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A THESIS ENTITLED
"PHENANTHRENE SYNTHESIS AND THE
BIOSYNTHESIS OF MOLLISIN"

Submitted to the University of Glasgow
for the Degree of Doctor of Philosophy
in the Faculty of Science

by

ANNE MARIE BYTH, B.Sc.

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I am also indebted to the Departmental technical staff for the analytical services they supplied and to the Mycology Unit for assisting in the biosynthetic work.

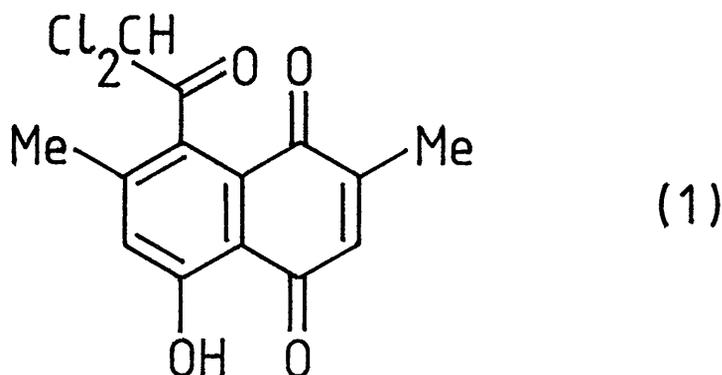
Finally, I thank the University of Glasgow for the award of a Scholarship.

TABLE OF CONTENTS

	Page No.
<u>Summary</u>	ii
<u>Introduction</u>	1
 <u>Results and Discussion</u>	
 CHAPTER 1 : The Biosynthesis of Mollisin	 33
 CHAPTER 2 : The Synthesis, Properties and Photochemistry of 2-Halo- and 2,6-Dihalo- α -cyanostilbenes	 47
 CHAPTER 3 : The Synthesis and Decarbomethoxylation of a 9-Carbomethoxyphenanthrene	 140
 CHAPTER 4 : The Synthesis and Photocyclisation of a 2-Benzyloxystilbene	 169
 <u>Experimental</u>	 183
 <u>References</u>	 232

SUMMARY

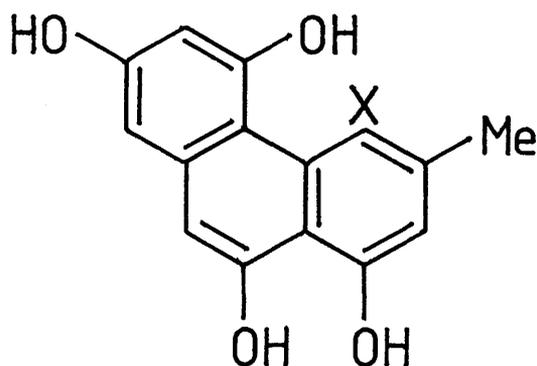
Mollisin (1)^{4,5} is derived via the polyketide pathway in the fungus Mollisia caesia and is the only known natural product to contain an aromatic dichloroacetyl moiety. Since its discovery⁴ in 1956 several groups⁵⁰⁻⁵⁴ have attempted to unravel the biosynthesis of mollisin because of its unique structure. The ultimate aim of the work described in this thesis was to elucidate the biogenesis of this unusual fungal metabolite and is in part a continuation of the work performed by A.A. Finnie⁵⁰ in this laboratory.



The Introduction gives a brief account of the polyketide pathway and discusses biological chlorination, a common in vivo modification in the biosynthesis of polyketides and other classes of metabolite. The Introduction also describes in detail the mechanism for the formation of phenanthrenes via stilbene photocyclisation. This is relevant to subsequent chapters dealing with synthetic strategies to

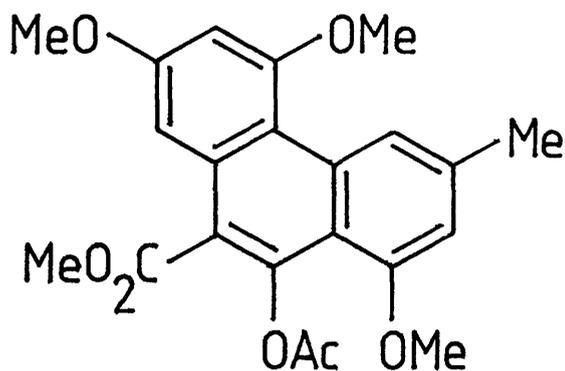
the phenanthrene derivatives which are postulated intermediates in the biosynthesis of mollisin. Practical aspects of stilbene photocyclisations are outlined in the final section of the Introduction.

The biosynthesis of mollisin is discussed in Chapter 1 and is proposed to involve chlorination and then ring degradation of a polyketide derived phenanthrene (14), (15) or (16). Chapter 1 also records the disappointing result of feeding sodium $[2\text{-}^2\text{H}_3, 1\text{-}^{13}\text{C}]$ -acetate to malt agar cultures of *M. caesia* during the present investigation. Thus it was proposed to study the biosynthesis of mollisin by feeding deuterium labelled phenanthenes (14) - (16) to the fungal medium.



(14) $X = \text{H}$, (15) $X = \text{OH}$, (16) $X = \text{CO}_2\text{H}$

Chapters 2, 3 and 4 describe attempts to synthesise the postulated biosynthetic intermediates. The synthesis, properties and photochemistry of ortho-halostilbenes with α' -acetoxy- α -cyano or α' -acetoxy- α -carbomethoxy substituents are recorded in Chapters 2 and 3 respectively. The evidence from the photochemical experiments indicates that an ortho-halo substituent cannot be used to regiochemically control the cyclisation step in these systems. As outlined in Chapter 3, a significant result was the finding that the 9-carbomethoxyl group of phenanthrene (173) can be easily removed with simultaneous hydrolysis of the 10-acetoxy group upon treatment with aqueous base. Chapter 4 mainly deals with attempts to synthesise phenanthrene (14) using benzyl protecting groups for the phenolic substituents in the starting materials. Unfortunately, no feeding experiments employing deuterium labelled phenanthrenes were conducted. However, many interesting results were obtained in connection with the photochemical synthesis of phenanthrenes.



(173)

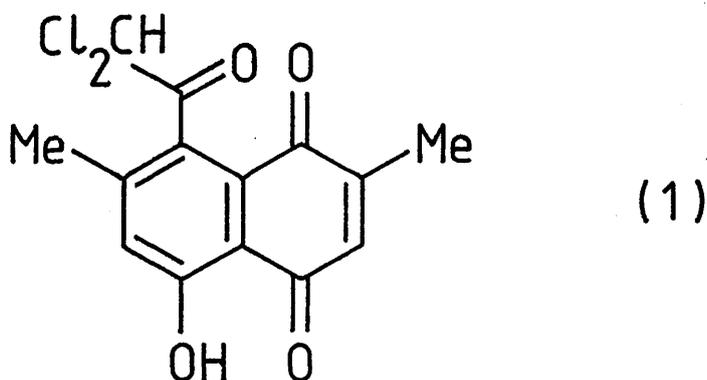
1. Background

Ever since 1769-85 when Carl Wilhelm Scheele first isolated tartaric acid in pure form from grapes, citric acid from lemons, malic acid from apples and gallic acid from gall nuts, chemists have been interested in the molecular structure, chemical properties, synthesis and biosynthesis of natural products.¹

Living organisms synthesise and degrade chemical compounds by means of a series of enzyme mediated chemical reactions known as metabolism. All organisms have some metabolic pathways in common that are essential for their survival, for example those through which amino acids, sugars, common fatty acids and nucleotides are constructed. In addition to such primary metabolites, a considerably greater body of substances - alkaloids, terpenes, polyenes, pigments, phenols, myco-toxins and so forth - occur throughout nature and are often specific to a particular species of organism. Such secondary metabolites are biosynthesised from primary metabolites and are the end products of a long line of complex functionalisation requiring a large number of specific enzymes.

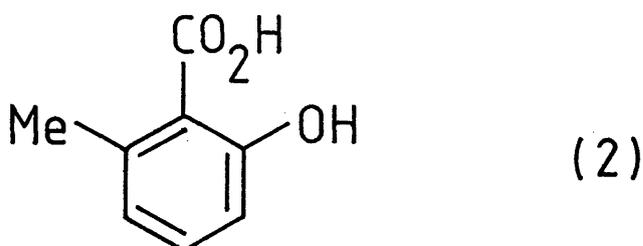
Many theories have been proposed to account for the presence of secondary metabolites.² One view is that they are simply waste products, another that they can be used as a food reservoir in times when the organism faces nutritional deficiencies. It has also been suggested that they can act as toxic protectors against predators. Whatever their role, to date many hundreds of secondary metabolites have been isolated from fungi and novel structural types continue to be discovered.³ This thesis is concerned with the biosynthesis of the

fungal metabolite mollisin (1), produced by Mollisia caesia and M. fallens.^{4,5}



2. The Polyketide or Acylpolymalonate Pathway

One of the most important biosynthetic routes in the secondary metabolism of fungi is the polyketide or acylpolymalonate pathway. The idea that naturally occurring, polyoxygenated compounds may arise from the condensation of acetate units was first suggested by Collie⁶ in 1893. However, this speculation was largely ignored until it was restated by Birch et al.^{7,8} over fifty years later. They supported the proposition with the experimental evidence that ¹⁴C-labelled acetate was incorporated into 6-methylsalicylic acid (2), a metabolite of Penicillium griseofulvum and other fungi.



The basic concepts which underline the acetate hypothesis can be summarised thus:

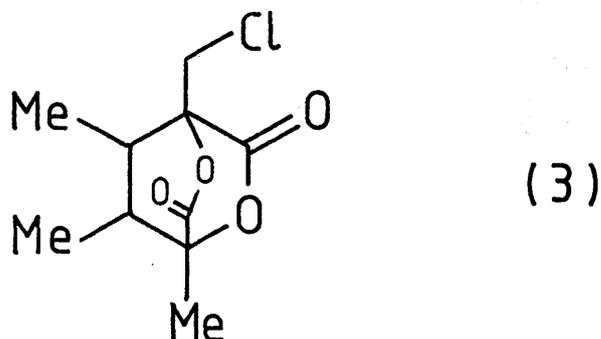
- (a) Acetic acid units are joined by the formal elimination of water in head-to-tail linkages with each other or with other naturally occurring carboxylic acids to form β -polyketomethylene chains.
- (b) The β -polyketomethylene chains may undergo secondary changes, notably cyclisations of the Claisen or Aldol type to form aromatic rings.
- (c) The carbon skeleton so formed may be modified by the introduction of alkyl groups.
- (d) Secondary processes of reduction and oxidation may occur either before or after cyclisation.

3. Chlorometabolites

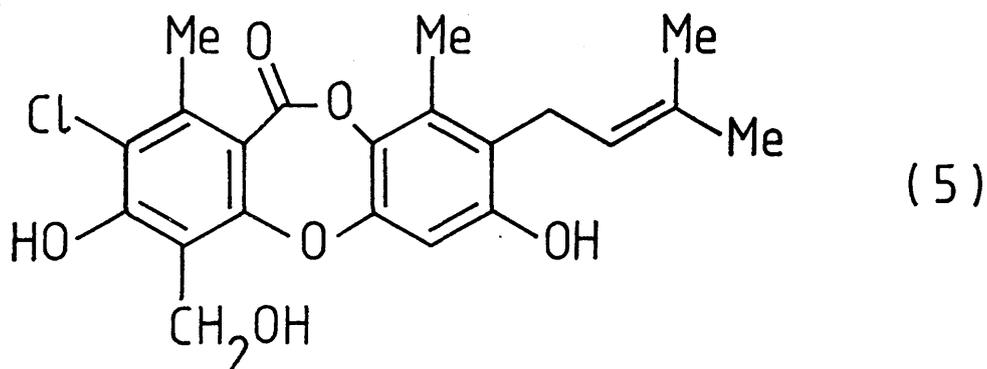
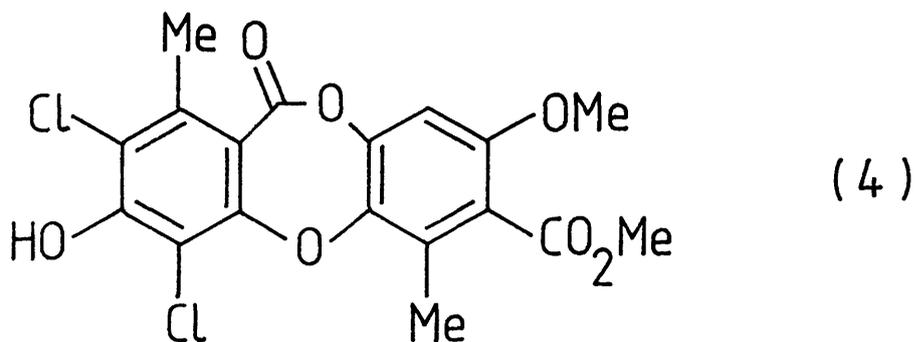
3.1 Natural Occurrence

Of the many known in vivo modifications of polyketides and other classes of metabolite, chlorination is frequently encountered.^{9,10} More than 130 chlorine containing compounds have been isolated from higher plants and ferns; about half are polyacetylenes, thiophenes and sesquiterpene lactones from the Asteraceae. Some plant chlorometabolites show strong biological activity, either within the plant itself as hormones or against other organisms as antifeedants or toxins. The first plant compound to be discovered to contain covalently bound chlorine was sceleratinic acid lactone (3) from the highly toxic Senecio

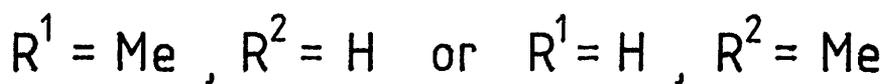
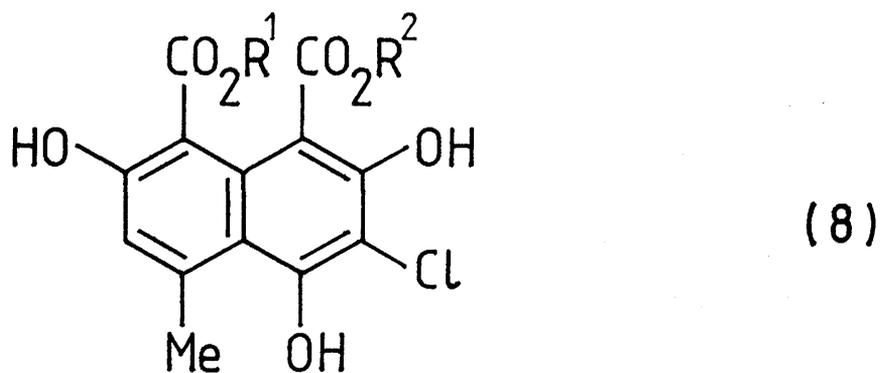
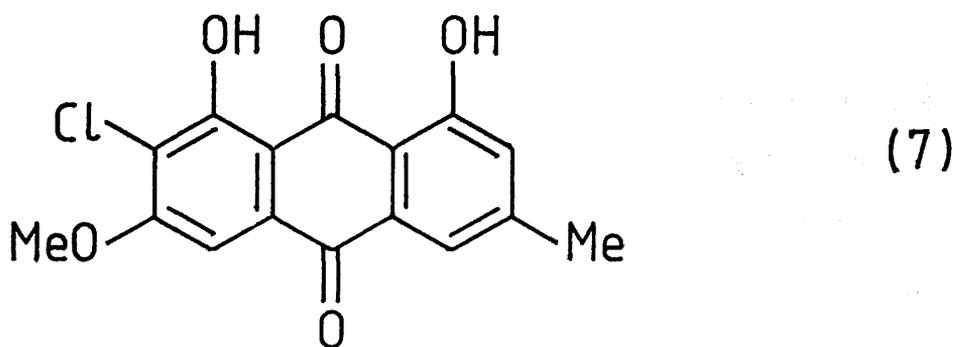
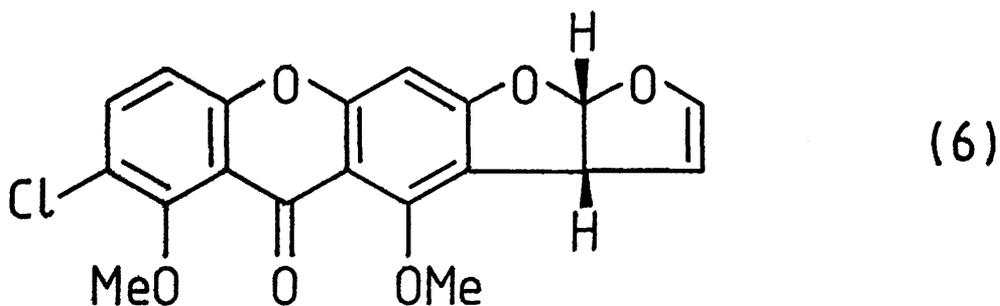
sceleratus,¹¹ although its structure was only clarified later.^{12,13}



Chlorometabolites are more common in fungi, lichens and marine algae. Among many known examples are the depsidones gangaleoidin (4) from the lichen Lecanora gangaleoides¹⁴ and mollicelin D (5) from the fungus Chaetominium mollicellum.¹⁵



Many chlorine containing products of polyketide origin have been isolated: the xanthone austocystin A (6) from maize meal cultures of *Aspergillus ustus*,¹⁶ the anthraquinone fragilin (7) from the *Caloplaca* genus of lichen¹⁷ and the chloronaphthalic ester (8) produced from a phenalenone type compound in *Verticillium lamellicola*.¹⁸

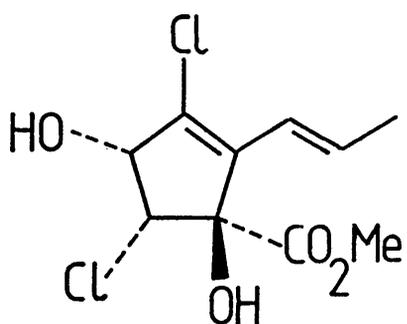


Most chloro compounds of polyketide origin have an aromatic bonded chlorine atom. Non-aromatic fungal chlorometabolites of polyketide origin are often derived via ring degradation of an aromatic precursor. For example, cryptosporiopsinol (9) is derived from the chloroisocoumarin (10) in the fungus Periconia macrospinosa.¹⁹

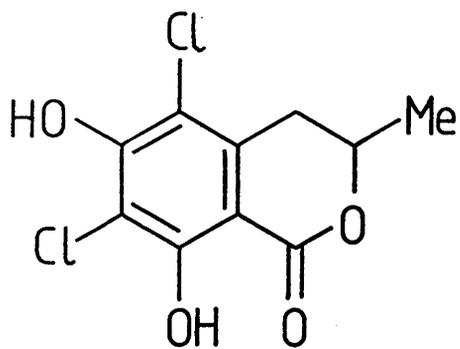
Many chlorometabolites have antibiotic, fungicidal, herbicidal or pesticidal properties. Chloramphenicol (11) (Streptomyces venezuelae), griseofulvin (12) (Penicillium urticae) and chlorotetracycline (13) (Streptomyces aureofaciens) are clinically important antibiotics.²⁰

3.2 The Mechanism of Biological Chlorination

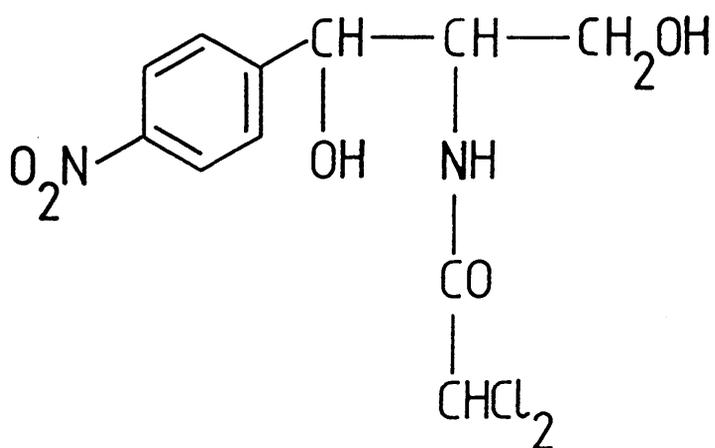
Little is known about the mechanism of biological chlorination. The process is thought to involve the oxidation of chloride to chlorine cations, or some equivalent. This could be accomplished by a chloroperoxidase enzyme together with a suitable oxidising agent. Such an enzyme has been isolated from the mould Caldariomyces fumago.²¹ The purified preparation was shown to catalyse the formation of carbon-halogen bonds in the presence of hydrogen peroxide. Details of the structure of the enzyme are known: it contains one mole of ferriprotoporphyrin IX as a prosthetic group and has a molecular weight of 42,000 of which 25-30% is carbohydrate. However, details of the structure of the active site and the mechanism by which the halogen atom is transferred to the substrate are lacking. Specifically, the nature of the group to which the halogen atom is added during transfer is not known. In studies of the C. fumago chloroperoxidase the relative non-specificity of the enzyme was noted: it catalysed the



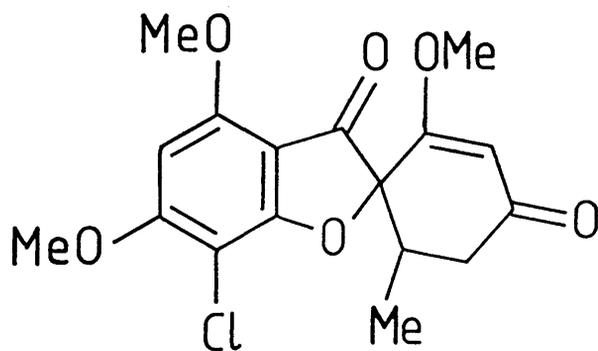
(9)



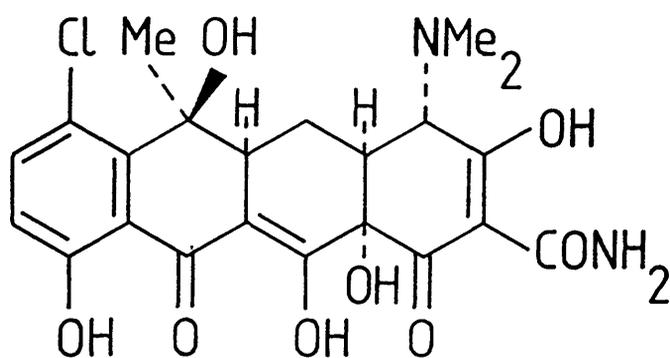
(10)



(11)



(12)



(13)

chlorination, bromination and iodination of a number of cyclic and acyclic 1,3-dicarbonyl compounds.

3.3 Dichloroacetyl Metabolites

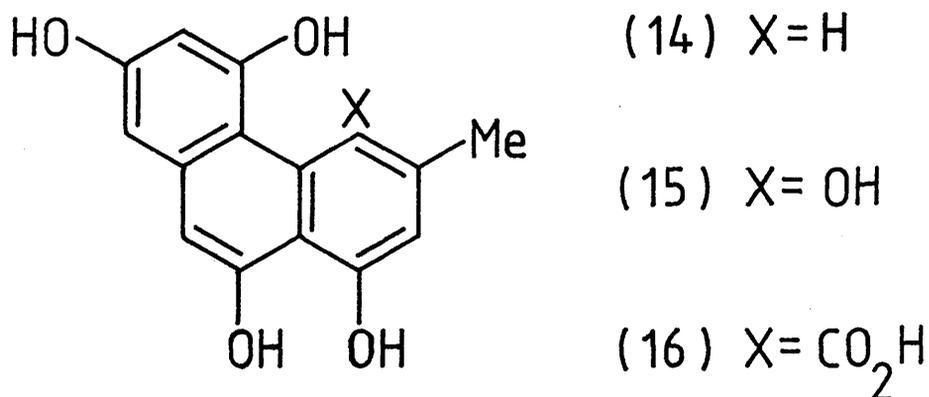
A structurally unique polyketide chlorometabolite is the naphthoquinone pigment mollisin (1), isolated from fungi of the genus Mollisia.^{4,5} It was the first natural product to be discovered to contain a dichloroacetyl group directly attached to carbon and it remains the only known natural product to contain an aromatic dichloroacetyl group.

Dichloroacetyl groups are not unknown in secondary metabolites but they are extremely rare from fungal sources. One of the few examples is chloramphenicol (11) which has a dichloroacetamide group. The origin of this group is unclear but it does not appear to arise either from the chlorination of an acetamide or via the formation of an amide from dichloroacetic acid in S. venezuelae. It has been suggested that biosynthesis proceeds through the fixation of carbon dioxide into a three carbon unit followed by chlorination of the resultant four carbon compound or its derivative.²⁰

Marine algae are a more abundant source of dichloroacetyl moieties and of halo compounds generally.²² Chlorocarbons are thought to play an important role in the regulation of atmospheric ozone density and marine plants have been suggested as the source of such air-borne compounds.²³ Among the volatile components of the Hawaiian seaweed Asparagopsis taxiformis, identified by GC-MS, were five dihaloacetamides, seven halogenated but-3-en-2-ols and twenty halogenated isopropanols.²⁴

Mollisin (1), with a unique aromatic dichloroacetyl group is of biosynthetic interest and is the subject of this thesis. Chapter 1

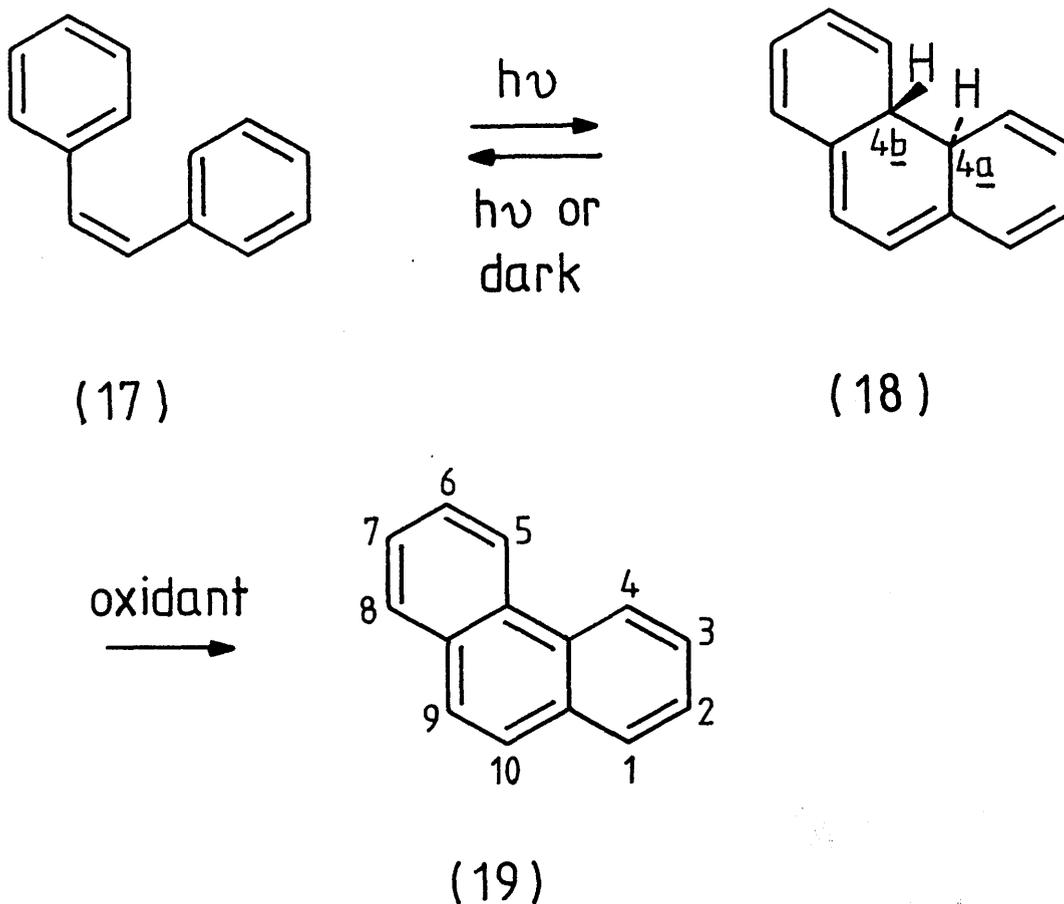
discusses the biosynthesis of mollisin (1) and is proposed to involve chlorination then ring degradation of a polyketide derived phenanthrene compound (14), (15) or (16). One way of testing this theory would be to feed isotopically labelled compounds (14)-(16) separately to the fungus, followed by isolation of mollisin (1) which is monitored for incorporation of the isotopic label. Thus synthetic routes to phenanthrenes (14), (15) and (16) are desired.



4. Phenanthrene Synthesis

Photocyclisation is the preferred method for the synthesis of phenanthrenes and many different polynuclear aromatic systems.

On irradiation in solution with ultraviolet (uv) light, cis-stilbene (17) undergoes reversible photocyclisation to give trans-4_a,4_b-dihydrophenanthrene (18), an intermediate that can be trapped oxidatively with hydrogen acceptors such as iodine, oxygen, tetracyanoethylene or diphenyl selenide to give phenanthrene (19) in high yield²⁵ [Scheme 1].



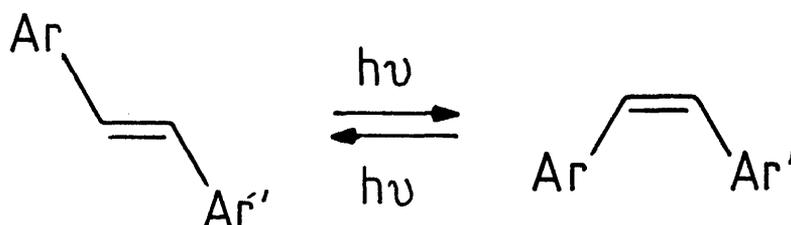
Scheme 1

4.1 The Mechanism of Stilbene Photocyclisation

The mechanism of the photocyclisation of stilbenes has been studied extensively.²⁵ The photocyclisation of stilbenes and the trapping of the resulting dihydrophenanthrenes are complicated transformations, and many mechanistic details are not yet firmly established.

4.1.1 Dihydrophenanthrenes from cis-Stilbenes

Photocyclisation reactions, with one possible exception,²⁶ proceed only by absorption of a photon by the cis-isomer and not by the trans-isomer of the stilbene derivative. However, the synthetically more accessible trans-isomer is commonly used as the starting material since reversible cis-trans photoisomerisation generates the mechanistically required cis-isomer [Scheme 2].



Scheme 2

Typically, stilbene photocyclisations are carried out at concentrations of 10^{-2} M or less to minimise the competing photodimerisation of the trans-isomer to give a 1,2,3,4-tetraarylcyclobutane derivative.²⁷ Photochemical [2+2] cycloaddition involving C-9 and C-10 of the product phenanthrene and the double bond of the starting stilbene, particularly the trans-isomer, is another potentially troublesome side reaction that is minimised at low concentrations.²⁸ Photocyclisations of stilbenes and related systems generally proceed only by way of molecules in their lowest excited singlet state.

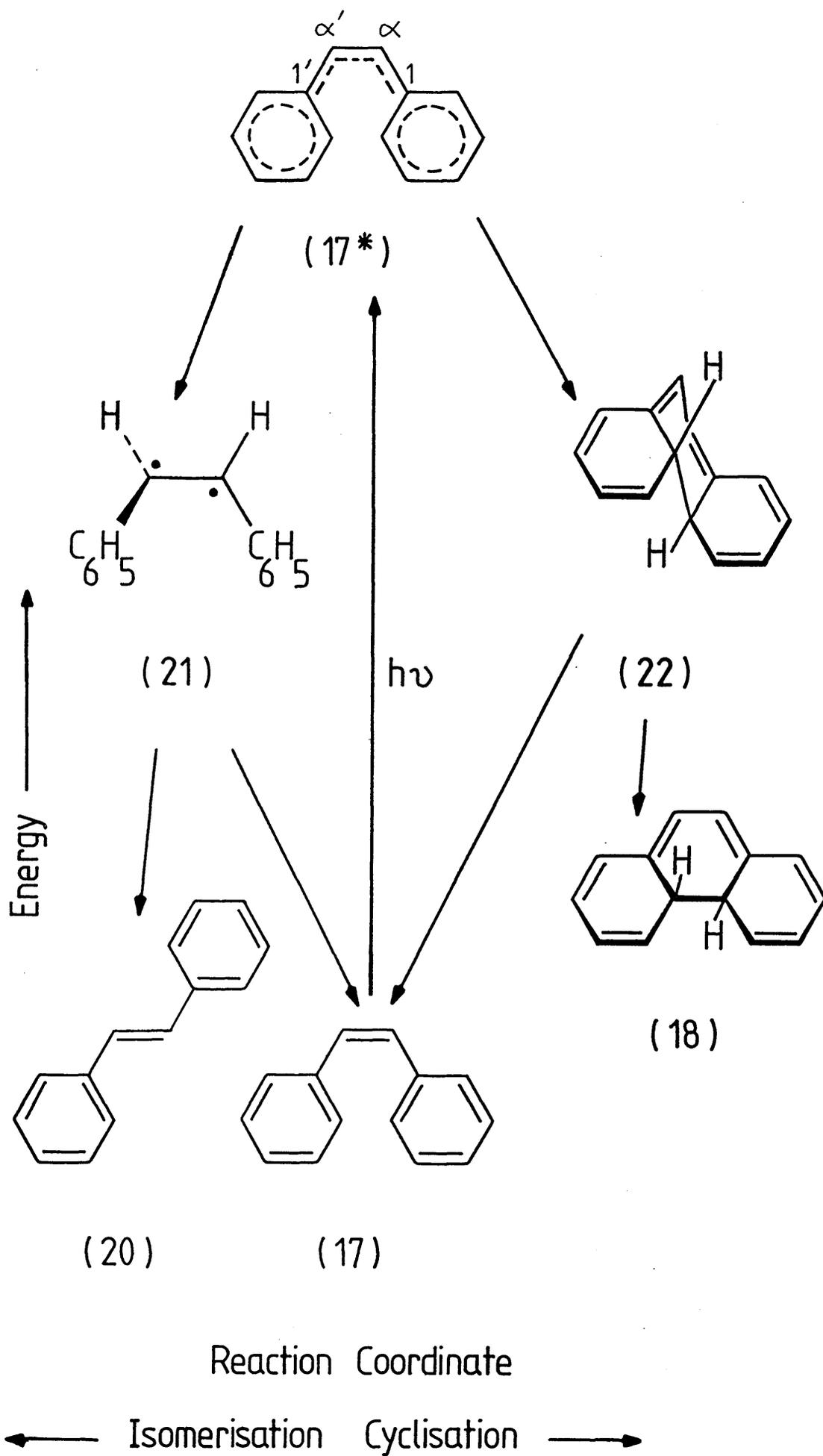
Photochemically produced dihydrophenanthrenes such as (18) are unstable because both photochemical and thermal ring opening reactions regenerate the starting cis-stilbene derivative. These dihydro-

phenanthrenes generally are not isolable, but under appropriate conditions many are sufficiently long lived in solution to study their chemical reactions and spectral properties.^{29,30} The assignment of trans rather than cis stereochemistry for the two allylic hydrogens on the carbon atoms at the site of ring closure is based on orbital symmetry considerations and on experimental evidence in a few systems.^{31,32}

A current view of the photocyclisation mechanism is illustrated for cis-stilbene (17) in Scheme 3. In this rough energy-reaction coordinate diagram, the important pathways are shown for both the photocyclisation of (17) to dihydrophenanthrene (18) and the competing photoisomerisation of (17) to trans-stilbene (20).

Photoexcitation of cis-stilbene (17) by absorption of a photon of uv light transforms the molecule from its ground singlet electronic state S_0 to its lowest excited singlet electronic state S_1 . The resulting excited species (17*) is drawn partly with dotted lines in Scheme 3 to indicate that the distribution of π -electron density in the S_1 state differs from that in the S_0 state. Calculations show that, in comparison to (17), (17*) has a smaller π -bond order between the two olefinic carbon atoms C- α and C- α' and a greater π -bond order between C- α and C-1 (and also between C- α' and C-1').²⁵

The excited cis-stilbene (17*) is thought to have two principal fates: rotation around the bond between C- α and C- α' followed by an $S_1 \rightarrow S_0$ electronic transition to give the twisted ground state stilbene species (21), and ring closure followed by an $S_1 \rightarrow S_0$ transition to give the skewed ground state dihydrophenanthrene species (22). Both (21) and (22) are at energy maxima on the ground state potential energy surface: (21) is considered identical with the transition state for the



Scheme 3

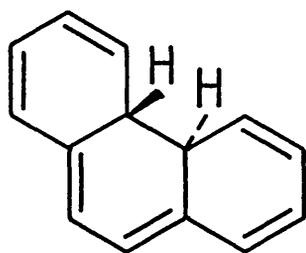
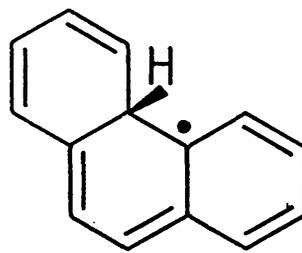
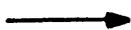
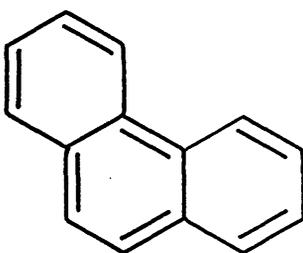
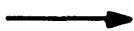
thermal cis-trans isomerisation reaction (17) \rightarrow (20), and (22) is considered identical with the transition state for the thermal ring opening reaction (18) \rightarrow (17). The dihedral angle between the bond from C- α to C-1 and the bond from C- α' to C-1' is assumed to be about 90° in the twisted stilbene (21). The bond between the saturated carbon atoms in the skewed dihydrophenanthrene (22) is regarded as abnormally long and weak compared to the corresponding bond in the relaxed dihydrophenanthrene (18). Species (21) relaxes rapidly to either (17) or (20), and species (22) relaxes rapidly to either (17) or (18).

4.1.2 Phenanthrenes from Dihydrophenanthrenes by Oxidative Trapping

The conversion of trans-4a,4b-dihydrophenanthrene (18) to phenanthrene (19) in air saturated solution proceeds by a radical mechanism involving two successive hydrogen abstractions with radical (23) as an intermediate^{33,34} [Scheme 4].

Although oxygen acts cleanly as the oxidant in the photocyclisations of very dilute solutions of stilbenes (10^{-5} - 10^{-4} M), its use with the more concentrated solutions (10^{-2} M) needed for practical preparative work often results in low yields of impure phenanthrenes. This problem may stem from unwanted reactions of the accumulated hydrogen peroxide.

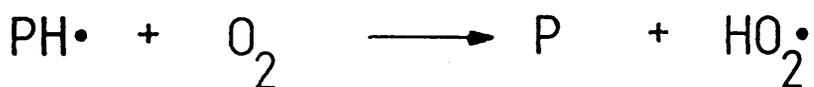
Usually it is advantageous to carry out preparative scale photocyclisations in an air saturated solution with a small amount of added iodine. This generally shortens the irradiation time for complete

(18) PH_2 (23) $\text{PH}\cdot$ (19) P

Initiation

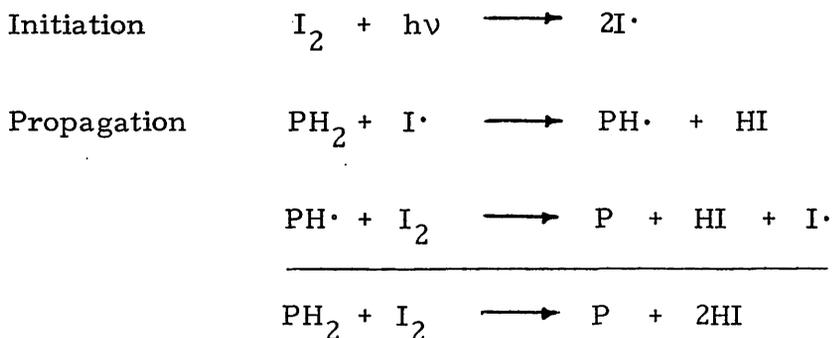


Propagation

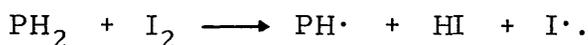


Scheme 4

conversion and gives a cleaner product in higher yield.²⁵ Iodine provides another chain mechanism for trapping dihydrophenanthrenes.



The photochemical dissociation of molecular iodine may involve predominantly the visible component of the emission from the light source used in the irradiation. The hydrogen iodide from the propagation steps may undergo oxidation under the reaction conditions to regenerate iodine. Another conceivable initiation step involving iodine is



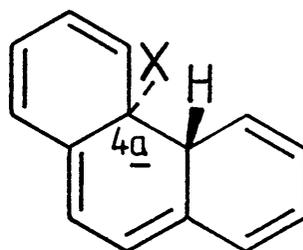
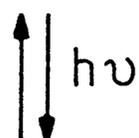
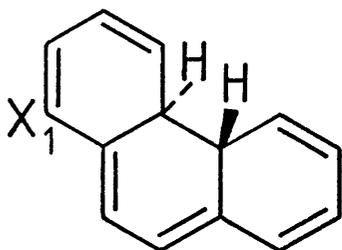
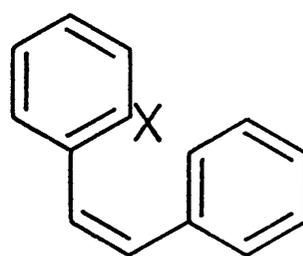
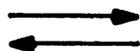
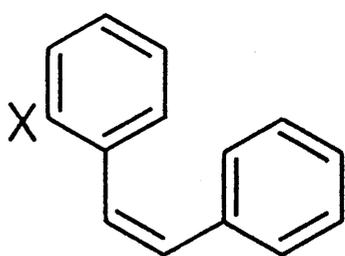
Hydrogen abstraction by iodine atoms is more exothermic than by oxygen molecules by 24 kcal/mol. [This is the difference in the bond dissociation energies of H - I (71 kcal/mol) and H - O₂· (47 kcal/mol).]³⁵ This accounts for the greater success of iodine as compared to oxygen in trapping certain dihydrophenanthrene derivatives for which the competing ring opening is especially fast.³⁶

Tetracyanoethylene³⁷ and diphenyl selenide³⁸ can also be used as dehydrogenating agents.

4.1.3 Phenanthrenes from Dihydrophenanthrenes by Non-oxidative Trapping

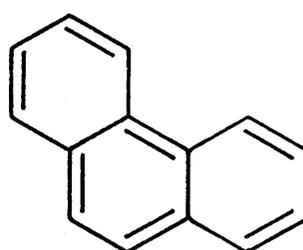
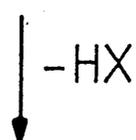
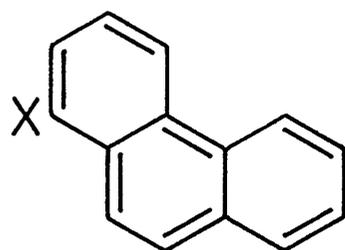
4a,4b-Dihydrophenanthrenes with suitably placed leaving groups can undergo elimination reactions leading to phenanthrenes in the absence of oxidants. This behaviour is found, for example, in the photocyclisation of certain ortho-substituted stilbenes. As shown in Scheme 5, an ortho-substituted stilbene exists in solution as a mixture of conformers (24a) and (24b); therefore, uv irradiation produces two isomeric dihydrophenanthrenes (25a) and (25b), respectively. For certain substituents X, dihydrophenanthrene (25b) can be trapped to give phenanthrene (19) by a highly exothermic elimination reaction; the trapping of the isomeric dihydrophenanthrene (25a) requires an oxidant. If oxidants are excluded during irradiation in such systems, the reversibility of formation of the 1-substituted dihydrophenanthrene (25a) allows the overall photoreaction to proceed in high yield by way of eliminative trapping of the 4a-substituted dihydrophenanthrene (25b). Thus stilbenes with ortho-methoxyl substituents photocyclise under a nitrogen atmosphere with elimination of methanol.³⁹

Elimination of HX involves abstraction of the 4b-hydrogen from the 4a-substituted dihydrophenanthrene (25b) (by O_2 , $HO_2\cdot$, $X\cdot$ or a solvent derived radical) to give a radical of type (27) that subsequently undergoes unimolecular expulsion of X. [Scheme 6]. This expulsion is estimated from bond dissociation energies to be exothermic for $X = CH_3$, CH_3O , Cl , Br and I but endothermic for $X = H$, F and C_6H_5 .³⁵



(25a)

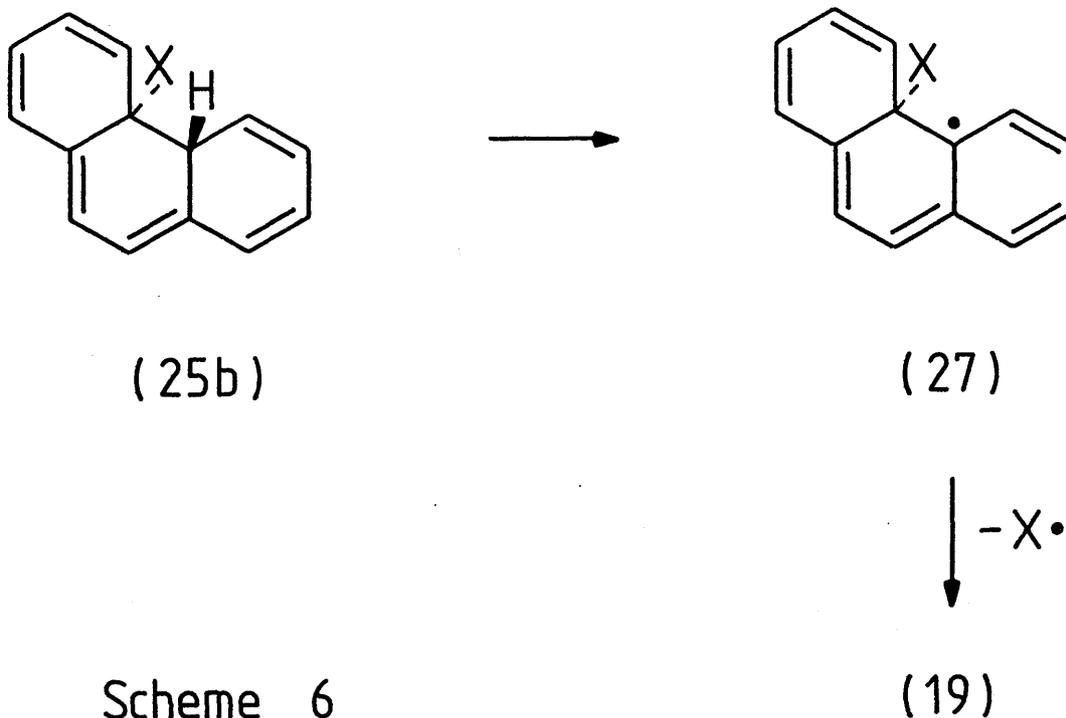
(25b)



(26)

(19)

Scheme 5

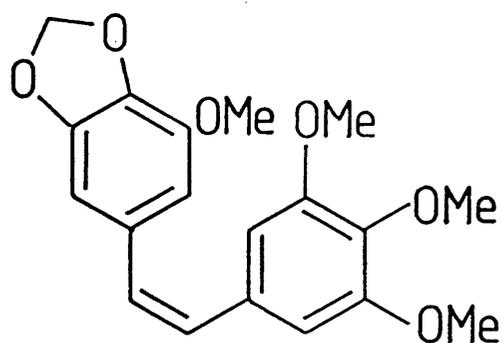


4.2 Phenanthrenes from 2-Halostilbenes

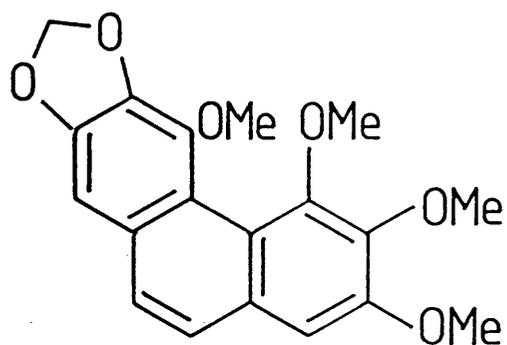
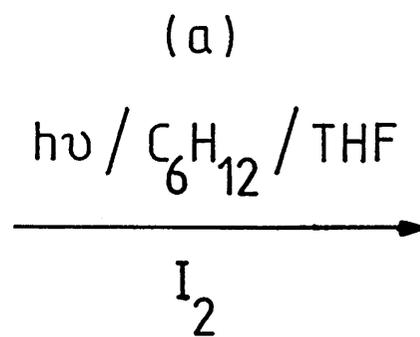
4.2.1 2-Bromostilbenes

Oxidative photocyclisation of stilbene (28) gives a 1:1 mixture of phenanthrenes (29) and (30) while stilbene (31), with a blocking 2-bromo substituent, gives phenanthrene (32) as the sole product under the same conditions⁴⁰ [Scheme 7]. To date, in the vast majority of systems investigated, oxidative photocyclisation of bromostilbenes has resulted in retention of the bromo substituent, irrespective of its position^{41,42,43} [Scheme 8].

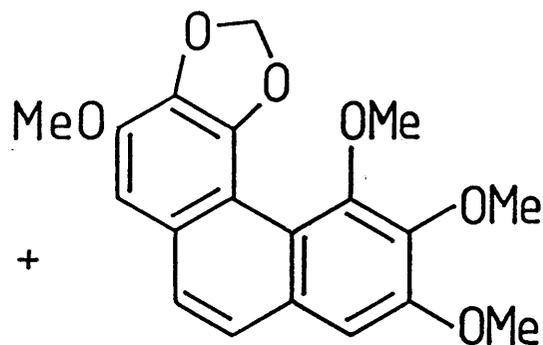
Non-oxidative photocyclisation of 2-bromostilbenes was first used by Cava's group⁴⁴ in 1970 for the synthesis of the aporphine alkaloid glaucine (41) [Scheme 9]. Calcium carbonate was used as an acid scavenger for hydrogen halide formed by aromatisation of the presumed dihydrophenanthrene intermediate. Three years later Cava's



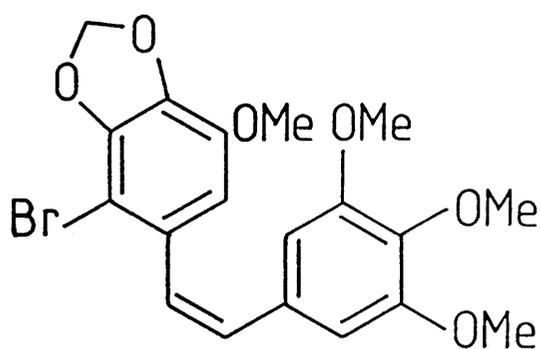
(28)



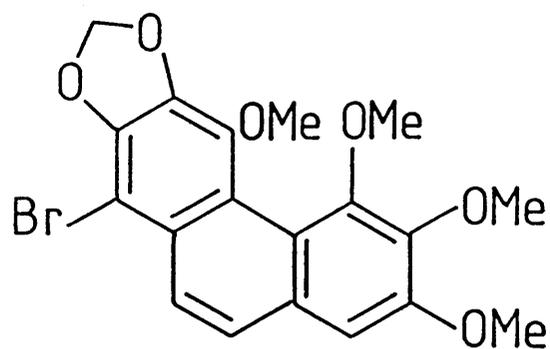
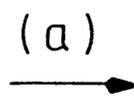
(29) 40%



(30) 40%



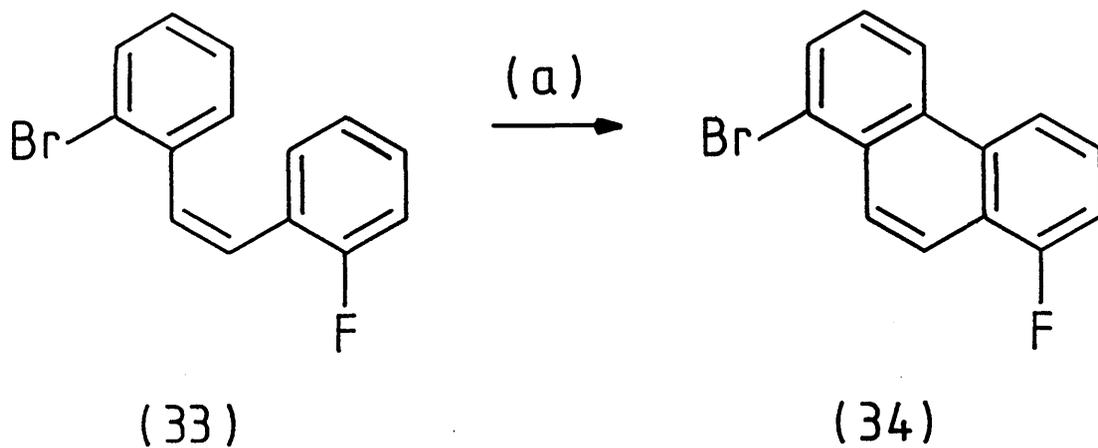
(31)



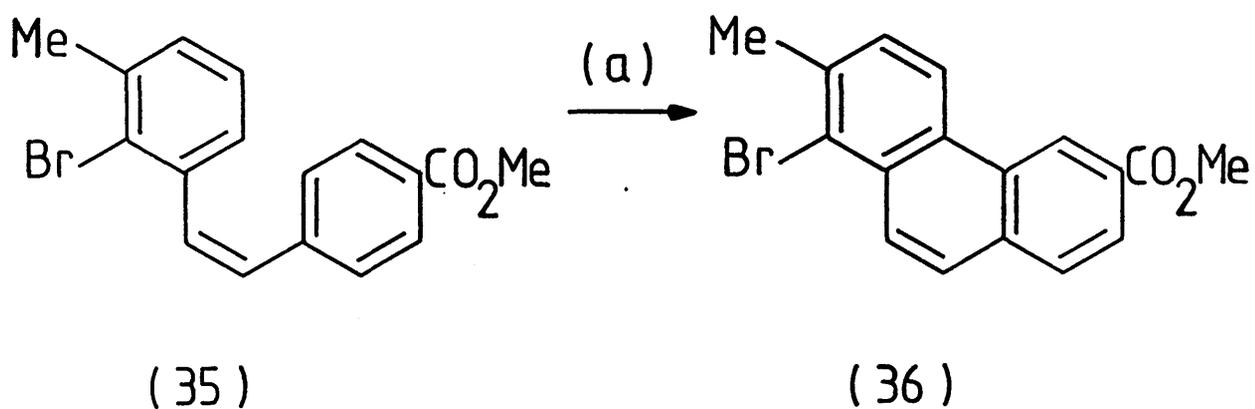
(32) 84%

Scheme 7

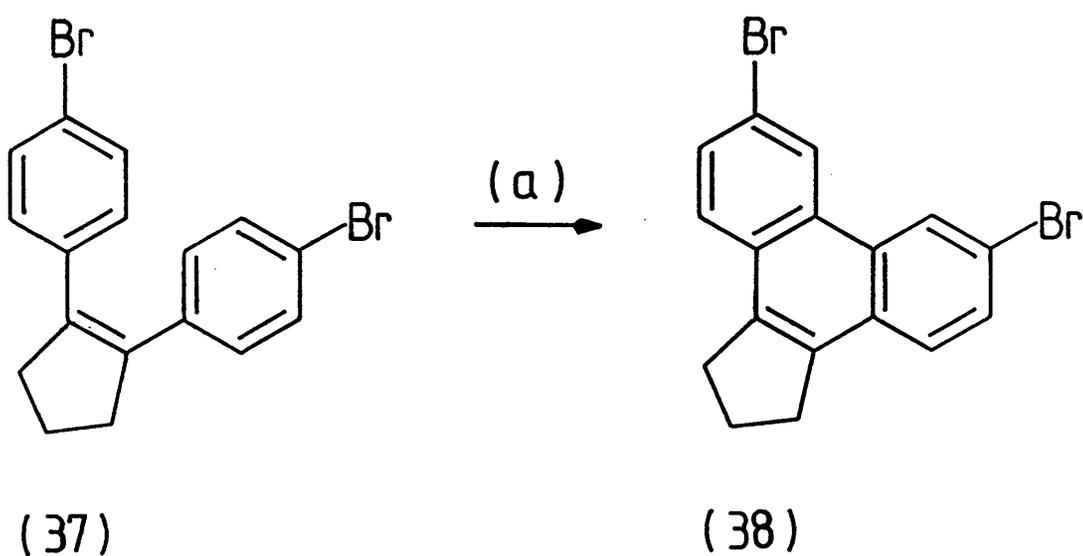
Ref. 41

(a) $h\nu / I_2 / C_6H_{12} / THF$ 

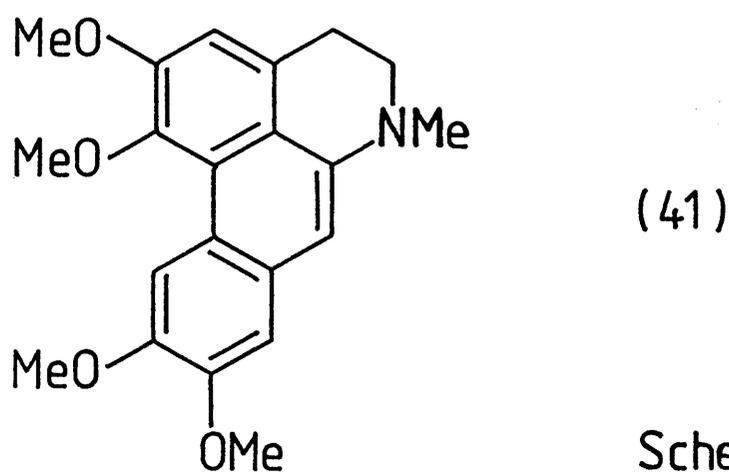
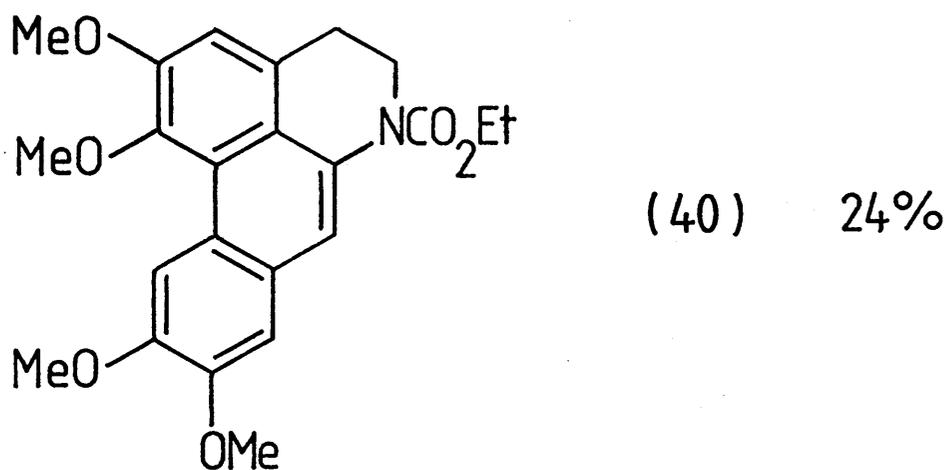
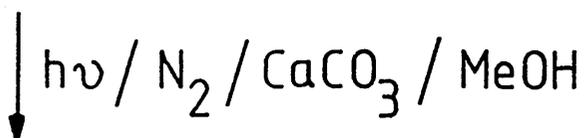
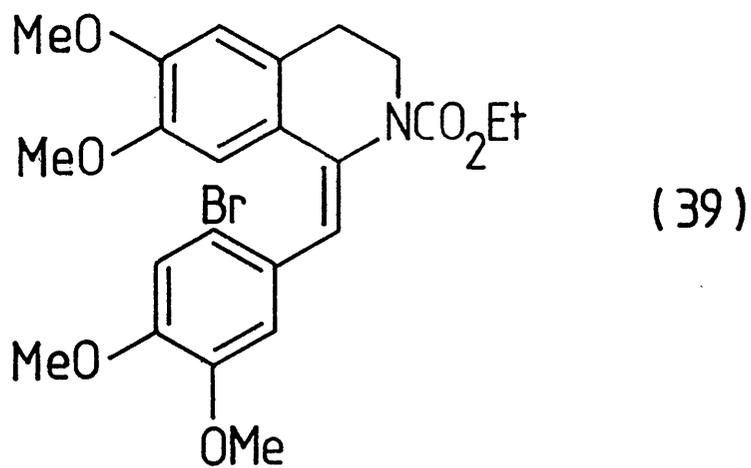
Ref. 42



Ref. 43



Scheme 8

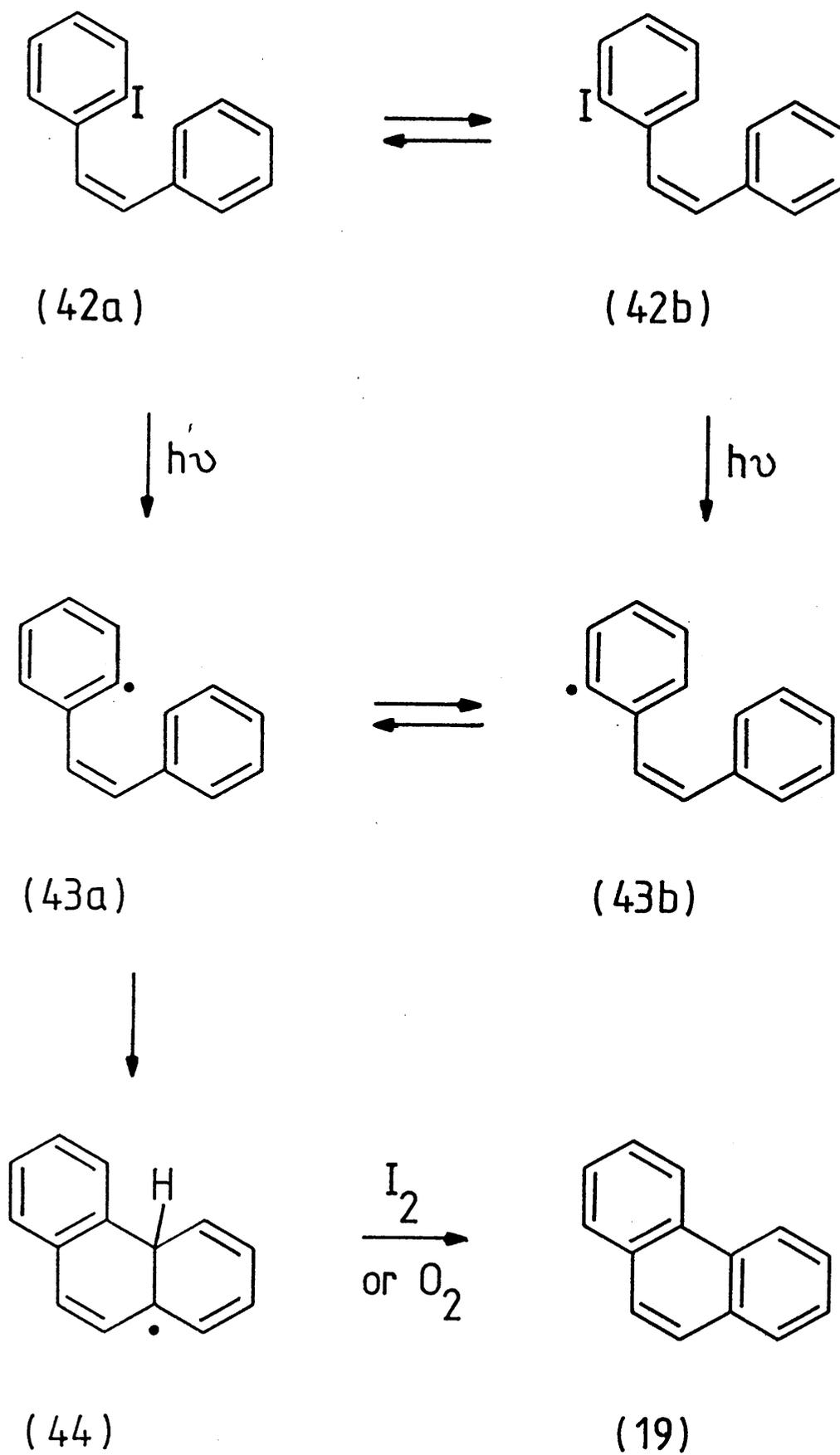


Scheme 9

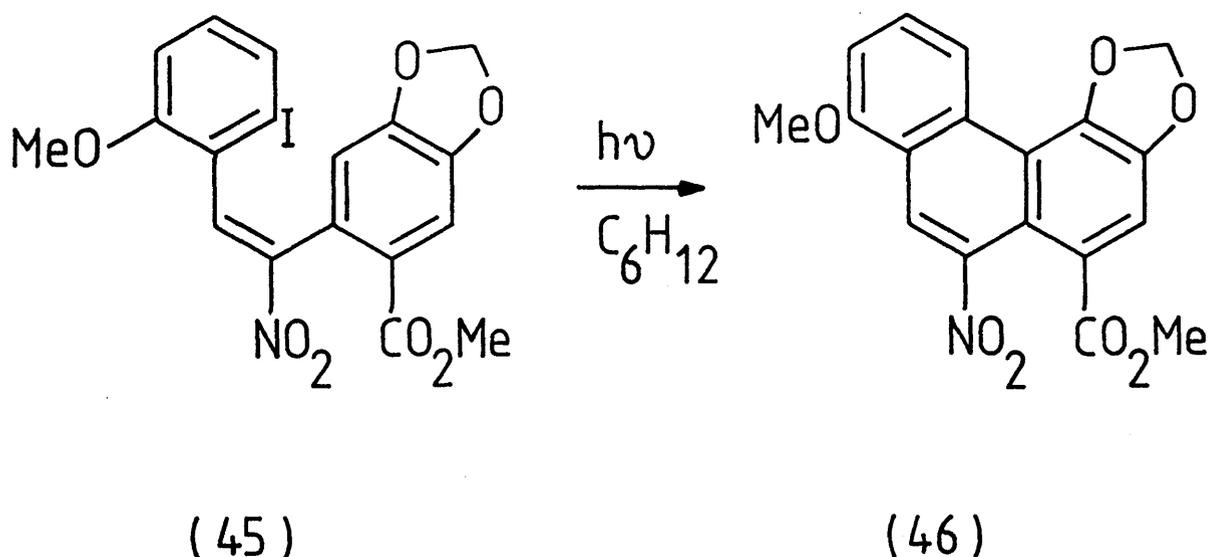
group⁴⁵ reported an improved yield (59%) of phenanthrene (40) from photocyclisation of 2-bromostilbene (39) in deoxygenated benzene/tert-butanol containing potassium tert-butoxide. Cava proposed that the presumed 4b-bromodihydrophenanthrene intermediate can smoothly undergo a concerted E2 elimination in the presence of tert-butoxide but can decompose only solvolytically (E1) in the presence of calcium carbonate, thus accounting for the improved yield of cyclised product.

