NEW APPROACHES TO THE SYNTHESIS OF BENZOPYRANOPYRANS

Thesis submitted in accordance with the requirements of the University of Liverpool for the Degree of Doctor of Philosophy by

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B.Sc. (Sheffield).

August, 1986.

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ACKNOWLEDGEMENTS

The author is grateful for the award of a Postgraduate Studentship from the University of Liverpool and to Professor I. O. Sutherland for the opportunity to carry out this study at the Robert Robinson Laboratories, University of Liverpool.

In addition, the Technical Staff are thanked for the excellent spectroscopic, analytical and support services.

PREFACE

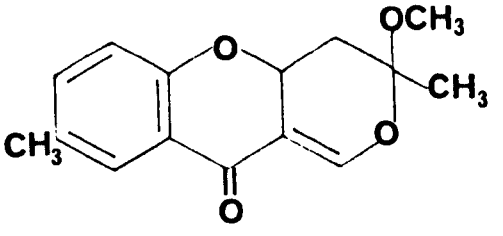
The author wishes to express his thanks to Dr. F. M. Dean for his enthusiasm, advice and encouragement throughout the course of this work.

To

Dad, Dandy and Pat

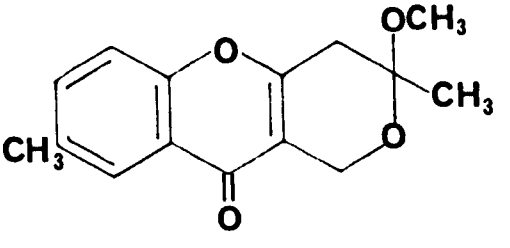
CONTENTS

Following this, Chapter Three describes construction of the key tricycle (4) via a Diels-Alder reaction between a 3-formylchromone (which may be variously substituted on the benzene ring) and 2-methoxypropene.



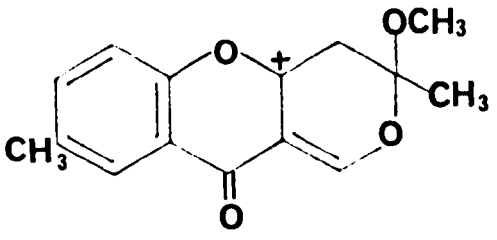
(4)

Tricycle (4) contains the same fused ring system as found in the target molecule (1) but this short and high yielding route to (4) was soon overshadowed by its lability towards acid or base. Accordingly, the following Chapter describes those attempts made to find neutral and mild reagents required to bring about a 1,3-hydrogen shift in adduct (4) generating the essential chromone (5).



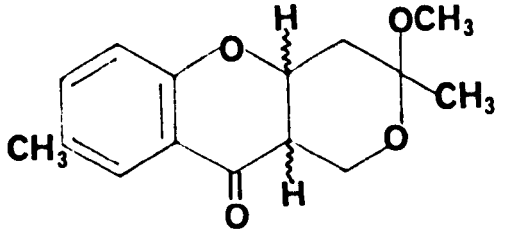
(5)

To this end, the use of homogeneous catalysis by transition metal complexes was investigated. In parallel with this work, the use of triphenylcarbenium salts as hydride acceptors was examined since, it was thought, loss of a hydride ion from (4) to such reagents might generate the allylic carbenium ion (6), attack of which by borohydride anion, for example, might generate (5).



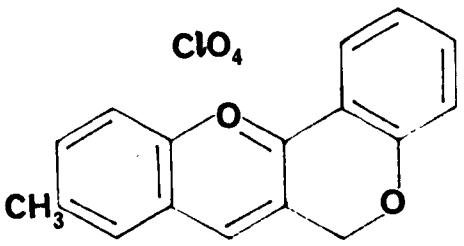
(6)

In the absence of useful results from these studies, however, a less direct conversion of (4) to (5) was sought and this work concentrated on the chemoselective reduction of (4) to the chromanone (7). This was to be followed by inducing a loss of hydrogen across the junction of the heterocyclic rings forming (5) in a sequential reduction-oxidation scheme.



(7)

The final Chapter describes an examination of pyrilium ions as models of the proposed intermediate (6). The salt (8) undergoes rearrangement to the homoisoflavone (9) under the action of borohydride ion in aqueous ethanol and it is shown here that the same bond isomerisation reaction may be brought about simply by admitting a trace of water to an acetonitrile solution of (8).



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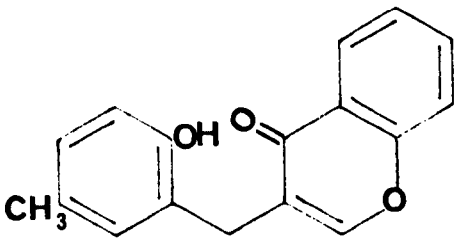
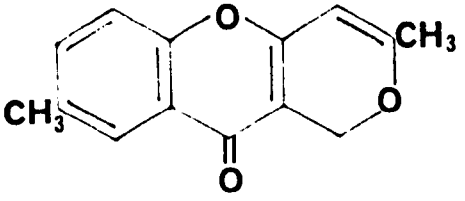


(9)

Salt (8) was one of a few oxonium ions tested as hydride abstracting reagents with adduct (4), one of which was successful. In this reaction, hydride ion was readmitted to the intermediate carbenium ion by means of the soft reducing agent, Hantzsch ester and, under the conditions of the reaction, methanol was eliminated and the elusive chromone (10) isolated in moderate yield.



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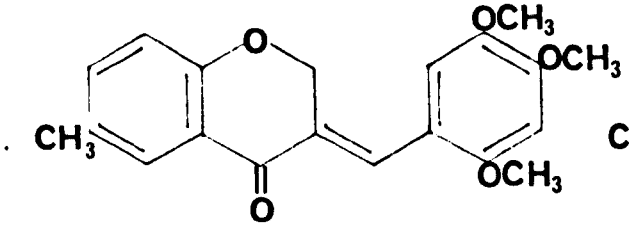
This novel bond isomerisation method was also successfully applied to the benzylidenechromanone (11), generating chromone (12) in 70% yield.



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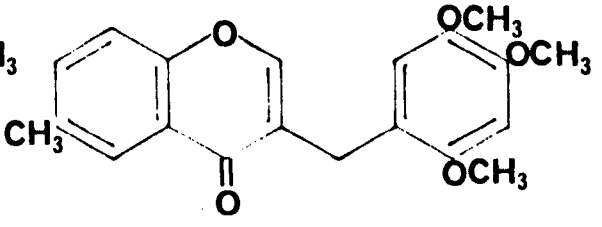

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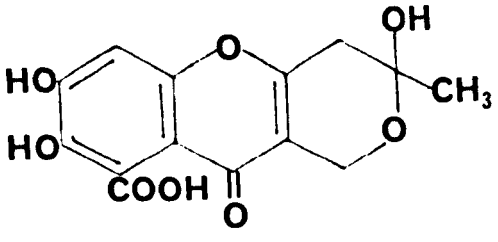
CHAPTER ONE

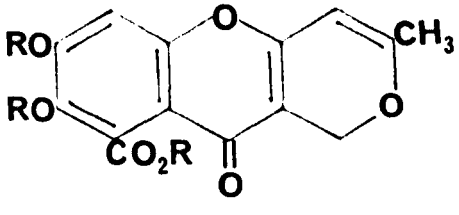
An Introduction to Fulvic Acid

Fulvic acid (1) is a yellow metabolite produced by several fungi including Penicillium, Carpenteles and Cereospora species and was first isolated by Raistrick[1] in 1935.



(1)

When heated in acetic acid, fulvic acid is smoothly transformed by dehydration into anhydrofulvic acid (2, R=H), $C_{14}H_{10}O_7$, isomeric with citromycetin[2] (3).



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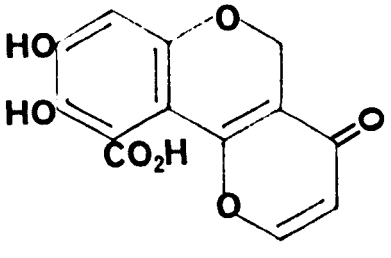
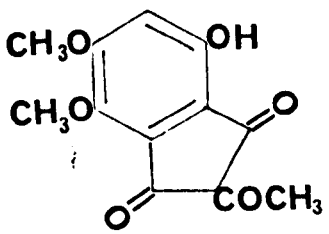


(3)

Structures for both fulvic acid and anhydrofulvic acid were proposed by Robertson et al[3] in 1957 though their correctness remained unverified until the advent of modern spectroscopic techniques some years later.[4] This delay in establishing the validity of the proposed structure for fulvic acid arose because none of the simpler degradation products retained

a chromone ring; alkaline hydrolysis of methylanhydro-O-methylfulvate (2, R=CH_3), for example, gives 2-acetyl-7-hydroxy-4,5-dimethoxyindan-1,3-dione (4).



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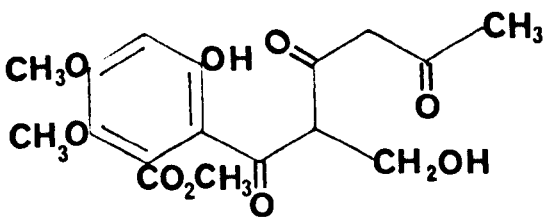
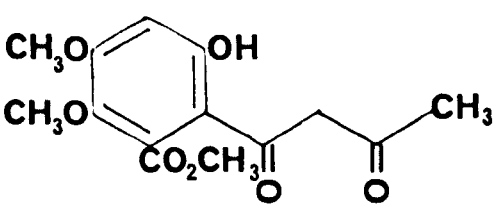


(5)

The formation of (4) is explained by considering the hydrolysis to involve the opening of both heterocyclic rings to give the (transitory) intermediate (5) which then undergoes both β-ketonic fission and retro-aldol condensation leading to an o-acetoacetylbenzoic ester (6).



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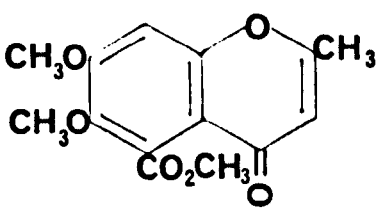
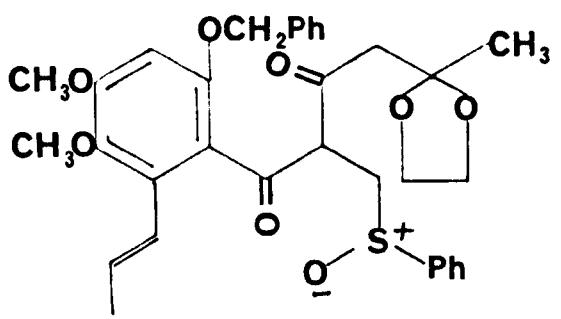


(7)

The β-ketonic side-chain then cyclises with the ester grouping by Claisen ester condensation to give the observed indanedione product. An alternative cyclisation pathway --that of the side-chain with the hydroxy group-- to give methyl 6,7-dimethoxy-2-methylchromone-5-carboxylate (7) does not occur. It has been shown[4] that chromone ester (7) produces the indanedione (4) when subjected to the experimental conditions used in

the alkaline degradation of the anhydrofulvate (2, R=CH_3). This experimental evidence, coupled with that provided by ultra violet, infra red and n.m.r. spectroscopy, left no doubt that fulvic acid does have structure (1).

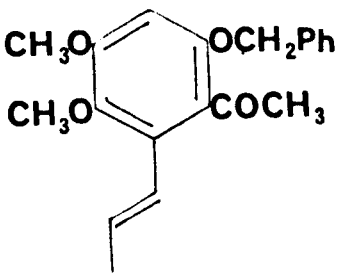
An analogue of the triketone (5), the speculative intermediate in the alkaline hydrolysis of methylanhydro-O-methylfulvate (2, R=CH_3), has been prepared and used as an intermediate in the first total synthesis of fulvic acid, described recently by Japanese workers.[5] This compound, the 2-methyl-sulphinylmethyl-1,3-dione (8) is a masked ene-trione and regioselective cyclisation generates the tricyclic skeleton of fulvic acid.



(8)

This synthesis of the metabolite, starting with vanillin, involves a total of 24 steps with an overall yield of 0.85%.

The acetophenone (9), chosen as a starting material, was prepared from vanillin via nine steps (32% overall yield) by a modification of Dean and Randells' method.[6] Aldol condensation of (9) with the aldehyde (10) afforded the hydroxyketone (11a).



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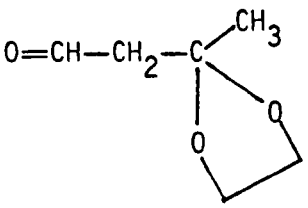
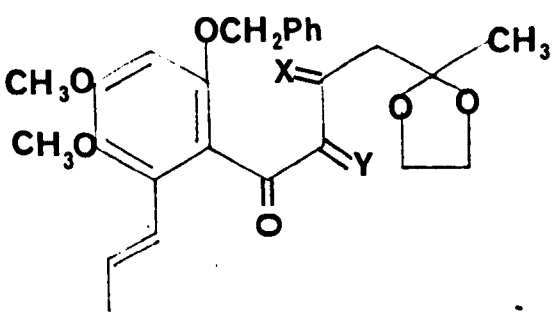
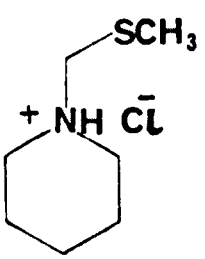


(10)

Conversion to the β-diketone (11b) was effected by treatment of (11a) with N-chlorosuccinimide and dimethyl sulphoxide followed by reduction with zinc dust and acetic acid. Alkylation of (11b) using methylthiomethylpiperidine hydrochloride[7] (12) in dioxane yielded the thiomethyldione (11c) which was oxidised to the sulphinylmethyl dione (8) by treatment with sodium metaperiodate in 72% total yield from (9).



(11a) X = H,OH; Y = H,H
(11b) X = O; Y = H,H
(11c) X = O; Y = H,CH_2SCH_3
(8) X = O; Y = H, $CH_2S(O)CH_3$



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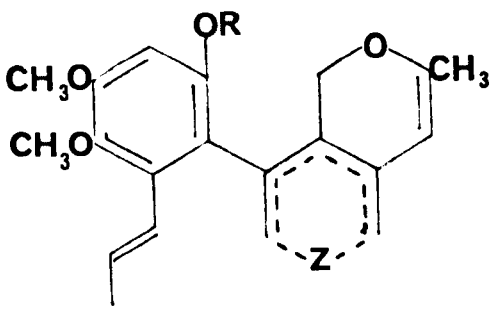
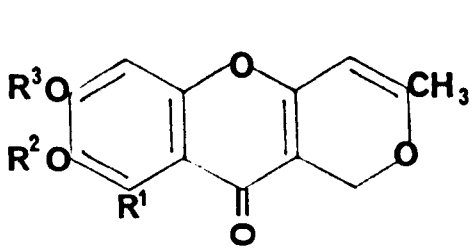
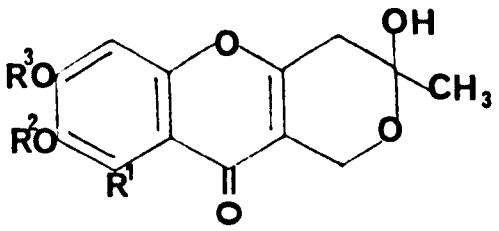
Dilute acid treatment of (8) caused regioselective cyclisation to the pyrone (13a) which was characterised as the BF_2-complex (13b).



(13a) R = CH_2Ph; Z = H
(13b) R = CH_2Ph; Z = BF_2
(13c) R = H; Z = BF_2

Debenzylation of (13b) was effected by boron trifluoride-diethyl etherate in a mixture of dimethyl sulphoxide and dichloromethane. Acid catalysed cyclisation of phenol (13c) afforded the pyrano[4,3-b][1]benzopyran (14a) in 22% yield from (8). Hydration of the pyrone (14a) to give the alcohol (15a), followed by ozonisation and reduction with dimethyl sulphide yielded the aldehyde (15b). Oxidation of (15b) with sulphamic acid and sodium chlorite and dehydration with a dilute sulphuric acid-acetone mixture afforded anhydrodi-O-methylfulvic acid (14b) in 74% yield. Double O-demethylation was effected by treatment of (14b) with aluminium chloride in dimethyl sulphide and dichloromethane at -10 ^{o}C. Finally, the conversion to fulvic acid (1), m.p. 242-244 ^{o}C, was achieved by hydration with a dilute hydrochloric acid-acetone mixture in 68% yield.





(14a) R^1 = $CH{=}CHCH_3$; $R^1{=}R^3{=}CH_3$
(14b) R^1 = CO_2H; $R^1{=}R^3{=}CH_3$

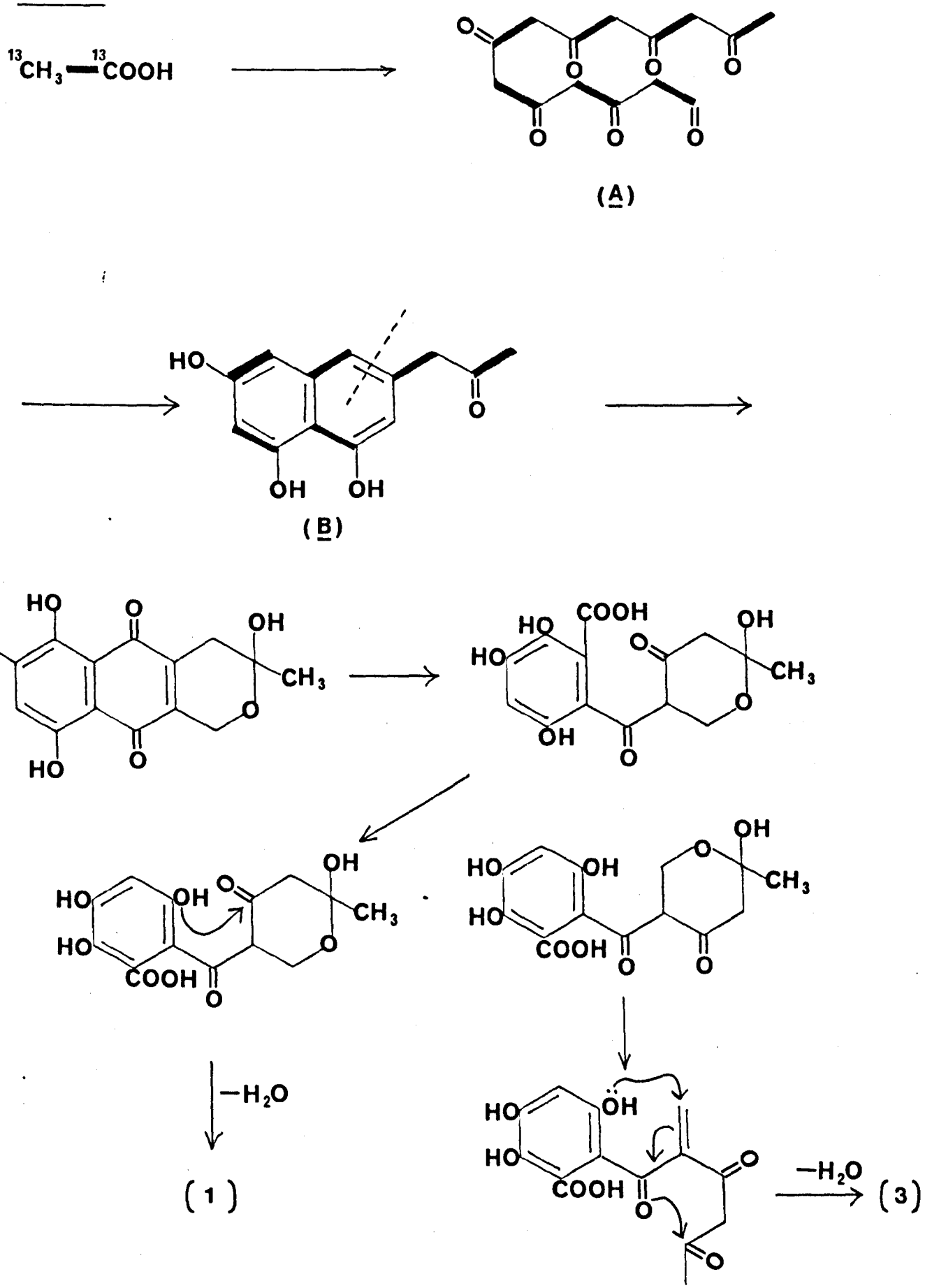
(15a) R^1= $CH{=}CHCH_3$; $R^2{=}R^3{=}CH_3$
(15b) R^1= $CH{=}O$; $R^2{=}R^3{=}CH_3$
(1) R^1= CO_2H; $R^2{=}R^3{=}H$

This method for the synthesis of fulvic acid constitutes a formal analogy to the biosynthetic pathway (vide infra).

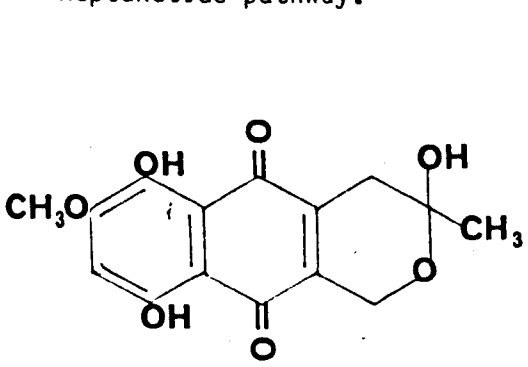
Fulvic acid (1), citromycetin (3) and fusarubin (16) have all been considered as having the same acyclic precursor (A in Scheme I). This progenitor can cyclise in three different modes, depending on organism-specific cyclising and processing reactions. Some workers[8] have postulated that the biosynthesis of fulvic acid (1) occurs via two, smaller poly-ketide chains.

^{13}C-Analysis of the regiochemistry of [1-^{13}C]acetate and [1,2-^{13}C]-acetate incorporation into fulvic acid (1) by Penicillium brefeldianum indicates that the metabolite is biosynthesised via a heptaketide intermediate;[9] these analyses suggest that this single-chain intermediate is folded in the manner shown in Scheme I. Intramolecular aldol cyclisation, to give intermediate (B), followed by oxidative fission of the indicated bond and appropriate bond reconnections, will give rise to (1), (3) and (16). In support of this hypothesis, fulvic acid (1) has recently been isolated

Scheme I



from Cercospora beticola Sacc.[10] -- an organism reported to produce cercosporin (17) which is known[11] to be synthesised through the simple heptaketide pathway.



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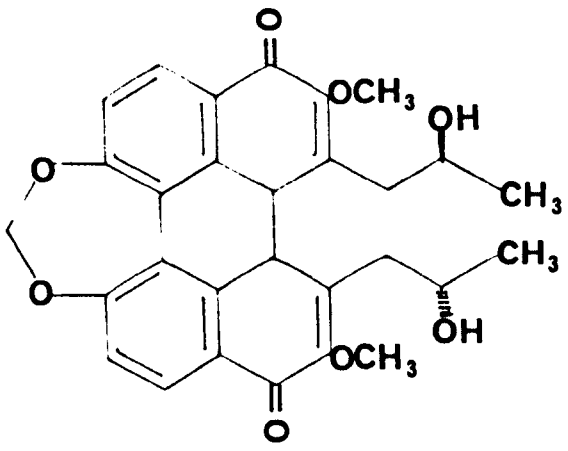
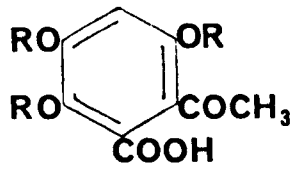


(17)

Fungi produce a number of metabolites that contain the pyranochromone nucleus found in fulvic acid and only few of these metabolites have been synthesised in the laboratory. Since chromones are valued for their anti-allergenic[12] and other activities, investigations of synthetical routes to pyranobenzopyrans of the chromone series have been undertaken in these laboratories. In so far as the total synthesis of fulvic acid or its anhydro-derivative (2, R=H), is concerned, these investigations have had two aims:

(i) the preparation of highly substituted o-acetylbenzoic acids of type (18, R=H,alkyl) suitable as starting materials for pyranopyrans, and;

(ii) the synthesis of the pyranopyran system (19) itself.



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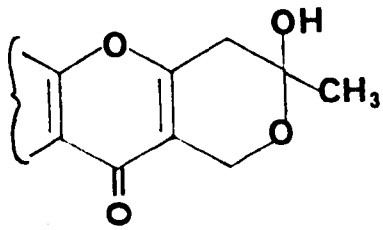
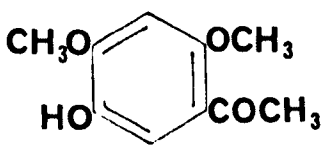


(19)

Earlier workers[13] had failed in their attempts to prepare o-acetylbenzoic acid derivatives from the phenolic ketone (20) or the hydroxy-acid (21) principally because of the resistance of these nuclei to electrophilic substitution.



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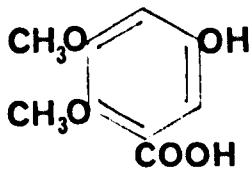
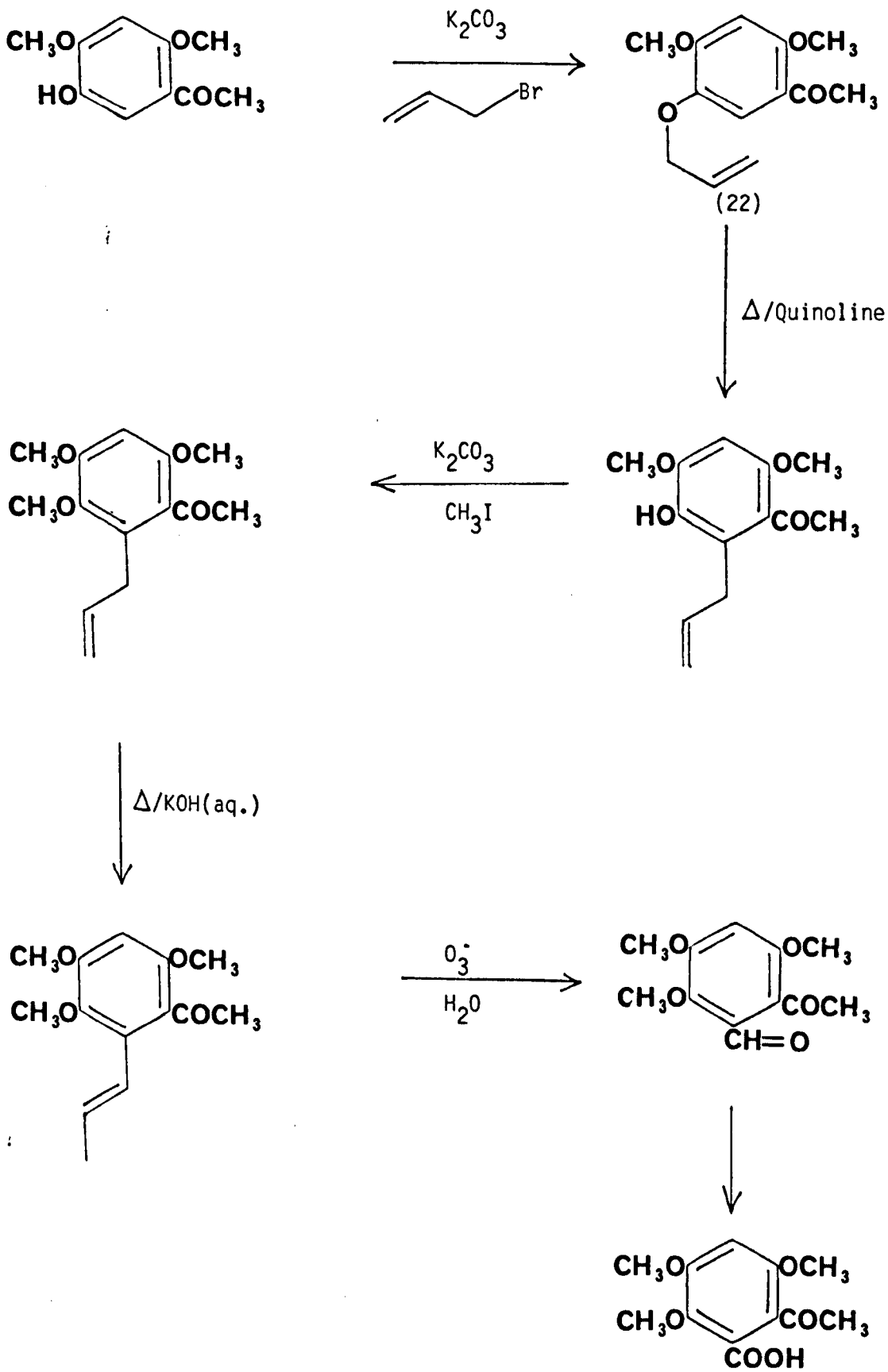


(21)

The synthesis of the benzoic acid (18, R=CH_3) was eventually achieved[14] by a long synthetical route (Scheme II) which had, as a key step, the Claisen rearrangement of the allylic ether (22). However, no attempt was made to elaborate the product to a benzopyranopyran principally because of inadequate yields in the last two steps shown in the Scheme.

The main complication in the synthesis of o-acetylbenzoic acids of the type (18) is the tendency of a free carboxylic function to react with an

Scheme II

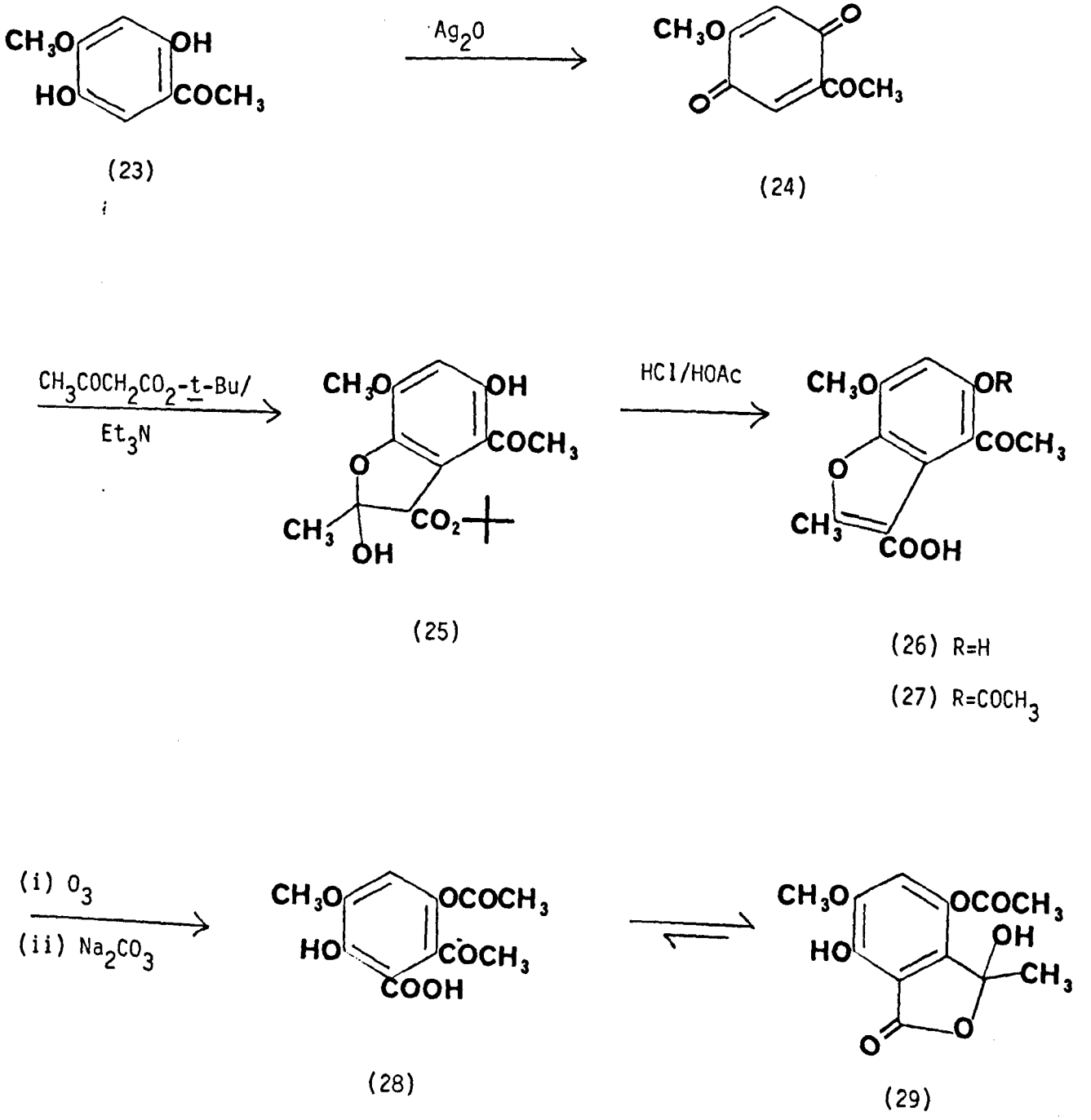

CH3O
OCH3
HO
COCH3
K2CO3
Br
O
(22)
Δ/Quinoline
HO
CH3I
CH3O
Δ/KOH(aq.)
O3
H2O
CH=O
COOH

o-acetyl grouping producing lactols. For example, the 2-acetylbenzoic acid (28) (Scheme III) exists predominantly as the lactol (29) making any elaboration of this substrate a rather tricky undertaking. Similarly, if the o-acetyl grouping is replaced by a ketonic side-chain, interaction with the free acid grouping will furnish an indanedione; as we have seen this occurence was responsible for confusion in earlier studies of the degradation of methylanhydro-O-methylfulvate (2, R=CH_3).

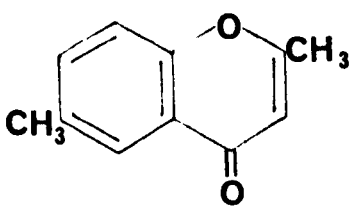
A later investigation[15] of the synthesis of the target o-acetylbenzoic acid, using benzofuran intermediates, was more effecient; the product (28) --existing predominantly as its tautomer (29)-- was prepared from vanillin in nine steps with an overall yield of 18%. The quinol (23), obtained in three steps from vanillin, was oxidised with silver oxide to provide the benzoquinone (24) and, following a method devised by Eugster,[16] its reaction t-butylacetoacetate in the presence of a catalytic amount of trietylamine, led to the hemiketal (25). Dehydration was effected by a mixture of acetic and hydrochloric acids; the resultant benzofurancarboxylic acid (26) was acetylated and, after alcoholysis, provided the benzofurancarboxylic acid (27). Finally, treatment of (27) with ozone followed by a work-up involving aqueous sodium carbonate solution furnished the target o-acetylbenzoic acid (28).

It is worthy of note in this sequence to 2-acetylbenzoic acids, the nuclear carboxylic function was masked until the ozonolysis reaction. Such protection avoids a possible cyclisation with the ketonic side-chain, leading to indanedione derivatives. Partly because (28) exists predominantly as the lactol (29), later synthetical work began with the immediate precursor of (29), the benzofurancarboxylic acid (27). The action of lithium bis(trimethylsilyl)amide on (27) effected a Baker-Venkataraman rearrangement to the dioxophenol (30) which, upon treatment with trifluoroacetic acid,

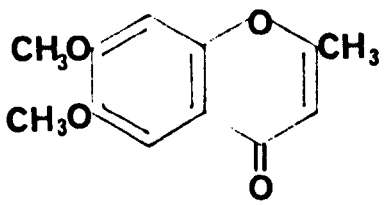
Scheme III


CH3O
OH
HO
COCH3
Ag2O
(23)
(24)
CH3COCH2CO2-t-Bu/
Et3N
HCl/HOAc
CO2
CH3
OH
OR
COOH
(25)
(26) R=H
(27) R=COCH3
(i) O3
(ii) Na2CO3
OCOCH3
(28)
(29)

afforded the furochromone (31), (Scheme IV). It was envisaged that (31) would then be converted into the 3-chlormethyl derivative (32) which, by selective ozonolysis[17] at the furan double-bond followed by appropriate work-up, might yield the 2-methyl-3-chloromethylchromonecarboxylic acid (33). As recent investigations in these laboratories[15] with less highly substituted 2-methyl-3-chloromethylchromones had established two routes to the pyrano-pyran system, it was thought that (33) might serve as a potential starting material for either of these. In practice, however, the synthesis of (32) could not be realised: the chloromethylation reagents and reaction conditions which had proved successful with simpler chromones --for example (34)-- had no effect when applied to (31) or the similarly substituted model (35).



(34)

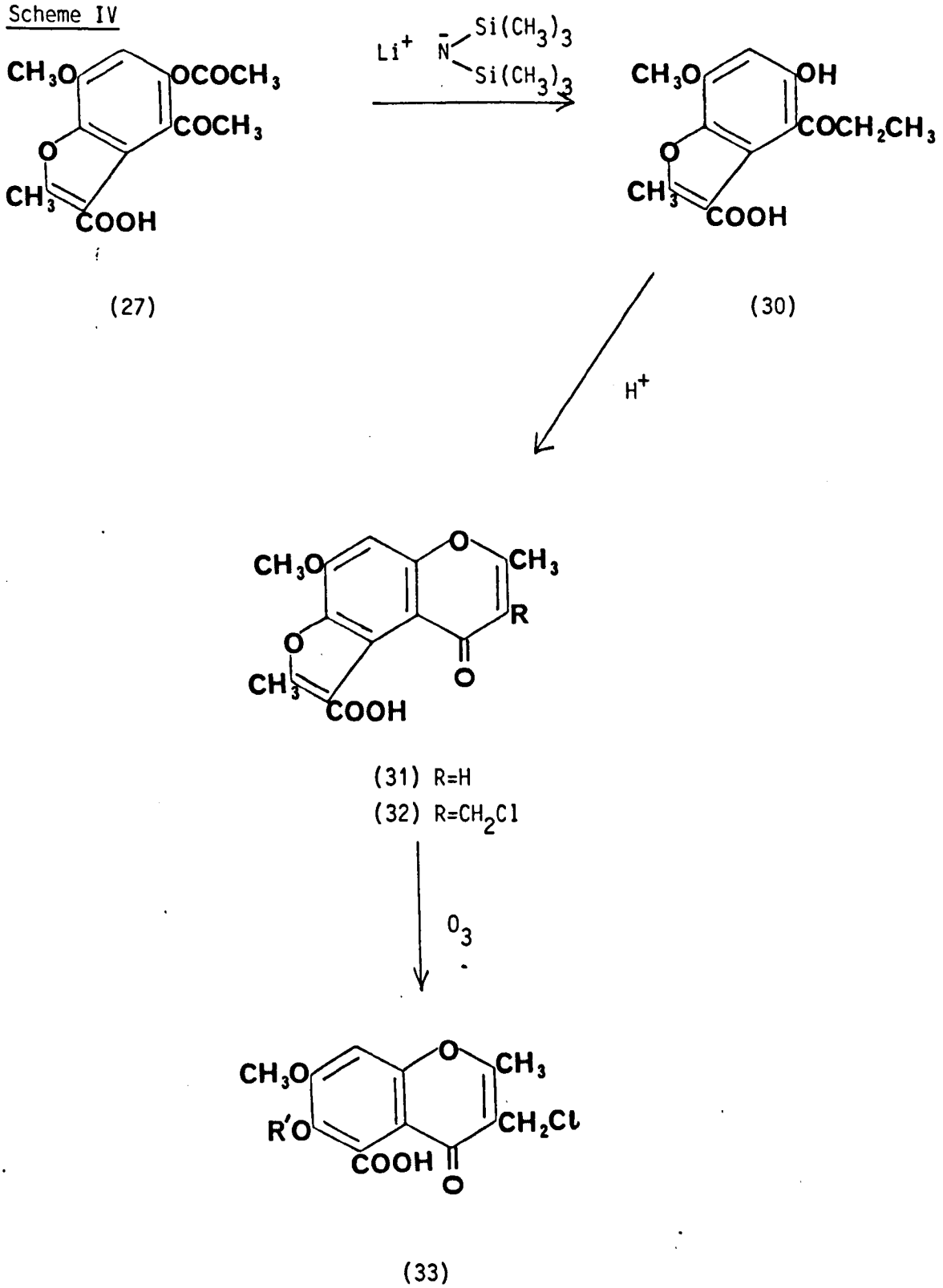


(35)

The reasons for the failure of the chloromethylation reaction will be discussed in Chapter 3 since they are central to the development of a new synthetical scheme which overcomes this difficulty and others arising from the use of such highly substituted precursors of the type (31) or (35).

As stated before, the construction of relatively simple derivatives of the pyrano[4,3-b][1]benzopyran nucleus characteristic of fulvic acid has been successful. In particular, a model of anhydrofulvic acid, i.e. 3,8-dimethyl-1H,10H-pyrano[4,3-b][1]benzopyran-10-one, has been synthesised

Scheme IV



(27)

(30)

(31) R=H

(32) R=CH_2Cl

(33)

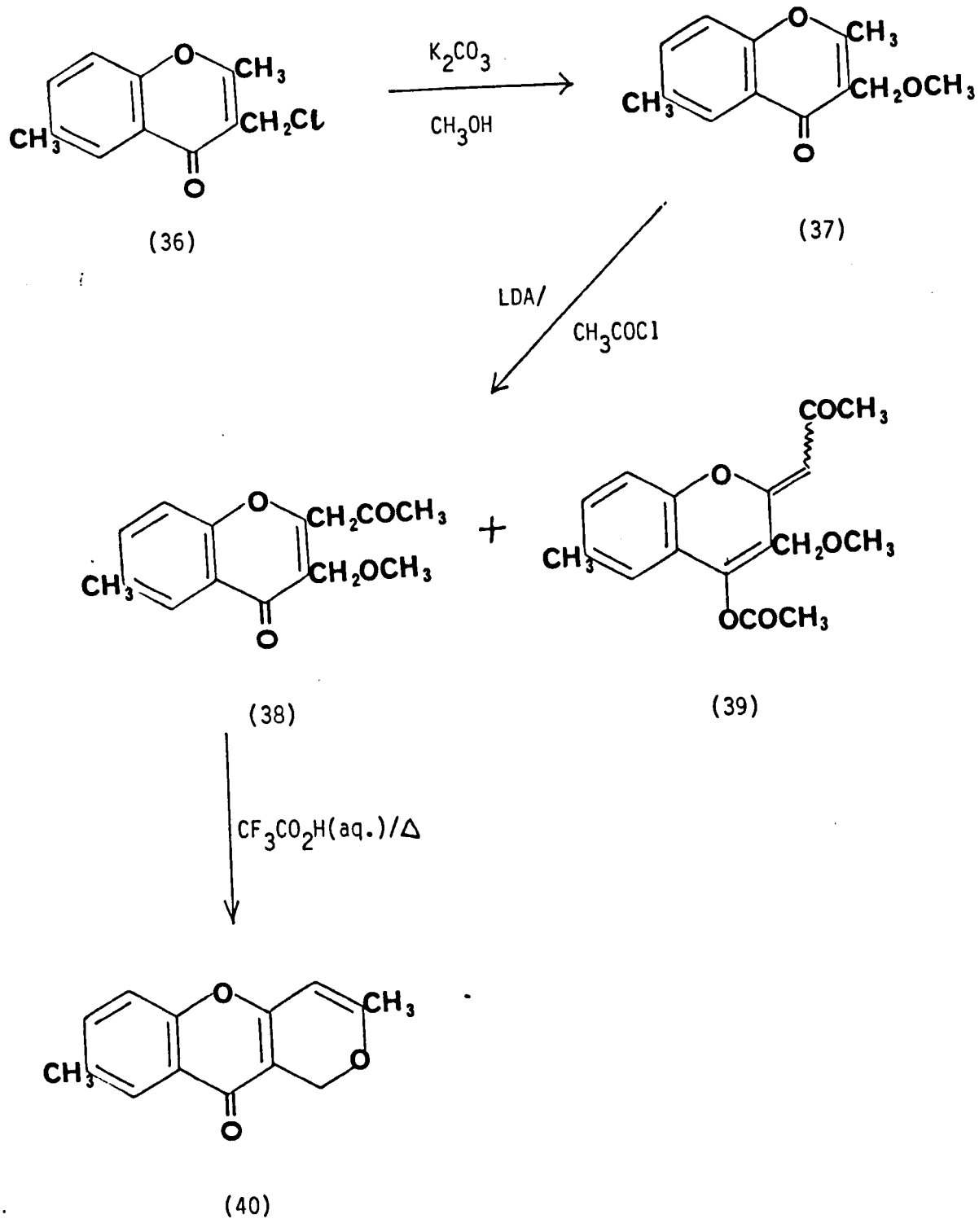
by two methods, each of which start with chromones. The common starting material for both routes is 3-chloromethyl-2,6-dimethylchromone (36) -- acquired by treatment of 2,6-dimethylchromone with gaseous hydrogen chloride and paraformaldehyde in hot, aqueous acetic acid.

In one of these routes, (Scheme V), the 3-chloromethyl derivative (36) is converted by brief treatment with methanol and base into the analogous 3-methoxymethyl compound (37). Lithiation of (37) (lithium diisopropylamide in tetrahydrofuran at -78 ^{o}C) and subsequent acetylation with acetyl chloride afforded the desired 2-acetylchromone (38) along with the diacylated compound (39). Hydrolysis of (38) with damp trifluoroacetic acid under reflux replaced OMe with OH thus permitting cyclodehydration to the required 3,8-dimethyl-1H,10H-pyrano[4,3-b][1]benzopyran-10-one (40) in a yield of 34% from (41).