4.2.2 2-Iodostilbenes

The photochemistry of stilbenes with 2-iodo substituents is complicated by another possible mechanistic pathway leading to phenanthrenes in addition to that proceeding by way of dihydrophenanthrene intermediates. This other pathway involves photolysis of the carbon-iodine bond followed by intramolecular free radical arylation as illustrated in Scheme 10 for the parent 2-iodostilbene system (42). Sometimes this route to phenanthrenes is advantageous synthetically. For example, nitro substituted phenanthrenes are not produced from the corresponding stilbenes by the electrocyclic pathway, but uv irradiation of the 2-iodo analogues results in cyclisation. This route was first used by Kupchan and Wormser⁴⁶ in 1965 for the synthesis of (46), the methyl ester of the natural product aristolochic acid I [Scheme 11].



Scheme 10

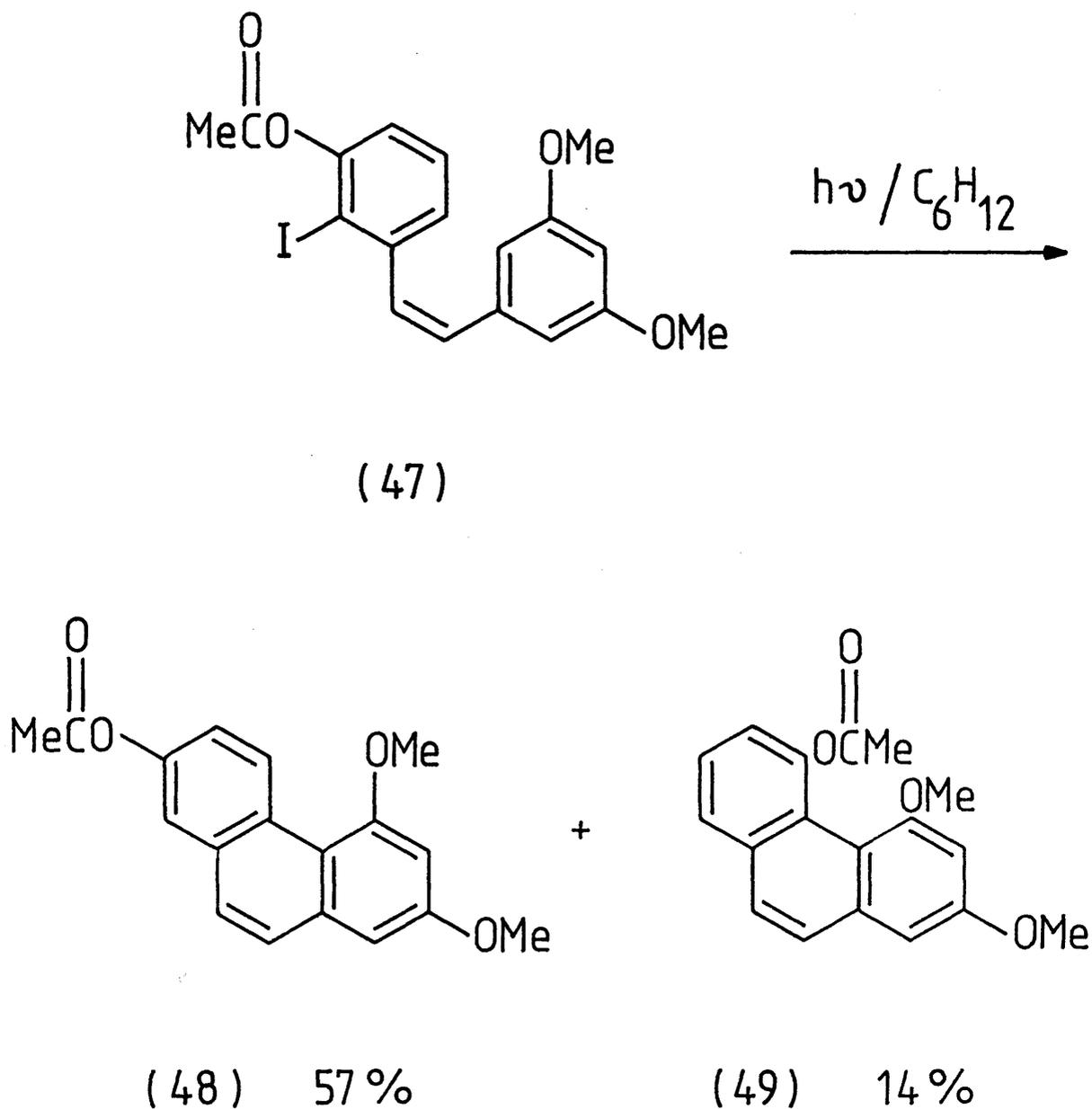


Scheme 11

In a solvent with easily abstractable hydrogen atoms (e.g. cyclohexane) the formation of phenanthrene (19) might follow one or more of the following pathways in which the 2-iodo substituent plays a trivial role:

- (a) photolysis of (42b) to give radical (43b) (Scheme 10), followed by hydrogen transfer from the solvent and oxidative photocyclisation of the resulting stilbene, perhaps with the iodine generated in situ serving as the oxidant;
- (b) a sequence analogous to pathway (a), starting with photolysis of the trans-isomer of the iodostilbene;
- (c) oxidative photocyclisation of stilbene (42b) to give 1-iodophenanthrene, with subsequent photolysis of the carbon-iodine bond and hydrogen transfer from the solvent to give phenanthrene (19).

At least one of the latter three types of pathway must be involved, for example, in the photocyclisation of the 3-acetoxy-2-iodostilbene (47) in cyclohexane because the major product is the 7-acetoxyphenanthrene (48) rather than the 5-acetoxy isomer (49)⁴⁷ [Scheme 12].



Scheme 12

The synthesis and photocyclisation of 2-halostilbenes is discussed in more detail in Chapters 2 and 3 of this thesis.

5. Practical Aspects of Stilbene Photocyclisations^{25,48}

5.1 Lamps

Many different commercially available mercury discharge lamps can be used as sources of uv light for stilbene photocyclisations on a preparative scale. Among the most popular of these are Hanovia medium pressure immersion lamps and Rayonet low pressure lamps. In medium pressure lamps the pressure of mercury lies in the range of 1 to 10 atmospheres, being determined by the amount of mercury introduced into the tube during manufacture, and the operating temperature of the lamp, which is in the region of 600 to 800°C. Low pressure lamps operate at a lamp tube temperature just above ambient (40-50°C usually being the optimum), at which the vapour pressure of mercury is around 10^{-5} atmospheres. High pressure lamps are also available at operating pressures from 10 to several hundred atmospheres. The high pressure lamp contents can be mercury, or a rare gas such as xenon, or a mixture of mercury and rare gas.

The fundamental requirement of the light source is emission in the wavelength region that corresponds to the appropriate electronic absorption band of the reactant. Medium and high pressure lamps emit throughout the region of 200-400 nm. The spectral distribution of the radiation emitted by an undoped medium pressure mercury lamp is mainly in the form of sharp, discrete lines (Fig. 1). Metal halide doped lamps

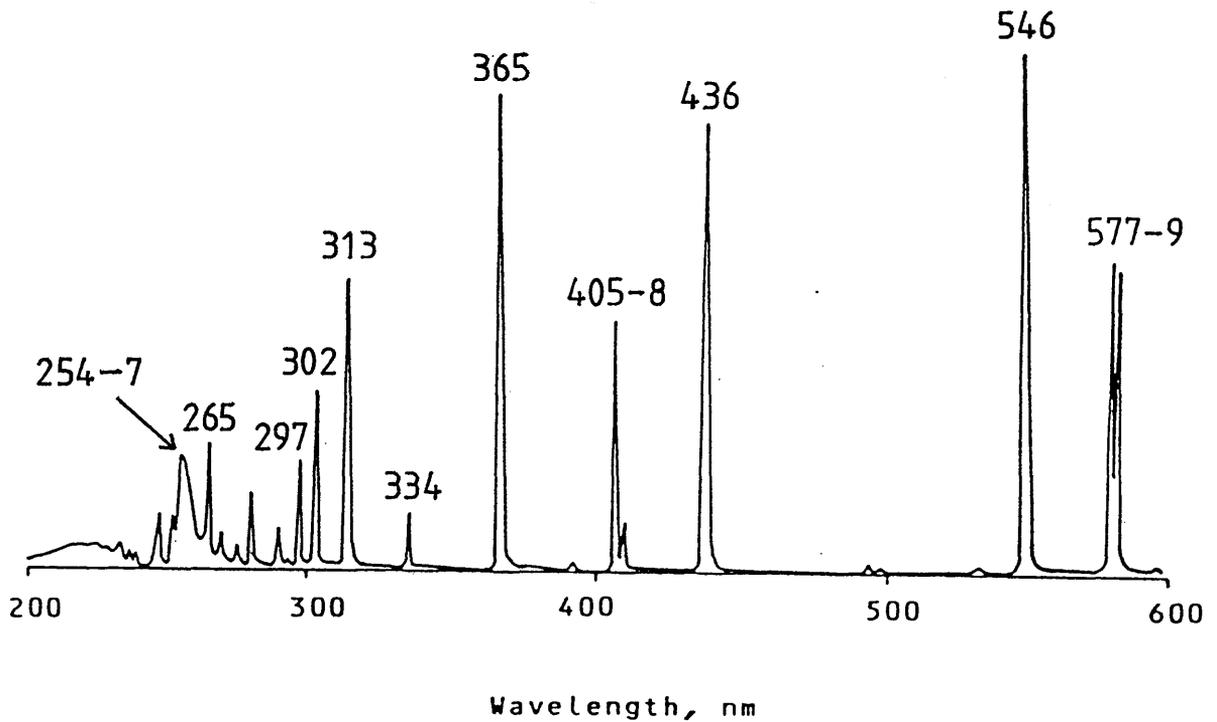


Fig. 1 Spectral output of undoped medium pressure mercury lamp

produce additional lines characteristic of the metal dopant (e.g. gallium, magnesium, iron, thallium). The main feature of the spectral distribution emitted by high pressure lamps is the presence of a strong continuum, which becomes more dominant for the higher operating pressures. Around 90% of the radiation emitted by low pressure mercury lamps consists of the mercury resonance lines at 254 nm and 185 nm, produced in the ratio of approximately 6:1. Thus these lamps are not well suited for stilbene photocyclisations because the products usually absorb more strongly than the reactants in the region of 200-300 nm. Satisfactory results are often obtained, however, with low pressure lamps that are coated on the inside with a material that absorbs the 254 nm radiation and subsequently emits its own characteristic fluorescence at longer wavelengths.

Some light sources are designed to be enclosed in a transparent well with a water cooled jacket and immersed in the solution to be irradiated. Surrounding of the light source by the reaction mixture in this way maximises the effectiveness with which the emitted photons are captured by the reactant molecules. Other light sources are designed to be mounted outside the reaction vessel.

The use of a quartz immersion well (or a quartz reaction vessel with an external light source) allows light of all wavelengths above about 200 nm to enter the reaction mixture. For some photocyclisations higher chemical yields are obtained by employing a Pyrex immersion well (or a Pyrex reaction vessel). This excludes from the reaction mixture light of wavelengths below about 300 nm and thereby protects the product from photochemical destruction.

5.2 Choice of Solvent

In stilbene photocyclisations and in photochemical reactions generally, the solvent must be transparent in the wavelength region that is effective in bringing about reaction. Fortunately there is a fairly wide choice of solvents which transmit down to quite short wavelengths including many alcohols, ethers, hydrocarbons and water. The wavelength below which a solvent is no longer transparent is called the cut-off wavelength. Cut-off wavelengths for a selection of solvents are given in Table 1.

Table 1. Cut-off wavelengths for a selection of solvents

Solvent	Cut-off wavelength, nm
water	< 190
acetonitrile	190
hexane	195
methanol	205
diisopropyl ether	220
1,2-dichloroethane	225
ethyl acetate	255
benzene	280
toluene	285
pyridine	305
acetone	330

Other requirements of the solvent are that it is free from impurities, especially those which absorb outside the solvent cut-off, and that it should not (unless desired) react with the photoexcited states or with other intermediates involved in the course of the reaction. For example if free radicals are involved, solvents labile to hydrogen abstraction by the free radicals need to be avoided. This can exclude alcohols, ethers and saturated hydrocarbons from consideration. Benzene, acetonitrile and tert-butanol are relatively, but not completely, unreactive towards free radicals.

5.3 General

The irradiation time required for optimal conversion of reactant to product in a photocyclisation reaction depends on several factors: the type of light source and its positioning relative to the reaction mixture; the transparency of the material through which the light enters the solution; the purity of the reactant and the solvent; the effectiveness with which the reaction mixture is stirred; and the scale of the reaction. Because so many factors are operative, the reported duration of irradiation in a published description of a particular photoreaction is not a reliable guide for prediction of the irradiation time that would be required for the repetition of the work by an independent investigator. Therefore, it is essential to monitor the progress of a photocyclisation to determine when to stop the irradiation. Any convenient analytical method can be employed, such as glc, tlc or uv spectroscopy.

During the course of a photoreaction the wall of the immersion well (or reaction vessel) through which the light enters the reaction

mixture often becomes coated with opaque material, thereby interfering with completion of the reaction (as revealed by monitoring). In this event the reaction should be interrupted and the immersion well and reaction vessel cleaned; it is also advisable to filter the reaction mixture through a short column of alumina to remove highly coloured or polymeric materials before returning the mixture to the cleaned reaction vessel for resumption of irradiation.

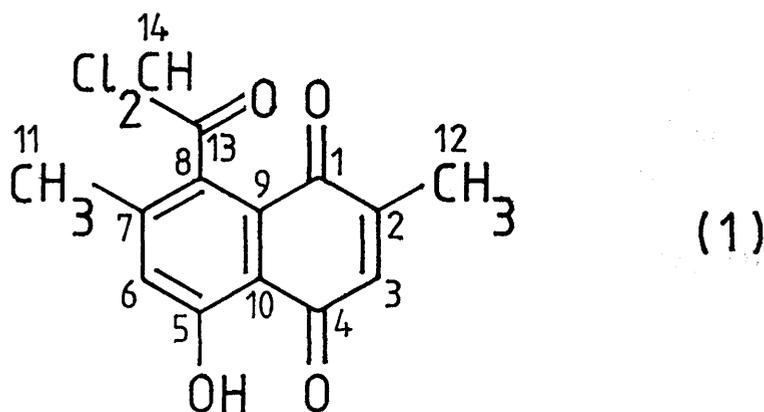
For some photocyclisations it is desirable to exclude dissolved oxygen. Three techniques can be employed for this purpose: degassing the solution under high vacuum by a series of freeze-thaw cycles and then sealing the reaction vessel before irradiation; heating the solution at reflux and then allowing it to cool under an atmosphere of an inert gas such as nitrogen or argon before irradiation; and continuously purging the solution with nitrogen or argon during irradiation. This last method is recommended for preparative scale work because of its simplicity and effectiveness.

In most preparative scale photoreactions the absorbance of the reactant is sufficiently high that the light penetrates only an extremely short distance into the reaction mixture. Thus stirring is very important in order to remove the product from this very thin reaction zone and bring in fresh reactant.

A more detailed discussion concerning experimental methods in photochemical syntheses is given elsewhere.⁴⁹

1.1 Introduction

In 1956 Gremmen⁴ described some new strains of the species Mollisia caesia and M. fallens which, when cultivated on malt agar, produced a characteristic yellow crystalline pigment in the medium. The pigment, named mollisin, showed strong antifungal activity on several types of mould. It was identified as 8-dichloroacetyl-5-hydroxy-2,7-dimethyl-1,4-naphthoquinone (1) by Overeem and van der Kerk⁵ in 1964 on the basis of chemical and spectroscopic evidence. Several groups⁵⁰⁻⁵⁴ have investigated the biosynthesis of mollisin (1) because of its unique structure; it is the only known natural product to contain an aromatic dichloroacetyl group.

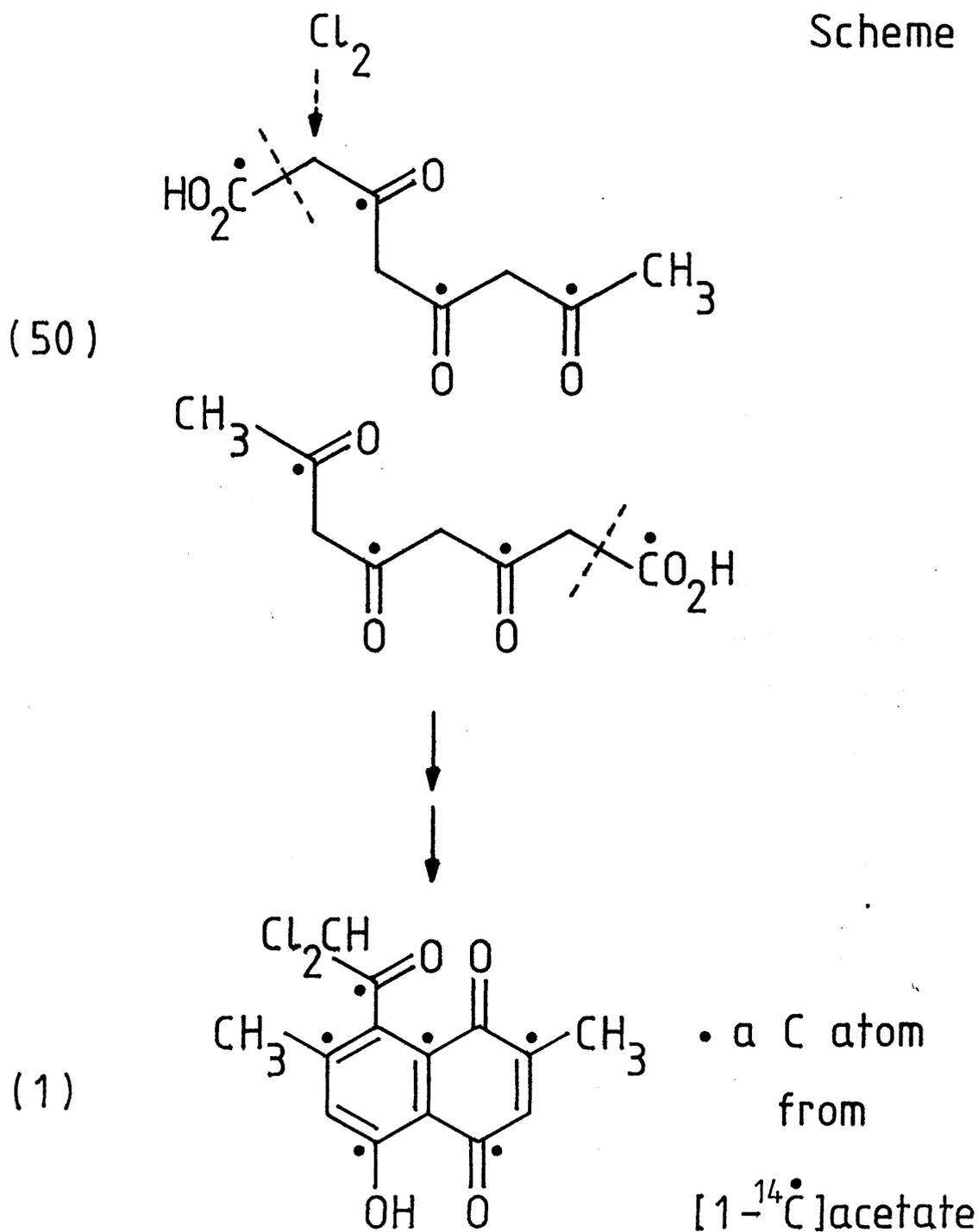


Mollisin has a relatively simple carbon framework and is highly oxygenated, therefore implying that it is derived from acetic acid via the polyketide pathway. This origin was first proposed by Overeem

and van der Kerk⁵ and was later confirmed by Bentley and Gatenbeck⁵¹ through addition of ¹⁴C-labelled substrates to malt agar cultures of *M. caesia*. [1-¹⁴C]Acetate and [1,3-¹⁴C]malonate were incorporated into mollisin and carbon atoms 2, 4, 5, 7, 9 and 13 were found to be labelled. [¹⁴CH₃]Methionine was not utilised for mollisin biosynthesis. Bentley and Gatenbeck stated that if the nucleus and dichloroacetyl side chain are constructed from a single polyketide chain, then at least one methyl group must be derived from a C₁ addition. The result of feeding [¹⁴CH₃]methionine ruled out the possibility of a C₁ addition and thus implies that C-11 and C-12 are derived from C-2 of acetate. To accommodate these results they proposed a two chain mechanism in which the dichloroacetyl group is formed by chlorination of an active methylene unit followed by decarboxylation [Scheme 13]. Although a relatively uncommon situation, it has been shown by Gatenbeck and Mosbach⁵⁵ that two chains are used in the biosynthesis of citromycetin; furthermore, the participation of an acetoacetyl unit as a second chain has been described in rotiorin biosynthesis by Holker *et al.*⁵⁶

In 1970, Tanabe and Seto⁵² used ¹H nmr spectroscopy to determine the labelling pattern in isotope enriched mollisin from [2-¹³C]acetate. The results demonstrated that carbon atoms 3, 6, 11, 12 and 14 of mollisin are derived from the methyl group of acetate. Carbon atoms 1, 8 and 10 were shown also to originate from the methyl group of acetate by Casey *et al.*⁵³ on repeating this experiment.

Three years later, Seto *et al.*⁵⁴ excluded Bentley and Gatenbeck's proposal for mollisin biosynthesis on evidence from feeding [1,2-¹³C]acetate to the fungal medium. The ¹³C nmr spectrum of



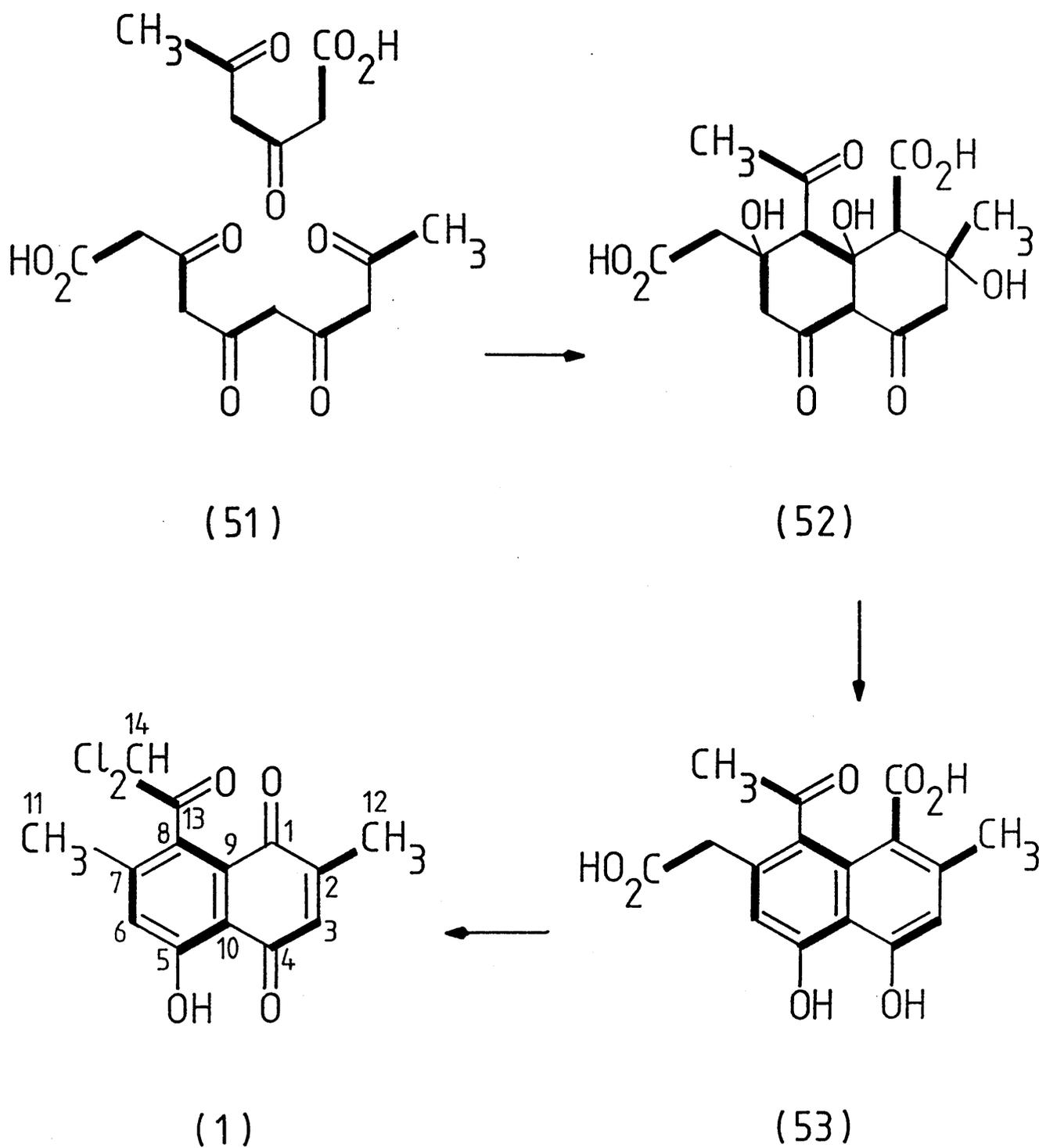
mollisin isolated in this experiment showed ^{13}C - ^{13}C coupling between C-2 and C-12, C-3 and C-4, C-5 and C-10, C-6 and C-7, C-8 and C-9, and C-13 and C-14. Thus these pairs of carbon atoms are derived from the same molecule of acetic acid. Coupling between C-13 and C-14

would not be expected on the basis of Bentley and Gatenbeck's proposal shown in Scheme 13. Seto *et al.* suggested that the pathway depicted in Scheme 14 is actually involved in the formation of mollisin (1).

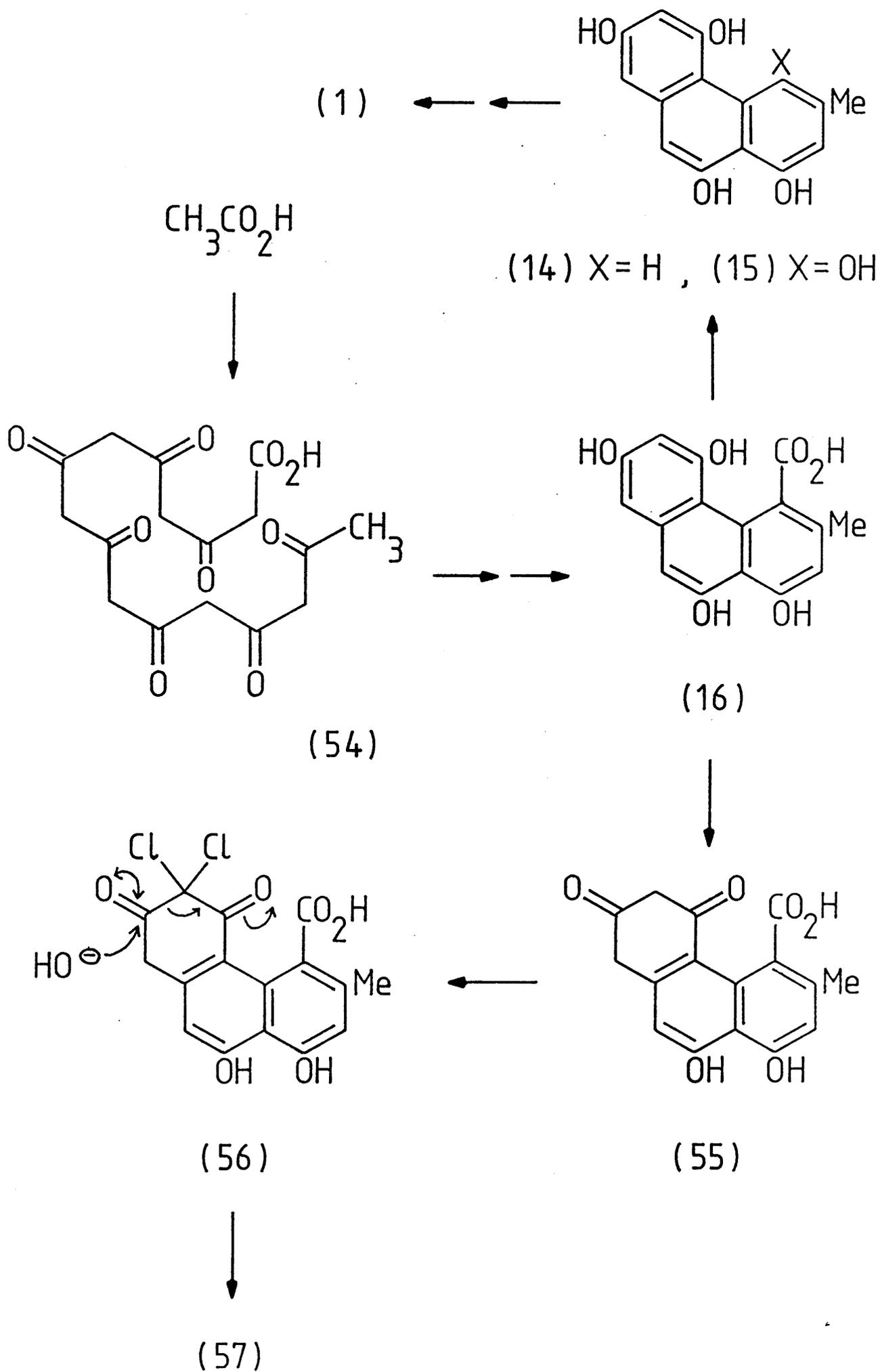
In 1975 McInnes and Wright⁵⁷ proposed that the biogenetic pathway depicted in Scheme 15 is also plausible. This pathway involves condensation of the octaketide chain (54) to produce the phenanthrene derivative (16). Tautomerism of (16) yields the 5,7-dioxo intermediate (55) which then undergoes chloroperoxidase enzyme mediated dichlorination at the active methylene group. Nucleophilic attack by hydroxyl at the C-7 carbonyl group cleaves the ring giving (57), then loss of carbon dioxide occurs followed by a proton shift to afford the naphthalene derivative (59). (59) is readily transformed into mollisin (1) by oxidative decarboxylation followed by dehydrogenation, controlled by the mono-oxygenase and dehydrogenase enzymes respectively. Alternatively, decarboxylation or oxidative decarboxylation of phenanthrene (16) might occur at the start of the sequence giving phenanthrenes (14) and (15) respectively. These phenanthrenes could yield mollisin via a mechanism similar to that outlined in Scheme 15.

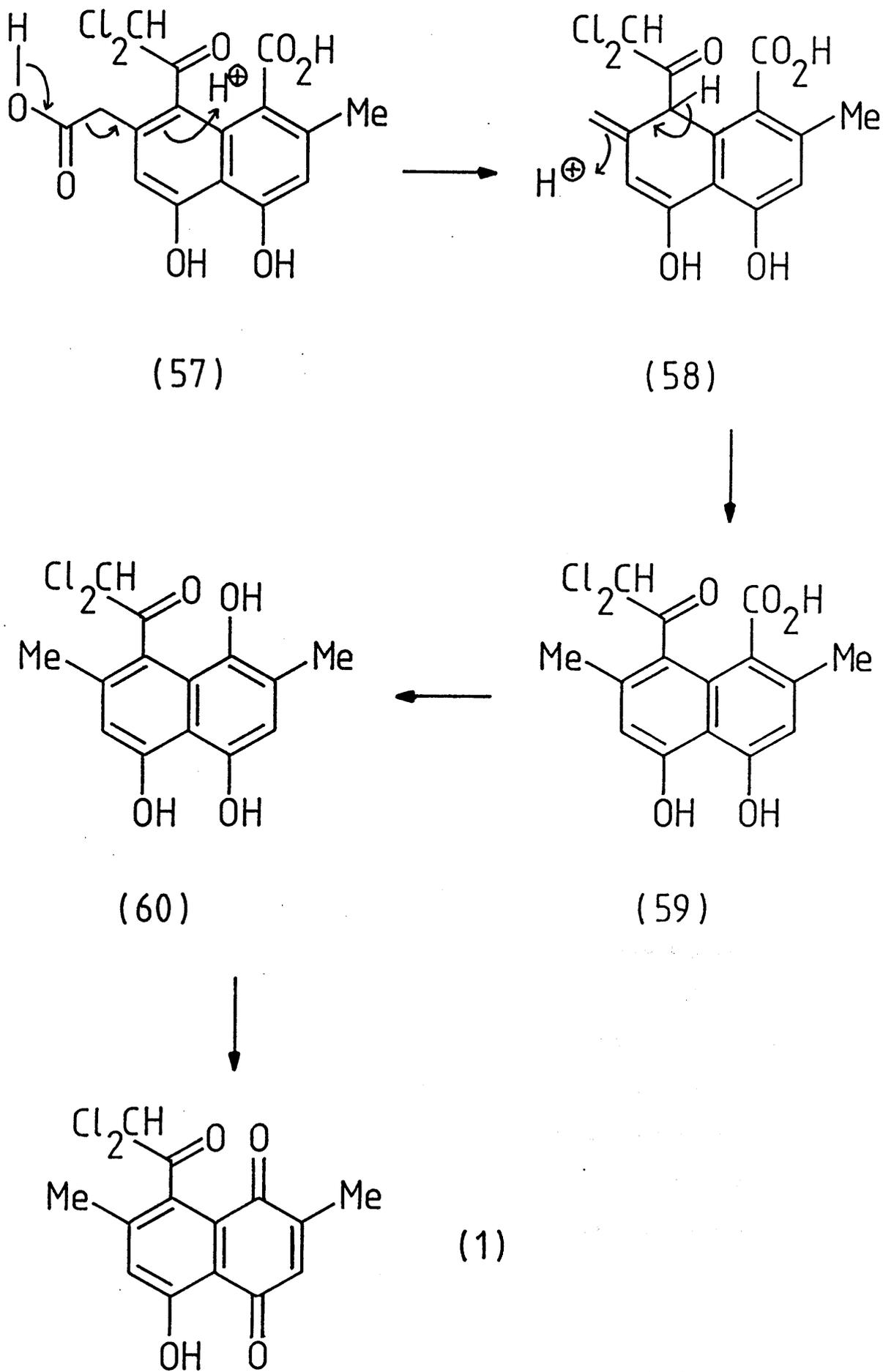
The proposal of McInnes and Wright was declared a null hypothesis by Casey *et al.*⁵³ in 1976, but Simpson⁵⁸ commented in 1977 that "the biosynthesis of mollisin by cleavage of a single octaketide chain would appear to be at least as likely as the two chain pathway proposal".

As described above, the *M. caesia* feeding experiments employing singly (¹³C or ¹⁴C) or doubly (¹³C) labelled acetate have been unable to distinguish between the two postulated biosynthetic routes to mollisin (1) (i.e. Schemes 14 and 15) since both routes are consistent



Scheme 14

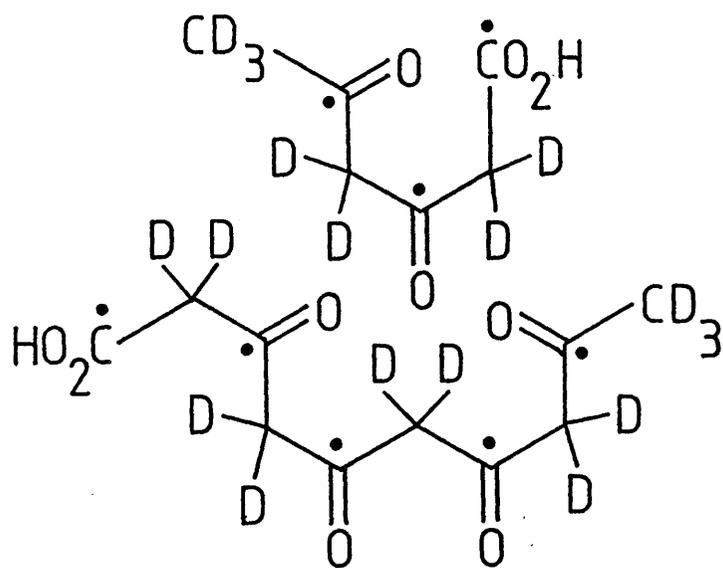




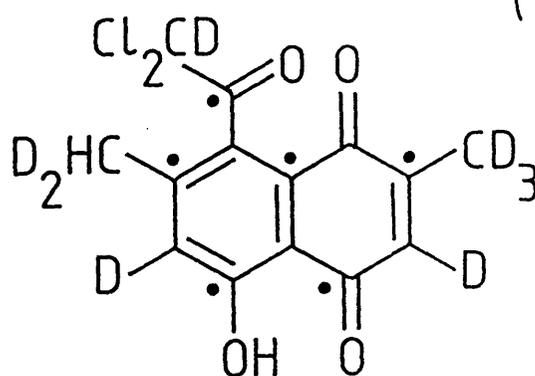
Scheme 15

with the observed labelling patterns. However, if [2- $^2\text{H}_3$, 1- ^{13}C]-acetate is fed to M. caesia then, assuming equal rates of $^1\text{H}/^2\text{H}$ exchange at all positions, the resulting mollisin would have an isotope distribution characteristic of one of the biosynthetic pathways [Scheme 16]. Of course $^1\text{H}/^2\text{H}$ exchange is unlikely to be equivalent at all sites, but (1a) and (1b) in Scheme 16 do represent the maximum possible extent of deuterium labelling in mollisin, provided that one of the two postulated biosyntheses does indeed operate.

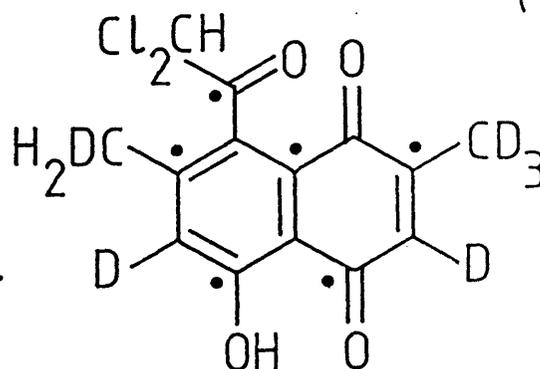
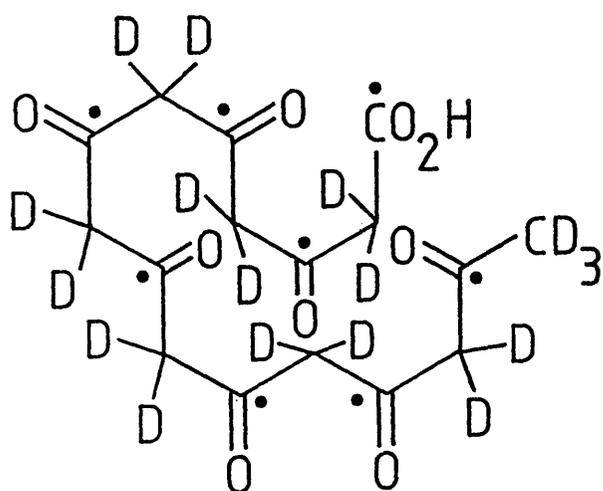
Finnie⁵⁰ fed aqueous solutions of sodium [2- $^2\text{H}_3$, 1- ^{13}C]-acetate after 10, 13, 16 and 19 days growth to malt agar cultures of M. caesia. After 26 days the combined cultures were extracted with ethyl acetate and the extract purified by chromatography to provide a sample of mollisin. This sample was carefully acetylated by the method of Casey et al.⁵³ to give mollisin acetate (61) which is appreciably more soluble than mollisin in organic solvents. ^{13}C nmr spectroscopy of the sample of (61) revealed that the level of enrichment of ^{13}C was only 0.2% above the 1.1% natural abundance background, too small to give a clear indication of the ^{13}C -labelling pattern. (Enrichments must usually be about 0.5-1.0% ^{13}C above natural abundance to be meaningful.⁵⁷) Close examination of the ^{13}C nmr spectrum for geminally shifted resonances indicated the presence of a single deuterium atom at C-6 and two deuterium atoms at C-12. This was confirmed by ^2H nmr spectroscopy. (See Section 1.3 for an explanation of this method of locating deuterium labels in an enriched metabolite). Finnie suggested that rapid $^1\text{H}/^2\text{H}$ exchange reactions in the polyketide might account for the fact that no deuterium was observed at sites (e.g. C-3) where



(1a)



(1b)



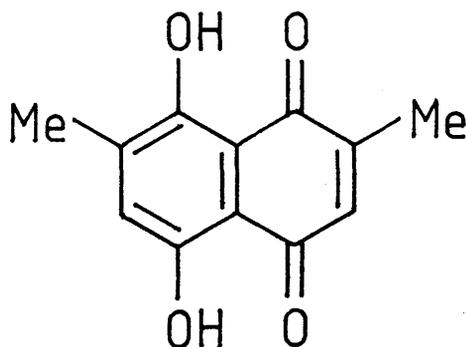
- denotes a carbon atom derived from $[2-^2\text{H}_3, 1-^{13}\text{C}]$ acetate

Results and Discussion

1.2 The Search for New Metabolites of Mollisia caesia

As the overall purpose of a biosynthetic study is, by definition, the identification of the precursors of a natural product, one obvious course is to isolate co-metabolites which can then be identified or rejected as precursors.

Surprisingly, few minor metabolites of M. caesia were detected and with the exception of a red oil which ran just ahead of mollisin on silica, none were present in sufficient amounts to permit characterisation. The red oil, which crystallised on standing, has previously been reported by Bentley and Gatenbeck⁵¹ and identified as 2,7-dimethylnaphthazarin (62). The naphthazarin (62) is proposed to arise through a biological degradation of mollisin and is not thought to be a biosynthetic precursor.⁵¹ Unfortunately, then, no new metabolites of M. caesia were identified.



(62)

1.3 Feeding of Sodium [2-²H₃, 1-¹³C]acetate to *Mollisia caesia*

A second approach to investigating the biosynthesis of a natural product is to feed an isotopically labelled postulated precursor to the organism, followed by isolation of the metabolite of interest, which is then monitored for incorporation of the isotopic label.

The fate of deuterium in biosynthesis may be monitored either directly by ²H nmr spectroscopy or indirectly by ¹³C nmr spectroscopy.^{59,60} If the deuteron is directly attached to a ¹³C atom then the ¹³C nmr signal for that carbon is shifted, normally upfield, and shows deuterium coupling. This technique is disadvantaged by the signal to noise ratio of the shifted signal being reduced by poor relaxation, signal multiplicity and loss of nuclear Overhauser effects. If the deuteron is placed β to the ¹³C nucleus, then again an upfield shift in the ¹³C nmr spectrum results but the ²H-¹³C coupling over two bonds is negligible, the shifted signal is therefore a singlet and the level of enrichment can more easily be determined as the problems with relaxation and NOE are avoided. Thus the ¹³C nmr spectrum of a metabolite enriched from [2-²H₃, 1-¹³C]acetate would show a geminal isotope shift of c. 0.1 ppm per deuteron β to the ¹³C nucleus and the magnitude of this shifted resonance would be proportional to the level of deuterium incorporation.

¹³C nmr spectroscopy also permits the ¹³C-labelling pattern in an enriched metabolite to be determined directly from differences in the intensities of corresponding resonances in the ¹³C nmr spectra of naturally occurring and labelled metabolites.⁵⁷ Enrichments must usually

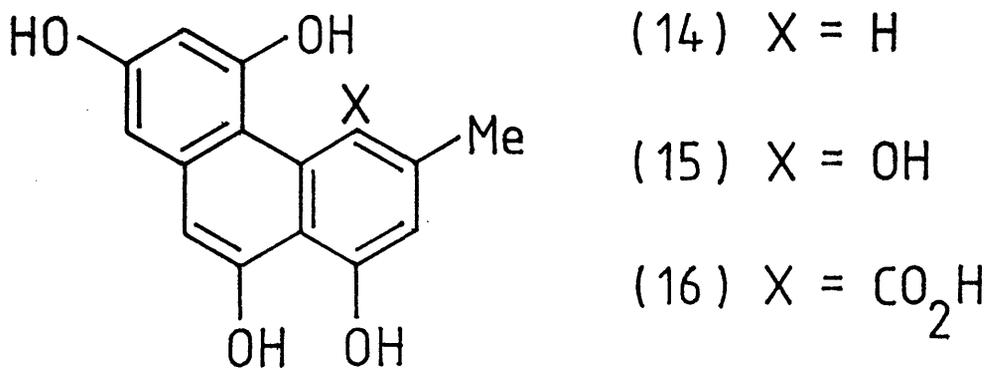
be about 0.5-1.0% ^{13}C above natural abundance to be detectable by the difference method. Thus ^{13}C nmr spectroscopy is a powerful tool in elucidating the ^{13}C - and ^2H -labelling patterns and levels of incorporation in a metabolite enriched from $[2\text{-}^2\text{H}_3, 1\text{-}^{13}\text{C}]\text{acetate}$.

Recall that Finnie⁵⁰ fed aqueous solutions of sodium $[2\text{-}^2\text{H}_3, 1\text{-}^{13}\text{C}]\text{acetate}$ after 10, 13, 16 and 19 days growth to agar cultures of M. caesia and after 26 days growth found that the resulting mollisin acetate contained a single deuterium atom at C-6 and two deuterium atoms at C-12. The ^{13}C -labelling pattern could not be determined as the level of enrichment of ^{13}C in the sample was only 0.2% above the 1.1% natural abundance background.

In the present study, it was thought that by varying the feeding technique better levels of incorporation might be achieved, enabling the ^{13}C - and ^2H -labelling patterns to be clearly established. The method of feeding used in the present study involved applying a water suspension of the M. caesia culture to the surface of Blakeslee malt extract agar containing sodium $[2\text{-}^2\text{H}_3, 1\text{-}^{13}\text{C}]\text{acetate}$ and incubating at 25°C for 21 days. The combined cultures were continuously extracted with ethyl acetate overnight and the organic extract purified by column chromatography over silica to afford mollisin. This sample was acetylated to give mollisin acetate and analysed by ^{13}C and ^2H nmr spectroscopy. Unfortunately, the level of ^{enrichment} incorporation of ^{13}C averaged only 0.1% (range 0.02-0.26%), again too low to give a clear indication of the ^{13}C -labelling pattern. The ^{13}C nmr spectrum contained no obvious β -shifts, even on expansion of the signals, but the ^2H nmr spectrum indicated the presence of deuterium

at the C-2 methyl group. Thus no new information about the biosynthesis of mollisin was derived from this experiment.

Hence it was proposed to prove or reject the ^{single} ~~two~~ chain pathway to mollisin depicted in Scheme 15 by conducting feeding experiments with the deuterium labelled phenanthrenes (14)-(16). Higher levels of incorporation into mollisin are likely to be achieved if the hypothesis is correct since these are late intermediates. Furthermore, these compounds are likely to be highly reactive owing to their polyphenolic nature and so require to be protected by acetylation. It is assumed that on feeding these acetate moieties would be enzymatically cleaved to give the free phenols.



Subsequent chapters discuss various synthetic strategies to the postulated biosynthetic intermediates (14)-(16).

CHAPTER 2

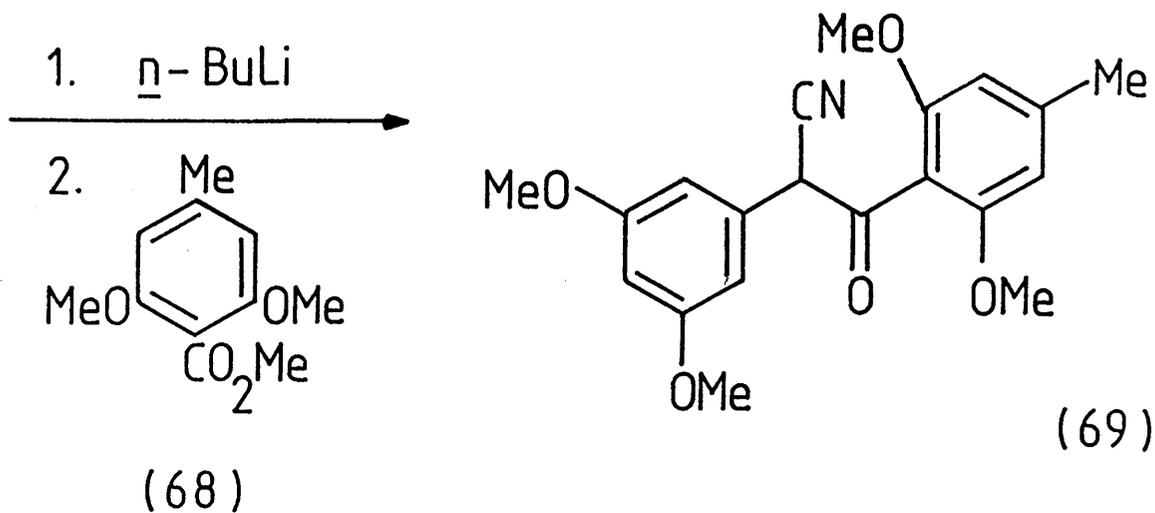
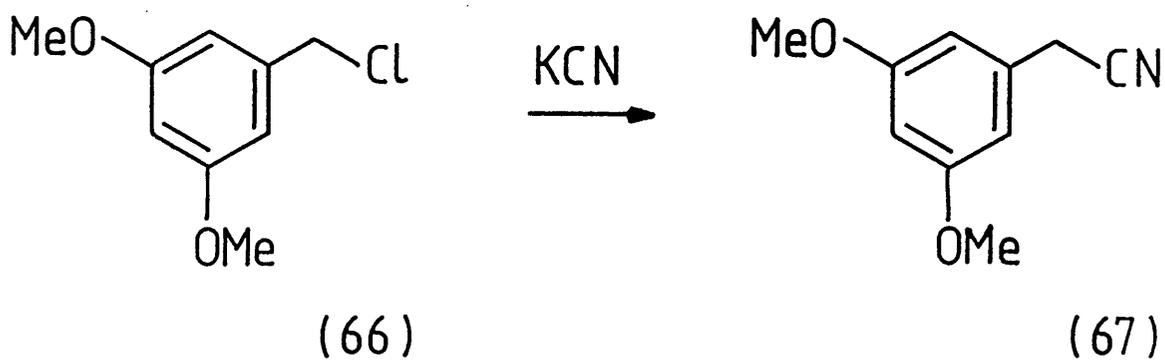
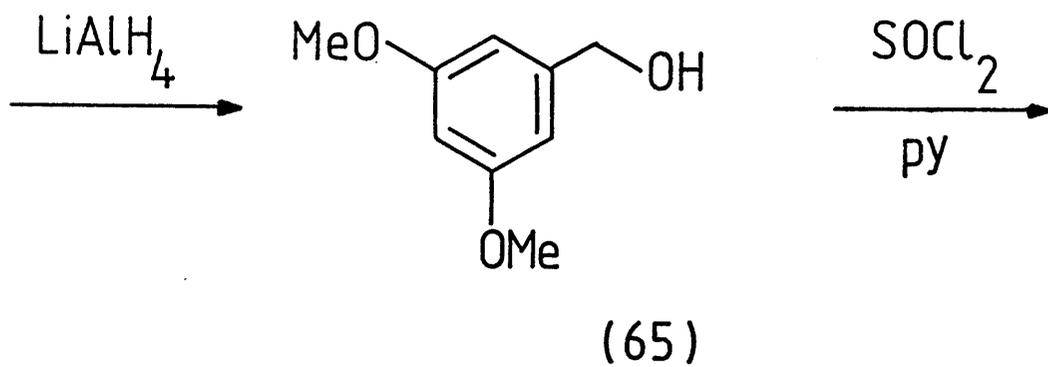
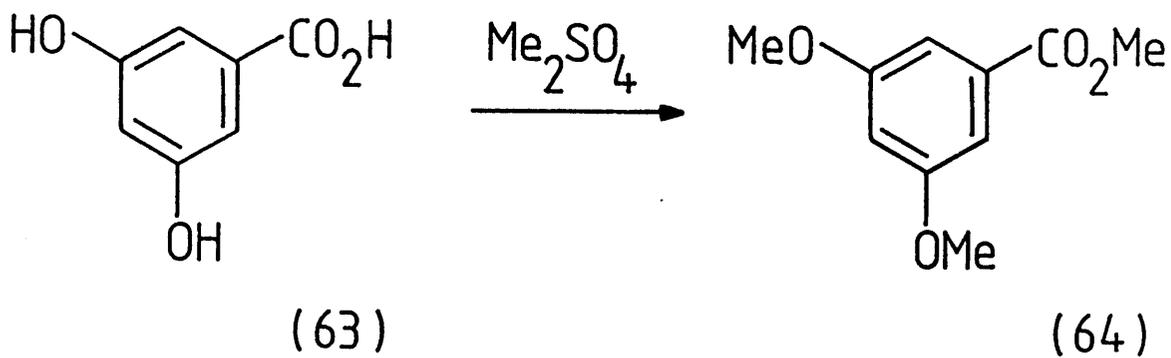
The Synthesis, Properties and Photochemistry of 2-Halo- and 2,6-Dihalo- α -cyanostilbenes

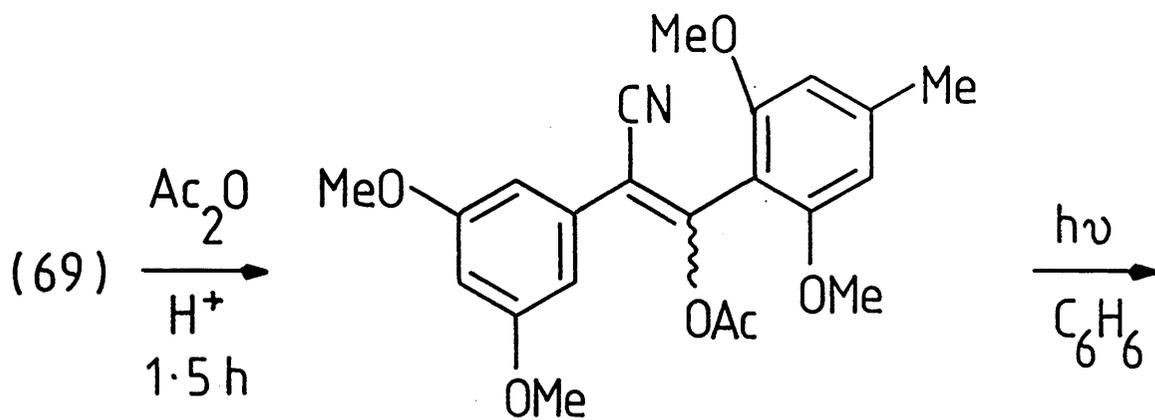
2.1 Introduction

As described in the previous chapter, the biosynthetic study of mollisin (1) requires the synthesis of deuterium labelled hydroxy-phenanthrenes.

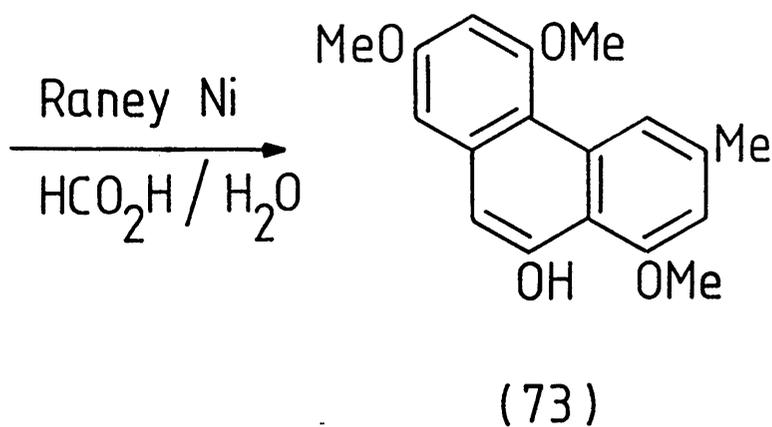
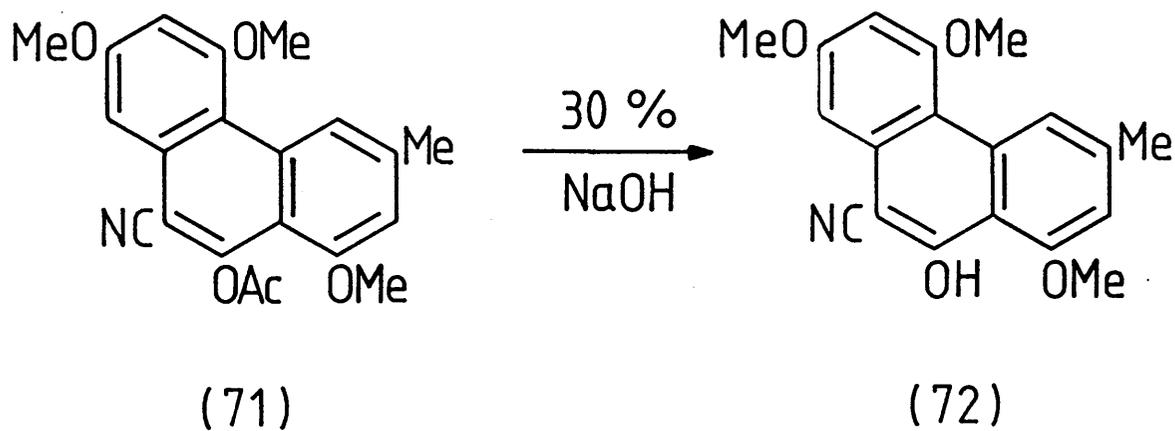
Also in connection with investigating the biosynthesis of mollisin (1), Finnie and Hill⁶¹ devised a synthesis of 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) involving photocyclisation of stilbene (70) as the key step [Scheme 17]. Unfortunately, treatment of (73) with boron tribromide or trimethylsilyl iodide failed to effect complete demethylation to give the target phenanthrene (14).⁵⁰ The synthesis involved production of 3,5-dimethoxybenzyl cyanide (67) from commercially available 3,5-dihydroxybenzoic acid (63) via the route of Hinchliffe.⁶² Treatment of the nitrile (67) with 2.2 equivalents of n-butyl lithium formed the dianion, which was acylated with methyl 2,6-dimethoxy-4-methylbenzoate (68) to give the β -keto nitrile (69) in 65% yield. A mixture of E- and Z-stilbenes (70) was obtained upon reaction of (69) with acetic anhydride in the presence of a catalytic amount of concentrated sulphuric acid for 1.5 hours. Irradiation of (70) in benzene yielded phenanthrene (71) via elimination of methanol from the Z-isomer. The acetoxy group of (71) was hydrolysed by base and then the cyano group of (72) was removed in 42% yield by reaction with Raney nickel in aqueous formic acid.

The synthesis outlined in Scheme 17 would be less efficient for the preparation of the 4-substituted phenanthrenes (15) and (16) since the Z-stilbene exists in solution as a mixture of two conformers [(74a) and (74b)] and so two products [(75a) and (75b)] would be formed in





(70) $\underline{E} : \underline{Z} = 3 : 1$



Scheme 17

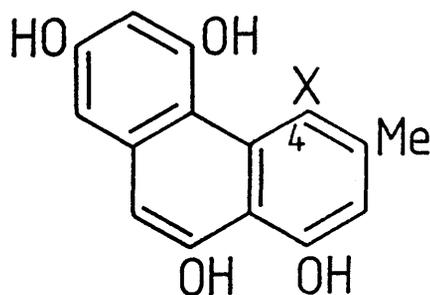
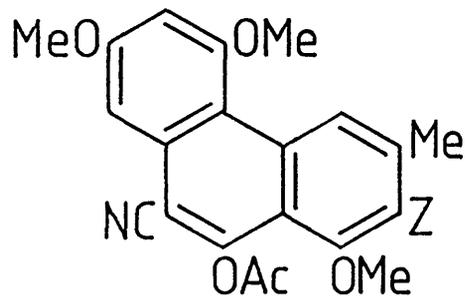
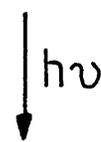
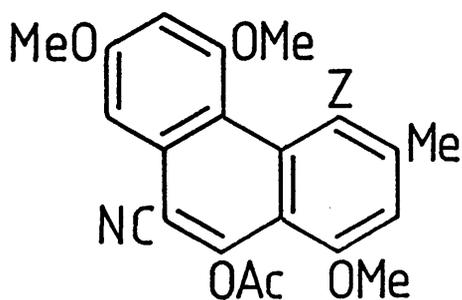
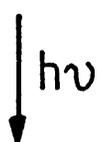
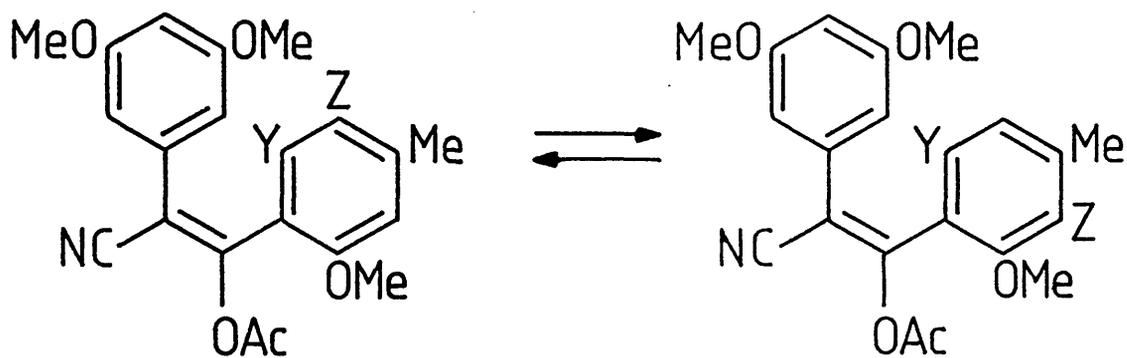
the cyclisation step [Scheme 18].

The work described in this and subsequent chapters was aimed at generating a general synthetic strategy that could be applied to the preparation of any of the target phenanthrenes (14), (15) or (16). The main objectives were:

1. To introduce regiochemical control into the cyclisation step so that a single phenanthrene product would be formed upon irradiation of each of the stilbene precursors of the target phenanthrenes (14)-(16). It was anticipated that this might be achieved by introducing an ortho-halo substituent into the appropriate stilbene system since irradiation of ortho-halostilbenes can result in preferential loss of hydrogen halide under suitable conditions.^{45,46} This would permit the photocyclisation of the 2-halostilbene (77) to the 4-substituted phenanthrene (75a) in comparable yield to the photocyclisation of (76) to phenanthrene (71) which lacks a substituent at position 4 [Scheme 19]. (The yield of the 4-substituted phenanthrene (75a) would probably be slightly lower than that of the corresponding unsubstituted phenanthrene (71) due to the unfavourable meta-meta' interaction in stilbene (77).)



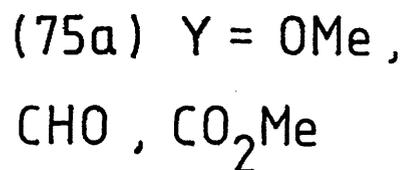
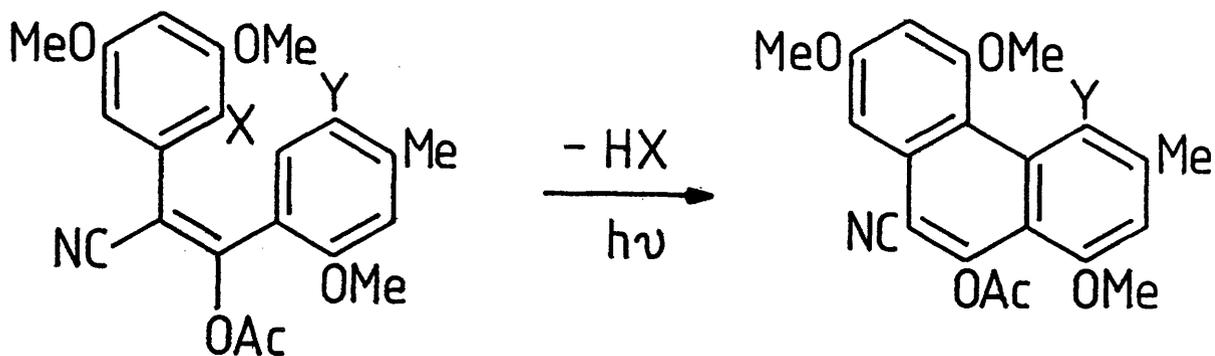
Y = OMe ; Z = OMe, CHO or CO₂Me



(15) X = OH

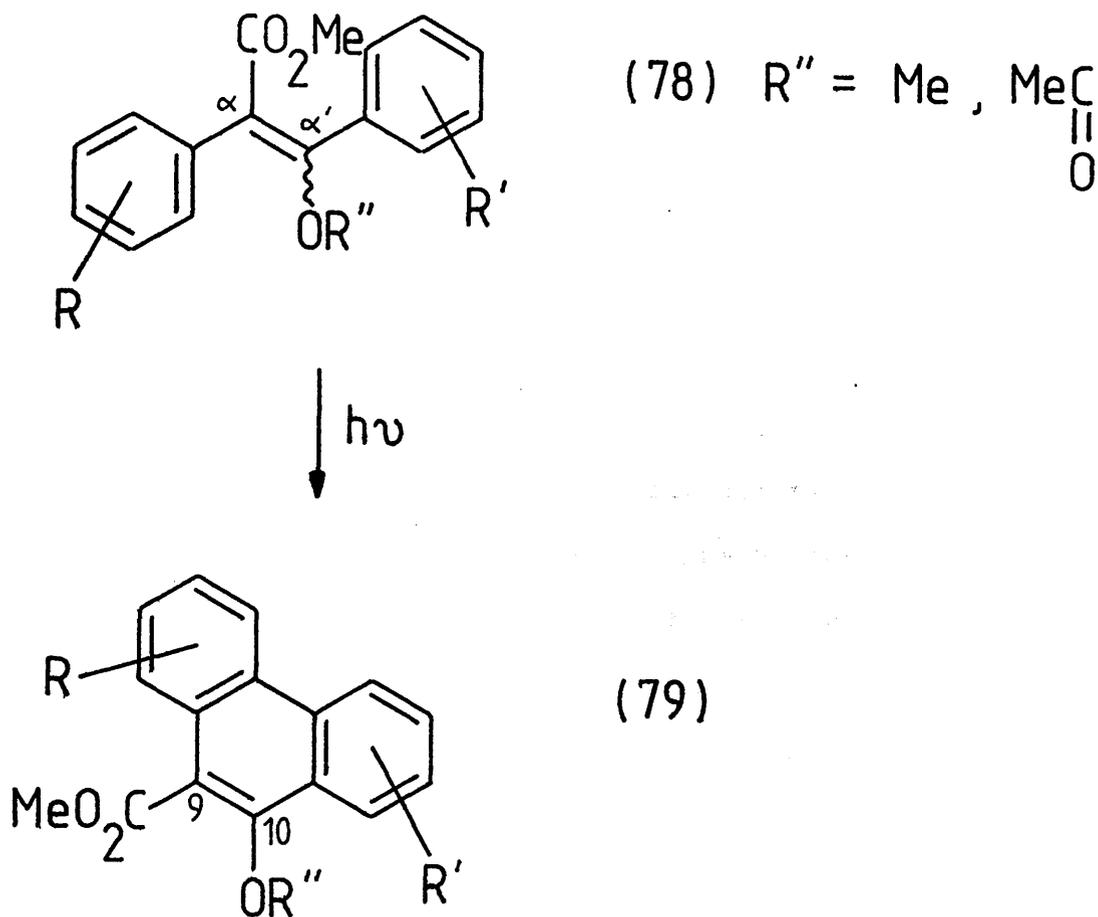
(16) X = CO₂H

Scheme 18



Scheme 19

2. To prepare suitable α -carbomethoxy- α' -oxystilbenes (78) for photocyclisation to 9-carbomethoxy-10-oxyphenanthrenes (79) [Scheme 20]. It was thought that the 9-carbomethoxyl group might be easily removed by hydrolysis/decarboxylation in contrast to the difficulty experienced in removing the 9-cyano group⁵⁰ (see Chapter 3). However, if the 9-carbomethoxyl group also proved difficult to remove, or if the yield of cyclised product was unacceptably low, then it was envisaged that either cyano or carbomethoxyl groups could be removed at an appropriate point prior to cyclisation.



Scheme 20

3. To accomplish demethylation of (73) to (14) (see Scheme 17) and to investigate other phenol protecting groups (e.g. benzyl) if a suitable demethylating agent could not be found.

The present chapter and part of the next chapter discusses the preparation, properties and photochemistry of ortho-halostilbenes (i.e. work related to topic 1 above). The next chapter also records the synthesis and photochemical behaviour of α' -acetoxy- α -carbomethoxy-stilbenes (topic 2). The work carried out in an attempt to overcome the difficulty experienced in demethylating phenanthrene (73) (topic 3) is described in the final chapter.

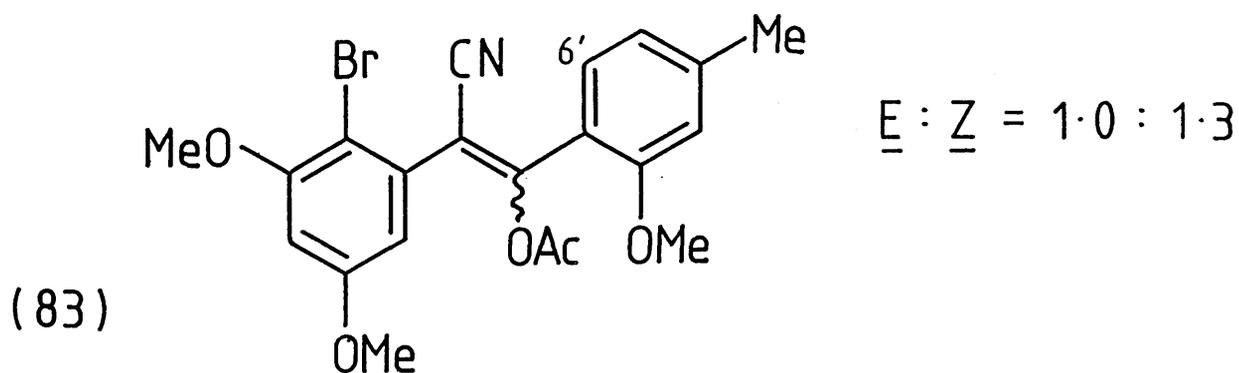
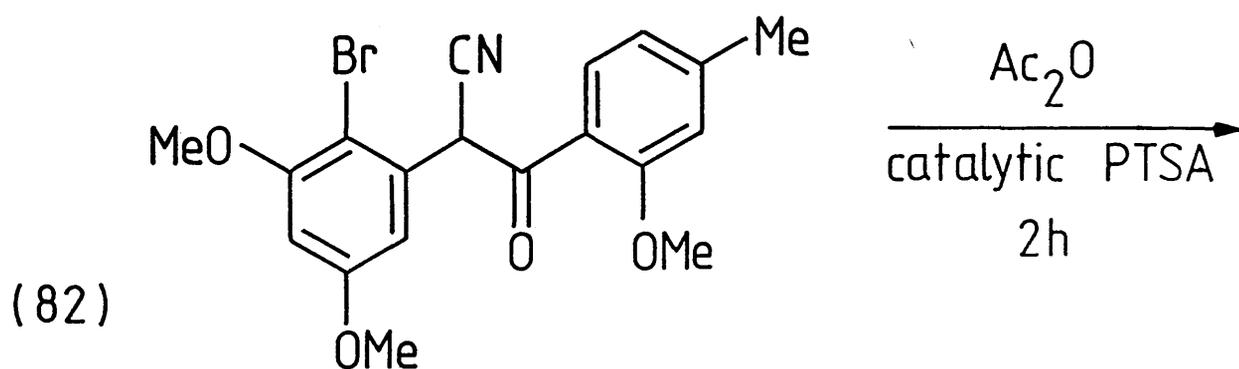
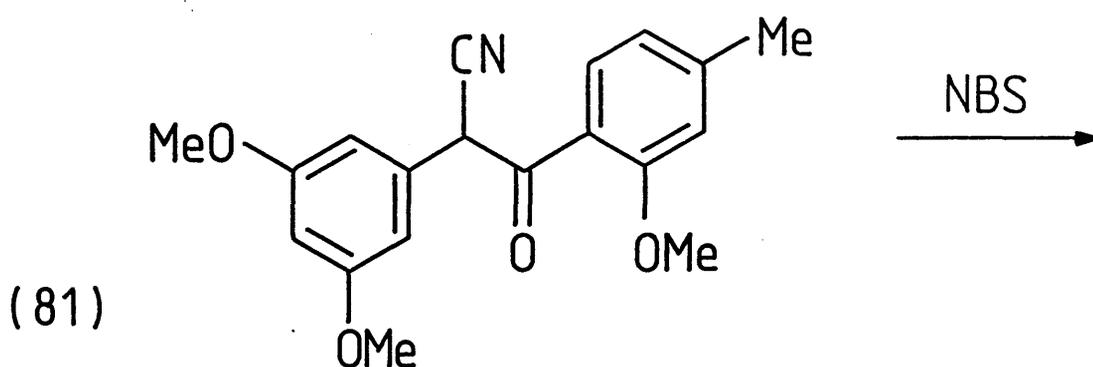
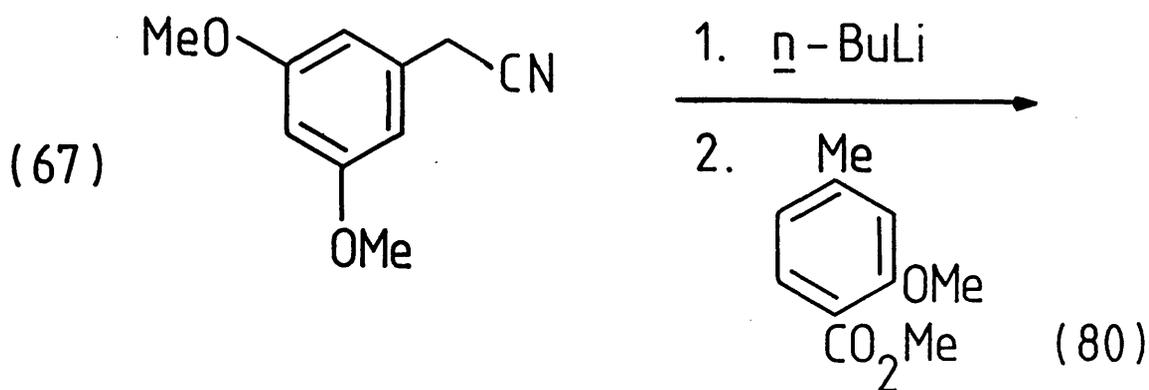
Results and Discussion

2.2 2-Bromostilbenes

2.2.1 Synthesis

The first halostilbene to be prepared was the 2-bromostilbene (83) via the route outlined in Scheme 21. The β -keto nitrile (81) was synthesised by condensation of the nitrile (67) with the ester (80) according to the procedure developed by Finnie and Hill.⁶¹ As predicted, the 2-bromo β -keto nitrile (82) was obtained by treatment of (81) with N-bromosuccinimide. Reaction of (82) with acetic anhydride containing a catalytic amount of p-toluenesulphonic acid for 2 hours afforded a mixture of E- and Z-enol acetates (83) in almost quantitative yield after chromatography. The 200 MHz ¹H nmr spectrum of the mixture of stereoisomers indicated that the isomers were present in the ratio of 1.0:1.3 from the integration of the H-6' doublets (J ~ 8 Hz) at δ 7.53 and 7.02 ppm respectively. Addition of ether caused crystallisation of most of the minor isomer and left a yellow gum consisting of the major isomer and 21% of the minor isomer. Figs. 2 and 3 show the 200 MHz ¹H nmr spectra of the minor isomer and the stereoisomeric mixture. It is well known that E-stilbenes are usually crystalline while Z-stilbenes are often gums.²⁵ On this basis, the minor isomer was predicted to be the E-stilbene and the major isomer the Z-stilbene.

Determination of the uv spectra of the minor isomer and the stereoisomeric mixture containing 21% of the minor isomer allowed the configuration of the isomers to be assigned. The uv spectra are



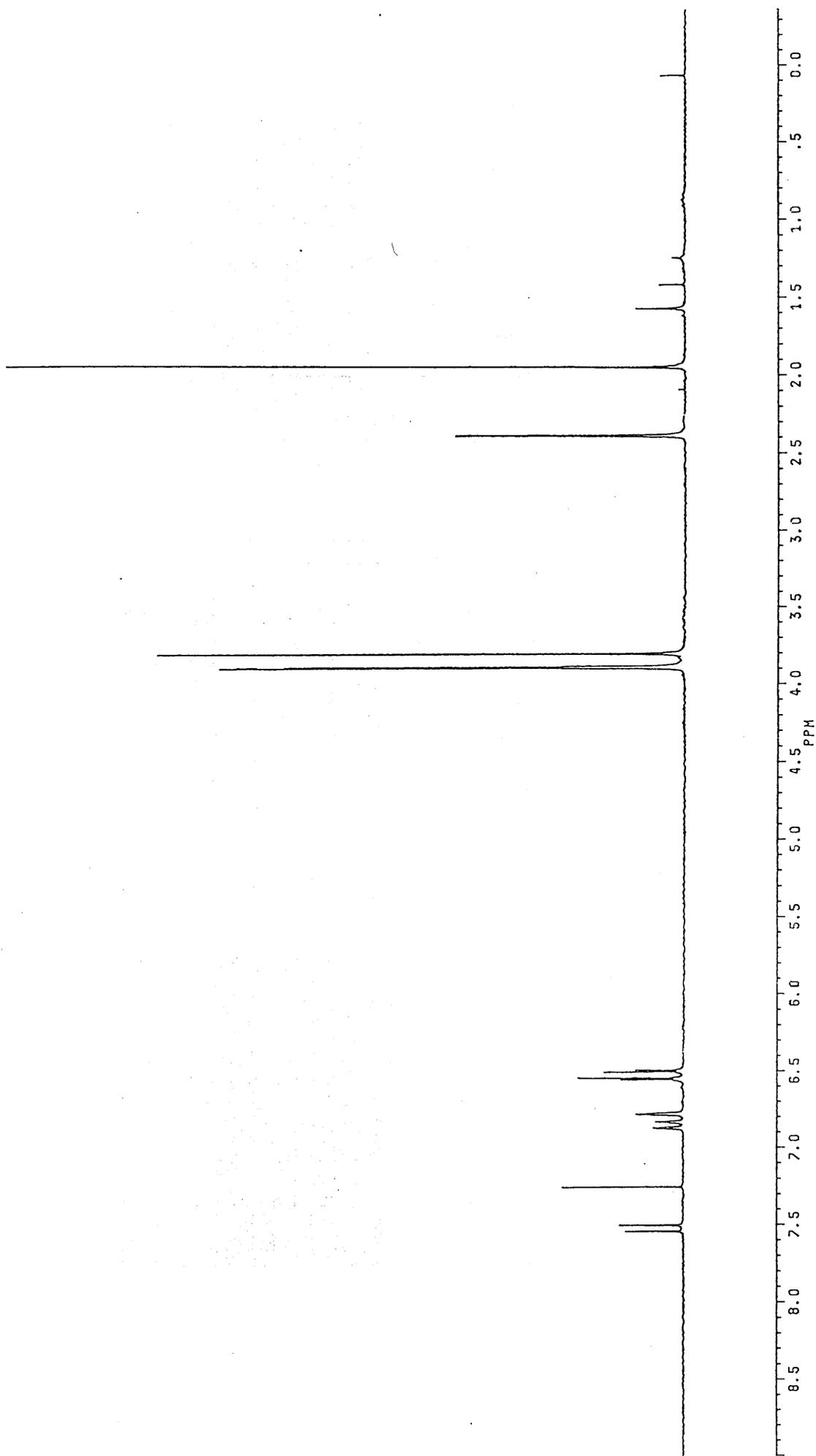


Fig. 2 200 MHz ^1H nmr spectrum of the E -2-bromostilbene (83) in CDCl_3

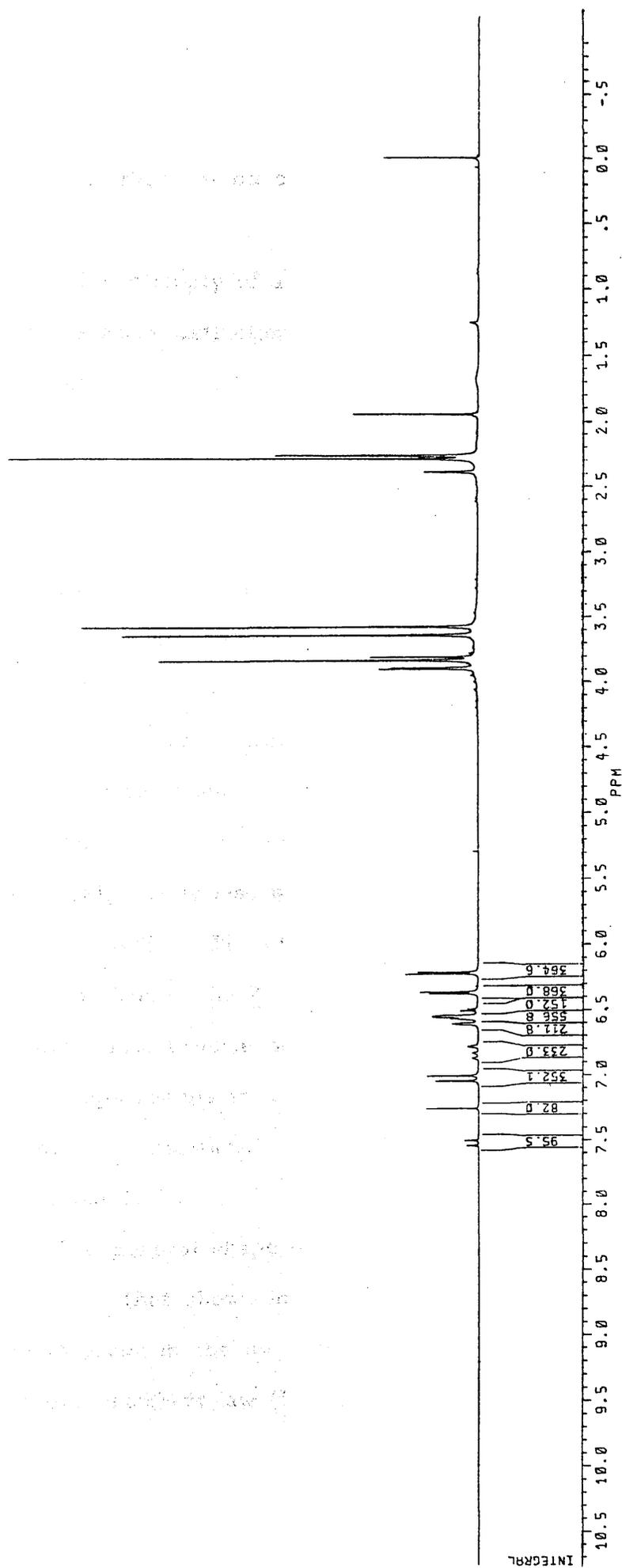


Fig. 3 200 MHz ^1H nmr spectrum of the E- and Z-2-bromostilbenes (83) in CDCl_3 (E : Z = 1.0 : 3.8)

reproduced in Figs. 4 and 5 and are discussed in more detail in Section 2.6.1.

The intensity of an absorption band is generally expressed in terms of the molar extinction coefficient, ϵ , which is calculated from the Beer-Lambert law [Equation 1].

$$A = \epsilon c \ell \quad \text{Equation 1}$$

The absorbance, A , has no units and is measured when the spectrum is recorded. c is the concentration of the absorbing solution in mol/l. ℓ is the path length in cm and is determined by the uv cell chosen to measure the spectrum. The units of ϵ are therefore 1,000 cm²/mol, but these are by convention never expressed.

The longest wavelength band of the uv spectrum of the mixture of isomers (Fig. 5) is less intense (ϵ 8,100) than that of the minor isomer (Fig. 4, ϵ 10,800). Therefore the minor isomer has the E-configuration and the major isomer the Z-configuration. This is because, in the Z-isomer, steric interference between the adjacent ortho-substituents of the two aryl groups results in a decrease in coplanarity and a reduction in the amount of conjugation. The lower the amount of conjugation, the weaker the band.

The general shape of the uv spectrum of the pure Z-isomer would resemble that shown in Fig. 5. The ϵ values of the three bands expected to occur in the uv spectrum of the Z-isomer can be estimated from the Beer-Lambert law (Equation 1) using the information contained in Figs. 4 and 5.

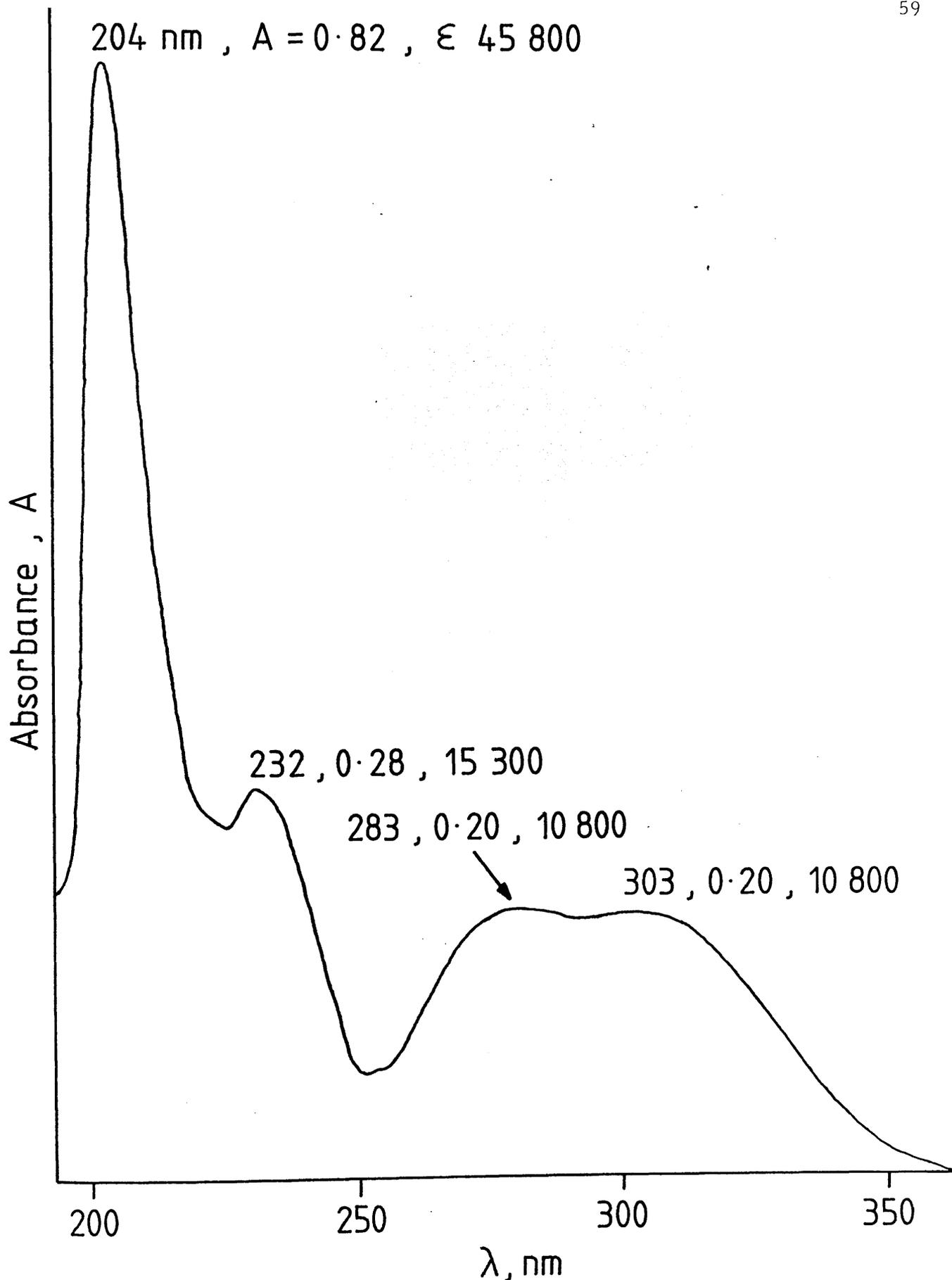


Fig. 4 Uv spectrum of the E-stilbene (83).

Path length = 1 cm . Conc. = 1.80×10^{-5} mol / l ethanol .

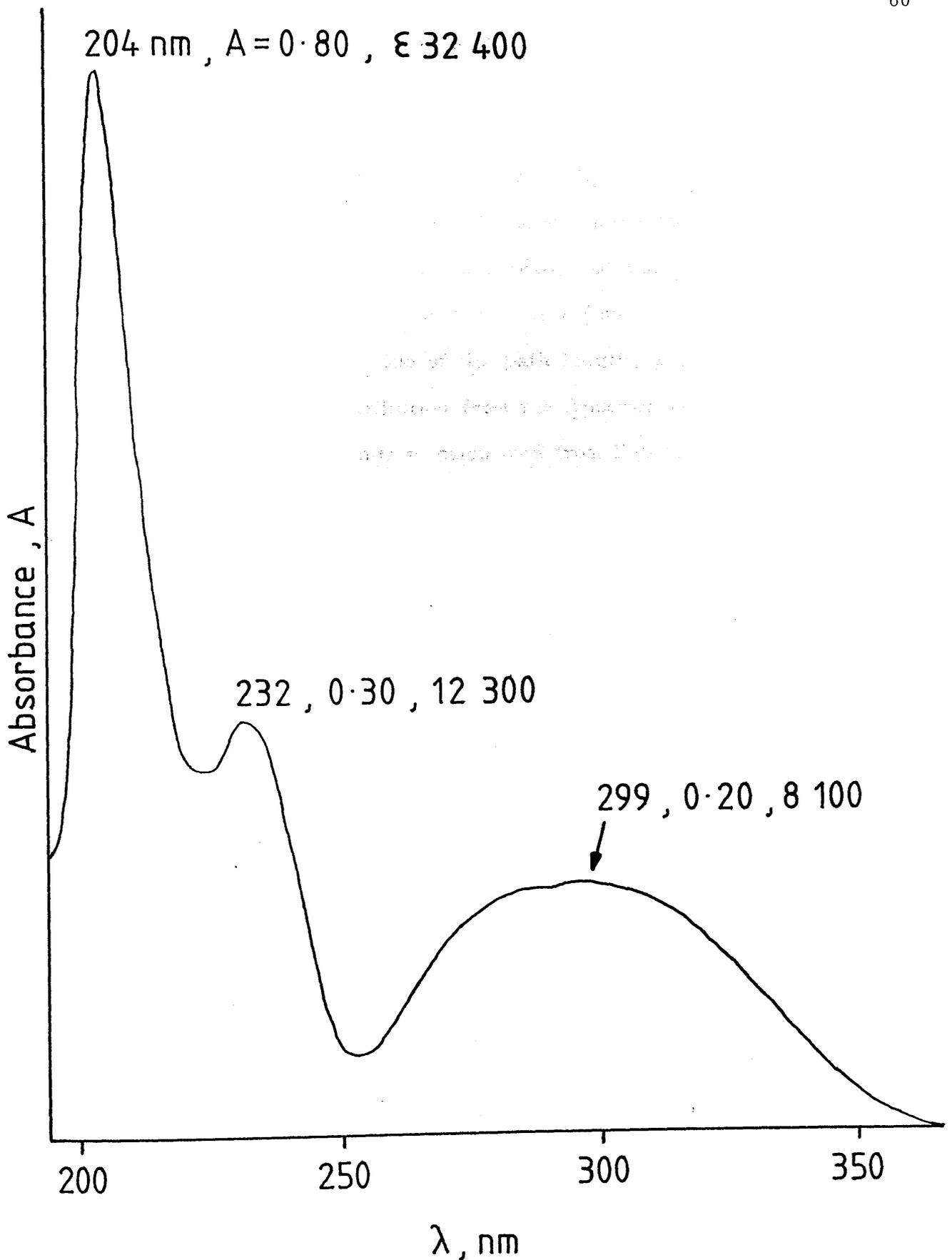


Fig. 5 Uv spectrum of the $\underline{E} : \underline{Z} = 1.0 : 3.8$ mixture of stilbenes (83). Path length = 1 cm. Conc. = 2.47×10^{-5} mol / l ethanol.

The concentration of the Z-isomer in Fig. 5 can be calculated from the concentration of the mixture of isomers since the ratio of isomers is known (E:Z = 1.0:3.8). The concentration of the Z-isomer is substituted in each of the three equations for ϵ (one equation for each band) along with the known value of the path length, ℓ .

In Fig. 5, the contribution from the Z-isomer (A_Z) to the absorbance of each of the bands is calculated from Equation 2.

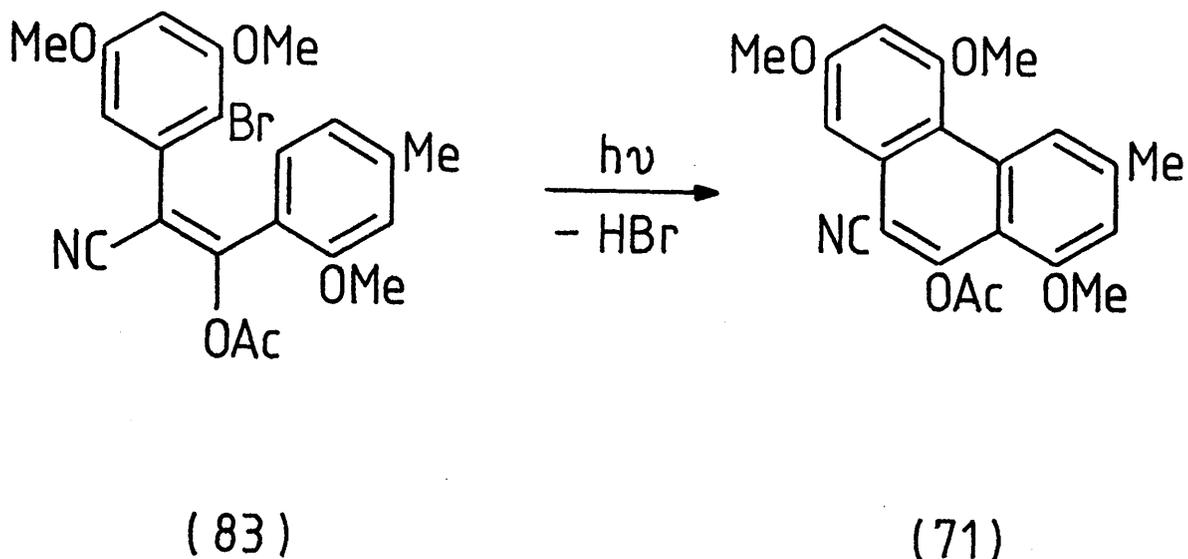
$$A_Z = A_{\text{mixt}} - A_E \quad \text{Equation 2}$$

A_{mixt} is the band absorbance of the mixture of isomers and A_E is the absorbance of the E-isomer. A_E is calculated from Equation 1 using the concentration of the E-isomer in Fig. 5, the known path length, ℓ , and the appropriate value of ϵ from Fig. 4.

Thus the three bands in the uv spectrum of the Z-2-bromostilbene (83), in order of decreasing wavelength, have calculated ϵ values of 7,400, 11,600 and 28,800.

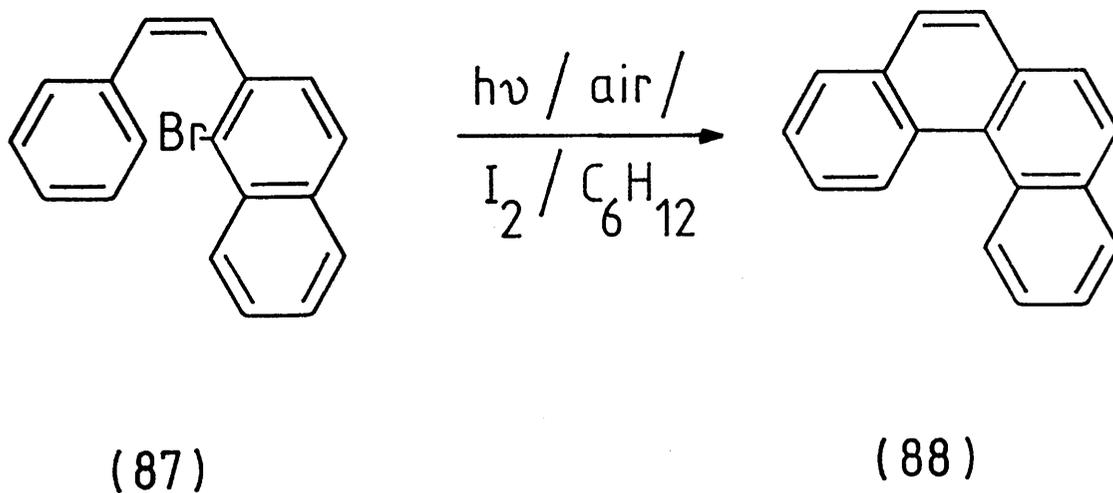
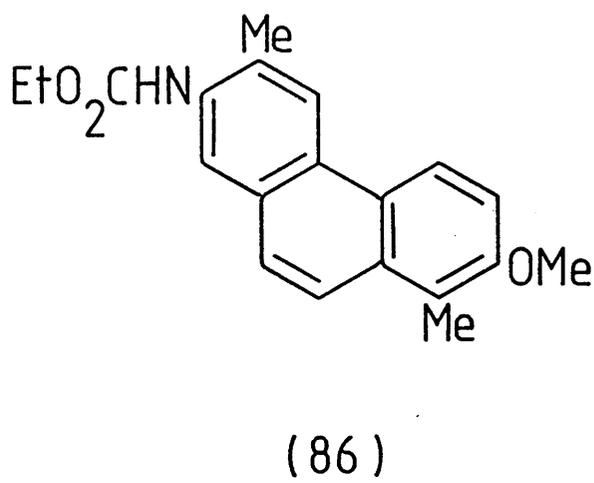
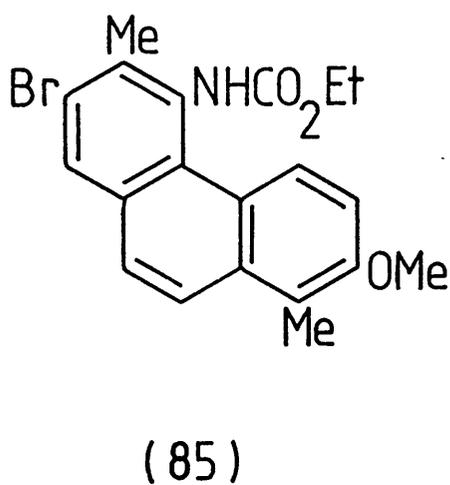
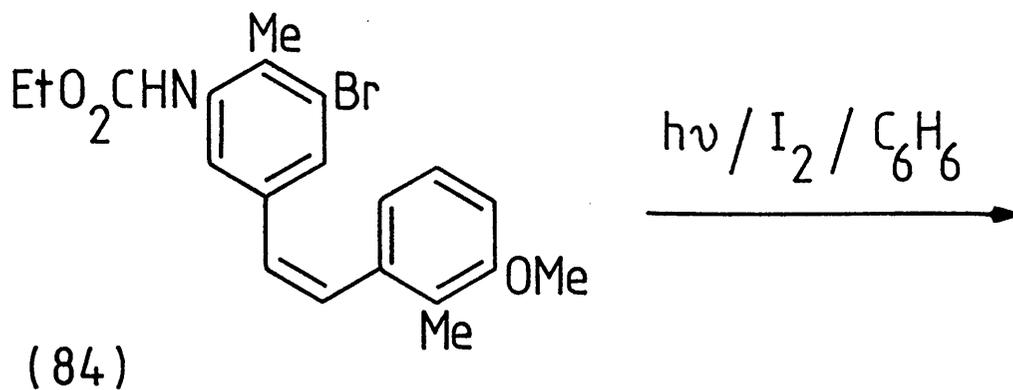
2.2.2 Photochemistry

A variety of photochemical experiments were conducted in an attempt to induce the 2-bromostilbene (83) to preferentially eliminate hydrogen bromide and give the desired phenanthrene (71) in good yield [Scheme 22].



Scheme 22

The literature contains many examples of oxidative and eliminative photocyclisations of bromostilbenes.²⁵ As mentioned in the Introduction and illustrated in Schemes 7-9 therein, photocyclisation of bromostilbenes under oxidising conditions (solvent, iodine and/or air) generally results in retention of the bromo substituent, even when it is at stilbene position 2, 2', 6 or 6' and thus could potentially be eliminated in the cyclisation step.⁴⁰⁻⁴² If more than one bromo substituent is present in the stilbene, then under oxidising conditions, generally both are retained in the phenanthrene product.⁴³ The examples depicted in Scheme 23 are exceptional. Irradiation of the 3-bromostilbene (84) in benzene containing a trace of iodine gives phenanthrene (85) via oxidative photocyclisation and phenanthrene (86) via loss of the bromo group before or after oxidative photocyclisation.⁶³ Also, irradiation of 1-bromo-2-styrylnaphthalene (87) in air saturated cyclohexane containing



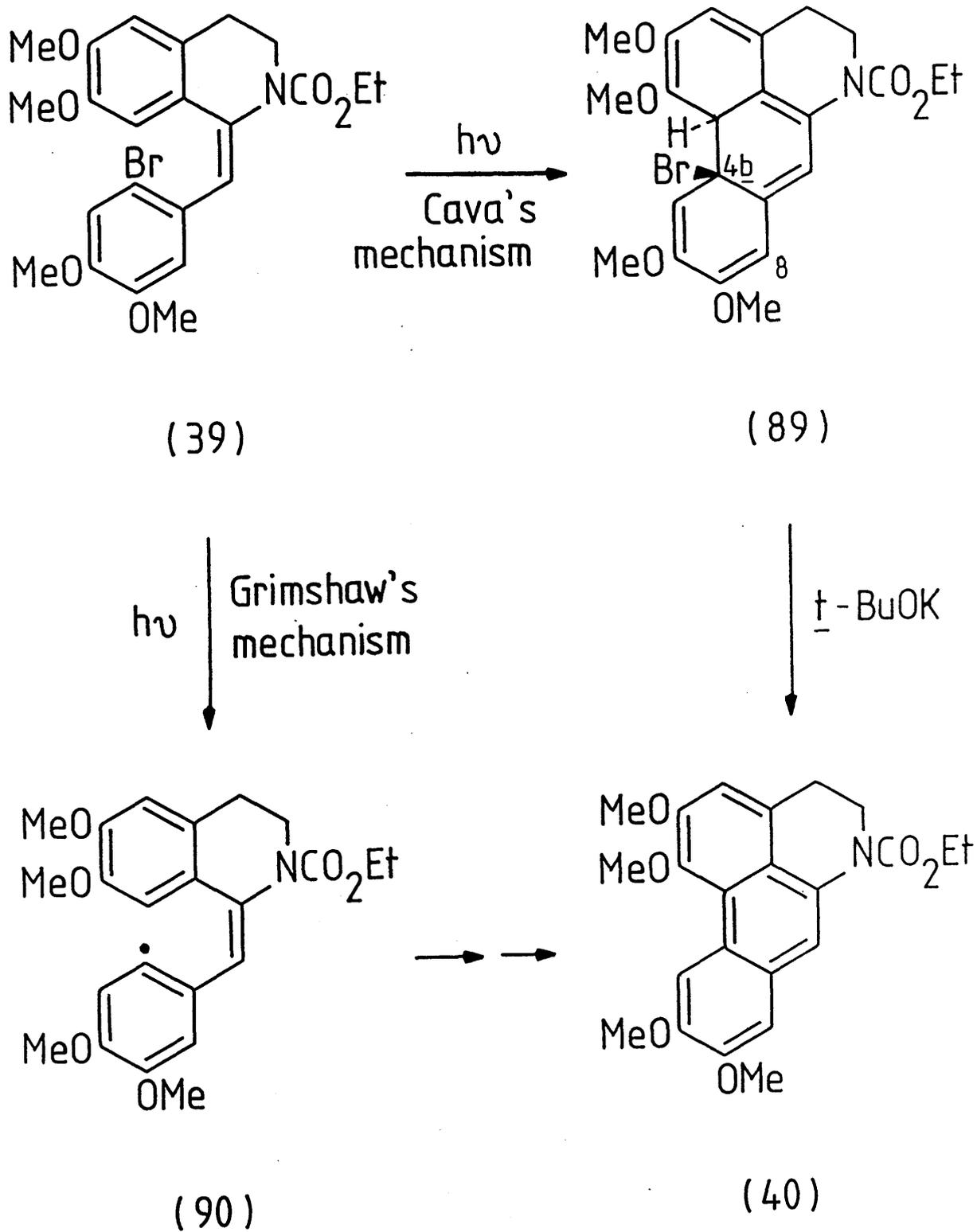
Scheme 23

iodine produces benzo[c]phenanthrene (88) in 18% yield.⁶⁴ Loss of the bromo group could occur before, during or after photocyclisation.

Loss of bromo substituents in stilbene photocyclisations most often occurs when the substituent is at position 2 and the irradiation is carried out under nitrogen or argon in the presence of a suitable trapping agent such as potassium tert-butoxide⁴⁵ or an aliphatic amine.⁶⁵ In Scheme 23, the photocyclisations of stilbenes (84) and (87) are unusual since they involve loss of a bromo group in the absence of a trapping agent. In (84) the bromo group is lost from position 3, while in (87) it is lost from position 2.

The cyclodehydrobromination of 2-bromostilbenes by irradiation in deoxygenated benzene/tert-butanol containing potassium tert-butoxide was discovered in 1973 by Cava's group⁴⁵ and has since been used to prepare a number of alkaloids.⁶⁶ One mechanistic suggestion, proposed by Cava and illustrated in Scheme 24 for the conversion of (39) to (40), is that irradiation of the 2-bromostilbene (39) under nitrogen leads reversibly to a mixture of dihydrophenanthrenes with the bromine atom at either C-8 or C-4_b. In the presence of potassium tert-butoxide the latter dihydrophenanthrene is trapped by an E2 elimination of hydrogen bromide. An alternative mechanism has been suggested by Grimshaw and de Silva,⁶⁷ involving as the first step photolysis of the carbon-bromine bond in the starting 2-bromostilbene (39) assisted by intramolecular radical complexation [Scheme 24].

When the 2-bromostilbene (83) was dissolved in dry benzene/tert-butanol and irradiated under anaerobic conditions in the presence of potassium tert-butoxide the major products were the β -keto nitrile



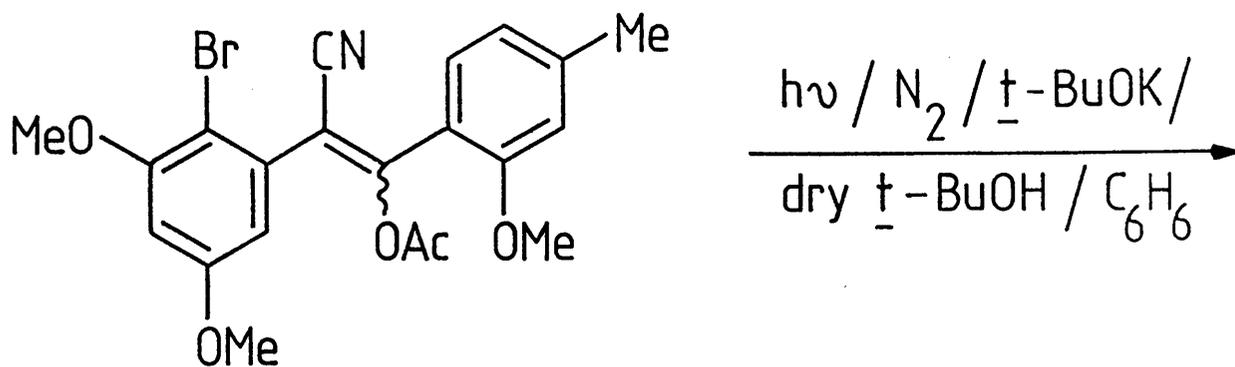
Scheme 24

(82) and the dimer (91) [Scheme 25].

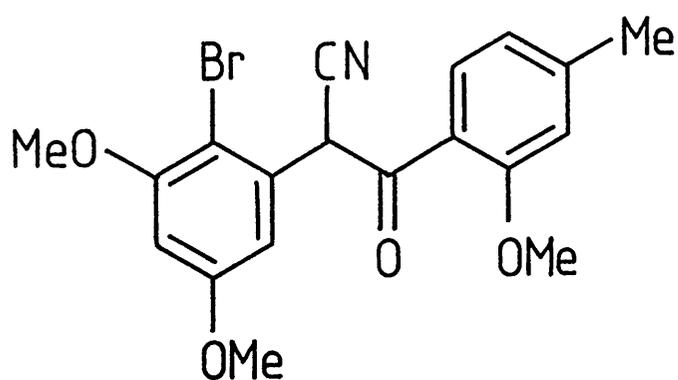
Since the reaction was carried out under anhydrous conditions, formation of (82) either involves base promoted elimination of ketene from the enol acetate system of stilbene (83), or simple O-acyl photofragmentation [Scheme 26]. This type of photochemical cleavage of enol acetates to give ketones is known.^{68,69} For example, Roberts⁶⁸ isolated desoxybenzoin (94) from the photoreaction of E- α -acetoxystilbene (93) in dry acetic acid. The other products were 9-acetoxyphenanthrene (95) and the Z-isomer of the starting stilbene [Scheme 27].