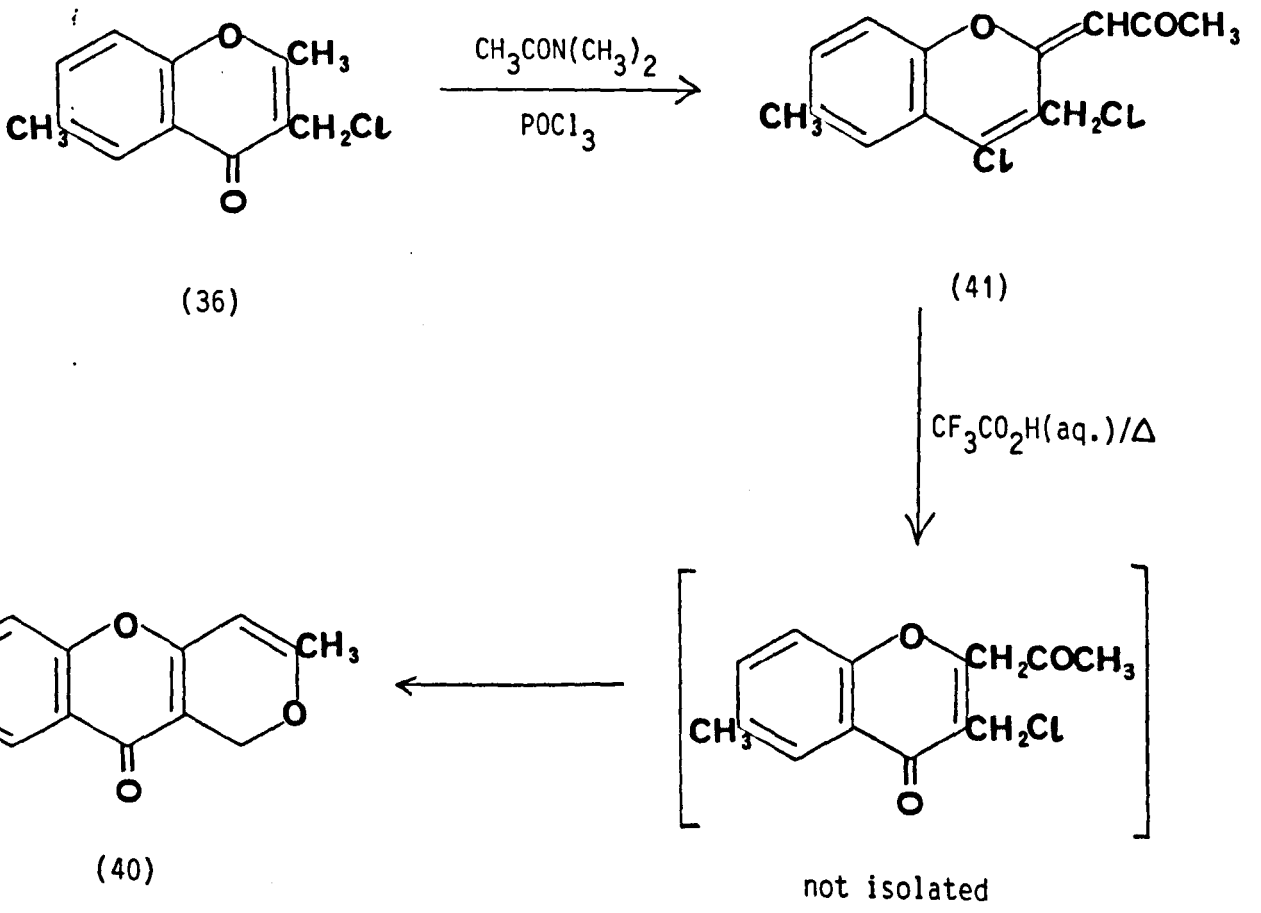
The other route to (40) involved the acid-catalysed acetylation of (36) with N,N-dimethylacetamide in the presence of phosphoryl chloride at 110 ^{o}C, (Scheme VI). The resultant imminium salt was converted into the chloro-chromene (41) by careful hydrolysis. Hydrolytic removal of halogen by damp trifluoroacetic acid under reflux resulted in the required pyranopyran (40) though in only 22% yield from (41).

Finally, another synthesis of the basic skeleton of fulvic acid which deserves mention here is that reported by Japanese workers in preliminary studies[18] directed towards their, eventually successful, total synthesis of the metabolite. Inasmuch as the starting block for this synthesis is the acetal (42) (Scheme VII) which subsequently undergoes a regioselective cyclisation, this scheme mimics the biogenesis of fulvic acid which has been discussed earlier. Dilute acid treatment of the acetal (42) at room temperature gave the pyrone (43) as a single cyclisation product in 97%

Scheme V


CH3
CH2Cl
O
K2CO3
CH3OH
CH3
CH2OCH3
(36)
(37)
LDA/
CH3COCl
CH2COCH3
CH2OCH3
COCH3
OCOCH3
(38)
(39)
CF3CO2H(aq.)/Δ
(40)

Scheme VI



(36)

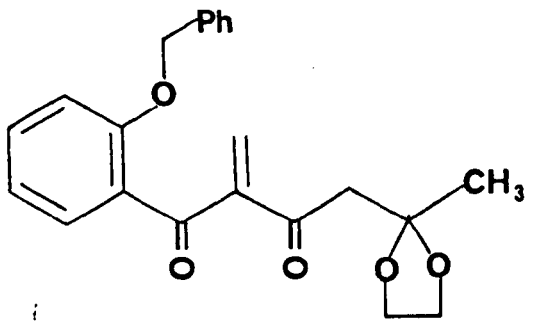
(41)

(40)

not isolated

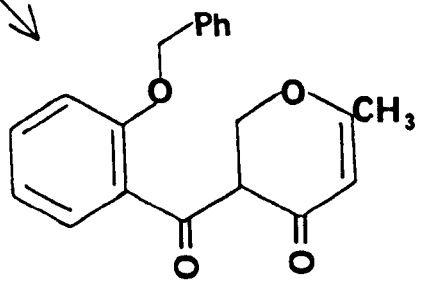
yield. Prior formation of the boron complex (44a) improved the yield in the debenzylation reaction to give product (44b). Acid catalysed cyclisation of this phenol gave the pyranobenzopyran (45) in 75% overall yield based on (42).

Scheme VII



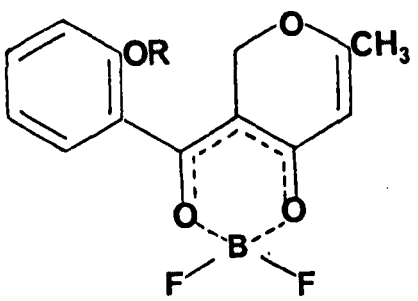
(42)

H^+



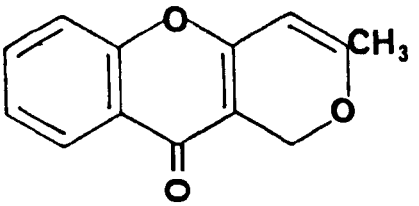
(43)

BF_3-Et_2O



(44a) R=CH_2Ph
(44b) R=H

HCl/HOAc (1:10)



(45)

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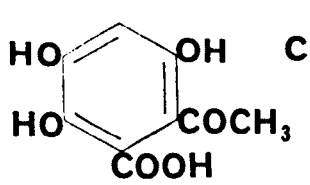
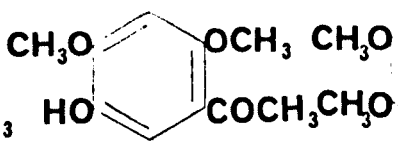
CHAPTER TWO

Synthesis of Derivatives of 3,5-Dihydroxybenzoic Acid

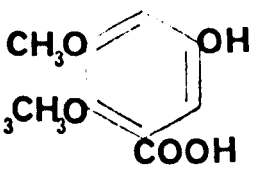
This Chapter describes attempts directed towards the synthesis of 2-acetyl-3,5,6-trihydroxybenzoic acid (1). As remarked in Chapter One, earlier attempts at the synthesis of similar 2-acetylbenzoic acids were inefficient because of the number of synthetical steps involved or the resistance of the phenolic ketone (2) or the hydroxyacid (3) to electrophilic attack.



(1)



(2)

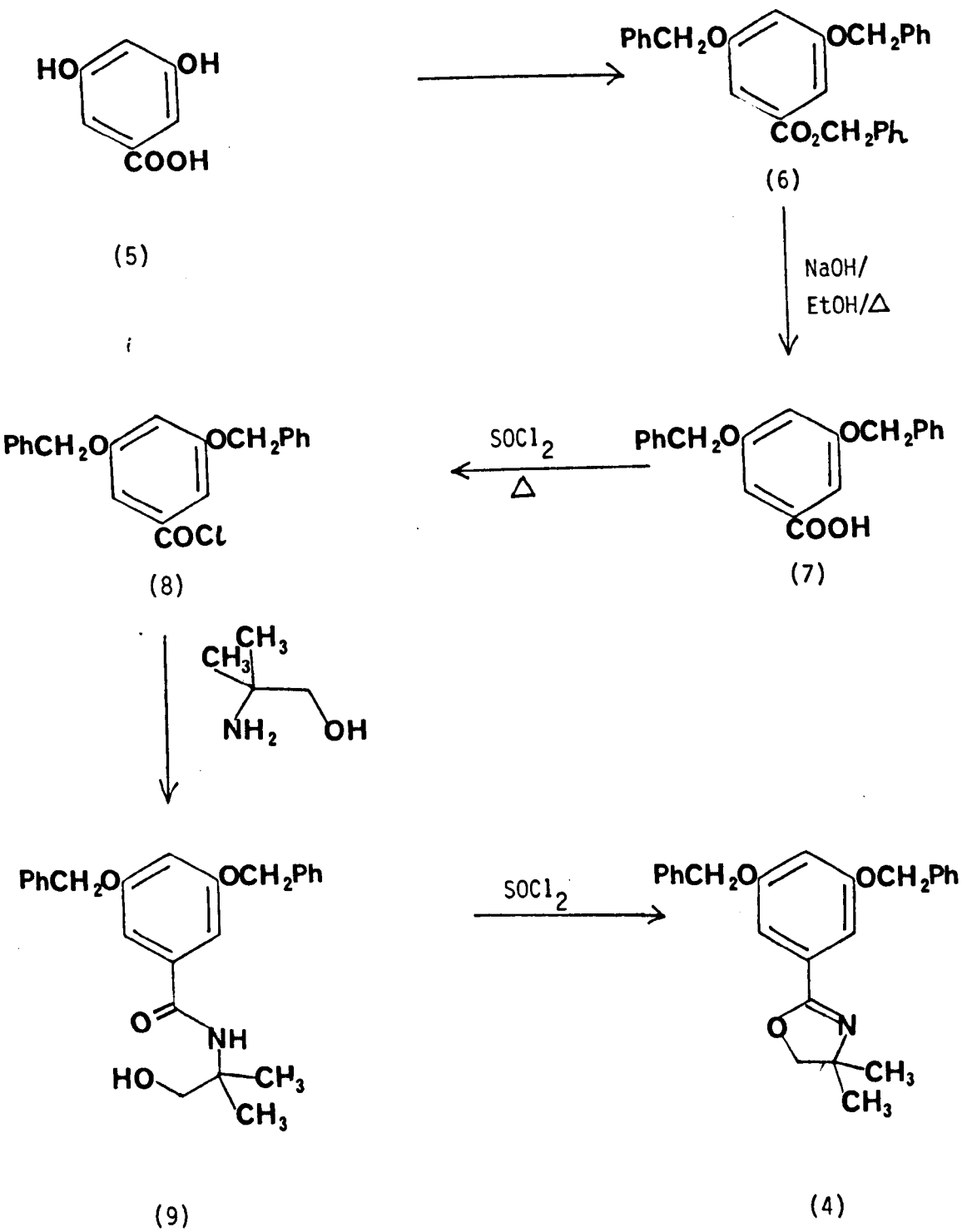


(3)

The present work describes an alternative approach in which the carboxylic group was to be masked as its oxazoline derivative. Starting from the readily available 3,5-dihydroxybenzoic acid, we hoped to construct the oxazoline (4) by the route shown in Scheme I. The synthetic utility of oxazolines in aromatic substitution is now well established, particularly with respect to the efficacy of this grouping as a director for o-lithiation of the benzene nucleus.[1] Ready access to the required 2,6-disubstituted benzoic acid should be realised by sequential metalations and treatment with the appropriate electrophiles, followed by hydrolysis of the oxazoline ring and debenzylation.

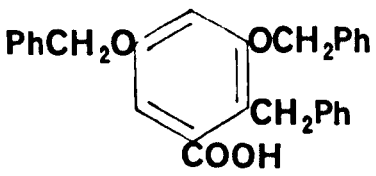
On a small scale, the synthesis of oxazoline (4) was successful. Reaction of the acid (5) with benzyl bromide in acetone in the presence of

Scheme I


HO
OH
COOH
(5)
PhCH2O
OCH2Ph
CO2CH2Ph
(6)
NaOH/
EtOH/Δ
PhCH2O
OCH2Ph
COOH
(7)
SOCl2
Δ
PhCH2O
OCH2Ph
COCl
(8)
CH3
CH3
NH2
OH
PhCH2O
OCH2Ph
O
NH
HO
CH3
CH3
(9)
SOCl2
PhCH2O
OCH2Ph
O
N
CH3
CH3
(4)

potassium carbonate gave the benzyl ester (6), which was hydrolysed with ethanolic sodium hydroxide solution to give the acid (7). Treatment of (7) with thionyl chloride gave the acyl chloride (8) in 80% yield from (5). The amide (9) was obtained by treatment of (8) with 2-amino-2-methyl-propan-1-ol at 0 °C and cyclised with thionyl chloride to afford the oxazoline (4).

Subsequent attempts to obtain (4) on a preparative scale using this sequence were hampered at an early stage by the production of the o-benzyl acid (10), along with the desired acid (7), from the hydrolysis of the benzyl ester (6).



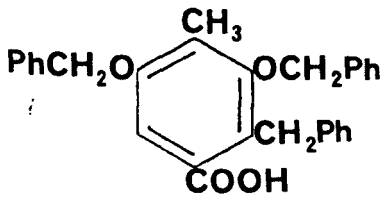
(10)

This compound was consistently obtained in unacceptably high yields on repeating the alcoholysis of (6) with modifications to the experimental conditions and the acidic work-up procedure. After many attempts it was found that best results were obtained by stirring the ester during one hour with 10% sodium hydroxide solution in a water-ethanol (1:5 v/v) mixture at reflux temperature and neutralising the mixture at 0 °C with hydrochloric acid (pH 3-4). This procedure afforded the o-benzyl acid (10) in 20% yield and the required acid (7) in 67% yield.

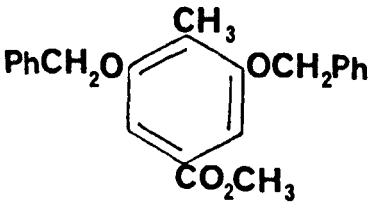
A brief survey of the literature revealed that other workers have encountered this problem of unwanted nuclear benzylation. Whalley and co-workers[2] describe the formation of 2-benzyl-3,5-dibenzyloxy-4-methyl-benzoic acid (11), obtained as a minor product in the alkaline hydrolysis of the parent **methyl** ester (12). Similarly, when we examined the hydrolysis of the methyl ester (13), under those conditions that had been found most advantageous with the benzyl ester (6), acidic work-up afforded a mixture of the required acid (7) and the undesired acid (10) in approximately a 9:1 ratio. Despite this improvement in the yield of (7), the separation of the two products could not be realised by fractional crystallisation and chromatographic separation of such large amounts of material proved laborious and too time-consuming to justify continuing with this route on the scale we would have liked.

Nevertheless, with a portion of the stock of (7) which had accrued during these experiments, it was decided to test the feasibility of the remainder of the synthetical sequence, i.e. from (7) to the oxazole (4), on a preparative scale. Similar complications to those outlined above, however, arose in the last step of the synthesis. Cyclisation of the amide (9) with thionyl chloride afforded a mixture of two products which were shown by n.m.r. analysis to be the required oxazole (4) and the o-benzyl oxazole (14). The yield of (14) was small though not negligible and its separation from (4) was only effective by silica gel column chromatography. While the yield of (14) could be reduced further by more rigorous purification of the thionyl chloride and dichloromethane/diethyl-ether solvent mixture, reaction conditions supplying (4) as the sole product were not realised.

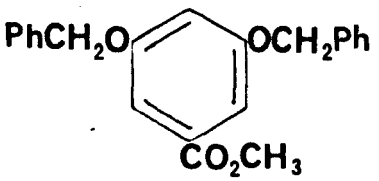
It appears that the presence of acid, either added to neutralise


CH3
PhCH2O
OCH2Ph
CH2Ph
COOH

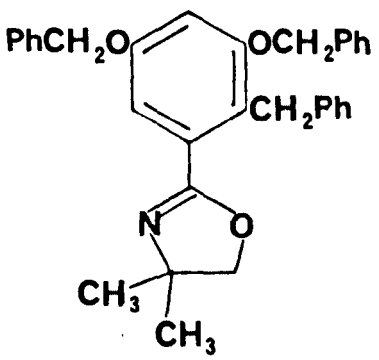
(11)


CH3
PhCH2O
OCH2Ph
CO2CH3

(12)

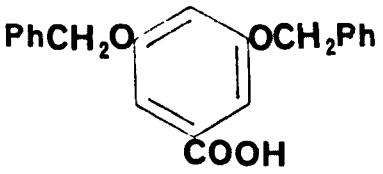

PhCH2O
OCH2Ph
CO2CH3

(13)

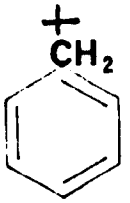

PhCH2O
OCH2Ph
CH2Ph
N
O
CH3
CH3

(14)

the alkaline slurry after hydrolysis of (6) or when produced in the thionyl chloride induced cyclisation of the amide (9) is responsible for the incidence of nuclear benzylation. Moreover, it is likely that the addition of even such a bulky electrophile as (15) to the already sterically hindered acid (7) is facilitated by electron release from the benzyloxy groups. Such electron release will increase the π-electron density at the free ortho positions of the benzoic acid and it is here that electrophiles will add in preference, for example, to the free para position. [In contrast to simple carbenium ions, ion (15) is readily formed and stabilised by charge delocalisation via the agency of the delocalised π orbitals of the benzene nucleus].

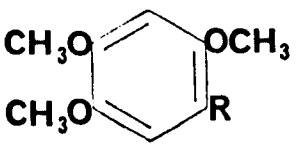


(7)

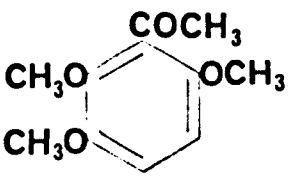


(15)

This phenomenon of electron release from alkoxy groups has been observed before, especially with hydroxy quinol and its ethers. It is reported,[3] for example, that under very mild conditions, acetic acid and polyphosphoric acid convert 1,2,4-trimethoxybenzene (16) into the ketone (17) and that, under the same conditions, the isomeric ketone (18) rearranges into (17).

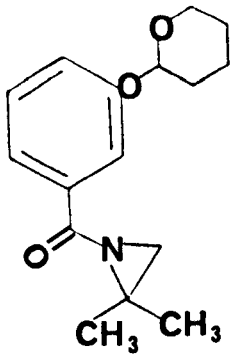


(16) R=H
(17) R=$COCH_3$

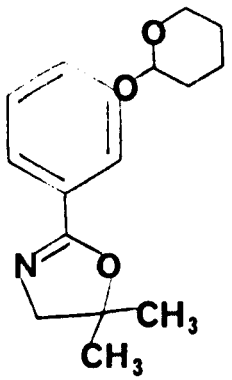


(18)

As the use of thionyl chloride in the final step of our synthetical sequence produces hydrochloric acid which promotes production of the undesired oxazole (14), we sought a means of constructing the oxazoline ring which avoids the use of thionyl chloride. An alternative method of constructing the ring system has been described by Meyers et al[4] which proceeds via rearrangement of an N-acyl aziridine. Although this rearrangement is acid-catalysed, these authors claim that the conditions employed are so mild that the acyl aziridine (19), for example, was successfully transformed into the isomeric oxazoline (20) without hydrolysis of the tetrahydropyranyl grouping.



(19)

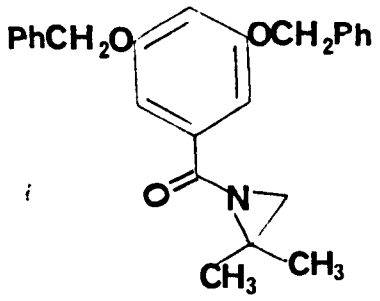


(20)

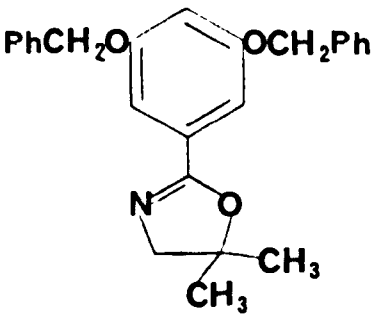
In view of the mild acid conditions of this reaction, we thought this method worth investigating whilst retaining the benzyl protecting groups for the hydroxy functions.

Reaction of the acyl chloride (8) with 2,2-dimethylaziridine in tetrahydrofuran (containing triethylamine) afforded the benzoylaziridine (21) in 58% yield. Subsequently, attempts to isomerise this compound to the required oxazoline (22) using the standard procedure proved fruitless:

addition of a catalytic amount of sulphuric acid in dichloromethane afforded an amorphous solid which resisted purification.



(21)



(22)

Perhaps the presence of acid might again be implicated in the failure of this reaction; the use of an alternative, less acid-labile protecting group for the hydroxy functions now appears an attractive proposition. Of those protecting groups considered initially, the benzyl grouping seemed most advantageous from a practical point of view. This moiety attributes 182 Daltons to each intermediate and the projected multi-step synthesis to the target (4) would be helped considerably by having plenty of material at each step. Additionally, the ease of removal of such groups (catalytically, under mild, neutral conditions) at the end of the sequence was taken into account.

Work on this project was ceased at this point in order to concentrate upon building the tricyclic skeleton of fulvic acid with less highly substituted precursors and an account of this work is given in the next Chapter.

EXPERIMENTAL

Unless otherwise stated:

Melting points were determined on a Köfler block and are uncorrected;

Product purity was checked by thin layer chromatography (t.l.c.) on Merck 10 x 2 cm aluminium-backed plates with 0.2 mm layer of kieselgel 60 F_{254}. Column chromatography was carried out over pre-activated silica gel 60 (E. Merck No. 9385), 40-63 μm, 400-230 mesh under nitrogen at 2 p.s.i.;

Nuclear magnetic resonance (n.m.r.) proton spectra (δ-scale; coupling constants, J quoted in Hertz) were recorded either on a Perkin-Elmer R34 (220 MHz) or a Bruker WM250 (250MHz) spectrometer. Spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard. The multiplicities of the resonances are given in the following manner: s(singlet); d(doublet); t(triplet); q(quartet); dd(double doublet) and m(multiplet);

Infra red spectra were measured on a Perkin-Elmer 125 spectrophotometer for KBr discs;

Ultra violet spectral measurements (λ_{max}, ϵ) were made on a Unicam SP800 spectrophotometer;

Mass spectra were recorded either on an A.E.I. MS902 or a V.G. Analytical 7070E Spectrometer;

All reaction solvents were distilled before use;

Ether refers to diethyl ether;

Light petroleum refers to that fraction boiling between 60-80 °C.

All glassare was flame-dried in a stream of dry nitrogen before use;

Nitrogen: passed alternately through concentrated sulphuric acid and potassium hydroxide pellets;

Acetone: dried over anhydrous sodium sulphate and distilled over freshly activated molecular sieves (type 4A);

Thionyl chloride: dried over calcium chloride overnight and distilled;

Benzene: dried over sodium wire and distilled from calcium hydride;

Toluene: as for benzene;

Triethylamine: distilled from calcium oxide and stored in the dark over molecular sieves (type 5A);

Tetrahydrofuran: twice distilled from lithium aluminium hydride;

2,2-Dimethylaziridine: prepared according to the method of Campbell, Campbell and Sommers[5] and distilled from potassium hydroxide pellets immediately before use.

3,5-Bis(benzyloxy)benzoic Acid (7)

To a solution of 3,5-dihydroxybenzoic acid (5) (2.5 g) in dry acetone (50 ml) was added potassium carbonate (13 g) and benzyl bromide (8.5 g). The reaction mixture was stirred at reflux temperature for 72 hours before the solvent was evaporated under reduced pressure to afford a colourless oil. This oil was dissolved in ether (250 ml) and the ether solution was washed with water (100 ml x 3), dried (Na_2SO_4) and evaporated. The resulting residue was refluxed with 10% ethanolic sodium hydroxide solution (200 ml) for one hour before being cooled and stirred at 0 °C while hydrochloric acid (pH 3-4) was added dropwise until the mixture reached pH 7. Solvent was evaporated under reduced pressure and the residue

extracted with ether (250 ml). The ether solution was washed with water (100 ml x 3), dried (Na_2SO_4) and evaporated to give the acid (7) which crystallised from ethyl acetate as colourless needles (4.1 g), m.p. 214-216 °C (lit:[6] 214-216 °C).

The above synthetical scheme was next carried out on a preparative scale. To 3,5-dihydroxybenzoic acid (5) (30 g) in dry acetone (500 ml) was added potassium carbonate (100 g) and benzyl bromide (73 g). The mixture was stirred at reflux for 72 hours and work-up in the manner described above afforded an off-white solid (65.2 g) which t.l.c. analysis indicated to be a mixture of two compounds. These were separated by silica gel column chromatography with toluene as eluant affording 3,5-bis(benzyloxy)benzoic acid (7) (43.6 g, 67%), m.p. 213-216 °C and the 2-benzyl acid derivative (10) (16.5 g, 20%) which crystallised from ethanol as colourless needles, m.p. 149-151 °C.

Found (EMAL 18888): C,79.22; H,5.81%

$C_{28}H_{24}O_2$ requires: C,79.21; H,5.70%

Accurate Mass found: 424.16964

$C_{28}H_{24}O_2$ requires: 424.16744.

ν_{max}: 2950br. (CO_2H); 1690 (C=O); 1600 (C=C) $cm.^{-1}$

δ ($CD_6C=O$): 4.42 [2H, s, C(2)CH_2Ph];

5.11 [2H, s, C(3)OCH_2Ph];

5.14 [2H, s, C(5)OCH_2Ph];

6.5-7.54 (17H, m, aromatic H).

The mother liquor of the 2-benylbenzoic acid (10) was left to stand at room temperature over 48 hours and deposited more crystals. These had separated as needles of ethyl 2-benzyl-3,5-bis(benzyloxy)benzoate (300 mg),

m.p. 75-77 °C.

Found (ML 22683): C,79.38; H,6.29%

$C_{30}H_{28}O_4$ requires: C,79.61; H,6.24%

Accurate Mass found: 452.20068

$C_{30}H_{28}O_4$ requires: 452.19873.

ν_{max}: 1695 (C=O); 1600 and 1575 (C=C) $cm.^{-1}$

δ : 1.19 (3H, t, J7Hz, $CH_2\underline{CH_3}$);

4.21 (2H, q, J7Hz, $\underline{CH_2}CH_3$);

4.30 [2H, s, C(2)$\underline{CH_2}$Ph];

4.91 [2H, s, C(3)O$\underline{CH_2}$Ph];

4.99 [2H, s, C(5)O$\underline{CH_2}$Ph];

6.70 [1H, d, J3Hz, C(4)H or C(6)H];

7.0-7.4 (16H, m, aromatic H).

N-(2,2-Dimethyl-3-hydroxypropyl)-3,5-bis(benzyloxy)benzamide (9)

A solution of 3,5-bis(benzyloxy)benzoic acid (7) (334 mg) in thionyl chloride (3 ml) was refluxed for two hours after which time excess thionyl chloride was removed by co-distillation with dry benzene. Trituration of the remaining dark oil with ether afforded the acyl chloride (8) as a granular, off-white solid (270 mg) which was used without further purification. A solution of acyl chloride (8) in dichloromethane (10 ml) was added dropwise during ten minutes to a stirred dichloromethane solution of 2-amino-2-methylpropan-1-ol (70 mg) at 0 °C. While stirring at this temperature for 2.5 hours, a white precipitate formed which was collected and washed with a little cold water. This solid was combined with that obtained by concentrating and cooling the dichloromethane filtrate and the benzamide (9) crystallised from ether

(charcoal treatment) as fine needles (368 mg), m.p. 93-95 °C.

Accurate Mass found: 405.193420

$C_{25}H_{27}N_1O_4$ requires: 405.194008

m/e: 387 (M^+-H_2O); 374 (M^+-OCH_3).

ν_{max}: 3310br. (NH,OH); 1625 (C=O) and 1590 (C=C) $cm.^{-1}$

δ : 1.30 (6H, s, $2xCH_3$);

3.12 (2H, s, $C\underline{H}_2OH$):

5.01 (4H, s, $2xOC\underline{H}_2Ph$);

6.18 (1H, br.s., NH, D_2O-exchangeable);

6.71 [1H, d, J2Hz, C(4)H];

6.95 [2H, d, J2Hz, C(2)H and C(6)H];

7.25-7.52 (10H, m, aromatic H).

2-[3,5-Bis(benzyloxy)phenyl]-4,4-dimethyl-2-oxazoline (4)

The amide (9) (387 mg, 1 mmol) was suspended in toluene (10 ml) at 0 °C and thionyl chloride (0.2 ml, 3 mmol) was added. After one hour, the yellow solution was poured into dry ether (100 ml) whereupon white crystals separated out and were filtered off. The hydrochloride salt was neutralised with two drops of cold 10% sodium hydroxide solution and extracted with ether (100 ml). The ether was dried (Na_2SO_4) and evaporated under reduced pressure to give oxazoline (4) as a white powder which was recrystallised twice from light petroleum (b.p. 40-60 °C) to afford prisms (317 mg), m.p. 86 °C.

Found (EMAL 18884): C,77.43; H,6.60; N,3.61%

$C_{25}H_{25}N_1O_3$ requires: C,77.48; H,6.51; N,3.61%

Accurate Mass found: 387.184799

$C_{25}H_{25}N_1O_3$ requires: 387.183443

m/e: 296 (M^+-$PhCH_2$); 268 (296-CO).

ν_{max}: 1645 (C=N); 1600 and 1580 (C=C) $cm.^{-1}$

δ : 1.33 (6H, s, 2 x CH_3);

4.06 [2H, s, $C\underline{H}_2C(CH_3)_2$];

5.02 (4H, s, 2 x $C\underline{H}_2Ph$);

6.70 [1H, s, C(4)H];

7.21 [2H, s, C(2)H and C(6)H];

7.3-7.6 (10H, m, aromatic H).

A preparative scale synthesis of the title compound was next attempted. The amide (9) (2.0 g) was suspended in toluene (60 ml) at 0-5 °C and treated with thionyl chloride (1.35 g). Work-up as described above gave a mixture of two (t.l.c.) compounds. These were separated by silica gel flash-column chromatography, eluting with toluene-ethyl acetate (9.5:0.5 v/v) affording oxazoline (4) (1.12 g, 59%), m.p. 86 °C and the 2-benzyloxazoline (14) (118 mg, 5%) which crystallised from ethanol as prisms, m.p. 85-86 °C.

Found (ML 22504): C,80.42; H,6.43%

$C_{32}H_{31}N_1O_3$ requires: C,80.46; H,6.54%

Accurate Mass found: 477.22949

$C_{32}H_{31}N_1O_3$ requires: 477.23037.

ν_{max}: 1638 (C=N); 1600 and 1580 (C=C) $cm.^{-1}$

δ: 1.30 (6H, s, 2 x CH_3);

4.02 [2H, s, $O\underline{C}H_2C(CH_3)_2$];

4.42 (2H, s, $C\underline{H}_2Ph$);

4.99 [2H, s, C(3)$O\underline{C}H_2Ph$];

5.09 [2H, s, C(5)$O\underline{C}H_2Ph$];

1-[3,5-Bis(benzyloxyphenyl)]-2,2-dimethylaziridine (21)

To a stirred solution of 2,2-dimethylaziridine[5] (71 mg) and triethylamine (8.6 g) in tetrahydrofuran (100 ml) at 5 °C was added dropwise a mixture of benzoyl chloride (8) (353 mg) in tetrahydrofuran (10 ml). The reaction mixture was stirred at room temperature overnight before being filtered. The filtrate was evaporated under reduced pressure to afford a brown oil which deposited colourless micro-needles when treated with hot light petroleum-benzene (1:1 v/v). The solid was collected and recrysallised from ether to furnish aziridine (21) as fine, white needles (226 mg), m.p. 104-105 °C.

Found (ML 22389): C,77.25; H,6.53; N,3.68%

$C_{25}H_{25}N_1O_3$ requires: C,77.48; H,6.51; N,3.62%

Accurate Mass found: 387.18134

$C_{25}H_{25}N_1O_3$ requires: 387.18342.

ν_{max}: 1645 (amide) and 1585 (C=C) $cm.^{-1}$

δ: 1.17 (6H, s, 2 x CH_3);

2.26 (2H, s, NCH_2);

5.06 (4H, s, 2 x OCH_2Ph);

6.80 [1H, d, J2Hz, C(4)H];

7.20 [2H, d, J2Hz, C(2)H and C(6)];

7.3-7.45 (10H, m, aromatic H).

Treatment of benzoylaziridine (21) with acid

A solution of amide (21) (387 mg) in dichloromethane (100 ml) was treated with concentrated sulphuric acid (0.1 ml) and stirred, under nitrogen, at room temperature. After 16 hours, sodium bicarbonate (1 g) was added to the mixture which was then filtered and the solvent removed

under reduced pressure to afford a dark brown gum (310 mg) which solidified on standing. This solid was insoluble in dichloromethane or chloroform and only slightly soluble in acetone. T.L.C. analysis showed mainly very polar components (at least five) and the reaction was not investigated further.

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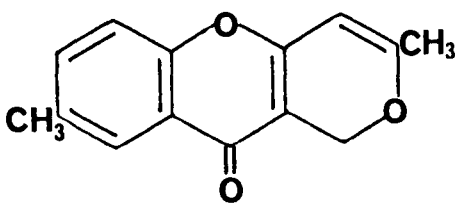
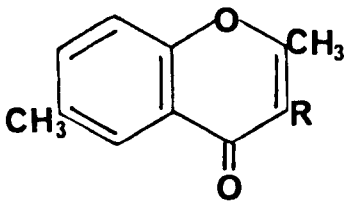
CHAPTER THREE

A new synthesis of the molecular skeleton of fulvic acid

It was stated in Chapter One that the common starting material in two routes to the pyrano[4,3-b][1]benzopyran system (1) developed in these laboratories[1] is 2,6-dimethyl-3-chloromethylchromone (2). This is obtained by treatment of 2,6-dimethylchromone (3) with formaldehyde and hydrogen chloride in hot, aqueous acetic acid.

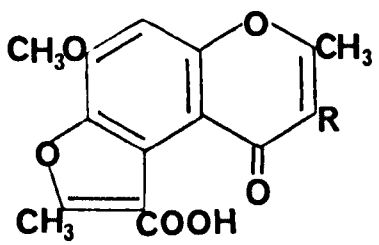


(1)



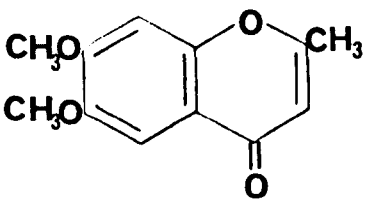
(2) R=CH_2Cl
(3) R=H

Both these routes were successful in transforming simple chromones such as (2) into the required pyranobenzopyran system, but now had to be applied to a precursor containing suitably masked oxygen functions on the benzene nucleus. The furochromone (4), synthesised by Costa,[2] seemed the proper choice as a starting material for either of these pathways provided that it could be converted first into the 3-chloromethylfurochromone (5).



(4) R=H
(5) R=CH_2Cl

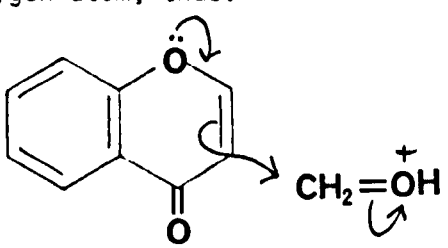
In practice, however, attempted introduction of the chloromethyl grouping (using a variety of chloromethylation reagents) at the 3-position of (4) proved fruitless: each of the conditions tried provided only unchanged starting material. The same was true also with attempted 3-chloromethylation of the model (6).



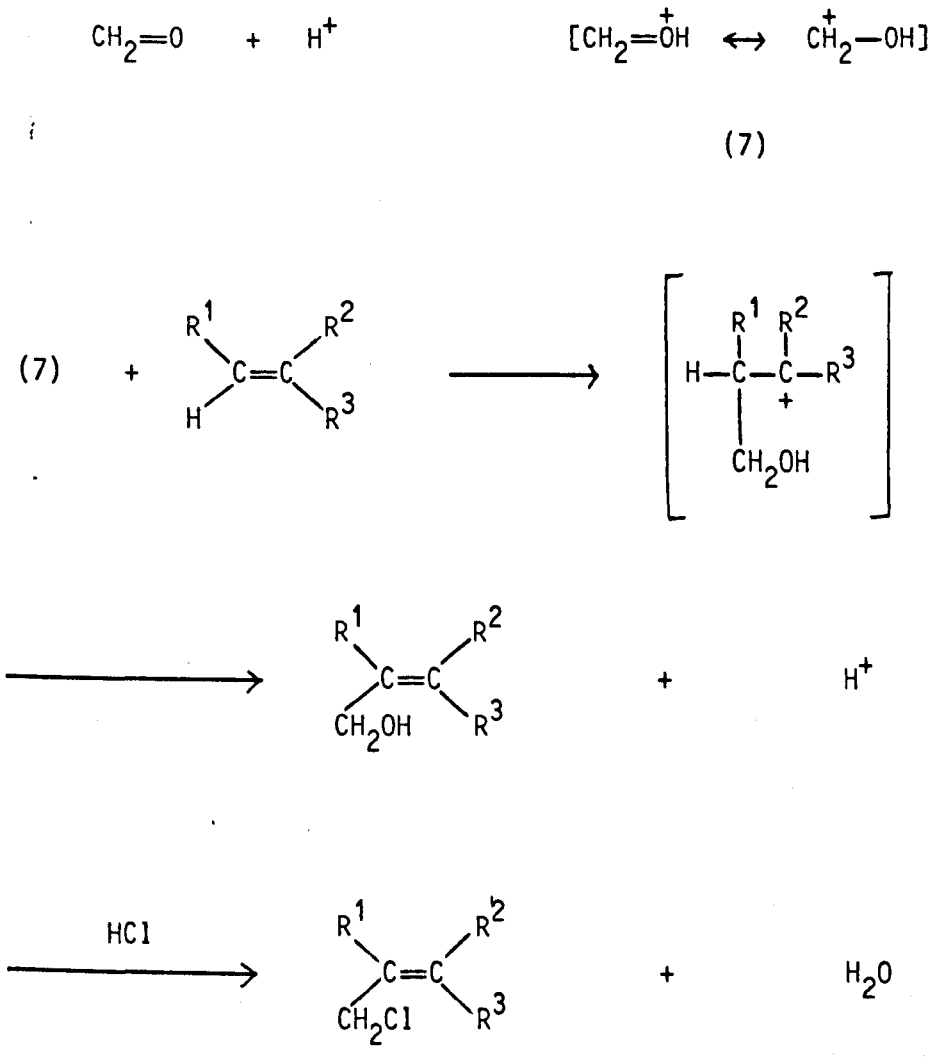
(6)

Studies[3] of the mechanism of chloromethylation by formaldehyde and hydrochloric acid (Scheme I) indicate that the electrophilic hydroxymethyl cation (7) attacks a double bond, the intermediate cation loses a proton giving an alcohol, and finally, replacement of the hydroxy group by a chlorine atom gives the product. It is obvious from this proposal that the proton concentration in the medium is important in determining the amount of reactive cation (7) available.

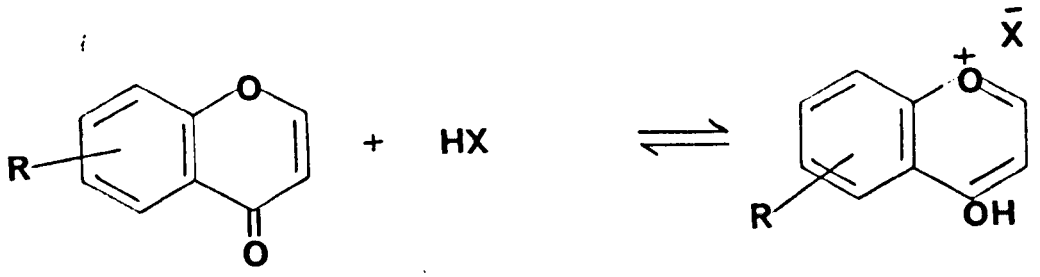
Normally, the 3-position on a chromone ring is the preferred site for chloromethylation since this position is activated by electron release from the heterocyclic oxygen atom, thus:



Scheme I


CH2=O + H+
[CH2=OH ↔ CH2—OH]
(7)
(7) +
R1 R2 C=C H R3
H—C—C—R3 R1 R2 + CH2OH
CH2OH R1 R2 C=C R3 + H+
HCl
CH2Cl R1 R2 C=C R3 + H2O

However, a competing reaction (Equation 1) occurs when the benzene nucleus is substituted with electron releasing groups (e.g. R=OCH_3). These make the chromone more basic than the unsubstituted chromone (R=H) and, under the acidic reaction conditions employed for chloromethylation, pyrilium salt formation is increased:



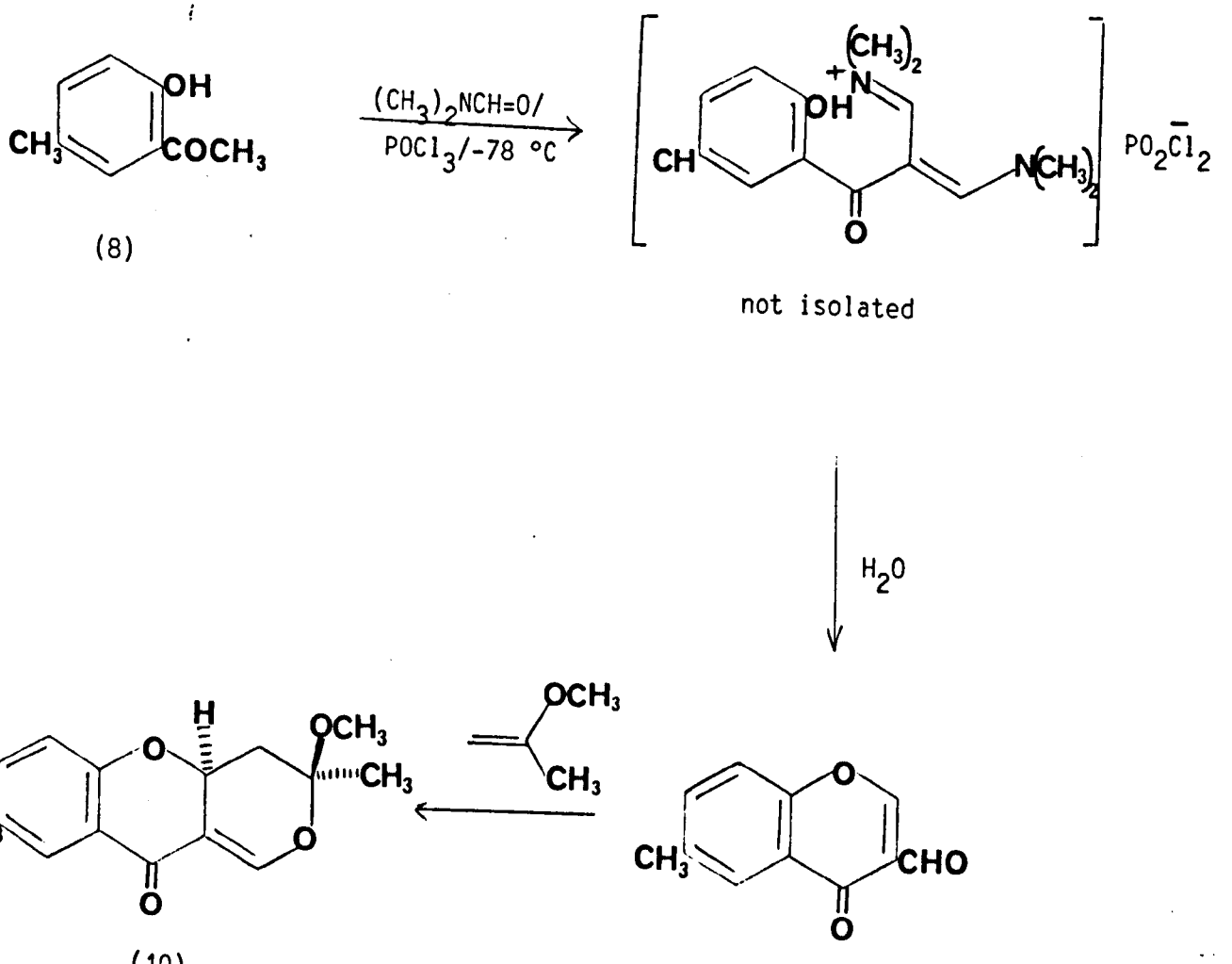
Equation 1

It seems that, in the numerous attempts directed towards 3-chloromethylation of the chromones (4) and (6), pyrilium salt formation was so complete that no non-protonated chromone was available for attack by the hydroxymethyl cation (7).

Since chloromethylation of chromones bearing electron releasing substituents on the benzene ring was unsuccessful, therefore, those routes requiring this transformation were abandoned and an alternative synthetical strategy investigated.

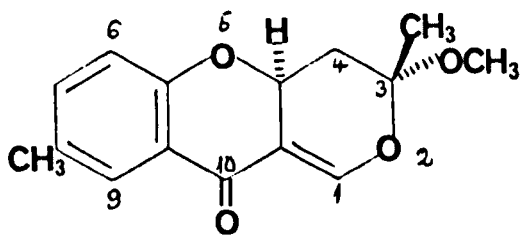
A key intermediate in this new synthetical approach is the tricycle (10) and its synthesis is illustrated in Scheme II. The precursor of (10), the 3-formylchromone (9) is obtained in 66% yield by treatment of 5-methyl-2-hydroxyacetophenone (8) with Vilsmeier reagent at low temperature. This method of producing 3-formylchromones was rigorously investigated only recently by Nohara and co-workers[4] who showed that it was general for several, more highly

Scheme II


OH
CH3
COCH3
(8)
(CH3)2NCH=O/
POCl3/-78 °C
(CH3)2
+N
OH
CH
N(CH3)2
O
PO2Cl2
not isolated
H2O
OCH3
CH3
H
O
OCH3
CH3
O
O
CH3
CHO
O
(10)
(9)

substituted o-hydroxyacetophenones. As we might expect from the account given earlier concerning the difficulties of chloromethylation in certain instances, those o-hydroxyacetophenones carrying an OMe group at the C-4 position (e.g. 4-methoxy-, 4,5-dimethoxy- and 4,6-dimethoxy-2-hydroxy-acetophenones) gave the desired products in low yields because of formylation on the benzene ring and formation of tarry material. Likewise, o-hydroxy-acetophenones carrying one more hydroxy group (e.g. 2,4-dihydroxy-acetophenone) also gave the desired hydroxy products in poor yields.

The next step in the Scheme involves an inverse electron demand Diels-Alder reaction in which formylchromone (9) undergoes a $4\pi+2\pi$ cyclo-addition with 2-methoxypropene to give the single isomer (10) in 66% yield. Reaction takes place at room temperature in chloroform and is complete (t.l.c.) after six days. Compound (11), the alternative epimer of (10), was obtained by treatment of a methanolic solution of (10) with a catalytic amount of 4-toluenesulphonic acid.