A possible mechanism for the dimerisation process is shown in Scheme 28. The steps involved are: 1. photolysis of the two carbon-bromine bonds and coupling of the radical centres, and 2. O-acyl bond cleavage and subsequent carbon-carbon bond formation. Steps 1 and 2 could, of course, be reversed. This mechanism is supported by the observations of Yogev *et al.*⁶⁹ on the reactivity of the enol acetate (98) upon irradiation in cyclohexane [Scheme 29]. The main changes are O-acyl bond fission followed by: 1. hydrogen atom abstraction to give the ketone (99), 2. acyl radical migration yielding the β -diketone (100), and 3. dimerisation via carbon-carbon bond formation.

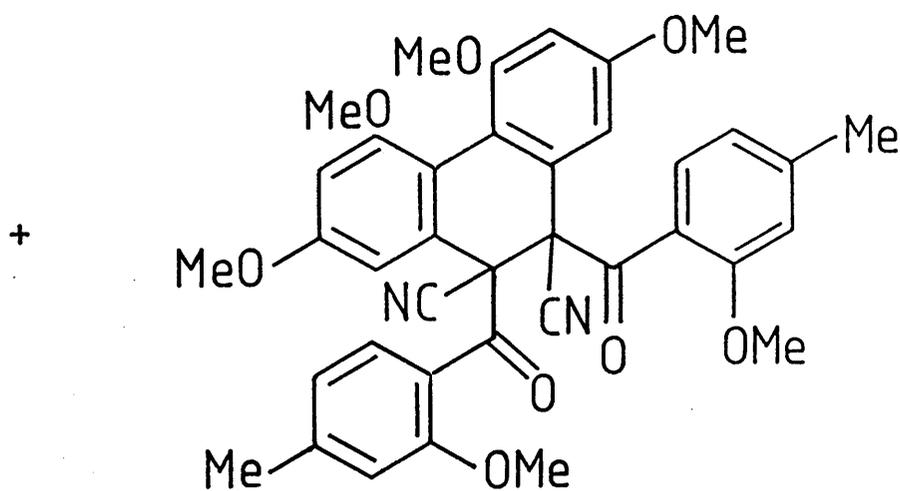
It was thought that stilbene (102) would perhaps undergo photodehydrobromination under the above irradiation conditions since the enol ether system of stilbene (102) would remain intact in the presence of uv light and potassium tert-butoxide, in contrast to the observed reactivity of the enol acetate moiety of stilbene (83) depicted in Scheme 25. Thus attempts were made to prepare stilbene (102), but these were unsuccessful.



(83)

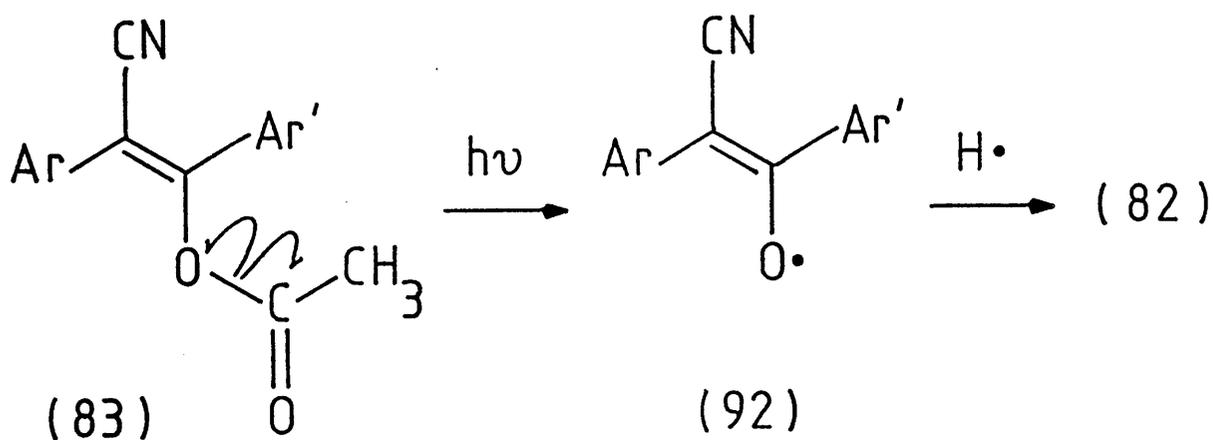
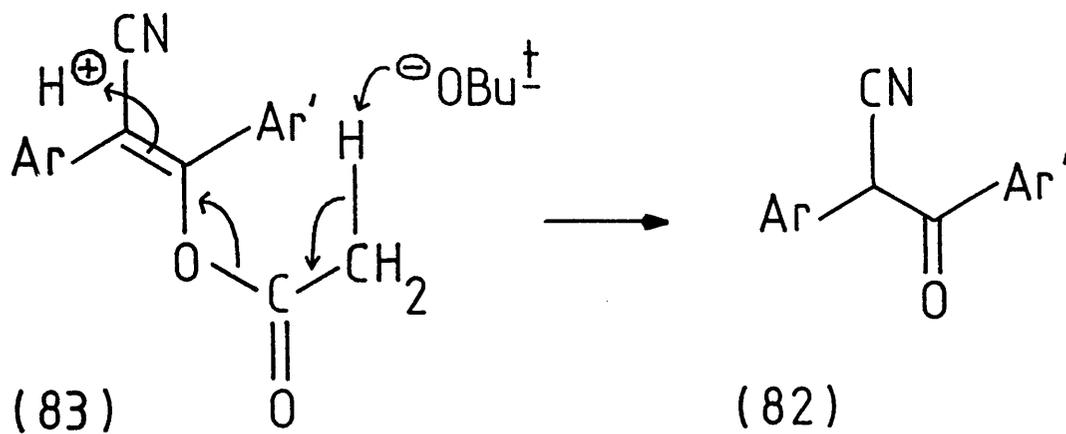


(82)

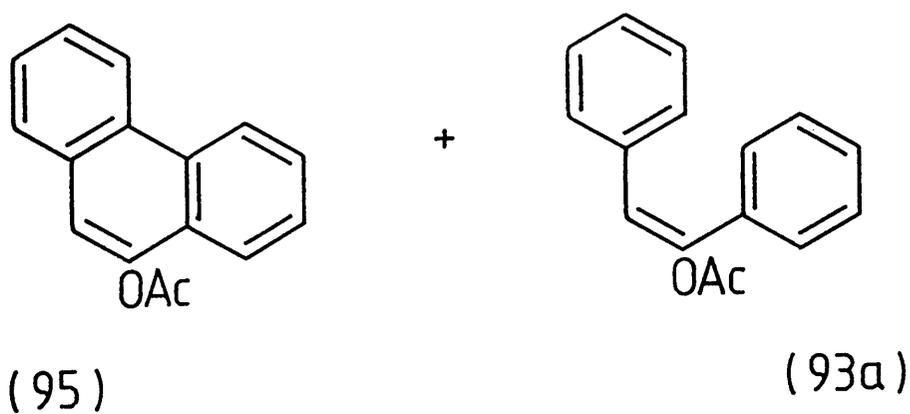
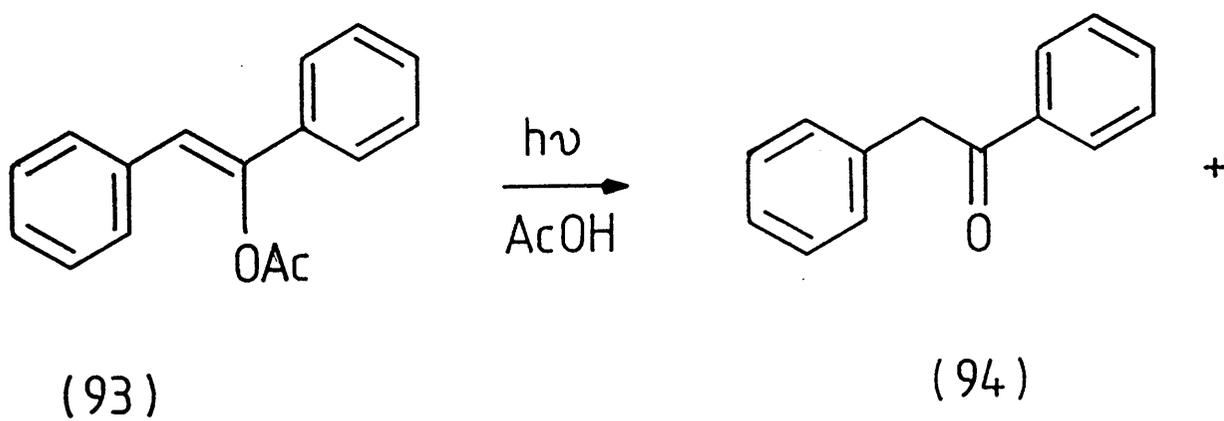


(91)

Scheme 25

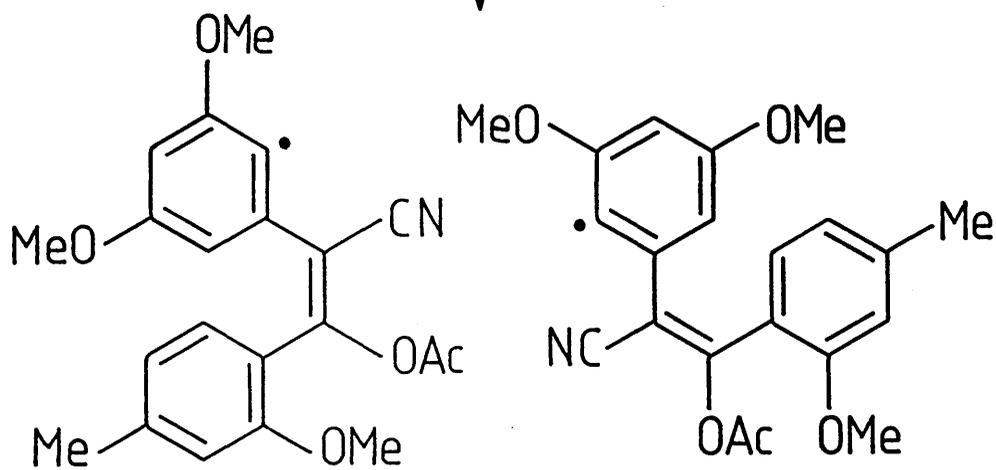
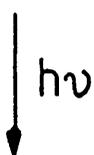


Scheme 26

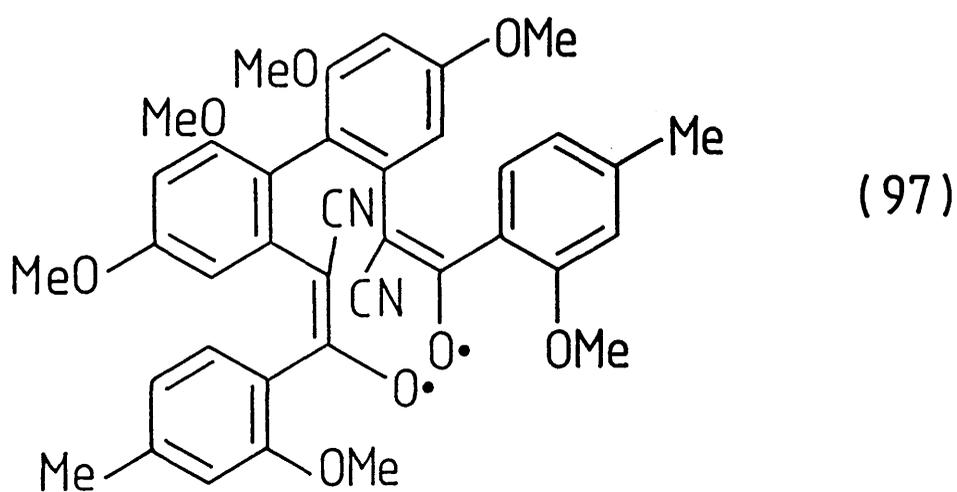


Scheme 27

2 (83)



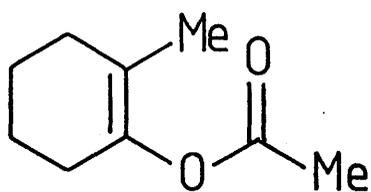
(96)



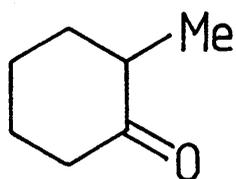
(97)



(91)

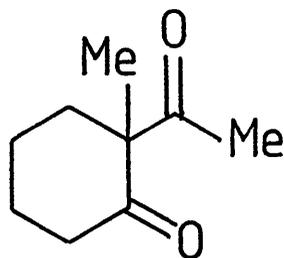


(98)

 $h\nu / \text{C}_6\text{H}_{12}$ 

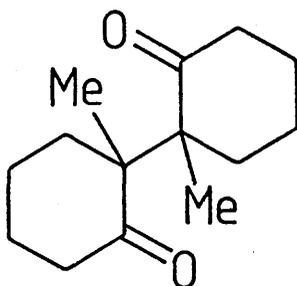
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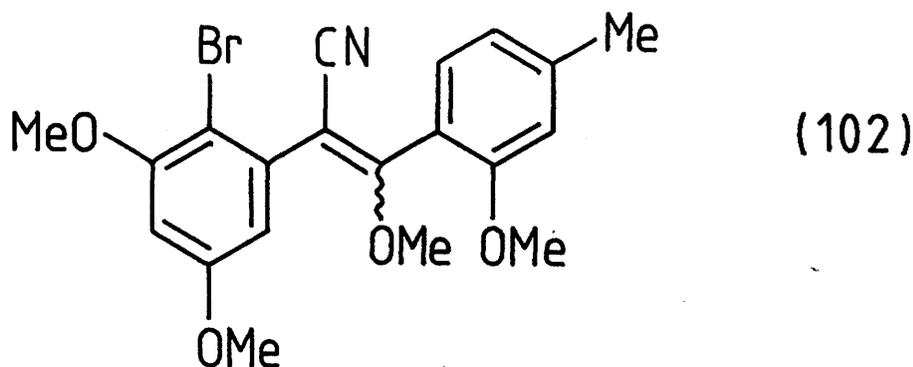
(100)

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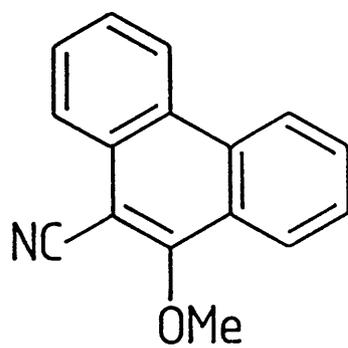
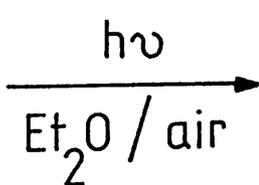
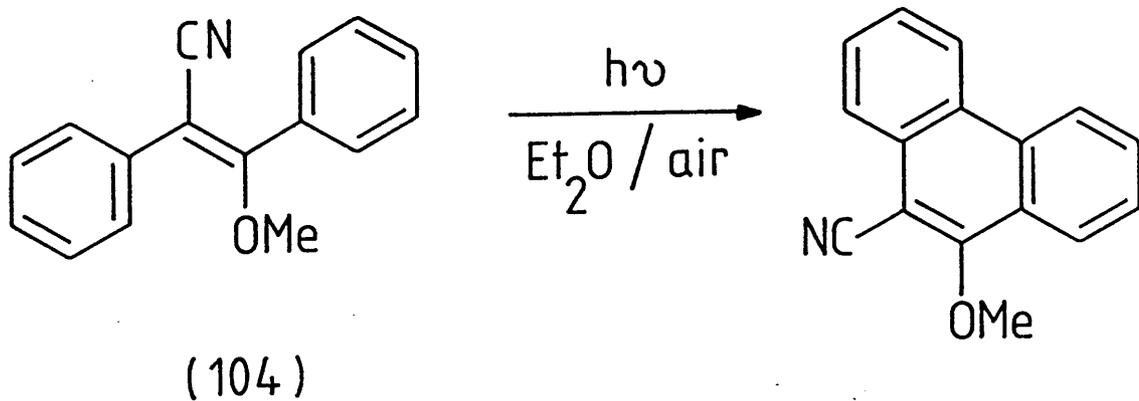
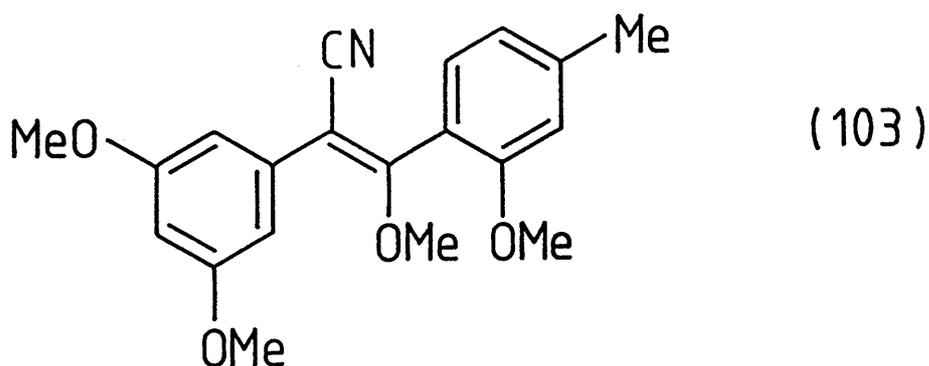
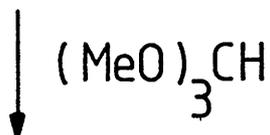
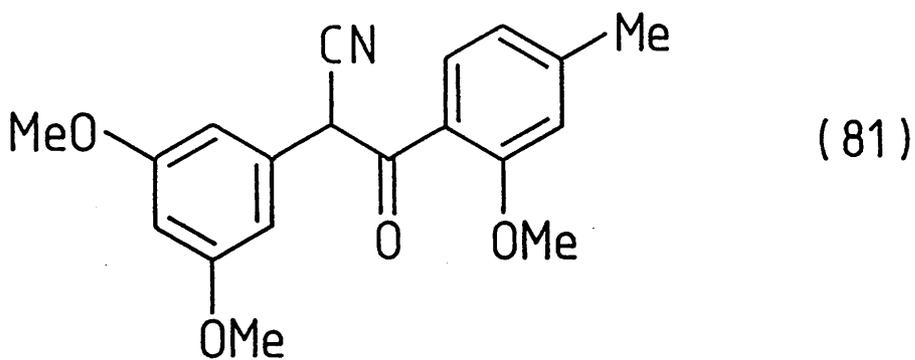
(101)

Scheme 29

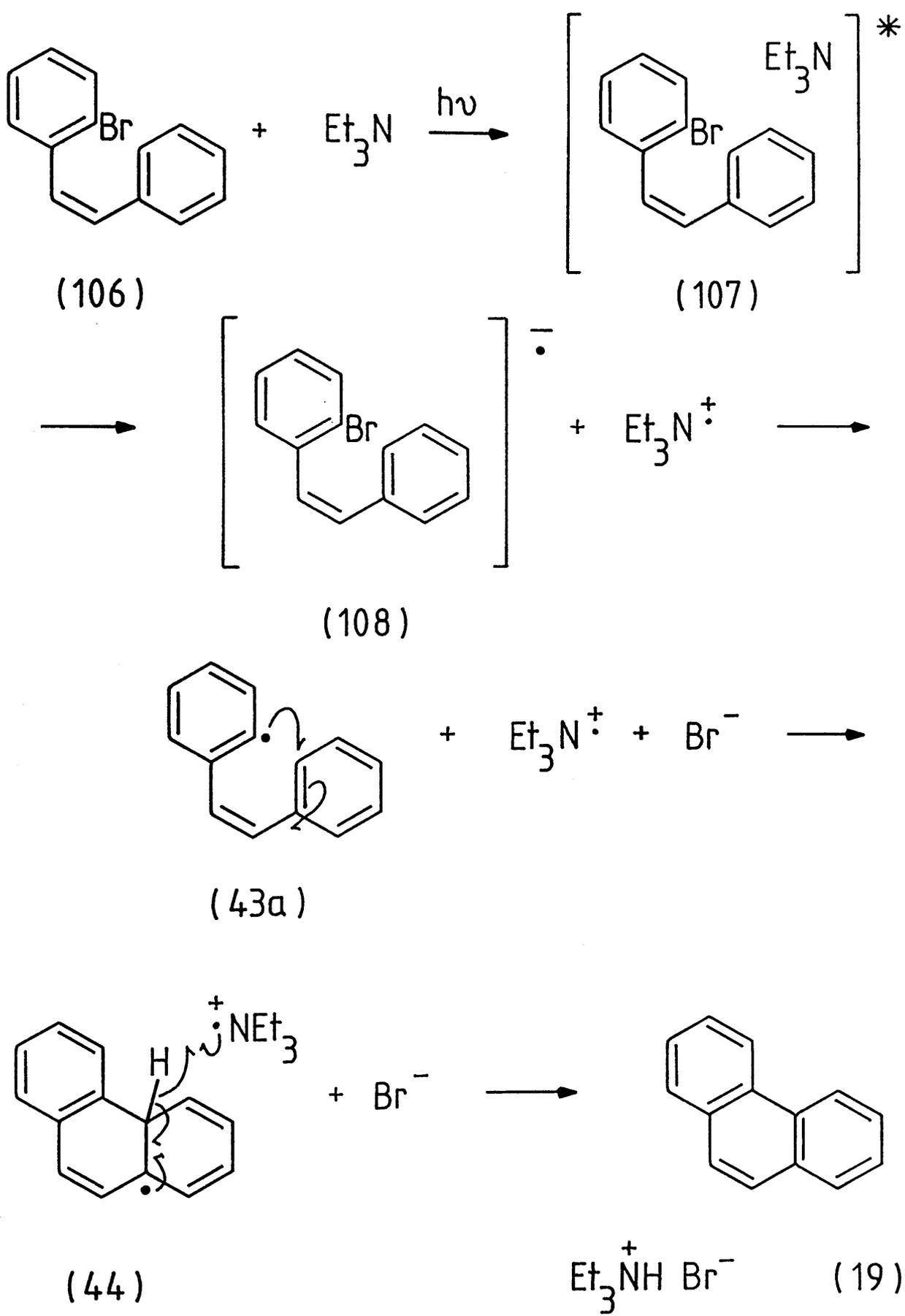


Finnie⁵⁰ synthesised stilbene (103) by reaction of the β -keto nitrile (81) with trimethyl orthoformate. However, (103) failed to cyclise under the same conditions ($h\nu$ /ether/oxidant) which afford 9-cyano-10-methoxyphenanthrene (105) in 65% yield from α -cyano- α' -methoxystilbene (104)⁷⁰ [Scheme 30]. When the corresponding 2-bromo β -keto nitrile (82) was treated with trimethyl orthoformate only starting material was recovered. Also, reaction of the enol ether (103) with N-bromosuccinimide gave a complex mixture of products which could not be resolved by chromatography over silica.

An aliphatic amine such as triethylamine or tert-butylamine can be used instead of potassium tert-butoxide as a scavenger for hydrogen halide in the photocyclisation of 2-halostilbenes.⁶⁵ Photodehalogenation of aryl halides by electron transfer from amines is well documented⁷¹⁻⁷³ and a similar mechanism is proposed to operate in the photocyclisation of 2-halostilbenes in the presence of an aliphatic amine.⁷⁴ This is illustrated in Scheme 31 for the photochemical ring closure of 2-bromostilbene (106) in the presence of triethylamine. It is thought⁷⁴ that irradiation of a mixture of (106) and triethylamine leads to an excited



Scheme 30

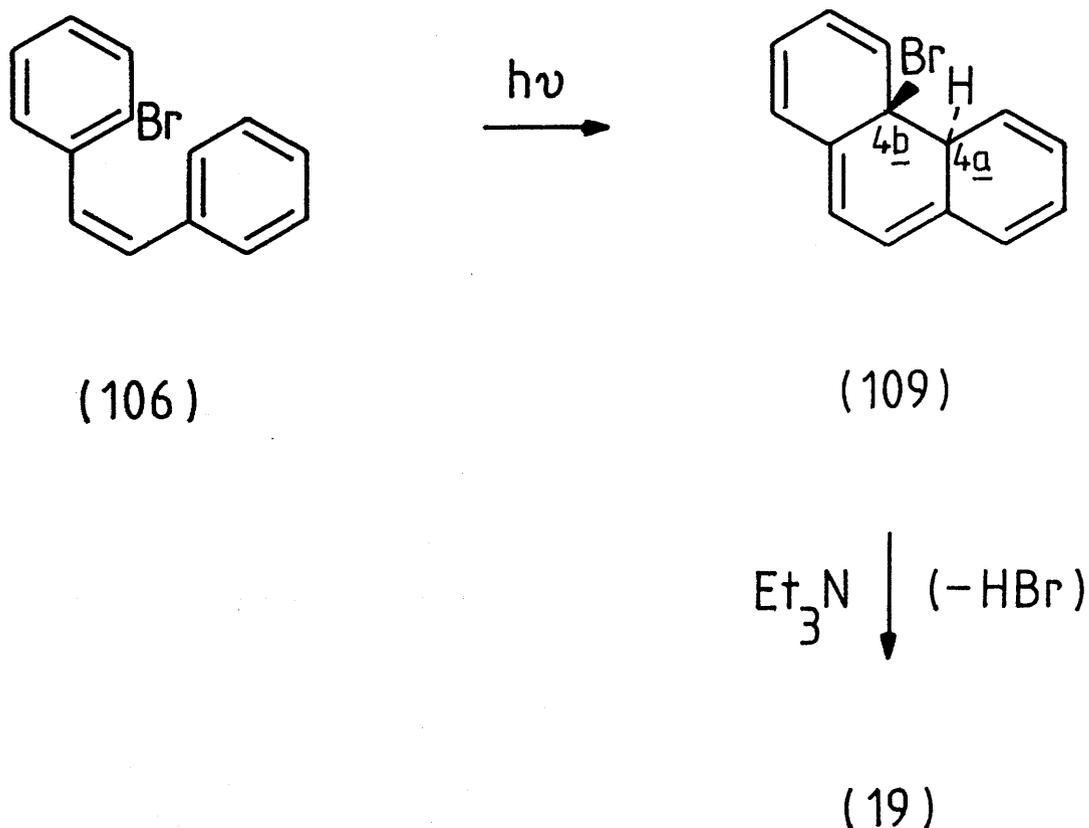


Scheme 31

state complex (or exciplex) between the excited state of the amine and the stilbene, followed by electron transfer from the amine.

Decomposition of the radical anion (108) and subsequent intramolecular radical cyclisation affords (44) which is converted to phenanthrene (19) upon hydrogen atom abstraction by $\text{Et}_3\text{N}^{+\bullet}$.

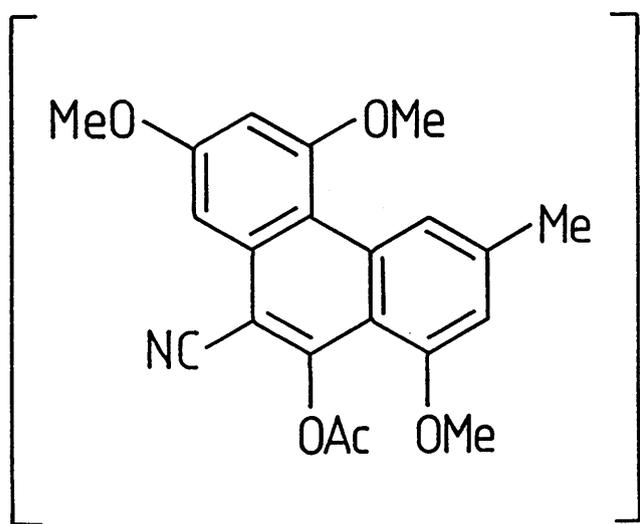
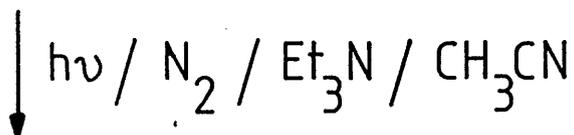
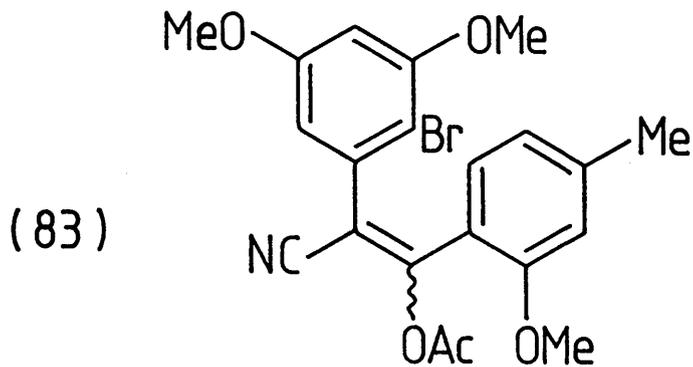
A mechanism similar to that shown in Scheme 24 in which the 4b-bromodihydrophenanthrene (109) is trapped by base promoted E2 elimination of hydrogen bromide is a plausible alternative to the electron transfer mechanism [Scheme 32].



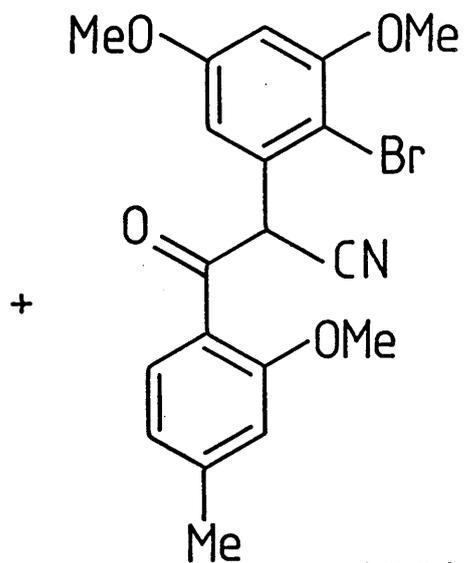
Scheme 32

When a mixture of the 2-bromostilbene (83) and triethylamine was irradiated in acetonitrile under nitrogen for 20 hours the 10-hydroxyphenanthrene (72) was isolated in 9% yield [Scheme 33]. The 10-hydroxyl substituent of (72) could have been formed by photochemical cleavage of the 10-acetoxy substituent of phenanthrene (71), or by simple ester hydrolysis of (71) during the reaction work-up (see the Experimental, p. 200). A small amount of the 2-bromo β -keto nitrile (82) was also formed in the reaction as evidenced by the singlet due to CHCN at $\delta 6.31$ ppm in the 90 MHz ^1H nmr spectrum of the crude reaction mixture.

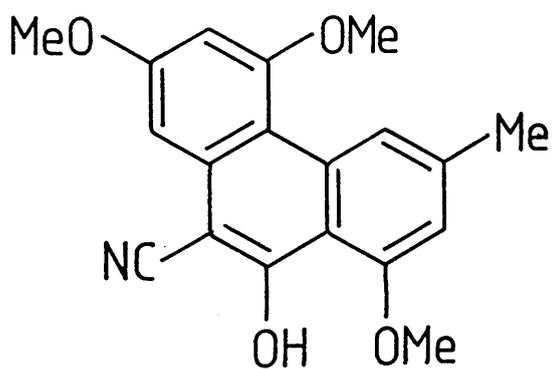
The final photochemical reaction of the 2-bromostilbene (83) involved irradiation in benzene under nitrogen and gave a mixture of the four phenanthrenes (110), (111), (71) and (112) in good overall yield [Scheme 34]. The protons at positions 4 and 5 of a phenanthrene occur in the ^1H nmr spectrum in the region of $\delta 8.5$ - 9.5 ppm due to angular crowding.⁷⁵ The integration of the singlets at $\delta 9.24$, 9.05, 8.90 and 8.68 ppm in the 90 MHz ^1H nmr spectrum of the crude mixture indicated that the four phenanthrenes (110), (111), (71) and (112) were present in the ratio of 1 : 2.5 : 2 : 2 respectively. When oxygen was rigorously removed in this reaction a 1.3 : 1.7 : 1.8 : 1.0 mixture of phenanthrenes (110), (111), (71) and (112) was obtained. The four phenanthrenes were separated by chromatography and identified by 200 MHz ^1H nmr and other techniques.



(71)

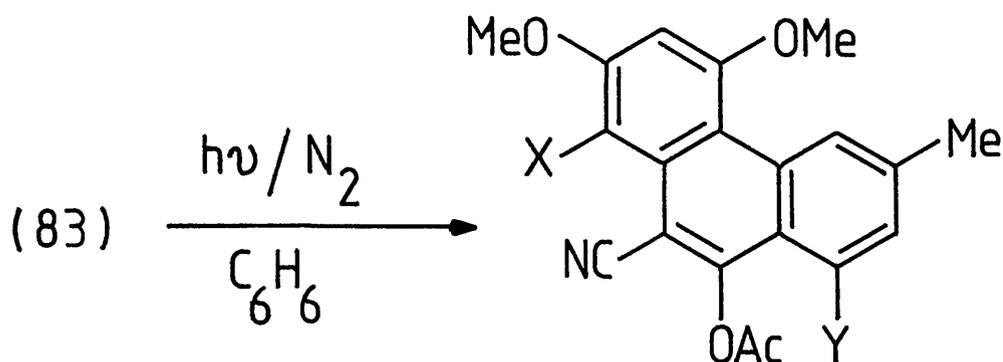


(82)



(72)

Scheme 33



(110) X = H , Y = H

(111) X = Br , Y = H

(71) X = H , Y = OMe

(112) X = Br , Y = OMe

Scheme 34

The uv spectrum of phenanthrene (71) is reproduced in Fig. 6. It is similar to the uv spectra of the other three phenanthrenes in that strong absorption occurs throughout the region of 200-400 nm. Comparison with Fig. 5 reveals that the phenanthrene products absorb uv light at least three times more strongly than the starting 2-bromostilbene (83) in the wavelength region (260-350 nm) that leads to photocyclisation. This means that as the amount of cyclised product increases as the photocyclisation proceeds, the amount of radiation

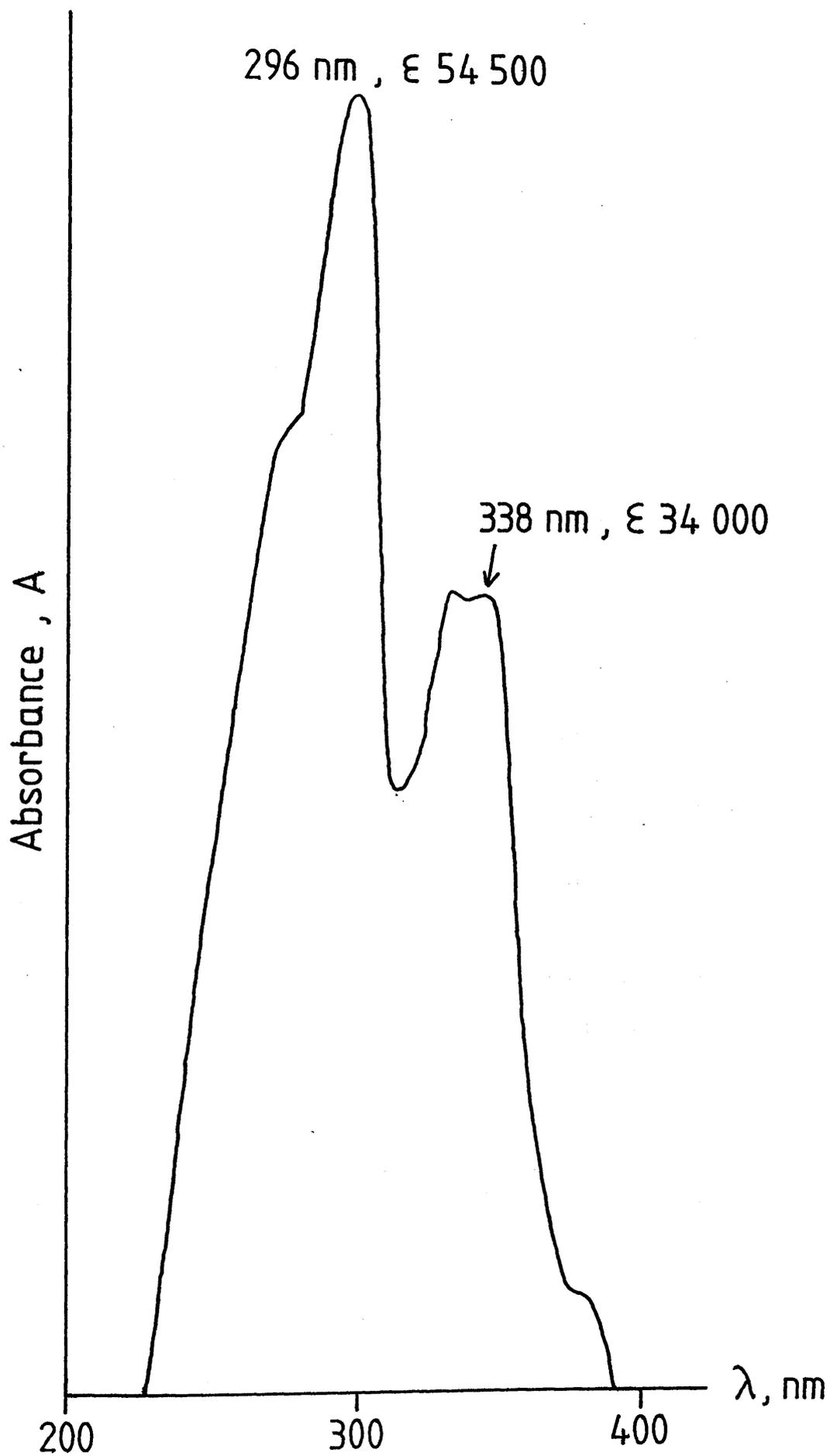
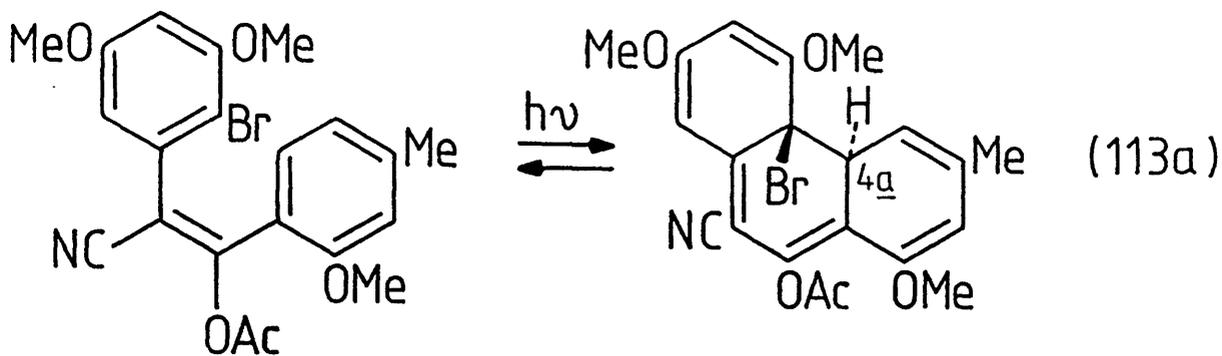


Fig. 6 Uv spectrum of phenanthrene (71) in MeOH

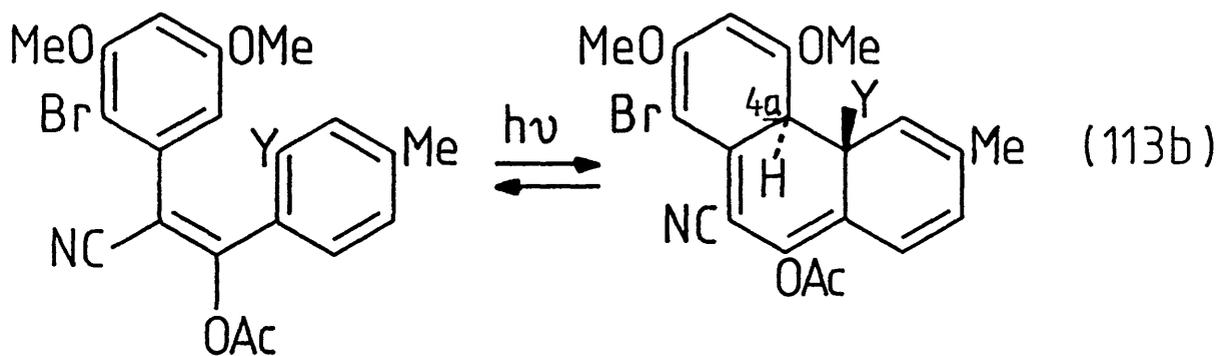
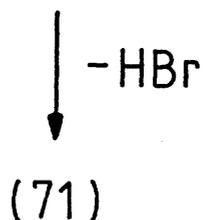
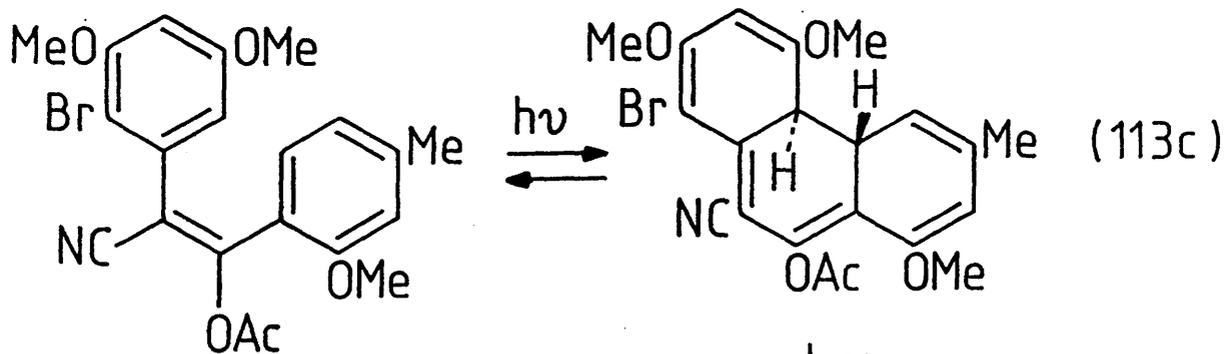
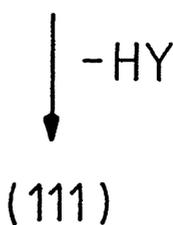
available to the starting material progressively diminishes and this can bring about premature cessation of the reaction.

Various mechanisms could account for the formation of these four phenanthrenes, although the mechanisms shown in Schemes 35 and 41 are considered to be the most likely ones. Scheme 35 involves electrocyclic reaction of the 2-bromostilbene (83) to give three isomeric dihydrophenanthrenes (113a)-(113c). Elimination of hydrogen bromide from (113a) and methanol from (113b) affords phenanthrenes (71) and (111) respectively. As explained in the Introduction (p.17), these eliminations proceed by abstraction of the 4_a-hydrogen from the appropriate dihydrophenanthrene followed by unimolecular expulsion of Br· or CH₃O·. In the presence of residual dissolved oxygen (the last traces of oxygen are difficult to remove), phenanthrene (112) is formed by dehydrogenation of dihydrophenanthrene (113c). This occurs via a radical mechanism involving two consecutive hydrogen abstractions^{33,34} (see p.14).

There is extensive literature precedent for the loss of hydrogen and methanol during photochemical electrocyclic reactions of stilbenes under both oxidising and non-oxidising conditions.²⁵ The elegant work of Begley and Grimshaw⁷⁶ shows that aryl bromides can undergo electrocyclic reactions to the exclusion of homolysis [Scheme 36]. They found that (114) photocyclises to give (116) as the only product. Electrochemical reduction of aryl halides results in the generation of aryl radicals; the formation of (118) must involve such species. The absence of (118) from the products of the photochemical reaction indicates that in this case the electrocyclic reaction takes precedence over the homolytic reaction.

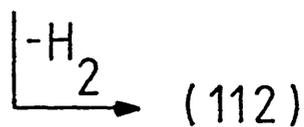


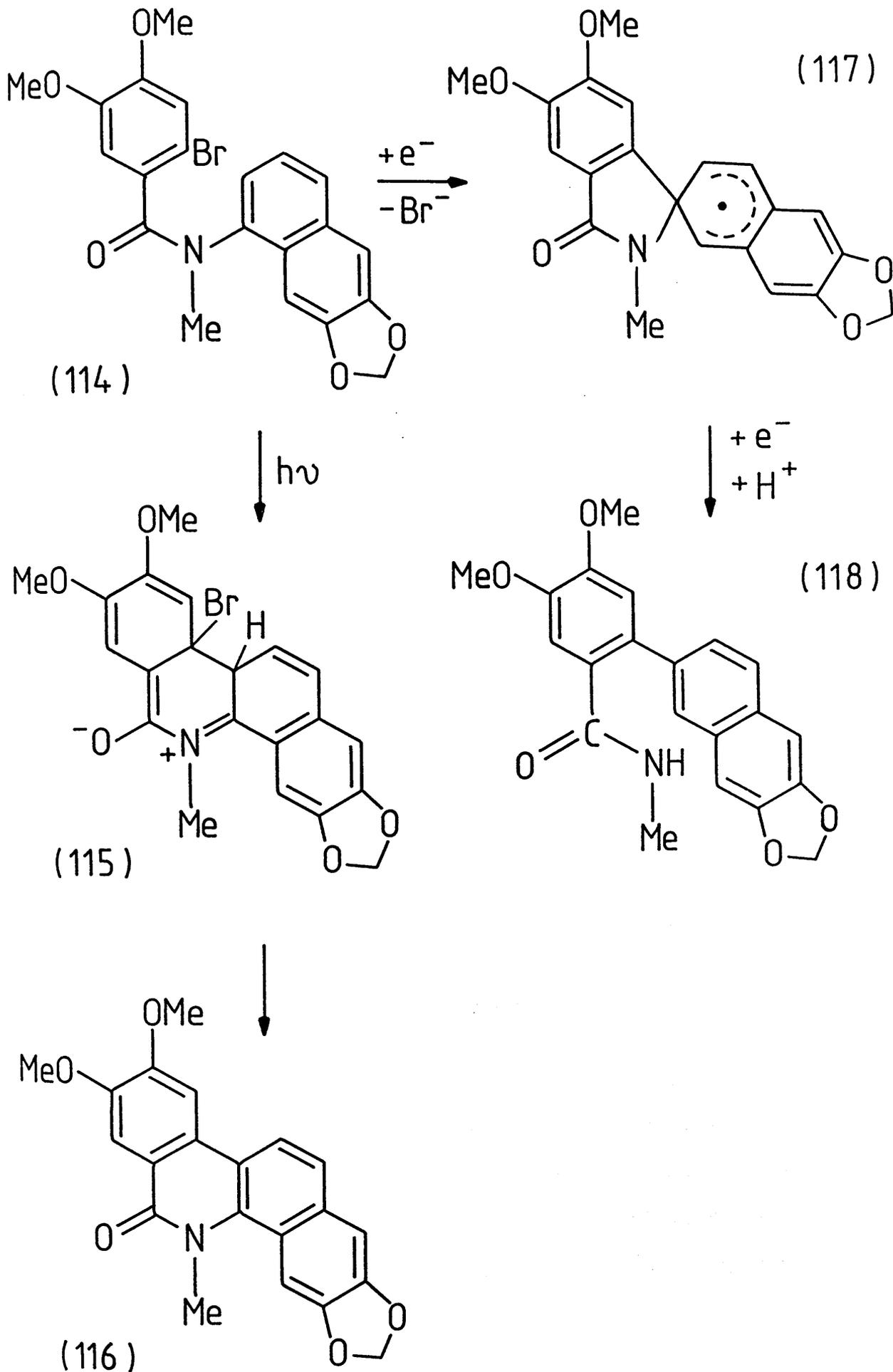
(83a)

(83b) $Y = OMe$ 

(83c)

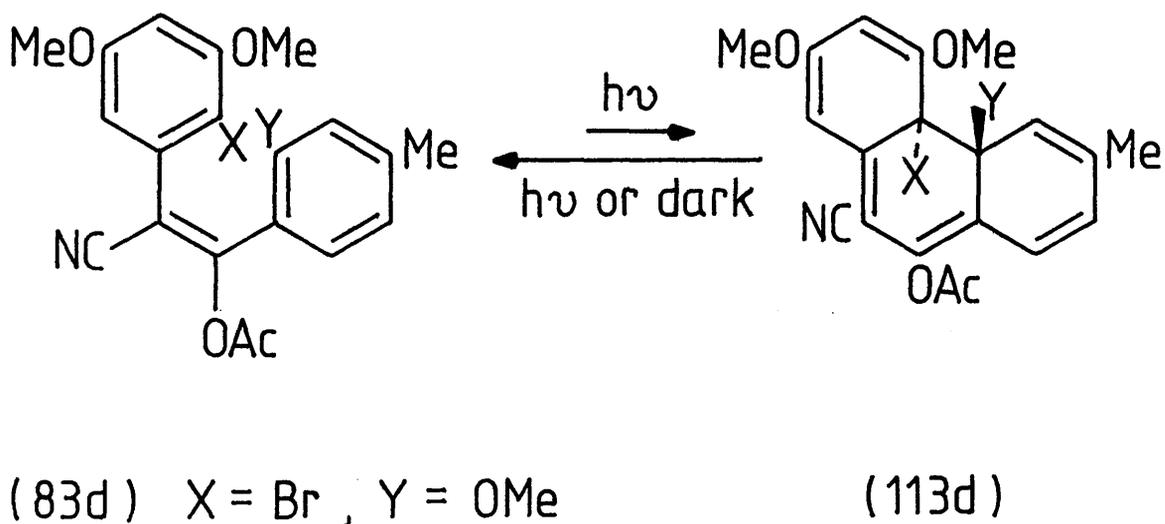
Scheme 35





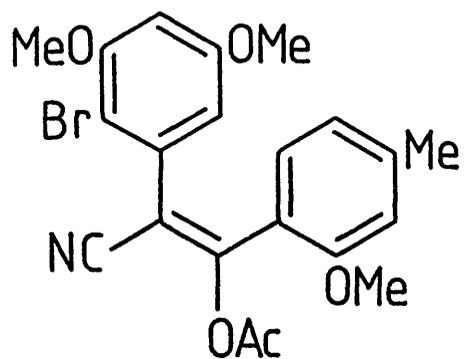
Scheme 36

Dihydrophenanthrene (113d) would probably undergo an especially rapid ring opening reaction to regenerate stilbene (83d) and thus escape trapping to phenanthrene (110) [Scheme 37]. Hence the electrocyclic pathway depicted in Scheme 35 can account for formation of phenanthrenes (71), (111) and (112), but cannot account for formation of phenanthrene (110).

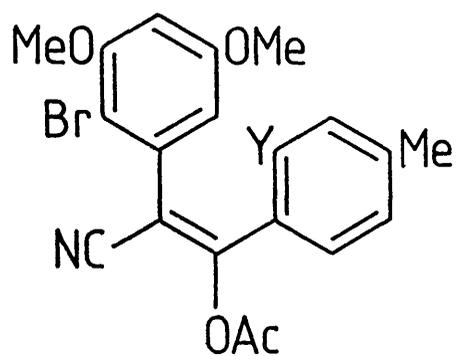
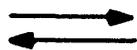


Scheme 37

The next possible mechanism can account for the production of phenanthrenes (71) and (110) [Scheme 38]. It involves electrocyclic cyclisation of the 2-bromostilbene (83) to the bromophenanthrenes (119) and (120), followed by carbon-bromine bond photolysis and hydrogen

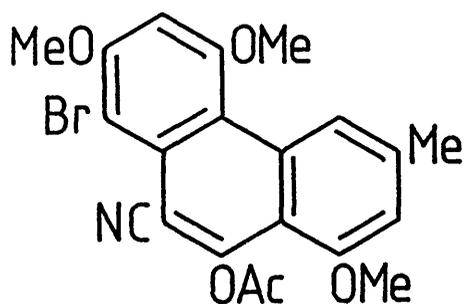
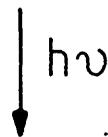
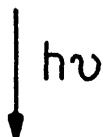


(83c)

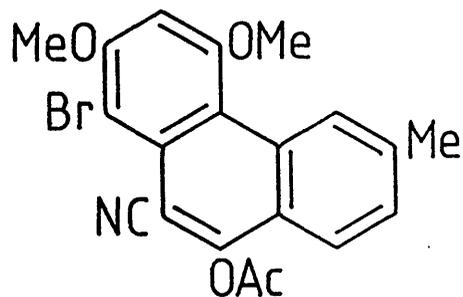


(83b)

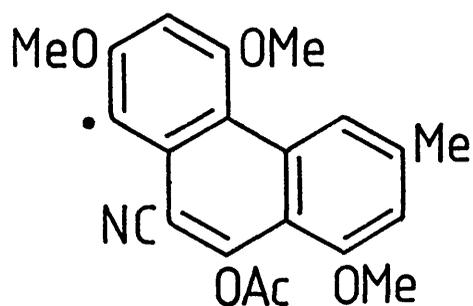
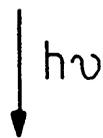
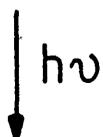
Y = OMe



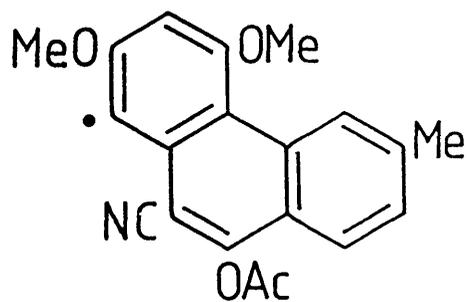
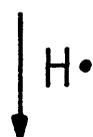
(119)



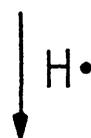
(120)



(121)



(122)

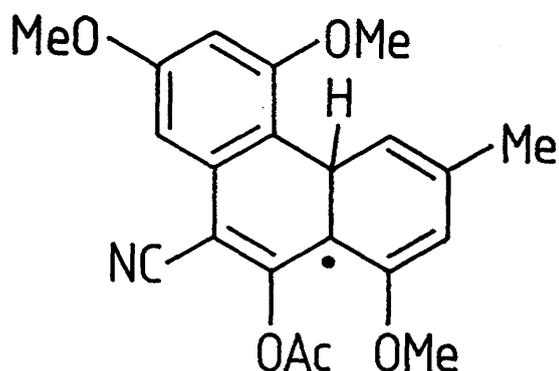


(71)

Scheme 38

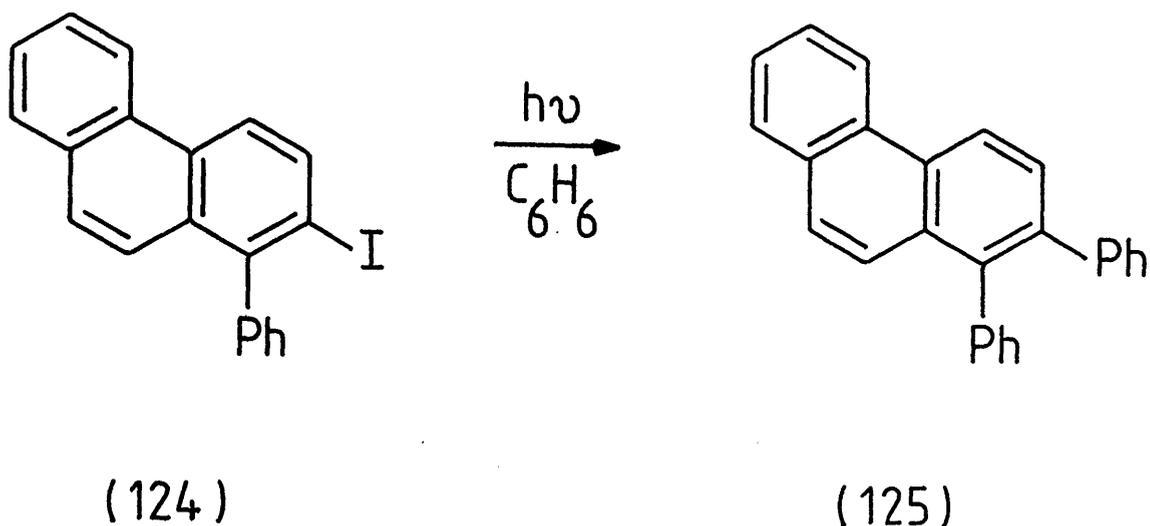
(110)

atom abstraction from methanol, hydrogen bromide, a solvent impurity or a radical of type (123a).



(123a)

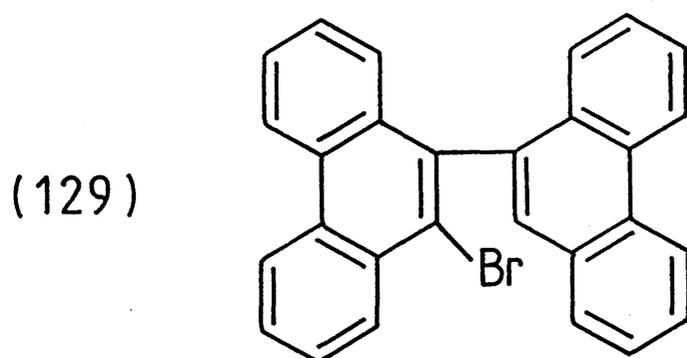
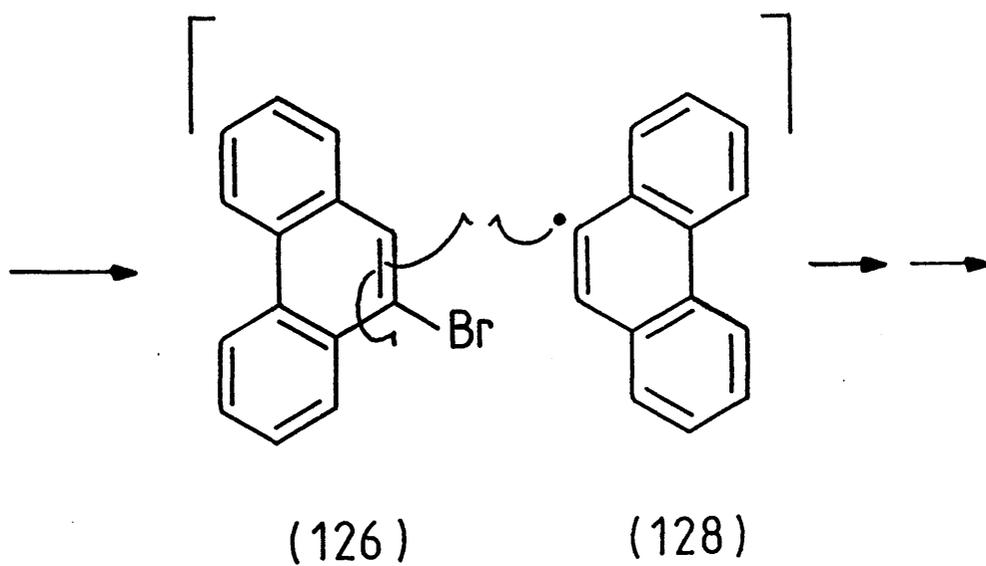
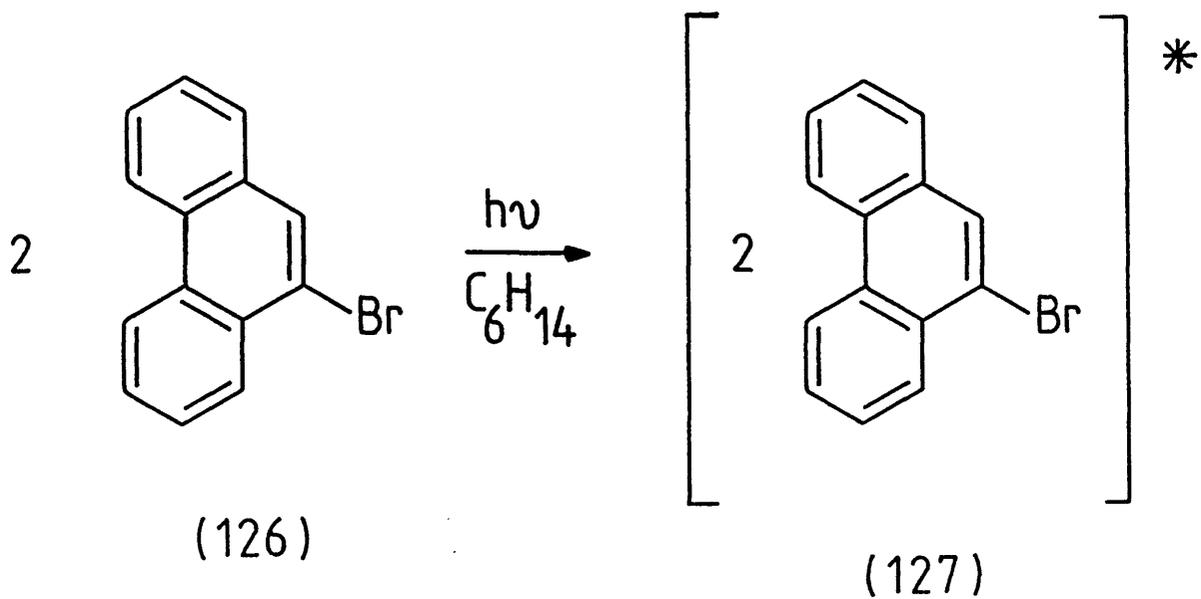
However, this is an unlikely mechanism for a number of reasons. First of all, in the vast majority of literature examples of photoinduced electrocyclisation of bromostilbenes in the absence of a trapping agent (potassium tert-butoxide, triethylamine or tert-butylamine) the carbon-bromine bond remains intact in the phenanthrene product.²⁵ (Scheme 38 involves cleavage of the carbon-bromine bond of phenanthrenes (119) and (120).) Furthermore, radicals (121) and (122) would be expected to interact with benzene (the solvent), by analogy with the formation of 1,2-diphenylphenanthrene (125) in 88% yield upon irradiation of 2-iodo-1-phenylphenanthrene (124) in benzene⁷⁷ [Scheme 39]. Similarly, radicals (121) and (122) would perhaps be



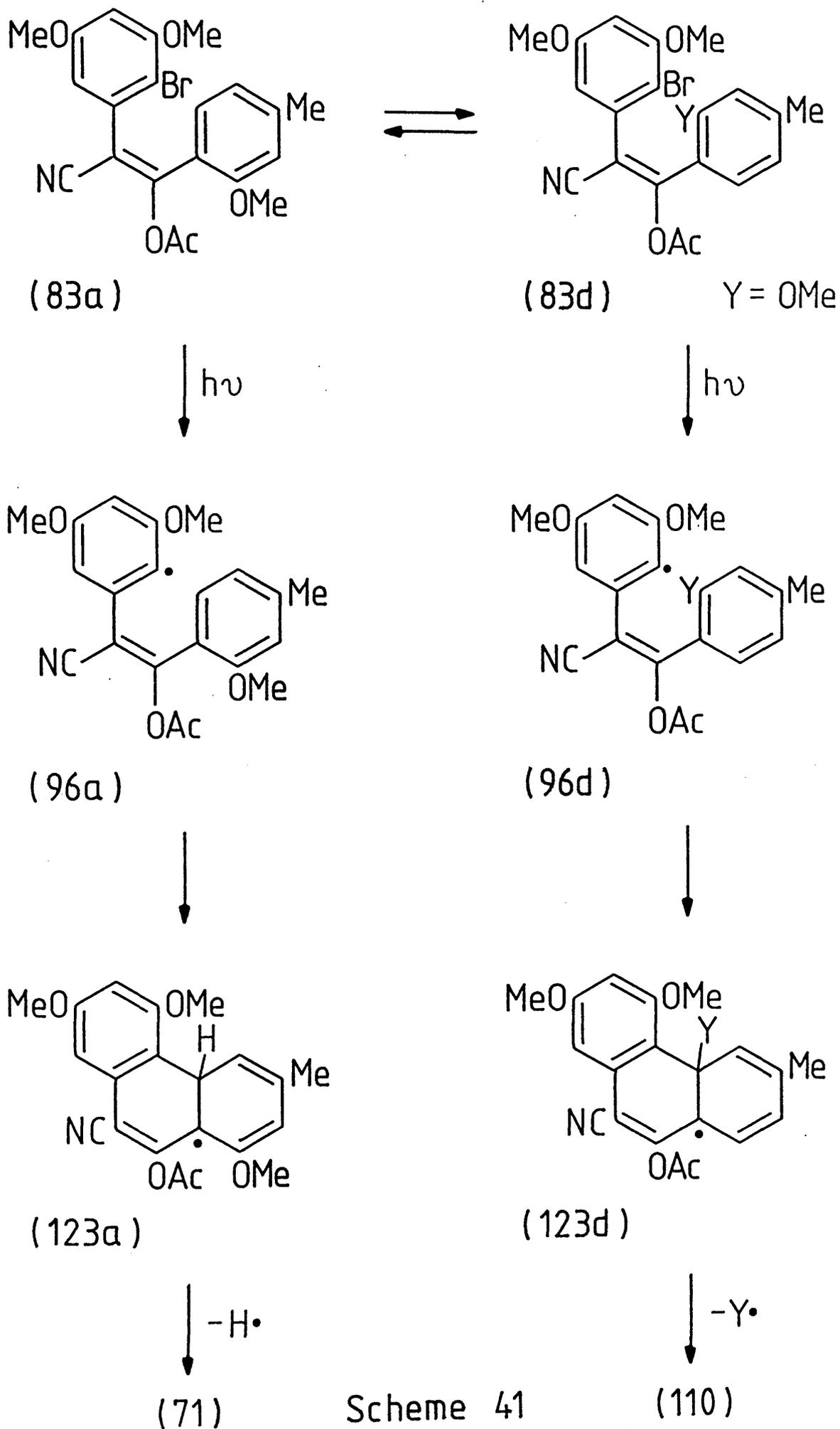
Scheme 39

expected to react in the same way as radical (128) as found by Weiss *et al.*⁷⁸ [Scheme 40]. As shown in Scheme 40, irradiation of 9-bromophenanthrene (126) in hexane forms an exciplex composed of two molecules of starting material. One of these molecules yields the corresponding 9-phenanthryl radical (128) which then attacks the second molecule to produce (129). The fact that reactions equivalent to those depicted in Schemes 39 and 40 did not occur upon irradiation of the 2-bromostilbene (83) in benzene is further evidence against the mechanism shown in Scheme 38.

The third mechanism that could operate in the photocyclisation of (83) involves photolysis of the carbon-bromine bond in the starting 2-bromostilbene followed by two competing intramolecular radical cyclisations [Scheme 41]. Trapping of radical (123d) to give phenan-



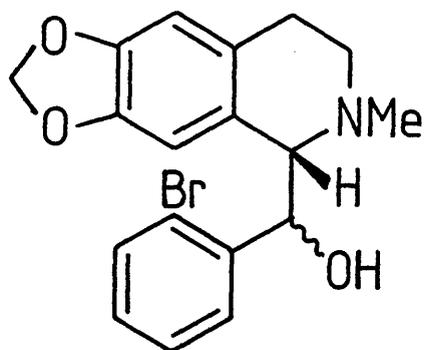
Scheme 40



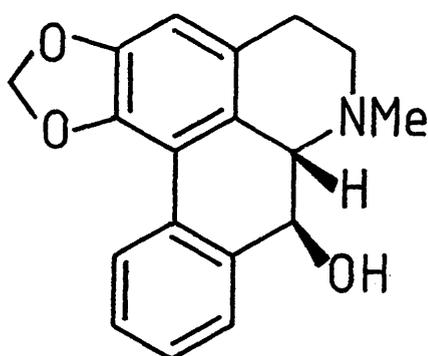
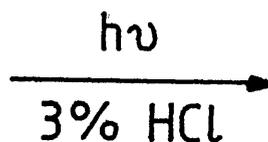
threne (110) occurs spontaneously by unimolecular expulsion of $\text{CH}_3\text{O}\cdot$ while formation of phenanthrene (71) involves hydrogen atom transfer from radical (123a) to a suitable acceptor (e.g. O_2 , $\text{HO}_2\cdot$, $\text{CH}_3\text{O}\cdot$, $\text{Br}\cdot$, etc.). (Consult the Introduction, pp. 14, 17).

Support for the radical nature of this mechanism comes from the synthesis of aporphine alkaloids by the photocyclisation of substrates bearing non-conjugated aromatic rings. Typically yields of 15-30% are obtained and photochemically induced fission of the carbon-halogen bond is assumed to be the first step.⁶⁷ This is illustrated in Scheme 42 for the conversion of (130) to the alkaloids oliveroline (131) and ushinsunine (132).⁷⁹

Photochemically induced homolysis reactions of the carbon-halogen bond have been known since around 1960, and bond reactivity follows the order expected from carbon-halogen bond energy considerations. Iodobenzene⁸⁰ was investigated first, and later bromobenzene⁸¹ was shown to undergo equivalent reactions, and chlorobenzene to react with a low quantum yield. There are two processes for energy transfer to the carbon-halogen bond leading to radicals, which may recombine before breaking from the solvent cage and forming products.⁷⁴ Firstly, homolytic fission in aryl iodides may arise from population of $n\sigma^*$ or $\sigma\sigma^*$ states. This mechanism is not available in the ordinary solution photochemistry of aryl bromides and chlorides, which do not possess a low energy σ^* orbital. Radiationless decay of the $\pi\pi^*$ state to a vibrationally excited ground state can also lead to homolysis of the weakest bond in the system before the vibrational energy is dispersed

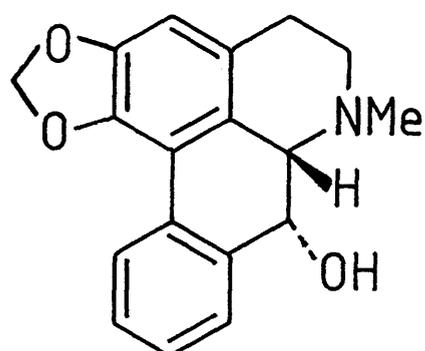


(130)



(131)

+



(132)

Scheme 42

as heat. In aryl iodides, bromides and chlorides the weakest bond is usually, but not necessarily, the carbon-halogen bond. Clearly, for simple homolysis to occur, the energy of the excited state must be greater than the bond energy. According to Grimshaw and de Silva⁶⁷ the energy requirement for homolysis is lowered when the resultant radical is complexed by an adjacent π -cloud. This is the situation in

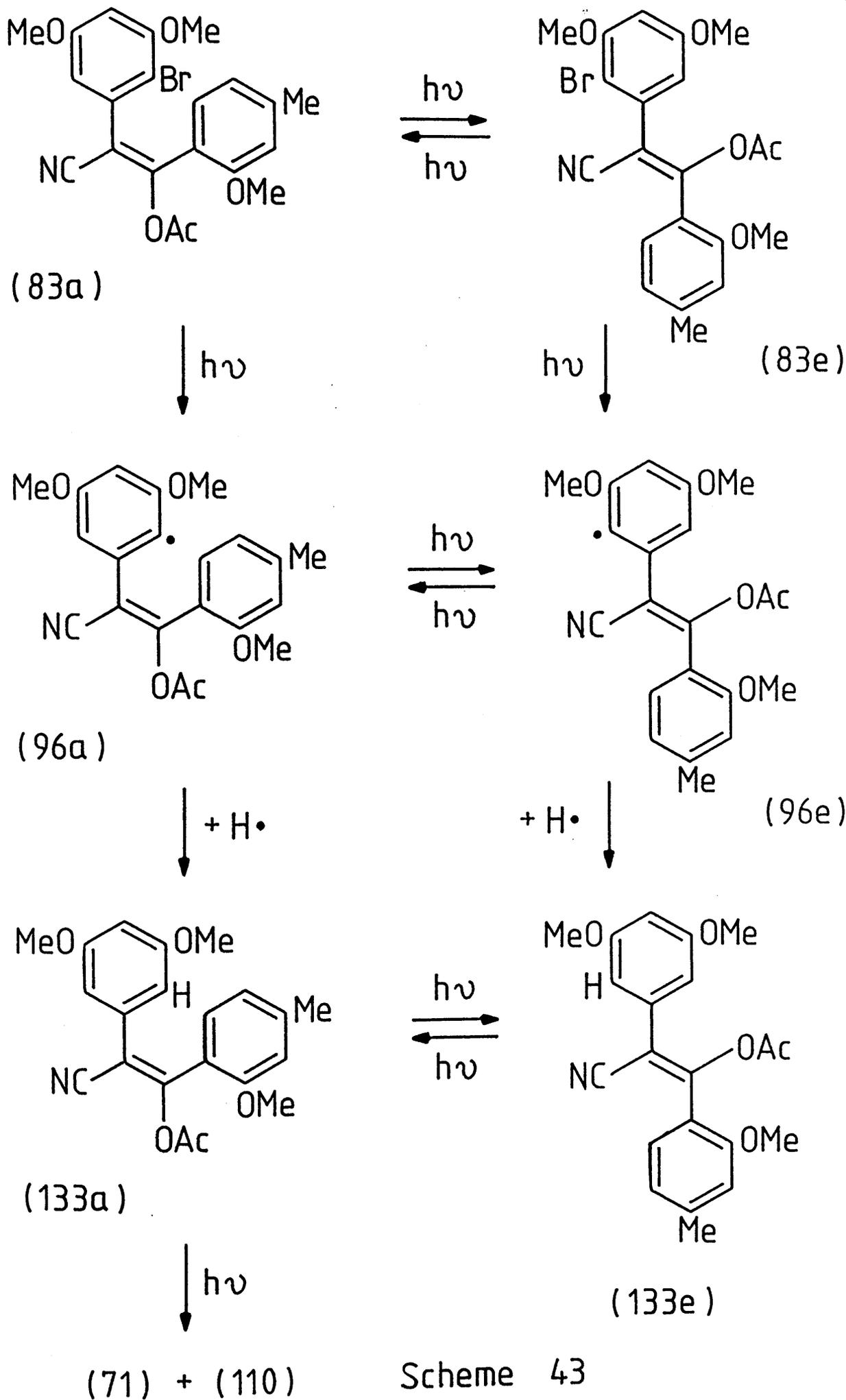
the photolysis of the 2-bromostilbene (83).

Scheme 43 outlines the final possible mechanism, in which the first step is again carbon-bromine bond photolysis. Radical (96a), derived from the Z-2-bromostilbene (83a), abstracts a hydrogen atom and then undergoes oxidative and eliminative photocyclisations to yield phenanthrenes (71) and (110) respectively. Radical (96e), derived from the E-isomer, also abstracts a hydrogen atom, and then isomerises to the Z-isomer and cyclises to phenanthrenes (71) and (110). However, this is unlikely to be a major pathway owing to the relatively low concentration of species capable of donating a hydrogen atom.

A possible side reaction in the photoreaction is arylation of radical (96e) by interaction with benzene.

In summary then, phenanthrene (110) could be formed by three of the four possible mechanisms (Schemes 38, 41 and 43), all of which involve carbon-bromine bond photolysis, either before or after cyclisation. The most likely photolytic pathway is Scheme 41, which involves intramolecular radical cyclisation as the key step. Phenanthrene (71) could be formed by all four mechanisms while phenanthrenes (111) and (112) can only be derived via the electrocyclic pathway shown in Scheme 35. Thus both electrocyclic and photolytic mechanisms are operating in this system.

The ability of an electrocyclic reaction to compete with a homolytic reaction depends upon the relative activation energies for the two processes and on the energy available for reaction. Steric factors are important in electrocyclic reactions since there is more steric overcrowding in the transition state. The homolytic reaction may well result in the relief of steric overcrowding in the rate determining step. The competition



between electrocyclic and homolytic processes also depends upon the nature of the halogen since homolysis becomes progressively easier as the substituent is changed $F \rightarrow Cl \rightarrow Br \rightarrow I$.

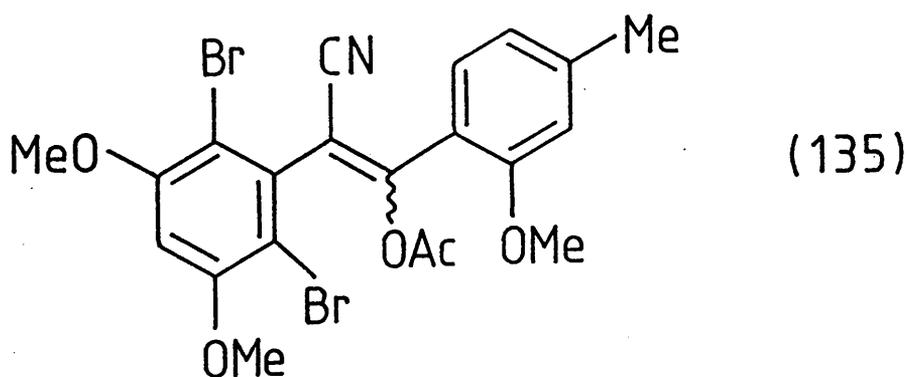
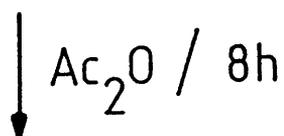
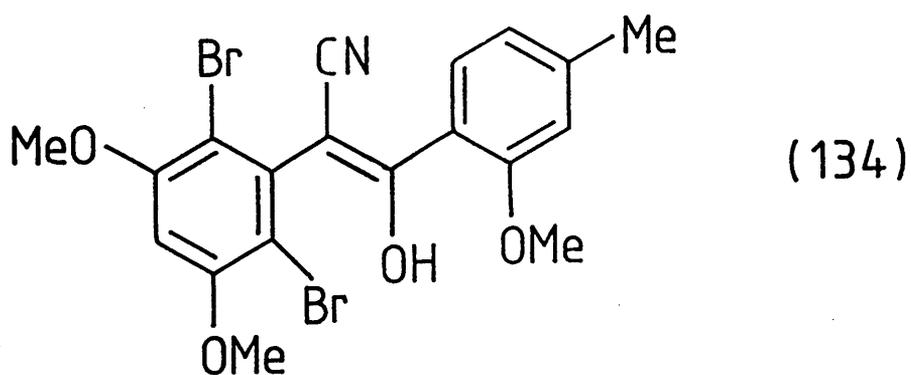
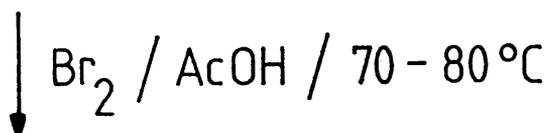
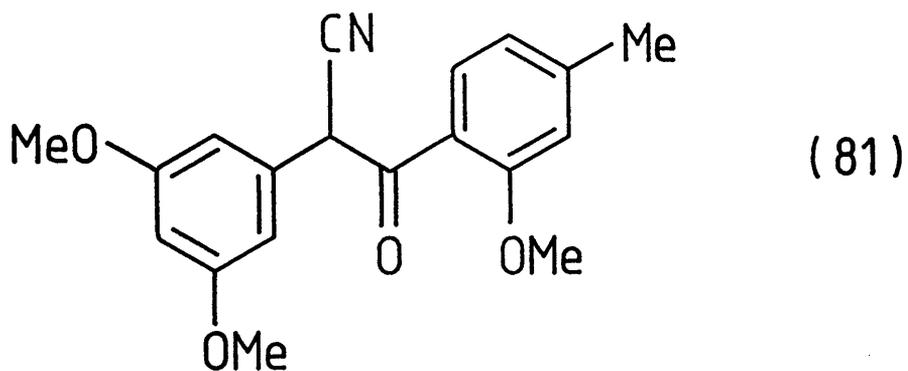
As described above, the 2-bromostilbene (83) photocyclises via both electrocyclic and photolytic pathways. However, the corresponding 2-iodostilbene (139) probably photocyclises via initial carbon-iodine bond photolysis (see Section 2.4.2). These results clearly demonstrate the effect of carbon-halogen bond energy and size of halogen in determining the mechanism of photocyclisation.

2.3 2,6-Dibromostilbenes

2.3.1 Synthesis

It was reasoned that the 2,6-dibromostilbene (135) would give fewer photoproducts than the corresponding 2-bromostilbene (83) because of the symmetry of the pentasubstituted aromatic ring and so this stilbene became the next synthetic target.

Treatment of the β -keto nitrile (81) with two equivalents of N-bromosuccinimide gave a complex mixture of inseparable products. However, the desired dibromo derivative (134) was obtained in 77% yield upon reaction of (81) with bromine in acetic acid at 70–80°C [Scheme 44]. The dibromo compound (134) was shown by 1H nmr (d_6 -dmsO) and ir (KBr disc) to exist entirely in the enol form: the 1H nmr spectrum lacks a signal corresponding to $CHCN$ and the ir spectrum shows a strong O-H absorption and no C=O absorption. The reason for this preference for the enol form is explained in Section 2.5.1. When



$$\underline{E} : \underline{Z} = 2.3 : 1.0$$

compound (134) was refluxed in acetic anhydride for 8 hours the E-enol acetate (135) crystallised out from the solution upon cooling and the Z-isomer remained as a white crystalline solid upon removal of the acetic anhydride as an azeotrope with toluene. The ratio of stereoisomers was E : Z = 2.3 : 1.0 after recrystallisation. The E and Z assignments were made on the basis of uv measurements in the same way as for the 2-bromostilbene (83). The molar extinction coefficient, ϵ , of the longest wavelength band of Fig. 7 is greater than that of Fig. 8. Thus Fig. 7 is the uv spectrum of the E-isomer and Fig. 8 the uv spectrum of the Z-isomer.

2.3.2 Photochemistry

When the 2,6-dibromostilbene (135) was irradiated in benzene only starting material was recovered. Introduction of potassium tert-butoxide or triethylamine into the reaction mixture caused a complex mixture of products to form. The lack of signals in the region of δ 8.5-9.5 ppm in the ^1H nmr spectrum of the crude reaction mixture implied that photocyclisation had not occurred. Failure to cyclise by the electrocyclic pathway might be due to inefficiency of overlapping of the hexatriene system. This was proposed to account for the failure of the 2-bromostilbene (136) to undergo photochemical electrocycloisat⁸². The corresponding 2-iodo derivative (137) cyclised in 25% yield via a radical mechanism. In addition, halogen substituents increase inter-system crossing from both the excited singlet to the triplet state and from the triplet state to the singlet ground state.⁸³ Therefore, electrocyclic and homolytic processes from the S_1 excited state of the

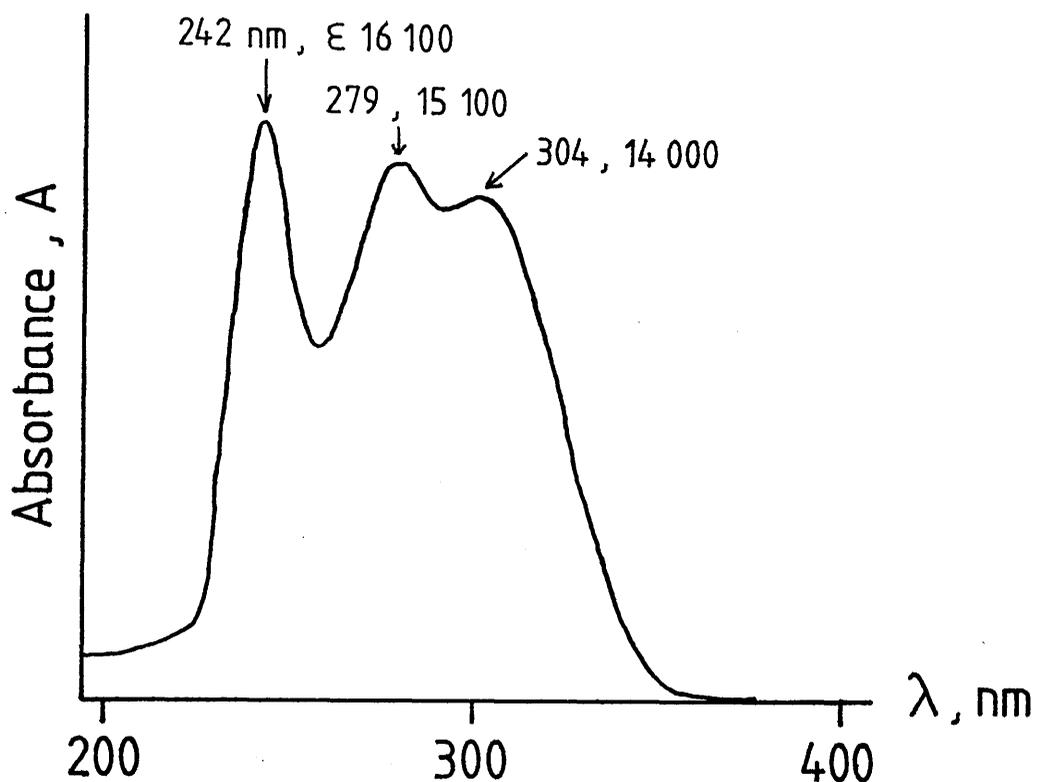


Fig. 7 Uv spectrum of the E-stilbene (135) in CH₂Cl₂

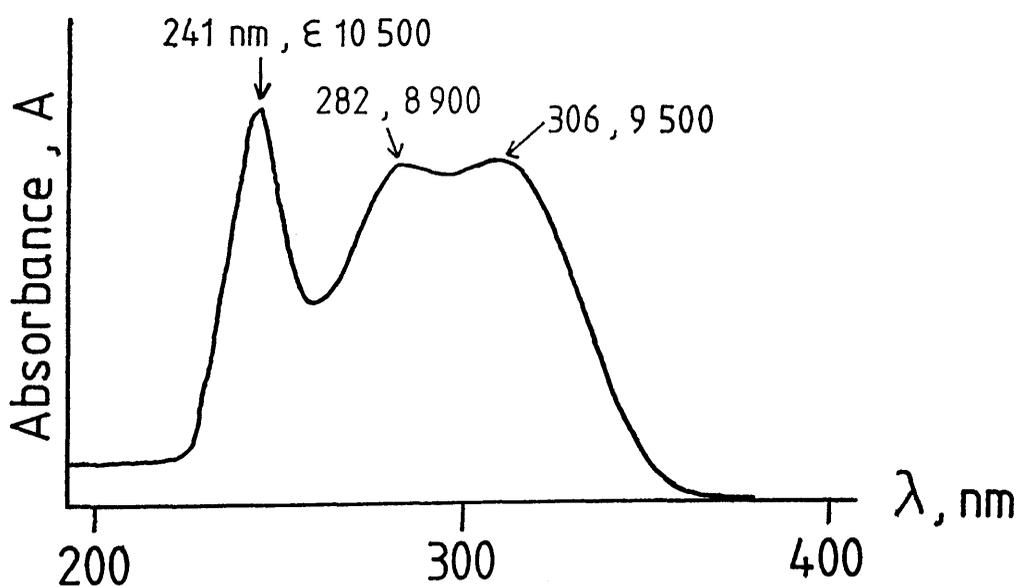
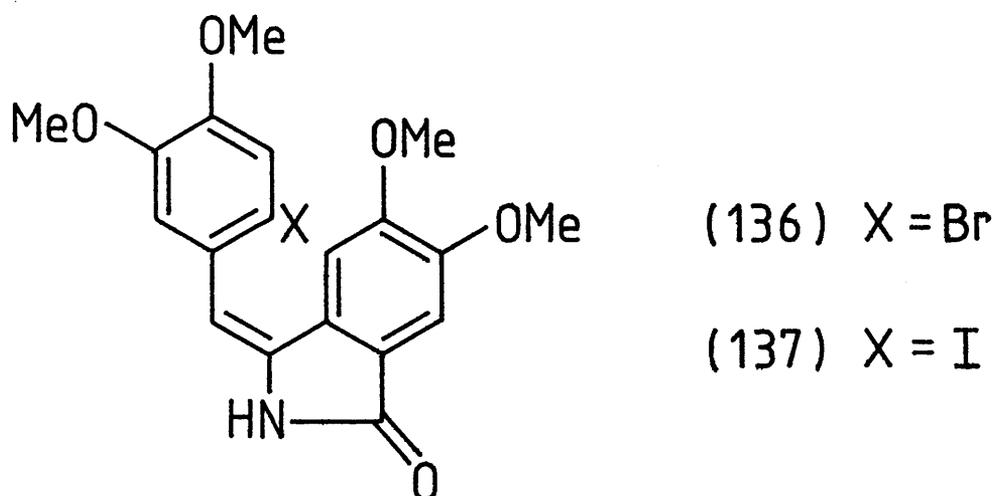


Fig. 8 Uv spectrum of the Z-stilbene (135) in CH₂Cl₂

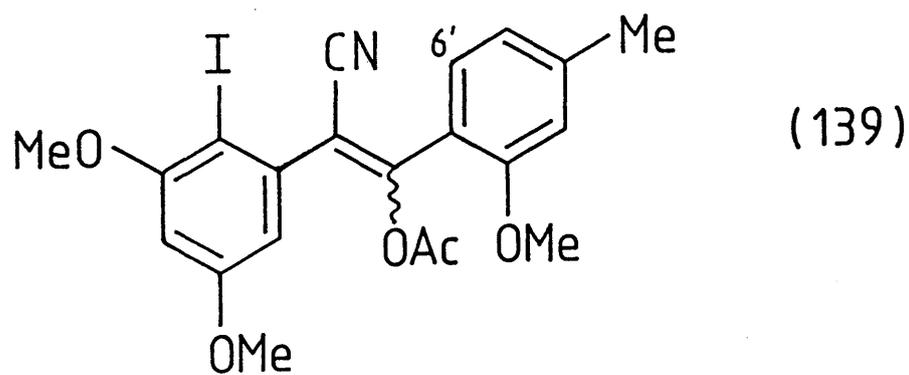
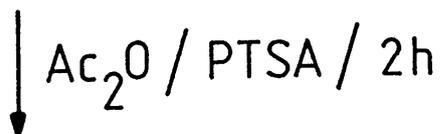
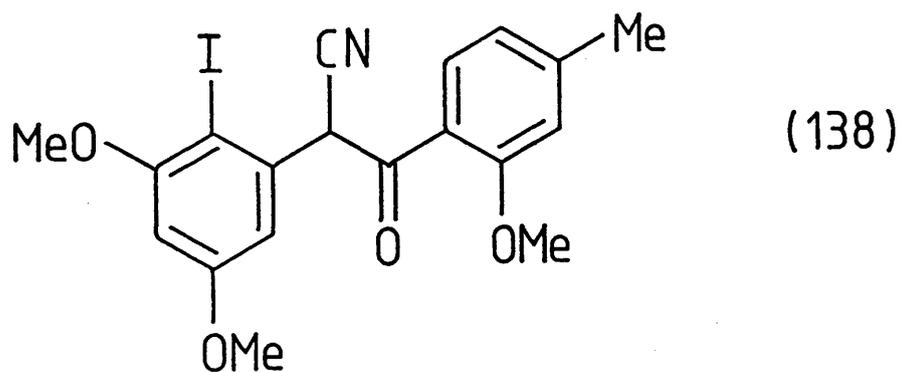
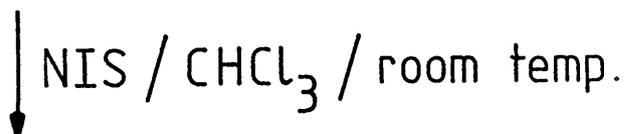
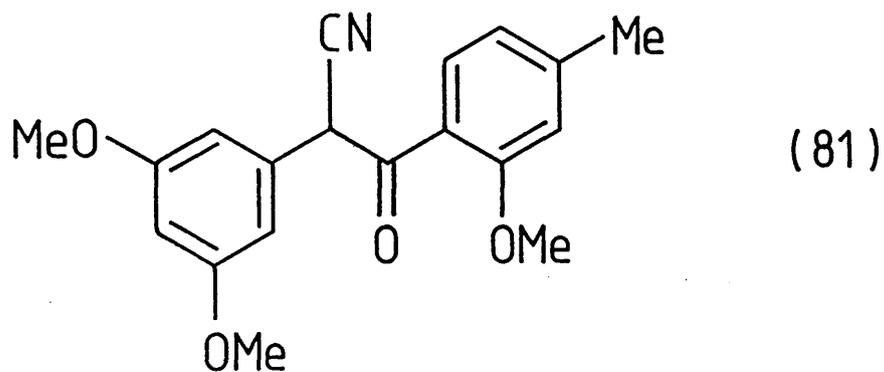
dibromostilbene (135) may be unable to compete effectively with very fast intersystem crossing.



2.4 2-Iodostilbenes

2.4.1 Synthesis

Next, attention was turned to the 2-iodostilbene (139), which was conveniently prepared in two steps from the β -keto nitrile (81) [Scheme 45]. The first step involved iodination of (81) with precisely one equivalent of N-iodosuccinimide (added in small portions over 1½ hours) in chloroform at room temperature for 10½ hours. Much experimentation was required to optimise the conditions of the iodination reaction to give an acceptable yield of the 2-iodo β -keto nitrile (138).



E : Z = 1.0 : 1.0

Scheme 45

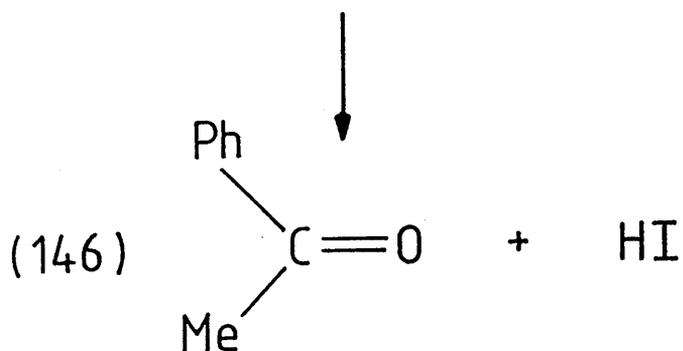
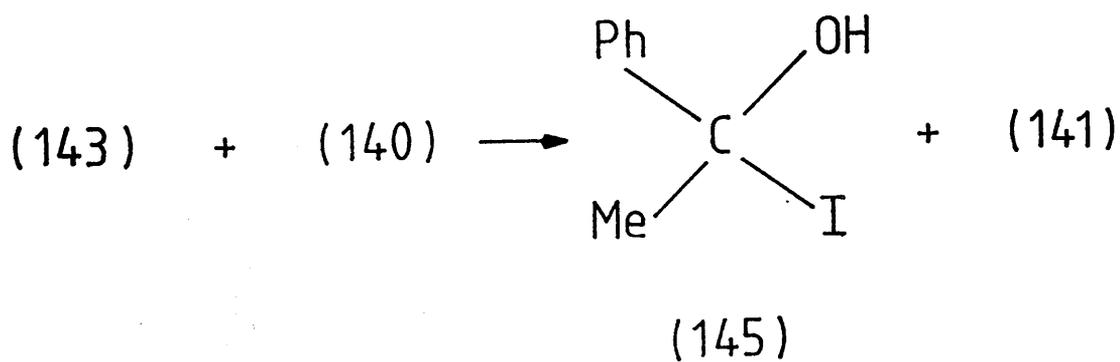
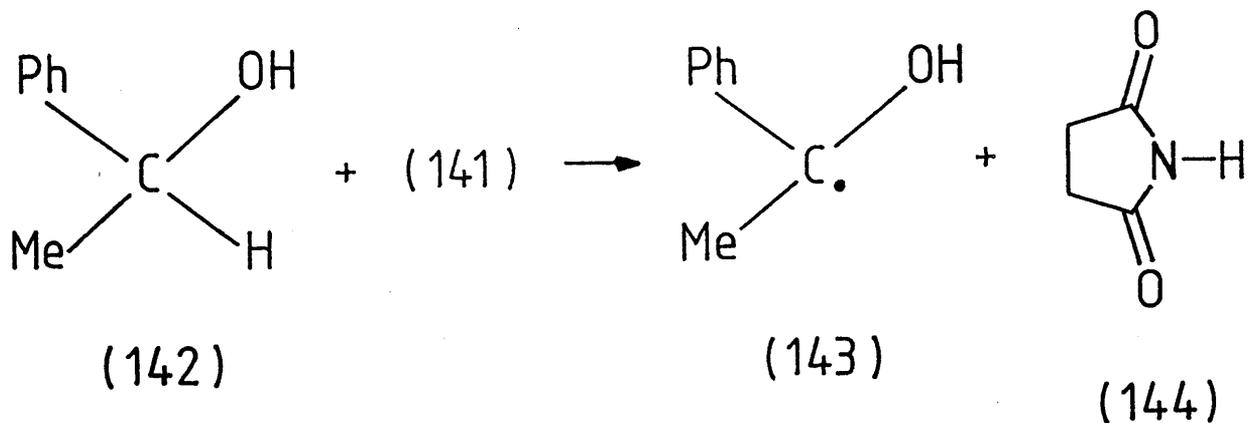
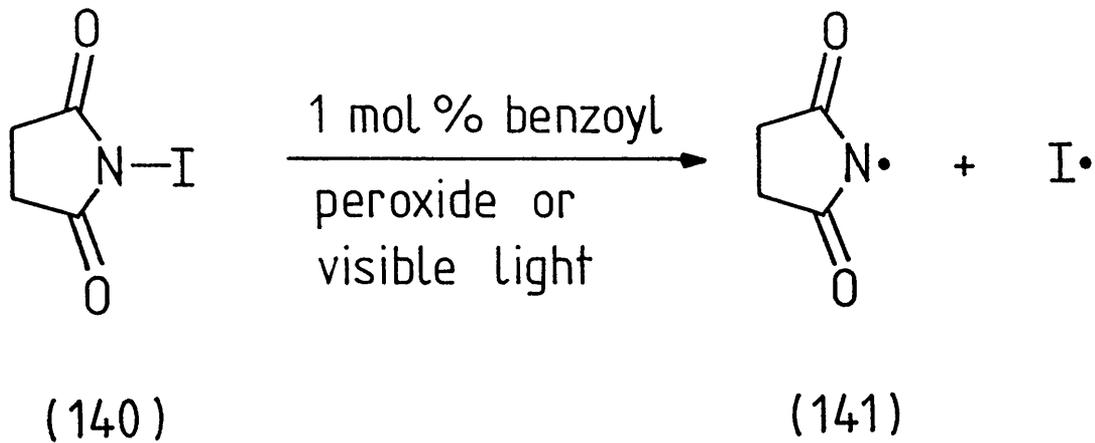
The first time the reaction was carried out the precaution was taken to exclude light from the reaction mixture since NIS is light sensitive. NIS was added in one portion at the beginning of the reaction to a chloroform solution of (81) and the solution was refluxed for 3 hours. After cooling, the red solution was washed successively with 20% aqueous sodium thiosulphate and brine, then dried and evaporated to leave an amber gum. This crystallised on adding ether and gave the 2-iodo β -keto nitrile (138) in 40% yield after recrystallisation from chloroform/hexane. When the reaction was repeated using carbon tetrachloride as the solvent, a lower yield (< 20%) of (138) was obtained, even when the NIS was added over a period of 3 hours. Two simple experiments were conducted in an attempt to account for the low yield of (138). First of all, a chloroform solution of (138) was refluxed in the dark for 3 hours, whereupon the solution developed a red colouration due to liberated iodine. That de-iodination had indeed occurred was confirmed by ^1H nmr spectroscopy of the residue after evaporation of the solvent. The spectrum displayed a small peak at $\delta 5.85$ ppm due to CHCN of the β -keto nitrile (81). (The corresponding peak of the 2-iodo β -keto nitrile (138) occurs at $\delta 6.34$ ppm). A small amount of de-iodination also occurred when a chloroform solution of (138) was washed with 20% aqueous sodium thiosulphate. No iodination of (81) occurred when treated with one equivalent of NIS in chloroform at room temperature in the dark for 4 hours. However, addition of NIS to a chloroform solution of (81) over $1\frac{1}{2}$ hours and reaction for a further 9 hours at room temperature in the diffuse laboratory light led to an 84% yield of (138).

These results suggest that the iodination reaction proceeds via a heat or light initiated radical mechanism. Radical^{84,85} as well as ionic⁸⁶ mechanisms for iodination by NIS have been proposed in earlier works. The mechanism for iodination of (81) may be similar to that suggested by Beebe and Howard⁸⁴ in 1969 for the oxidation of 1-phenylethanol (142) by NIS. They carried out a set of experiments which led to the mechanistic proposal shown in Scheme 46 in which the succinimidyl radical (141) is the chain carrier. Scheme 47 outlines the proposed mechanism for the reaction of (81) with NIS. The site of iodination is mainly controlled by the methoxyl and carbonyl groups of (81). These groups are ortho/para directors in radical processes and so iodination occurs at position 2 preferentially.

As depicted in Scheme 45, the 2-iodo β -keto nitrile (138) was reacted with acetic anhydride in the presence of a catalytic amount of p-toluenesulphonic acid to afford a mixture of E- and Z-2-iodostilbenes (139) which were inseparable by crystallisation or silica gel chromatography. The 200 MHz ¹H nmr spectrum of the mixture of geometric isomers was assigned by comparison with the spectra of E- and Z-2-bromostilbenes (83). The integration of the H-6' doublet of the E-isomer at δ 7.56 ppm relative to that of the Z-isomer at δ 7.04 ppm indicated that the ratio of isomers was E : Z = 1.0 : 1.0.

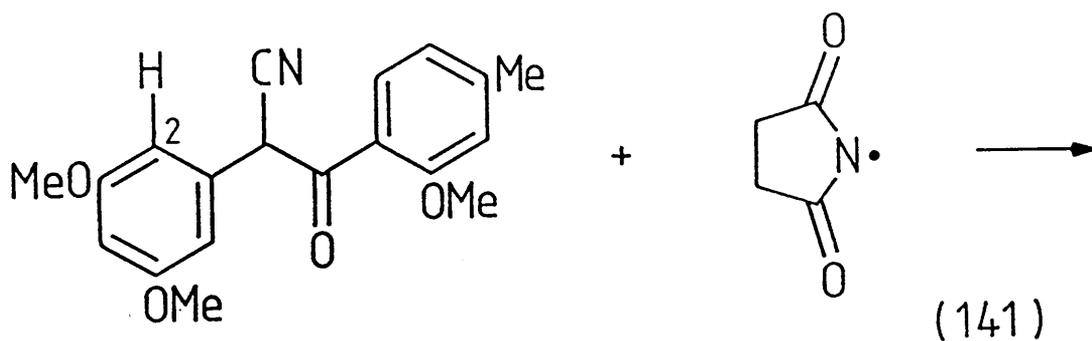
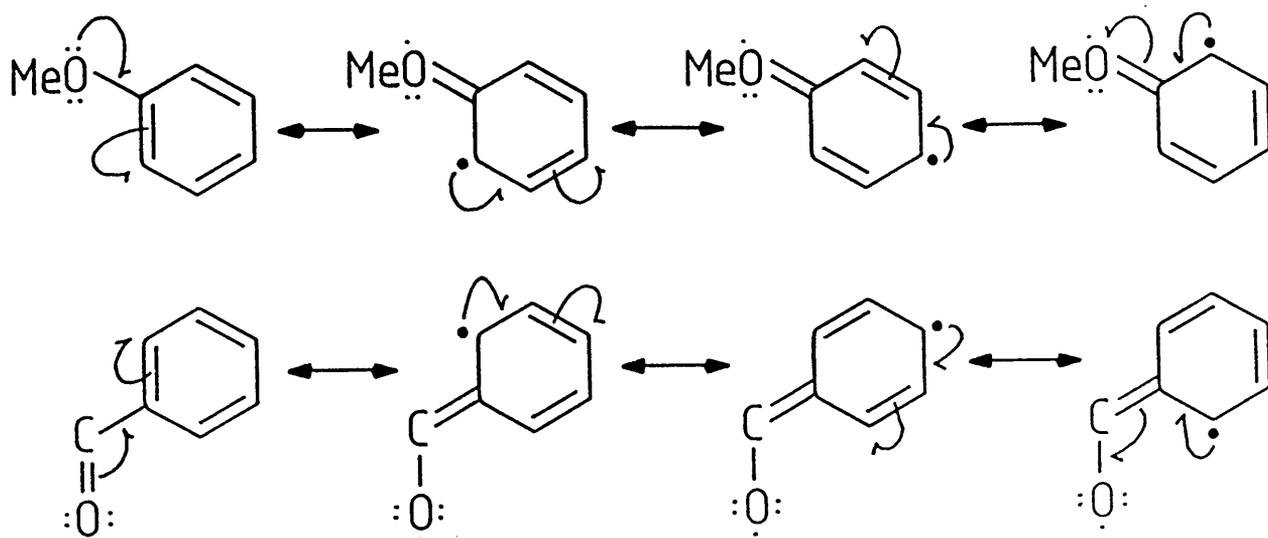
2.4.2 Photochemistry

In 1965 Kupchan and Wormser⁴⁶ published a new general synthesis of substituted phenanthrenes involving photocyclisation of 2-iodostilbenes. They detected radical intermediates in the photo-

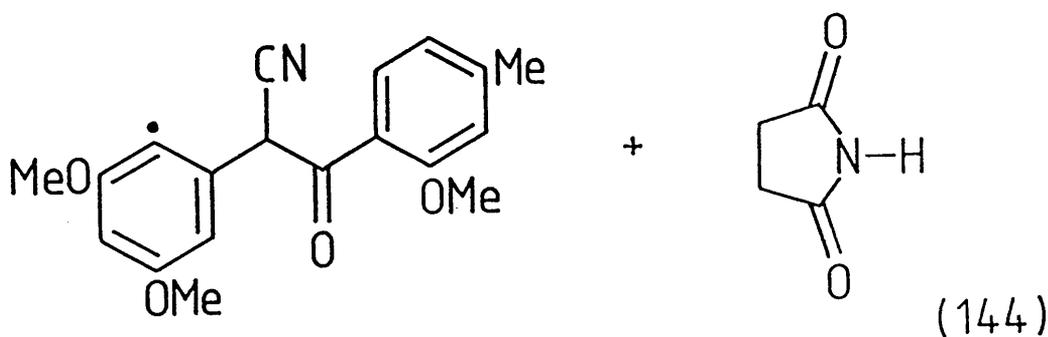


Scheme 46

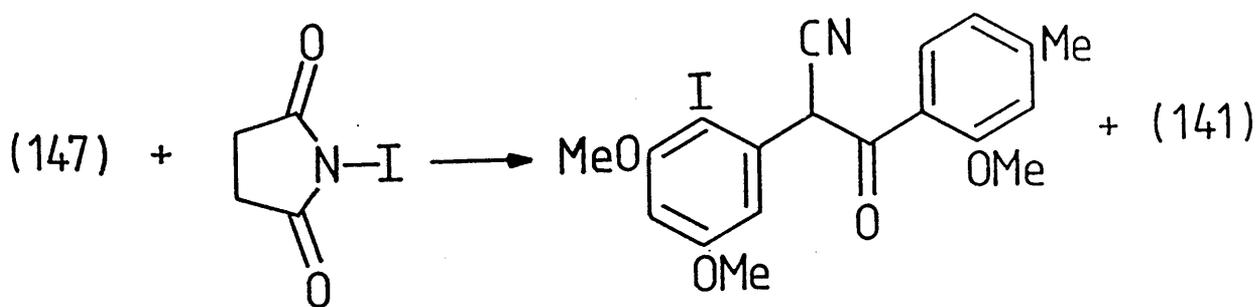
MeO and C=O are o/p directors in radical processes



(81)



(147)



(140)

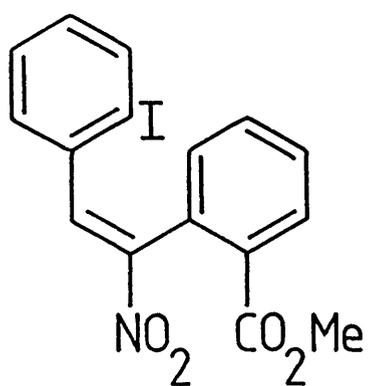
(138)

process by electron spin resonance and devised experiments to evaluate the integrity of the free radical formed upon photolysis of the carbon-iodine bond of the stilbene. They reasoned that 2-, 3- or 4-iodostilbenes would yield a common product if rearrangement of the aryl radical occurs. Scheme 48 shows the results of these experiments. The 2-iodostilbene (148) gave phenanthrene (149) in 50% yield while the 3-iodo and 4-iodo isomers of (148) did not photocyclise, clearly demonstrating that rearrangement of the aryl radical does not occur.

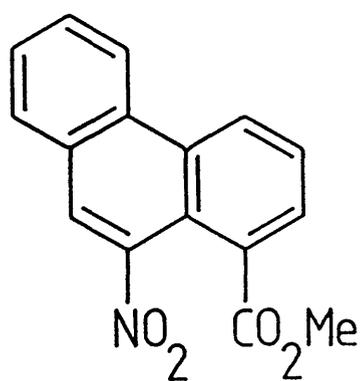
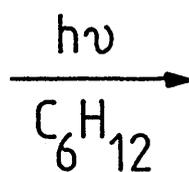
The photocyclisation of iodostilbenes is always accompanied by loss of the iodo substituent irrespective of its position.²⁵ This reflects the ease with which aryl iodides undergo carbon-iodine bond photolysis upon uv irradiation.

In the present study, the 2-iodostilbene (139) was irradiated in deoxygenated benzene whereupon a 50% yield of the desired phenanthrene (71) was obtained in addition to a 15% yield of phenanthrene (110) [Scheme 49]. The formation of these products very likely involves initial photolysis of the carbon-iodine bond of stilbene (139) and subsequent intramolecular radical cyclisation. Radical (123a) is trapped oxidatively by iodine generated *in situ* or by residual traces of dissolved oxygen, while trapping of radical (123d) occurs by unimolecular expulsion of $\text{CH}_3\text{O}\cdot$.

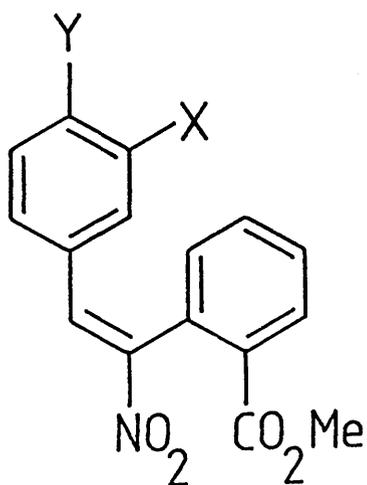
A related intramolecular arylation reaction was observed for the 2-iodo β -keto nitrile (138) upon uv irradiation in deaerated acetonitrile containing two equivalents of iodine [Scheme 50]. A complex mixture of inseparable products was obtained, although one of these was identified as phenanthrene (72) by the presence of a singlet at



(148)

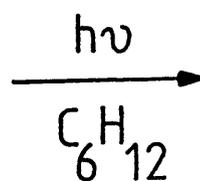


(149)

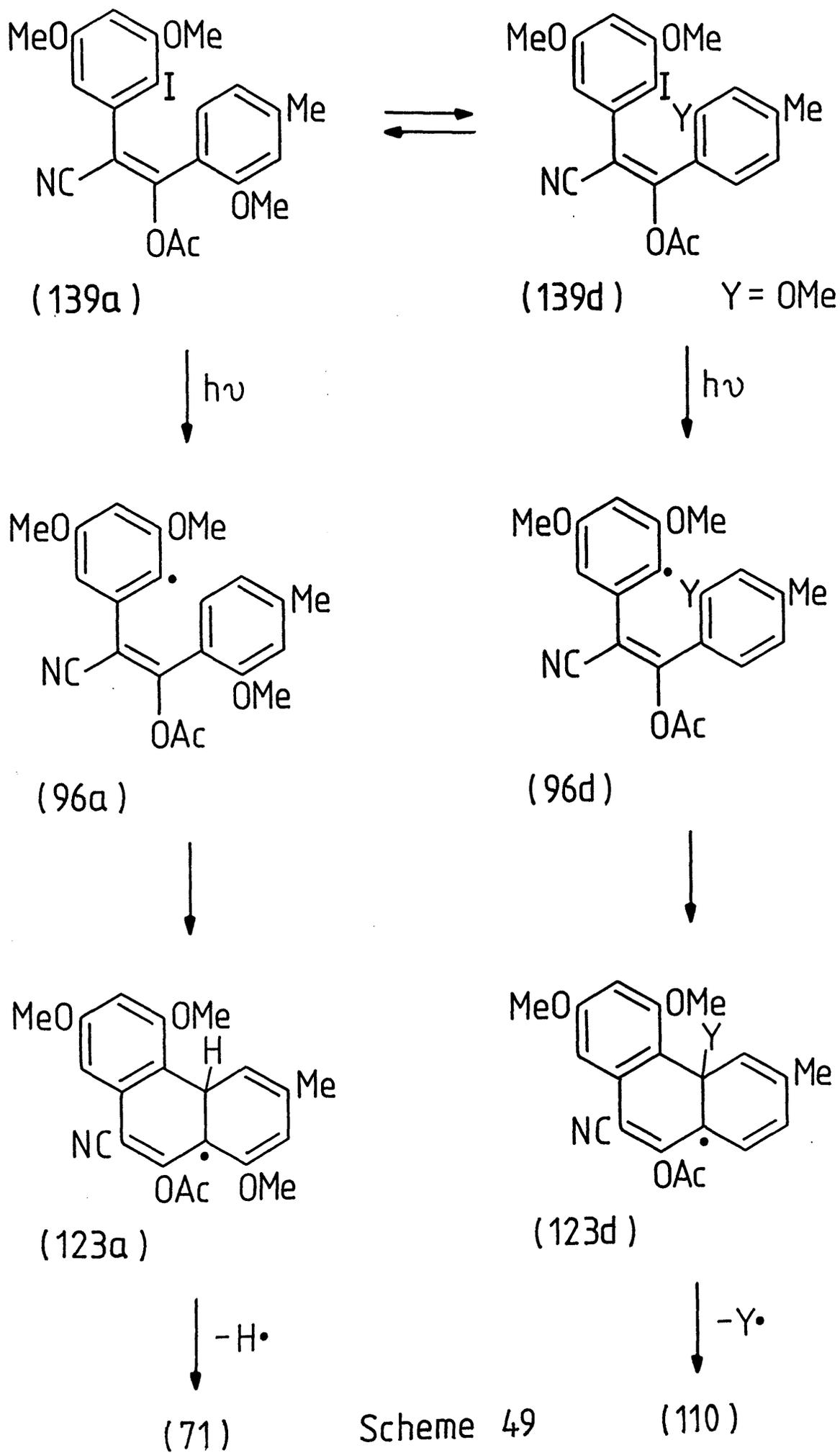


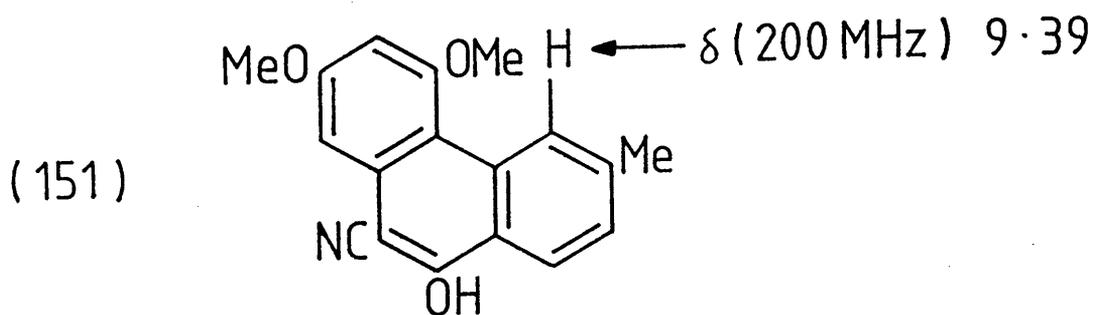
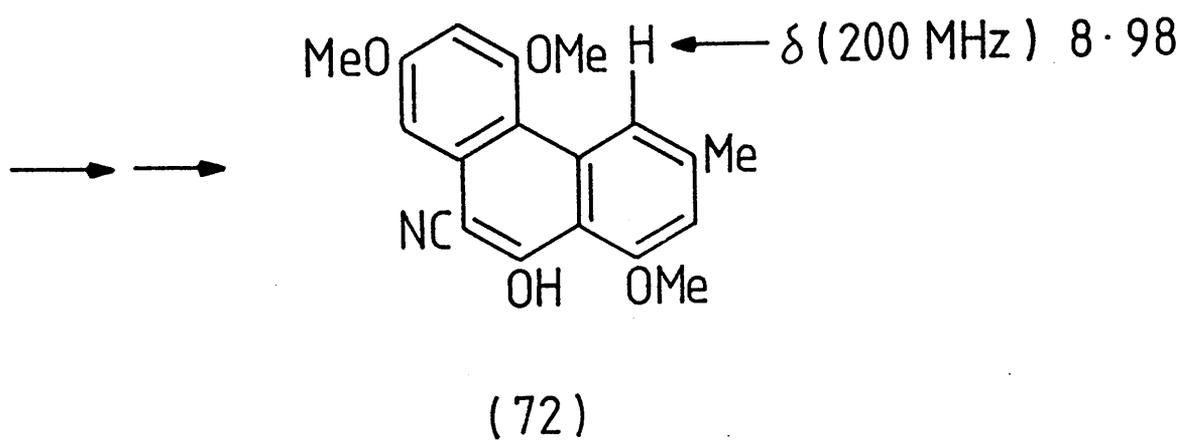
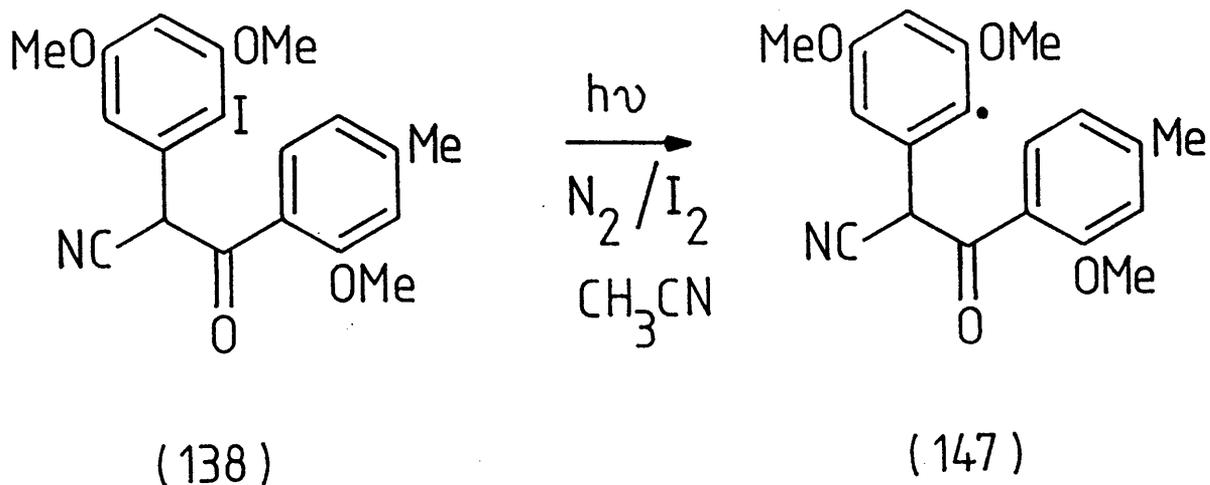
(150) X = I , Y = H

or X = H , Y = I

no phenanthrene
products

Scheme 48





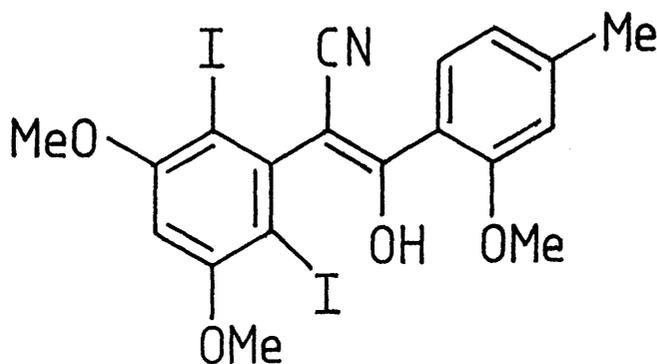
None of this was detected

δ 8.90 ppm in the 90 MHz ^1H nmr spectrum of the crude reaction mixture. Surprisingly, none of the alternative photocyclisation product (151) was detected.