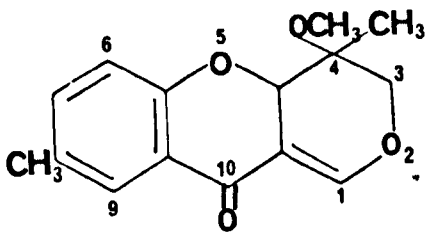


(11)

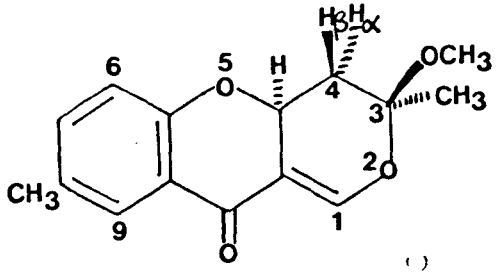
Both new compounds (10) (m.p. 118 °C) and (11) (m.p. 122 °C) could be crystallised from ethanol as needles and had the same R_f value on silica gel t.l.c. in a number of different solvent mixtures, e.g. R_f 0.5 in benzene-ethyl acetate (5:1 v/v) and R_f 0.35 in light petroleum 40/60-acetone (4:1 v/v).

The infra red carbonyl absorption frequencies [i.e. (10):1665; (11):1670 cm^{-1}] were similar and the electron impact mass spectra for both compounds showed M^+ at m/e 260 and peaks at m/e 229 and m/e 189 consistent with loss of OCH_3 and the retro Diels-Alder product respectively. Fast atom bombardment (F.A.B.) mass spectra showed M^+ for (10) at m/e 260.10485 and M^+ for (11) at m/e 260.10540. The combustion analyses for the two compounds were in accordance with the molecular ion determinations in that each compound analysed as $C_{15}H_{16}O_4$.

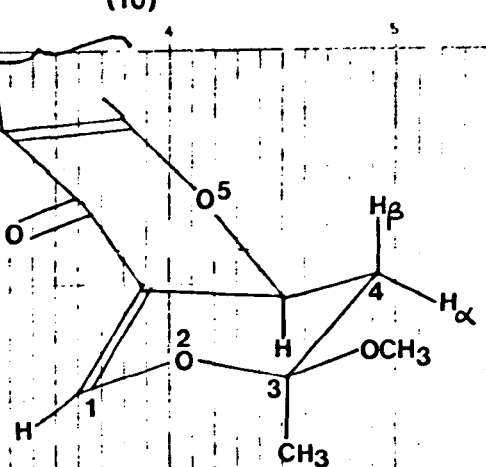
The proton n.m.r. spectra of compounds (10) and (11) are depicted on the following two pages and each spectrum clearly shows three singlets for the methyl groups and a "doublet of doublets" at ca. δ 5.0 for the C-4a methine hydrogens. There is no evidence of an aldehydic hydrogen in the downfield region in either spectrum; the hydrogen at C-1 resonates at ca.δ7.55 as a singlet very slightly broadened by allylic coupling with C-4aH. Had addition of 2-methoxypropene to the formylchromone taken place in such a manner as to afford (12), among the changed resonances in its n.m.r. spectrum, we would have expected to see an AB quartet for the methylene protons at C-3.



(12)


Hβ Hα
6
5
H
4
OCH3
3
CH3
2
O
CH3
9
1
O

(10)


O5
Hβ
O
4
Hα
2
O
H
OCH3
3
1
H
CH3

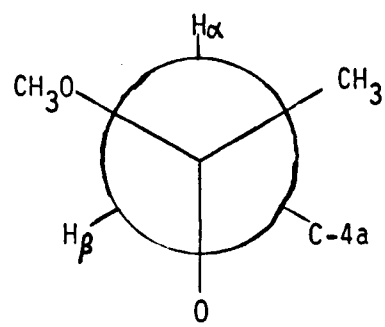
8
7
6
5
4
3
2

(11)

While all of these analyses taken together indicate that the Diels-Alder reaction has taken place to give a cycloadduct with the regiochemistry as depicted in (10), the stereochemistry of epimers (10) and (11) at the anomeric 3-positions can be only tentatively deduced from analysis of the n.m.r. spectra.

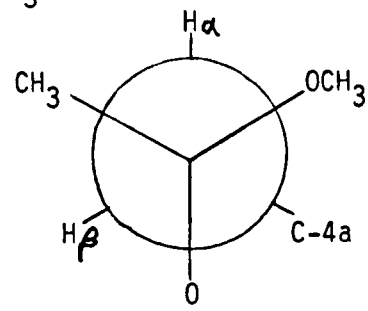
The main difference between the spectra is the position and appearance of those signals arising from the axial-equatorial and trans-diaxial interactions, C4a-H--H_α and C4a-H--H_β respectively in each compound. In (10), the H_β and H_α methylene protons are partly masked by the aromatic methyl signal but can be seen to consist of a doublet (J=14 Hz), centred at δ2.38, each line of which is split by coupling with the vicinal axial C4a-H ($J_{4a\text{-}H,H\beta}$ = 9; $J_{4a\text{-}H,H\alpha}$ =7 Hz). The signals for the corresponding proton interactions in (11) are similar and well clear of the aromatic methyl signal; the geminal coupling constant is 15 Hz and the coupling values for the C4a-H--C3H_β and C4a-H--C3H_α interactions are 9 and 8 Hz respectively. These values are very similar in magnitude to those observed for the same interactions in (10).

The analysis becomes a little clearer with the aid of molecular models and from such a model of cycloadduct (10) a Newman projection along the bond between carbon atoms 3 and 4 may be drawn, thus:



Here it can be seen that the OCH_3 group bisects the plane containing H_β and H_α and, as a result, both these protons experience neither a net

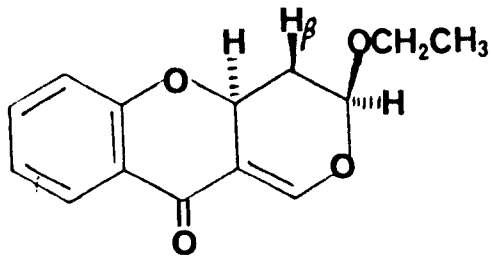
shielding or deshielding effect so the fact that there is no significant separation in the n.m.r. signals for these protons is not surprising. In contrast to this, the Newman projection along carbons 3 and 4 in epimer (11) shows H_β <u>anti</u> to the OCH_3 group:



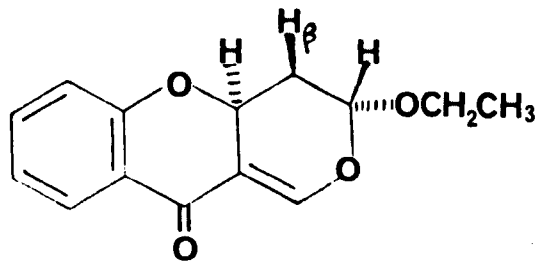
Electron donation from the C-OCH_3 bond to the C-H_β bond may be expected to result in H_β being slightly shielded (relative to H_α) in the applied magnetic field and so it is the highfield double doublet at δ 2.06 in the spectrum of (11) which we assign to H_β . H_α is <u>syn</u> to the axial OCH_3 and appears as a double doublet at δ 2.55. These shielding-deshielding effects will be only very small in magnitude as is reflected in the small separation of the signals corresponding to H_α and H_β in either spectrum. Furthermore, since Newman projections for other conformers of (10) and (11) may be drawn, the n.m.r. assignments of the methylene protons in (10) and (11) are offered only tentatively. In fact, the similarity of the two n.m.r. spectra is such that any claim that each one taken alone provides sufficient evidence for an unequivocable assignment of the stereochemistry is dubious. Fortunately, the precedent set by other workers who have studied Diels-Alder additions of enol ethers to α,β -unsaturated carbonyl compounds and the deductions that can be made from the theory of thermal pericyclic reactions may be cited to aid interpretation of the stereo- and regiochemistry of cycloadducts (10) and (11).

A recent study by Wallace and co-worker[5] has shown that treatment of

3-formylchromone with ethyl vinyl ether resulted in the formation of cyclo-addition adduct (13) in 75% yield. Chromatography of the crystallisation mother liquors of (13) led to recovery of (14) in 17% yield.



(13)



(14)

The advantage of using ethyl vinyl ether as dienophile (as opposed to 2-methoxypropene) is that anlaysis of the coupling values for H_β and the proton at C-3 enables a much more reliable definition to be made of the stereochemistry of these products than that made for (10) and (11). The major product (13) had a coupling constant value of 10 Hz for $J_{H\beta,3\text{-}H}$ --indicating a trans-diaxial arrangement-- and in (14) the same protons coupled with a value of 2.8 Hz -- indicating an axial-equatorial arrangement.

The stereochemistry assigned to adducts (10) and (11) seems more reasonable in the light of Wallace's assertion[5] that similar stereoselectivity to that shown in the formation of (13) and (14) was observed in the reaction of a series of substituted 3-formylchromones with ethyl vinyl ether and the minor cycloaddition adduct formed in each reaction could be obtained independently by acid equilibration of the major adduct.

It is well known that the rate of reaction of "normal" Diels-Alder additions is increased by electron attracting groups in the dienophile and decreased by electron donating groups. In this case, the dienophile reacts as the electron deficient component and the diene as the electron rich component. The reaction between formylchromone (9) and 2-methoxypropene,

however, represents a Diels-Alder addition with "inverse" electron demand since the "diene" (i.e. formylchromone) acts as the electron deficient component and the dienophile (i.e. 2-methoxypropene) as the component with excess electrons. Both these types of Diels-Alder additions may be represented schematically in a way which shows the attractions between the appropriate frontier molecular orbitals of the diene and dienophile. This kind of representation utilises the "frontier orbital approximation" first advocated by Fukui.[6] His theory states that, for a thermal cycloaddition, the orbitals which interact most are those which overlap best and are closest in energy and, furthermore, that the smaller the energy gap between the interacting orbitals, the faster the reaction goes. Figure 1 shows the frontier molecular orbital energies[7] in the normal Diels-Alder reaction between isoprene and acrylonitrile and it can be seen that the addition reaction is dominated by the interaction of the Highest Occupied Molecular Orbital (HOMO) of the diene (at -8.89 eV) and the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile (at -0.02 eV). The difference in energy is 8.87 eV, whereas the difference in energy of the LUMO of the diene (at 0.8 eV) and the HOMO of the dienophile (at -10.92 eV) is 10.12 eV.

In the reaction of formylchromone (9) with 2-methoxypropene (Figure 2), the carbonyl group in the α-position of the heterodiene lowers the energy of both the HOMO and LUMO whereas the methoxy and methyl groups on the dienophile raise the energy of both the HOMO and LUMO. (This lowering and raising of the frontier orbital energies is relative to the energies for the same orbitals in the unsubstituted heterodiene and dienophile). Now it can be seen that the important interaction in this inverse Diels-Alder reaction is that between the HOMO of the dienophile and the LUMO of the heterodiene.

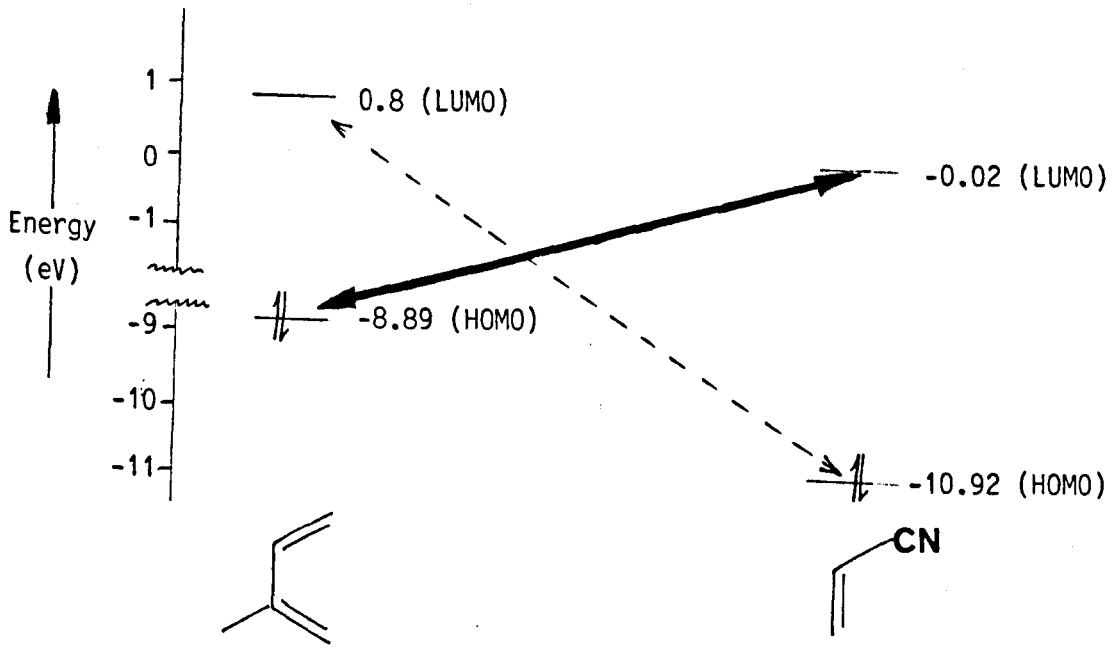


Figure 1

(The energy values shown here are typical for a diene with an electron withdrawing group and a dieneophile with an electron donating group.[8])

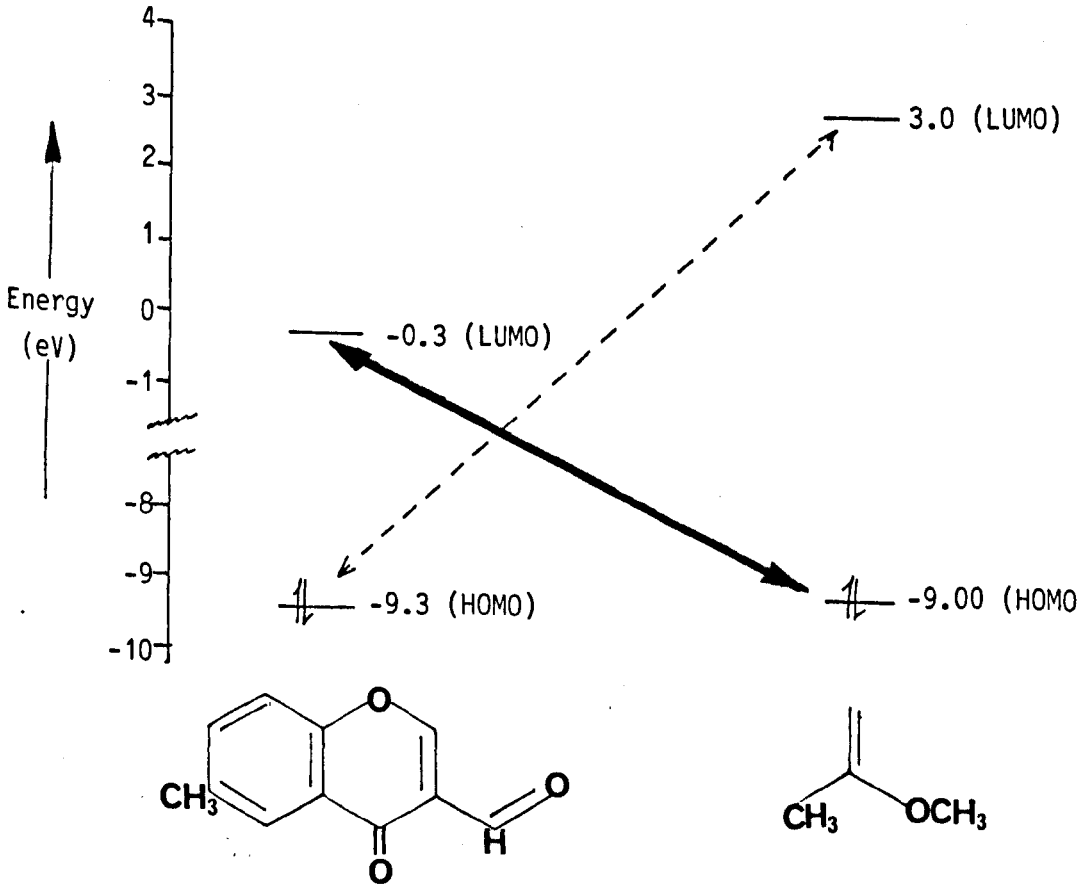


Figure 2

In terms of orbital energy considerations, therefore, the cycloaddition reaction between (9) and 2-methoxypropene is favourable. Moreover, dipole moment and infra red measurements indicate that the formylchromone (9) has an S-cis- configuration (as shown in Figure 2) which is stabilised by intramolecular hydrogen bonding[9] so the stereochemical requirement for the Diels-Alder addition is satisfied too.

The regiochemistry of the cycloaddition is determined by the relative sizes of the coefficients of the atomic orbitals at the atoms involved in forming new bonds. Unfortunately, though, a survey of the chemical literature did not reveal the values for the pertinent atomic orbital coefficients in our cycloaddition reactants. However, on the basis of spectral analyses, it seems a reasonable conclusion that the general rule governing regio-selectivity was obeyed in that the larger atomic orbital coefficients on the dienophile were matched with those on the diene to produce the cycloadduct with regiochemistry as shown in (10).

The transition state for the $4\pi + 2\pi$ cycloaddition between formylchromone (9) and 2-methoxypropene leading to the expected endo addition product might be represented by Figure 3 where the + and - signs represent the plus and minus lobes of the molecular orbitals in each reactant.

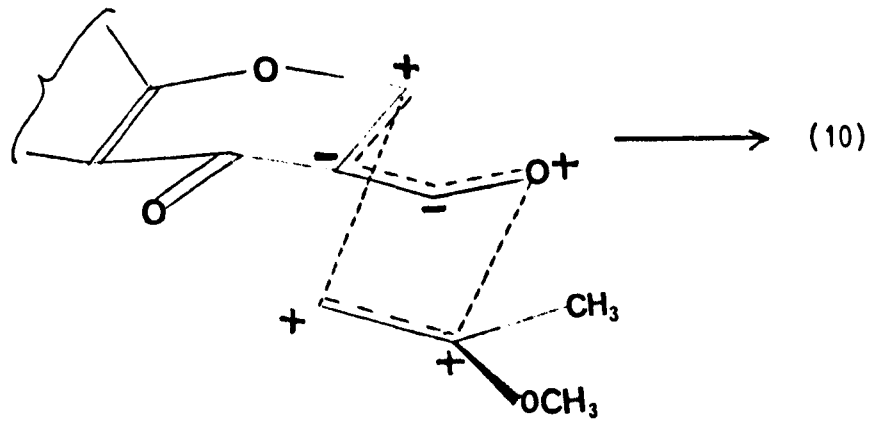


Figure 3

It is usually explained that endo (as opposed to exo) addition is promoted by secondary orbital interactions which lead to a lowering of the energy of the endo transition state relative to the exo transition state. This is the reason given, for example, for the predominance of the endo product in the classical Diels-Alder addition between maleic anhydride and cyclopentadiene. This explanation is only really applicable, however, where the dienophile possesses additional π-orbitals (as in maleic anhydride) to those involved in the primary orbital interaction. Clearly, therefore, another explanation needs to be found for the observed exclusive formation of the endo product (10).

It appears from a large body of studies[10] which have been undertaken to elucidate Alder's endo rule[11] that a number of forces are in operation in the transition state (besides secondary orbital interactions) which promote endo orientation. In most of these studies, the investigators have commented on the importance of intermolecular dispersion forces and steric repulsions at the transition state. There certainly seems to be some justification for including the effect of steric repulsions since Wallace[5] has shown that increasing the bulk of R in the enol ether (15) leads to an increase in the proportion of the exo product found in the reaction of (15) with 3-formylchromones. For example, in the reaction of ethyl vinyl ether (15, R=Et) with 3-formylchromone, the ratio of endo to exo addition products is 75:25 whereas with t-butyl vinyl ether (15, R=t-Bu) and 3-formylchromone, the endo-exo product ratio is reduced to 55:45. Moreover, the reaction with t-butyl vinyl ether is slower than that observed with less sterically bulky dienophiles.

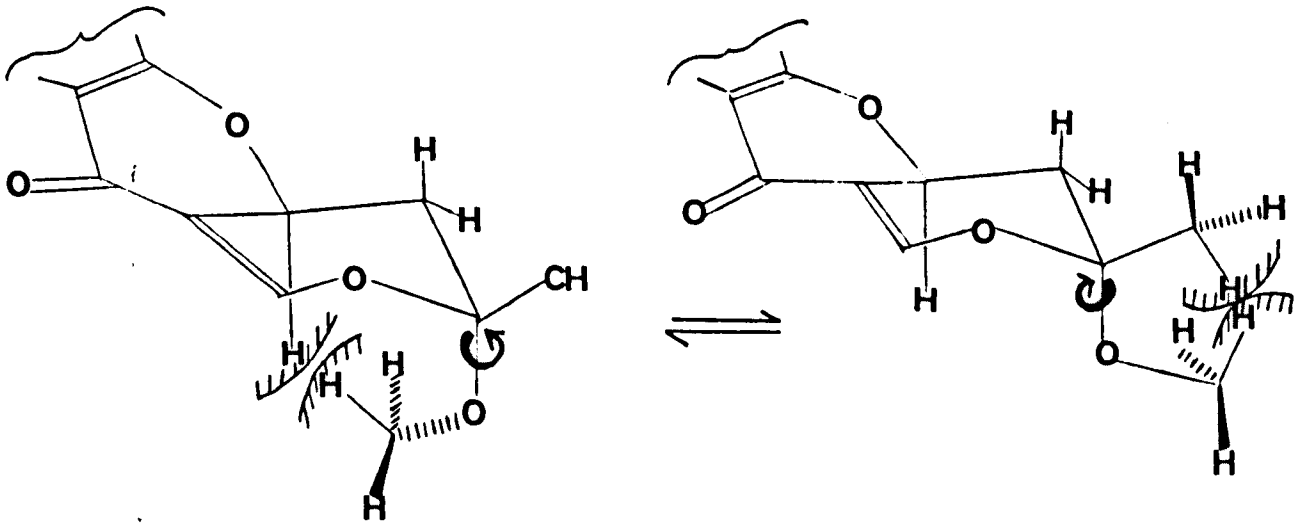
(15)

Wallace's work, therefore, has shown a connection between steric bulk in the dienophile and the stereochemistry of the addition product. Put another way; steric interactions at the transition state of the cyclo-addition reaction have an influence in determining the ratio of kinetically and thermodynamically controlled reaction products observed. These observations may go some way towards explaining why, in the reaction of formylchromone (9) with 2-methoxypropene (hardly a 'bulky' dienophile), the endo cycloaddition product **only** is observed. A more explicit explanation would be useful, however, and the following discussion goes some way towards this.

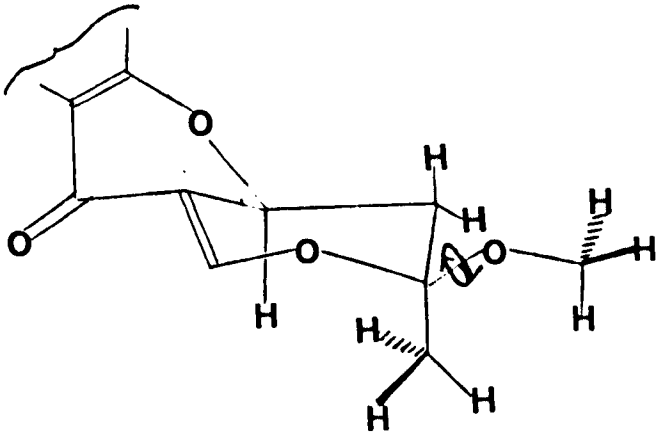
The reaction between (9) and 2-methoxypropene leads to an overall loss of entropy. Allied to this, the change in hybridisation (i.e. $sp^2 \rightarrow sp^3$) in the dienophile which occurs on its reaction with (9) leads to a closer (in space) approach of the OCH_3 and CH_3 groupings since the CH_3--C--OCH_3 bond angle is reduced from 120 °C to ca. 109 °C. At the transition state, therefore, restrictions placed on free rotation about the C--OCH_3 bond because of steric or other interactions (e.g. Van der Waals', dispersion forces) become important in determining the stereochemistry in the product. In fact, molecular models of (10) and (11) show that the extent to which the C--OCH_3 bond is able to rotate may be the key to explaining the exlusive formation of (10) which was observed.

In (11) (see below), rotation of the axial OCH_3 group is restricted by the axial C-4a methine proton and the C-3 methyl group hydrogens as shown. In fact, the approach of the methoxy group hydrogens to the C-4a methine and C-3 methyl group hydrogens is so close in the molecular model that unrestricted 360° rotation about the C--OCH_3 bond is impossible. In contrast to this, in epimer (10), the hydrogens on the equatorial methoxy grouping are orientated so as to allow completely free, through space, rotation about

the C--OCH_3 bond. In this case, the C-4a methine hydrogen atom is too distant to interfere and 360° locii for the methoxy hydrogens may be drawn which are not traversed by the C-4 geminal hydrogens.



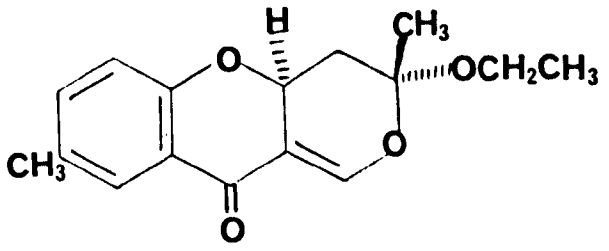
(11)



(10)

Presumably, the easy conversion of (10) to (11), observed under the influence of a catalytic amount of acid on (10), means that the lack of free rotation about the C--OCH_3 bond in the product is compensated for by anomeric

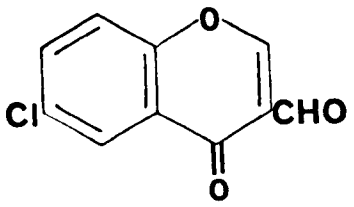
oxygen stabilisation.[12] The essence of the anomeric effect is that the antiperiplanar relationship of a lone-pair of electrons on the heterocyclic oxygen of the pyran ring to the C--OCH_3 bond in (11) facilitates an n--σ^* interaction which stabilises this molecule relative to (10). This effect may also be invoked to explain the formation of adduct (16) which occurred via ether exchange on treating an ethanolic solution of (10) with a catalytic amount of 4-toluenesulphonic acid.



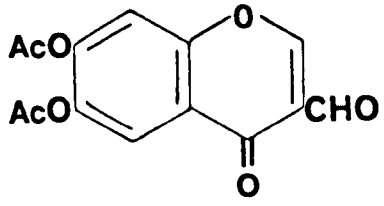
(16)

While this is not an important reaction in terms of the overall synthetical scheme it is interesting in that it represents a method for transforming the product obtained by kinetic control in the Diels-Alder reaction into the thermodynamically more stable cycloadduct.

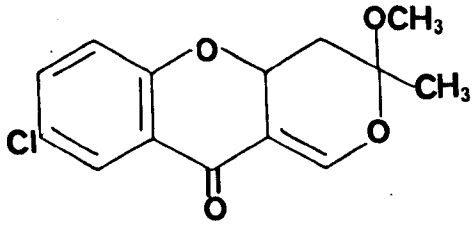
The formylchromones (17) and (18) were used in the synthesis of two more cycloaddition adducts, (19) and (20). The latter of these is the more important because it contains two masked hydroxy groups with the same substitution pattern as found on the benzene ring in the ultimate synthetic target, fulvic acid.



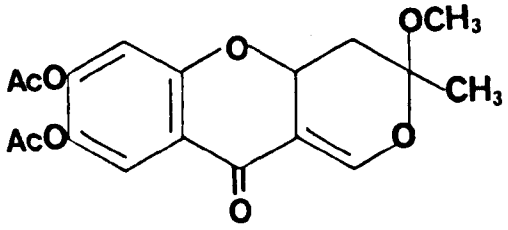
(17)



(18)



(19)



(20)

The use of lanthanide reagents such as $Yb(fod)_3$, which have been reported by Danishefsky[13] to catalyse cycloadditions of α,β -unsaturated aldehydes with enol ethers was found not to be useful. The use of $Yb(fod)_3$ was found to accelerate the reaction between formylchromone (9) and 2-methoxypropene but the reagent is expensive to buy or prepare and its recovery complicated purification of the product. In any case, the more important reaction for our purposes, that between 6,7-diacetyloxy-3-formyl-chromone (18) and 2-methoxypropene, producing (20), was complete after only 24 hours without the use of lanthanide catalysis.

While 3-formylchromone has received much attention[14] from chemists over a number of years, principally because of the pharmacological activities of its derivatives, its use as a heterodiene in Diels-Alder reactions has only

recently been explored.[15] The value of this reaction in our synthetical scheme may be summarised:

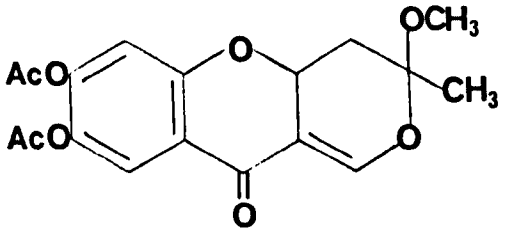
(i) in one step, two ring bonds are formed;

(ii) the reaction is not adversely affected by substituents on the benzene ring, i.e. the complications encountered in previous routes owing to extensive electron release from 6,7-oxygen substituents are not observed;

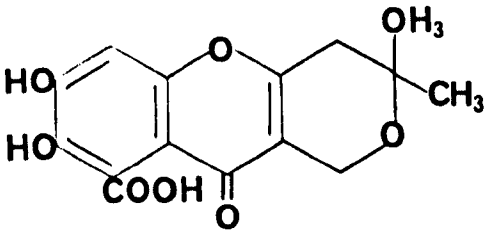
(iii) the reaction is clean and affords a high conversion to product;

(iv) less importantly, the reaction is both regio- and stereospecific so separation of mixtures is avoided.

We are now in a position to look in a little more depth at the structural similarities between model compound (20) and fulvic acid (21)

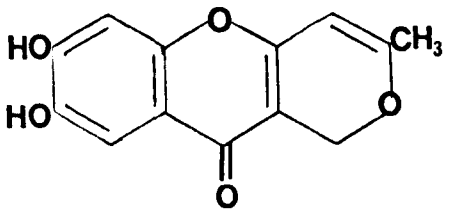


(20)

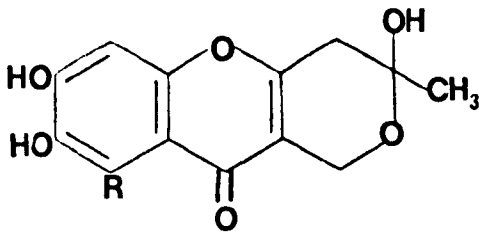


(21)

It was stated earlier that the acetyloxy groups on the benzene ring of (20) mask the necessary hydroxy groups. The use of 2-methoxypropene in the synthesis of (20) introduced the essential 3-methyl group and, after moving the heterocyclic carbon-carbon double-bond to regain the required chromone nucleus, careful acid hydrolysis of the hemiacetal and acetyloxy functions might lead to decarboxylated anhydrofulvic acid (22).



(22)

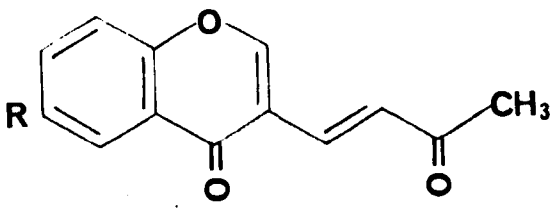


(22a) R=CH=CH_3
(22b) R=CH=O
(22c) R=CO_2H

As the experimental conditions for the equilibration of anhydrofulvic acid to fulvic acid are known,[16] we are left with the problem of when and how to introduce the 9-carboxylic acid function. This problem was addressed in the previous Chapter and while the results were disappointing, a better result might be forthcoming if the acid function has its origin as shown in the "styrene" (22a). Here, ozonisation followed by oxidation of the resultant aldehyde (22b) would lead to the required anhydrofulvic acid (22c). This was, in fact, the technique used by Japanese workers in a recently published paper[16] describing the first total synthesis of fulvic acid. Previous workers in these laboratories have used much the same method for the synthesis of highly substituted 2-acetylbenzoic acids, (c.f. Scheme II, Chapter One).

Given, therefore, that there are established procedures for introducing the carboxylic acid function, it was decided that the priority in the synthetical work would become the manoeuvring of the heterocyclic carbon-carbon double-bond into the required position. First, however, we looked at

the more elementary chemistry of the cycloaddition adducts, in particular the reaction of (10) and (19) with acid and base. We have already seen that the action of a catalytic amount of acid on (10) in methanol furnishes the alternative epimer. When (10) was subjected to aqueous acid conditions (i.e. a 10% aqueous acetic acid solution at 50 °C) the starting material was consumed in only ten minutes and the unsaturated ketone (23) produced in high yield. Similarly, when the 8-chloroadduct (19) was subjected to the same experimental conditions, the product obtained was the 5-chloro-chromone derivative (24).

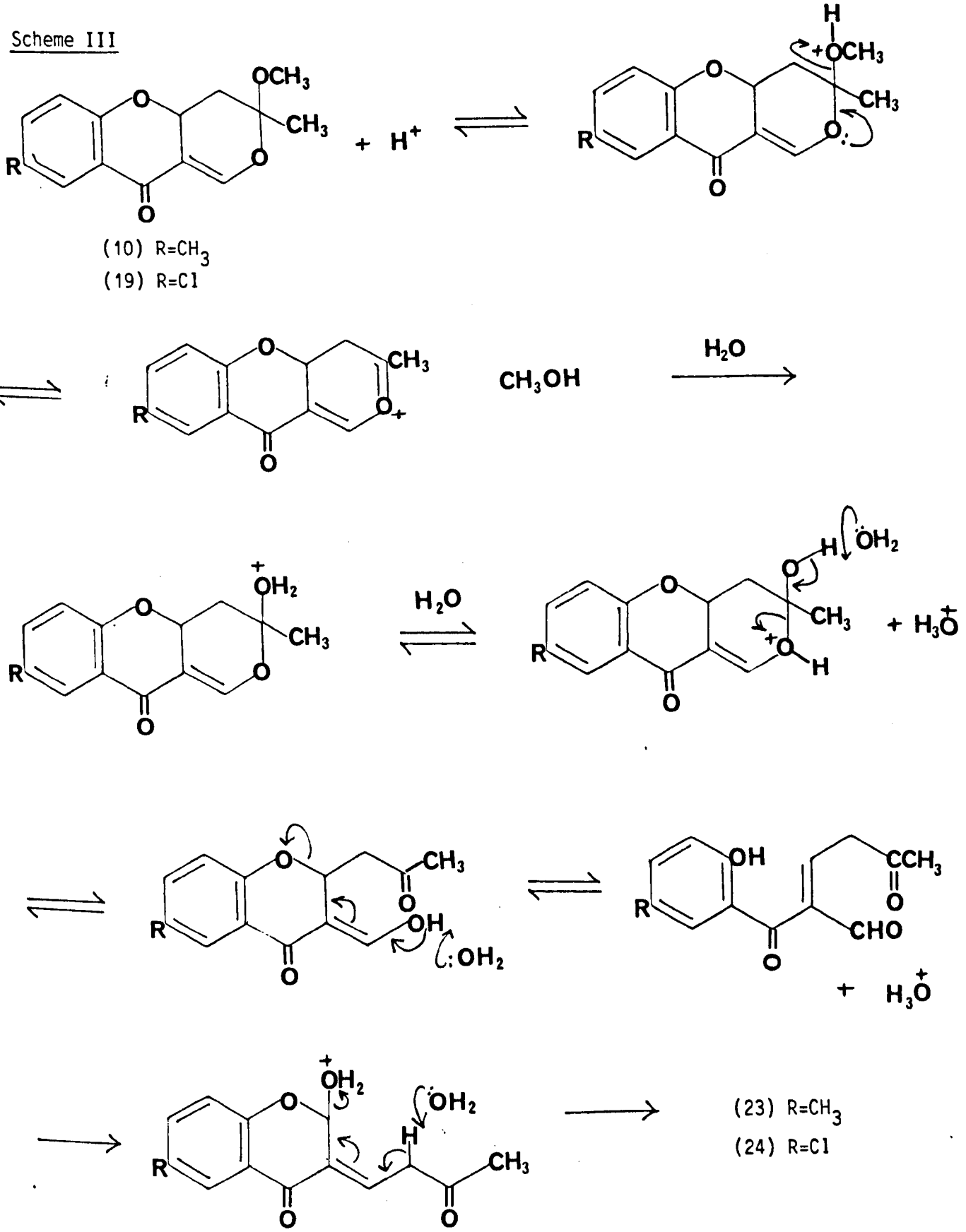


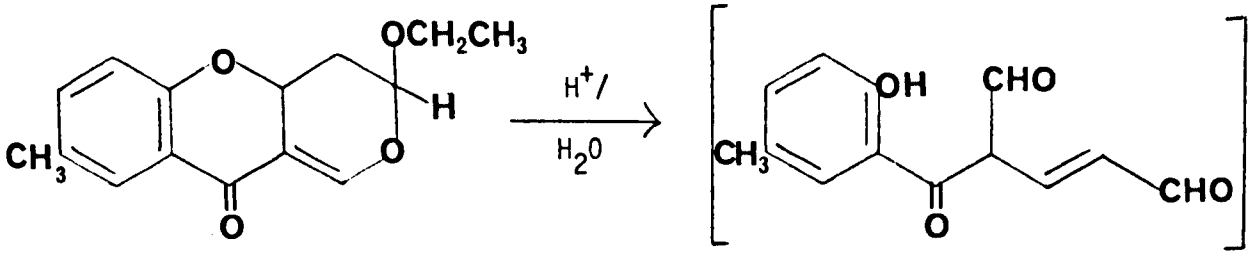
(23) R=CH_3

(24) R=Cl

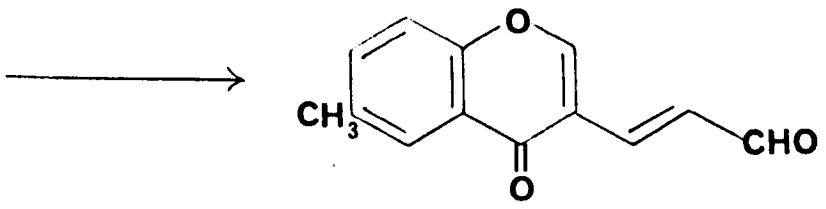
That such products result is not surprising when we consider that the starting materials contain a hemi-acetal function which is labile to attack by acid. A mechanism that may account for this transformation is shown in Scheme III. The ease with which this acid catalysed reaction takes place has been exploited by Ghosh and co-workers[15] to provide a convenient route to β-(4-oxo-4H[1]benzopyran-3-yl)acroleins. In this case, the starting material is the adduct (25) --formed by cycloaddition of 3-formylchromone (9) with ethyl vinyl ether. Dilute acid treatment furnished the acrolein (26) in moderate yield, presumably by recyclisation of the intermediate (27).

Scheme III


OCH3
CH3
R
O
+ H+
H
+OCH3
CH3
(10) R=CH3
(19) R=Cl
CH3
CH3OH
H2O
+OH2
H2O
+ H3O+
OH
CCH3
CHO
+ H3O+
(23) R=CH3
(24) R=Cl



(25) (27)

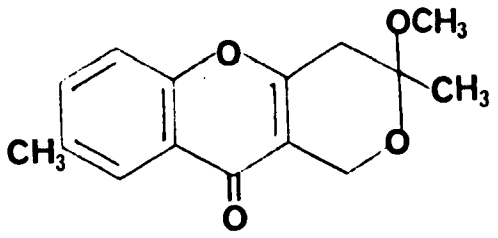


(26)

Treatment of the heterocycles (10) or (19) with bases generated a complex, highly coloured mixture. When a few drops of bench, aqueous sodium hydroxide solution made contact with a warm ethanolic solution of (10), the mixture immediately turned from colourless to deep red. T.L.C. examination of the mixture indicated that all the starting material had reacted to give mostly baseline, polar material. There was evidence (by co-t.l.c.) for the formation of the 3-formylchromone (9) and the unsaturated ketone (23) though these too were degraded into more polar material after a further hour had elapsed. Degradation of adduct (10) in the presence of base was accelerated by heating and work-up almost invariably produced an immobile, red oil which was shown by n.m.r. and t.l.c. analyses to be multi-component in composition. This deep red coloured solution was observed on numerous occasions thereafter when the adduct (10) came into contact with reagents or reaction conditions having basic character. The lability of formylchromone (9) and the

unsaturated ketone (23) in basic conditions is not surprising: chromones are well known[17] to be base-labile, the heterocyclic ring undergoing fissions in aqueous or alcoholic alkali to give hydroxyketones and carboxylic acids.

One implication of the acid-sensitivity of (10) is that acidic reagents or reaction conditions would be undesirable in any attempt to move the double-bond in (10) to form chromone (28) -- a model for the same fused ring system as found in fulvic acid.

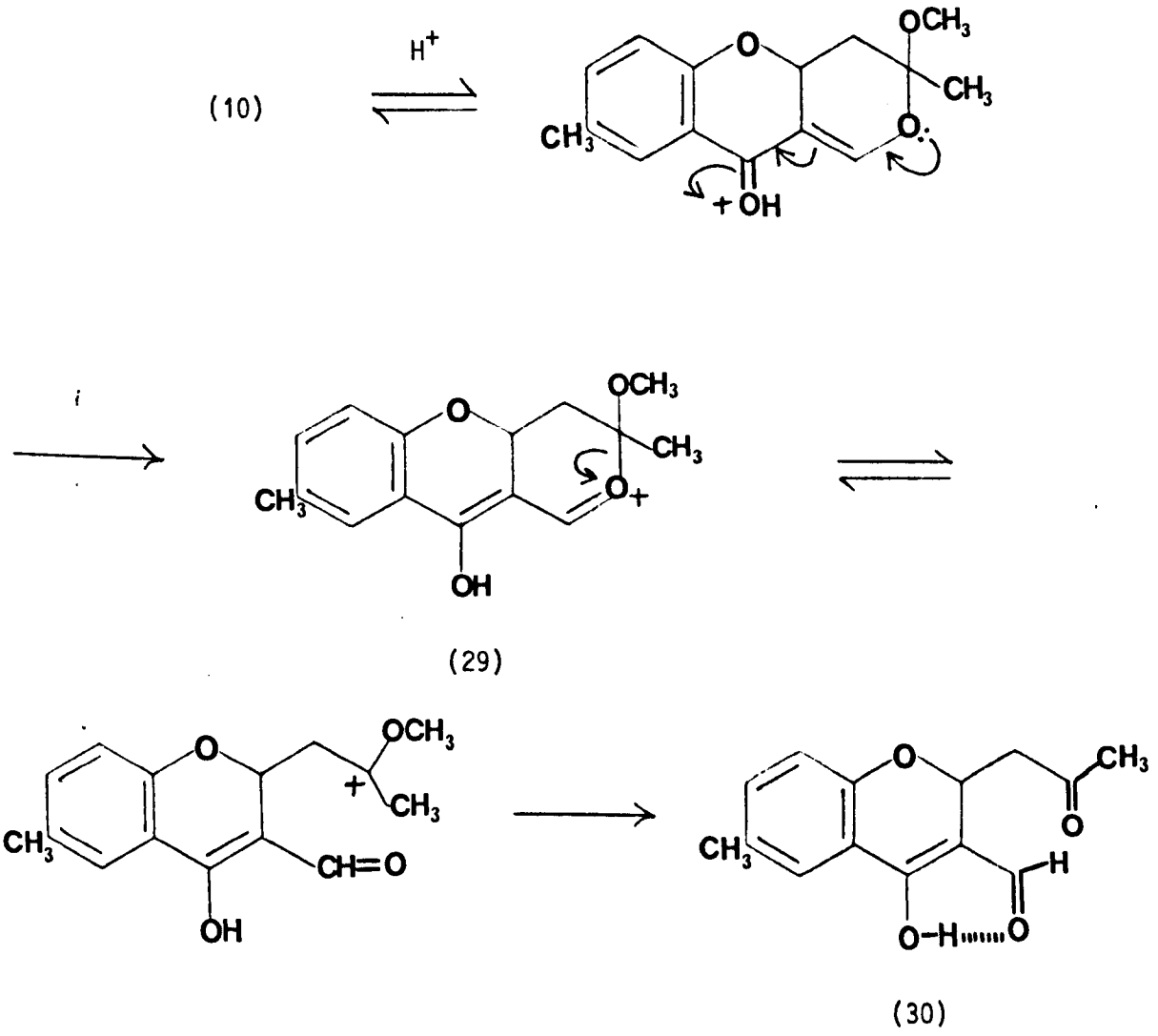


(28)

However, given that many of the reagents subsequently used in attempts to bring about the required conversion had electrophilic character, it is important to consider here the other electron-rich sites on (10) to which an electrophile could add and the subsequent rearrangement or cleavage reactions that might occur as a result of this. For the sake of convenience in the following speculative reaction mechanisms and discussion, H^+ shall be used to represent an electrohile.

Firstly, addition of an electrophile to the carbonyl group in (10) (Scheme IV) could be expected to lead to the conjugated system (29) which, after ring-opening and loss of methanol, would furnish the β-hydroxyaldehyde (30) which is shown stabilised by intra-molecular hydrogen bonding.