2.5 2,6-Diiodostilbenes

2.5.1 Synthesis

It was discovered that treatment of the β -keto nitrile (81) with precisely two equivalents of N-iodosuccinimide affords the diiodo derivative (152). This diiodo compound and the corresponding dibromo



(152)

compound (134) exist in the enol form in the solid state and in solution. The ir spectra of potassium bromide discs of (134) and (152) exhibit strong O-H absorption and no C=O absorption (see Table 2), clearly demonstrating that these compounds exist entirely in the enol form in the solid state. The solution ir spectra of (134) and (152) could not be recorded because they are insoluble in all common solvents except dimethyl

sulphoxide and tetrahydrofuran. Evidence for the enol form in solution is provided by ^1H nmr: the spectra of (134) and (152) in d_6 -dimethyl sulphoxide lack a signal due to CHCN and the spectrum of (152) at 200 MHz shows a broad singlet at $\delta 10.00$ ppm due to OH .

Table 2. Ir data for compounds (69), (134) and (152);

s - strong, m - medium, w - weak

Compound	$\nu(\text{KBr}), \text{cm}^{-1}$	$\nu(\text{CHCl}_3), \text{cm}^{-1}$
tetramethoxy (69)	3650-3030 m, 2210 m, 1635 s, 1610 s, 1585 s	3620-3140 very w, 2250 w, 2210 w, 1715 m, 1610 s
dibromo (134)	3630-3030 s, 2210 m, 1640 m, 1610 m, 1570 s	
diiodo (152)	3640-3020 s, 2205 s, 1630 s, 1610 m	

The enol tautomer is also preferred by the tetramethoxy compound (69) in the solid state as shown by ir spectroscopy (refer to Table 2) and X-ray analysis [Fig. 9]. As expected, the two aromatic rings adopt the trans-configuration. Table 3 shows that the rings are

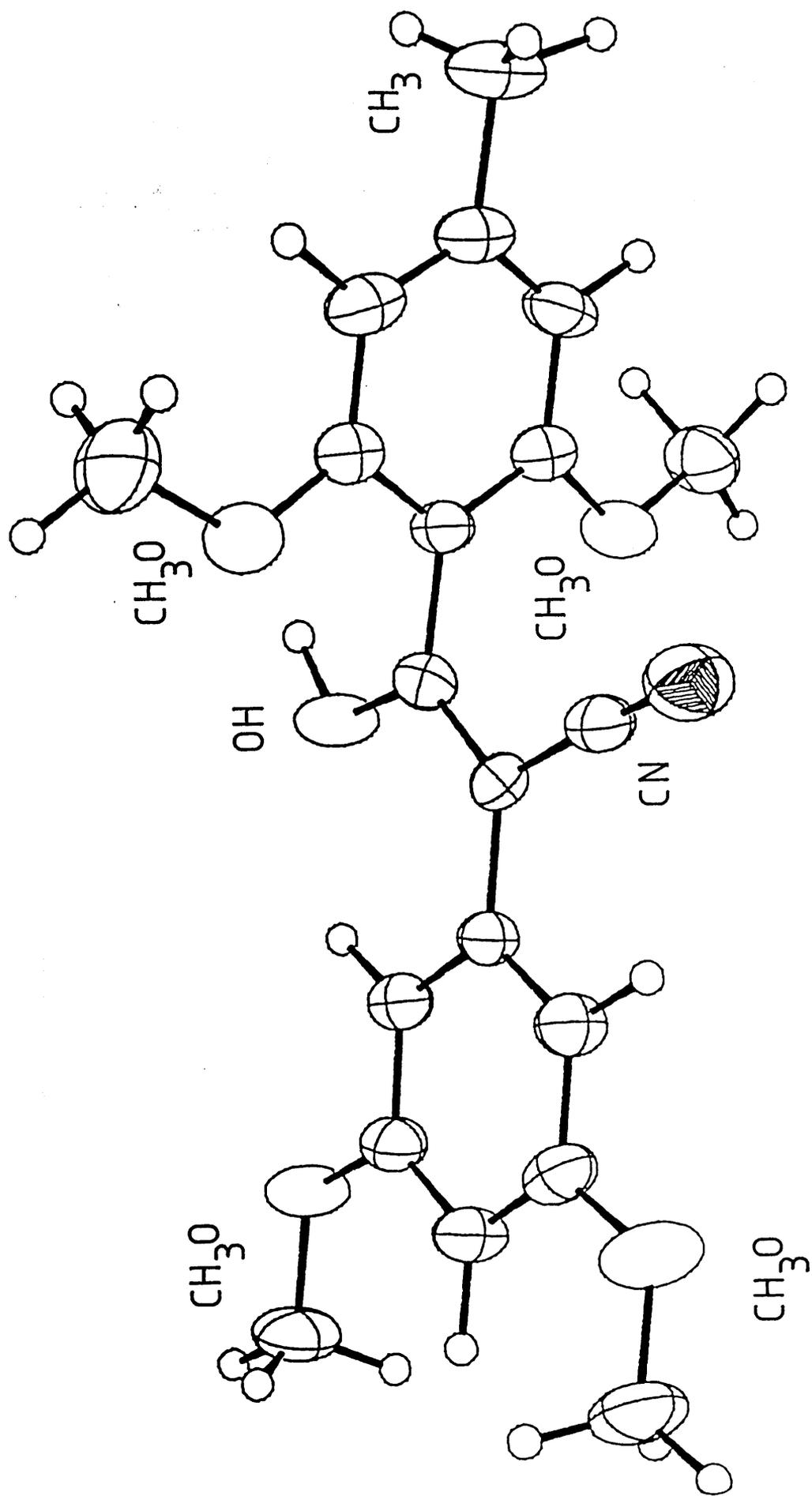
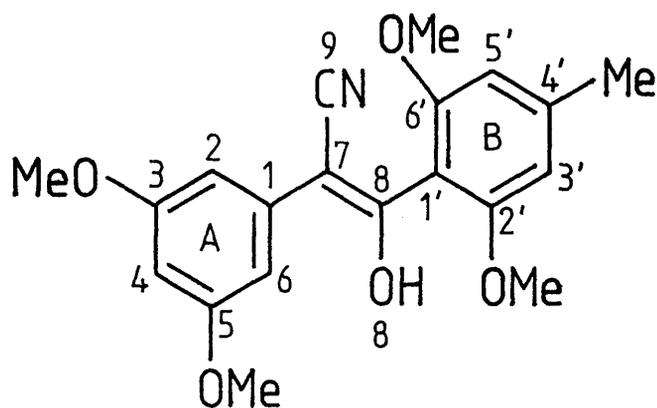


Fig. 9 X-ray crystal structure analysis of the tetramethoxy enol (69)

orientated at 91.16° to each other and that the tetrasubstituted ring (ring B) is twisted out of the plane of the remaining styrene system.



(69)

Table 3. Angles between selected planes in the tetramethoxy compound (69)

Plane	Atoms in the plane	Angle between normals or lines
(1)	ring A	(1)+(2) = 91.16° , (1)+(3) = 4.90°
(2)	ring B	(1)+(4) = 4.00° , (1)+(5) = 3.39°
(3)	C(1')C(7)C(8)O(8)	(2)+(3) = 93.85° , (2)+(4) = 94.09°
(4)	C(7) C(8)C(9)O(8)	(2)+(5) = 94.25° , (3)+(4) = 1.40°
(5)	C(1)C(7)C(8)C(9)	(3)+(5) = 2.72° , (4)+(5) = 1.32°

The behaviour of (69) in solution is more complicated. The ^1H nmr spectrum of (69) was determined at 90 MHz in a variety of solvents. In d_6 -acetone, d_6 -dimethyl sulphoxide and d_4 -methanol compound (69) appears to exist in more than one tautomeric form. The 200 MHz ^1H nmr spectrum of (69) in d_6 -acetone is shown in Fig. 10. The 90 MHz ^1H nmr spectrum of (69) in d_1 -chloroform was recorded three times with varying results. The first time the spectrum was recorded a peak occurred at $\delta 6.63$ ppm which disappeared upon addition of D_2O . The position of this peak shifted to $\delta 6.51$ ppm when the spectrum was recorded for the second time, then it was completely absent from the final spectrum. These results imply that the enol tautomer is preferred in chloroform solution. It was hoped that this would be confirmed by the ^{13}C DEPT experiment which allows ^{13}C nmr signals to be identified as corresponding to primary, secondary or tertiary carbons. Three $\underline{\text{CH}}$ signals are expected for the enol form and four for the keto form. When this experiment was performed the spectrum illustrated in Fig. 11 was obtained. Four major $\underline{\text{CH}}$ signals are present: the peak at $\delta 51.54$ ppm is probably due to $\underline{\text{CHCN}}$ of the keto form since a similar peak occurs at $\delta 49.85$ ppm in the ^{13}C nmr spectrum of the corresponding trimethoxy β -keto nitrile (81) [Fig. 12]. Other minor $\underline{\text{CH}}$ peaks are present, but it does seem likely that the keto form is predominant in this experiment. It is difficult to explain the contrasting conclusions from the DEPT experiment and the 90 MHz ^1H nmr experiments in d_1 -chloroform. It is also not clear why the 200 MHz ^1H nmr spectrum of (69) in d_1 -chloroform changed substantially when D_2O was added [Figs. 13 and 14]. It may be a solvent

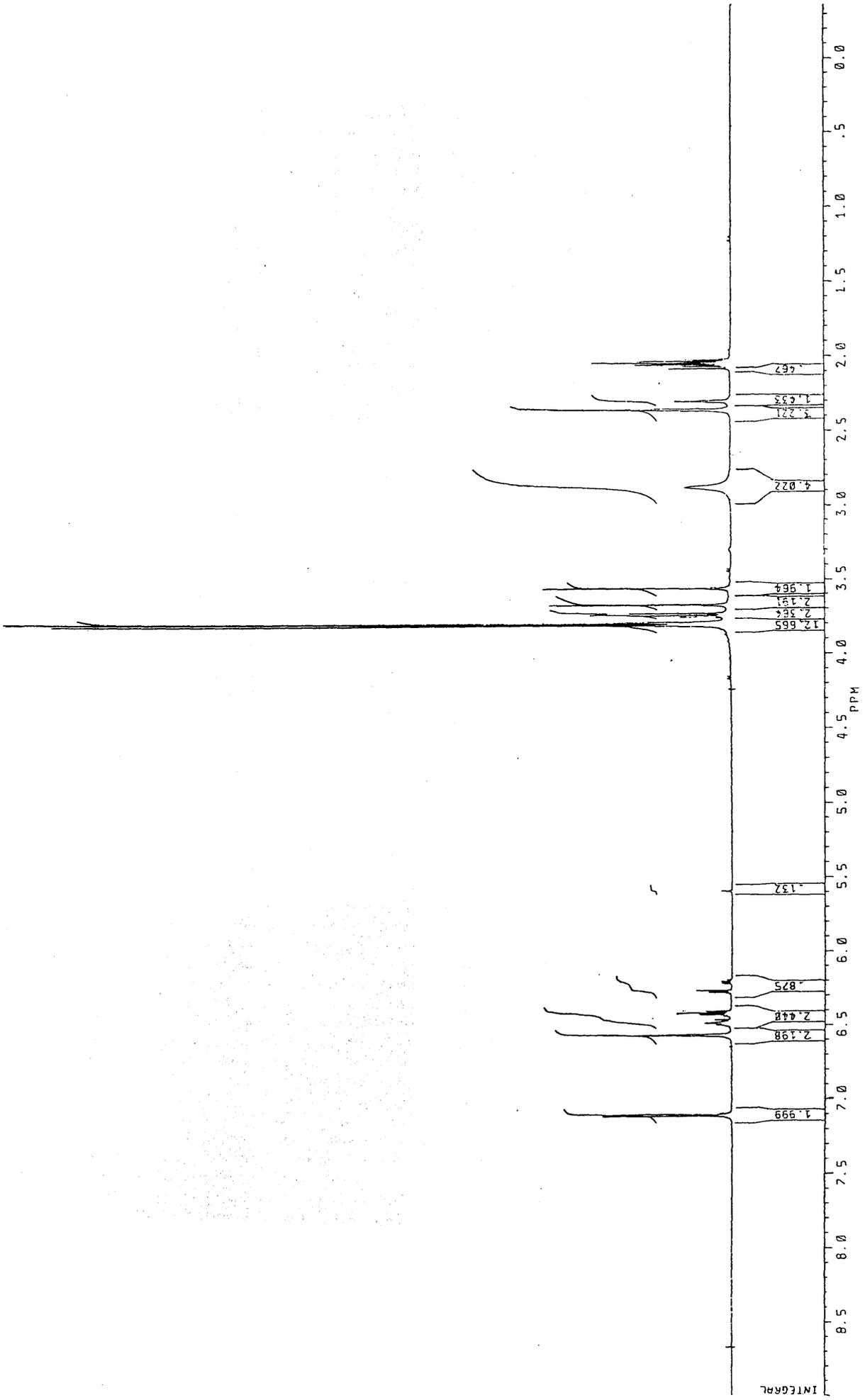


Fig. 10 200 MHz ^1H nmr spectrum of compound (69) in d_6 -acetone

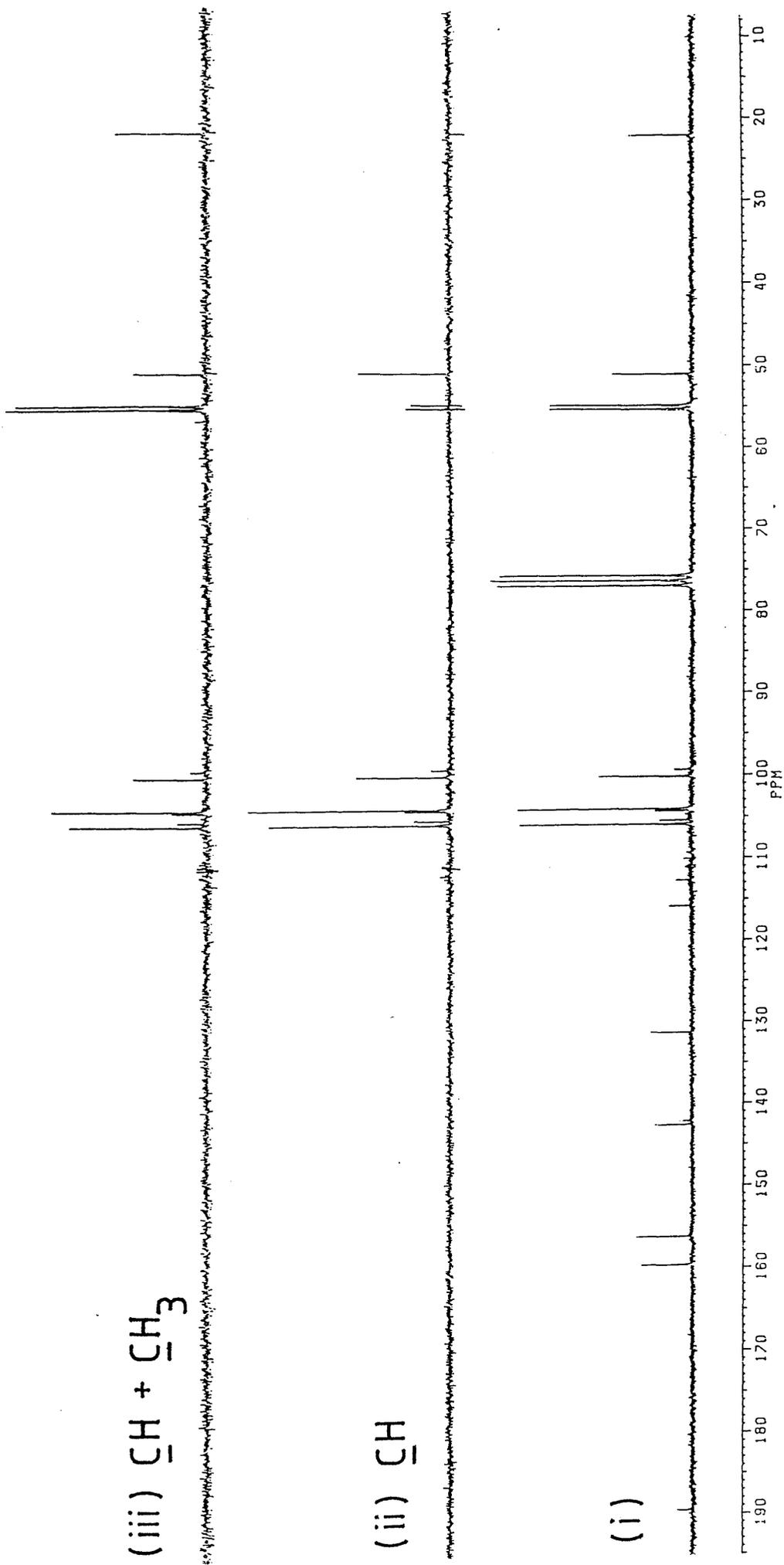


Fig. 11 (i) ^{13}C nmr spectrum of compound (69) in CDCl_3 . (ii) DEPT $\theta = 90^\circ$.

(iii) DEPT $\theta = 135^\circ$.

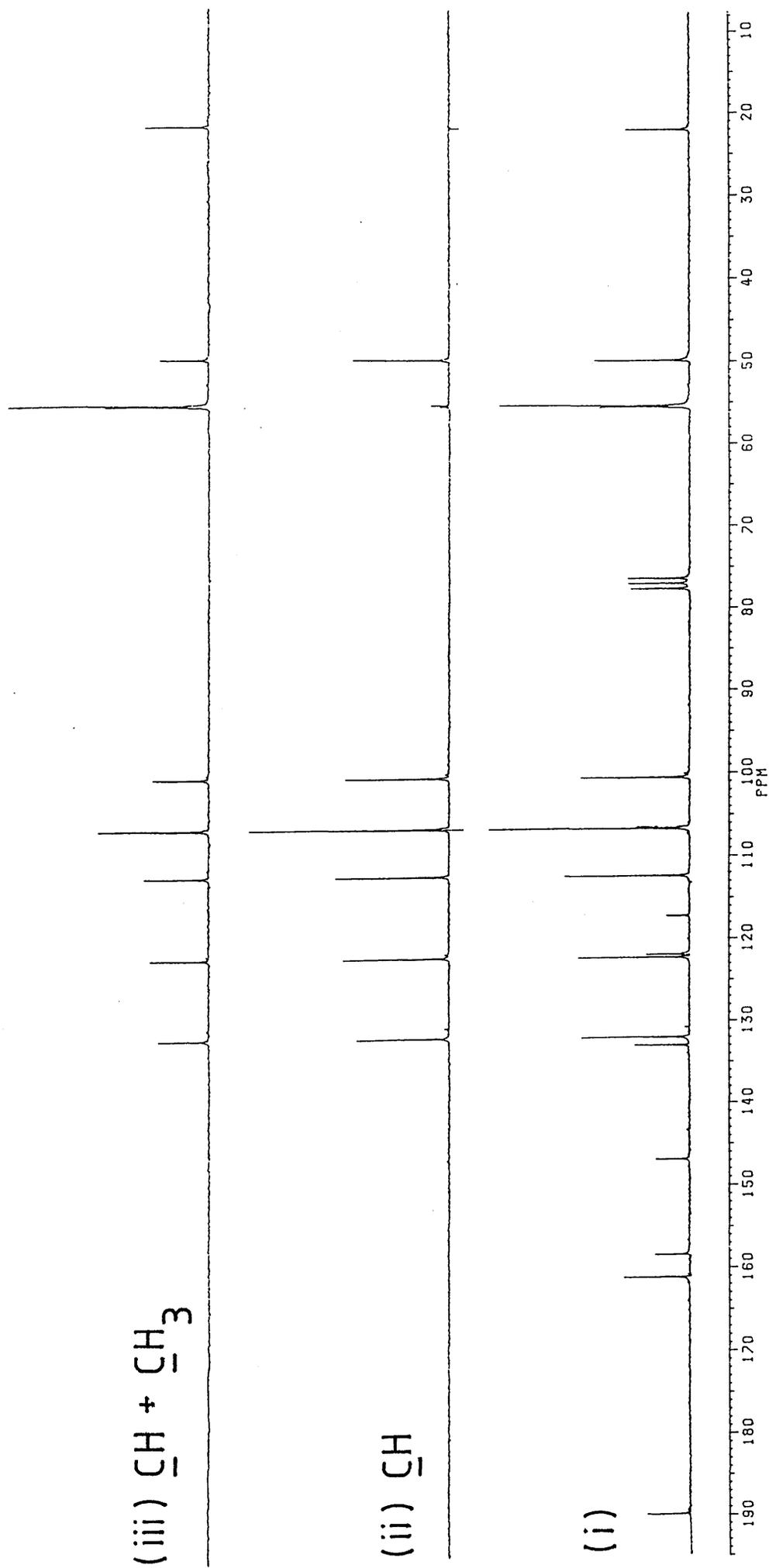


Fig. 12 (i) ^{13}C nmr spectrum of the β -keto nitrile (81) in CDCl_3 . (ii) DEPT $\theta = 90^\circ$.

(iii) DEPT $\theta = 135^\circ$.

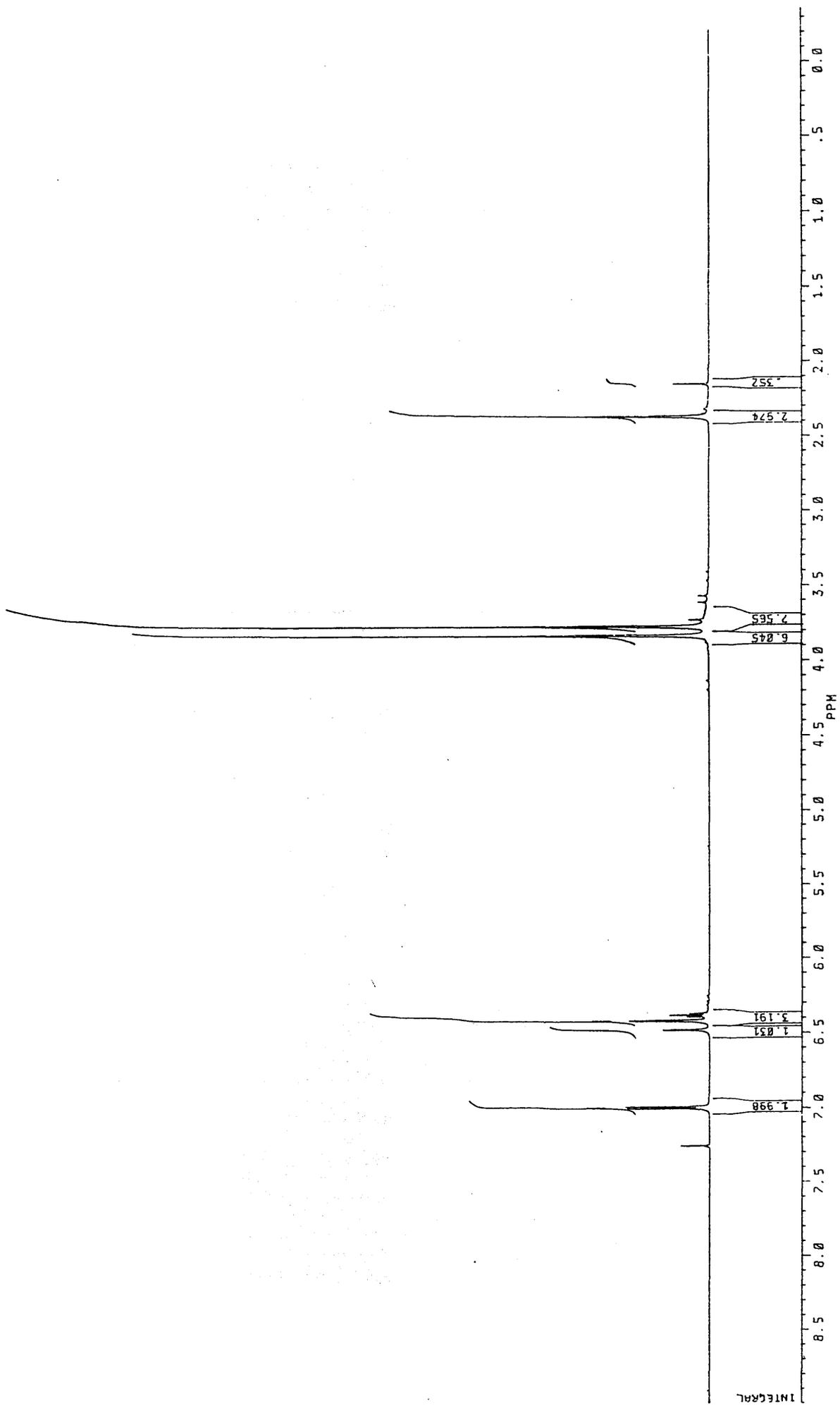


Fig. 13 200 MHz ¹H nmr spectrum of compound (69) in CDCl₃

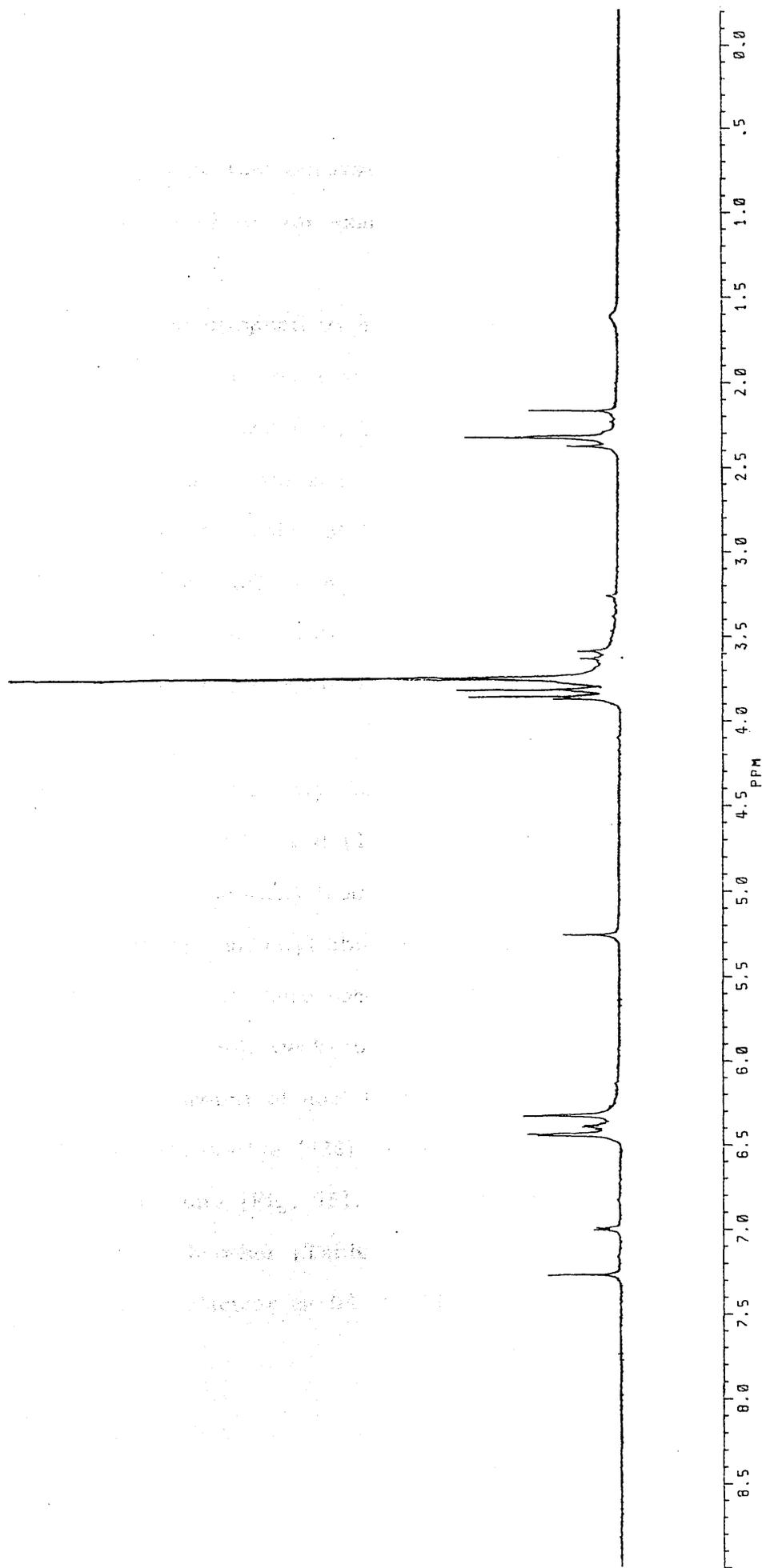


Fig. 14 200 MHz ^1H nmr spectrum of compound (69) in CDCl_3 + a few drops of D_2O

effect similar to that observed on changing from d_1 -chloroform (one tautomeric form) to, for example, d_6 -acetone (more than one tautomeric form).

The ir spectrum of (69) in chloroform also implies that the keto tautomer is predominant in solution. The spectrum (see Table 2) displays only a very weak broad absorption centred at 3550 cm^{-1} and a peak of medium intensity at 1715 cm^{-1} . This carbonyl absorption is approximately one third of the intensity of the aromatic peak at 1610 cm^{-1} and its position differs significantly from that of the β -keto nitriles (81), (82) and (138) (see Table 4). Two nitrile peaks are present, one probably due to the major keto tautomer and the other due to the minor enol tautomer.

The trimethoxy compound (81) and its monobromo and mono-iodo derivatives (82) and (138) respectively prefer to exist in the keto form. This is evident from the ^1H singlet due to CHCN in the ^1H nmr and the strong carbonyl absorption in the solid state and solution ir spectra of each of these compounds [Table 4]. The chloroform ir spectra also exhibit weak absorption at $3640\text{--}3220\text{ cm}^{-1}$ which indicates that a small amount of enol tautomer is also present. X-ray analysis of the iodo derivative (138) confirmed that it exists as the keto tautomer in the solid state [Fig. 15]. The two aromatic rings are inclined at 101.85° to each other [Table 5]. The torsion angles in Table 6 allow an accurate molecular model of (138) to be constructed.

Table 4. Ir and 90 MHz ^1H nmr data for β -keto nitriles (81), (82) and (138); s - strong, m - medium, w - weak

β -Keto nitrile	$\nu(\text{KBr}), \text{cm}^{-1}$	$\nu(\text{CHCl}_3), \text{cm}^{-1}$	$\delta_{\text{CHCN}}(\text{CDCl}_3),$ (ppm)
trimethoxy (81)	2240 w 1680 s 1610 s	3640-3220 very w 2250 w 1680 m 1610 s	5.85
2-bromo (82)	2250 w 1670 s 1610 s 1580 s	3640-3220 w 2250 w 1680 s 1610 s 1590 s	6.33
2-iodo (138)	2240 w 1680 s 1610 s 1585 s	3640-3220 w 2240 w 1680 s 1610 s 1585 s	6.34

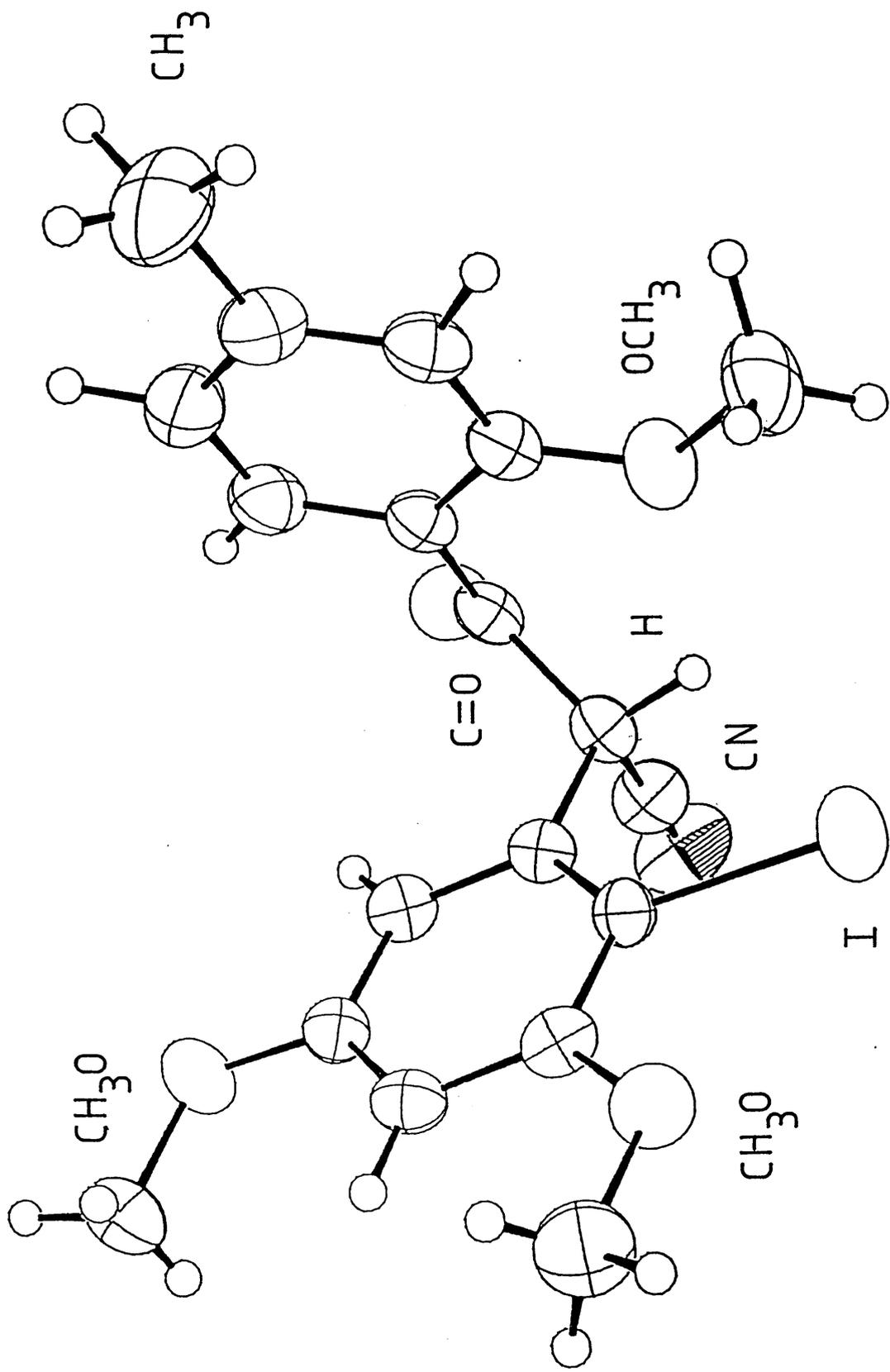
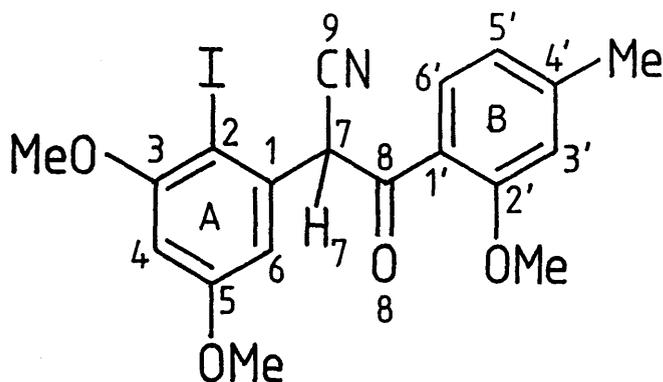


Fig. 15 X-ray crystal structure analysis of the 2-iodo β -keto nitrile (138)

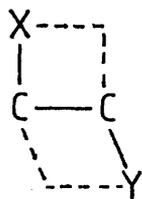


(138)

Table 5. Angles between selected planes in the 2-iodo β -keto nitrile (138)

Plane	Atoms in the plane	Angle between normals or lines
(1)	ring A	(1) + (2) = 101.85°
(2)	ring B	(1) + (3) = 104.63°
(3)	C(1')C(7)C(8)O(8)	(2) + (3) = 136.94°

Thus compounds (69), (134) and (152) containing 2',6'-dimethoxy, 2,6-dibromo and 2,6-diiodo substituents respectively, prefer to exist in the enol form. In contrast, compounds (81), (82) and (138), in which the 2 and 6 positions of the same aromatic ring do not both have substituents, prefer to exist in the keto form. The reason for

Table 6. Torsion angles for the 2-iodo β -keto nitrile (138)

torsion angle = angle between

XCC plane and CCY plane

+ clockwise - anticlockwise

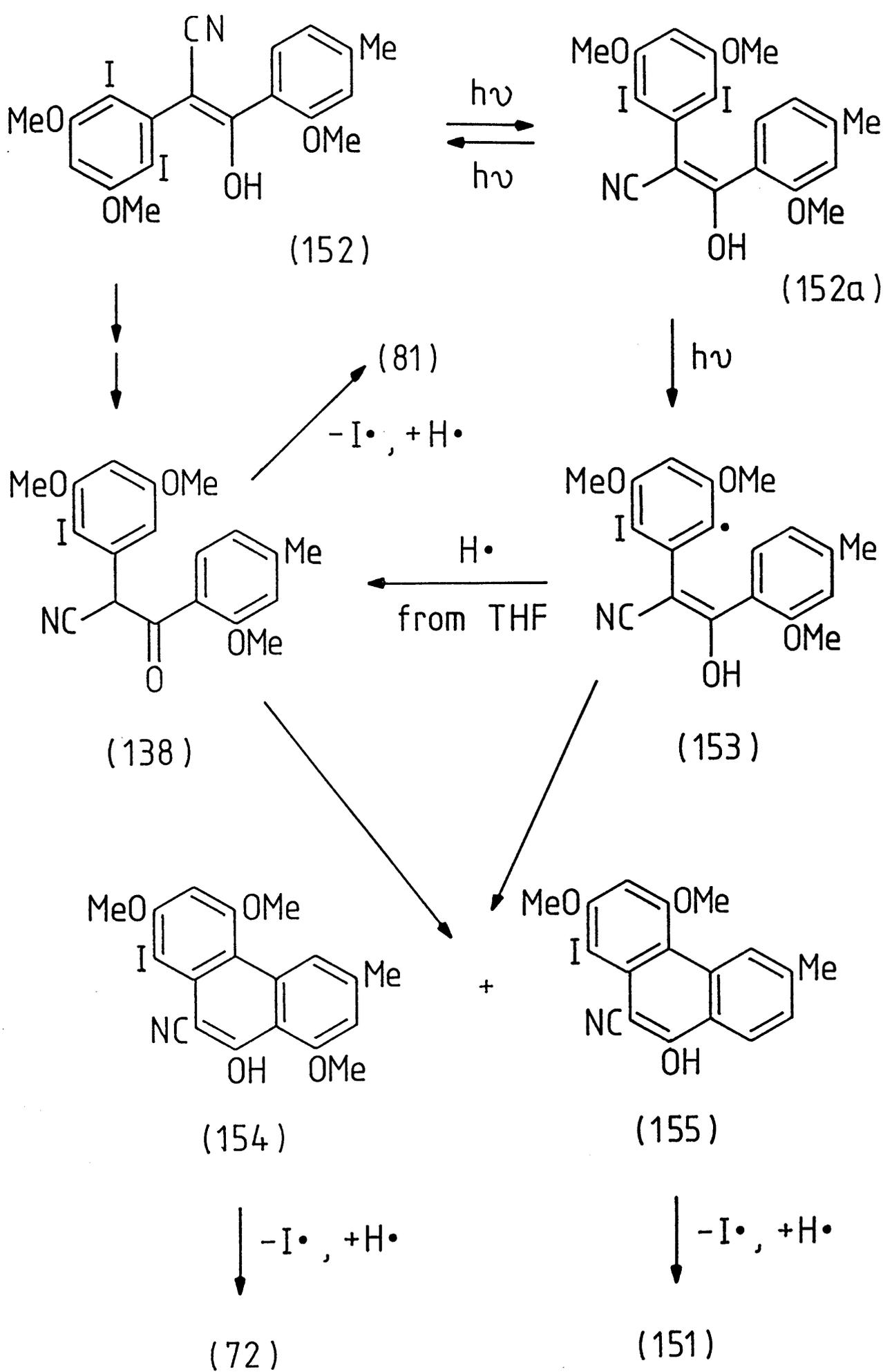
Angle	Degrees ($^{\circ}$)
C(2) - C(1) - C(7) - C(8)	- 136.6
C(2) - C(1) - C(7) - C(9)	+ 102.3
C(2) - C(1) - C(7) - H(7)	- 17.7
C(6) - C(1) - C(7) - C(8)	+ 45.1
C(6) - C(1) - C(7) - C(9)	- 75.9
C(6) - C(1) - C(7) - H(7)	+ 164.0
C(2') - C(1') - C(8) - C(7)	+ 45.7
C(2') - C(1') - C(8) - O(8)	- 137.5
C(6') - C(1') - C(8) - C(7)	- 136.4
C(6') - C(1') - C(8) - O(8)	+ 40.4
C(9) - C(7) - C(8) - O(8)	+ 4.2
H(7) - C(7) - C(8) - O(8)	+ 123.0
H(7) - C(7) - C(8) - C(1')	- 60.2

this difference can be understood from models. In the keto form of compounds (69), (134) and (152) there is severe steric crowding between the cyano and carbonyl groups and the adjacent aromatic substituents, irrespective of the orientation of the 2,6-substituted aromatic ring. In the more rigid enol form the steric congestion is significantly reduced. Compounds (81), (82) and (138) exist in the keto form with fairly free rotation about the tetrahedral carbon atom.

The decrease in the ϵ values (21,500 \rightarrow 9,600 \rightarrow 3,300) of the major band in the uv spectra of the 2',6'-dimethoxy, 2,6-dibromo and 2,6-diiodo compounds shows that the steric congestion increases on going from $\text{CH}_3\text{O} \rightarrow \text{Br} \rightarrow \text{I}$. Hence the driving force for enol formation (i.e. reduction in steric congestion) is not as great in the 2',6'-dimethoxy compound (69) as in the 2,6-diiodo compound (152). This accounts for the fine balance between the different tautomeric forms of (69) observed in solution.

2.5.2 Photochemistry

Phenanthrenes (72) and (151) were isolated in 20% and 10% yields respectively upon irradiation of the 2,6-diiodo species (152) in deaerated tetrahydrofuran [Scheme 51]. Intramolecular free radical arylation probably predominates in this reaction. Indeed formation of phenanthrene (151) must proceed by initial photolysis of one of the carbon-iodine bonds since it involves loss of the methoxyl group at stilbene position 2'. In competition with radical cyclisation of (153) is hydrogen atom transfer from tetrahydrofuran to give the 2-iodo



Scheme 51

β -keto nitrile (138) which has two fates: intramolecular cyclisation and reductive dehalogenation. A small amount of the β -keto nitrile (81) was detected in the 90 MHz ^1H nmr of the crude reaction product through the presence of a singlet at $\delta 5.85$ ppm due to CHCN .

2.6 Spectral Properties of α' -Acetoxy- α -cyanostilbenes

2.6.1 Ultraviolet Spectra

The uv spectra of E- and Z-stilbene in ethanol solution⁸⁷ are presented in Figs. 16 and 17. The uv absorption spectrum of a compound can provide useful information about the electronic transitions that occur since bands corresponding to $\pi \rightarrow \pi^*$ transitions are usually more intense (ϵ 5,000 - 100,000) than those corresponding to $n \rightarrow \sigma^*$ (ϵ 100 - 1,000) or $n \rightarrow \pi^*$ transitions (ϵ 1 - 400).⁸⁸ Therefore all of the uv absorption bands of E- and Z-stilbene are the result of $\pi \rightarrow \pi^*$ transitions.

The lowest energy excited singlet state of Z-stilbene is responsible for photocyclisation. A value for the energy of a lowest excited singlet state can be estimated from the uv absorption spectrum of a molecule. If vibrational fine structure is apparent, as in the spectrum of E-stilbene in Fig. 16, the longest wavelength band in the spectrum is often the one that corresponds to the energy required [since energy and wavelength are inversely related thus: E (kJ mol^{-1}) = $1.19 \times 10^5 / \lambda$ (nm)], and the wavelength can be converted to its equivalent energy. Spectra for most organic compounds in solution show little or no vibrational fine structure because of inter-

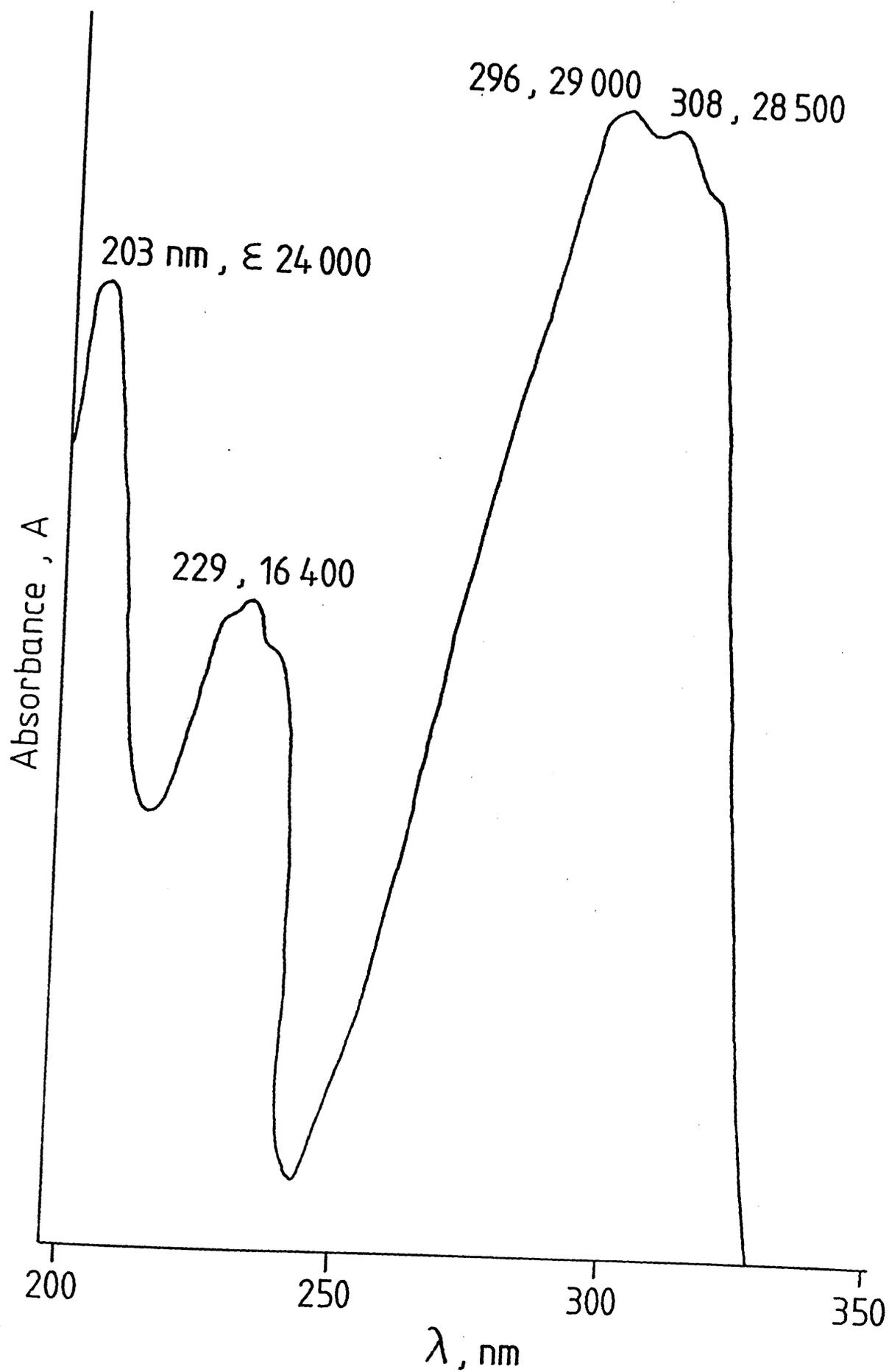


Fig. 16 Uv spectrum of E-stilbene in ethanol

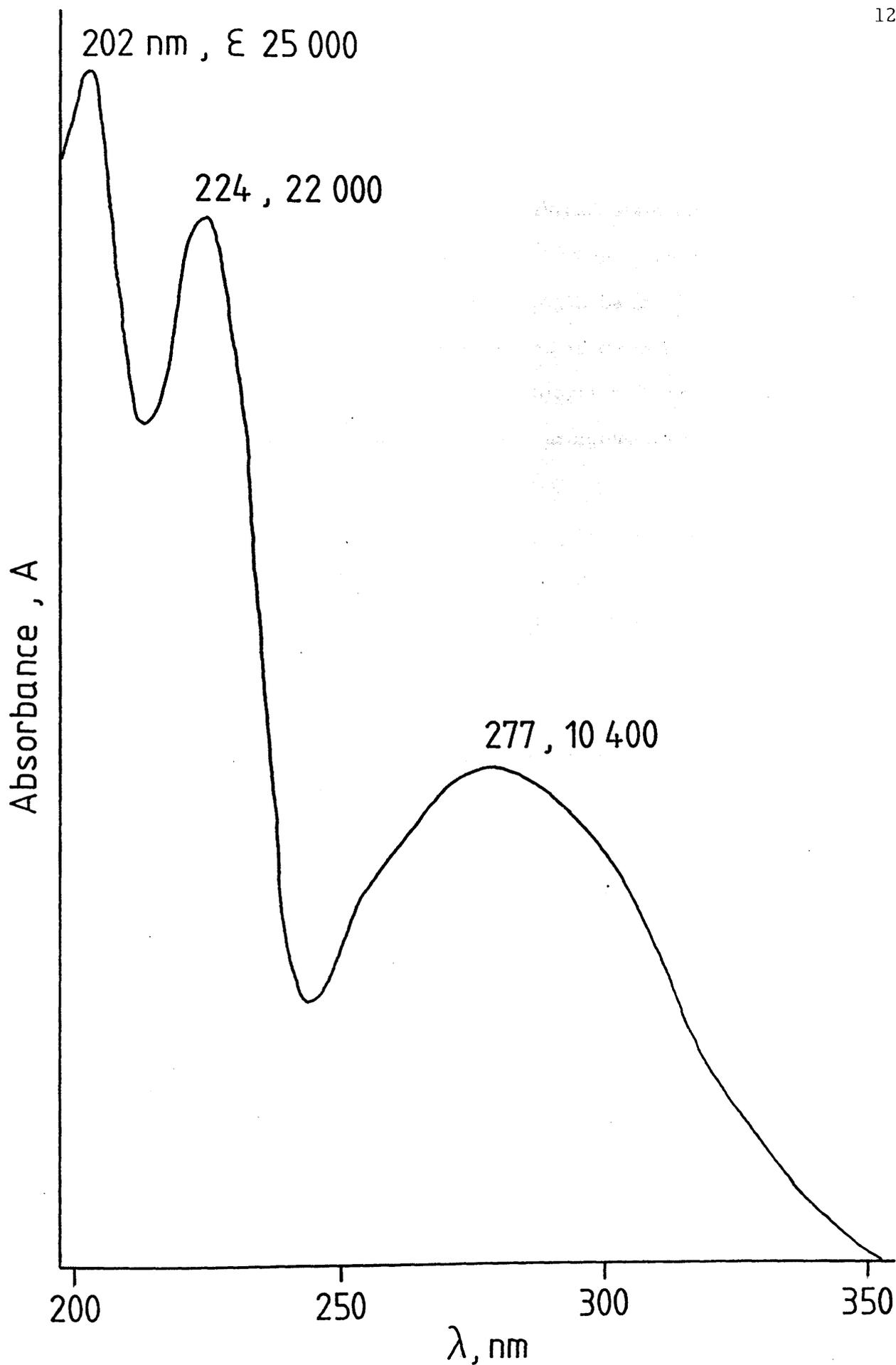


Fig. 17 Uv spectrum of Z-stilbene in ethanol

actions of solute with solvent molecules. In these cases (e.g. Fig. 17) a reasonable guess for the lowest excited singlet state energy can be made. Note that the absorption maximum does not correspond to the excited state energy. The longest wavelength band of Figs. 16 and 17 corresponds to the stilbene chromophore and is termed the conjugation band. Irradiation anywhere within the conjugation band of Z-stilbene leads to photocyclisation. The other band assignments are the subject of some controversy.⁸⁹

The lower values of λ_{\max} and ϵ_{\max} of the longest wavelength band of Z-stilbene compared to E-stilbene are ascribed to the shorter length of the conjugated system in the Z-configuration, owing to the reduction in coplanarity caused by steric interference between the ortho-hydrogen atoms of the phenyl groups.⁹⁰

The uv absorption spectrum of a conjugated compound differs from that expected for a planar model when the molecule is sufficiently crowded to render coplanarity of the conjugated atoms difficult or impossible.⁹¹ The degree of deviation from the expected spectrum seems to increase with the degree of steric crowding, and on this basis, three types of behaviour of the longest wavelength band have frequently been distinguished:

- (1) Slight crowding, the spectroscopic result of which is an intensity decrease (hypochromic effect);
- (2) Moderate crowding, resulting in both an intensity decrease and a shift of λ_{\max} to a shorter wavelength (hypsochromic shift);

- (3) Severe crowding, resulting in a spectrum quite different from that expected for a planar model. The severity of the steric crowding determines the appearance of the observed spectrum: the conjugation band (or longest wavelength band) due to the extended chromophore may not be present if the crowding is particularly severe since coplanarity of the conjugated atoms is no longer possible. In this event the observed spectrum is the summation of the spectra of the two isolated chromophores.

Z-Stilbene belongs to the second category and its uv spectrum is representative of a moderately crowded stilbene. The uv spectra of the E-isomer and the stereoisomeric mixture (E : Z = 1.0 : 3.8) of isomers of the 2-bromostilbene (83) shown in Figs. 4 and 5 have the characteristic shape of a moderately crowded stilbene. The uv spectra of the 2-iodostilbene (139) and the tetramethoxystilbene (70) show that these are also moderately crowded stilbenes.

The E- and Z-isomers of the 2,6-dibromostilbene (135) belong to the third category as evidenced by the uv spectra in Figs. 7 and 8. The perfect coplanarity of the molecular configuration is not prerequisite to the occurrence of conjugation and hence not prerequisite to the appearance of the conjugation band.⁹² Therefore, the two longest wavelength bands of Figs. 7 and 8 may correspond to the stilbene chromophore while the 241/242 nm bands may correspond to the partial styrene chromophore since styrenes display a characteristic band in the 250 nm region.⁹³

2.6.2 ¹H Nmr Spectra

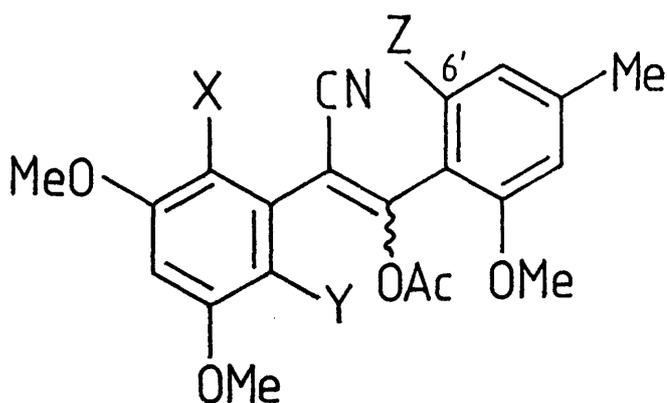
The data contained in Table 7 show that the ¹H nmr signal due to the proton at position 6' in a Z-α'-acetoxy-α-cyanostilbene occurs upfield relative to the same signal in the E-stilbene. This is caused by shielding of H-6' in the Z-isomer by the neighbouring anisotropic aromatic ring. Also, the E-stilbene acetoxy protons resonate at higher field than the Z-stilbene acetoxy protons owing to a greater degree of shielding of these protons by the aromatic rings in the E-isomer compared to the Z-isomer. In each of the E- and Z-isomers the signal corresponding to the aromatic methyl group is broader than the acetoxy signal due to interaction with the ortho-protons, and in this way these signals can be distinguished.