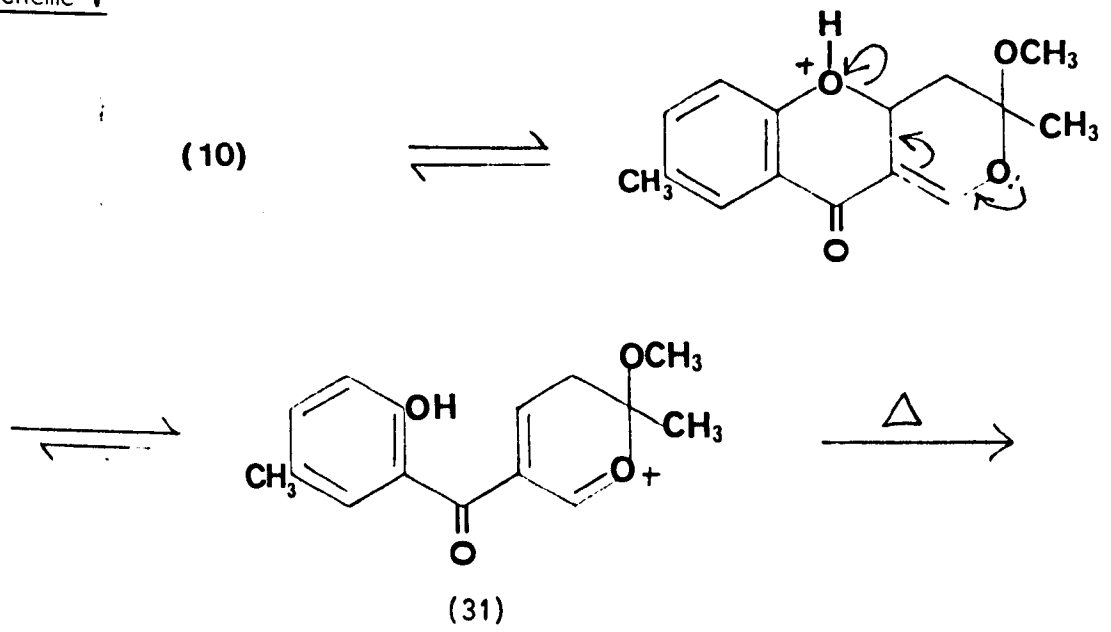
Scheme IV

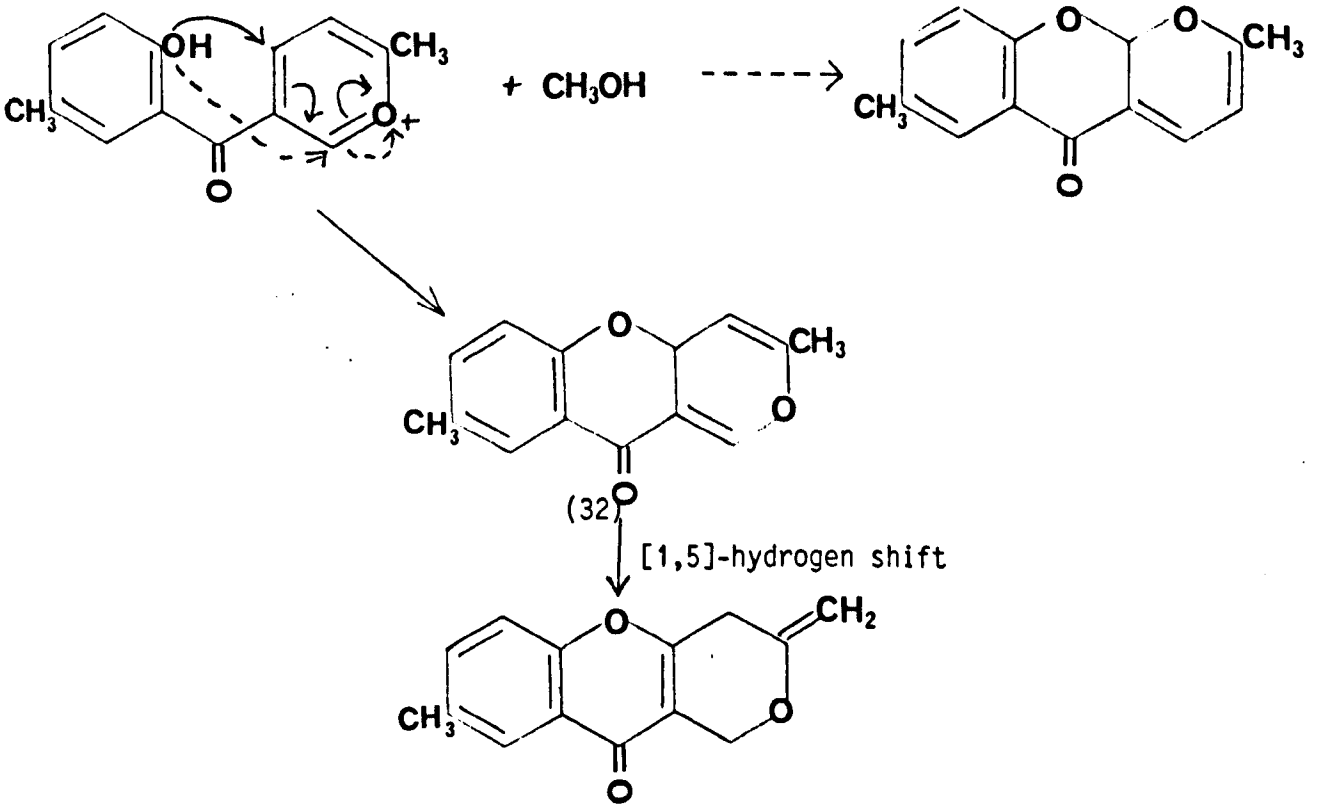


In another instance (Scheme V), the electrophile might add to the heterocyclic oxygen of the pyrone ring and electron movement as shown would lead to the oxonium ion (31). This is an interesting heterocyclic system since loss of methanol (induced perhaps under thermal reaction conditions) results in the formation of the aromatic pyrilium ion which might then undergo intramolecular attack by the hydroxy group at C-2 or C-4 leading to the heterocycles shown. Both these ring-closure reactions involve a "6-endo-trigonal" reaction which Baldwin's rules[18] predict to be a favoured

pathway for ring formation. Of these compounds, (32) is perhaps the more interesting since we can draw on it a 1,5-hydrogen shift which is thermally allowed by Woodward-Hoffmann rules whereas the direct 1,3-hydrogen shift required to transform (10) into (28) is thermally forbidden.

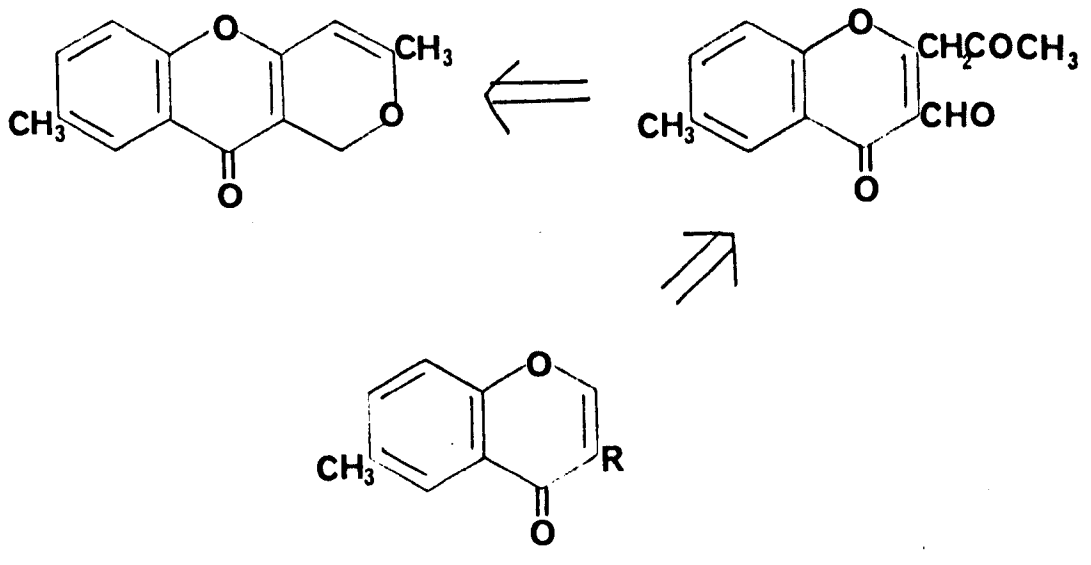
Scheme V





At an early stage it had become obvious that acidic or basic reagents or reaction conditions would be undesirable in any attempt to move the double-bond in (10) to give (28). In fact, this acid- and base-sensitivity of (10) was to have a profound effect in all subsequent attempts to bring about its direct conversion into (28).

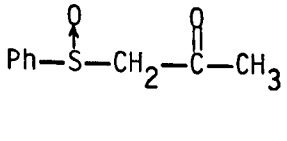
While it was our intention to concentrate further synthetical work on the elaboration of adduct (10), the procurement of multi-gram quantities of its immediate precursor, i.e. (9), prompted a brief study of this compound as a potential building block for a model compound of fulvic acid. Perhaps the most profitable way of constructing a linear tricycle from formylchromone (9) is to introduce functionality at the 2-position. An idealised sequence would involve addition of an acetone anion (i.e. "$\bar{C}H_2COCH_3$") to (9) followed by cyclisation of the product to a model of anhydrofulvic acid as the following retrosynthetic analysis illustrates:



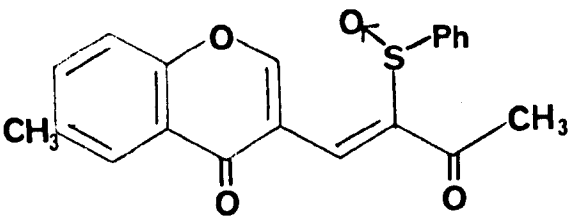
(9) R=CH=O

(35) R=CH(O)(O)

In the event, reaction of the anion of the β-ketosulphoxide (33) with (9) furnished a high yield of the 1,2-addition product (34).



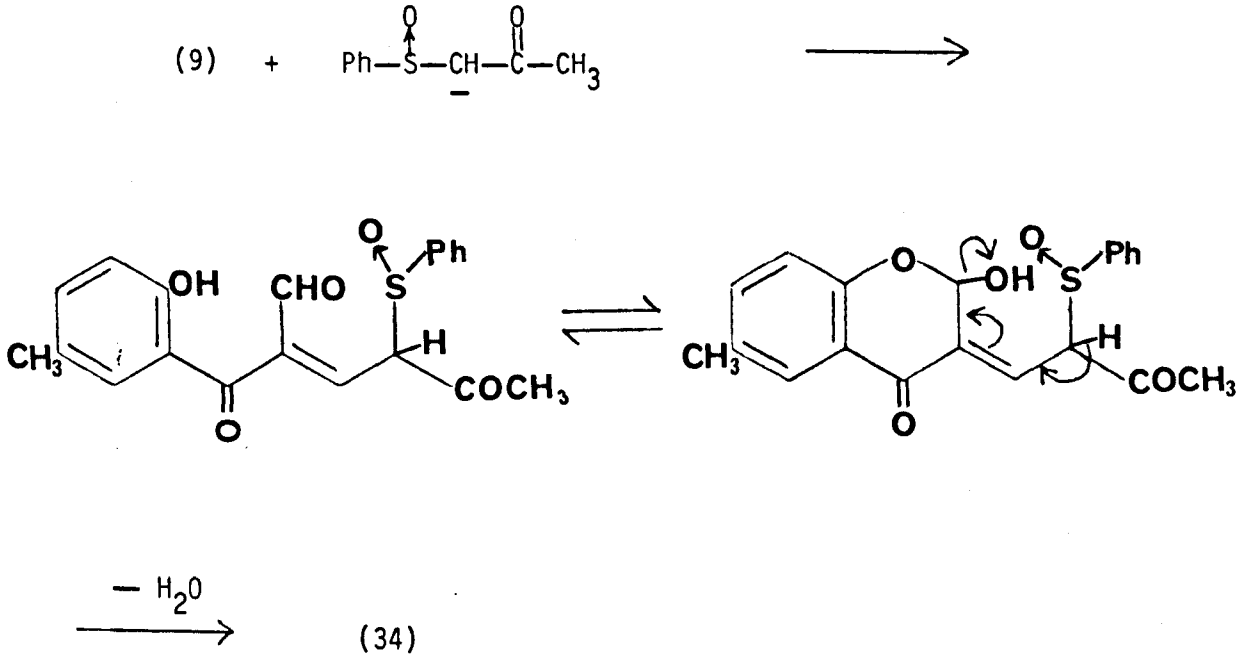
(33)



(34)

In an effort to avoid aldol condensation, the aldehyde function of (9) was protected as its ethylene acetal[19] (35). Reaction of (33) with (35) under the same experimental conditions as before, however, led to the recovery of starting materials and some of the free formylchromone (9) owing to acetal hydrolysis during work-up.

The formation of (34) is not surprising in the circumstances since the reaction of 3-formylchromones with nucleophiles or active methylene compounds (in conjunction with an appropriate base) is well known to give such condensation products and is usually explained by straight forward 1,2-addition to the electron deficient aldehydic carbon. However, since the C-2 site on (9) is also electron deficient, an alternative route to product (34) may be envisaged which proceeds via initial 1,4-addition of the nucleophile with concomitant opening of the pyrone ring and subsequent recyclisation of the intermediate phenol, see over.



(9) + Ph—S(=O)—CH(−)—C(=O)—CH$_3$ ⟶

(34)

After this brief aside, we returned to exploring the chemical manipulation of the Diels-Alder cycloadduct (10). In particular, the behaviour of (10) towards mild and neutral reagents required for the conversion to the required chromone structure was investigated and the results are described in the next Chapter.

EXPERIMENTAL

General conditions as described on page 32.

N,N-Dimethylformamide: Stirred over calcium oxide for 16 hours before being distilled at reduced pressure. The first and last 10% of the distillate was rejected;

Phosphoryl chloride: Distilled immediately before use;

2-Methoxypropene: Synthesised according to the method of M. S. Newman and M. C. V. Zwan[20] before becoming commercially available (ALDRICH).

2-Hydroxy-5-methylacetophenone (8)

p-Cresol (108.1 g, 1 mol) was dissolved in acetic anhydride (112 g, 1.1 mol) and magnesium perchlorate (0.62 g, 0.005 mol) was added. After 0.5 hours, the initial exothermic reaction had subsided and aluminium chloride (267 g, 2 mol) was added in small portions so as to maintain the temperature of the vigorously stirred solution at 70-80 °C. After addition of all the aluminium chloride was complete, the reaction mixture was heated to 170 °C and maintained at this temperature for 45 minutes. The mixture was then allowed to cool to 100 °C and 10% aqueous hydrochloric acid (200 ml) was added. The solution was left overnight at room temperature before extraction with ether (150 ml x 3). The combined ether extracts were washed with 10% aqueous sodium carbonate solution (200 ml x 2), water (150 ml x 3) and dried ($CaCl_2$). Evaporation of the ether under reduced pressure afforded a dark-brown oil which was distilled. The distillate boiling at 238-242 °C solidified to give acetophenone (8) as colourless needles, (119 g, 79%), m.p. 48-50 °C, (lit.[21] 48-50 °C).

6-Methyl-4-oxo-4H[1]benzopyran-3-carboxaldehyde (9)

To a stirred solution of 2-hydroxy-5-methylacetophenone (8) (40 g, 0.27 mol) in N,N-dimethylformamide (165 ml) at -20 °C was added phosphoryl chloride (169 g, 1.1 mol) dropwise over 30 minutes. The ice-methanol cooling bath was then removed and the temperature allowed to rise to 70 °C by an exothermic reaction. After a further 30 minutes, the solution was cooled to 15°C before being carefully poured onto ice-water (2 l). The resulting precipitate was collected and crystallised from acetone to afford the 3-formylchromone (9) as lemon-yellow needles (31 g, 66%), m.p. 173-174 °C, (lit.[4] 174-175 °C).

(3S)-4,4a-Dihydro-3,8-dimethyl-3-methoxy-3H,10H-benzopyrano[2,3-d][1]pyran-10-one (10)

The formylchromone (9) (2.5 g, 13.3 mmol) in chloroform (60 ml) was treated with 2-methoxypropene (19 g, 20 equiv.) and the mixture left to stand in the dark at room temperature for six days. During this time the solution turned dark red in colour. Solvent was evaporated under reduced pressure to afford a viscous red oil which solidified upon trituration with ether. The pyranone (10) crystallised from methanol as thick needles, (2.28 g, 66%), m.p. 116-118 °C.

Found (ML 22848): C,69.18; H,6.35%

$C_{15}H_{16}O_4$ requires: C,69.26; H,6.20%

Accurate Mass found: 260.10218

$C_{15}H_{16}O_4$ requires: 260.10485

m/e: 245 (M^+-CH_3); 229 (M^+-OCH_3); 200 (229-CHO)

ν_{max}: 1665 (C=O) and 1620 (C=C) $cm.^{-1}$

$^1H, \delta$: 1.47 (3H, s, CH_3)

2.29 (3H, s, $ArCH_3$);

3.41 (3H, s, OCH_3);

2.31 [1H, dd, J14 and 7Hz, C(4)];

2.45 [1H, dd, J14 and 9Hz, C(4)];

5.02 [1H, ddd, J7, 9 and 1.5Hz, C(4a)H];

6.82 [1H, d, J8Hz, C(6)H];

7.23 [1H, dd, J8 and 2.5Hz, C(7)H];

7.55 [1H, dd, J1.5Hz, C(1)H];

7.73 [1H, d, J2.5Hz, C(9)H].

$^1C, \delta$: 181.00 (s, C=O);

158.58 (s, C-10a);

151.28 (d, C-1);

135.91 (d, C-9);
131.12 (s, C-3);
126.77 (d, C-7);
122.35 (d, C-9a);
117.35 (d, C-6);
110.56 (s, C-5a);
103.81 (s, C-8);
71.43 (d, C-4a);
49.79 (q, O$\underline{C}H_3$);
35.65 (t, 4-$\underline{C}H_2$);
21.41 (8 lines, Ar$\underline{C}H_3$ and 3-$\underline{C}H_3$).

Pyranobenzopyranone (10) by lanthanide catalysis

The formylchromone (9) (1.05 g, 5.6 mmol) in chloroform (15 ml) was treated with 2-methoxypropene (2.4 g, 6 equiv.) followed by tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (0.3 g, 0.28 mmol). The reaction mixture was left to stand in the dark and reaction was shown to be complete (t.l.c.) after 24 hours. Solvent was removed under reduced pressure and the residue flash-chromatographed with dichloromethane-ethyl acetate (9:1 v/v) as eluant to afford pyranobenzopyranone (10) (856 mg, 59%) identical in all respects (t.l.c., n.m.r.) to that produced without employing ytterbium catalysis.

6,7-Diacetyloxy-4-oxo-4H[1]benzopyran-3-carboxaldehyde (18)

A solution of acetic anhydride (90 g, 0.88 mol) and concentrated sulphuric acid (2.5 g) was stirred at 40-50 °C while small portions of p-benzoquinone (30 g, 0.12 mol) were added. After addition of quinone was complete, the temperature of the mixture was raised to 135 °C and water (15 ml)

added dropwise during 10 minutes. After this time, more water (250 ml) was added and the mixture boiled for five minutes before being left to cool. The crystals which separated from the cooled solution were collected and recrystallised from aqueous ethanol to afford red needles of 2,4,5-trihydroxyacetophenone (27.9 g, 60%), m.p. 200-202 °C (lit.[22] 200-202 °C). This compound was acetylated with acetic anhydride (32.9 g, 0.32 mol) and pyridine (10 ml) at 0 °C. The reaction mixture was poured onto ice-water and the precipitate collected and recrystallised from ethanol to afford 4,5-diacetyloxy-2-hydroxyacetophenone as white tablets (21 g, 50%), m.p. 100-101 °C, (lit.[4] 100-102 °C). To a stirred solution of 4,5-diacetyloxy-2-hydroxyacetophenone (11.8 g, 47 mmol) in N,N-dimethylformamide (65 ml), phosphoryl chloride (28.8 g, 187 mmol) was added dropwise over the course of 15 minutes with cooling by a dry-ice acetone bath. The reaction mixture was then cooled at 0 °C for 20 minutes and then brought to room temperature for two hours, before being poured carefully onto ice-water (500 ml). The yellow precipitate was filtered off, washed with cold water and left to dry in air. Recrystallisation from acetone afforded the formylchromone (18) as colourless scales (8.2 g, 60%), m.p. 138-140 °C, (lit.[4] 140-141 °C).

(3S)-7,8-Diacetyloxy-4,4a-dihydro-3-methoxy-3-methyl-3H,10H-benzopyrano[2,3][1]-pyran-10-one (20)

To a solution of formylchromone (18) (1 g, 3.44 mmol) dissolved in chloroform (15 ml) at 0 °C, 2-methoxypropene (1.49 g, 6 equiv) was added and the reaction mixture left in the dark for 24 hours. T.L.C. then showed no starting material remained and the blood-red solution was concentrated under reduced pressure to afford a viscous red oil from which pyranobenzopyranone (20) separated on trituration with ether and crystallised from ethanol as needles, (674 mg, 54%), m.p. 125-126 °C.

Found (ML 22082): C,59.71; H,5.01%

$C_{18}H_{18}O_8$ requires: C,59.65; H,5.01%

Accurate Mass found: 362.1003

$C_{18}H_{18}O_8$ requires: 362.1001

m/e: 320 (M^+-CH_2CO); 291 (320-CHO); 262 (291-CHO)

ν_{max}: 1778 and 1759 ($ArCOCH_3$); 1665 (pyrone, C=O);
1620 and 2590 (C=C) $cm.^{-1}$

δ: 1.42 (3H, s, CH_3);
2.23 (3H, s, 2 x $OCOCH_3$);
3.37 (3H, s, OCH_3);
2.29 [1H, dd, J14 and 7Hz, C(4)H];
2.42 [1H, dd, J14 and 9Hz, C(4)H];
5.07 [1H, ddd, J7, 9 and 1.5Hz, C(4a)H];
6.84 [1H, s, C(6)H];
7.54 [1H, d, J1.5Hz, C(1)H];
7.72 [1H, s, C(9)H].

3(S)-8-Chloro-4,4a-dihydro-3-methoxy-3-methyl-3H,10H-benzopyrano[2,3-d][1]-pyran-10-one (19)

To 6-chlorochromone-3-carboxaldehyde (5 g, 23.9 mmol) in dichloromethane (125 ml) stirred at 0 °C, 2-methoxypropene (10.5 g, 6 equiv.) was added dropwise over five minutes and the reaction mixture then left to stand at room temperature and in the dark for 72 hours. Solvent was removed under reduced pressure to afford a cream-coloured granular solid which was recrystallised twice from ethanol to afford the 8-chlorobenzopyranone (19) as white flakes (4.87 g, 72%), m.p. 152.5-154 °C.

Found (ML 22400): C,60.03; H,4.63; Cl,12.54%

$C_{14}H_{13}ClO_4$ requires: C,59.88; H4.67; Cl,12.64%

m/e: 280 and 282 M^+, two isotopes of chlorine);

265 (M^+-CH_3); 248 (M^+-CH_3OH): 237 (M^+-CH_3CO).

ν_{max}: 1660 (C=O) and 1590br. (C=C) $cm.^{-1}$

δ: 1.43 (3H, s, CH_3);

3.38 (3H, s, CH_3);

2.31 [1H, dd, J14 and 7Hz, C(4)H];

2.45 [1H, dd, J14 and 7Hz, C(4)H];

5.03 [1H, ddd, J7, 7 and 2Hz, C(4a)H];

6.89 [1H, d, J8Hz, C(6)H];

7,36 [1H, dd, J8 and 3Hz, C(7)H];

7.57 [1H, d, J2Hz, C(1)H];

7.88 [1H, d, J3Hz, C(9)H].

(3R)-4,4a-Dihydro-3,8-dimethyl-3-methoxy-3H,10H-benzopyrano[2,3-d][1]pyran-10-one (11)

To benzopyranone (10) (520 mg) in benzene-methanol (30 ml, 2:1 v/v) was added 4-toluenesulphonic acid (30 mg) and the mixture left to stand at room temperature overnight. Removal of solvent under reduced pressure afforded a red gum. This was dissolved in dichloromethane and filtered through a short column containing celite. Evaporation of the eluant gave epimer (11) which crystallised from methanol as needles (157 mg), m.p. 120-122 °C.

Found (EMAL): C,69.36; H,6.17%

$C_{15}H_{16}O_4$ requires: C,69.20; H,6.19%

Accurate Mass found: 260.10540

$C_{15}H_{16}O_4$ requires: 260.10485

m/e: 245 (M^+-CH_3); 229 (M^+-OCH_3); 217 (M^+-CH_3CO)

ν_{max}: 1670 (C=O); 1610 and 1595 (C=C) $cm.^{-1}$

δ: 1.54 (3H, S, CH_3);

2.30 (3H, s, $ArCH_3$);

3.25 (3H, s, OCH_3):

2.06 [1H, dd, J15 and 9Hz, C(4)H];

2.55 [1H, dd, J15 and 8Hz, C(4)H];

5.13 [1H, ddd, J9, 8 and 2Hz, C(4a)H];

6.83 [1H, d, J8Hz, C(6)H];

7.24 [1H, dd, J9 and 3Hz, C(7)H];

7.50 [1H, d, J1.5Hz, C(1)H];

7.75 [1H, d, J3Hz, C(9)H].

(3S)-4,4a-Dihydro-3,8-dimethyl-3-ethoxy-3H,10H-benzopyrano[2,3-d][1]pyran-10-one (16)

To benzopyranone (10) (520 mg) in benzene-ethanol (30 ml, 2:1 v/v) was added 4-toluenesulphonic acid (50 mg). The reaction mixture was left to stand at room temperature for 16 hours. The work-up was the same as that described for epimer (11) and provided the 3-ethoxy epimer (16) as needles, (155 mg), m.p. 138-140 °C (EtOH).

Found (ML 22410): C69.92; H,6.42%

$C_{16}H_{18}O_4$ requires: C70.01; H,6.62%

Accurate Mass found: 274.11835

$C_{16}H_{18}O_4$ requires: 274.12049

m/e: 259 (M^+-CH_3); 246 ($M^+-C_2H_4$); 231 (M^+-CH_3CO)

ν_{max}: 1660 (C=O); 1615 and 1595 (C=C) $cm.^{-1}$

δ: 1.11 (3H, t, J9Hz, $OCH_2\underline{CH_3}$);

1.59 (3H, s, CH_3);

2.06 [1H, dd, J14 and 11Hz, C(4)H];

2.28 (3H, s, CH_3);

2.54 [1H, dd, J14 and 7Hz, C(4)H];

3.54 (2H, q, J7Hz, $O\underline{CH_2}CH_3$);

5.16 [1H, ddd, J11, 7 and 2Hz, C(4a)H];

6.82 [1H, d, J8Hz, C(6)H];

7.24 [1H, dd, J8 and 2Hz, C(7)H];

7.49 [1H, d, J2Hz, C(1)H];

7.72 [1H, d, J2Hz, C(9)].

3-(6-Methyl-4-oxo-4H[1]benzopyran)-but-1-en-3-one (23)

The benzopyranone (10) (500 mg) in an acetic acid-ethanol-water mixture (1:0.5:9 v/v) was heated on a water-bath at 50 °C. After ten minutes, t.l.c. indicated no starting material remained and the reaction mixture was poured into ice-water (40 ml). The precipitate was filtered off and crystallised from ethanol to afford ketone (23) as white needles, (280 mg), m.p. 179 °C.

Found (ML 22163): C,73.60; H,5.57%

$C_{14}H_{12}O_3$ requires: C,73.66; H,5.30%

m/e: 213 (M^+-CH_3); 199 (M^+-CHO); 185 (M^+-CH_3CO)

ν_{max}: 1660 ($COCH_3$); 1640 (pyrone, C=O);
1615 (C=C) $cm.^{-1}$

δ: 2.34 (3H, s, $ArCH_3$?);

2.45 (3H, s, $COCH_3$?);

7.27-7.45 [3H, m, C(8)H and CH=CH-CHO];

7.51 [1H, dd, J8 and 2Hz, C(7)H];

8.08 [1H, ill-defined d, C(5)H];

8.18 [1H, s, C(2)H].

3-(6-Chloro-4-oxo-4H[1]benzopyran)-but-1-en-3-one (24)

Benzopyranone (19) (500 mg) was subjected to the same experimental conditions as that described for the formation of ketone (23). Ketone (24) was recrystallised twice from methanol to afford yellow flakes (256 mg), m.p. 175-177 °C.

Found (ML 22680): C,62.81; H,3.73%

$C_{13}H_9ClO_3$ requires: C,62.77; H,3.66%

Accurate Mass requires: 248.02307

$C_{13}H_9ClO_3$ requires: 248.02401

m/e: 248 and 250 (M^+, two isotopes of chlorine);

233 (M^+-CH_3); 207 ($233-C_2H_2$).

ν_{max}: 1645br ($COCH_3$) and 1605 (pyrone, C=0) $cm.^{-1}$

δ : 2.30 (3H, s, 4'-CH_3);

7.27 [1H, d, J16Hz, C(1')H];

7.43 [1H, d, J8Hz, C(8)H];

7.47 [1H, d, J16Hz, C(2')H];

7.61 [1H, dd, J8 and 2.5Hz, C(7)H];

8.13 [1H, s, C(2)H];

8.18 [1H, d, J2.5Hz, C(5)H].

3-(6-Methyl-4-oxo-4H[1]benzopyran-3-yl)-but-1-en-2-(phenylsulphoxide)-3-one (34)

The anion of phenylsulphinyl acetone[23] (33) (546 mg) was generated in tetrahydrofuran with sodium hydride (50% dispersion in oil, 130 mg) and the solution was added dropwise to 3-formylchromone (9) (564 mg) stirred in tetrahydrofuran (30 ml) at room temperature. After addition was complete, the clear, red solution was allowed to stir for a further three hours before being added to ice-water (200 ml) containing concentrated hydrochloric acid (2 ml). The fine, yellow precipitate was extracted with ether (100 ml x 3) and the combined ether extracts were washed with water (50 ml x 2), brine (50 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a yellow-orange oil (1.16 g) which was flash-chromatographed over silica eluting with toluene-ethyl acetate (83:17 v/v). Evaporation of the eluants afforded unchanged 3-formylchromone (9) (263 mg) and an orange gum (113 mg) which was purified by recrystallisation from ethanol twice

Found (ML 22938): C,68.22; H,4.76%

$C_{20}H_{16}O_4S$ requires: C,68.17; H,4.58%

Accurate Mass found: 352.07693

$C_{20}H_{16}O_4S$ requires: 352.07691

m/e: 227 (M^+-PhSO); 185 (227-CH_2CO).

ν_{max}: 1680 ($COCH_3$); 1650 (pyrone, C=O);
1615 (C=C) and 1045 (S=O) $cm.^{-1}$

δ: 1.94 (3H, s, $ArCH_3$);

2.45 (3H, s, $COCH_3$);

7.23 [1H, d, J1.5Hz, C(1')H];

7.40 [1H, d, J8Hz, C(8)H];

7.51 [4H, m, o- and p-H of PhSO];

7.70 [2H, m, C(7)H and p-H of PhSO];

8.03 [1H, ill-defined d, C(5)H];

8.28 [1H, s, C(2)H].

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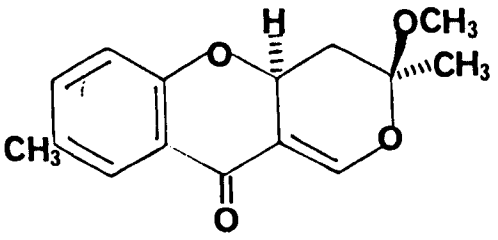
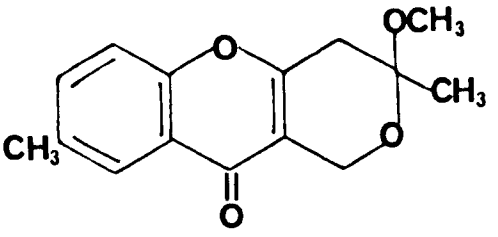
CHAPTER FOUR

A study of carbon-carbon double-bond isomerisation in benzopyranopyrans

The synthetical chemistry investigated up to this point had established a three step reaction pathway leading to adduct (1) in multi-gram quantities. The next task was to shift the heterocyclic carbon-carbon double-bond in this molecule to provide chromone (2).



(1)



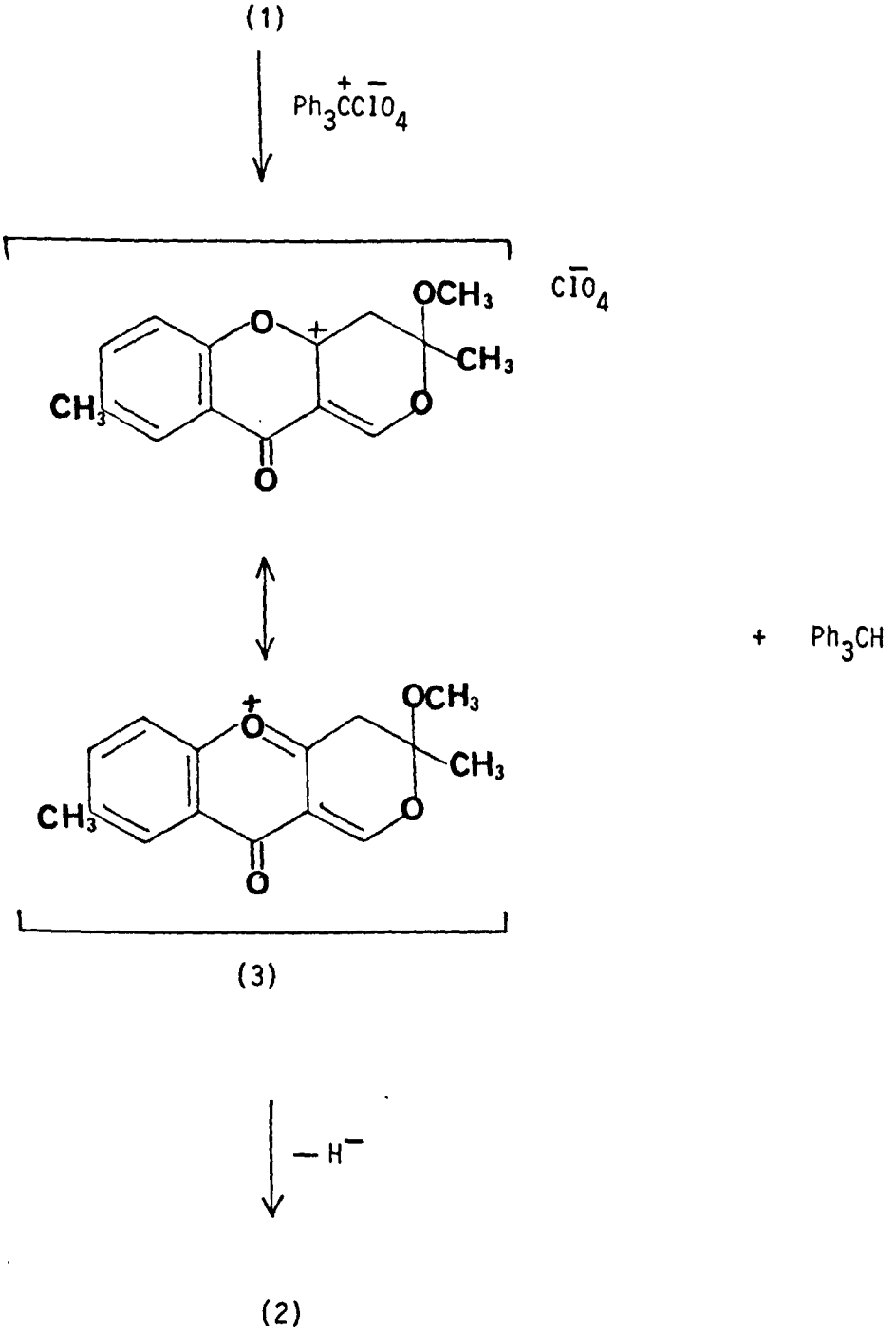
(2)

Classical methods of inducing bond migration usually require drastic conditions (i.e. strong bases or acids or high temperature, heterogeneous catalysis[1]) and, since treatment of adduct (1) with either mild base or acid leads to degradation or rearrangement of the molecular skeleton, we needed to look to reagents and conditions which are neutral and preferably mild.

The first method considered involved removal of the allylic hydrogen at position 4a as a hydride ion with triphenylcarbenium perchlorate, $Ph_3C^+ClO_4^-$, to give the intermediate carbenium ion (3), (Scheme I). For subsequent **mild** hydride reduction of (3) to furnish the required chromone (2), the site of attack for hydride ion must be position 1 and not position 4a as this would merely regenerate starting material.

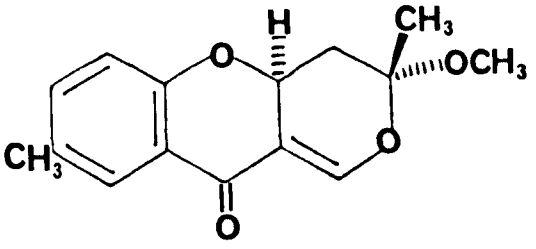
Triphenylcarbenium ions are well documented as hydride ion acceptors and have found preparative use in, for example, the dehydrogenation of

Scheme I


(1)
$Ph_3\overset{+}{C}\overset{-}{C}lO_4$
OCH3
CH3
CH3
O
O
O
$\overset{-}{C}lO_4$
+ Ph_3CH
OCH3
CH3
CH3
O
O
O
(3)
$-H^-$
(2)

cycloheptatriene to tropylium ion,[2] oxidation of ketone acetals and ethers by hydride transfer,[3] and for the oxidation of alcohols to ketones and aldehydes, via the trimethylsilyl ethers of the alcohols.[4] Moreover, all of these transformations occur under mild experimental conditions affording products in near quantitative yields.

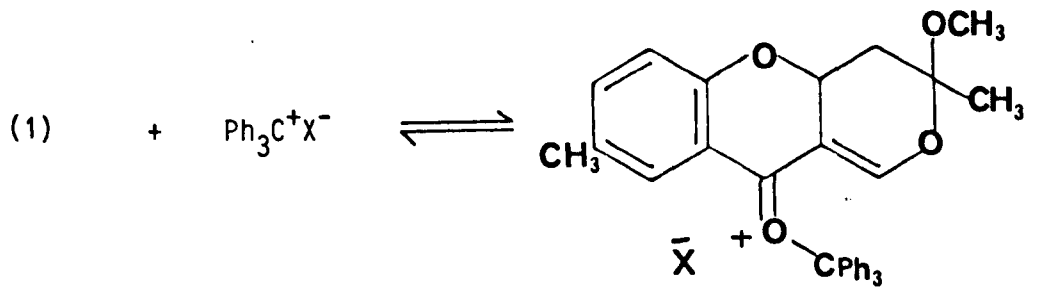
In practice, the addition of triphenylcarbenium perchlorate to a dichloromethane solution of (1) afforded a red coloured solution and careful addition of sodium borohydride provided (4), i.e. the alternative C-3 epimer of (1), and a quantitative yield of triphenylmethane. The same result was observed whatever the counter-ion of the triphenylcarbenium salt: the use of $Ph_3C^+BF_4^-$ or $Ph_3C^+SbCl_6^-$ gave (4) in 35 - 50% yield and a virtually quantitative yield of triphenylmethane.



(4)

That the stereochemistry about the anomeric centre of (1) is reversed to furnish the alternative epimer (4) could be due to the triphenylcarbenium salt not having been freed from traces of acid used in its preparation. Any trace of perchloric or hydrofluoric acid, for example, is likely to be sufficient to catalyse this reaction: in the previous Chapter it was reported that a trace of 4-toluenesulphonic acid in a methanolic solution of adduct (1) produces (4).

Reaction of adduct (1) with any of these triphenylcarbenium salts under forcing conditions did not provide any useful result. Heating a mixture of (1) and Ph_3CBF_4 in acetonitrile, for example, resulted in isolation of an intractable red oil upon work-up, whether sodium borohydride was added or not. The red colour which invariably occurred on mixing an equimolar amount of $Ph_3C^+X^-$ (where $X^- = ClO_4^-$, BF_4^-, $SbCl_6^-$) with adduct (1) in dichloromethane (or methylcyanide) may be due to the formation of ion (5) in a dynamic equilibrium reaction as shown in Equation 1.



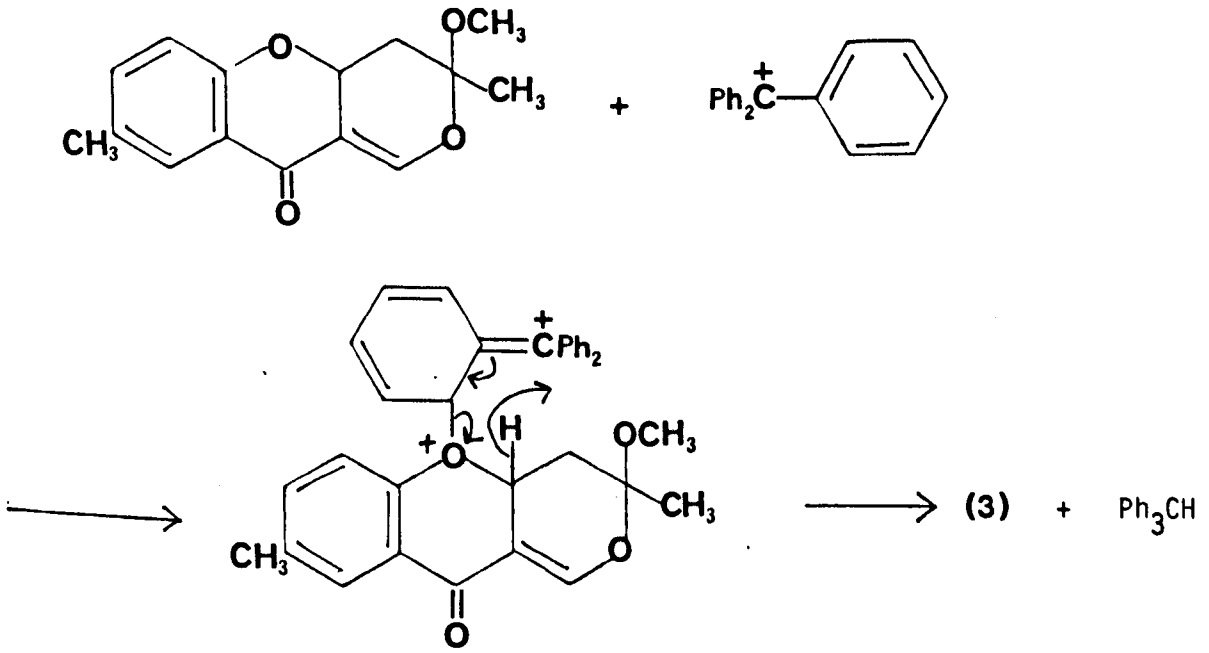
(5)

Equation 1

Under mild experimental conditions, the addition of borohydride ion may cause this equilibrium to lie more to the reactant side; the Ph_3C^+ electrophile then reacting with a "hard" nucleophile (i.e. H^-) rather than the relatively "soft" carbonyl oxygen. Alternatively, when more forcing conditions were employed, it may be that oxonium ion (3) was produced by hydride abstraction from C-4a on adduct (1). Indeed, we might expect ion (3) to have a red colour but perhaps this ion is unstable and degrades before or during the addition of borohydride ion. In either case, the formation of triphenylmethane occurs and so a question remains as to whether the triphenylcarbenium ion, Ph_3C^+, abstracts hydride ion from C-4a on adduct (1) or from borohydride anion. One way of investigating the origin of the hydride ion would be to substitute

a deuterium atom for the C-4a hydrogen on (1) and analyse the triphenylmethane product by high resolution n.m.r. spectroscopy for ^{1}H or ^{2}H content. Unfortunately though, none of the published[5] methods for the preparation of 3-formylchromones is suitable for incorporation of the desired specific labelling.

In the previous Chapter, speculative reaction schemes were drawn for the attack of an electrophile at the carbonyl grouping on (1) and other electron rich sites. Any of these schemes may be in operation in addition to those considered above in the reaction of (1) with Ph_3C^+ species. In fact, the idea of simple hydride transfer to Ph_3C^+ which has usually been proposed as the mechanism by which such reactions proceed has recently been shown to be incorrect.[6] The new proposal is that there is direct addition of Ph_3C^+ to the substrate, followed by intramolecular rearrangement and cleavage forming the oxonium ion and triphenylmethane. If we apply the proposed mechanism to our system, reaction would need to proceed in the following manner for the formation of carbenium ion (3):



There is no obvious reason to rule out this pathway, although the use of a smaller --i.e. "harder"-- carbenium ion would result in a less sterically crowded intermediate. This attempt to produce chromone (2) via an initial hydride transfer to triphenylcarbenium salts was not abandoned before a rigorous investigation in which numerous experiments varied not only the counter-ion of the salt but the other reaction parameters too. In the end, the repeated failure of such experiments forced us to examine an alternative method of moving the double-bond.

Viewed as a 1,3-hydrogen shift, the conversion of the adduct (1) to positional isomer (2) is thermally forbidden by Woodward-Hoffmann rules[7] unless it can proceed via the sterically unfavourable antarafacial mode. 1,3-Hydrogen shifts have been effected, however, via a low energy route involving catalysis by various transition metal complexes.[8] In essence, it is thought that interaction of appropriate metal orbitals with those of the alkene form a new set of occupied molecular orbitals which provide a symmetry-allowed (suprafacial) reaction pathway.[9] Unfortunately, there exists no close example in the chemical literature of double-bond isomerisation in molecules of type (1); most investigations of catalytic systems have centred on their structure and mode of action in hydrogenations -- isomerisations sometimes being reported as undesired side-reactions. Furthermore, of the wide variety of isomerisations which have been achieved using transition metal species, it is not surprising that the most important and extensively studied have been those involving carbon-carbon bond fission.

Nevertheless, before we consider potentially useful examples of double-bond migration which were gleaned from the chemical literature, we shall briefly examine the mechanisms of catalytic alkene isomerisation. These were to have a bearing on the type of catalyst chosen and the reaction conditions

in which they were employed in the attempts that were directed towards achieving the required isomerisation.

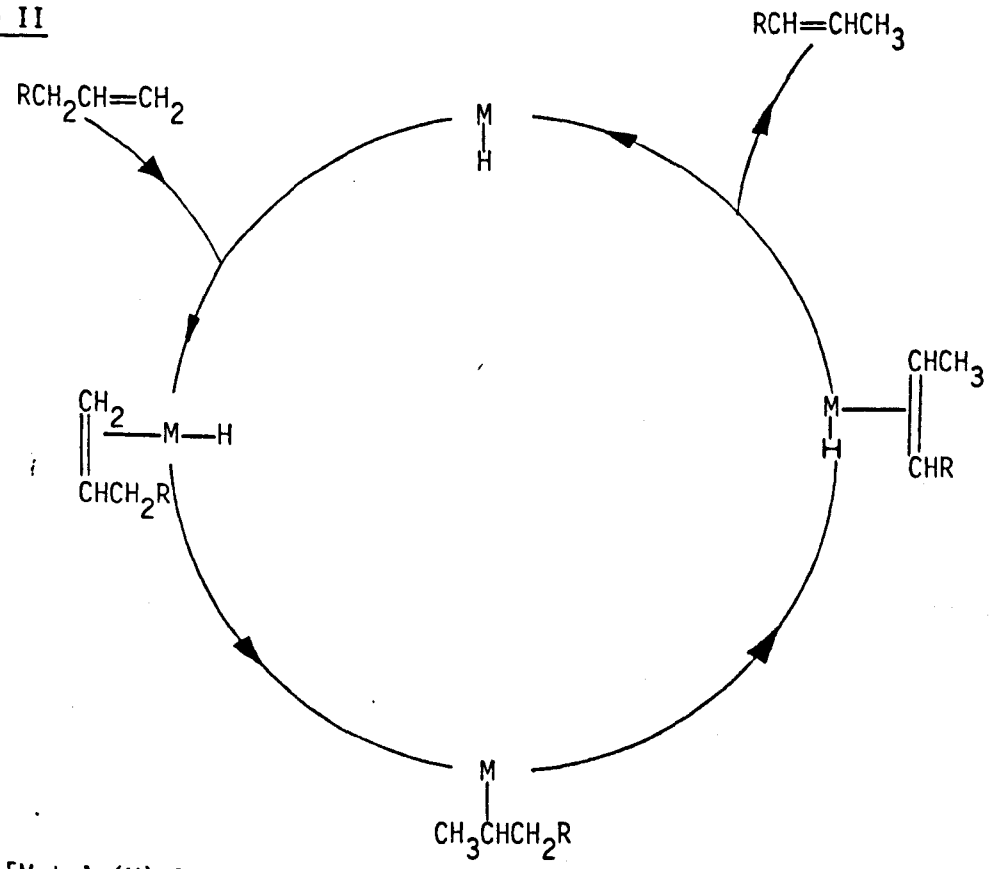
We note that two important mechanisms have been established for double-bond migration in alkenes (i.e. hydrogen migration reactions) catalysed by homogeneous transition metal compounds.[10] Isomerisation induced by metals in heterogeneous conditions will not be considered here since they are not usually suited to organic syntheses under normal laboratory conditions.

One mechanism (depicted in Scheme II) involves addition of an alkene to a metal hydride to form a metal alkyl, followed by a β-elimination, reforming an alkene in which the double-bond has migrated by a 1,2-hydrogen shift. This mechanism is common in isomerisations catalysed by rhodium compounds.

The second mechanism (Scheme III) involves formation of a π-allyl intermediate which facilitates a 1,3-hydrogen shift, rather than the 1,2-shift of the metal-alkyl mechanism. The metal π-allyl route requires a metal centre with two available oxidation states (n and n+2) since a redox process is operating at the metal centre. Among the better known examples of hydrogen migrations of this kind are those catalysed by palladium complexes and by iron carbonyls.

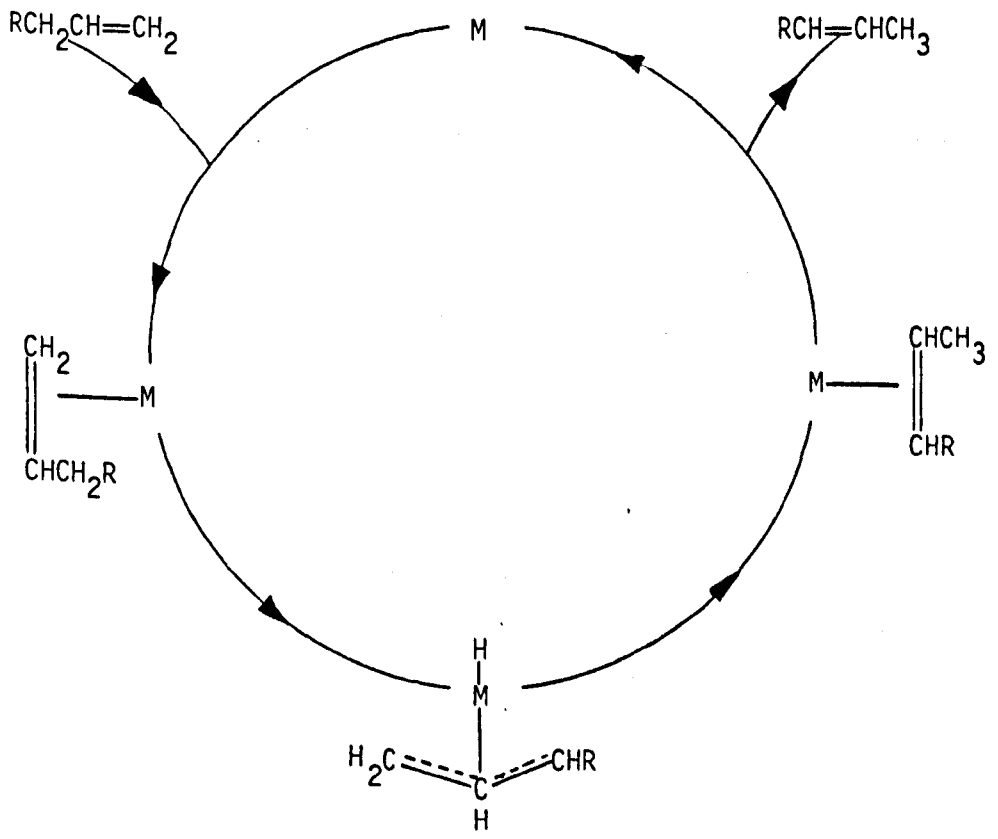
While these two mechanisms very likely explain the bulk of double-bond migration chemistry, it should be borne in mind that there are many cases[11] which appear to be inconsistent with the exchange of hydrogen atoms between the metal and alkene substrate, a process intrinsic to both the above mechanisms. In addition, solvent molecules undoubtedly play an active rôle in the overall process, principally by occupying vacant sites on the metal atom at different stages during the catalytic cycle.

Scheme II



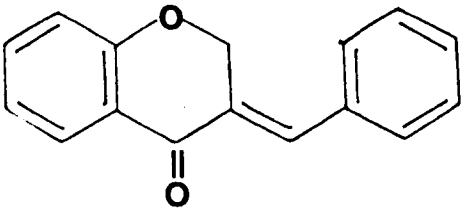
[Metal (M) ligands have been omitted for clarity]

Scheme III

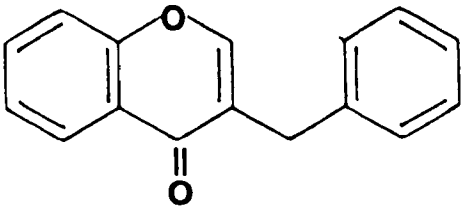


Apart from a consideration of the mechanisms and theory of 1,3-hydrogen migrations, the greatest incentive to explore the use of transition metal derived reagents was the belief that such a reagent (probably rhodium-derived) had already been used[12] in the successful transformation of adduct (1) to the chromone derivative (2). A previous research student of these laboratories had tackled the same synthetical problem and allegedly found success in converting (1) to (2) by using a certain transition metal based catalyst. Unfortunately, this student is now held incommunicado in an Iraqi gaol and his notebooks containing details of the particular reagent and the reaction conditions in which it was employed are similarly unobtainable. The only material evidence that the direct conversion of (1) to (2) had been effected via transition metal catalysis was a ^1H n.m.r. spectrum, (the signals in which are in agreement with structure (2)), and the presence in the laboratory of a box containing numerous samples of Rh-, Pd-, Pt- and Ir-complexes. So, accepting the fact that one crucial bit of information was missing, this synthetical problem was re-investigated.

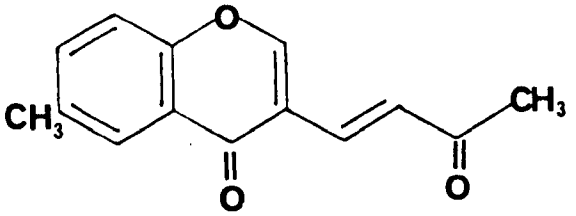
Our attention turned first to rhodium(III) chloride trihydrate, $RhCl_3.3H_2O$, which had been used in mild, homogeneous conditions by Barton and co-workers[13] to effect exocyclic to endocyclic double-bond migrations in arylmethylenechroman-4-ones. For example, the rearrangement of (6) to (7) was brought about simply by boiling (6) in an ethanol-chloroform-water mixture containing the catalyst for 24 hours. Moreover, the report states that this method of bond isomerisation was successfully applied to more complex molecules too. However, refluxing a mixture of adduct (1) and a catalytic amount of the rhodium salt in an ethanol-chloroform mixture for two hours afforded the ring-opened, unsaturated ketone (8) as the sole product.



(6)



(7)



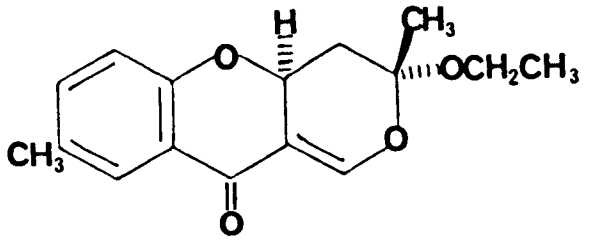
(8)

The formation of (8) is explained by the following. It is known[14] that rhodium trichloride oxidises ethanol to give a catalytically active rhodium hydride species with concomitant production of hydrogen chloride:

$$RhCl_3.3H_2O + CH_3CH_2OH \longrightarrow H\text{-}RhCl_2 + 3H_2O + HCl + CH_3CH{=}O$$

The acid produced in this reaction is responisble for the hydrolysis of the hemi-acetal function of (1) which is followed by ring-opening and reclosure ending in the ketone (8). (For the mechanism of this reaction, c.f. Scheme III of the previous Chapter). The hydrated trichlorides of ruthenium and iridium similarly afforded ketone (8) as the only product under these reaction conditions. Reaction of (1) with $RhCl_3.3H_2O$ in t-butanol instead of ethanol or the use of calcium carbonate in the reaction mixture to remove hydrogen chloride as generated resulted in starting materials being

recovered. Substituting anhydrous rhodium(III) chloride for $RhCl_3.3H_2O$ also converted (1) into (8) though much more slowly and if the reaction was performed in an ethanol-benzene solvent mixture and halted after four hours, the intermediate acetal (9) could be isolated in high yield.



(9)

As described in Chapter 3, the same product could be obtained by treatment of an ethanolic solution of (1) with a catalytic amount of 4-toluenesulphonic acid. An attempt to regain starting material (1) by boiling a methanolic solution of (9) containing $RhCl_3$ for four hours failed and longer reflux times produced only the unsaturated ketone (8).

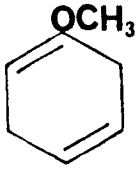
Since these initial efforts to form (2) with $RhCl_3.3H_2O$ were thwarted mainly because of the production of acid in the reaction mixture, we next looked to transition metal complexes which might avoid this problem.

One compound which has received considerable attention for its use in laboratory synthesis (especially in the selective hydrogenation of alkenes containing other reducible functional groups) is tris(triphenylphoshine)-rhodium(I) chloride, or Wilkinson's compound, as it is more commonly known. This compound has been reported by Corey[15] to catalyse the isomerisation of allyl ethers (10) to 1-propenyl ethers (11) in neutral, aprotic conditions.

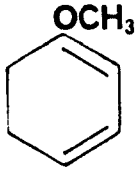
$$ROCH_2CH{=}CH_2 \xrightarrow{(Ph_3P)_3RhCl} ROCH{=}CHCH_3$$

(10) $R{=}CH_3$; $CH_3(CH_2)_9$; $PhCH_2$ (11)

Furthermore, a study by Birch et al[16] has shown that the $(Ph_3P)_3RhCl$ complex is an excellent reagent for inducing the isomerisation of (12) to its more stable conjugated isomer (13).



(12)

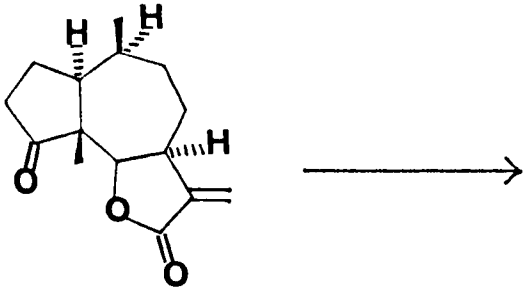


(13)

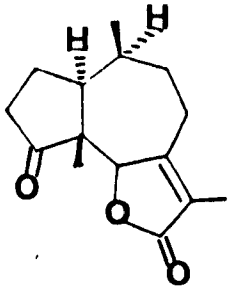
Corey's method involves boiling the allyl ether and Wilkinson's compound (10% by weight) in 10% aqueous ethanol for three hours. For our purposes, this method was modified by excluding water from the reaction mixture but after three hours of boiling a neat ethanolic solution of adduct (1) and the catalyst under an inert atmosphere, no reaction had occurred. Similarly, longer reflux periods or varying the amount of Wilkinson's compound used until it was present in stoichiometric quantities, also proved fruitless. Birch's method of effecting the isomerisation of (12) to (13) comprises of boiling (12) in chloroform for two hours with 1% by weight of the catalyst. This change in solvent and quantity of catalyst used also failed when applied to adduct (1). In fact, chlorinated solvents are not recommended for use

with $(Ph_3P)_3RhCl$ since they have been reported to deactivate the catalyst by chlorine addition.

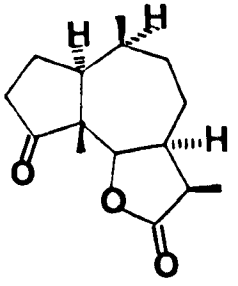
In the initial work on the homogeneous hydrogenation of alkenes over $(Ph_3P)_3RhCl$, Wilkinson reported[17] that no double-bond isomerisation was observed though reports which appeared later conflict with this assertion. For example, the attempted hydrogenation of damsin (14) using $(Ph_3P)_3RhCl$ gives iso-damsin (15) as the major product along with only a small quantity of the required dihydrodamsin[18] (16). No isomerisation of (14) to (15) occurs with $(Ph_3P)_3RhCl$ alone: addition of hydrogen as a co-catalyst is required to induce the reaction (14) ⟶ (15).



(14)



(15) Major product



(16)

That the use of molecular hydrogen in conjunction with $(Ph_3P)_3RhCl$ is able to bring about such an isomerisation tallies with the established mechanism for rhodium-promoted isomerisation depicted in Scheme II. Here it is shown that a metal hydride species is required and it is known that

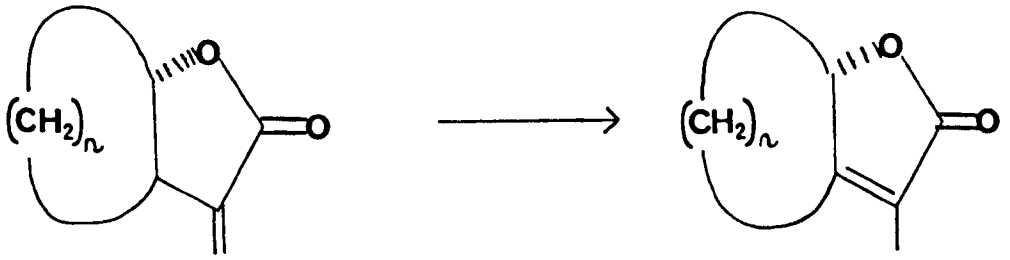
presaturating a solution of $(Ph_3P)_3RhCl$ with hydrogen gas, before introduction of the alkene, forms a metal dihydride complex.[17] However, molecular hydrogen bubbled at one atmosphere pressure into a solution containing $(Ph_3P)_3RhCl$ had no effect on adduct (1).

Not surprisingly perhaps, the extent to which isomerisation may occur during hydrogenation with Wilkinson's catalyst has been shown to depend on the experimental conditions. Augustine and Van Peppen,[19] for example, have reported that whilst there is no significant isomerisation of 1-heptene using Wilkinson's catalyst in benzene, use of a benzene-ethanol solvent mixture leads to formation of cis- and trans-2-heptene at an early stage in hydrogenation. Furthermore (and in contradiction to much of the previous two paragraphs) these workers report that in experimental studies of 1-heptene and 1-methylene-4-t-butylcyclohexane, isomerisation is much reduced if the Rh-complex is first equilibrated with hydrogen and promoted in the presence of oxygen. Accordingly, the meticulous exclusion of air which had been ensured in previous experimental procedures was abandoned though still to no avail; aerated benzene-ethanol solutions of $(Ph_3P)_3RhCl$ also failed to isomerise adduct (1) and starting materials were recovered.

The bromo-analogue of Wilkinson's compound, tris(triphenylphosphine)-rhodium(I) bromide, was prepared and substituted for $(Ph_3P)_3RhCl$ in many of the previously described experiments though again, no different effect was observed. (Wilkinson reports[17] an increase in the catalytic activity of $(Ph_3P)_3RhX$ in the order X=Cl<Br<I).

The last rhodium complex to be investigated in this study for its potential as an isomerisation reagent was carbonyltris(triphenylphosphine)-rhodium(I) hydride, $(Ph_3P)_3Rh(H)CO$ -- a metal hydride known to be an

excellent double-bond isomerisation catalyst.[20] This complex has found application, for example, in the quantitative conversion of exocyclic methylene lactones of the type (17) to the endocyclic isomers (18).



(17) (18)

No molecular hydrogen was required for this conversion and the method consisted simply of mixing the lactone (17) with an equimolar amount of the rhodium hydride complex in dioxane and leaving the mixture at room temperature for two days.

When this complex proved unsuccessful in bringing about the required change in (1), it was a particular disappointment since all of the rhodium-derived compounds present in the laboratory when this author took up the project had been examined for their potential as double-bond isomerisation reagents. It was suspected (c.f. page 95) that at least one of these compounds might have been used in the successful, direct conversion of (1) to the chromone[12] (2). Of course, it may be that one of these rhodium compounds was indeed used for the conversion of (1) to (2) but in this investigation the compound had been used in experimental conditions in which it was inert towards (1). Alternatively, it may be that some other route (i.e. one not involving transition metal catalysis) to chromone (2) was found. In fact the failure of the experiments described above to bring about the desired conversion forced us to examine the possibility that we might be

mistaken in assuming that chromone (2) ought to be more stable (i.e. thermodynamically and/or electronically) than adduct (1). If it transpires from an experimental investigation of adduct (1) and chromone (2) that the former is the more stable, then it may be that the hypothetical intermediate shown below has been formed at the transition state in our experiments and then followed the lowest energy path available, i.e. to regenerate starting materials. On the other hand, it may be argued that if chromone (2) is more stable than adduct (1), then the transition state shown below was simply not reached in any of our experiments.

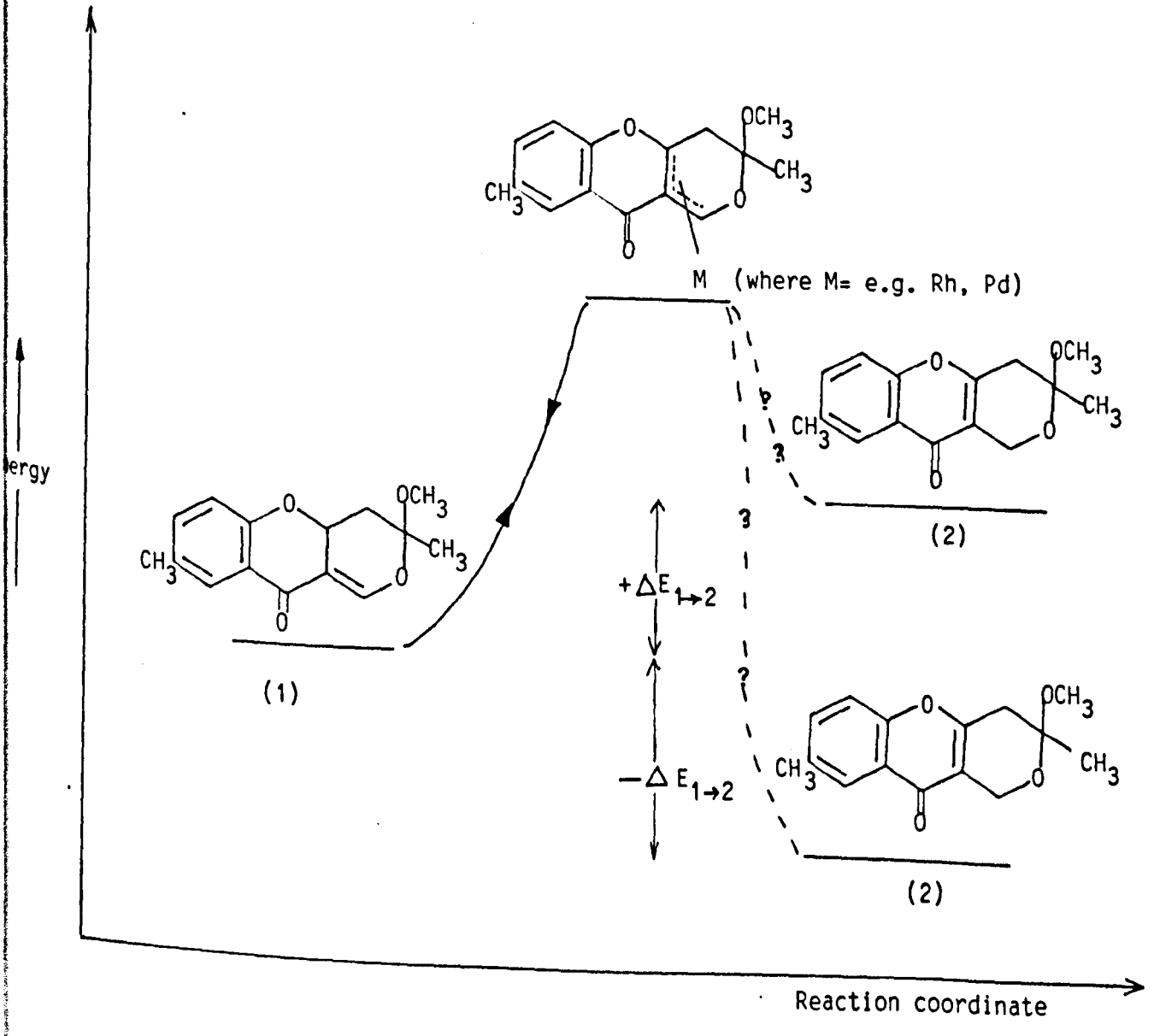


Diagram 1

Before commencing any experimental work, however, a survey of the chemical literature very quickly provided an important clue as to which of (1) or (2) (which differ structurally only in the orientation of the oxyvinylketone grouping, O-C=C-C=O) is likely to be the more stable. Studies[21] which have focused on compounds containing the O-C=C-C=O grouping as found with the geometry shown in chromone (2) (which we shall refer to as a 'cis' orientated chromone) are in a marked abundance compared with the very few studies of the ('trans' orientated) O-C=C-C=O grouping as found in adduct (1). The main reason for this, of course, is the prevelance of naturally occuring compounds containing the cis O-C=C-C=O grouping, e.g. chromones, flavones, rotenoids, etc. For this reason alone, we might justifiably have assumed that 'cis' chromone (2) would be more stable than 'trans' chromone (1). However, a quantitative, rather than a qualitative analysis of the relative stability of cis and trans O-C=C-C=O groupings would be useful since we might then be more able to predict which of the energy profiles from transition state to product shown in diagram 1 would be the most favourable.

Many of the investigations of chromones and substituted chromones which have been published have centred on analysing the aromaticity of these compounds. In chromone itself, for example, the strong resonance interaction between the etheric oxygen and the carbonyl group is evidenced by the basicity, $pk'_a = -2.05$, and the dipole moment, $\mu = 5.05D$, on the carbonyl oxygen.[22] It is clear, therefore, that the mesomeric effect operating in (1) is likely to be of a much lower magnitude than that found in (2) [see diagram 2] which, at the extreme, represents an aromatic pyrilium ring.

It is known that in groups of ketones that are close in structure, there exists a direct relation between basicity and the characteristic vibration frequencies of the carbonyl group. This fact can be exploited to provide

a method of assessing the basicity of chromone and chromone-like compounds.

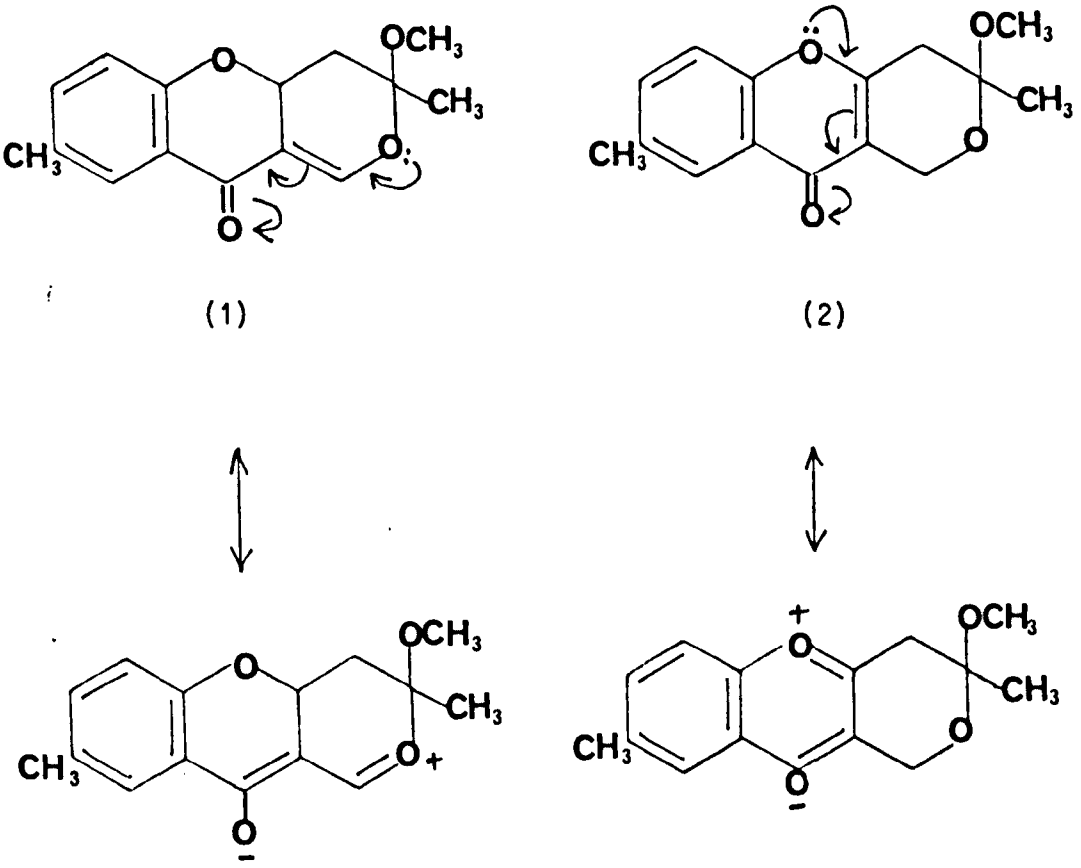
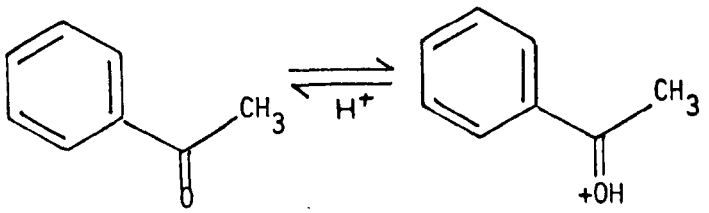
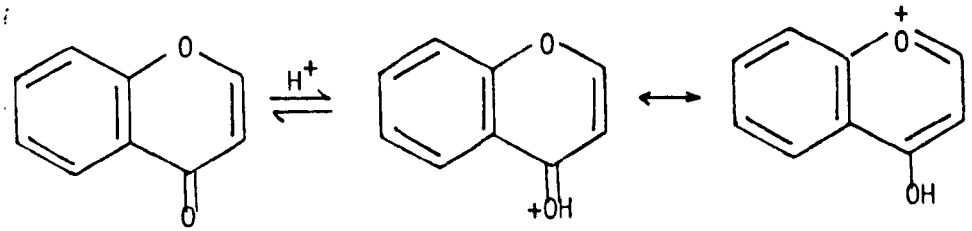
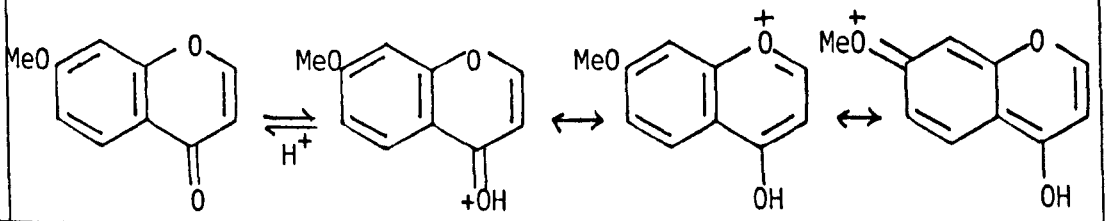
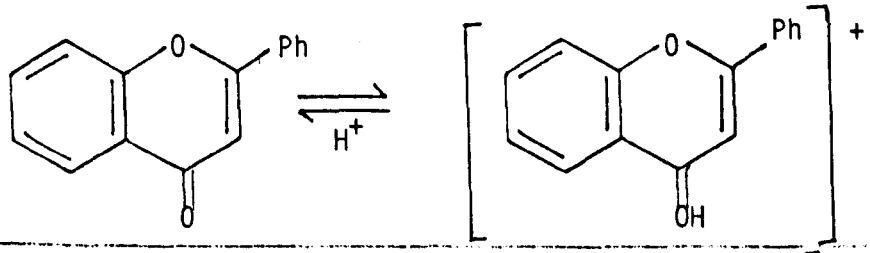
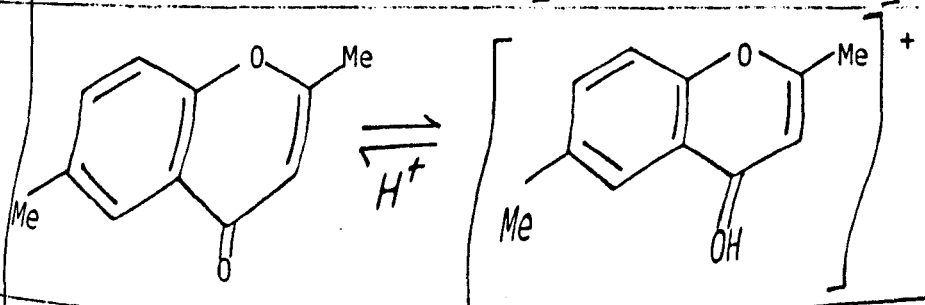
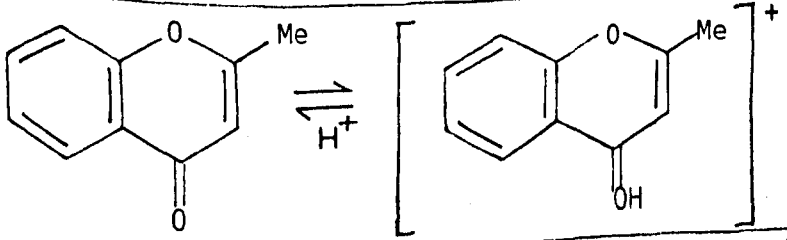
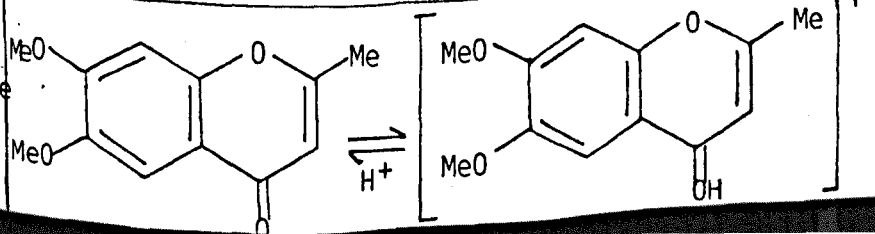


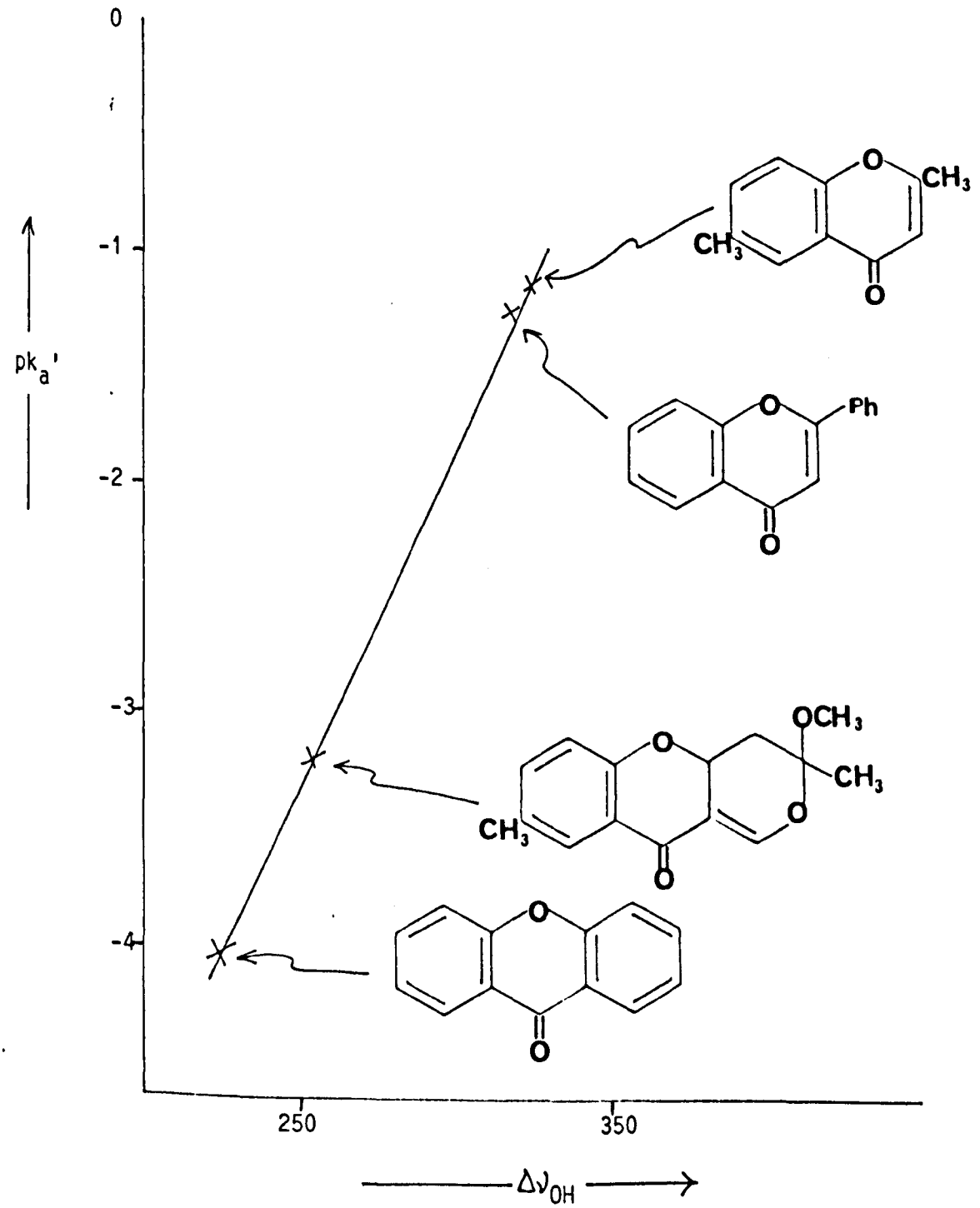
Diagram 2

Russian workers,[23] for example, have measured the frequencies of hydrogen bonds formed between chromones and phenol in carbon tetrachloride solution, (see Table 1). A linear correlation exists between the OH frequency shift and the pk_a' of the carbonyl acceptor and, not surprisingly, this hydrogen bonding becomes more pronounced with chromones bearing electron releasing substitutents on the benzene nucleus. For our purposes, however, we were interested in using the method described by the Russians to compare the pk_a' values obtained for 'trans' chromone (1) and [in the absence of (2)] the 'cis' chromones, 2,6-dimethylchromone, flavone and xanthone.

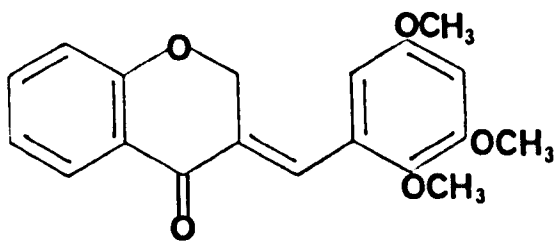
TABLE 1

BASE	EQUILIBRIUM	pk_a'
Acetophenone		-6.05
Chromone		-2.00
7-MeO-Chromone		-1.38
Flavone		-1.33
2,6-diMe-Chromone		-1.26
2-Me-Chromone		1.16
2,6-diMe-2-Me Chromone		-0.55

Confirming first the infra red shifts reported by the Russian workers for flavone and xanthone as being accurate, we used the same technique for the '<u>cis</u>' chromone, 2,6-dimethylchromone and the '<u>trans</u>' chromone (1). By extrapolation in the graph, we obtained the approximate value: $pk_a'(1) = -3.2$



The graph shows that there is a reduction in basicity along the series 2,6-dimethylchromone > flavone > adduct (1) > xanthone. This may be explained by considering the conjugation between cyclic and acyclic oxygen atoms to be disturbed by annelation of the pyrone ring with a benzene ring (as occurs in xanthone) or another pyran ring as in adduct (1). It is clear from the position that adduct (1) occupies in the graph that there is some electron donation from the cyclic oxygen of the pyran ring into the pyranone ring. The importance of this donation, with respect to the overall basicity of the compound, can be seen by considering the lower value (pk_a' = -4.2) which we obtained for the basicity of '<u>trans</u>' chromone (19). This compound contains no similar exocyclic etheric oxygen atom and, it appears, the electron rich, trisubstituted benzene nucleus adjacent to the double-bond does not even compensate for this.



(19)

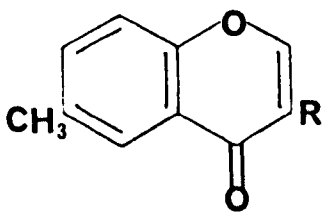
In terms of the relative basicities of the compounds shown in the graph, we may draw a tentative conclusion that, under the right chemical conditions, the heterocyclic double-bond in (1) should migrate to form the chromone proper.

A consideration of the mechanism of 1,3-hydrogen migration catalysed by homogeneous transition metal complexes indicated that the use of palladium complexes or iron carbonyls would be worth investigating.

Bis(benzonitrile)palladium(II) chloride, a compound reported[24] to catalyse the isomerisation of simple alkenes in homogeneous conditions, gave no reaction when dissolved in a benzene solution of (1) and left at room temperature for one week. Boiling this mixture under nitrogen for five hours, however, afforded a uselessly complex red oil. Presumably the affinity of palladium for the oxygen in adduct (1) caused disproportionation under these conditions giving the mixture observed.

The use of iron pentacarbonyl,[25,26] $HCo(CO)_4$,[26] and $(Ph_3P)_3RuH_2$[26] were similarly unsuccessful in promoting the isomerisation of (1) to (2).

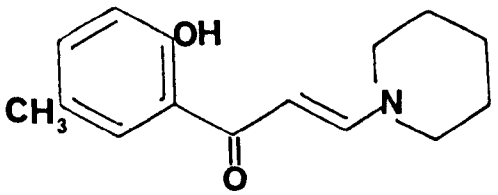
In a departure from the use of homogeneous conditions, the adduct (1) was heated in toluene in the presence of palladium metal on barium sulphate. It seems that these forcing conditions caused the adduct to dissociate to the 3-formylchromone (20) which was then decarbonylated to yield 6-methylchromone (21) in 81% yield. [A separate experiment confirmed that the formylchromone (20) is indeed decarbonylated under these experimental conditions producing (21) in near quantitative yield].



(20) R=CH=O
(21) R=H

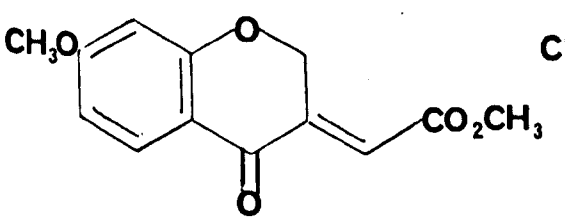
While the decarbonylation of aldehydes using palladium metal catalysts is known,[27] this method of defunctionalising 3-formylchromones has no precedent;

previously, removal of the formyl group of (20) has always been effected[28] by reaction with piperidine and the product isolated only as the ring-opened, enamino ketone (22).

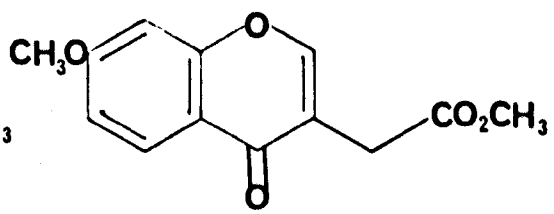


(22)

The final attempt to catalyse double-bond migration again involved heterogeneous conditions. Indian workers have reported[29] that treatment of (5) with Raney nickel afforded a mixture of the endocyclic double-bond isomer (6) and the reduced homoisoflavone. In addition, these workers claim that the ester (23) was smoothly isomerised to the chromone (24) on boiling in xylene in the presence of Raney nickel for three hours. (It may be, however, that this reaction was catalysed by alkali since the preparation of Raney nickel involves the use of strong alkali, complete removal of which is difficult).



(23)

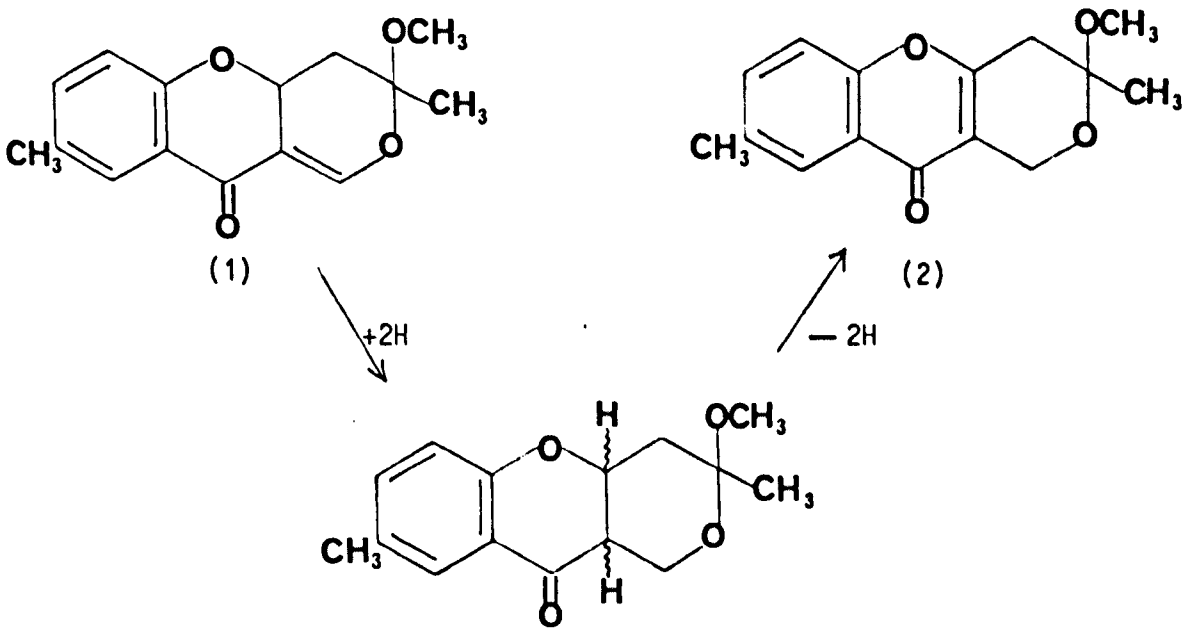


(24)

Adduct (1) remained intact after treatment with boiling xylene (b.p. 139 °C) alone for one hour but when Raney nickel was added and the mixture reheated, t.l.c. analysis soon showed that the adduct was dissociating. NMR analysis of the residue obtained on work-up confirmed the presence of the formyl-chromone (20) in an approximately 1:1-mixture with starting material (1). It may be that, under longer reflux times, nickel would mimic palladium in effecting deformylation of (20) but this was not investigated.

Given the failure, so far, of this authors' efforts to obtain the desired isomer (2) it was decided to pursue an alternative synthetical strategy not involving the use of transition metals or reagents derived therefrom.

The rearrangement of (1) to (2) is conceivable <u>via</u> a two step reaction pathway in which hydrogen is added to the molecule to furnish a chromanone and, in a separate reaction, dehydrogenation of this chromanone is induced to afford chromone (2):



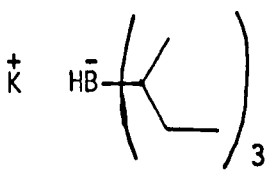
This then represents a sequential reduction-oxidation pathway and relies for its successful completion on two important criteria:

(i) The selective reduction of the carbon-carbon double-bond in the presence of the reducible carbonyl moiety;

(ii) dehydrogenation occuring only across the junction of the heterocyclic rings.

There are many different hydride donating reagents and hydrogenation catalysts which have been investigated in recent years in order to find conditions under which a given group will be reduced selectively. The most common broad-spectrum reducing agents, i.e. sodium borohydride and lithium aluminium hydride, were quickly shown to be useless in bringing about selective reduction of (1) because they gave a complex mixture of products resulting not only from indiscriminate reduction but also because of the basic nature of these reagents.

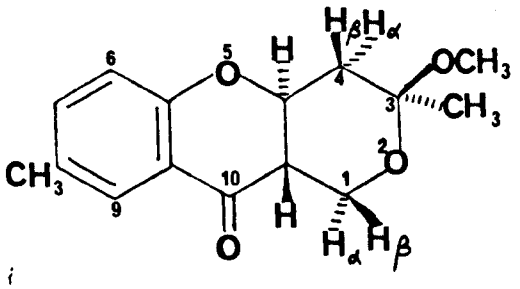
Replacing some of the hydrogens of $NaBH_4$ with alkyl or alkoxy groups results in reagents which are less reactive and hence more selective. Several such reagents are now commercially available and in common use. One such reducing agent is the borane complex, potassium tri-s-butyl-borohydride, or "K-Selectride" (25).



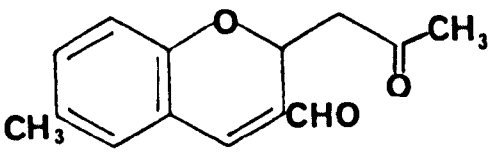
(25)

Reaction of one equivalent of (25) with adduct (1) at -78 °C in tetrahydrofuran, followed by oxidative work-up with 10% sodium hydroxide and 30% hydrogen peroxide solution (to destroy the borane by-product) afforded a 22% yield of the required chromanone (26) and, unexpectedly, the intensely

yellow 3-formylchromene (27) in 70% yield.