The E- and Z-configurations were determined by various means. Sections 2.2.1 and 2.3.1 described the assignment of the configuration of the geometric isomers of the 2-bromostilbene (83) and the 2,6-dibromostilbene (135) on the basis of uv measurements. As mentioned in Section 2.4.1, the ¹H nmr spectrum of the mixture of geometric isomers of the corresponding 2-iodostilbene (139) was assigned by comparison with the spectra of the E- and Z-2-bromostilbenes (83).

Reaction of the β-keto nitrile (81) with acetic anhydride/ catalytic p-toluenesulphonic acid for 2 hours afforded a 1.0 : 1.4 mixture of E- and Z-trimethoxystilbenes (156) respectively. The ratio of E- and Z-isomers was determined from the integration of the H-6' doublets in the 200 MHz ¹H nmr spectrum. The major isomer was assumed to have the Z-configuration since it corresponded to the upfield H-6' doublet and the downfield acetoxy signal.

Table 7. 200 MHz ^1H nmr chemical shifts for α' -acetoxy- α -cyanostilbenes

Stilbene	$\delta(\text{CDCl}_3)$, ppm	
	H-6'	CH_3CO
(70) <u>E</u>		2.07
<u>Z</u>		2.22
(83) <u>E</u>	7.53	1.95
<u>Z</u>	7.02	2.28
(135) <u>E</u>	7.59	1.95
<u>Z</u>	7.00	2.29
(139) <u>E</u>	7.56	1.92
<u>Z</u>	7.04	2.28
(156) <u>E</u>	7.43	2.09
<u>Z</u>	7.11	2.26



(70) X = Y = H , Z = OMe

(83) X = Br , Y = Z = H

(135) X = Y = Br , Z = H

(139) X = I , Y = Z = H

(156) X = Y = Z = H

Finnie⁵⁰ assigned the configuration of the geometric isomers of the tetramethoxystilbene (70) in the following way. The ¹H nmr spectrum of the mixture of isomers indicated that the isomers were present in the ratio of 2:1. Irradiation of this mixture afforded phenanthrene (71) which was isolated by addition of methanol to the crude reaction product. The second batch of crystals was shown to be the major geometric isomer from its ¹H nmr spectrum. The gummy residue consisted mainly of the minor geometric isomer. Thus the major isomer was proposed to have the E-configuration since E-stilbenes are usually crystalline while Z-stilbenes are often gums.²⁵ On the basis of this proposal, the acetoxy signal of the E-isomer occurs upfield from that of the Z-isomer, in agreement with the other E/Z pairs of α' -acetoxy- α -cyanostilbenes.

Evidence is presented in Chapter 3 which shows that the E- and Z-isomer H-6' and acetoxy resonances in α' -acetoxy- α -carbomethoxy-stilbenes have the same relative positions as in α' -acetoxy- α -cyano-stilbenes.

2.7 Enol Acetate Derivatives of 2,3-Diaryl-3-oxopropanenitriles

Examples of enol acetate derivatives of 2,3-diaryl-3-oxopropanenitriles (157) (i.e. α' -acetoxy- α -cyanostilbenes) occur throughout this chapter. A more detailed discussion of the derivatisation reaction based on the results contained in Table 8 now follows.

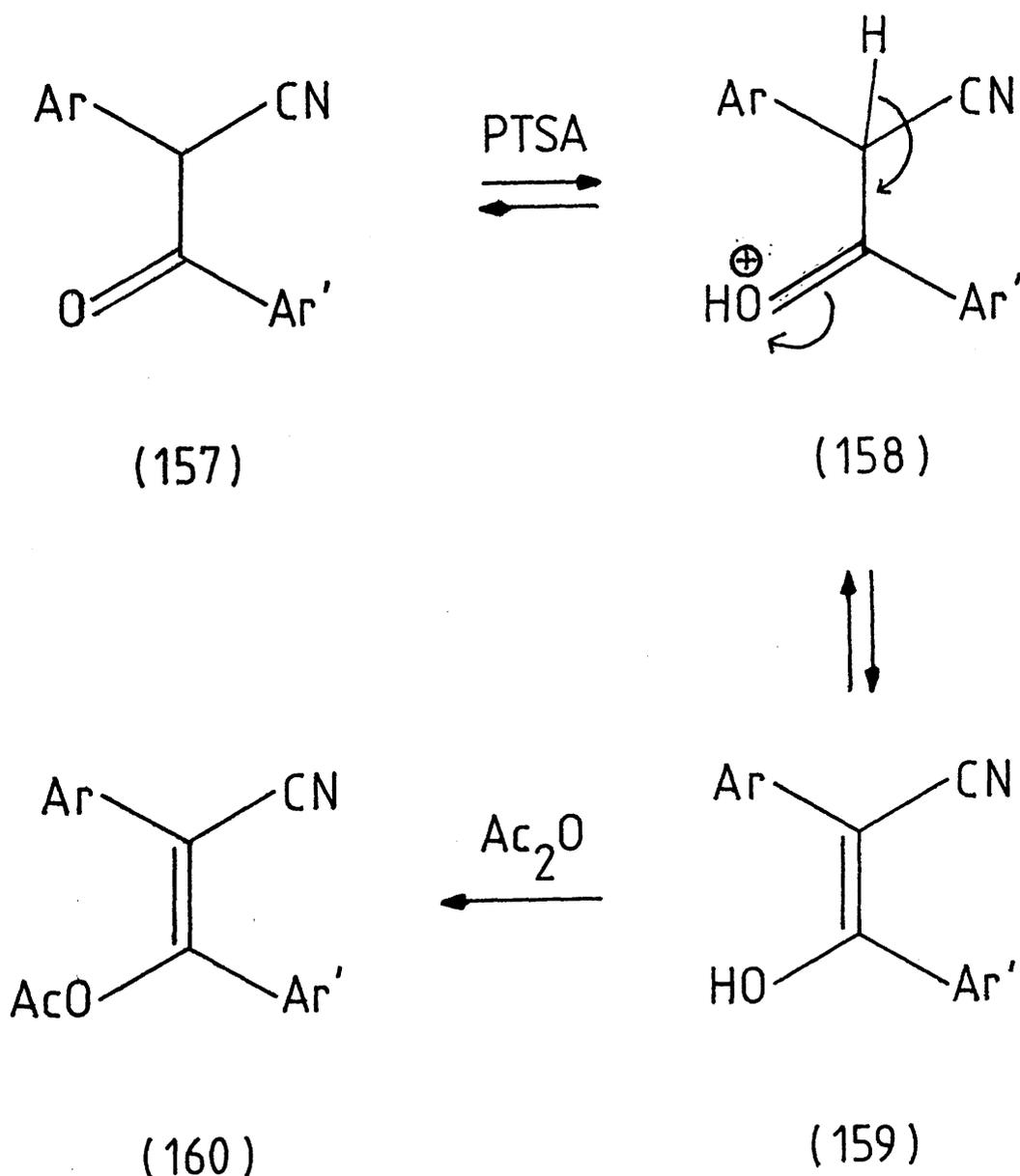
The general procedure for preparation of the enol acetate derivatives consists of refluxing a solution of the β -keto nitrile in acetic

Table 8. Enol acetate derivatives of 2,3-diaryl-3-oxopropanenitriles

Enol acetate	Reaction time	Ratio of isomers, <u>E</u> : <u>Z</u>	Yield, %
(156)	5 min	1.0 : 1.0	80
	30 min	1.0 : 1.1	
	1 h	1.0 : 1.2	
	2 h	1.0 : 1.4	
	7 h	1.0 : 1.5	
(83)	2 h	1.0 : 1.3	98
	24 h	1.0 : 1.8	
(139)	2 h	1.0 : 1.0	62
(70)	5 min	1.3 : 1.0	83
	30 min	1.2 : 1.0	
	2 h	1.0 : 1.1	
	5 h	1.0 : 1.1	
	(a)	1.0 : 1.3	
(135)	8 h	2.3 : 1.0	85

Note (a): The mixture of geometric isomers obtained after 2 hours was refluxed in Ac_2O /catalytic PTSA for a further 7 hours.

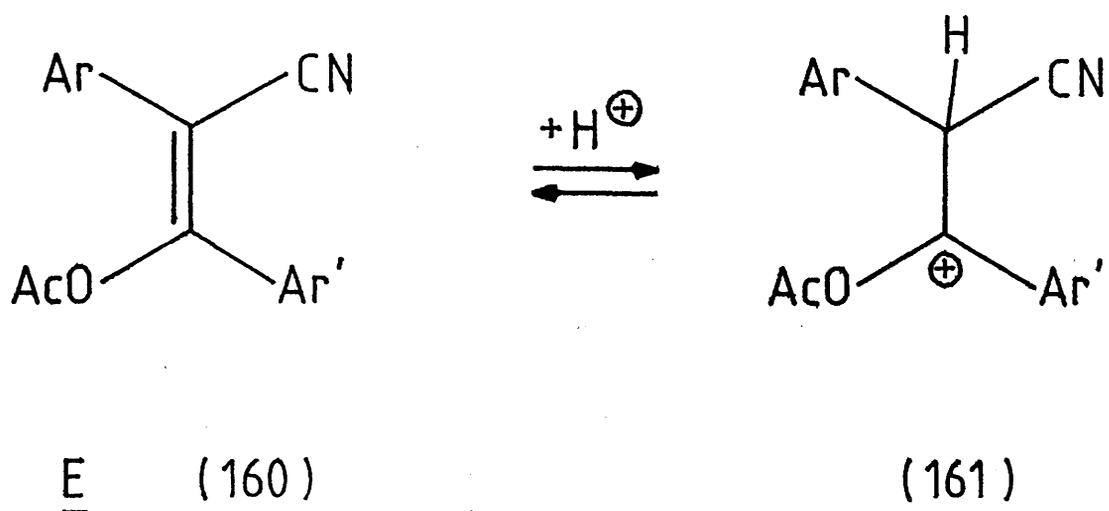
anhydride containing a few crystals of *p*-toluenesulphonic acid monohydrate (PTSA). The purpose of the PTSA is to promote tautomerism of the initial keto form to the corresponding enol form, which then reacts with acetic anhydride to give the enol acetate as outlined in Scheme 52. Since the 2,6-dibromo compound (134) already exists as the enol tautomer, no acid is employed in the preparation of its enol acetate derivative (135).



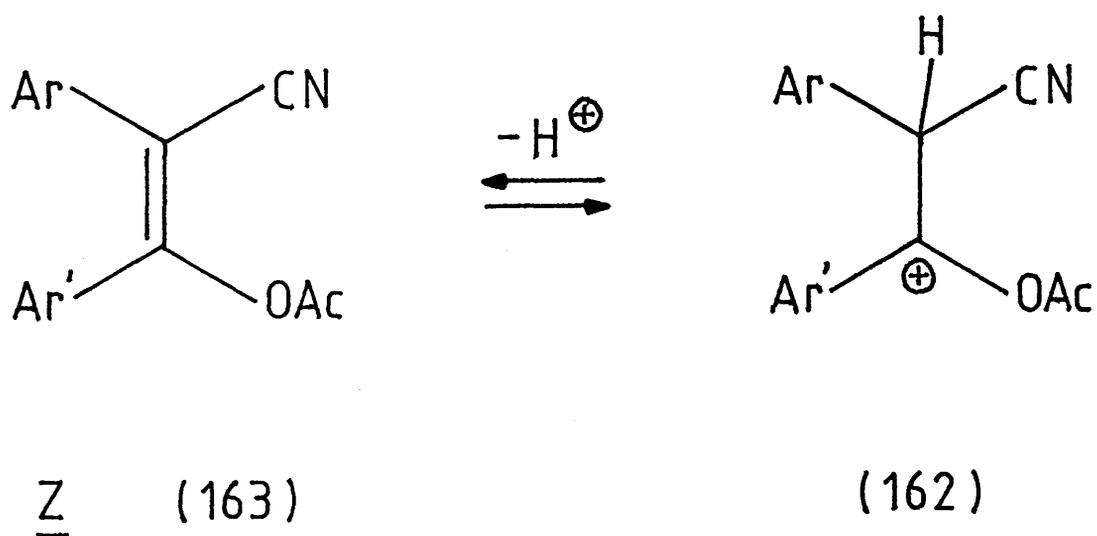
Scheme 52

In each case the ratio of geometric isomers was determined from the ^1H nmr integration. For enol acetates (83), (135), (139) and (156) the ratio of isomers was estimated from the integration of the downfield H-6' doublet of the E-isomer relative to that of the upfield H-6' doublet of the Z-isomer. The ratio of E- and Z-isomers of enol acetate (70) was calculated from the integration of the acetoxy signal of the E-isomer relative to that of the Z-isomer at lower field.

The conditions employed in the acetylation reactions equilibrate E- and Z-forms to give a thermodynamically controlled mixture, i.e. a mixture rich in the more thermodynamically stable isomer [Scheme 53]. Z-Stilbenes are generally less thermodynamically stable than E-stilbenes owing to steric crowding between the adjacent ortho-substituents of the two aryl groups.²⁵ Thus, on steric grounds the E-enol acetate would be predicted to be the major isomer. However, after 2 hours, there was a preponderance of the Z-isomer of enol acetates (70), (83) and (156) and the E- and Z-isomers of enol acetate (139) were present in equal amounts. Furthermore, the proportion of Z-isomer increased at the expense of the E-isomer upon long reaction times in the case of enol acetates (70), (83) and (156). (On prolonged reaction the iodo enol acetate (139) was unstable). After 2 hours the ratio of geometric isomers of (70) was E : Z = 1.0 : 1.1. When this mixture was refluxed in acetic anhydride containing a catalytic amount of PTSA for a further 7 hours the ratio of isomers changed to E : Z = 1.0 : 1.3. These results suggest that the Z-isomer of enol acetates (70), (83) and (156) (and probably also (139)) is more thermodynamically stable than the E-isomer.

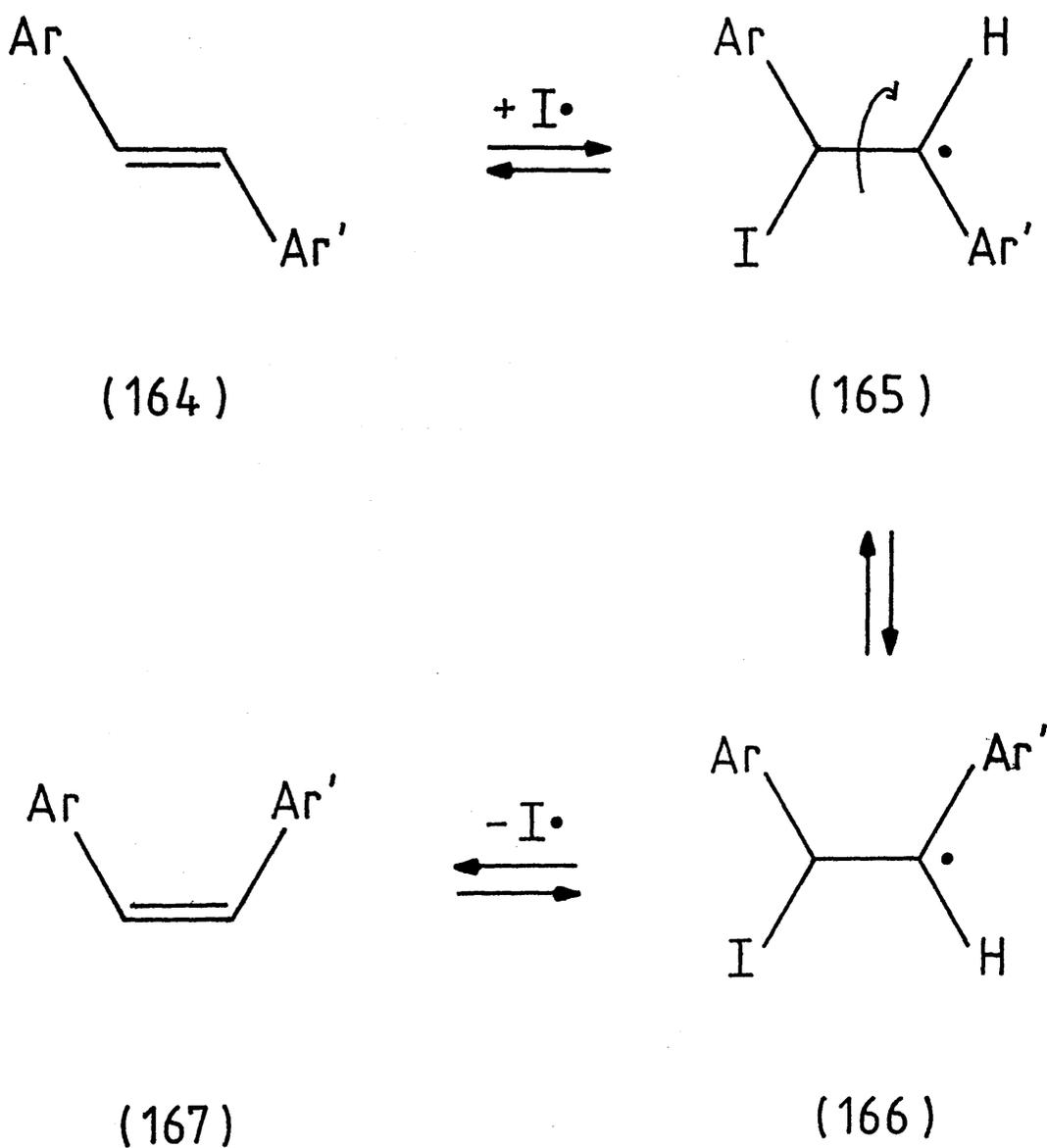


rotation about
 the tetrahedral
 C atom



Scheme 53

Irradiation of a benzene solution containing a mixture of E- and Z-stilbenes and a trace of iodine with visible light equilibrates the E- and Z-isomers to give a mixture which is rich in the more thermodynamically stable isomer²⁵ [Scheme 54]. However, only a small amount



Scheme 54

of isomerisation to the Z-isomer occurred when a benzene solution of the E-bromo enol acetate (83) and iodine was irradiated with visible light and heated at gentle reflux for 24 hours. No change was observed when a mixture (E : Z = 1.0 : 3.8) of the E- and Z-bromo enol acetates (83) or when either the E- or Z-dibromo enol acetate (135) were treated in the same way.

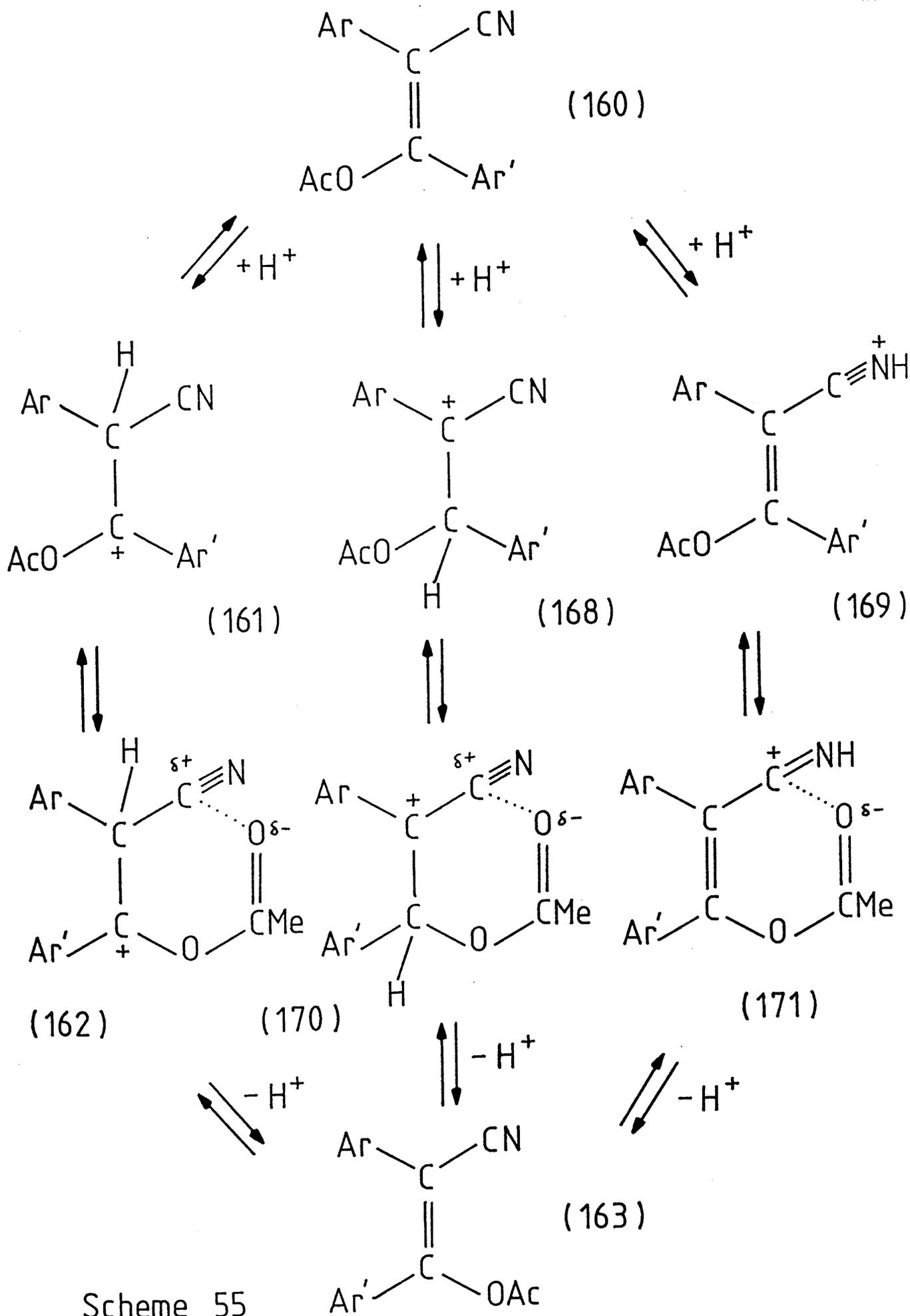
It was thought that the E-enol acetate would probably be the product of kinetic control, i.e. the major product after short reaction times. To test this proposition, the β -keto nitrile (81) was refluxed in acetic anhydride/catalytic PTSA for 5 minutes whereupon a 1.0 : 1.0 mixture of E- and Z-enol acetates (156) was obtained. Unreacted β -keto nitrile remained (as evidenced by the presence of a doublet at $\delta 7.60$ ppm due to H-6') and the ratio of either isomer to starting material was 1.0 : 1.4. A rapid rate of E \rightarrow Z isomerisation might account for the observed ratio of geometric isomers of (156) after 5 minutes. It was thought that the rate of isomerisation in the more crowded enol acetate (70) would be slower, and this appears to be the case since the ratio of isomers was E : Z = 1.3 : 1.0 after 5 minutes. Thus it seems likely that the E-enol acetate is the product of kinetic control. The 1.3 : 1.0 ratio of E- and Z-isomers of (70) progressively changed with time in favour of the Z-isomer and this is consistent with the greater thermodynamic stability of the Z-isomer compared to the E-isomer.

When the 2,6-dibromo enolic compound (134) was heated at reflux in acetic anhydride for 8 hours the E- and Z-enol acetates (135) were produced in the ratio of 2.3 : 1.0 respectively. This shows that

the E-isomer of (135) is more thermodynamically stable than the Z-isomer.

In the solid state the dibromo enol (134) very likely has the E-configuration since this is the configuration of the tetramethoxy enol (69) in the solid state as revealed by X-ray analysis (see Fig. 9). The configuration of (134) in solution is probably also E and so one would expect the E-enol acetate (135) to be formed initially and then to equilibrate giving a thermodynamically controlled mixture of E- and Z-isomers. It is unlikely that a slow rate of E \rightarrow Z isomerisation accounts for the observed ratio of geometric isomers since the reaction time was relatively long (8 hours). Scheme 55 forms the basis of a possible explanation for the unexpected finding that Z-enol acetates are formed preferentially in the reaction of β -keto nitriles (69), (81), (82) and (138) with acetic anhydride under acid catalysis, while the E-enol acetate (135) is formed preferentially upon refluxing (134) in acetic anhydride.

In Scheme 55, the E-enol acetate (160) can be protonated at three possible sites giving (161), (168) and (169). Rotation about the tetrahedral carbon atom in (161) and (168) and rotation about the partial double bond in (169) give (162), (170) and (171) respectively, which yield the Z-enol acetate (163) upon deprotonation. If Ar and Ar' are not too bulky, then (162), (170) and (171) will probably be more stable than (161), (168) and (169) owing to favourable electronic interaction between the carbonyl oxygen and the carbon of the cyano group. Thus, if Ar and Ar' are not too bulky, the Z-isomer will be the major isomer. The uv spectra of enol acetates (70), (83), (139) and (156) show that these are only moderately crowded (see Section 2.6.1) and



so one would predict the major isomer to be the Z-isomer on the basis of the above reasoning. Similarly, one would predict the E-isomer to be the major isomer in the case of the dibromo enol acetate (135) since the uv spectra of its geometric isomers show that it is severely crowded. These predictions agree with the experimental findings. Therefore the major factor influencing the ratio of stereoisomers in slight or moderately crowded α' -acetoxy- α -cyanostilbenes is electronic and the Z-isomer is the major isomer. As expected, the amount of Z-isomer relative to the amount of E-isomer diminishes as the steric hinderance is increased: this is apparent from the E : Z ratios for enol acetates (156), (83) and (139) after 2 hours. In contrast, in severely crowded stilbenes of this type the favourable electronic interaction is not strong enough to compete with the unfavourable steric interaction and so the less hindered E-isomer is the major isomer.

Many of the principles underlying the synthesis, properties and photochemistry of α' -acetoxy- α -cyanostilbenes described in this chapter are relevant to the discussion of α' -acetoxy- α -carbomethoxy-stilbenes presented in the next chapter.

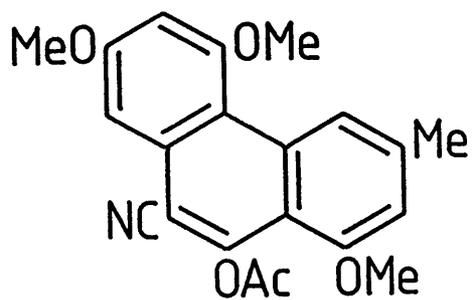
CHAPTER 3

The Synthesis and Decarbomethoxylation of a 9-Carbomethoxyphenanthrene

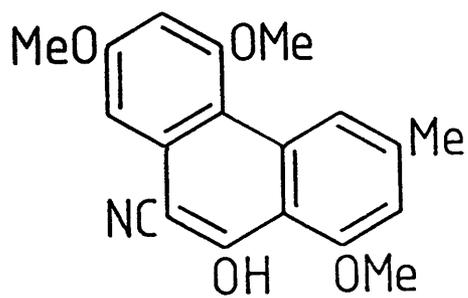
3.1 Introduction

The previous chapter outlined the synthesis of 10-acetoxy-9-cyano-1,5,7-trimethoxy-3-methylphenanthrene (71) devised by Finnie and Hill⁶¹ (see Scheme 17). This phenanthrene was converted to 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) upon hydrolysis of the acetoxy group and removal of the cyano group using Raney nickel in aqueous formic acid. The yield in this latter reaction was at best only 42% and, as described below, represented a great deal of effort on the part of the researchers.

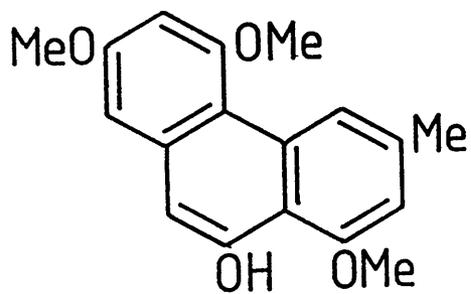
The cyano group of phenanthrene (71) proved extremely resistant to simple acid or base hydrolysis and only the 10-hydroxyphenanthrene (72) was obtained under these conditions. Similarly, no reaction of the cyano group occurred during attempted hydrolysis of the 9-cyano-10-methoxyphenanthrene (172), prepared by methylation of (72). These results are consistent with the reported resistance of ortho-oxygenated aryl cyanides to hydrolysis.⁹⁴ The cyano group of the hydroxyphenanthrene (72) could not be removed by pyrolysis of its calcium salt and all three compounds (71), (72) and (172) failed to show any decyanation when heated in sodium hydroxide/ethanol at 200°C in a sealed tube, or reacted with polyphosphoric acid or sodium in liquid ammonia.⁵⁰ An alternative approach is to convert the cyano group into a different functional group which may be easier to remove. However, amide formation with basic hydrogen peroxide and thioamide formation with basic hydrogen sulphide were unsuccessful in the case of phenanthrene (172). In an attempt to reduce the cyano group to an aldehyde, phenanthrene (72) was treated with Raney nickel in aqueous



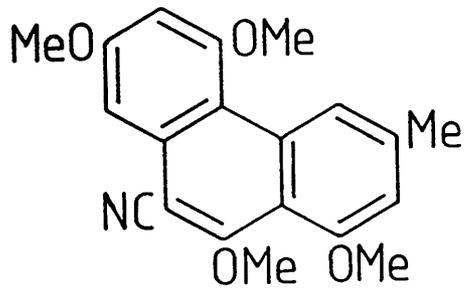
(71)



(72)



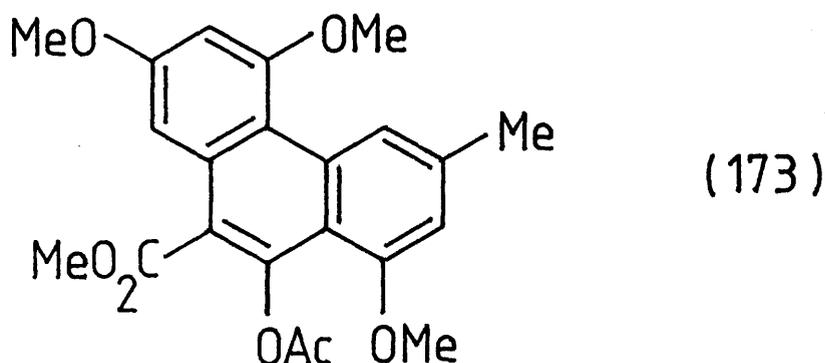
(73)



(172)

formic acid under a nitrogen balloon in a modification of Staskun and Backeberg's⁹⁵ procedure. Surprisingly this gave a 42% yield of the desired phenanthrene (73), although the yield was rather variable. It was initially thought that decyanation might be occurring via hydrogenation of the 9,10-double bond and subsequent loss of hydrogen cyanide. However all attempts to catalytically reduce this bond of phenanthrene (72) failed, even under high pressure conditions. Thus it was postulated that loss of the cyano group occurs by a radical mechanism similar to that suggested for related reactions using dissolving metal reductions.⁹⁵

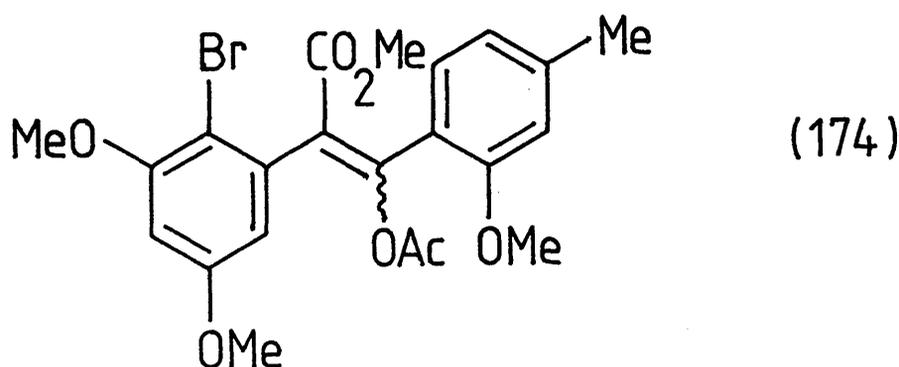
The work described in this chapter was aimed at avoiding the low yielding decyanation step. It was thought that the 9-carbomethoxyl group of phenanthrene (173) might be easily removed by simple acid or base hydrolysis/decarboxylation and so an efficient synthesis of this phenanthrene was desired. At the outset it was realised that if the 9-carbomethoxyl group proved difficult to remove, or if the yield of cyclised product (173) was unacceptably low, then cyano or carbomethoxyl groups could perhaps be removed at an appropriate point prior to cyclisation.



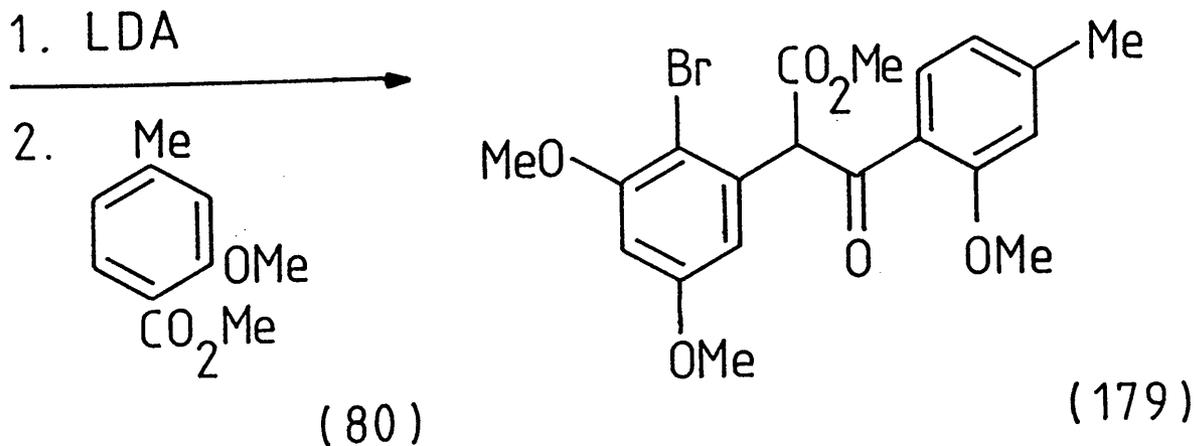
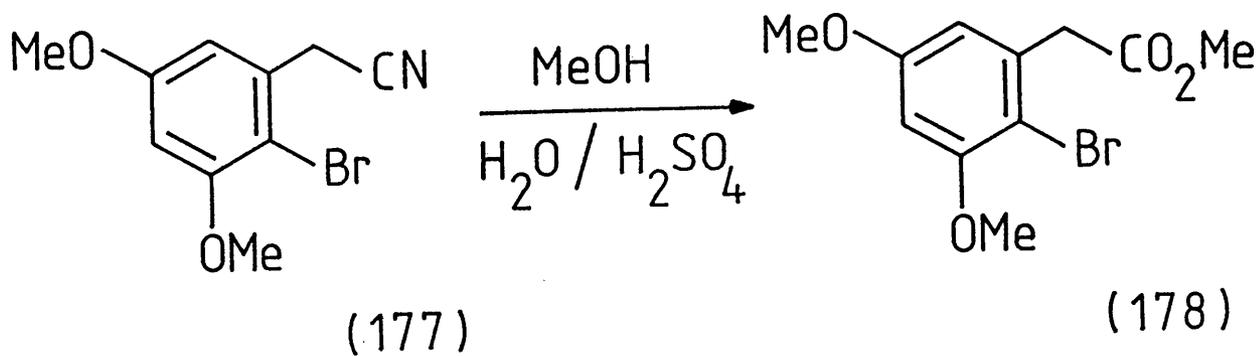
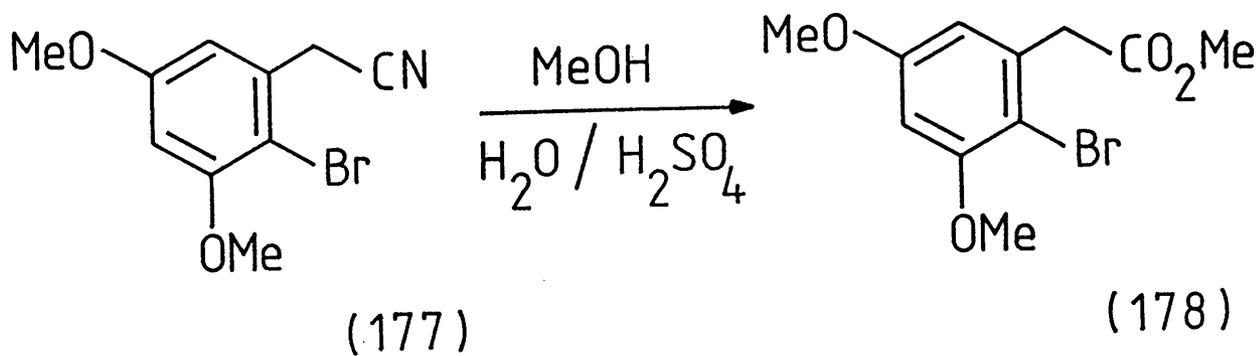
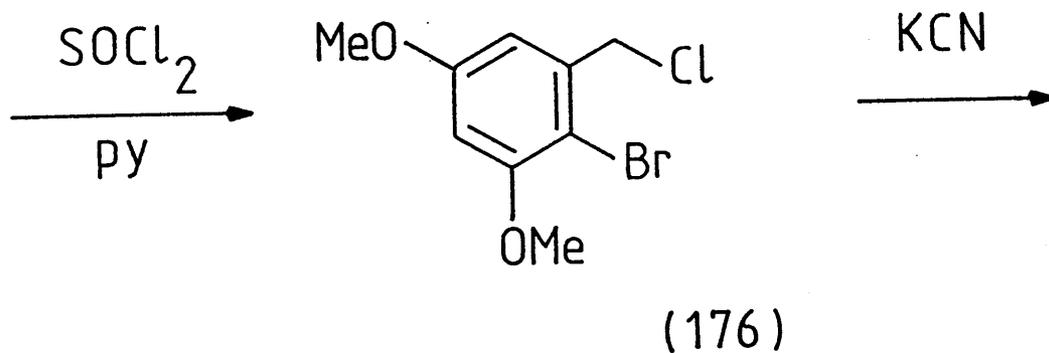
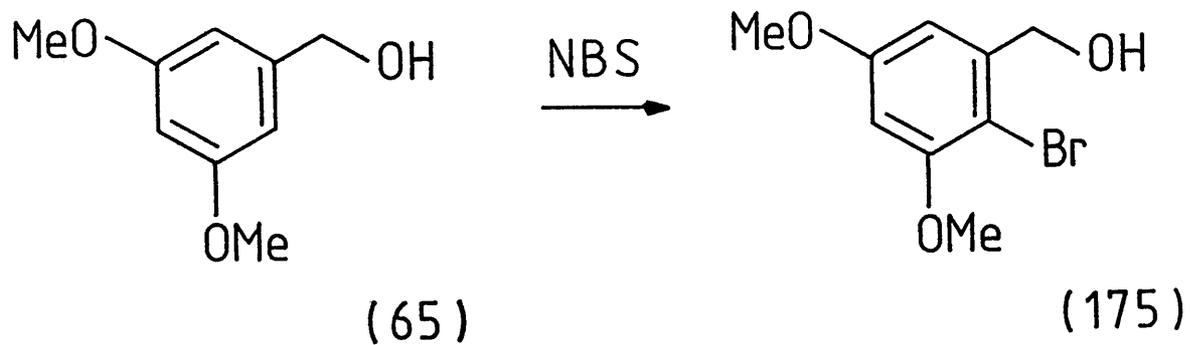
Results and Discussion

3.2 Synthesis of α' -Acetoxy- α -carbomethoxystilbenes

The initial synthetic target en route to the 9-carbomethoxyphenanthrene (173) was the 2-bromostilbene (174). The 2-bromo β -



keto ester precursor (179) of this stilbene was prepared by the reaction sequence depicted in Scheme 56. As described by Noire and Franck,⁹⁶ 3,5-dimethoxybenzyl alcohol (65) was brominated using *N*-bromosuccinimide to give compound (175), which was converted in three steps to the phenylacetic ester (178). Acylation of this ester with methyl 2-methoxy-4-methylbenzoate (80) could not be effected using sodium methoxide as the base and only ester starting materials were recovered unchanged. However, when lithium diisopropylamide was used a 22% yield of the 2-bromo β -keto ester (179) was obtained. A likely side reaction is halogen-metal exchange affording methyl 3,5-dimethoxy-

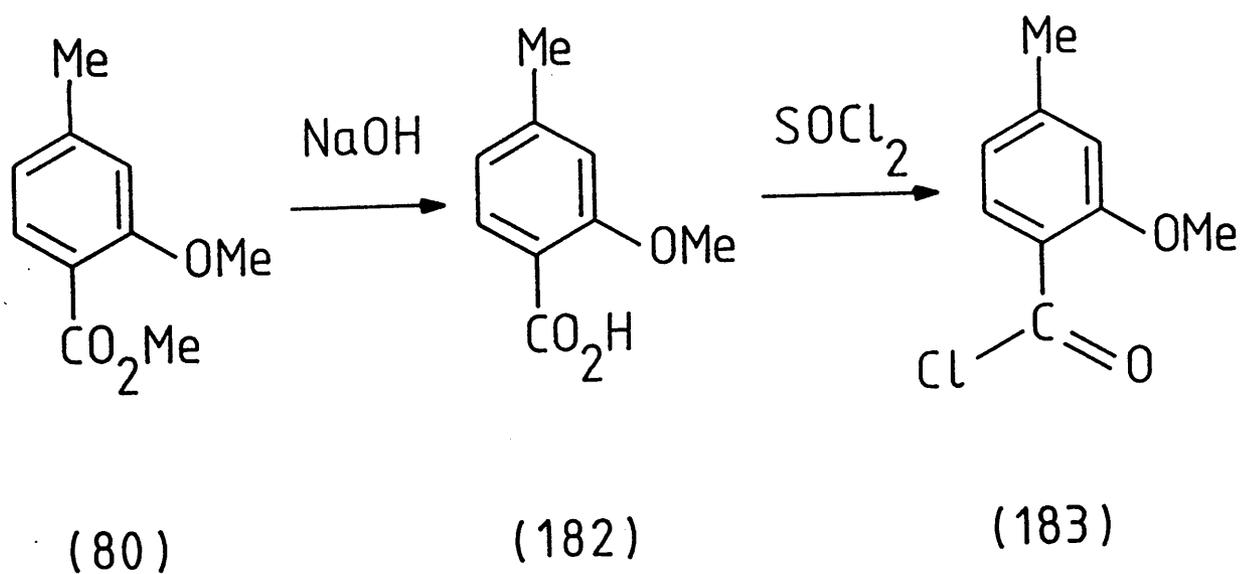
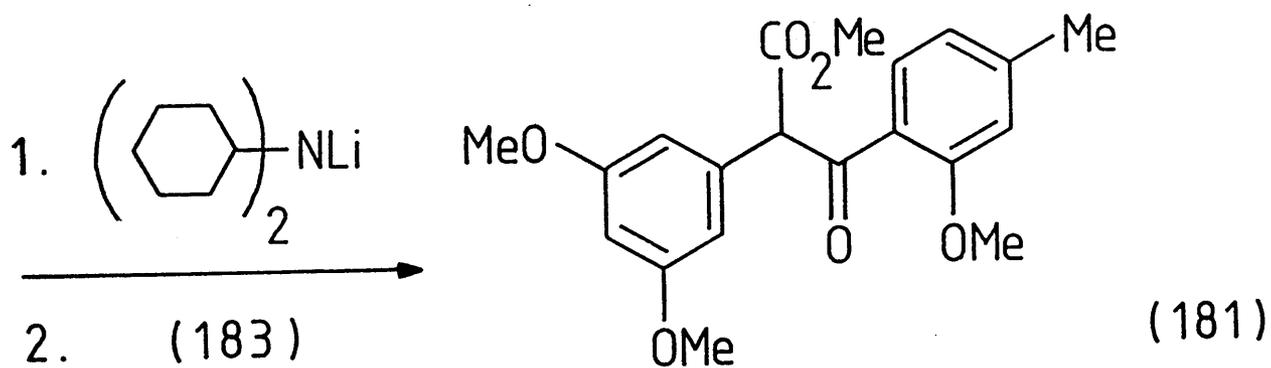
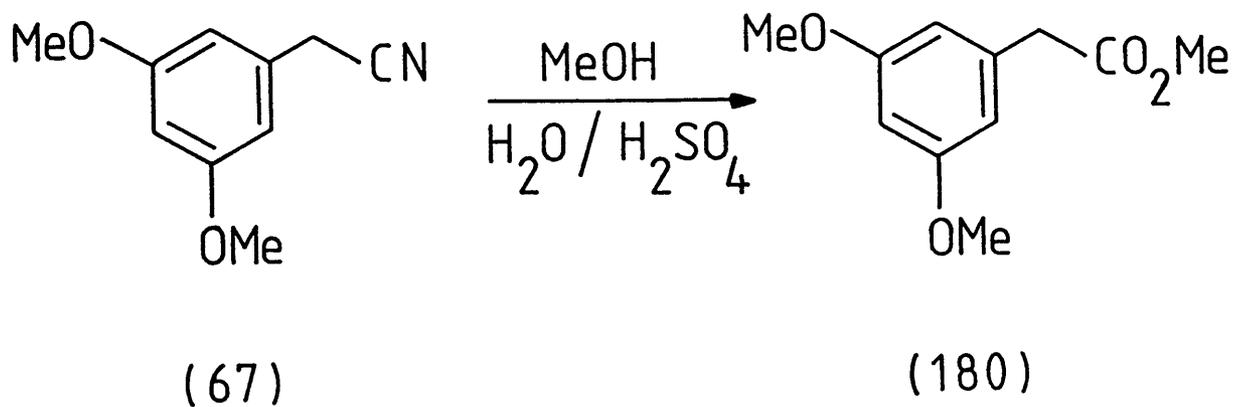


Scheme 56

phenylacetate (180) during the reaction work-up. Owing to the low yield in this reaction the synthesis was abandoned at this stage and a more efficient route to the 9-carbomethoxyphenanthrene (173) was sought.

Methyl 3,5-dimethoxyphenylacetate (180) was prepared by methanolysis of the nitrile (67) [Scheme 57]. Acylation of this ester with the benzoate ester (80) using sodium methoxide, sodium hydride, lithium diisopropylamide or lithium dicyclohexylamide as the base was investigated under a variety of reaction conditions, but the yield of the desired β -keto ester (181) was at best only 4%. A high yielding (84%) synthesis of (181) was developed which involved treatment of the ester (180) with lithium dicyclohexylamide at low temperature, followed by reaction with the acid chloride (183) at room temperature for 2 hours. The acid chloride (183) was prepared from the corresponding carboxylic acid (182) using thionyl chloride. The acylation reaction is an adaptation of Rathke and Deitch's⁹⁷ procedure for the synthesis of β -keto esters involving reaction of lithium ester enolates, prepared by treatment of esters with lithium isopropylcyclohexylamide at -78°C , with acid chlorides at this same low temperature.

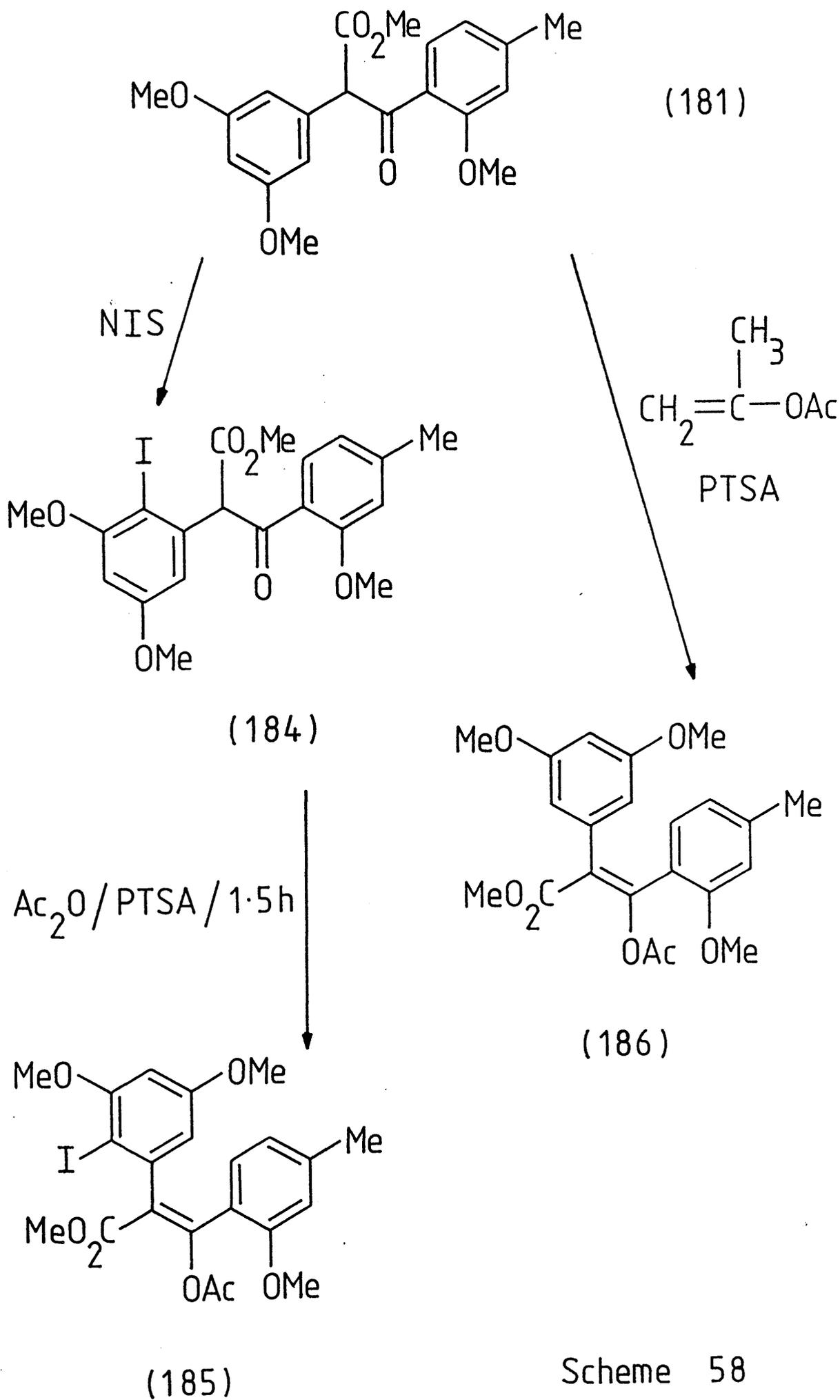
Two stilbenes were synthesised from the β -keto ester (181). The first of these was the Z-2-iodostilbene (185) but, as the next section describes, it soon became apparent that photocyclisation of (185) to the target phenanthrene (173) proceeds in unacceptably low yield. Thus the Z-stilbene (186) was synthesised in the hope that it would photocyclise to give phenanthrene (173) as the major product under oxidising conditions.



Scheme 57

The Z-2-iodostilbene (185) was easily prepared in two steps from the β -keto ester (181) [Scheme 58]. Iodination of (181) with N-iodosuccinimide in chloroform at room temperature afforded a 69% yield of the 2-iodo derivative (184). When (184) was refluxed in acetic anhydride/catalytic p-toluenesulphonic acid for 1½ hours a single geometric isomer of the 2-iodostilbene was isolated in 68% yield as a white crystalline solid. The next section describes how this was shown to be the Z-isomer. None of the E-isomer could be detected amongst the minor products formed in the reaction. Surprisingly, the Z-stilbene (186) could not be prepared satisfactorily under the same conditions since multiple products were obtained. An alternative method of preparing enol acetates involves using isopropenyl acetate and a strong acid catalyst.^{98,99} This is a particularly mild method and often allows high yields of products to be obtained. When the β -keto ester (181) was reacted with isopropenyl acetate in the presence of p-toluenesulphonic acid for 11 hours a 95% yield of a crystalline stereoisomer of the α' -acetoxy- α -carbomethoxystilbene was isolated.

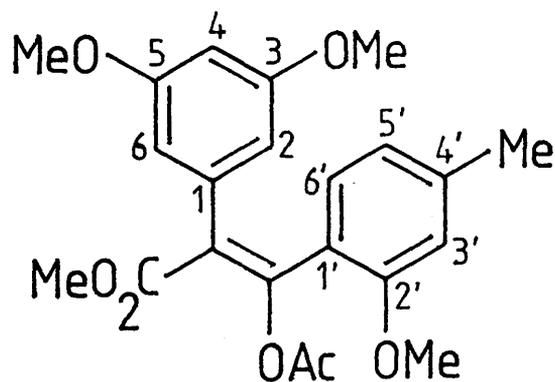
The configuration of this stilbene stereoisomer was determined to be Z by NOE difference spectroscopy. The ¹H nmr spectrum of the stereoisomer was recorded at 360 MHz and most of the signals in the spectrum were irradiated in turn and the resulting NOE enhancements measured [Tables 9 and 10]. Irradiation of the aromatic methyl signal caused enhancement of the H-3' and H-5' signals and irradiation of the 6H singlet due to the methoxyls at positions 3 and 5 enhanced the 3H singlet corresponding to H-2, H-4 and H-6. These NOE enhancements would be expected for both stilbene stereoisomers. The relatively



Scheme 58

Table 9. 360 MHz ^1H nmr data for the Z-stilbene (186)

$\delta(\text{CDCl}_3)$, ppm	Signal Multiplicity	Integral	Assignment
7.05	d, $\underline{J} = 7.6$ Hz	1H	H-6'
6.58	d, $\underline{J} = 7.6$ Hz	1H	H-5'
6.55	s	1H	H-3'
6.25	s	3H	H-2, H-4, H-6
3.76	s	3H	CO_2CH_3
3.62	s	3H	2'- CH_3O
3.59	s	6H	3- CH_3O , 5- CH_3O
2.26	s	3H	Ar CH_3
2.17	s	3H	CH_3CO



(186)

Table 10. NOE enhancements for the Z-stilbene (186)

Signal Irradiated	Signal(s) Enhanced	Size of NOE, %
ArCH ₃	H-3'	7
	H-5'	7
3-CH ₃ O, 5-CH ₃ O	H-2, H-4, H-6	15
2'-CH ₃ O	H-3'	12
CO ₂ CH ₃	none	
H-2, H-4, H-6	3-CH ₃ O, 5-CH ₃ O	1
	H-6'	small (< 1%)
H-6'	H-5'	5
	H-2, H-4, H-6	small (< 1%)

large NOE observed for H-3' when the 2'-methoxyl was irradiated probably suggests that this methoxyl substituent is orientated syn to H-3'. No enhanced signals were obtained when the carbomethoxyl resonance was irradiated. Models indicate that the probability of observing an NOE when the carbomethoxyl signal is irradiated is greater in the E-isomer than in the Z-isomer. However, the failure to observe an NOE when this signal was irradiated does not necessarily mean that the isomer has the Z-configuration since this situation could still arise in the case of the E-isomer.

As expected, the crucial experiments which determined the configuration of the isomer were irradiation of the 3H singlet due to H-2, H-4 and H-6 and irradiation of H-6'. When the former irradiation was performed a small NOE (< 1%) was observed for H-6' and when H-6' was irradiated a similar small (< 1%) enhancement of the H-2, H-4, H-6 signal was obtained. The fact that these NOE enhancements occurred at all is significant since they would not be observed if the isomer had the E-configuration. The small enhancements are probably due to the relatively large distance between H-2 or H-6 and H-6' because the ring containing H-6' is likely to be twisted out of the plane of the remaining styrene system for steric reasons.

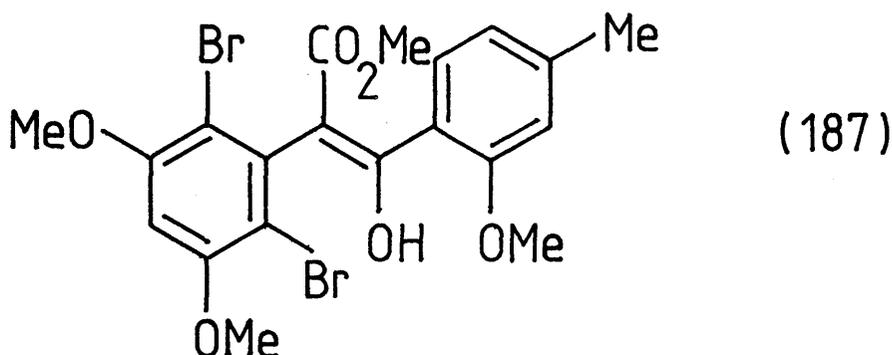
Recall that α' -acetoxy- α -cyanostilbenes are formed as a stereoisomeric mixture and the ratio of stereoisomers depends upon the steric hinderance in the stilbene since this determines which stereoisomer is the most thermodynamically stable (see Section 2.7). The Z-stilbene is more thermodynamically stable than the E-stilbene provided the steric interference between the two aryl groups in the Z-isomer is not too great. This may be due to a favourable electronic interaction between the cyano and acetoxy groups in the Z-stilbene which is not available in the E-stilbene. In this situation the Z-isomer predominates in the stereoisomeric mixture, provided the reaction time is sufficiently long for the E- and Z-forms to reach thermodynamic equilibrium. If the steric interference between the two aryl groups is great, then the favourable electronic interaction between the cyano and acetoxy groups in the Z-isomer is not strong enough to compete with the unfavourable steric interaction between the aryl groups. In this

case the less hindered E-stilbene is more thermodynamically stable and so it predominates in the stereoisomeric mixture.

It is interesting that the Z- α' -acetoxy- α -carbomethoxystilbenes (185) and (186) are formed to the exclusion of any E-isomer. This implies that these Z-stilbenes are significantly more thermodynamically stable than the corresponding E-stilbenes and this may be due to a particularly favourable electronic interaction between the carbomethoxyl and acetoxy groups in the Z-isomers. The uv spectra of the Z-stilbenes (185) and (186) have the characteristic shape of a moderately crowded stilbene and so the steric interference between the two aryl groups is not very great. This means that the unfavourable steric interaction between the aryl groups is not strong enough to overcome the favourable electronic interaction in the Z-isomers (185) and (186). Presumably the electronic interaction between the carbomethoxyl and acetoxy groups is greater than that between the cyano and acetoxy groups since only the Z- α' -acetoxy- α -carbomethoxystilbenes are formed while both the E- and the Z- α' -acetoxy- α -cyanostilbenes are formed.