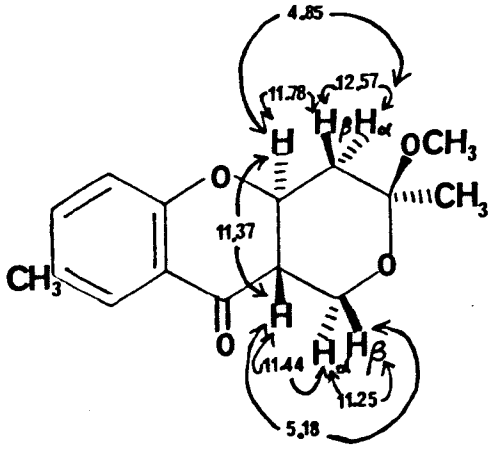


(26)



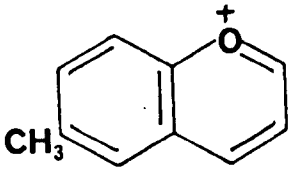
(27)

Compound (26) crstallised from methanol as colourless needles, m.p. 113 °C, and gave a molecular ion at m/e 262.12035 by F.A.B. mass spectrometry. Elemental analysis confirmed the empirical formula as $C_{15}H_{18}O_4$ and strong absorptions at 1675 and at 1615 and 1575 $cm.^{-1}$ in the infra red spectrum suggested the presence of a conjugated chromanone carbonyl grouping and aromatic C=C bonds respectively. The 250 MHz ^1H n.m.r. spectrum (shown overleaf) showed 18 hydrogens and a noticeable pattern of symmetry for the signals due to the methine and non-equivalent methylene hydrogens at C-4a, C-10a and C-1, C-4 respectively. The C-10a methine hydrogen resonates out of the deshielding cone of the carbonyl grouping as a multiplet centred at δ 2.74. Decoupling of this signal caused removal of ca. 11 Hz coupling to C-1H_α (t at δ 3.62) and of a ca. 4 Hz coupling to C-1H_β (dd at δ 4.21) and a change in the signal at δ 4.61 due to the C-4a methine hydrogen. Decoupling of this signal resulted in a similar loss of coupling values with the axial and equatorial C-4 geminal hydrogens and established the trans diaxial nature of the C-4a and C-10a hydrogens ($J_{4aH-10aH}$ = 11.4 Hz). The C-9 hydrogen appeared with characteristic separation from the other aromatic hydrogens as a singlet at δ 7.62.



(26) — with coupling values shown in Hz

The formylchromene (27) was isolated as an intensely yellow oil which degraded to a dark brown gum on attempted distillation at low pressure. The infra red spectrum of (27) showed strong absorptions at 1710 and 1665 $cm.^{-1}$ and ^{13}C n.m.r. signals at δ189.39 and δ204.48 indicated the presence of a conjugated aldehyde and a ketone grouping respectively. Among the important peaks in the F.A.B. mass spectrum (e.g. M^+ at 230.09477; $C_{14}H_{14}O_3$ requires 230.09428) was a prominent one at m/e 145 corresponding to the 6-methyl-benzopyrilium ion (27a).

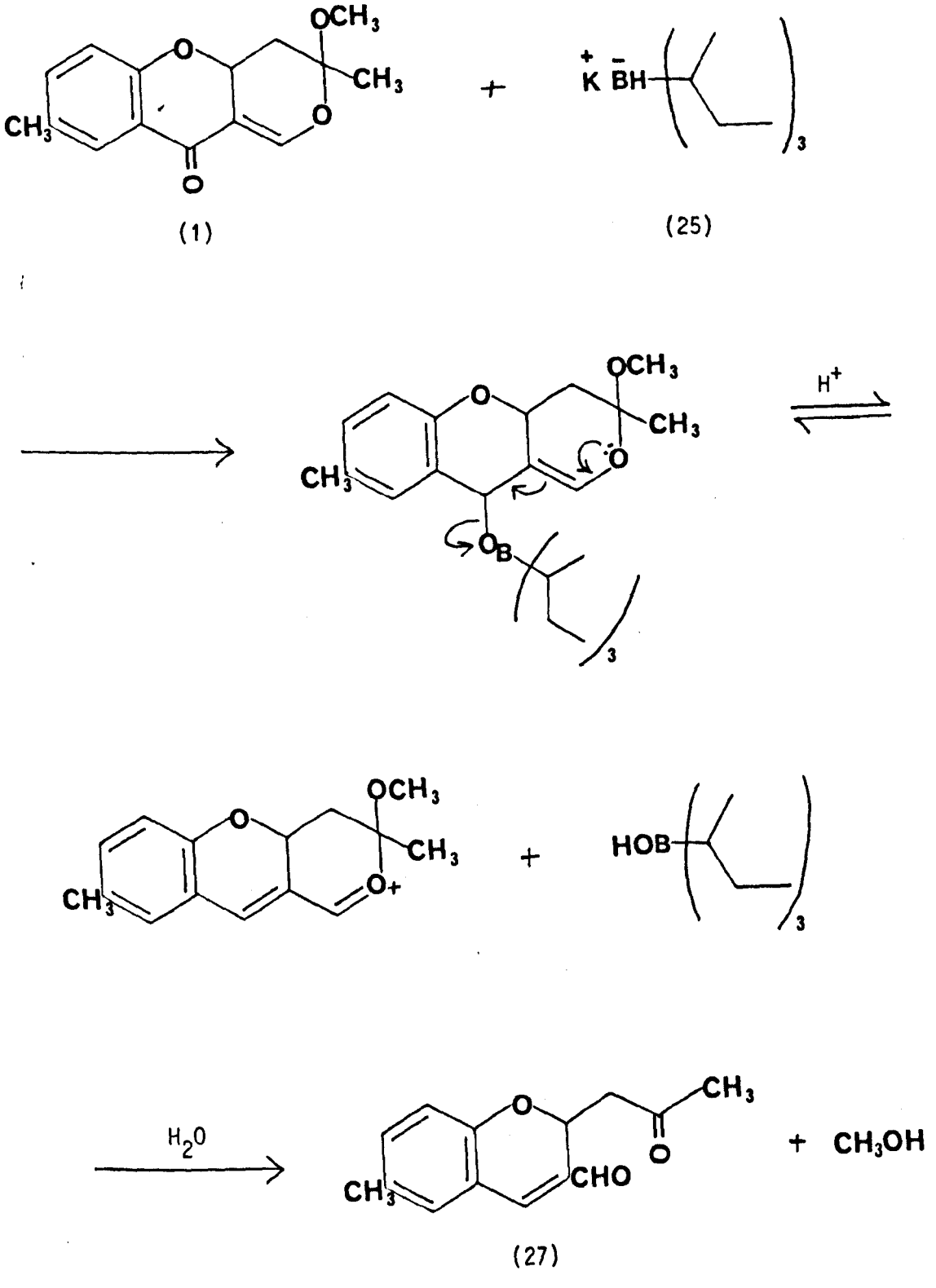


(27a)

In the ^1H n.m.r. spectrum, the aldehydic hydrogen signal was well separated from all others and appeared as a singlet at δ9.48. The vicinal couplings between C-2H (dd at δ5.68, J 3.5 and 10 Hz) and the C-1' geminal hydrogens (both dd at δ2.42 and δ2.84; J=16 and 3; 10 and 3.5 Hz respectively) constitute an ABX system. The conjugated alkene C-4 hydrogen resonates as a singlet at δ7.16. A plausible mechanistic account for the production of the formylchromene (27) is shown in Scheme IV. The carbonyl group in (1) is reduced instead of the carbon-carbon double-bond and a secondary transformtion occurs during the aqueous work-up of the reaction mixture. Here, an oxidised borane is expelled from the intermediate with concomitant double-bond migration to form a chromene. Acid catalysed hydrolysis of the acetal function completes the sequence.

In a detailed study of the reduction of α,β-unsaturated carbonyl

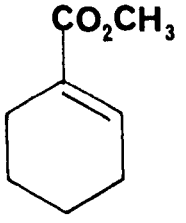
Scheme IV



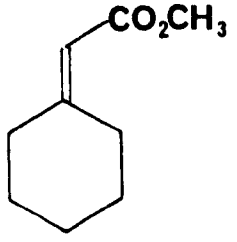
(1) (25)

(27)

compounds by K- and L-Selectride (lithium tri-s-butylborohydride), Ganem and Fortunato[30] report the effect of varying certain reaction parameters (such as solvent, duration and temperature of reaction, etc.) with a view to maximising 1,4-reduction as opposed to the competing 1,2-reduction. The report looks in particular at the reduction of α,β -unsaturated esters directly to saturated esters and it is noted that trialkylborohydrides were not very successful in reducing enoates such as (28) or (29) where the conjugated alkene is exo- or endocyclic; in these instances, complex mixtures were generally formed.



(28)



(29)

Changes in the solvent used for these reactions was also explored though no dramatic reactivity changes were apparent if pyridine or toluene, for example, was substituted for tetrahydrofuran. However, it was observed that the Selectride reagents had appreciable lifetimes in alcoholic solvents such as 2-propanol, ethanol and t-butanol. A useful application of this fact was in avoiding Claisen condensation in the attempted conjugate reduction of methyl nonenoate (30), for example; the first formed enolate (31) being rapidly protonated in a t-butanol-tetrahydrofuran reaction mixture.

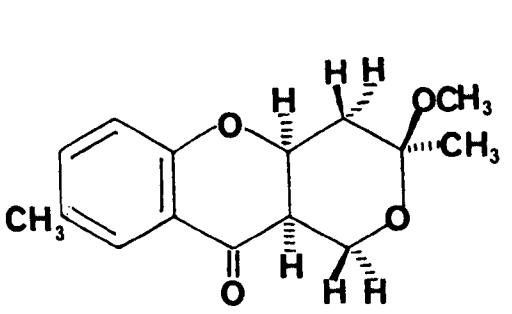
$$C_6H_{13}CH{=}CHCO_2CH_3 \xrightarrow{(25)} [C_7H_{15}\bar{C}H{-}CO_2CH_3] \xrightarrow{t\text{-BuOH/THF}} C_8H_{17}{-}CO_2CH_3$$

(30) (31)

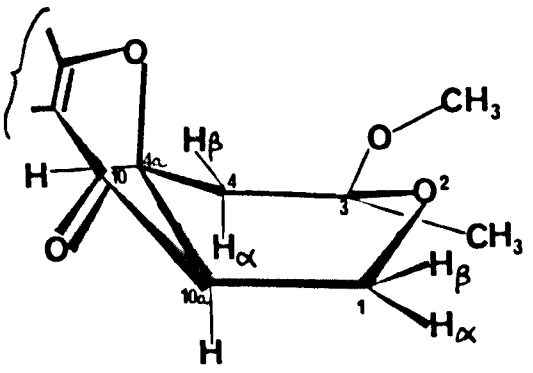
In contrast to these authors' recommendation of such protic solvents, however, the use of t-butanol in the attempted conjugate reduction of (1) with K-Selectride was not useful. As a solvent on its own, t-butanol (m.p. 25 °C) froze out in the reaction pot at -78 °C and also when diluted with tetahydrofuran to form a 1:3 t-butanol/tetrahydrofuran mixture. Substituting s-butanol (m.p. -115 °C) resulted in recovery of starting material (1) as well as a small amount of formylchromene (27).

In all the cases that Ganem and Fortunato studied, the work-up procedure remained the same, i.e. an oxidising mixture of aqueous sodium hydroxide and hydrogen peroxide was used to destroy the tri-s-butylborohydride product. Since we are seeking to increase the yield of the chromanone (26), and it is known that chromanones are base-labile, it was decided to change the work-up procedure to one not involving the use of aqueous sodium hydroxide solution. To this end, a tetrahydrofuran solution of the oxidising agent m-chloroperoxybenzoic acid was used in the work-up of subsequent experiments and there was indeed a small increase (5-10%) in the yield of the desired product (26) but the undesired formylchromene (27) remained the major product. With this slightly improved procedure, however, it was of interest to see if a further increase in the yield of (26) might be obtained by using L-Selectride instead of K-Selectride. This change in the counter-ion did indeed give an interesting result; t.l.c. examination showed a mixture of three reaction products which were separated by silica gel column chromatography followed by fractional crystallisation. Two of these products were the previously observed chromanone (26) and the formyl-

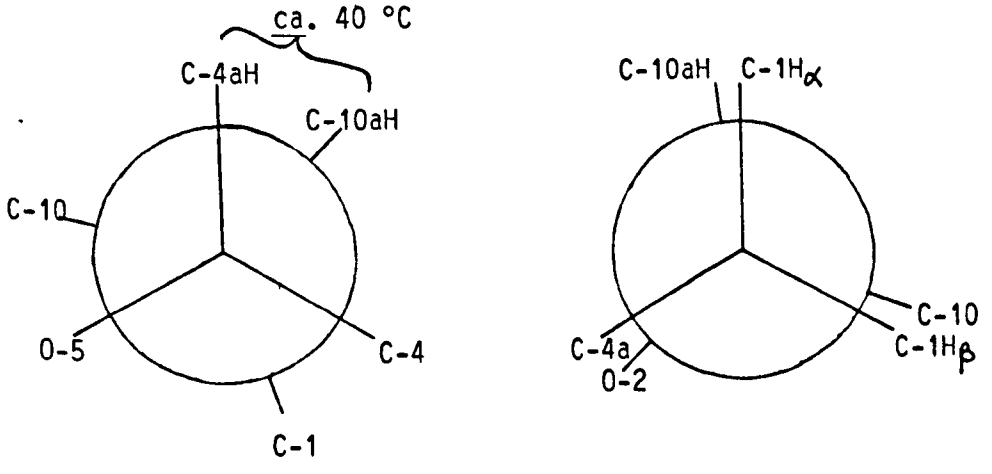
chromene (27). The third and most polar compound, obtained in 6% yield, was a new chromanone (32), the proton n.m.r. spectrum of which appears overleaf.



(32)

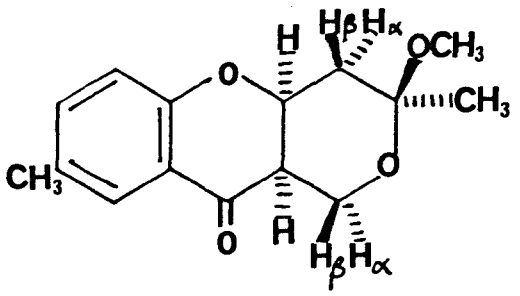


(32a)



(32b)

Comparison of the ^1H n.m.r. spectra of (32) and (26) (both compounds analysed in $CDCl_3$) immediately shows the loss of 'symmetry' in the former. In (32), the signals corresponding to the methine and methylene hydrogens are no longer arranged in a manner that allows them to be superimposed as they may be for the corresponding signals in the spectrum of (26). This loss of symmetry, however, provides an important clue as to the likely stereochemistry of chromanone (32), i.e. the arrangement of its hydrogens is one which permits, a priori, assignment of cis fused pyranone-pyran rings, c.f. (32a). The broadening of the signal due to the C-4a methine hydrogen at δ4.70 is so

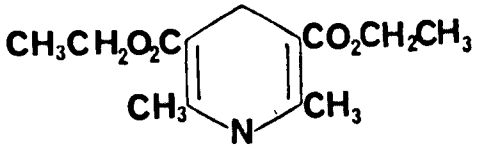


(32)

slight as to suggest this hydrogen is orientated gauche to both the vicinal C-10a hydrogen (multiplet at ca. δ2.8) and the C-4 geminal hydrogens, C-4H$_\alpha$ and C-4H$_\beta$ (both dd, δ2.36, J=16 and 2.5 Hz; δ1.84, J=16 and 4 Hz respectively). In contrast, the C-10a hydrogen, while gauche to C-4aH, is almost eclipsed by one of the vicinal C-1 hydrogens (i.e. C-1H$_\alpha$ at δ3.64, dd, J=12 and 6 Hz) and approximately trans diaxial to C-1H$_\beta$ (δ3.96, t, J=12 Hz). These assignments were confirmed by proton decoupling experiments which also showed the coupling value for C10a-H—C4a-H to be 3.9 Hz which is clearly too small for a trans diaxial relationship and confirms the cis nature of the pyranone-pyran ring junction. [A molecular model shows a dihedral angle between C4a-H and C10a-H of approximately 40° (c.f. (32b)) and inserting a value of J=3.9 Hz into the Karplus equation[31] leads to a calculated dihedral angle of 45°].

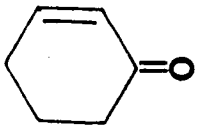
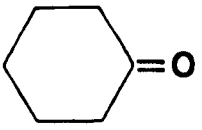
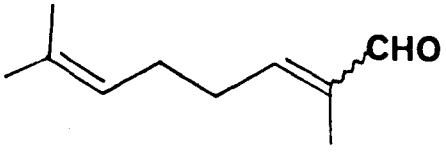
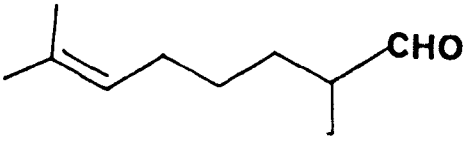
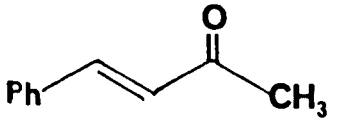
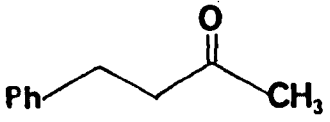
This investigation of the use of potassium and lithium trialkylborohydrides in the selective reduction of adduct (1) was interesting in that the formylchromene (27), the trans fused chromanone (26) and the less stable, cis fused chromanone (32) were obtained but the yields of the last two products were too low for this method to by synthetically useful.

Another reagent which is finding increasing use in the chemoselective reduction of olefinic double-bonds[32] in α,β -unsaturated carbonyl or nitro compounds is diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate or Hantzsch ester (33).

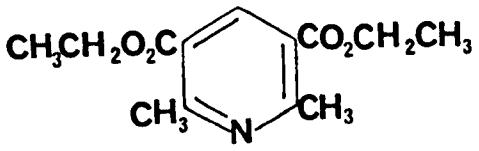


(33)

There are a number of reports in the chemical literature on the use of Hantzsch ester as an NADH model; (33) and other 1,4-dihydropyridine derivatives used in the presence of zinc ion mimic the role of coenzymes which reduce olefins in enzymatic systems. Japanese workers[33] report, for example, that Hantzsch ester reduces carbon-carbon double-bonds in simple α,β-unsaturated ketones and aldehydes in the presence of silica gel as catalyst. Although a detailed mechanism of the reduction process is not proposed by these workers, they describe the role of silica gel both as an acid catalyst and an absorbent to increase local concentration of reactants. A few representative examples of this method of reduction are reproduced below.

Substrate	Product	Yield (%)
		88
		67
		100

Accordingly, Hantzsch ester (33) was reacted with adduct (1) in the presence of silica gel in refluxing benzene during 16 hours. Work-up showed that although the ester had lost hydrogen to give the pyridine derivative (34), the adduct (1) was unaffected.



(34)

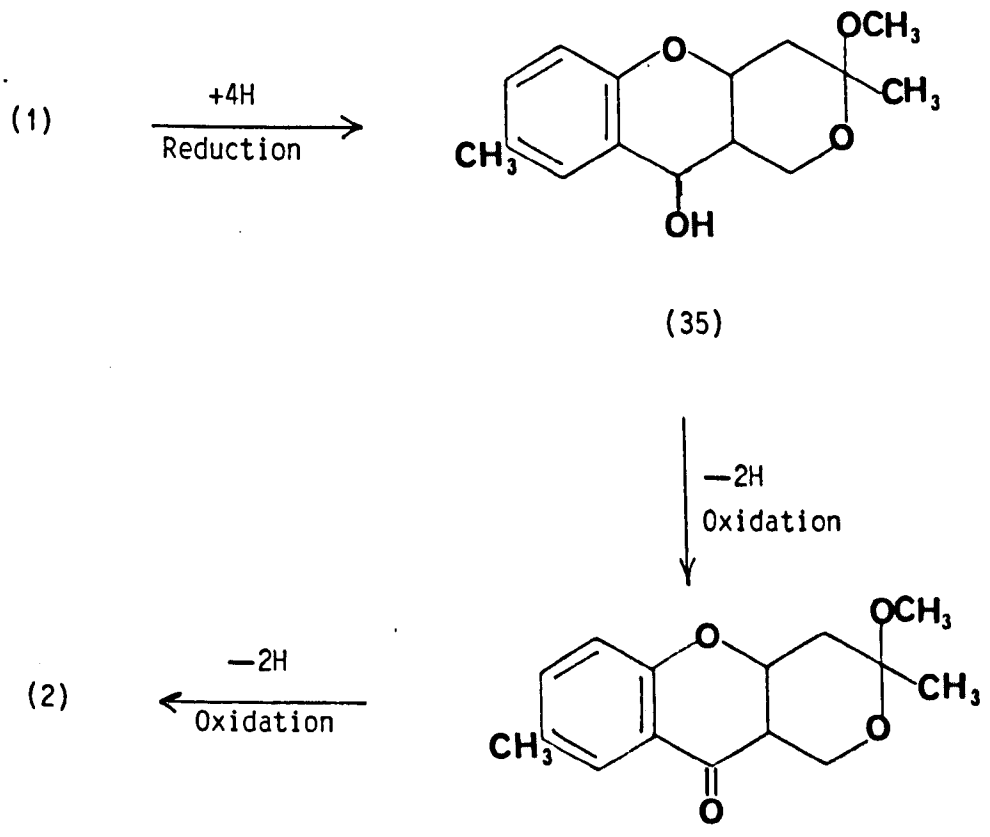
The failure of (33) to effect reduction of (1) is not altogether surprising. Hantzsch ester is a "softer" reducing agent than K- or L-Selectride and the fact that the carbon-carbon double-bond in (1) is trisubstituted and made further electron rich by the adjacent oxygen atom does not help matters. Nevertheless, the preparation of Hantzsch ester was not in vain as it was to find a much more rewarding application as a mild and selective reducing agent in later synthetical work, c.f. Chapter 5.

Since the chief drawback in the attempted direct reduction of (1) with Selectride reagents was their lack of selectivity, another possibility worth investigating was the use of other hydride donating reagents for the reduction of **both** the carbon-carbon double-bond **and** the carbonyl group in (1), (Scheme V). The saturated, secondary alcohol formed might then be oxidised to the required ketone before a second oxidation reaction generating chromone (2). This route to (2) again involves a sequential reduction-oxidation process though the synthesis of the chromanone intermediate would be achieved in two stages rather than by a one-pot, (but inefficient) direct reduction of (1) with Selectride reagents.

For the reduction of (1) to the alcohol (35), therefore, we are no longer concerned so much with the selectivity as with the mildness of the reagent which brings about reduction. It was stated earlier that sodium

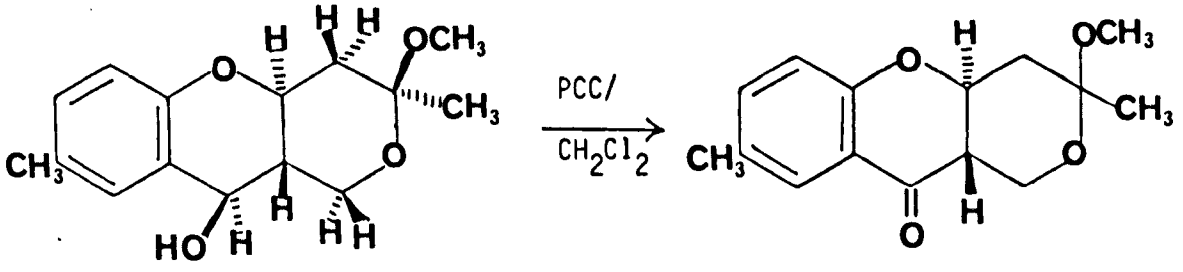
borohydride proved too powerful a reducing agent though substituting alkyl groups for hydrogen atoms in the borohydride ion formed a less reactive and more selective reducing agent. Similarly, a change in the nature of the cation in the borohydride reagent has been shown to be beneficial. For example, the commercially available reagents, tetraethyl- and tetra-n-butylammonium borohydrides (i.e. Et_4NBH_4 and n-Bu_4NBH_4 respectively) have found use in synthetical organic chemistry where mild and selective reducing agents are required largely because of their solubility in solvents of relatively low polarity such as benzene and dichloromethane.

Scheme V



When adduct (1) and tetra-n-butylammonium borohydride were dissolved in dichloromethane and left at room temperature for seven days, a 21% yield

of the desired saturated alcohol (35a) was isolated upon work-up; leaving the mixture a further 14 days increased the yield to 27%. Warming the dichloromethane solution did not seem to speed-up the reaction nor affect the yield and reaction of (1) with a single equivalent of borohydride ion was too slow to be useful. Similarly, the yield of (35a) was poor when tetraethylammonium borohydride was used as reductant under the same experimental conditions.



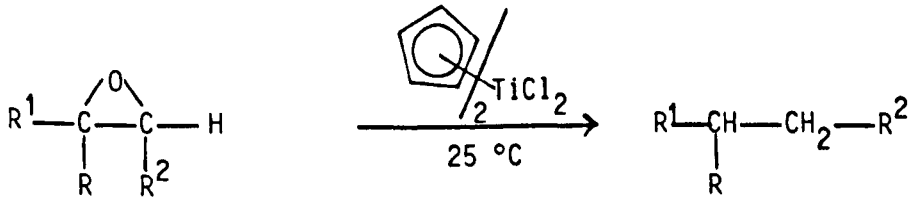
(35a) (26)

The infra red spectrum of (35a) showed an absorption at 3220 $cm.^{-1}$ indicative of a secondary hydroxy grouping and high resolution mass measurement of the molecular ion showed the exact mass to be m/e 264.13483 which was consistent with the formula $C_{15}H_{20}O_4$ (264.13614). The ^1H n.m.r. spectrum showed 20 hydrogens, one of which (δ1.73 br. s.) was exchangeable with D_2O. The C-9 hydrogen resonated as a singlet at δ7.26, i.e. at higher field than the corresponding hydrogens in any of the compounds so far examined in this study of benzopyranopyrans. Three singlets appeared for the tertiary methyl groups (δ3.21, OCH_3; δ2.27, $ArCH_3$; and δ1.39, C,3-CH_3) and the C-10 hydrogen appeared as a sharp doublet at δ4.48 and coupled to C10a-H (δ1.84, m) with $J_{C10\text{-}H,C10a\text{-}H}$= 10 Hz. When the doublet was saturated in a decoupling experiment, the only significant loss of coupling

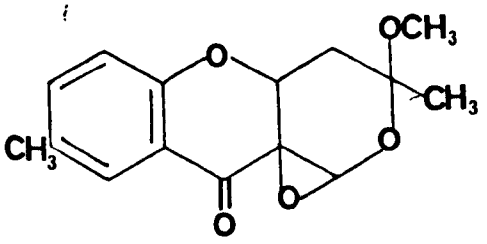
(ca. 10 Hz) was in the multiplet at δ1.84 suggesting a trans diaxial orientation of hydrogens at C10 and C10a. A triplet at δ3.44 (J=11.4 Hz) was assigned to the axial C-1 hydrogen; this triplet collapsed to a perturbed doublet ($J_{C1H_\alpha, C1H_\beta}$= 8 Hz) on saturation of the δ1.84 multiplet. Another multiplet at ca. δ4.25 integrated as two hydrogens and could be discerned as an overlapping double doublet (C1H$_\beta$, J=13.7 and 4.9 Hz) and a double 'double of doublets' (C4a-H, J=10.9, 5.5 and 2.5 Hz).

The trans nature of the pyranone-pyran ring junction was unambiguously confirmed by oxidation of (35a) with pyridinium chlorochromate (PCC) in dichloromethane affording the (trans) chromanone (26) which had been produced in earlier experiments with the K-Selectride reducing agent. This two-step reaction to chromanone (26), however, offerred no advantage in terms of the yield of product to the one step reaction involving chemoselective reduction of (1) to (26) with K-Selectride.

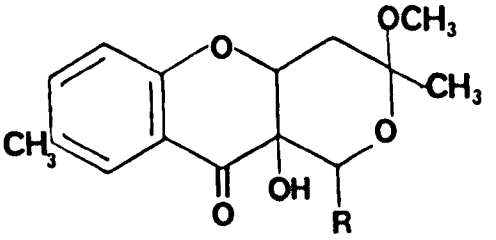
Another reaction worth investigating was epoxidation of the double-bond since an epoxide (or oxiran) is a readily adaptable functionality and compounds containing it may act, for example, as precursors for β-hydroxyalkanethiols, vic-glycols and β-hydroxyethers. Another interesting reaction which trisubstituted epoxides have been shown to undergo is total reduction to alkanes in the presence of the organometallic reagent, titanocene dichloride:[34]



This type of reduction has relevance to our study since if it was applied successfully to epoxide (36), it would generate the chromanone intermediate which was the target of numerous synthetical efforts reported earlier. An alternative pathway to chromone (2) might involve epoxide ring-opening to form the intermediate tertiary alcohol (37a).



(36)



(37a) R=H; (37b) R=SCH_3

(38) R=OCH_3

(39) R=OCH_2CH_3

The R appendage would ideally be a hydrogen atom though the conventional method of opening epoxide rings to saturated alcohols using lithium aluminium hydride would clearly be inappropriate in this case. The group R might also represent an alkylthio substituent originating from reaction of (36) with an alkanethiol. If (37b), for example, was obtained with ease, the remainder of the pathway to (2) might involve dehydration (perhaps via the tertiary tosylate) followed by cleavage of the ring-sulphur bond with Raney nickel.

In the event, epoxidation of (1) succeeded although it met with the difficulties expected from a reaction conducted under basic conditions; in most experiments much useless red oil was produced. The crude (36) (obtained in 50% yield) could not be recrystallised from methanol because the sensitivity

of the strained three-membered ring permitted total conversion into the β-hydroxymethyl ether (38). Attempted purification of (36) from ethanol similarly caused alcoholysis of the epoxide though to a lesser extent than that observed with methanol and this time, separation of (36) from ether (39) was easily achieved.

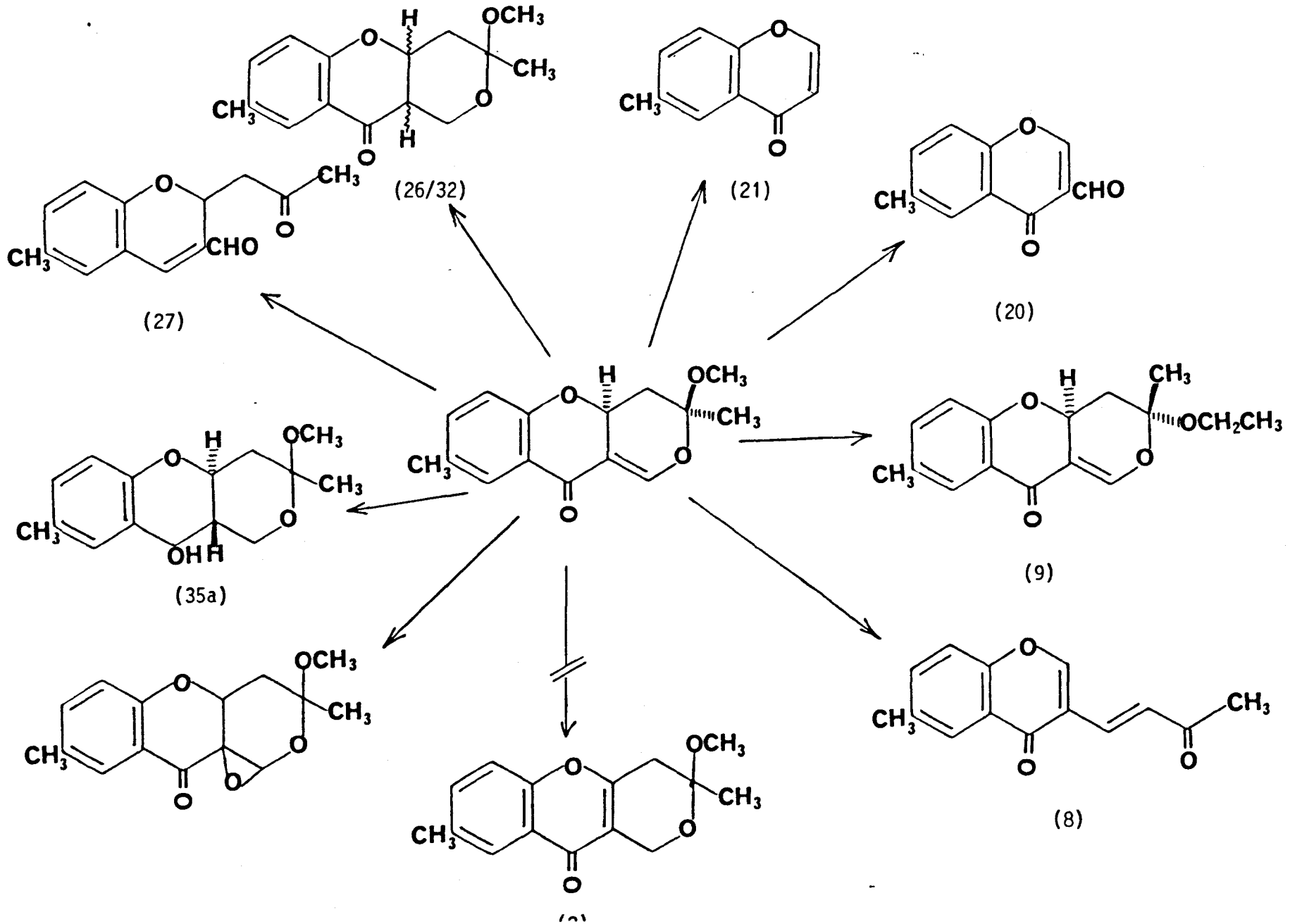
In view of the poor yield of epoxide, it was judged not worthwhile continuing with a particular study of this compound either in its reduction to the chromanone using titanocene dichloride or in any elaboration involving alkanethiol reagents.

At this stage, a brief resumé of the reactions which adduct (1) had undergone may serve to illuminate its versatility. This is depicted schematically overleaf and it can be seen that while the molecule undergoes oxidation and reduction reactions, dissociation, rearrangement of the molecular skeleton and ether exchange at the anomeric 3-position, the most important bond isomerisation step generating chromone (2) had still not been realised.

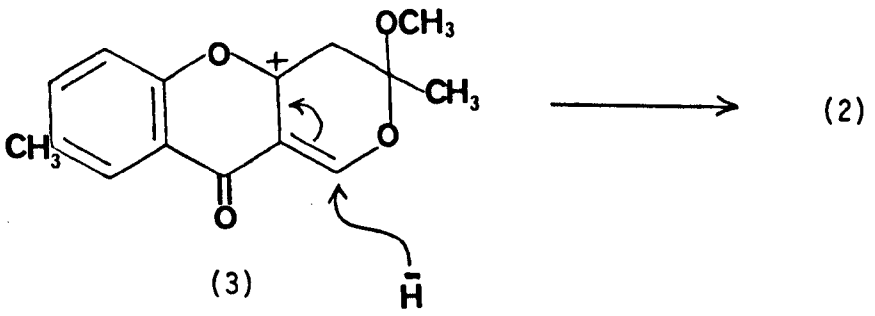
Apart from those attempts to produce (2) using transition metals (or their derivatives) and triphenylcarbenium salts, all other attempts have involved multi-step synthetical routes *via* intermediates derived from (1). Precisely because such circuitous routes to (2) had proved fruitless, it was decided to look again at means which might be employed to bring about a direct, one-pot conversion of (1) to (2). In this respect, we return to two basic strategies:

(i) reinvestigating the application of transition metals and/or their derivatives in bringing about the required conversion, or;

(ii) reinvestigating the use of hydride-removing reagents to generate an intermediate carbenium ion of the type (3) followed


(26/32)
(21)
(27)
(20)
(35a)
(9)
(8)

by its immediate reduction at position 1 as shown below.



(3) (2)

Possibility (i) had been thoroughly investigated without success. Moreover, the theoretical foundation on which transition metal-mediated isomerisations are based remains a fertile area of research and it was decided that no definite conclusions could be drawn as to which reagent(s) or conditions might be successfully applied to solve our problem. So, in spite of our belief that a transition metal species had been used to promote the desired transformation, this study was discontinued altogether.

Possibility (ii), however, deserved more attention since there are numerous reagents other than triphenylcarbenium salts which have been shown to abstract hydride ion from organic substrates. An examination of potential hydride abstracting reagents and their connection with the theoretical intermediate (3) will form the basis of the next Chapter.

EXPERIMENTAL

General conditions as described on pages 32 and 73.

Acetonitrile: Dried over anhydrous potassium carbonate and distilled from lithium aluminium hydride;

Dichloromethane: Dried over calcium chloride and distilled from phosphorus pentoxide;

Dioxane: Distilled from lithium aluminium hydride.

(3R)-4,4a-Dihydro-3,8-dimethyl-3-methoxy-3H,10H-benzopyrano[2,3-d][1]pyran-10-one (4)

Triphenylcarbenium perchlorate (686 mg, 2 mmol) in dichloromethane (10 ml) was added to benzopyranone (1) (520 mg, 2 mmol) in the same solvent (10 ml) and the reaction mixture stirred at room temperature for 0.5 hour before sodium borohydride (23 mg, 0.6 mmol) in 1,2-dimethoxyethane (2 ml) was added. After ten minutes, acetone (0.5 ml) was added and the mixture poured into water (50 ml) and extracted with dichloromethane (50 ml x 3). The combined dichloromethane extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford an off-white solid (940 mg) which was absorbed on silica (1 g) and placed at the top of a short silica gel-containing column. The column was eluted first with dichloromethane and then with ethyl acetate. The dichloromethane eluant provided triphenylmethane (480 mg, 98%), m.p. 92-94 °C and the ethyl acetate eluant provided epimer (4) (239 mg, 46%), which was identical (t.l.c., i.r. and n.m.r.) to the product obtained on treatment of benzopyanone (1) with a catalytic amount of 4-toluenesulphonic acid, c.f. Experimental of previous Chapter.

3-(6-Methyl-4H[1]benzopyran-4-one)-but-1-en-3-one (8)

Benzopyranone (1) (520 mg) and rhodium (III)chloride trihydrate (50 mg) were dissolved in an ethanol-chloroform solvent mixture (30 ml, 1:1 v/v) and stirred at reflux temperature, under a nitrogen atmosphere, for two hours. The mixture was then poured into water (50 ml) and extracted with chloroform (50 ml x 2). The combined chloroform extracts were washed with brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give a red gum which was filtered through a plug of celite eluting with ether. Evaporation of the ether left a white powder which crystallised from ethanol to afford ketone (8) as white needles, m.p. 179 °C and was identical in all respects to the product obtained from acid treatment of benzopyranone (1), c.f.

Experimental of previous Chapter.

(3S)-4,4a-Dihydro-3,8-dimethyl-3-ethoxy-3H,10H-benzopyrano[2,3-d][1]pyran-10-one (9)

Benzopyranone (1) (520 mg) and rhodium(III) chloride (50 mg) were dissolved in an ethanol-chloroform mixture (30 ml, 1:1 v/v) and stirred under a nitrogen atmosphere at reflux temperature for four hours. The work-up was the same as that described for the previous experiment and furnished benzopyranone (9) as needles, m.p: 139-140 °C which was identical in all respects to the product obtained from action of 4-toluenesulphonic acid on an ethanolic solution of (1), c.f. Experimental of previous Chapter.

Organometallic Compounds as Potential Isomerisation Reagents (i)-(vii)

(i) Tris(triphenylphosphine)rhodium(I) chloride

(i)a To benzopyranone (1) (520 mg) in ethanol (30 ml) was added tris(triphenylphosphine)rhodium(I) chloride (50 mg) and the mixture was stirred at reflux temperature, under a dry nitrogen atmosphere, for three hours. The mixture was then poured into water and the usual work-up afforded an off-white solid (480 mg) which was shown (t.l.c. and n.m.r.) to be unchanged benzopyranone (1).

(i)b The above experiment was repeated but the reflux time was extended to 24 hours. Work-up afforded benzopyranone (1) (t.l.c. and n.m.r.) as the only product.

(i)c Benzopyranone (1) (520 mg) was added to tris(triphenylphosphine)-rhodium(I) chloride (1.85 g) in ethanol (50 ml). The mixture was stirred at reflux temperature for three hours. After this time, t.l.c. showed no change so reflux was continued for a further 21 hours. The mixture was then poured into water and the usual work-up afforded unchanged (1) (478 mg) and triphenylphosphine (511 mg), m.p. 80 °C.

(i)d Dry hydrogen gas was bubbled through a stirred solution of benzopyranone (1) (520 mg) and the rhodium complex (50 mg) in aerated ethanol-benzene (50 ml, 1:1 v/v) for 16 hours. Work-up afforded unchanged (1) (500 mg) as the only product.

(ii) Tris(triphenylphosphine)rhodium(I) bromide

Rhodium(III) chloride trihydrate (500 mg) in ethanol (75 ml) was added to triphenylphosphine (3 g) dissolved hot ethanol (50 ml). After refluxing under dry nitrogen for five minutes, the solution became lighter in colour and lithium bromide (2 g) in hot ethanol (25 ml) was added and the mixture heated under reflux for one hour before being left to cool to room temperature overnight. The following morning, the red precipitate was filtered off, washed with degassed ether and dried *in vacuo* to afford the title compound (1.56 g) as micro-needles, m.p. 130-133 °C, (lit:[17] 133-134 °C).

This compound was substituted for tris(triphenylphosphine)rhodium(I) chloride in experiments (i)a-(i)d above though, in each case, work-up afforded benzopyranone (1) starting material in high yield, identified by t.l.c. and n.m.r.

(iii) Carbonyltris(triphenylphosphine)rhodium(I) hydride

Benzopyranone (1) (520 mg) and the rhodium complex (786 mg) were dissolved in dioxane (15 ml) and the mixture stirred under a nitrogen atmosphere for 48 hours. Solvent was evaporated under reduced pressure and the residue filtered through a short, neutral alumina column (eluting with dichloromethane) to afford unchanged benzopyranone (500 mg) by t.l.c. and n.m.r.

(iv) Bis(benzonitrile)palladium(II) chloride

The palladium complex (50 mg) and benzopyranone (1) (520 mg) were

dissolved in benzene (30 ml) and the flask flushed with nitrogen, sealed, and left at room temperature for seven days. After this time, t.l.c. showed unchanged starting material. The mixture was refluxed under dry nitrogen for five hours before evaporation of solvent under reduced pressure afforded a viscous red oil (562 mg) which was shown by t.l.c. to contain at least seven components and much polar, base-line material. This oil was not examined further.

(v) Pentacarbonyl iron

To benzopyranone (1) (520 mg) in dry acetonitrile (80 ml) was pentacarbonyl iron (1.5 g) and the mixture refluxed (under nitrogen) by exposure to u.v. light (253.7 nm) for 16 hours. The cooled solution was filtered through a short plug of alumina and the n.m.r. spectrum of the residue (500 mg) obtained on evaporation of the acetonitrile showed unchanged benzopyranone starting material (1) only.

(vi) Tetracarbonylcobolt hydride

d_6-Benzene (3 ml) was degassed (freeze-thaw method) and saturated with hydrogen gas in a round-bottomed flask equipped with septums holding syringe needles for inlet and exit of gas. Dicobolt octacarbonyl (50 mg) was added to the benzene solution and hydrogen gas bubbled through the mixture for ten minutes before benzopyranone (1) (200 mg) in d_6-benzene (3 ml) was added. Hydrogen gas was bubbled through the mixture for a further ten minutes after which time the n.m.r. spectrum (0-10δ) showed unchanged benzopyranone (1). The spectrum remained unchanged after the benzene solution had been held at 65 °C for 15 minutes.

(vii) Tetrakis(triphenylphosphine)ruthenium dihydride

The benzopyranone (1) (200 mg) was added, under a dry argon atmosphere,

to the ruthenium complex (100 mg) in d_6-benzene (5 ml). The mixture was stirred for two minutes to dissolve the solids, whereupon a portion of the solution was transferred to an argon-flushed n.m.r. tube. The n.m.r. spectrum (0-10δ) showed benzopyranone (1) only. After the sample tube was held at 65 °C for 15 minutes, the n.m.r. spectrum of the mixture remained unchanged.

6-Methyl-4H[1]benzopyran-4-one (21)

A mixture of benzopyranone (1) (520 mg) and 10% palladium on barium sulphate (150 mg) in m-xylene (30 ml) was stirred, under dry nitrogen, at reflux temperature for 24 hours. The cooled mixture was filtered and concentrated under reduced pressure to afford a black paste which was filtered through a plug of alumina (eluting with ethyl acetate). Evaporation of the eluant afforded a yellow solid which was recrystallised twice from light petroleum to afford pale yellow needles of chromone (21) (259 mg, 81%), m.p. 86-87 °C.

ν_{max}: 1640 (C=O) and 1615 (C=C) $cm.^{-1}$

δ : 2.39 (3H, s, CH_3);
6.28 [1H, d, J6Hz, C(3)H];
7.30 [1H, d, J8Hz, C(8)H];
7.44 [1H, dd, J7 and 2.5Hz, C(7)H];
7.79 [1H, d, J6Hz, C(2)H];
7.96 [1H, d, J2Hz, C(5)H].

(3S,4aS,10aR)-4a,10a-Dihydro-3,8-dimethyl-3-methoxy-1H,10H-pyrano[4,3-b][1]-benzopyran-10-one (26)

K-Selectride (25) (6 ml, 0.5M solution in tetrahydrofuran) was added dropwise to benzopyranone (1) (780 mg) in dry tetrahydrofuran (30 ml) stirred

at -78 °C. After one hour, the low temperature bath was replaced by an ice-bath and a mixture of ice-cold, aqueous, 10% sodium hydroxide solution (10 ml) and hydrogen peroxide (5 ml, 30% w/w) was added and the mixture left to stir overnight at room temperature. The aqueous and organic layers were separated and the former extracted with ether (20 ml x 3). The combined ether extracts were combined with the organic phase and washed with water (20 ml x 2), saturated sodium bisulphate solution (20 ml x 2), brine (20 ml) and dried (Na_2SO_4) and concentrated under reduced pressure to afford a foul-smelling yellow oil (661 mg). This oil was flash-chromatographed with toluene-ethyl acetate (95:5 v/v) as eluant and afforded pyranochromanone (26) which crysallised from methanol as colourless needles (173 mg, 22%), m.p. 111-113 °C.

Found (ML 23110): C,68.41; H,6.94%

$C_{15}H_{18}O_4$ requires: C,68.67; H,6.92%

Accurate Mass found: 262.12035

$C_{15}H_{18}O_4$ requires: 262.12049

ν_{max}: 1675 (C=O); 1615 and 1575 (C=C) $cm.^{-1}$

δ: 1.40 (3H, s, CH_3);

2.28 (3H, s, $ArCH_3$);

3.18 (3H, s, OCH_3);

1.88 [1H, t, J11.8Hz, $C(4)H_{eq}$];

2.35 [1H, dd, J12.6 and 4.9Hz, $C(4)H_{ax}$];

2.74 [1H, ddd, J11.5, 11.4 and 5.2Hz, C(10a)H];

3.62 [1H, t, J11.3Hz, $C(1)H_{eq}$];

4.21 [1H, dd, J11.3 and 5.2Hz, $C(1)H_{ax}$];

4.61 [1H, ddd, J11.8, 11.4 and 4.9Hz, C(4a)H];

6.84 [1H, d, J8.4Hz, C(6)H];

7.26 [1H, dd, J8.6 and 2Hz, C(7)H];

7.62 [1H, s, C(9)H].

Also eluted from the column was 2-(2H[1]-benzopyran-3-carboxaldehyde)-propanone (27) as a viscous yellow oil (485 mg, 70%) which turned semi-solid after being kept at room temperature over 48 hours. (Attempted distillation at 0.05 mmHg caused decomposition).

Accurate Mass found: 230.09474

$C_{14}H_{14}O_3$ requires: 230.09428

ν_{max}: 1710 (CH=O); 1665 (C=O); 1630 and 1570 (C=C) $cm.^{-1}$

$^1H\delta$: 2.07 (3H, s, CH_3);

2.16 (3H, s, $COCH_3$);

2.42 [1H, dd, J16 and 3Hz, C(1')H];

2.84 [1H, dd, J16 and 10Hz, C(1')H];

5.68 [1H, dd, J10 and 3.5Hz, C(2)H];

6.68 [1H, d, J7.5Hz, C(8)H];

6.97 [1H, s, C(5)H];

7.06 [1H, dd, J8 and 2Hz, C(7)H];

7.16 [1H, s, C(4)H];

9.48 (1H, s, C<u>H</u>=O).

$^{13}C\delta$: 20.323, Ar<u>C</u>H_3;

30.161, C3';

46.655, C1';

69.373, C8;

116.904, C7;

119.403, C6;

129.336, C2;

131.551, C-4a;

133.389, C-8a;

134.287, C-5;

141.137, C-4;

151.444, C-3;

189.398, CH=O;

204.488, C2'.

(3S,4aS,10aS)-4a,10a-Dihydro-3,8-dimethyl-3-methoxy-1H,10H-pyrano[4,3-b][1]-benzopyran-10-one (32)

L-Selectride (4 ml 1M solution in tetrahydrofuran) was added dropwise over five minutes to a tetrahydrofuran solution (25 ml) of benzopyranone (1) (1.04 g), stirred at -78 °C. After one hour, the mixture was brought to 0 °C before m-chloroperoxybenzoic acid (690 mg) in tetrahydrofuran (5 ml) was added. The mixture was left to stir at room temperature overnight before solvent was removed under reduced pressure to afford a bright red gum (2.53 g). This was extracted with ether (50 ml x 2), and the combined ether extracts washed with water (20 ml x 2), aqueous sodium bisulphate solution (20 ml x 2) and brine (20 ml). The ether was dried (Na_2SO_4) and evaporated under reduced pressure to afford a red oil (1.54 g) which was flash-chromatographed eluting with toluene-ethyl acetate (95:5 v/v). Evaporation of the eluants afforded a white solid (273 mg) and the formylchromene (27) (608 mg, 66%) as a yellow oil which was homogeneous on t.l.c. and identified by n.m.r. and i.r. spectroscopy. The white solid was shown by t.l.c. to be a mixture of two components, and crystallisation from methanol afforded pyranochromanone (26), (136 mg, 13%) as needles, m.p. 110-113 °C. The mother liquor, after being left to stand at room temperature for 16 hours, deposited pyranochromanone (32), as feathery, white needles, (63 mg, 6%), m.p. 129-131 °C.

Found (ML 22768): C,68.58; H,6.97%

$C_{15}H_{18}O_4$ requires: C,68.67; H,6.92%

Accurate Mass found: 262.12009

$C_{15}H_{18}O_4$ requires: 262.12049

m/e: 247 (M^+-CH_3); 231 (M^+-OCH_3).

ν_{max}: 1665 (C=O); 1615 and 1570 (C=C) $cm.^{-1}$

δ: 1.36 (3H, s, CH_3);

2.27 (3H, s, $ArCH_3$);

3.20 (3H, s, OCH_3):

1.84 [1H, dd, J16 and 4Hz, C(4)H_{ax} or H_{eq}];

2.36 [1H, dd, J16 and 2.5Hz, C(4)H_{eq} or H_{ax}];

2.79 [1H, ddd, J8, 6 and 2.5Hz, C(10a)H];

3.64 [1H, ddd, J12, 6 and 1.5Hz, C(1)H_{ax}];

3.96 [1H, t, J12Hz, C(1)H_{eq}];

4.70 [1H, m, C(4a)H];

7.01 [1H, d, J8Hz, C(6)H];

7.32 [1H, dd, J8 and 2.5Hz, C(7)H];

7.66 [1H, d, J2Hz, C(9)H].

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (33)

A mixture of formaldehyde (45 g, 40% aq., 0.6 mol) and diethylamine (2.8 g) was added to ethyl acetoacetate (150 g, 1.15 mol) cooled to 0 °C and the mixture was held at this temperature for six hours before the cooling bath was removed. After 40 hours at room temperature, the lower, oily layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether extracts were then added to the oily layer and dried ($CaCl_2$). Solvent was removed under reduced pressure and the remaining clear oil was diluted with ethanol (200 ml) before being cooled with stirring at 0 °C. Ammonia gas was bubbled through the solution for four hours and the solution was left to stand at room temperature for 48 hours. Solvent was evaporated to afford a sticky, bright yellow mass which was collected, washed with dry ether (50 ml x 4) and crystallised from ethyl acetate to afford

Hantzsch ester (33), (117 g, 80%) as yellow needles, m.p. 185 °C, (lit[35] 185 °C).

Reaction of Benzopyranone (1) with Hantzsch ester (33)

A mixture of benzopyranone (1) (780 mg), Hantzsch ester (33) (1.14 g) and silica gel 60 (2g, 40-63 μm, 400-230 mesh) was stirred in benzene (50 ml) at 80 °C for 17 hours under a nitrogen atmosphere. The solution was filtered while still hot and evaporation of the benzene under reduced pressure afforded a yellow solid (1.45 g) which was flash-chromatographed, eluting with toluene-ethyl acetate (85:15 v/v). Three components were obtained, two of which were shown by t.l.c. and n.m.r. to be benzopyranone (1) (468 mg) and Hantzsch ester (33) (248 mg). The third component was diethyl 2,6-dimethyl-3,5-dicarboxylate (34) which crystallised from hexane as white plates (535 mg), m.p. 71-73 °C (lit:[36] 72-73 °C).

(3S,4aS,10R,10aR)-4a,10a-Dihydro-3,8-dimethyl-3-methoxy-1H,10H-pyrano[4,3-b][1]-benzopyan-10-ol (35a)

To benzopyranone (1) (1.04 g) in dichloromethane (100 ml) was added tetra-n-butylammonium borohydride (580 mg) and the flask flushed with nitrogen and sealed. After seven days, the mixture was concentrated under reduced pressure to afford a yellow oil which was extracted with dichloromethane (50 ml x 3), washed with water (50 ml x 2), 3% aqeous hydrochloric acid (50 ml), brine (50 ml) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure to afford a yellow solid (822 mg) which crystallised from methanol as clumps of white needles of the benzopyranol (35a), (222 mg, 21%), m.p. 175-177 °C.

Found (ML 22465): C,68.03; H,7.42%

$C_{15}H_{20}O_4$ requires: C,68.14; H,7.63%

m/e: 264 (M^+); 249 (M^+-CH_3); 246 (M^+-OH_2); 233 (M^+-OCH_3).

ν_{max}: 3220br. (OH), 1495 and 1455 (C=C) $cm.^{-1}$

δ [$(CD_3)_2$=O]: 1.39 (3H, s, CH_3);

1.72 [1H, ill-defined t, J8.1Hz, C(4)H_{ax}];

1.73 [1H, ill-defined s, C(10)O<u>H</u>];

1.86 [1H, 3-lines, C(10a)H_{ax}];

2.27 [3H, s, $ArCH_3$);

2.29 [1H, t, hidden by $ArCH_3$ signal, J5.2Hz, C(4)H_{eq}];

3.21 (3H, s, OCH_3);

3.44 [1H, t, J11.2Hz, C(1)H_{ax}];

4.14 [1H, dd, J13.7 and 4.9Hz, C(1)H_{eq}];

4.22 [1H, ddd, J10.9, 5.5 and 2.5Hz, C(4a)H_{ax}];

4.48 [1H, d, J10.01Hz, C(10)H];

6.69 [1H, d, J8.3Hz, C(6)H];

6.98 [1H, d, J8.2Hz, C(7)H];

7.26 [1H, s, C(9)H].

<u>Oxidation of benzopyranol (35a) with pyridinium chlorochromate</u>

To benzopyranol (35a) (320 mg) in dichloromethane (20 ml) was added pyridinium chlorochromate (392 mg) and the mixture was stirred vigorously under nitrogen for two hours. The mixture was then filtered through a short column containing charcoal eluting with dichloromethane. The dichloromethane eluant was then evaporated affording a white solid which was recrystallised from methanol as white needles of <u>pyranochromanone</u> (26) (173 mg, 55%), m.p. 111-113 °C which was identical (t.l.c., i.r. and n.m.r.) to the product obtained on K-Selectride reduction of benzopyranone (1), <u>vide supra</u>.

<u>Determination of the basicity of chromones and pseudo-chromones</u>

Phenol, flavone, 2,6-dimethylchromone, benzopyranone (1) and 2,4,5-

trimethoxybenzylidenechroman-4-one (19) were crystallised and dried in vacuo over phosphorus pentoxide overnight before use. Spectra were recorded on a Perkin-Elmer 125 Spectrophotometer for carbon tetrachloride solutions where the substrate concentration was 0.1M. The values obtained for the shifts of the hydroxy band of phenol ($\Delta\nu_{OH}$) are shown below. These figures were used to plot the graph shown in the text and the pk_a' of benzopyranone (1) obtained by extrapolation in the graph was shown to have the value -3.2

Substrate	$\Delta\nu_{OH}$	pk_a'
Xanthone	225	-4.08
2,6-dimethylchromone	320	-1.25
Benzylidenechroman-4-one (19)	205	-----

Epoxidation of benzopyranone (1)

To a stirred mixture of benzopyranone (1) (500 mg) in acetone (20 ml) at -11 °C, hydrogen peroxide (0.7 ml, 30% w/w) was added followed by 10% sodium hydroxide solution (1 ml). The mixture was stirred at 0 °C for two hours and then left to stir at room temperature overnight before being poured into ice-water (100 ml). The white precipitate was extracted with ether (50 ml x 3) and the combined ether extracts were washed with water (50 ml x 3) and dried (Na_2SO_4). Evaporation of the ether afforded a reddish semi-solid (344 mg) which was purified from methanol, affording acetal (38) (213 mg, 36%), m.p. 216-219 °C as the sole product.

Found (ML 22444): C,62.50; H,6.50%

$C_{16}H_{19}O_6$ requires: C,62.51; H,6.24%

Accurate Mass found: 308.12598

$C_{16}H_{19}O_6$ requires: 308.12597

m/e: 227 (M^+-OCH_3); 248 (277-CHO); 216 (248-CH_3OH).

ν_{max}: 3390 (OH), 1670 (C=O), 1615 and 1575 (C=C) $cm.^{-1}$

δ: 1.46 (3H, s, CH_3);

2.29 (3H, s, $ArCH_3$);

3.25 (3H, s, 1-OCH_3?);

3.30 (3H, s, 3-OCH_3);

2.22 [1H, dd, J14 and 3.5Hz, C(4)H];

2.40 [1H, dd, J14 and 2.5Hz, C(4)H];

3.78 [1H, s, D_2O-exchangeable, OH];

4.39 [1H, ill-defined s, C(4a)H];

4.53 [1H, s, C(1)H];

6.96 [1H, d, J8Hz, C(6)H];

7.29 [1H, dd, J8 and 2.5Hz, C(7)H];

7.63 [1H, s, C(9)H].

When the experiment was repeated using ethanol as the recrystallisation solvent, feathery, white needles of epoxide (36) (280 mg, 53%), m.p. 154-156 °C were obtained.

Found (ML 22153): C,65.31; H,5.85%

$C_{15}H_{16}O_3$ requires: C,65.19; H,5.85%

m/e: 276 (M^+); 261 (M^+-CH_3); 247 (M^+-CHO); 229 (247-H_2O)

ν_{max}: 1680 (C=O), 1615 and 1575 (C=C) $cm.^{-1}$

δ: 1.40 (3H, s, CH_3);

2.30 (3H, s, $ArCH_3$);

3.26 (3H, s, OCH_3);

2.26 [1H, dd, J16 and 6Hz, C(4)H];

2.39 [1H, dd, J8 and 2Hz, C(4)H];

5.08 [1H, d, J1.5Hz, C(1)H];

5.10 [1H, d, J8Hz, C(4a)H];

7.08 [1H, d, J8Hz, C(6)H];

7.44 [1H, dd, J8 and 2Hz, C(7)H];

7.79 [1H, s, C(9)H].

When the mother liquor was cooled in the refrigerator overnight, brilliant, diamond-shaped crystals of ethyl acetal (39) (37 mg) separated, m.p. 171 °C

Found: C,63.09; H,6.71%

$C_{17}H_{22}O_8$ requires: C,63.32; H,6,88%

Accurate Mass found: 322.14163

$C_{17}H_{22}O_8$ requires: 322.14162

m/e: 291 (M^+-OCH_3); 248 (291-CH_3CO)

ν_{max}: 3395br. (OH); 1665 (C=O); 1610 and 1575 (C=C) $cm.^{-1}$

δ: 0.68 (1H, t, J9Hz, $OCH_2\underline{CH_3}$);

1.39 (3H, s, CH_3);

2.27 (3H, s, $ArCH_3$);

3.26 (3H, s, OCH_3);

2.23 [1H, dd, J14 and 3Hz, C(4)H];

2.37 [1H, dd, J14 and 2.4Hz, C(4)H];

3.70 [2H, q, J7Hz, $O\underline{CH_2}CH_3$];

3.78 [1H, s, D_2O-exchangeable, $\underline{OH}$];

4.40 [1H, ill-defined s, C(4a)H];

4.59 [1H, s, C(1)H];

6.96 [1H, d, J8Hz, C(6)H];

7.30 [1H, dd, J8 and 2Hz, C(7)H];

7.63 [1H, s, C(9)H].

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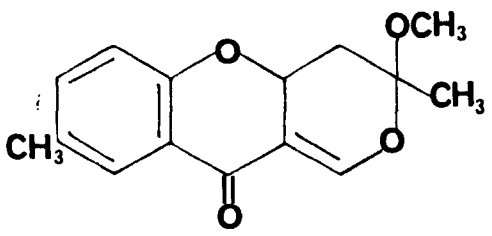
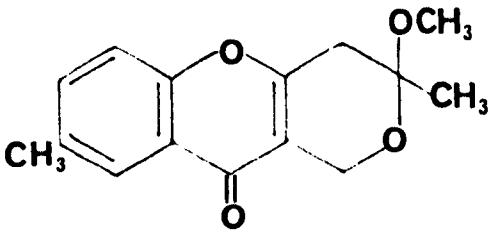
CHAPTER FIVE

Carbon-carbon double-bond isomerisation in oxygen heterocycles

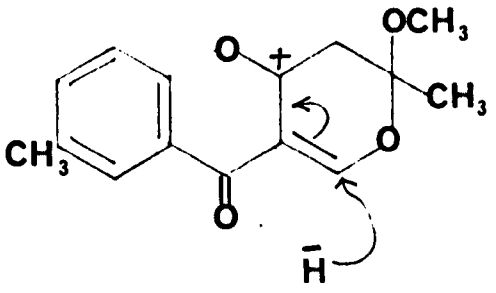
Following our failure to isomerise compound (1) directly, we decided to look again at the possibility of removing a hydride ion thus generating carbenium ion (2), selective reduction (i.e. hydride addition at position 1 only; see below) of which should afford the desired chromone (3).



(1)

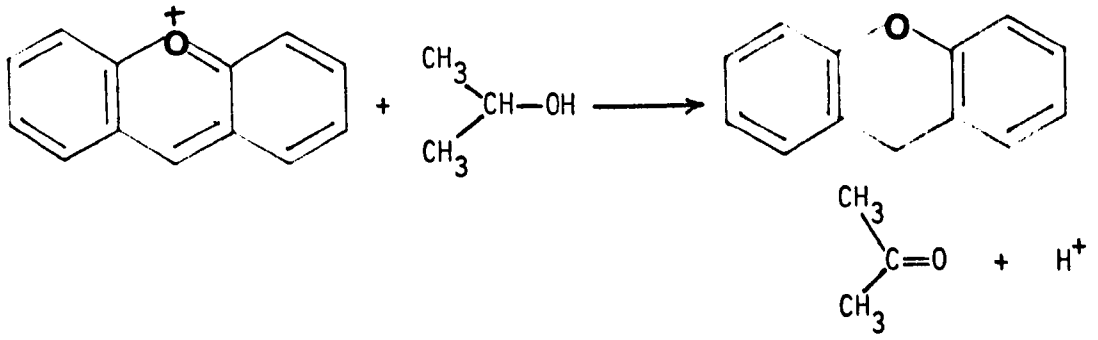


(3)

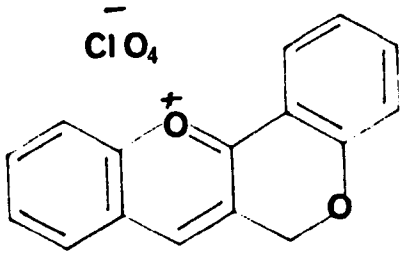


(2)

Since our investigations with triphenylcarbenium salts as hydride acceptors had failed to produce the required result, we thought that application of a pyrilium ion might be useful since such species have the capacity to induce oxidations as the following, simple example illustrates:

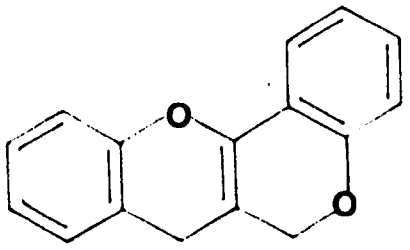


Interestingly, French workers[1] have studied the pyrilium salt (4) which has a structural similarity to adduct (1) by virtue of the position of the etheric oxygen atoms and is a close relation of the proposed intermediate --i.e. ion (2)-- in our synthetical scheme.

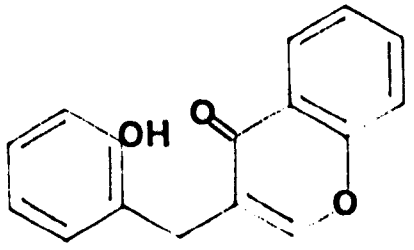


(4)

Of particular importance to us was the report of these workers concerning the behaviour of (4) towards reduction in different solvents. In dry tetrahydrofuran, (4) was reduced by potassium borohydride to the flavene (5) but when 95% ethanol was used as solvent, there was no reduction and the only product was the homoisoflavone (6) which was identified on the basis of its n.m.r. and u.v. spectra



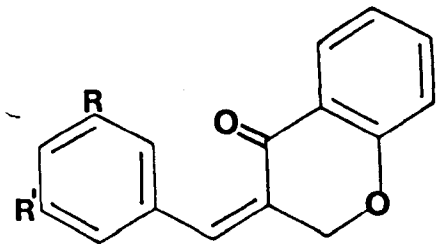
(5)



(6)

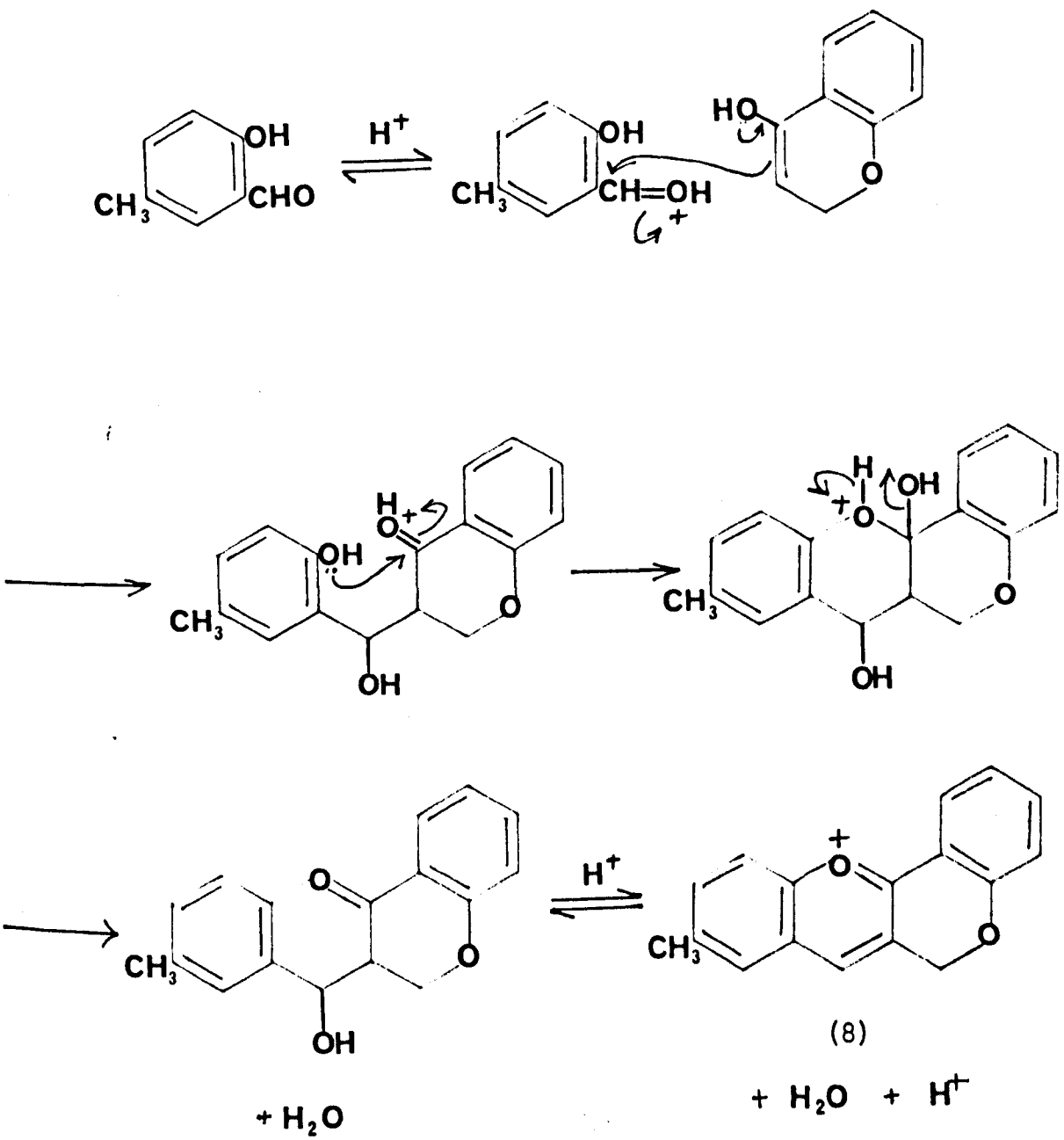
To corroborate structure (6), the French chemists also examined the n.m.r.

and u.v. spectra of compounds (7a,b,c) which are similar to (6) though they contain an endocyclic (rather than exocyclic) carbon-carbon double-bond.



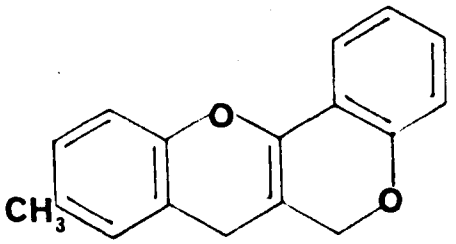
(7a) R=H R'=H
(7b) R=OH R'=H
(7c) R=$\overset{+}{N}H(CH_3)_2$ R'=H

Formally, the homoisoflavone (6) appears to be produced by a 1,3-hydrogen shift though no mechanism was proposed by the French chemists. They seem to have believed the double-bond migration to be promoted by base since shaking a solution of (4) with a dilute aqueous potassium acetate solution gave the same product. The ease with which the transformation occurs seems remarkable in view of the difficulties we had encountered in our own work and so we decided to investigate the chemistry of (4) ourselves. Accordingly, condensation of 5-methylsalicylaldehyde and 4-chromanone in perchloric acid afforded the brilliant red pyrilium salt (8), (see over).

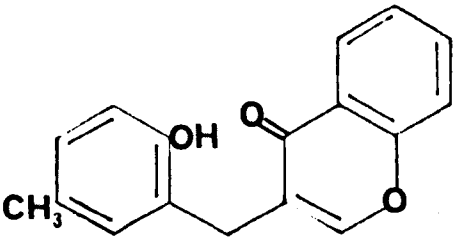


Reduction of (8) with sodium borohydride in dry tetrahydrofuran furnished the flavene (9) in 70% yield in the manner reported by the French workers. Our attempt at the reduction of (8) in 95% ethanol, however, met with poor results and only 10% of the desired chromone (10) was obtained, the major product being a thick, green oil. A similar result followed on shaking an aqueous ethanolic solution of (8) with dilute aqueous potassium acetate

solution.

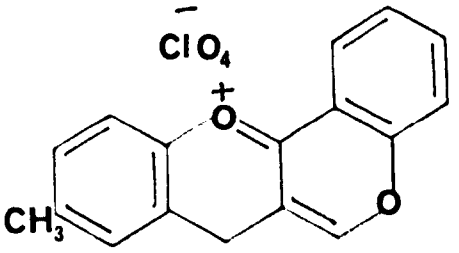


(9)



(10)

It is clear that the conversion of salt (8) into the chromone (10) includes a double-bond migration, but this might have occurred during salt formation, and not at a later stage. That is, the salt might actually have structure (11) rather than structure (8). To check this point, the chromone (10) was treated with perchloric acid generating the new oxonium ion (11) which is orange in colour contrasting with the brilliant red of the original salt (8).

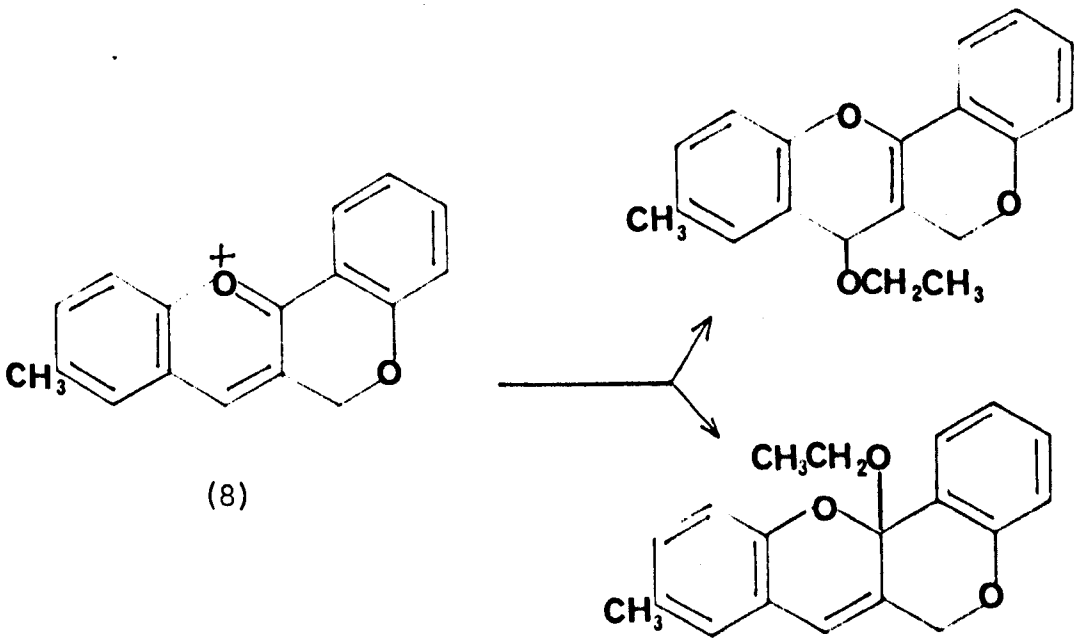


(11)

The methylene group in (11), now no longer adjacent to an etheric oxygen atom, appears at higher field (δ 4.42) in the n.m.r. spectrum than observed (δ 5.80) for the methylene in salt (8) (both salts in a 1:1 mixture of

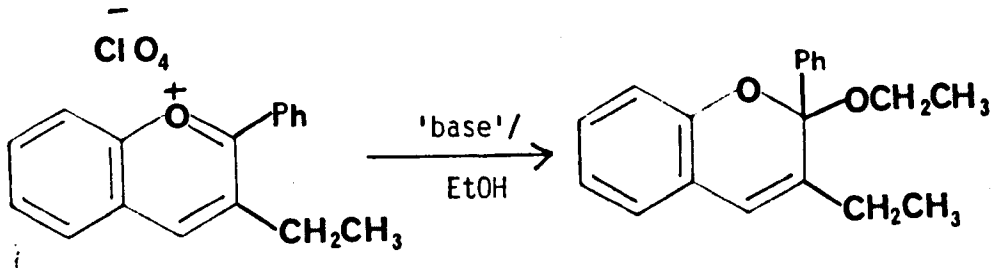
deuterochloroform-trifluoroacetic acid). The identity of (8) is, therefore, beyond question.

The green oil which had been produced as the major product from reaction of (8) with alkali was shown by t.l.c. to consist of at least five products and the n.m.r. spectrum contained a mass of complex aromatic signals. At higher field in the spectrum there appeared not only aromatic methyl signals but also signals consistent with an ethoxy grouping. The low solubility of pyrilium salt (8) in ethanol would ensure that there would always be some (8) available for nucleophilic attack by ethanol. This side-reaction is shown below and the products resulting therefrom would be consistent with the appearance of signals in the n.m.r. spectrum for ethoxy groupings.



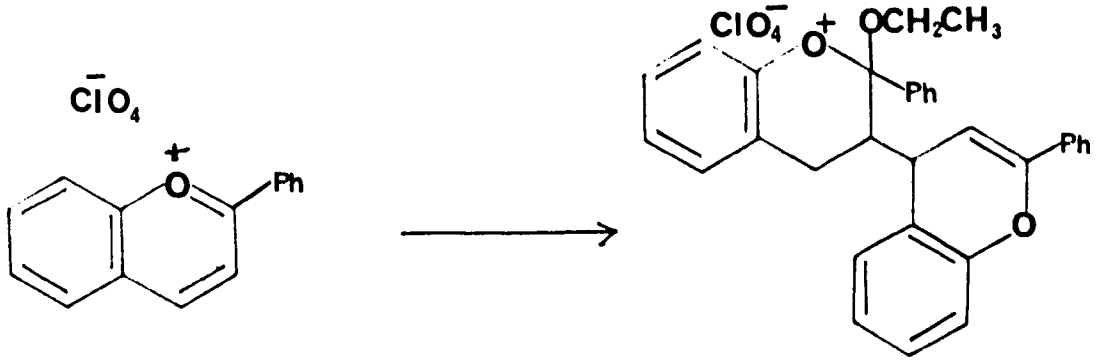
Reynolds and Van Allan[2] have shown that the reduction of 3-ethylflavilium perchlorate (12) with sodium borohydride in ethanol produces (13). In this

case, the reducing agent was acting only as a base since the same product was obtained by treating (12) with sodium hydroxide in ethanol.



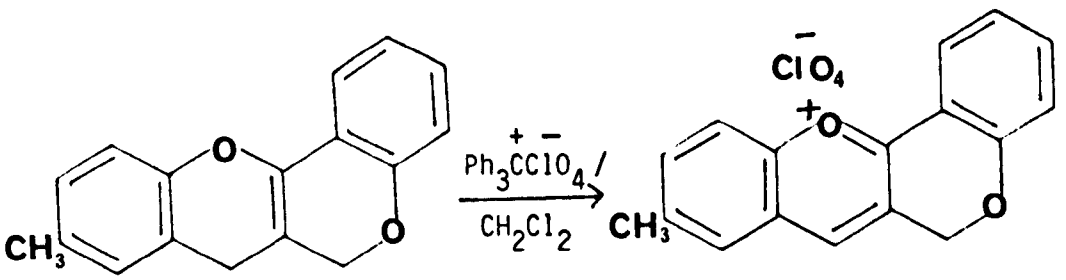
(12) (13)

Furthermore, these workers showed more complex structures are readily formed in the reduction of flavilium salts in alcohol solvents. For example, the reduction of flavilium perchlorate (14) with sodium borohydride in ethanol produces (15). The possibility of salt (8) forming similar compounds by the same mechanism is less likely because of steric factors



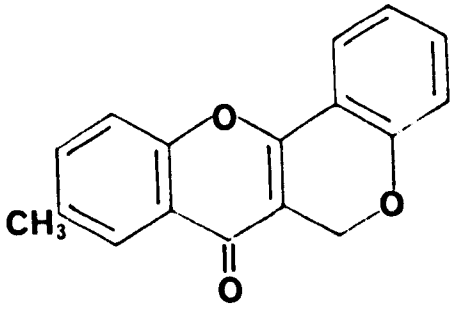
(14) (15)

Following another experiment performed by the French workers, we converted flavene (9) back to its precursor (8) by the action of triphenylcarbenium perchlorate in dichloromethane.



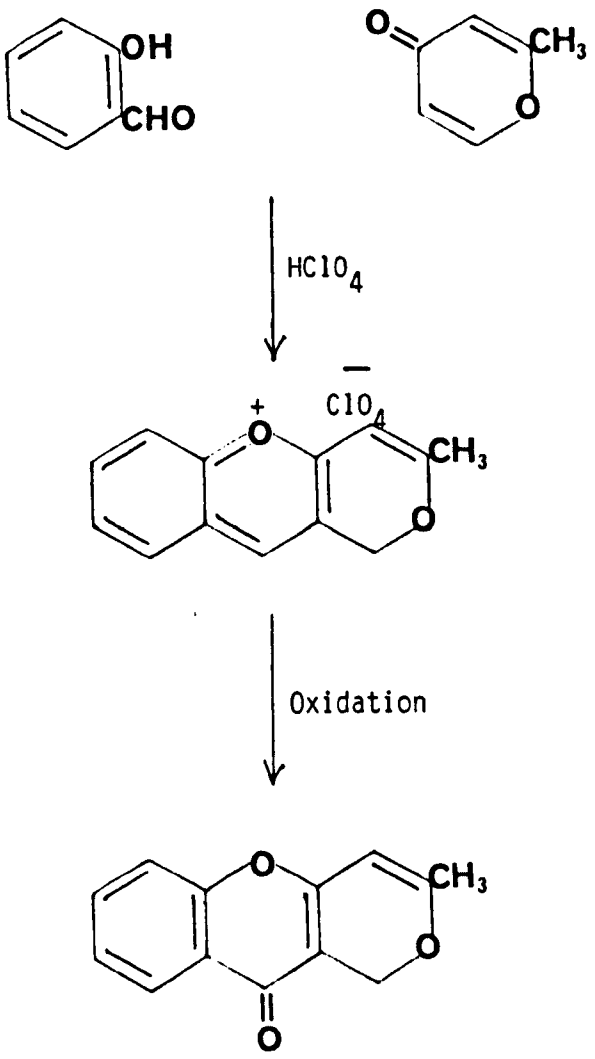
(9) (8)

The structure of pyrilium salt (8) and the ease with which it can be prepared suggested exploring a possible oxidation to the ketone (16).

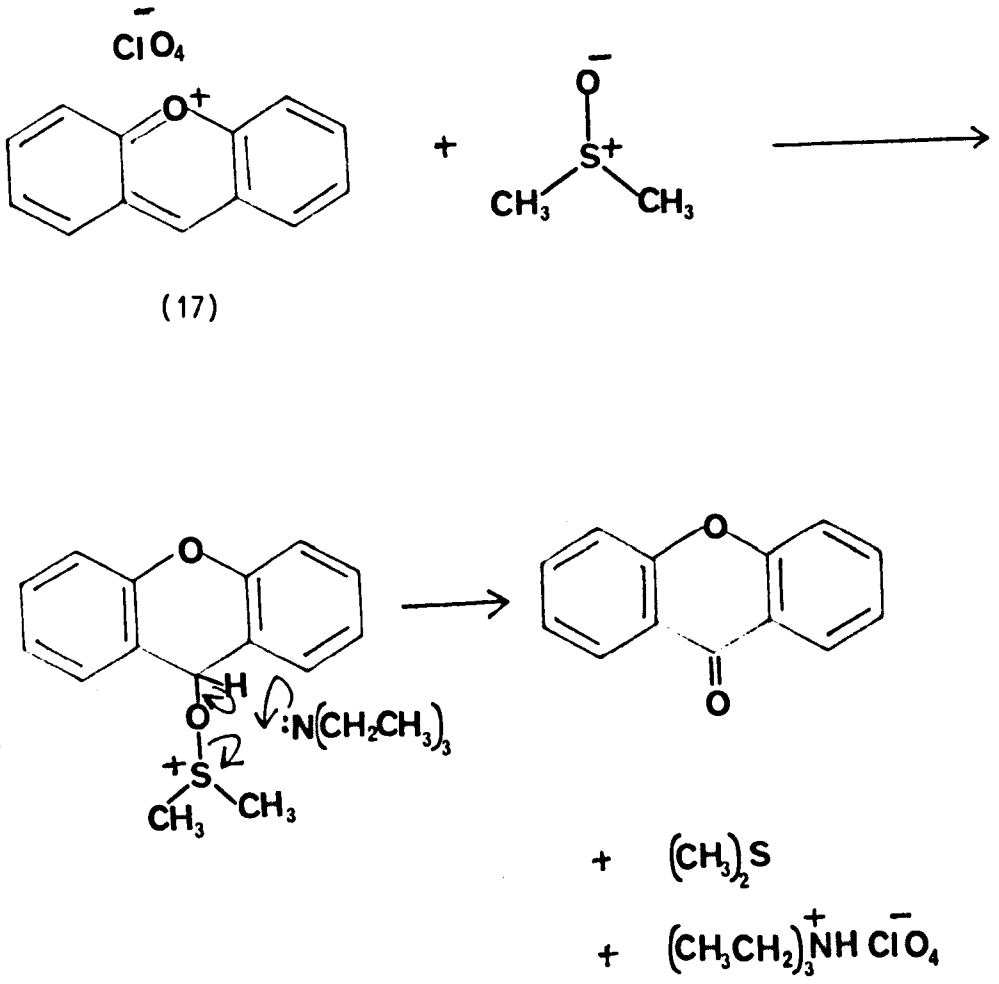


(16)

This would put us in a position to consider investigating an alternative synthesis of the skeleton of fulvic acid involving acid-catalysed condensation of salicylaldehyde and a 2-methylpyranone followed by oxidation according to the diagram overleaf.



To this end, xanthylium perchlorate (17) was chosen as a simpler model of (8). This model compound was oxidised with a mixture of dimethyl sulphoxide and triethylamine to afford xanthone in 90% yield, the reaction probably proceding according to the following pathway, (see over):



Application of the dimethyl sulphoxide--triethylamine oxidising mixture to (8), however, resulted in only a 30% yield of (16) along with much complex, brown oil. Substitution of the S atom in dimethyl sulphoxide for selenium would result in a reagent (dimethyl selenoxide) which is more nucleophilic and more easily cleaved from the reaction intermediate since the O-Se bond is weaker than the O-S bond. However, while this speculation may well be sound in practice, dimethyl selenoxide is an obnoxious chemical and its preparation is not as straightforward as that of the potentially equally meritorious reagent, potassium benzeneselenite,[3] $PhSeO_2K$, which is an odour-free,

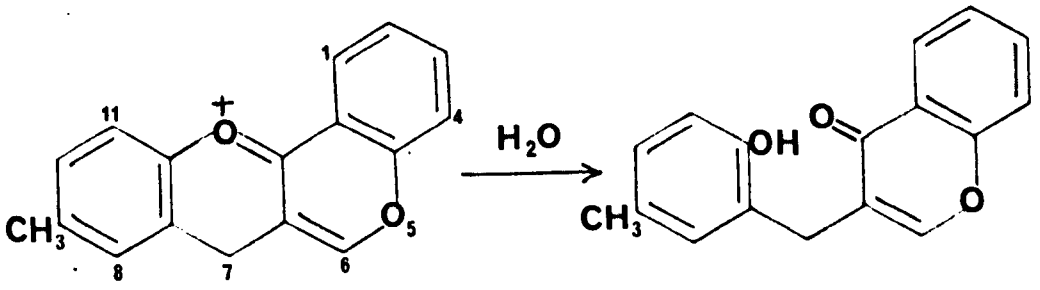
chemically stable and non-hygroscopic solid. In practice, reaction of this reagent with (17) in a mixture of 2-methoxyethanol and acetonitrile afforded xanthone in near quantitative yield. Application of the selenium salt in the same solvent mixture to pyrilium salt (8) furnished the chromone (16) in 70% yield.

Another reagent which we had investigated for its potential as an oxidising reagent was pyridine N-oxide. Addition of this reagent to the salt (8), dissolved in acetonitrile, produced no colour change (indicating that the pyrilium ion was still intact) and, after addition of triethylamine, work-up afforded a useless red oil. However, when the salt (8) and one equivalent of pyridine N-oxide were dissolved in acetonitrile and left undisturbed overnight, it was observed that crystals had come out of solution. These were collected and shown to be the chromone (10). Reaction with two equivalents of pyridine oxide doubled the yield to 60%. It is unlikely that this reaction involves base-promoted isomerisation (as advocated by the French workers) since the basicity of pyridine N-oxide is about three orders of magnitude less than that of acetate ion, for example.

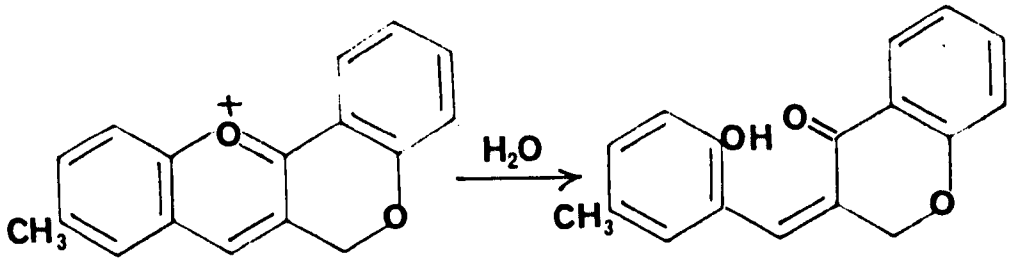
The pyridine oxide which had been employed in these experiments is supplied commercially and looks wet: presumably the suppliers synthesise this compound by oxidation of pyridine with aqueous hydrogen peroxide solution. The idea that water adhering to the pyridine oxide crystals might in some way be responsible for the observed reaction was tested by adding a trace of water to an acetonitrile solution of (8). When the mixture was left for a week, a steady accumulation of crystals could be seen at the bottom of the flask and, when collected, were shown to be the chromone (10).

The same product resulted from the action of pyridine oxide on oxonium ion (11).

While we believe we have established water as being responsible for this slow conversion of the pyrilium and oxonium ions (8) and (11) to chromone (10), there remains uncertainty about the mechanism in operation. The hydrolysis of oxonium ion (11) could be viewed as proceding by attack of water at position 12a leading to chromone (10) but a similar mechanism operating on pyrilium salt (8) ought to produce the chalcone derivative (18):



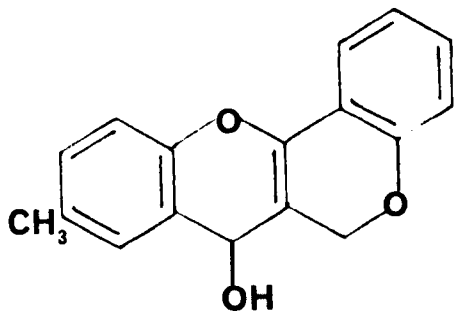
(11) (10)



(8) (18)

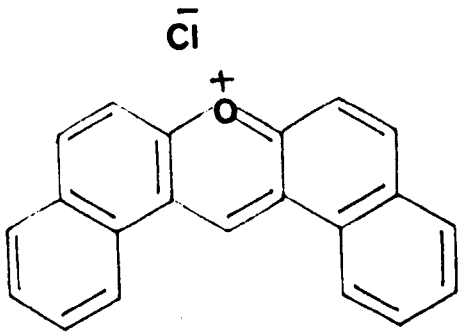
The presence of (18) was not observed at all, however, Moreover, 2,6-disubstituted pyrilium rings are not normally attacked by nucleophiles at their C-4, the least hindered site,[4,5] and if this had occurred we might have expected to see carbinol (19) though again this was not observed in

any of the experiments we performed.

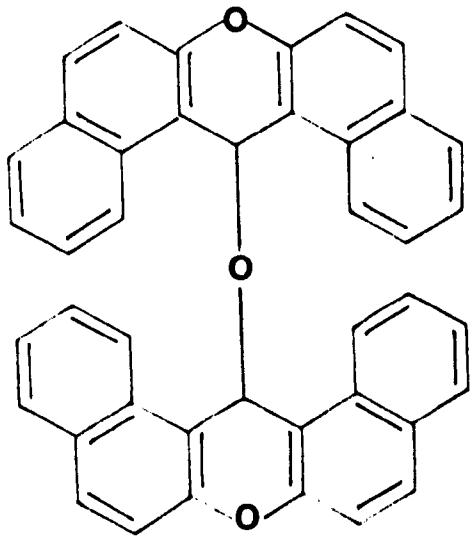


(19)

Even the hindered dinapthapyrilium salt[6] (20) (which we were studying at the time in independent work) readily underwent attack by water at position C-14 and then reacted further with pyrilium ion to form the dinapthapyranyl ether[7] (21) (obtained pure for the first time, c.f. Experimental).



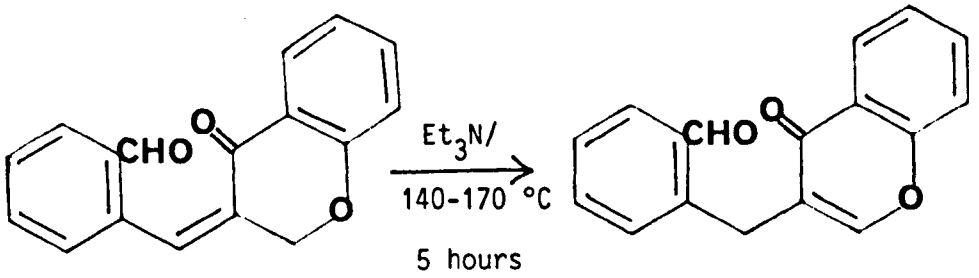
(20)



(21)

The idea that chalcone (18) is an intermediate in our conversion of salt (8) to chromone (10) becomes even less attractive in the light of a report[8]

describing the isomerisation of chalcone (22) to chromone (23). In this case, the conversion was achieved only under very severe reaction conditions, i.e. heating (22) in triethylamine at 140-170 °C for five hours.

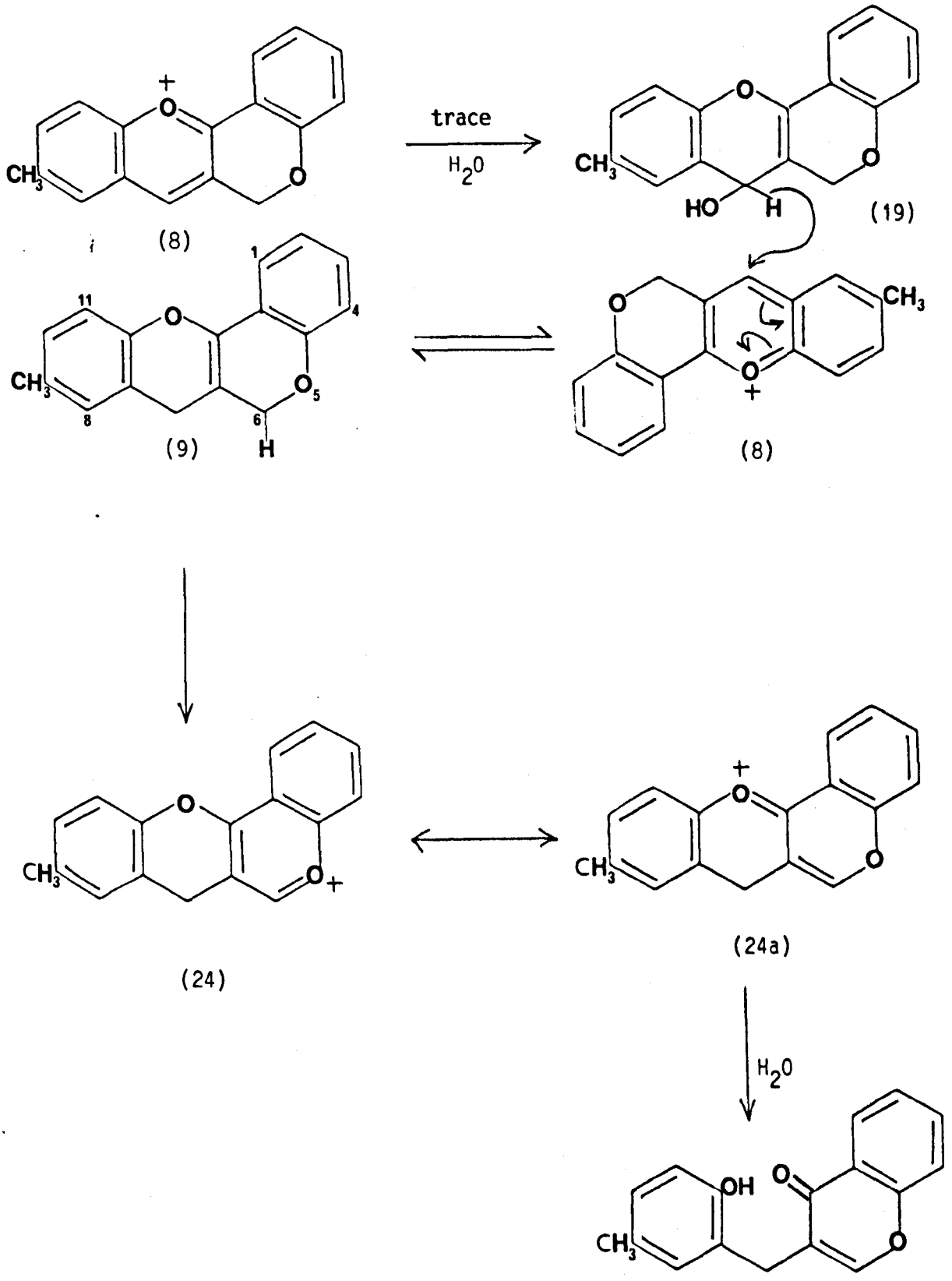


(22) (23)

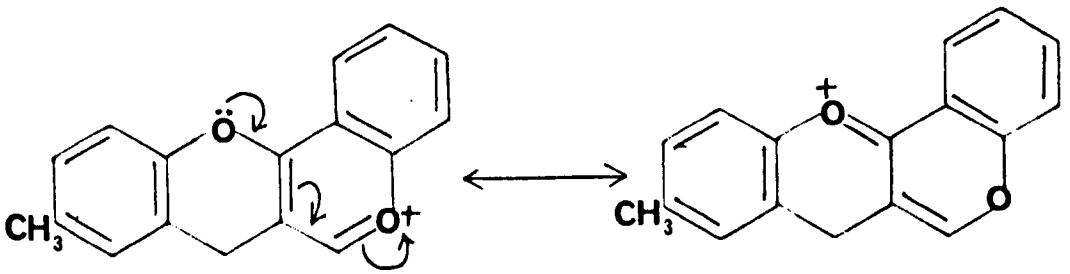
It might be that a trace of water does indeed form the carbinol (19) which then donates hydride ion (from position 7) to the parent ion (8), (Scheme I). The flavene (9) thus formed might itself donate hydride ion (this time from position 6) to salt (8) (present in large excess in this mixture) thus setting up an equilibrium mixture of hydride donor (9) and hydride acceptor (8). Ion (24) now becomes the target for two nucleophiles; hydride ion from (9) or water. Bearing in mind that (24) can equally well be represented by the canonical form (24a), attack of water on this species will generate the chromone (10) actually found.

An abortive attempt was made to follow this reaction using u.v. spectroscopy. An acetonitrile solution of (8) containing a trace of water was monitored over 36 hours though the spectrum remained unchanged from that observed for a solution of (8) in anhydrous acetonitrile over the same period. Rather than refuting the reaction mechanism we propose, this result might be interpreted as confirming merely that the reaction is extremely slow: we do know that water alone is sufficient to bring about the production of (10) and doubling the amount of (wet) pyridine oxide employed in the

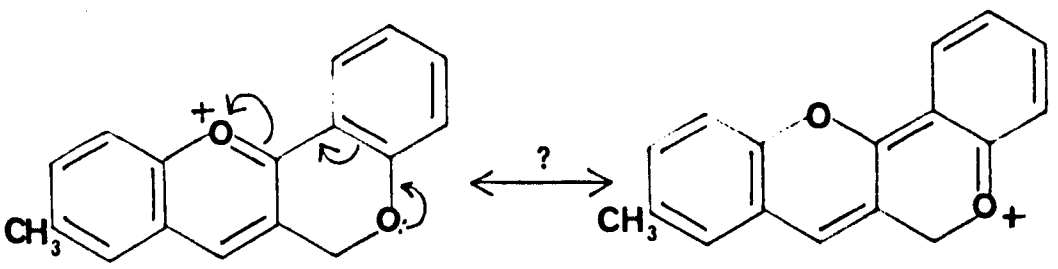
Scheme I



original experiment led to a two-fold increase in the yield of (10). A more informative result may be forthcoming from a study of the u.v. spectrum of an equimolar mixture of xanthylium salt (8) and flavene (9) containing a trace of water. One of the more interesting (or perhaps the most fundamental) assumptions of our scheme rests on the relative stability of ions (24) and (8). "Curly arrow" electron movements certainly seem to favour the greater relative stability of (24) (see below) since with this system the aromaticity of the 'angular' benzene ring is not disturbed.



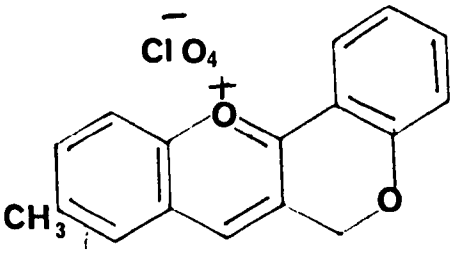
(24) (11)



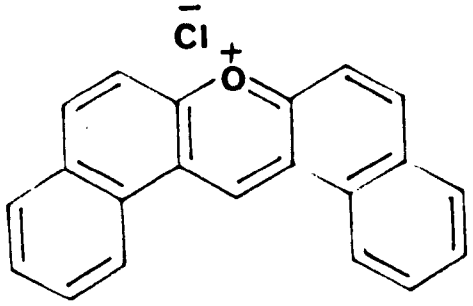
(8)

Unfortunately, shortage of time again got the better of our desire to experiment and we were forced to return to examining that which we had classed as a priority as the outset of this work with pyrilium salts, i.e. an investigation of their potential to act as hydride acceptors for adduct (1).

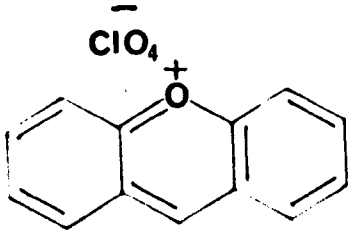
We had three pyrilium salts available, namely the pyranobenzopyrilium salt (8), the dinapthapyrilium salt (20) and xanthylium perchlorate (17).



(8)



(20)

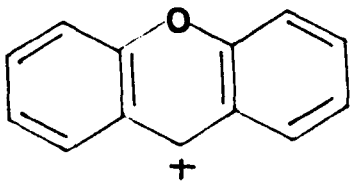


(17)

Pyrilium salt (8) failed to act as a hydride acceptor for adduct (1) and also failed to oxidise iso-propanol to propanone: both these results reflecting the stability of the salt owing to extensive delocalisation of the positive charge. Although the dinapthapyrilium salt (20) did oxidise iso-propanol to propanone, with adduct (1) in hot acetonitrile it caused degradation of the adduct and aqueous work-up afforded ether (21) as the only isolable product.

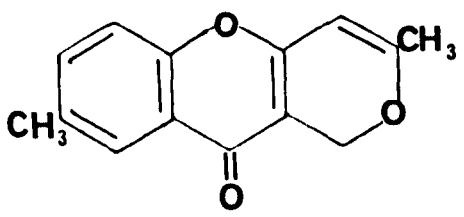
Xanthylium perchlorate was thought to be a much better prospect for this reaction because it is less sterically encumbered than (20) and it is known that attack of nucleophiles (e.g. hydride ion) takes place exclusively at C-9. In fact, the properties of xanthylium salts[9] are markedly different from those of simple pyrilium salts and tend to follow those of

triarylmethylcarbenium ions; so much so that they are best thought of in terms of the carbenium ion structure (26) rather than the pyrilium ion (17).

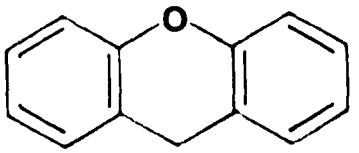


(26)

In the event, reaction of xanthylium perchlorate (26) with adduct (1) in boiling acetonitrile generated a very dark red coloured solution which, when cooled, was made translucent by addition of sodium borohydride in acetonitrile. Work-up afforded the chromone (27) --a model for anhydrofulvic acid-- in 7% yield, xanthene (28) and much useless, polar material.



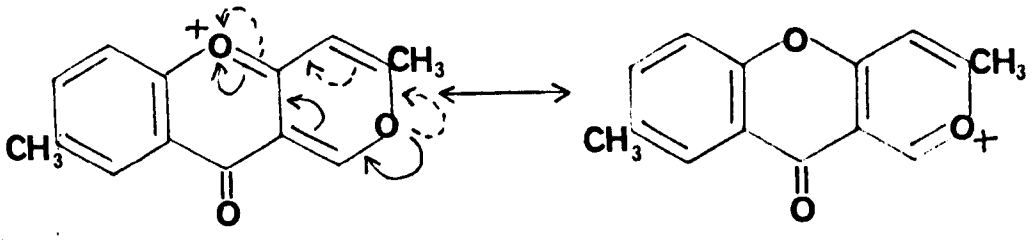
(27)



(28)

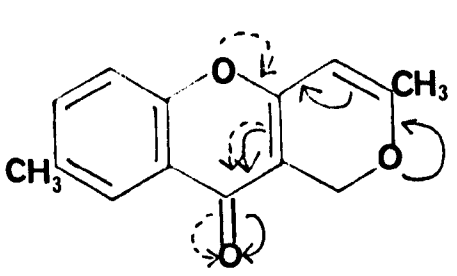
Evidently, the carbenium ion (26) had been able to effect hydride abstraction and borohydride ion had replaced hydrogen at position 1 as required. Since methanol had been lost from adduct (1) during this reaction, it may be that an intermediate such as (29) is involved. Such an ion ought

to have greater stability than the carbenium ion (2) since it contains two pathways through which positive charge may be delocalised leading to the aromatic pyrilium system (30) as shown below.

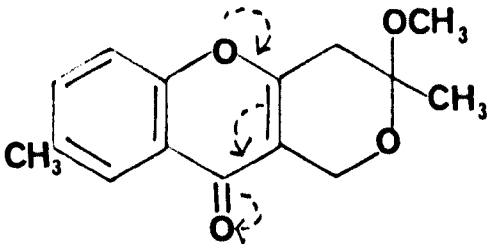


(29) (30)

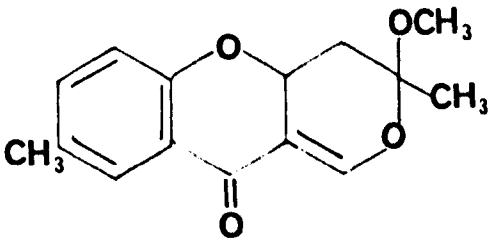
Now, a comparison of pyranobenzopyrans (27), (3),and (1) shows that extra stabilisation may be conferred on the first because there exists two positions from which electron donation may originate:



(27)



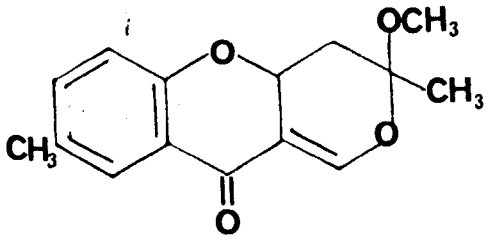
(3)



(1)

Hence a nucleophile (hydride ion) should attack ion (29) at position 1 and not position 4a so as to preserve both these interactions.

Finally, methanol containing 4-toluenesulphonic acid afforded the elusive chromone (3) so we now have, albeit in low yield, a two step reaction from (1) to (3):



(i) Hydride abstraction, i.e. oxidation

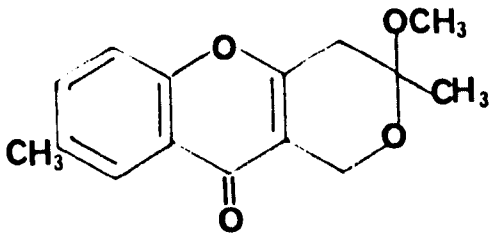
(ii) Hydride addition, i.e. reduction

(27)

(1)

CH_3OH

p-TsOH



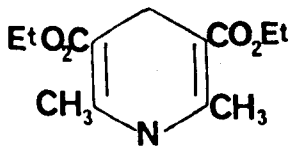
(3)

The product (3) has an n.m.r. spectrum identical to that of the chromone allegedly produced[10] by rhodium induced double-bond isomerisation of (1).

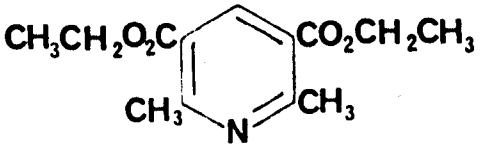
In the remaining time available, our efforts were concentrated on improving the yield of (27). In this respect, we looked especially at the hydride addition (i.e. reduction) step involved in the transformation of (1) to (27). It was found that using n-tetrabutyl- or tetraethyl-ammonium borohydrides gave (27) in a similar yield (5-10%) to that found with sodium borohydride. As with the study of selective reduction of (1) with complex boranes (c.f. Chapter 4), we were now again concerned with choosing a "soft" reducing agent, i.e. one that would deliver hydride ion

to reduce the intermediate ion (29) without reacting further with (in particular) the carbonyl function. In earlier work, we had encountered a similar problem (c.f. page 120) which we had thought might be resolved by the use of Hantzsch ester (31). Since (31) is easily prepared, we reexamined its use here.

Reaction of (1) with xanthylium perchlorate followed by (31) furnished the chromone (27) in 28% yield and xanthene (28) and the pyridine derivative (32) both in near quantitative yield.



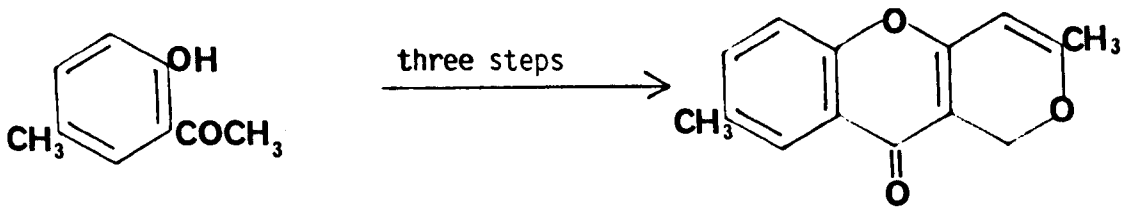
(31)



(32)

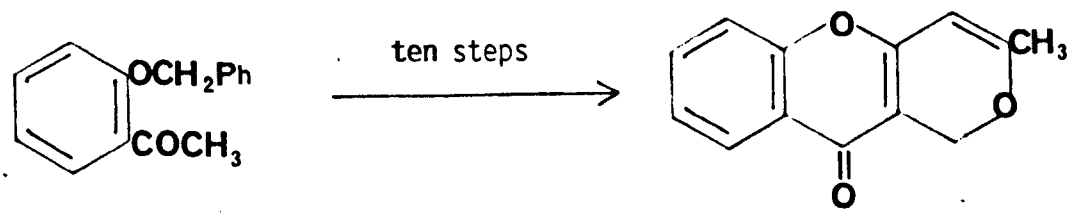
Much time was invested in trying to increase the yield of (27) further by this method without success. Nevertheless, a 28% yield is not at all bad when it is considered that we had initially viewed the bond isomerisation reaction as the fundamental step in our projected synthesis of fulvic acid.

At this point we can make a comparison between our synthesis of (27) and the synthesis of the similar compound (33) reported by Japanese workers in a study which was developed into a total synthesis[11] of fulvic acid. Compound (27) is obtained in 15% overall yield *via* a three step reaction beginning with acetophenone (34); compound (33) is obtained in 19% overall yield *via* a ten step reaction beginning with (35).



(34) (27)

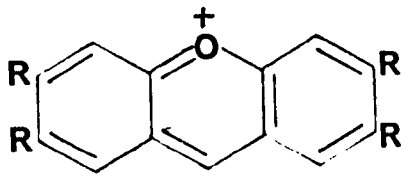
15% overall yield



(35) (33)

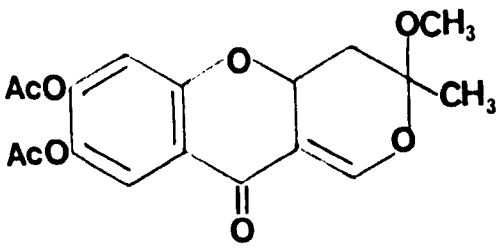
19% overall yield

Whilst the yields of (27) and (33) are similar, our reaction scheme is both less laborious and less time-consuming. Moreover, the yield of the critical step in our scheme (i.e. hydride abstraction) might be improved by modifying the xanthylium perchlorate reagent so that it acts as a more efficient hydride abstracting agent. A xanthylium salt containing electron withdrawing groups --such as (36), for example-- ought to have an electron-hungry nucleus to which hydride ion might be more readily donated than to the unsubstituted salt (17).

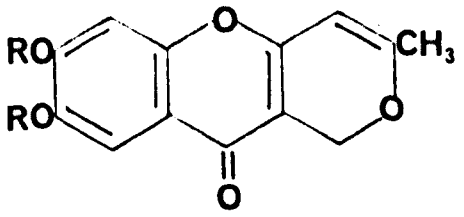


(36) R=F, CN

When our sequential oxidation-reduction method was applied to adduct (37), n.m.r. analysis of the residue obtained on work-up clearly showed signals corresponding to the chromone (38) which, however, was not actually isolated so that the nature of the R-groups is uncertain and it is possible that they may have been hydrolysed during column chromatography leading to the diphenolic chromone (38, R=H).

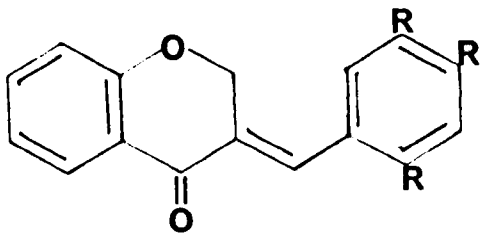


(37)



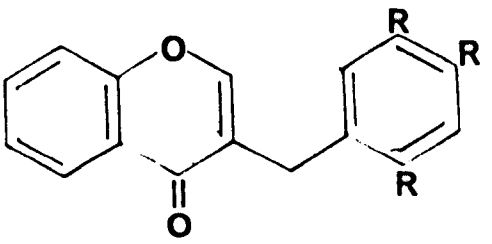
(38)

It was of interest to us to see if our method of isomerising compound (1) to (27) might have wider applicability. Barton and co-workers[12] report that refluxing an ethanol-chloroform solution of (39a) containing a catalytic amount of $RhCl.3H_2O$ over 24 hours produces a quantitative yield of (40a). We repeated this experiment and verified the result.



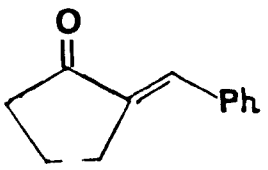
(39a) R=H

(39b) R=OCH_3



(40a) R=H

(40b) R=OCH_3



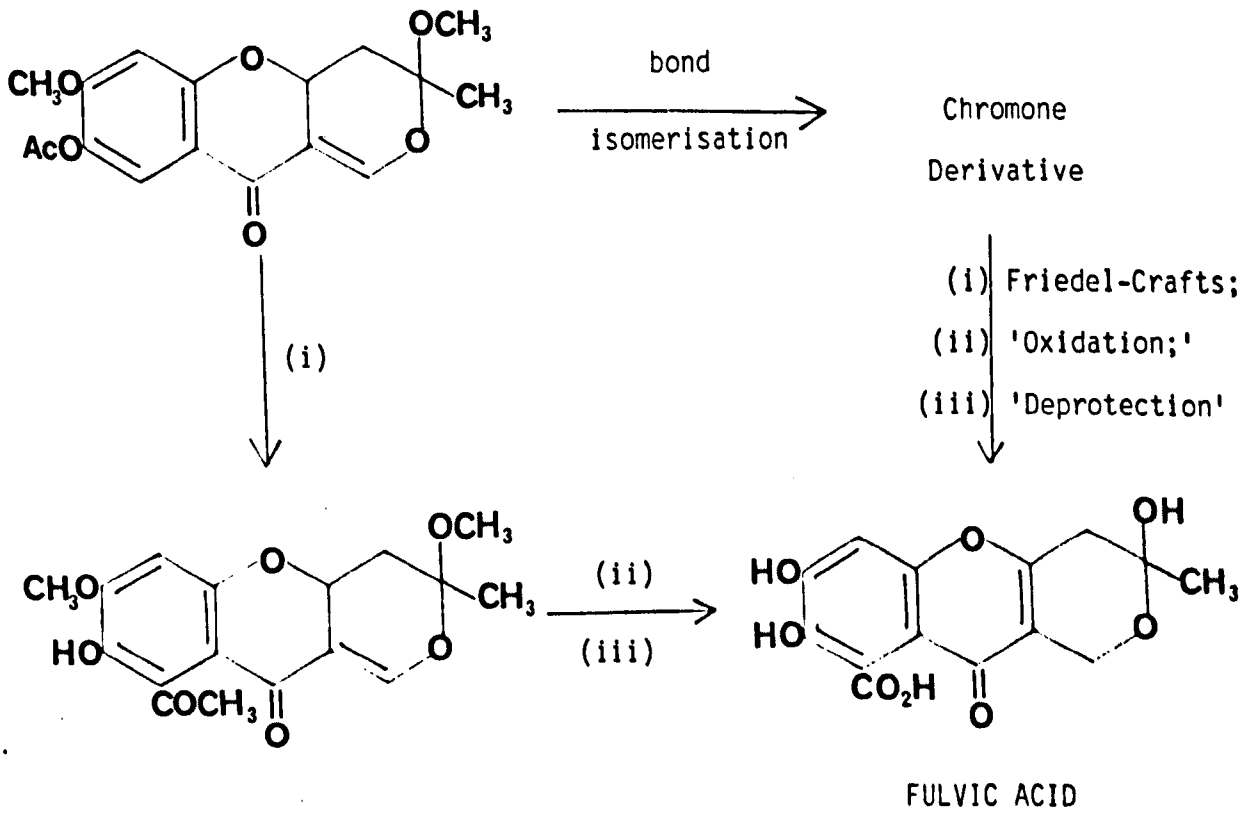
(41)

Application of our method of bond isomerisation was unsuccessful, however: a refluxing acetonitrile solution of (39a) and xanthylium perchlorate (17) showed no change over four hours. We observed a similar result on applying the same conditions to the benzylidene-cyclopentanone (41). A much more fruitful result came from substituting the more electron-rich chalcone (39b) to the same experimental conditions, however. After four hours reflux, the cooled mixture was decolourised by addition of Hantzsch ester and work-up afforded a 70% yield of (40b) along with 20% of unreacted (39b). Shortage of time prevented us from investigating those reaction conditions which might lead to a higher yield of (40b) though our method for inducing this transformation compares favourably with Barton's in that ours is quicker, does not rely on an expensive transition metal reagent (which is not easily recoverable at the end of the reaction) and may have more generality it that it should be applicable to acid-sensitive substrates.

The fact that xanthylium perchlorate is able to abstract hydride ion

from (39b) but not from (39a) or (41) reflects the importance of electron donation from the etheric oxygen atoms in adduct (1). This electron donation had been held responsible for the chromone-like character of adduct (1) discussed in the previous Chapter.

We have shown that the 6,7-disubstituted benzopyranopyran (37) isomerises to a similarly substituted chromone under the influence of xanthylium perchlorate and Hantzsch ester and the principal synthetical problem now remaining in any projected total synthesis of fulvic acid using this methodology is the introduction of the carboxylic acid grouping at position 9. The synthetical route outlined below illustrates two tentative approaches that may be explored in order to overcome this difficulty.



EXPERIMENTAL

General conditions as described on pages 32, 73 and 130.

Ethyl acetate: Dried over anhydrous sodium sulphate and distilled;

Methanol: Distilled from lithium aluminium hydride immediately before use.

9-Methyl-6H,7H[1]benzopyrano[4,3-b][1]benzopy-12-ylium perchlorate (8)

An anhydrous perchloric acid solution was made by the dropwise addition of 70% perchloric acid (200 g) to acetic anhydride (340 g) stirred at -11 °C. A portion of this solution (9.3 ml, equivalent to 18 mmol perchloric acid) was added dropwise to a stirred mixture of 5-methylsalicylaldehyde[13] (2.2 g, 16.2 mmol) and 4-chromanone (2.18 g, 14.7 mmol) in acetic acid (15 ml) at 10 °C. After five minutes, dry ether (150 ml) was added and the precipitated red powder filtered and washed with ether and crystallised from a large volume of acetic acid to afford brilliant red plates of the benzopyrilium perchlorate (8), (4.52 g, 80%), m.p. 210 °C (dec).

Found (ML 22922): C,58.23; H,3.77%

$C_{17}H_{13}O_2.ClO_4$ requires: C,58.53; H,3.76%

$\lambda_{max}(HClO_4)$: 455 nm, (ϵ=747);
373 nm, (ϵ=421);
283 nm, (ϵ=349);
265 nm, (ϵ=410).

$\delta(CDCl_3+TFA)$: 2.70 (3H, s, CH_3);
5.80 (2H, s, CH_2-O-);
7.29 [1H, d, J8Hz, C(4)H];
7.43 [1H, t, J7Hz, C(3)H];
7.94 [1H, t, J7Hz, C(2)H];
8.06 [1H, s, C(1)H];
8.17 [2H, s, C(7), C(8)H];
8.35 [1H, d, J8Hz, C(10)H];
8.99 [1H, s, C(11)H].

9-Methyl-6H,7H[1]benzopyrano[4,3-b][1]benzopyran (9)

Sodium borohydride (190 mg) in tetrahydrofuran (5 ml) was added to a vigorously stirred mixture of benzopyrilium salt (8) (1 g) in the same solvent (40 ml) at 0 °C. After 30 minutes, the reaction mixture was poured into a mixture of ice-cold water (50 ml) and conc. hydrochloric acid (2 ml) and extracted with ether (100 ml x 3). The combined ether extracts were washed with water (50 ml x 2), dried (Na_2SO_4) and evaporation of solvent under reduced pressure afforded benzopyran (9) as a white solid which crystallised from ethanol as colourless needles, (501 mg, 70%), m.p. 75 °C.

Found (ML 104): C,81.51; H,5.57%

$C_{17}H_{14}O_2$ requires: C,81.56; H,5.64%

Accurate Mass found: 250.098823

$C_{17}H_{14}O_2$ requires: 250.09936

m/e: 249 (M^+-H); 235 (M^+-CH_3).

ν_{max}: 1695, 1600, 1585 and 1575 (C=C) $cm.^{-1}$

$\lambda_{max}(CH_3CN)$: 339 nm (ϵ=131);

323 nm (ϵ=197).

δ : 6.82-7.05 [4H, m, C(3, 4, 10, 11)H];

7.19 [1H, t, J7.5Hz, C(2)H];

7.29 [1H, s, C(8)H];

7.52 [1H, dd, J7.5 and 2Hz, C(1)H].

3-(2'-Hydroxybenzyl)-6-methyl-4-oxo-4H[1]benzopyran (10)

Sodium borohydride (109 mg) in 95% ethanol (5 ml) was added to a stirred solution of benzopyrilium salt (8) (1 g) in the same solvent (50 ml). The mixture was stirred thoroughly at room temperature for twenty minutes before being poured onto ice-water (100 ml) containing conc. hydrochloric acid (2 ml) and extracted with ether (50 ml x 3). The combined ether

extracts were washed with water (50 ml x 2), brine (50 ml) and dried (Na_2SO_4). Solvent was removed under reduced pressure to afford a dark green semi-solid which was flash-chromatographed eluting with toluene-ethyl acetate (9:1 v/v). First to be eluted from the column was the chromone (10) which was purified by crystallisation from iso-propanol to afford needles (80 mg, 60%), m.p. 182 °C.

Found (ML 22968): C,76.68; H,5.32%

$C_{17}H_{14}O_3$ requires: C,76.66; H,5.30%

Accurate Mass found: 266.09429

$C_{17}H_{14}O_3$ requires: 266.09428

m/e: 249 (M^+-OH); 159 (249-C_7H_6); 145 (159-CH_2).

ν_{max}: 3110br. (OH); 1620(C=O); 1590 and 1565 (C=C) $cm.^{-1}$

δ : 6.85-6.99 [3H, m, C(11), (12), (14)H];

7.41 [1H, t, J7.5Hz, C(7)H];

7.47 [1H, d, J8Hz, C(8)H];

7.68 [1H, t, J7.5Hz, C(6)H];

8.09 [1H, s, C(2)H];

8.14 [1H, dd, J8 and 2.5Hz, C(5)H];

9.23 [1H, s, OH, D_2O-exchangeable].

Further elution of the column with toluene-ethyl acetate (1:1 v/v) afforded a green oil (536 mg) which was shown by t.l.c. to consist of at least six compenents which were more polar than chromone (10). Separation of this mixture by further silica gel column chromatography was unsuccessful.

9-Methyl-7H[1]benzopyrano[4,3-b][1]benzopy-12-ylium perchlorate (11)

To the chromone (10) (540 mg) in a mixture of acetic acid (20 ml) and ethyl acetate (5 ml) at 0 °C was added perchloric acid (1 ml) and the

flask flushed with nitrogen, stoppered and left to stand at room temperature. After 16 hours, dry ether (100 ml) was added and the yellow-orange precipitate filtered and crystallised from a large volume of acetic acid to afford benzopyrilium perchlorate (11) as orange micro-needles, (361 mg, 51%), m.p. 245 °C (dec). Despite drying in vacuo over phosphorus pentoxide for 48 hours, water of crystallisation could not be removed from (11).

Found (ML 23,061): C57.03; H,3.95%

$C_{17}H_{13}O_3.ClO_4+\frac{1}{2}H_2O$ requires: C,58.52; H,3.76%

ν_{max}: 1625, 1610 and 1600 (C=C) and 1080br. (ClO_4^-) $cm.^{-1}$

$\lambda_{max}(HClO_4)$: 378 nm (ϵ=196);
308 nm (ϵ=245).

δ ($CDCl_3$+TFA): 2.42 (3H, s, CH_3);
4.43 (2H, s, 7-CH_2);
7.22-7.39 [3H, m, C(8),(10),(11)H];
8.05 [1H, t, J7Hz, C(3)H];
8.17 [1H, dd, J8 and 2Hz, C(4)H];
8.34 [1H, t, J7Hz, C(2)H];
8.64 [1H, dd, J8 and 2Hz, C(1)H];
9.27 [1H, s, C(6)H].

Reaction of triphenylcarbenium perchlorate with benzopyran (9)

Triphenylcarbenium perchlorate (690 mg) in dichloromethane (10 ml) was added to benzopyan (9) (508 mg) in the same solvent (10 ml) affording an immediate deep red coloured solution. Solvent was evaporated providing a red gum which soldified on treatment with dry ether. The red solid was filtered and washed thoroughly with dry ether affording 9-methyl-6H,7H[1]-benzopyran[4,3-b][1]benzopy-12-ylium perchlorate (8) as a red powder (660 mg)

which was identical (m.p., t.l.c., n.m.r.) with independently synthesised (8). Evaporation of the ether mother liquor afforded triphenylmethane as an off-white solid (450 mg), m.p. 92-94 °C.

Xanthylium perchlorate (17)

Xanthydrol (2 g) was dissolved in ether (200 ml) and the solution stirred at -78 °C under a dry nitrogen atmosphere. Perchloric acid (1 g) was added dropwise and the yellow perchlorate salt (17) immediately precipitated. After one hour at room temperature, the salt was collected and washed with dry ether to afford a yellow powder (2.47 g, 87%), m.p. 239 °C (dec), (lit:[14] 237 °C).

9-Methyl-6H,7H[1]benzopyrano[4,3-b][1]benzopyran-7-one (16)

To a dark red mixture of benzopyrilium perchlorate (8) (1.4 g) in dimethyl sulphoxide (20 ml) at room temperature was added triethylamine (0.6 ml) which immediately decolourised the solution. The mixture was poured onto ice-water (100 ml) and extracted with ether (50 ml x 3). The combined ether extracts were washed with water (50 ml x 2), brine (50 ml) and dried ($CaCl_2$). Evaporation of the solvent afforded a brown oil which was flash-chromatographed with toluene-ethyl acetate (9:1 v/v) as eluant affording benzopyranone (16) as white needles (471.3 mg, 31%), m.p. 145 °C. A chloroform solution of this compound exhibits a purple fluorescence.

Found (ML 23048): C,77.32; H,4.75%

$C_{17}H_{12}O_3$ requires: C,77.25; H,4.58%

Accurate Mass found: 264.08013

$C_{17}H_{12}O_3$ requires: 264.07863

m/e: 235 (M^+-CHO); 205 (235-CH_2O).

ν_{max}: 1635 (C=O); 1610 and 1600 (C=C) $cm.^{-1}$

δ : 2.42 (3H, s, $ArCH_3$);

5.32 (2H, s, OCH_2);

6.93 [1H, dd, J8 and 1.5Hz, C( )H];

7.04 [1H, t, J7.5Hz, C(3)H];

7.36 [1H, t, J7.5Hz, C(2)H];

7.40-7.50 [2H, m, C(1),(11)H];

7.78 [1H, dd, J8 and 2Hz, C(10)H];

7.97 [1H, s, C(8)H].

9-Methyl-6H,7H[1]benzopyrano[4,3-b][1]benzopyran-7-one (16)

To the perchlorate salt (8) (700 mg) in acetonitrile (40 ml) was added potassium benzeneselenite[3] (680 mg, freshly crystallised from N,N-dimethylformamide) in 2-methoxyethanol (20 ml). After the near colourless solution was left to stand at room temperature for one hour, it was poured onto ice-water (100 ml) and work-up as described above produced benzopyranone (16) as colourless needles (370 mg, 70%), m.p. 144-145 °C spectroscopically identical to a sample prepared as described in the previous experimental procedure to this one.

3-(2'-Hydroxybenzyl)-6-methyl-4H[1]benzopyan-4-one (10)

(i) To the perchlorate salt (8) (700 mg) in acetonitrile (30 ml) was added pyridine N-oxide (190 mg, ALDRICH) in the same solvent (5 ml). The flask was flushed with nitrogen, stoppered and left at room temperature for 16 hours. Crystals (wide plates) formed during this time and were collected and washed with a small amount of cold ether. A second crop of crystals was obtained on chilling the mother liquor at 5 °C for five hours. Both crops of crystals were combined to afford chromone (10) (159 mg, 30%), m.p. 180-182 °C which was identical (m.p., t.l.c. in three different

solvent systems and n.m.r.) to the same compound prepared as described on page .

(ii) To perchlorate salt (8) (700 mg) in acetonitrile (20 ml) was added distilled water (10μl). The flask was flushed with nitrogen, sealed and left at room temperature for seven days, during which time the red solution precipitated crystals. These were filtered off and shown by the usual analyses to be chromone (10), (221 mg, 42%), m.p. 179-182 °C.

(iii) The title compound was obtained (279 mg, 53%) m.p. 181-182 °C, by submitting the orange perchlorate salt (11) (700 mg) to those conditions described in (i) above except, in this case, two mole equivalents of pyridine N-oxide (381 mg) was employed. After filtration of chromone (10), evaporation of the mother liquor under reduced pressure afforded a thick, red gum which could not be purified further. Similarly, quenching the reaction mixture with ice-water (20 ml) led to the formation of globules of a red oil which was shown by t.l.c. to consist of mostly very polar, base-line material and was not investigated further.

Di-(1,2,7,8-dibenzo-9-xanthyl) ether (21)

Dinapthapyrilium chloride[6] (3 g) in water (50 ml) was boiled for ten minutes before being filtered to afford ether (21) as a pink, granular solid (2.73 g). This solid was continuously extracted with toluene in a soxhlet apparatus over 48 hours. The cooled solvent deposited clumps of white needles which were collected as dinapthapyrl ether (21), (2.21 g, 83%), m.p. 250 °C, (lit:[7] 250-252 °C).

Found (ML 22923): C,87.16; H,4.76%

$C_{42}H_{26}O_3$ requires: C,87.17; H,4.53%

m/e: 281 (100%; $C_{21}H_{12}OH^+$)

ν max: 1615, 1585 and 1510 (C=C) cm.-1

3,8-Dimethyl-1H,10H-pyrano[4,3-b][1]benzopyan-10-one (27)

(i) To benzopyranone (1) (520 mg) in acetonitrile (10 ml) was added xanthylium perchlorate (562 mg) in the same solvent (20 ml). The reaction mixture was boiled for two minutes (effecting a change from colourless to very dark red) and, when cooled to room temperature, sodium borohydride (21 mg) in acetonitrile (5 ml) was added with vigorous swirling. After five minutes, the mixture was poured into ice-water (100 ml) and extracted with dichloromethane (50 ml x 4). The combined dichloromethane extracts were washed with water (50 ml x 3), brine (50 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a viscous brown oil (758 mg) which was flash-chromatographed with toluene-ethyl acetate (85:15 v/v) as eluant. Evaporation of the eluant afforded xanthene (28) (362.7 mg, 99%), m.p. 102 °C and benzopyranone (27) (32 mg, 7%) which crystallised from ether-ethyl acetate (ca 20:1 v/v) as light brown coloured micro-needles, m.p. 153-155 °C.

Found (ML 18193): C,73.5; H,5.4%

$C_{14}H_{12}O_3$ requires: C,73.7; H,5.3%

Accurate Mass found: 288.07843

$C_{14}H_{12}O_3$ requires: 288.07863

m/e: 273 (M^+-CH_3); 199 (M^+-CHO); 185 (M^+-CH_2CHO).

ν_{max}: 1650 (C=O); 1605 and 1590 (C=C) $cm.^{-1}$

δ : 2.00 [3H, s, C(3)CH_3];

2.42 [3H, s, C(8)CH_3];

5.29 [2H, s, C(1)H];

5.42 [1H, s, C(4)H];

7.26 [1H, d, J8Hz, C(6)H];

7.38 [1H, dd, J8 and 2Hz, C(7)H];

7.94 [1H, d, J2Hz, C(9)H].

(ii) To benzopyranone (1) (520 mg) in acetonitrile (10 ml) was added xanthylium perchlorate (17) (562 mg) in acetonitrile (20 ml) and the reaction mixture was boiled for two minutes. When cool, Hantzsch ester (31) (504 mg) was added with vigorous swirling for five minutes before the mixture was poured into ice-water (100 ml). Work-up as described in (i) above afforded a brown oil (1.08 g) which, after flash-chromatography, (eluting with toluene-ethyl acetate, 85:15 v/v), afforded benzopyranone (27), (128 mg, 28%) m.p. 152-155 °C which was identical (t.l.c., i.r. and n.m.r.) with a sample as prepared according to (i) above. Also eluted from the column were xanthene (28) (357 mg, 98%), m.p. 100-102 °C and the pyridine diester (32) which crystallised from hexane as white plates (457 mg, 91%), m.p. 72-73 °C.

3,8-Dimethyl-3-methoxy-1H,10H-pyrano[4,3-b][1]benzopyran-10-one (3)

Benzopyranone (1) (500 mg) was dissolved in methanol (5 ml) and the solution saturated with 4-toluenesulphonic acid (ca 1 g). The flask was stoppered and left at room temperature for five days during which time flakes precipitated. These were filtered off (90 mg) and shown by n.m.r. analysis to be a mixture containing the title compound (3) and a minute amount of benzopyranone (1). The latter was removed by one crystallisation of the mixture from methanol affording benzopyranone (3) (56 mg) as light brown coloured needles, m.p. 117-119 °C.

Accurate Mass found: 260.1047821

$C_{15}H_{16}O_4$ requires: 260.1048496

m/e: 245 (M^+-CH_3); 228 (M^+-CH_3OH); 213 (228-CH_3).

ν_{max}: 1650br. (C=O); 1630 and 1610 (C=C) $cm.^{-1}$

δ : 1.55 (3H, s, CH_3);
2.45 (3H, s, $ArCH_3$);
3.34 (3H, s, OCH_3);
2.73 [1H, d, J17Hz, C(4)H];
2.88 [1H, d, J17Hz, C(4)H];
4.47 [1H, d, J15Hz, C(1)H];
4.78 [1H, d, J15Hz, C(1)H];
7.26 [1H, d, J8Hz, C(6)H];
7.45 [1H, dd, J8 and 2.5Hz, C(7)H];
7.94 [1H, s, C(9)H].

7,8-Dihydroxy-3-methyl-1H,10H-pyrano[4,3-b][1]benzopyran-10-one? (38, R=H)

To the diacetyloxybenzopyranone (37) (639 mg) in acetonitrile (10 ml) was added xanthylium perchlorate (17) (534 mg) in acetonitrile (15 ml). The reaction mixture was boiled for five minutes and, when cool, Hantzsch ester (31) (479 mg) was added with vigorous swirling. After ten minutes, the mixture was poured into ice-water (100 ml), extracted with ether (100 ml x 3) and the combined ether extracts washed with water (100 ml x 2), brine (100 ml) and dried ($CaCl_2$). Evaporation of the solvent afforded a red oil (1.44 g) from which all but a fraction of the pyridine diester (32) was extracted by treatment with hot pentane and decanting. The residue was absorbed on silica (1 g) and placed at the top of a short, silica gel column and eluted with toluene --to afford xanthene (297 mg, 86%)-- and a light yellow coloured gum (170.9 mg). The n.m.r. spectrum of this gum showed a mass of indecipherable signals in the high field region, the only distinct signals being those in accord with a chromone structure (38, R=H?).

δ : 5.29 [2H, s, C(1)H];
5.43 [1H, s, C(4)H];

7.34 [1H, s, C(6)H];

7.94 [1H, s, C(9)H].

3-(2,4,5-Trimethoxybenzylidene)-4-chromanone (39b)

2,4,5-Trimethoxybenzaldehyde (1.5 g) was added to 4-chromanone (1.2 g) in benzene (30 ml) and piperidine (3 ml). The reaction mixture was refluxed and the water removed by means of a Dean-Stark trap. After 24 hours, the crude mixture was eluted with benzene through a short column of neutral alumina to afford benzylidene-4-chromanone (39b) which crystallised from ethanol as chunky needles, (1.96 g, 79%), m.p. 137-138 °C, (lit:[12] 136-138 °C).

3-(2,4,5-Trimethoxybenzyl)-4-chromone (40b)

To the benzylidenechromanone (39b) (326 mg) in acetonitrile (10 ml) was added xanthylium perchlorate (17) (281 mg) in the same solvent (15 ml). The reaction mixture was refluxed for four hours and when cool, Hantzsch ester (31) (253 mg) was added with vigorous swirling. After ten minutes, the mixture was poured into ice-water (100 ml) and extracted with ether (50 ml x 2). The combined ether extracts were washed with water (30 ml x 3), brine (20 ml), dried (Na_2SO_4) and evaporated to afford a yellow oil (736 mg) which solidified after being left at room temperature for 16 hours. This residue was dissolved in toluene and filtered through a short column of acidic alumina (10 g). Evaporation of the eluant afforded xanthene (180 mg), m.p. 101-102 °C and further elution afforded a mixture (n.m.r.) of the pyridine diester (32) and unchanged benzylidenechromanone (39b). Last to be eluted from the column was the benzyl-4-chromone (40b) which crystallised from ether-hexane as brilliant yellow needles (229 mg), m.p. 116-118 °C, (lit:[12] 117-118 °C).

δ : 3.76 [2H, s, C(1')H];

3.82 (3H, s, OCH_3);

3.84 (3H, s, OCH_3);

3.89 (3H, s, OCH_3);

6.57 [1H, s, C(7')H];

6.95 [1H, s, C(4')H];

7.38 [1H, t, J7Hz, C(7)H];

7.40 [1H, d, J8Hz, C(8)H];

8.12 [1H, t, J7Hz, C(6)H];

8.16 [1H, s, C(2)H];

8.25 [1H, dd, J8 and 2Hz, C(5)H].

2-(Benzylidene)-cyclopentanone (41)

A mixture of 4-(1-cyclopenten-1-yl)morpholine (24 g) (0.15 mol) and benzaldehyde (15 g, 0.14 mol) in benzene (30 ml) was stirred at reflux temperature for 12 hours and the water removed in a Dean-Stark trap. To the cooled reaction mixture a mixture of conc. hydrochloric acid (15 ml) and water (15 ml) was added dropwise with stirring. A further 30 ml of benzene was added and the mixture stirred at room temperature for one hour before the organic and aqueous layers were separated. The aqueous phase was extracted with benzene (50 ml) and the combined organic extracts washed with water (50 ml x 3) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure afforded a residue which was distilled under reduced pressure. The fraction boiling at 120 °C/0.1 mmHg solidified on standing and crystallised from ligroin as chunky, light-yellow prisms, (5.23 g, 19%), m.p. 70-71 °C (lit:[15] 71 °C).

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