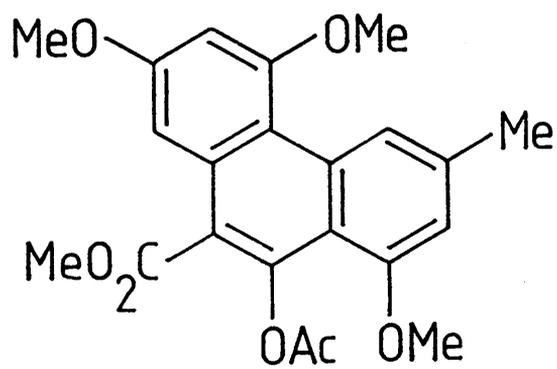
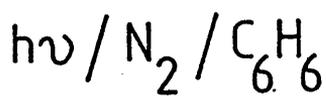
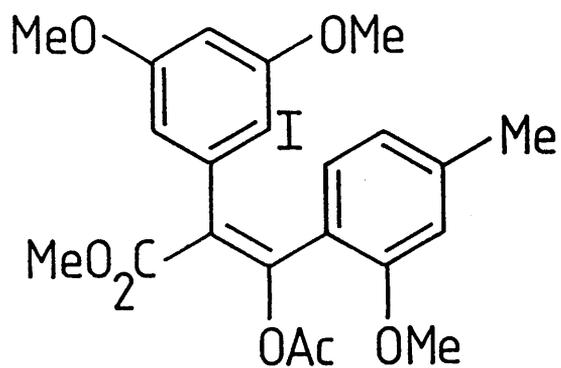
One might expect a mixture of E- and Z- α' -acetoxy- α -carbomethoxystilbenes to be formed if the steric interference between the aryl groups is large. It was hoped that this would be confirmed by the formation of a mixture of geometric isomers in the acetylation reaction of the crowded 2,6-dibromo compound (187), prepared by reaction of the β -keto ester (181) with bromine in acetic acid. The potassium bromide disc ir spectrum and 200 MHz ^1H nmr spectrum of (187) show that it exists in the enol form in the solid state and in d_6 -dimethyl sulphoxide. Unfortunately, reaction of (187) with acetic

anhydride afforded a complex mixture of inseparable products. Thus no confirmation or otherwise of the above expectation was derived from this experiment.

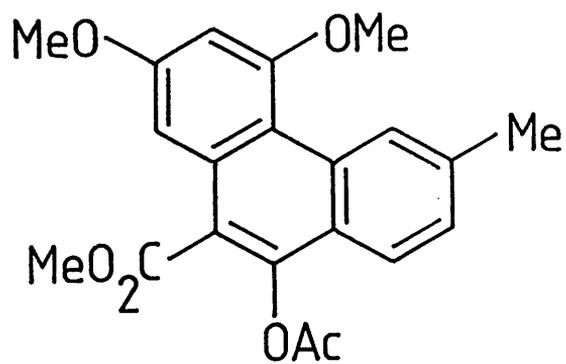


3.3 Photochemistry of α' -Acetoxy- α -carbomethoxystilbenes

The 2-iodostilbene (185) was the first α' -acetoxy- α -carbomethoxystilbene to be investigated as a possible source of the target phenanthrene (173) upon photocyclisation. When (185) was irradiated with uv light in deoxygenated benzene for 22 hours a disappointing 23% yield of the required phenanthrene (173) was obtained in addition to a 6% yield of phenanthrene (188) [Scheme 59]. Compound (185) probably photocyclises via intramolecular free radical arylation in the same way as described for the corresponding α -cyanostilbene (139) in Section 2.4.2. Introduction of triethylamine into the reaction mixture resulted in 10% and 3% yields of phenanthrenes (173) and (188) after 20 hours. Finally, irradiation of the 2-iodostilbene stereoisomer



+



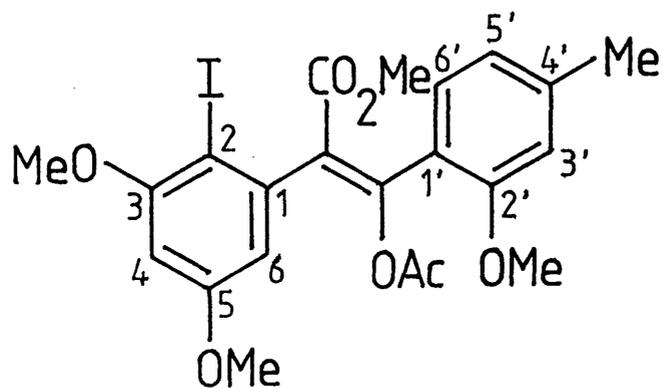
Scheme 59

(185) in benzene/triethylamine for 4 hours under anaerobic conditions resulted in a photostationary equilibrium of E- and Z-isomers. The opposite stereoisomer from (185) was subsequently isolated upon fractional crystallisation of the crude reaction product and shown to be the E-isomer (185a) by NOE difference spectroscopy (see below). Thus the configuration of the stereoisomer (185), formed by reaction of the β -keto ester (184) with acetic anhydride/catalytic PTSA, was clearly established as Z.

The ^1H nmr spectrum of the isomer (185a) produced in the photochemical experiment was recorded at 200 MHz and some of the signals in the spectrum were irradiated and the resulting NOE enhancements measured [Tables 11 and 12]. Irradiation of the H-6' signal caused enhancement of the H-5' signal only. Recall that in the Z-stilbene (186) a small NOE was observed for the 3H singlet due to H-2, H-4 and H-6 upon irradiation of H-6'. In the Z-stilbene (185) the 2-iodo substituent would probably not prohibit the small NOE expected to occur for H-6 upon irradiation of H-6'. Thus the failure to observe enhancement of H-6 when H-6' of the stilbene stereoisomer (185a) was irradiated suggests that it has the E-configuration. Irradiation of the doublet at $\delta 6.60$ ppm resulted in 2% and 0.8% enhancements of the methoxyl resonances at $\delta 3.79$ and 3.84 ppm respectively. Similarly, irradiation of the doublet at $\delta 6.40$ ppm caused 3% and 0.6% enhancements of the methoxyls at $\delta 3.87$ and 3.79 ppm respectively. It follows that the signal at $\delta 3.79$ ppm corresponds to the methoxyl substituent at position 5. The assignment of the other methoxyl signals is uncertain.

Table 11. 200 MHz ^1H nmr data for the E-stilbene (185a)

δ (CDCl ₃), ppm	Signal Multiplicity	Integral	Assignment
7.31	d, $J=7.7$ Hz	1H	H-6'
6.80	dq, $J=7.7, 0.7$ Hz	1H	H-5'
6.74	s	1H	H-3'
6.60	d, $J=2.7$ Hz	1H	ArH
6.40	d, $J=2.7$ Hz	1H	ArH
3.87	s	3H	CH ₃ O
3.84	s	3H	CH ₃ O
3.79	s	3H	CH ₃ O
3.57	s	3H	CH ₃ O
2.37	s	3H	ArCH ₃
1.85	s	3H	CH ₃ CO



(185a)

Table 12. NOE enhancements for the E-stilbene (185a)

Signal Irradiated	Signal(s) Enhanced	Size of NOE, %
H-6'	H-5'	10
doublet at $\delta 6.60$	CH_3O at $\delta 3.79$	2
	CH_3O at $\delta 3.84$	0.8
doublet at $\delta 6.40$	CH_3O at $\delta 3.87$	3
	CH_3O at $\delta 3.79$	0.6

The uv spectra of the Z-isomer (185) and the E-isomer (185a) of the 2-iodostilbene support these configuration assignments made on the basis of NOE difference of isomer (185a) since the longest wavelength band of the spectrum of (185) is less intense than that of (185a).

It is noteworthy that the ^1H nmr signal due to H-6' in the E-stilbene (185a) occurs downfield from that in the Z-stilbene (185) and that the acetoxy signal occurs at higher field in the E-isomer than in the Z-isomer. These relationships also exist in E- and Z- α' -acetoxy- α -cyanostilbenes (refer to Section 2.6.2).

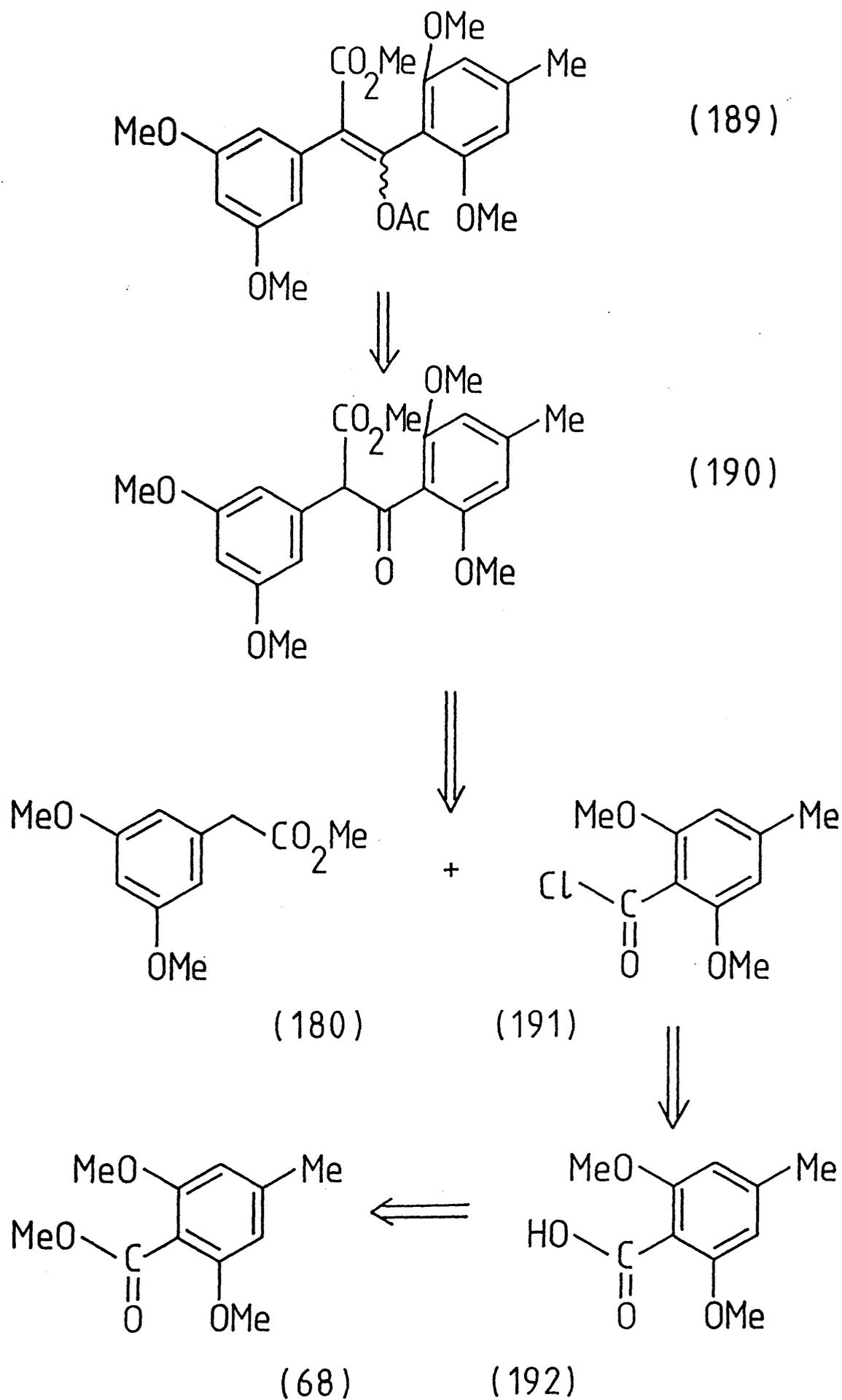
The poor yield of the desired phenanthrene (173) upon photocyclisation of the 2-iodostilbene (185) in benzene solution prompted the synthesis of stilbene (186). It was thought that this stilbene might afford phenanthrene (173) as the major photoproduct under oxidising conditions since there are numerous literature examples involving preferential loss of hydrogen from an ortho-methoxystilbene upon photo-

cyclisation in the presence of an oxidant.^{100,101} However, irradiation of stilbene (186) for 20 hours in air saturated cyclohexane containing iodine gave phenanthrene (173) in 21% yield and the eliminative photocyclisation product (188) in 56% yield. This result suggests that the corresponding 2',6'-dimethoxystilbene (189) would probably give a very good yield of the target compound (173). Unfortunately stilbene (189) could not be synthesised. The synthesis failed at an early stage owing to the difficulty experienced in preparing the acid chloride (191), required to acylate the phenylacetic ester (180) to give the β -keto ester (190) [Scheme 60]. The acid chloride (191) is a known compound,¹⁰² but in our hands, it could not be prepared from the corresponding carboxylic acid (192) using thionyl chloride, phosphorus pentachloride or oxalyl chloride under a variety of reaction conditions.

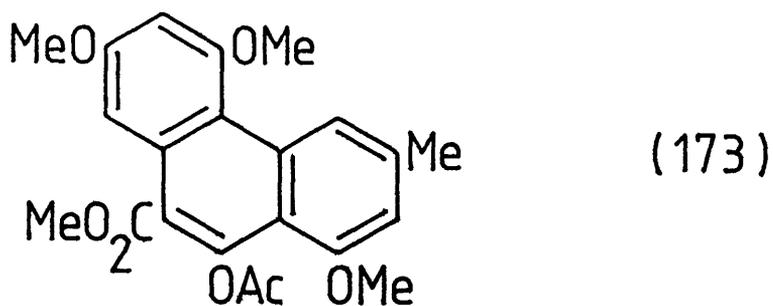
Evidence is presented in the next section which indicates that if the 2',6'-dimethoxystilbene (189) could be prepared and subsequently photocyclised, then the route would represent a very effective synthesis of the desired compound 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73).

3.4 Decarbomethoxylation of Phenanthrene (173)

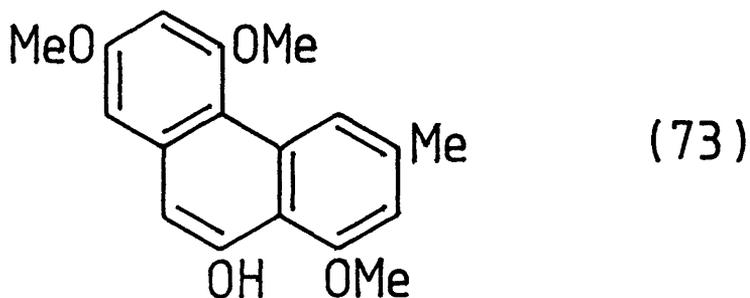
In contrast to the resistance of the 9-cyano group of phenanthrene (71) to a wide variety of reagents, the 9-carbomethoxyl group of the corresponding phenanthrene (173) could be easily removed with simultaneous hydrolysis of the 10-acetoxyl group to yield the desired phenanthrene (73) in very good yield [Scheme 61]. This latter



Scheme 60



↓
15% NaOH / MeOH / N₂

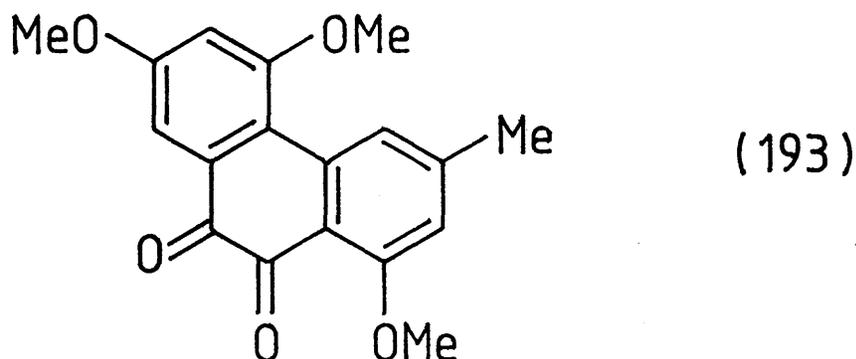


Scheme 61

phenanthrene was prepared in two steps from phenanthrene (71) by Finnie and Hill,⁶¹ although the second step involved variable and low yielding decyanation using Raney nickel in aqueous formic acid.

Conversion of the 9-carbomethoxyphenanthrene (173) to phenanthrene (73) was achieved by refluxing a solution of (173) in 15% aqueous sodium hydroxide/methanol under nitrogen for 6 hours. The yield of the crude product was 90%. The purpose of conducting the reaction under nitrogen was to prevent formation of the 9,10-quinone (193) which would occur upon heating (73) in air. The ¹H nmr spectrum of

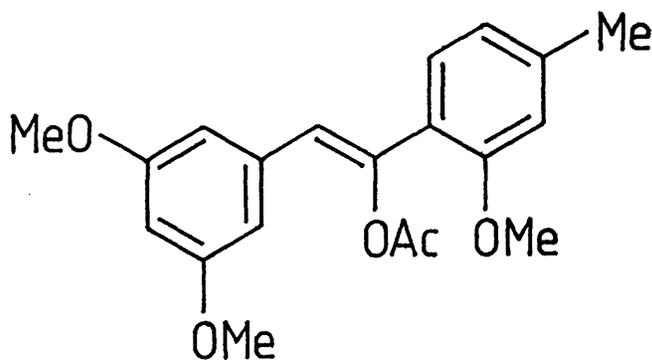
the crude product (73) was very clean, but on recrystallisation partial oxidation of (73) occurred. Immediate acetylation of the crude reaction product would prevent this happening, although this was not tried owing to a lack of time.



Thus decarbomethoxylation of phenanthrene (173) could be easily accomplished, but unfortunately the yield of (173) via photocyclisation of stilbene (185) or (186) is unacceptably low for the route to be synthetically useful. The next section describes an approach which was aimed at generating 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) via a route which gives a good yield of cyclised product and also avoids the low yielding decyanation step.

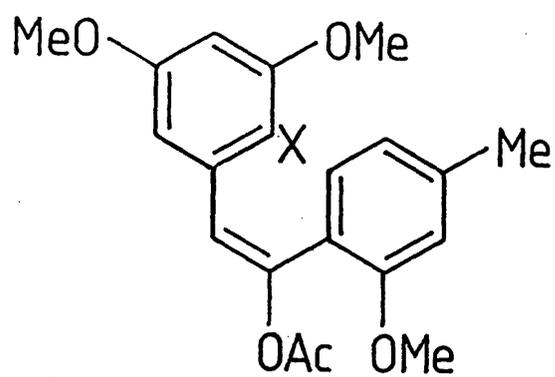
3.5 Desoxybenzoins via β -Keto Ester Hydrolysis/Decarboxylation

Scholz et al.¹⁰³ have attempted to explain the failure of certain stilbene photocyclisations by molecular orbital calculations and have implied that substituents play a crucial role in determining the yield of cyclised product. As an illustration of the effect a substituent can have, contrast the photoreactivity of the α' -acetoxy- α -carbomethoxy-stilbene (186) reported in Section 3.3 with the failure of the structurally related stilbene (194) (lacking the α -carbomethoxyl substituent) to photocyclise under the conditions investigated.⁵⁰

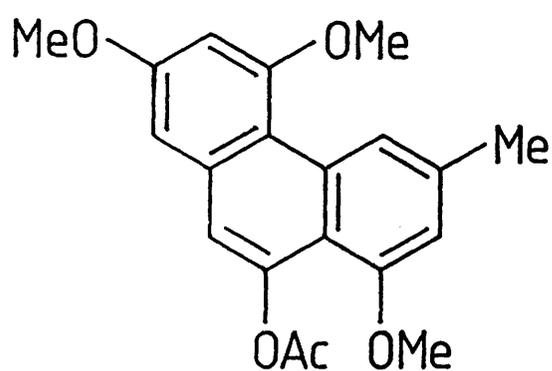
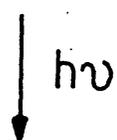


(194)

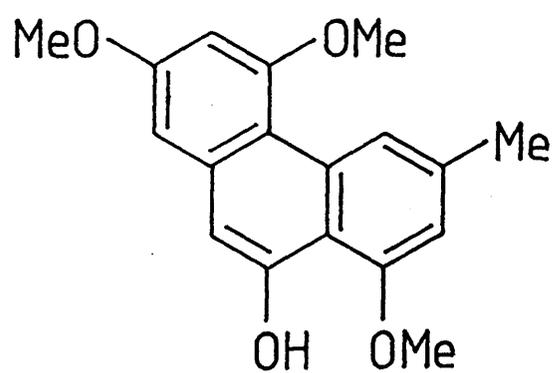
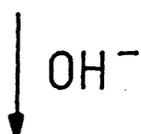
As shown in Scheme 62, uv irradiation of the 2-halo derivative (195) of stilbene (194) might induce ring closure to phenanthrene (196) and this synthetic route would avoid the need to perform decyanation or decarbomethoxylation subsequent to cyclisation.



(195) X = Br, I



(196)



(73)

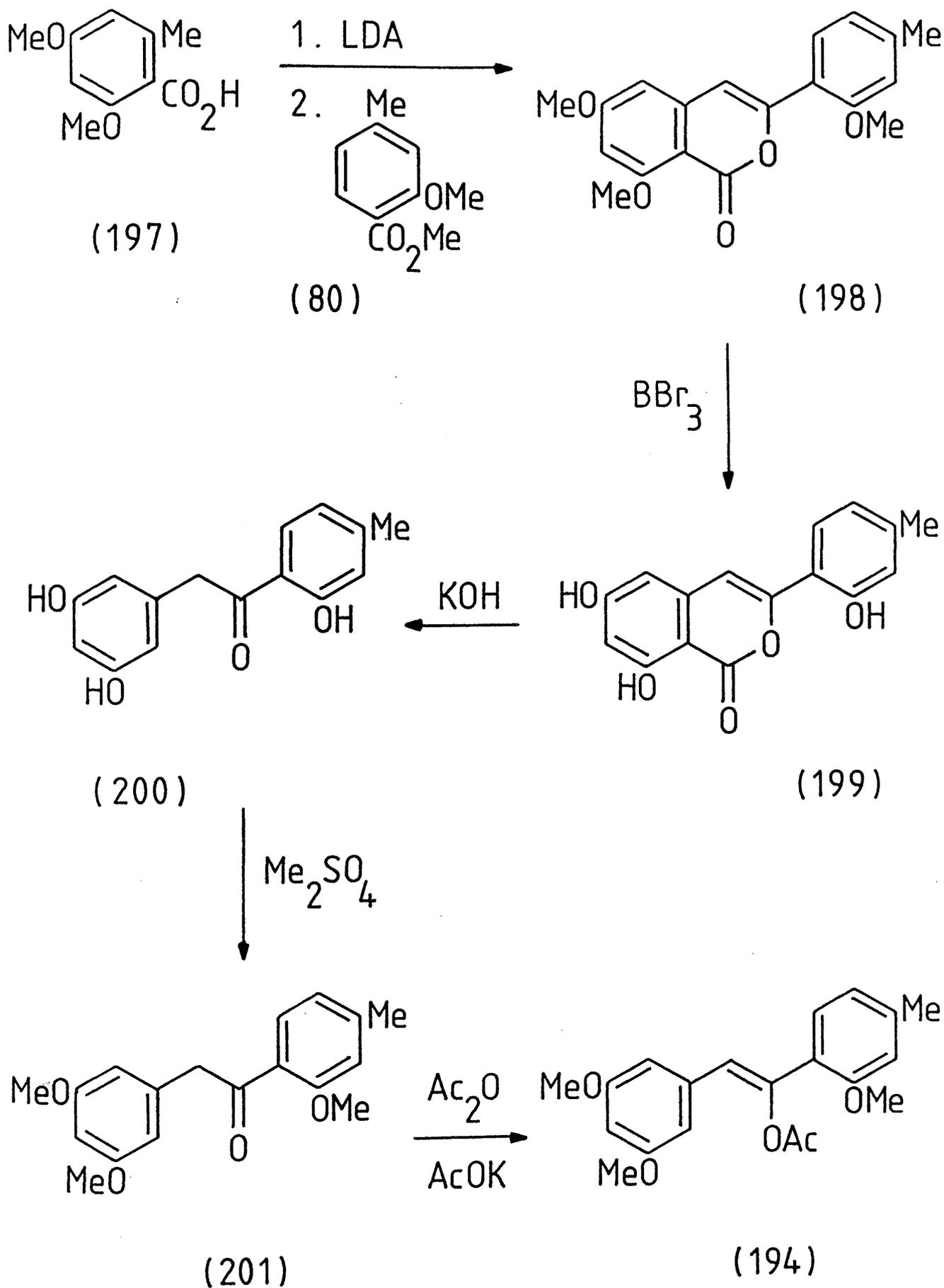
Scheme 62

Hydrolysis of the 10-acetoxy group of phenanthrene (196) would yield the target 10-hydroxyphenanthrene (73), C-9 of which is susceptible to oxidation. Therefore another advantage of the route shown in Scheme 62 is that it generates the target phenanthrene (73) as its 10-acetoxy derivative (196) and this prevents oxidation occurring at C-9. Thus stilbene (195), with a 2-substituent of either bromine or iodine, became the next synthetic target. It was hoped that a good yield of phenanthrene (196) would be obtained upon irradiation of one of these halostilbenes.

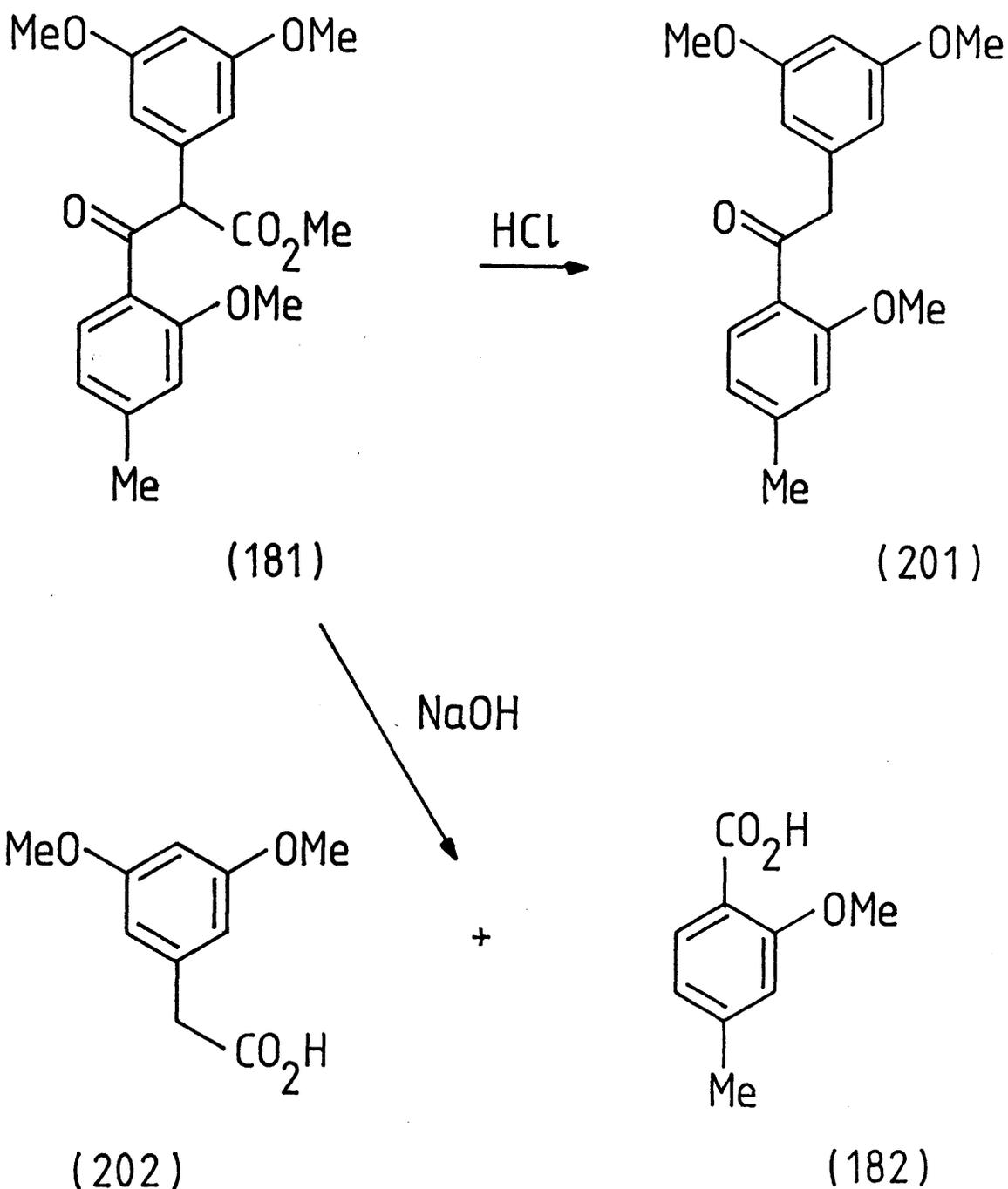
Finnie and Hill⁶¹ devised a synthesis of stilbene (194) in which the desoxybenzoin (201) was derived from the 3-arylisocoumarin (198) and then reacted with acetic anhydride/potassium acetate to give stilbene (194) in 52% yield [Scheme 63]. Repeated attempts to convert the β -keto nitrile (81) to the desoxybenzoin (201) in acidic or basic media were unsuccessful.

In the present study, the desoxybenzoin (201) was conveniently prepared by refluxing the β -keto ester (181) in 5M hydrochloric acid overnight [Scheme 64]. Upon refluxing in 10% aqueous sodium hydroxide, the β -keto ester (181) afforded 3,5-dimethoxyphenylacetic acid (202) and 2-methoxy-4-methylbenzoic acid (182) via a retro-Claisen type of reaction. Attempted bromination or iodination of the desoxybenzoin (201) using the N-halosuccinimides gave multiple products which could not be separated.

A more promising synthesis of the required 2-halostilbene (195) is shown in Scheme 65, although this route was not investigated due to a lack of time. It involves hydrolysis/decarboxylation of the

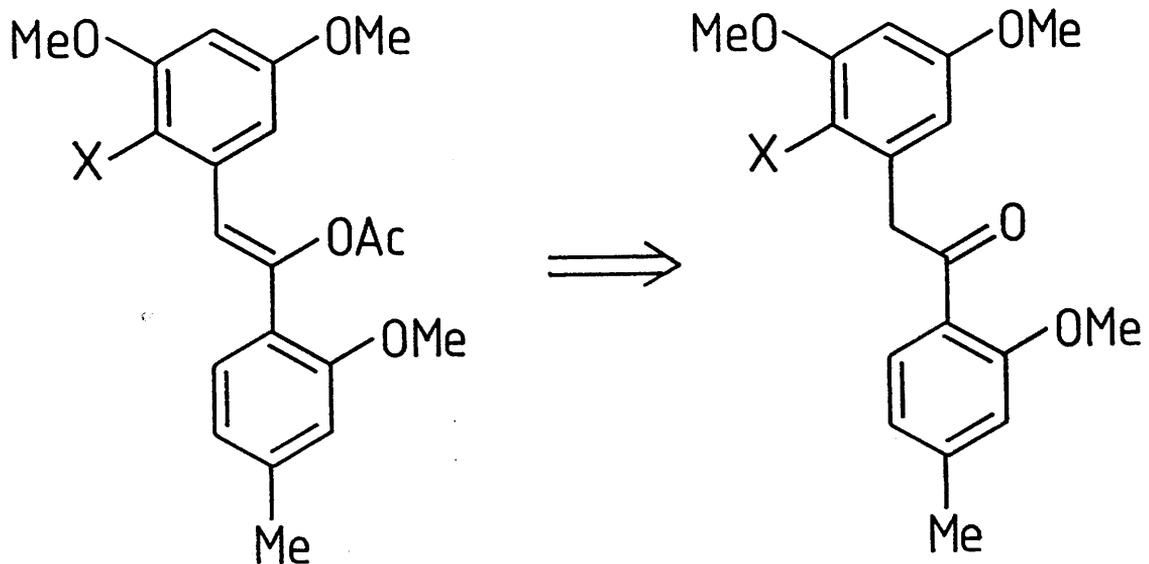


Scheme 63



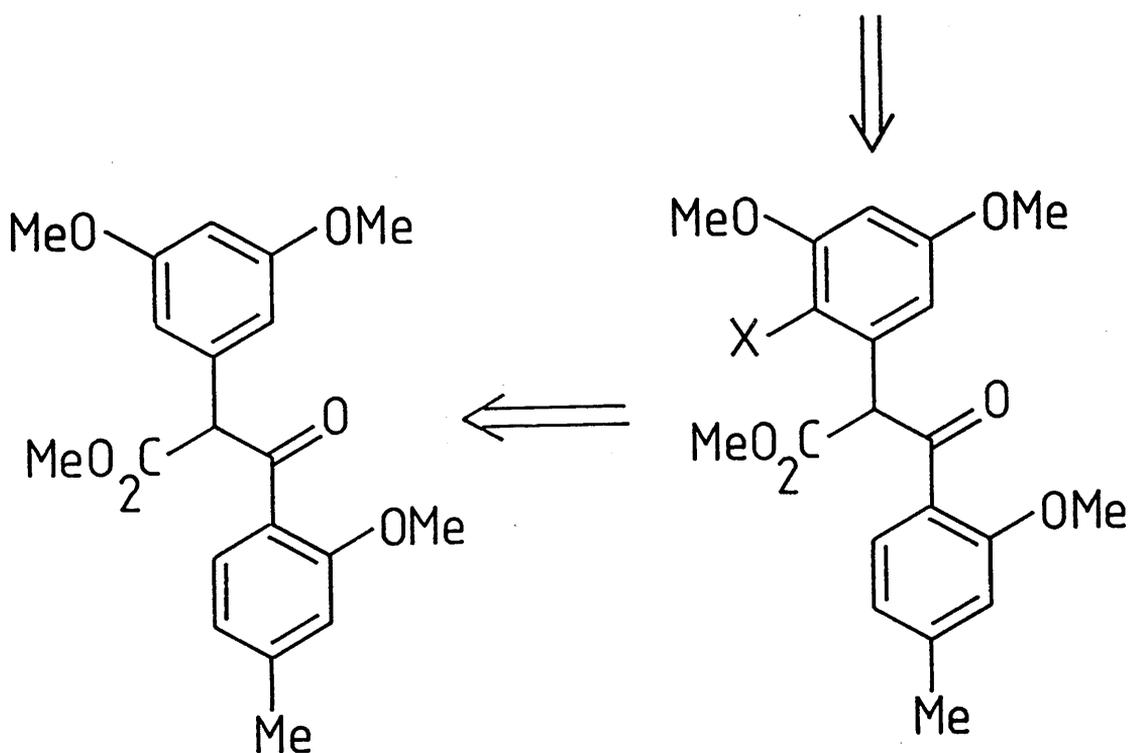
Scheme 64

2-halo β -keto ester (204) followed by enol acetate derivatisation. The 2-halo β -keto ester (204) is readily available via halogenation of the β -keto ester (181) using NBS or NIS (e.g. see p.147).



(195) X = Br, I

(203)



(181)

(204)

Scheme 65

As described in this and the previous chapter, 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) can be prepared from α -cyano- or α -carbomethoxystilbene intermediates. Attempted demethylation of (73) to provide phenanthrene (14), one of the postulated intermediates in the biosynthesis of mollisin (1), is discussed in the next chapter. The next chapter also describes attempts at synthesising phenanthrene (14) using benzyl protecting groups for the aromatic hydroxyl substituents in the starting materials.

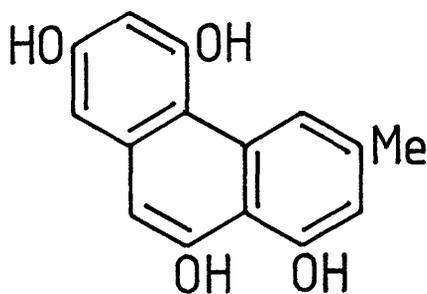
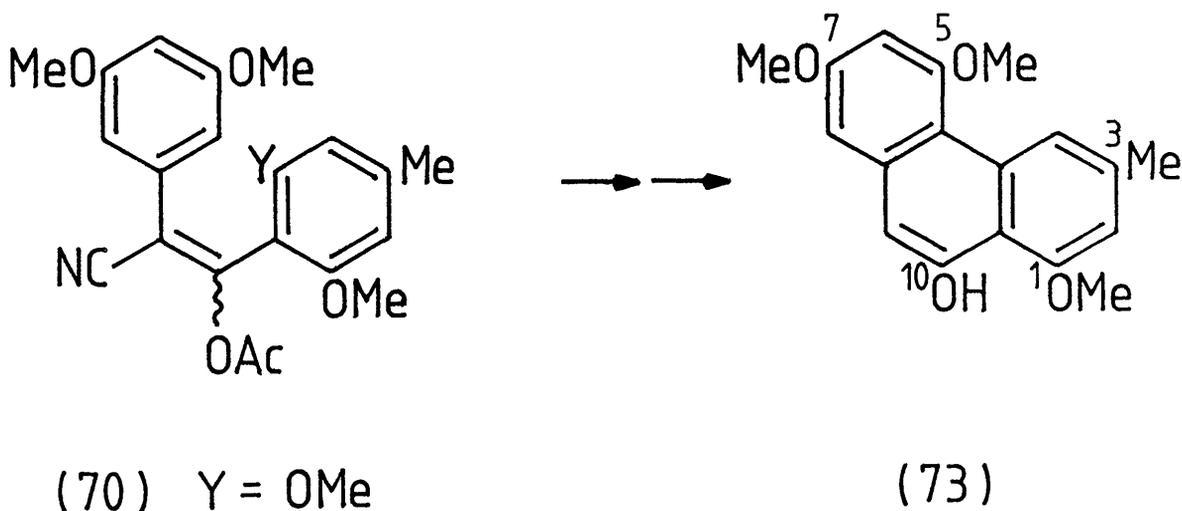
CHAPTER 4

The Synthesis and Photocyclisation of a 2-Benzyloxystilbene



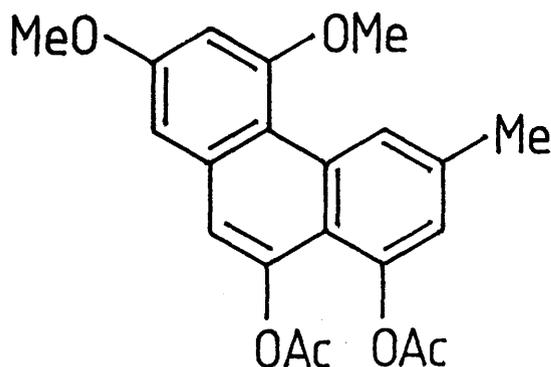
4.1 Introduction

In connection with an investigation of the biosynthesis of mollisin (1), Finnie and Hill⁶¹ devised a synthesis of 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) involving photocyclisation of the tetramethoxystilbene (70) as the key step (see Scheme 17). However, treatment of phenanthrene (73) with boron tribromide (BBr_3) or trimethylsilyl iodide (TMSI) failed to effect complete demethylation to give the target phenanthrene (14), one of the postulated biosynthetic intermediates.⁵⁰



(14)

There are a large number of reagents available for aromatic ether cleavage,¹⁰⁴ but the reagent of choice is often BBr_3 which is generally clean and effective. Cleavage of the methyl ethers of phenanthrene (73) using BBr_3 was not anticipated by Finnie⁵⁰ to be a problem, but because the tetrahydroxyphenanthrene (14) would be readily oxidised in air, the crude reaction product was immediately acetylated by reaction with acetic anhydride and pyridine. 1,10-Diacetoxy-5,7-dimethoxy-3-methylphenanthrene (205) was obtained when phenanthrene (73) was treated with a large molar excess of BBr_3 and the crude reaction mixture acetylated. This result was repeatable.

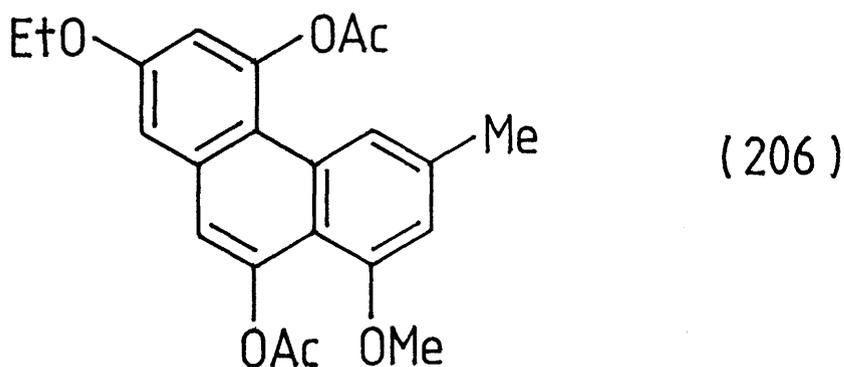


(205)

The failure of BBr_3 to fully demethylate phenanthrene (73) is somewhat surprising. The methoxyl at C-1 would be expected to be particularly labile towards BBr_3 because the peri-hydroxyl group would

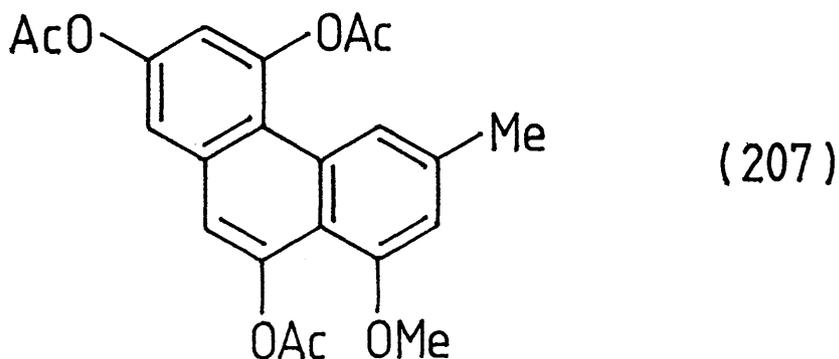
facilitate delivery of the borane moiety; this expectation agrees with the experimental evidence. The methoxyl at C-7 is unhindered and so it is difficult to understand why it is inert to BBr_3 . The methoxyl at C-5 is partially hindered due to its position in the aromatic bay region, but would still be predicted to be reactive towards BBr_3 .

One of the many alternative reagents available for the cleavage of ethers is TMSI, which is reported to result in clean, quantitative demethylation in many systems.¹⁰⁵ Treatment of phenanthrene (73) with a large molar excess of TMSI in refluxing chloroform under nitrogen, followed by chromatography of the acetylated crude reaction mixture, afforded 5,10-diacetoxy-7-ethoxy-1-methoxy-3-methylphenanthrene (206) as the major product in 40% yield. Thus cleavage of the methoxyls at C-5 and C-7 of phenanthrene (73) occurs in the presence of TMSI/chloroform, but because the C-7 methoxyl is unhindered it is ethylated under the reaction conditions. It is curious that ethyl ether formation occurs under conditions designed to promote ether cleavage.



A known reaction of aliphatic alcohols with TMSI is formation of the alkyl iodide.¹⁰⁶ Therefore the ethylating agent in the reaction of phenanthrene (73) with TMSI/chloroform is probably ethyl iodide, formed by the reaction of ethanol (present in chloroform as a stabiliser) with TMSI.

It is probable that 5,7,10-triacetoxy-1-methoxy-3-methylphenanthrene (207) would be obtained by carrying out the reaction of phenanthrene (73) with TMSI in ethanol-free chloroform. Subsequent treatment of this product with BBr_3 would probably cleave the final methyl ether, but it is likely that the poor yield obtained in each step would limit the synthetic value of such a route.



Recall that the ultimate aim of the research was to prepare deuterium labelled phenanthrenes (14)-(16) in acetylated form in order to investigate the biosynthesis of mollisin (1). One approach to the

synthesis of deuteriated compounds is to employ a route whereby the label is carried along from a deuteriated starting material over a multi-step sequence into the deuteriated product. A different approach involves synthesis of unlabelled material which is then made to undergo $^1\text{H}/^2\text{H}$ exchange within the finished molecular framework.

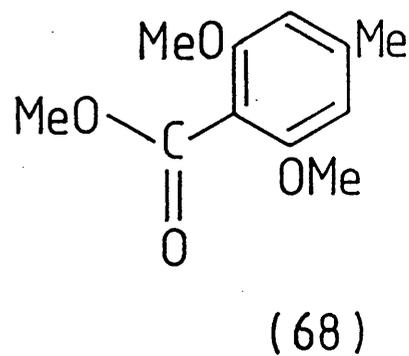
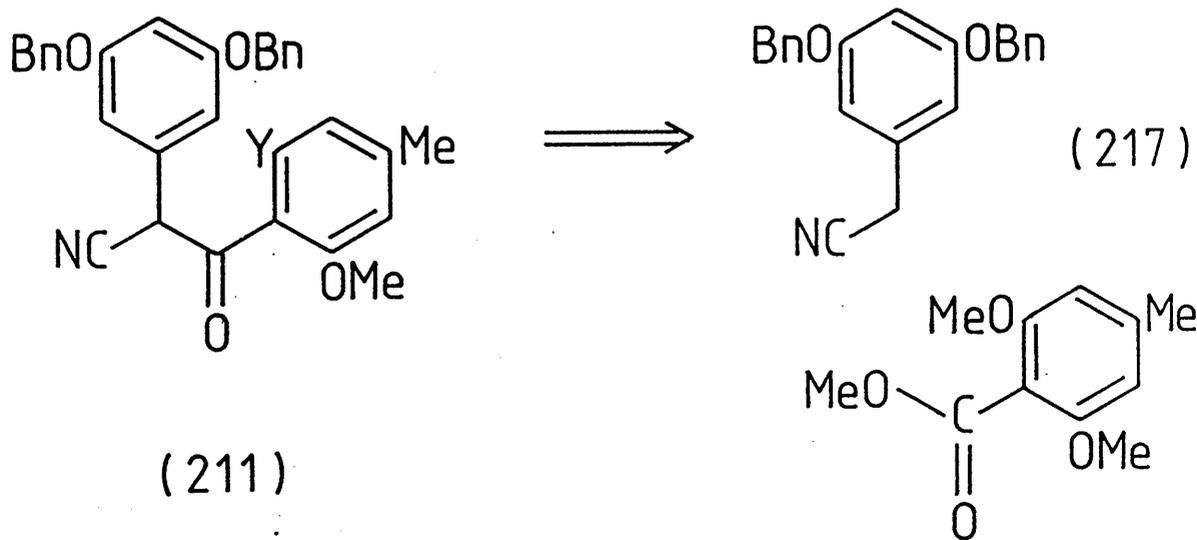
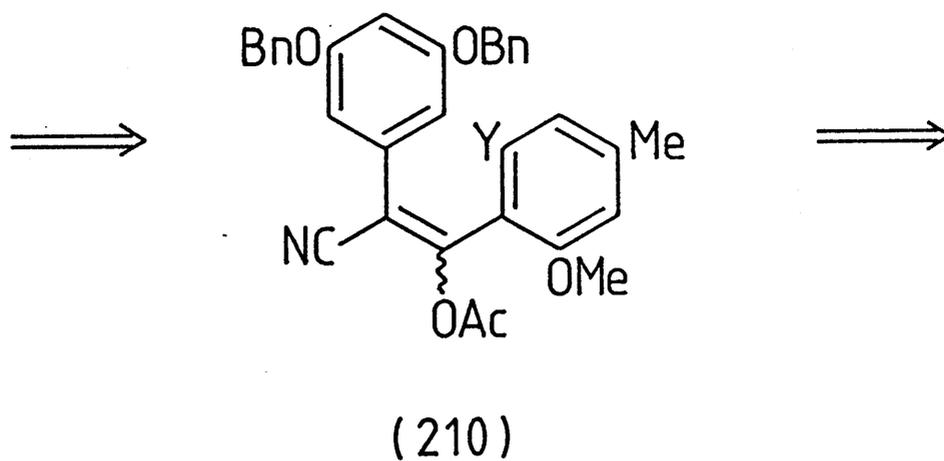
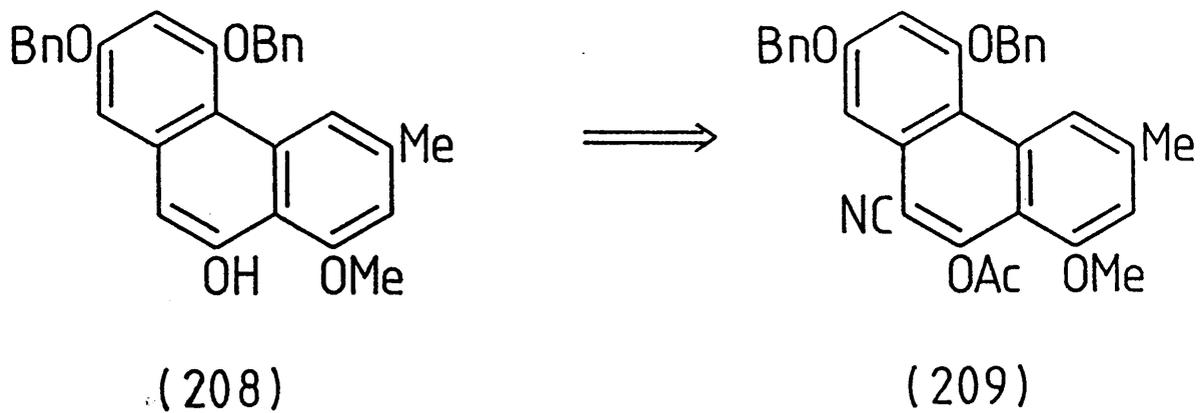
$^1\text{H}/^2\text{H}$ exchange in electron rich aromatic compounds can be achieved under acid or base catalysis and the choice of conditions is often determined by the stability of the substrate. Wähälä *et al.*¹⁰⁷ have shown that phenols undergo ortho and para exchange catalysed by deuterium bromide generated in situ from deuterium oxide and phosphorus tribromide. Yields are improved upon prior exchange of the acidic phenolic proton. Finnie⁵⁰ used this method to introduce deuterium labels into phenanthrene (73) after exchange of the proton of the 10-hydroxyl substituent by stirring a solution of (73) in deuteriochloroform/deuterium oxide at room temperature for 5 minutes. The level of deuterium incorporation after 60 hours was determined to be 77% by ^1H nmr integration. More prolonged reaction would perhaps increase the level of deuteriation.

The synthesis of the postulated biosynthetic precursor (14) in labelled form would be complete if a demethylating agent capable of cleaving the three methyl ethers of phenanthrene (73) could be found. The next section details demethylating agents which were examined in the course of the current investigation and also discusses attempts to synthesise phenanthrene (14) using benzyl protecting groups for the phenolic substituents in the starting materials.

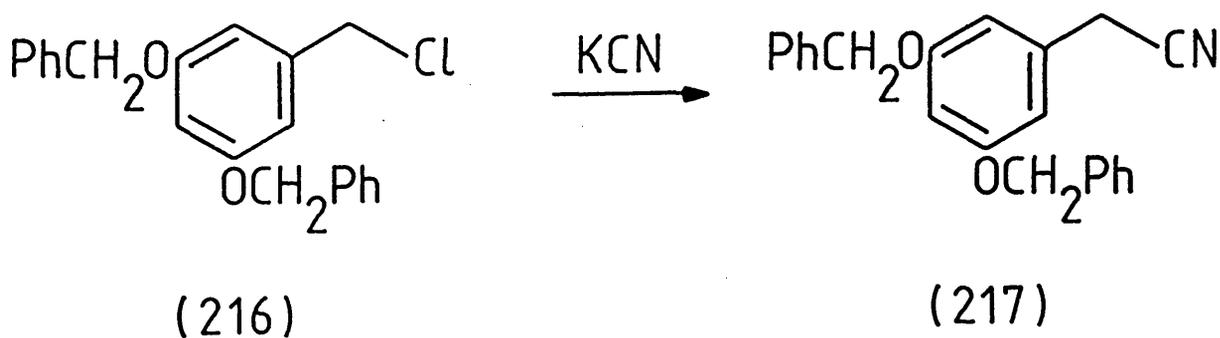
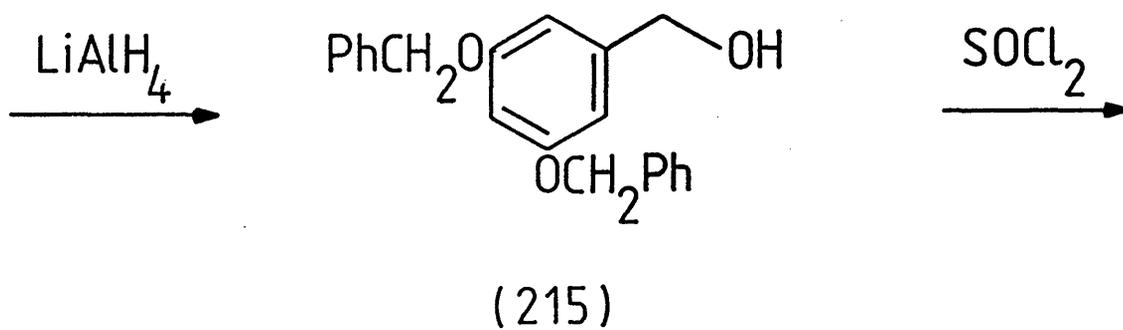
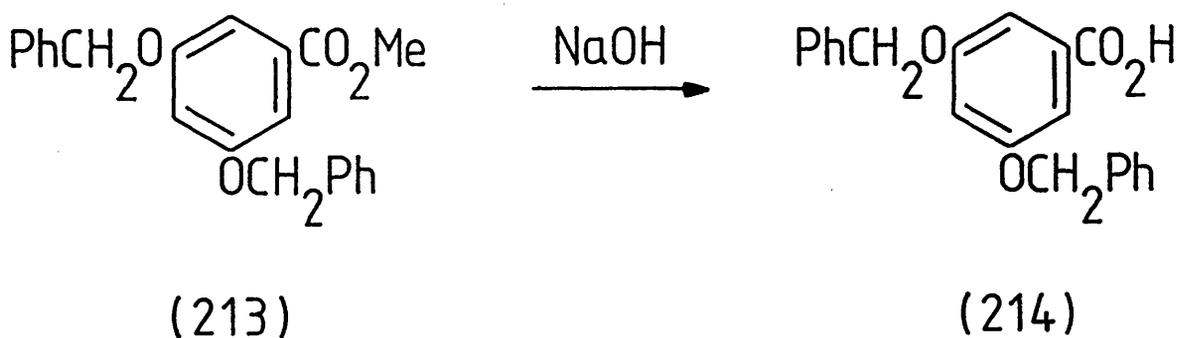
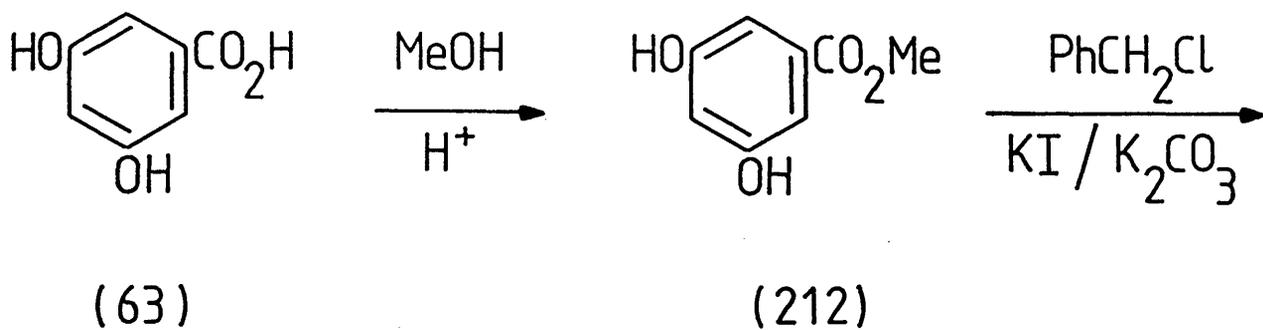
4.2 Results and Discussion

Two other reagents available for ether cleavage are dry lithium iodide/collidine¹⁰⁸ and aluminium trichloride/ethanethiol.¹⁰⁹ However, these reagents also proved ineffective in completely demethylating phenanthrene (73) to give the target phenanthrene (14).

It was reasoned that benzyl protecting groups might be more easily removed and so attention was turned to the synthesis and photocyclisation of benzyloxystilbenes. Since the methoxyls at C-5 and C-7 of phenanthrene (73) are resistant to BBr_3 , attempts were made to prepare the corresponding 5,7-dibenzyloxyphenanthrene (208). It was proposed to synthesise this compound in a similar manner to phenanthrene (73) (see Scheme 17) involving photocyclisation of stilbene (210) as the key step [Scheme 66]. Hence 3,5-dibenzyloxybenzyl cyanide (217) was prepared via the route of Hill¹¹⁰ [Scheme 67]. However, the synthesis of phenanthrene (208) failed owing to the difficulty experienced in preparing the β -keto nitrile precursor (211) of stilbene (210) by acylation of nitrile (217). The first attempt at preparing the β -keto nitrile (211) involved successive treatment of the nitrile (217) with n-butyl lithium and the benzoate ester (68). This resulted in the formation of multiple products which proved difficult to separate. Reaction of the methylene protons of the benzyloxy groups with n-butyl lithium might have been responsible for causing a mixture of products to be formed. It was thought that this might be avoided by using a more hindered base like lithium diisopropylamide (LDA) or a weaker base like sodium methoxide to effect the condensation. However, a



Bn = PhCH₂, Y = OMe



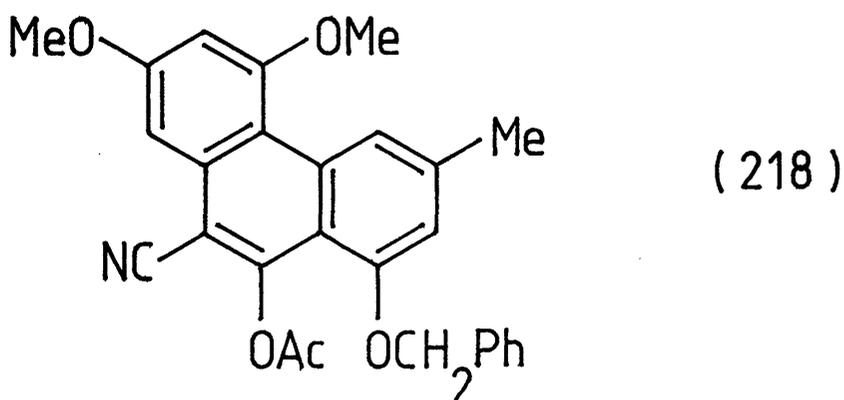
Scheme 67

complex product mixture was obtained when LDA was used and when the reaction was repeated using sodium methoxide only nitrile and ester starting materials were recovered unchanged.

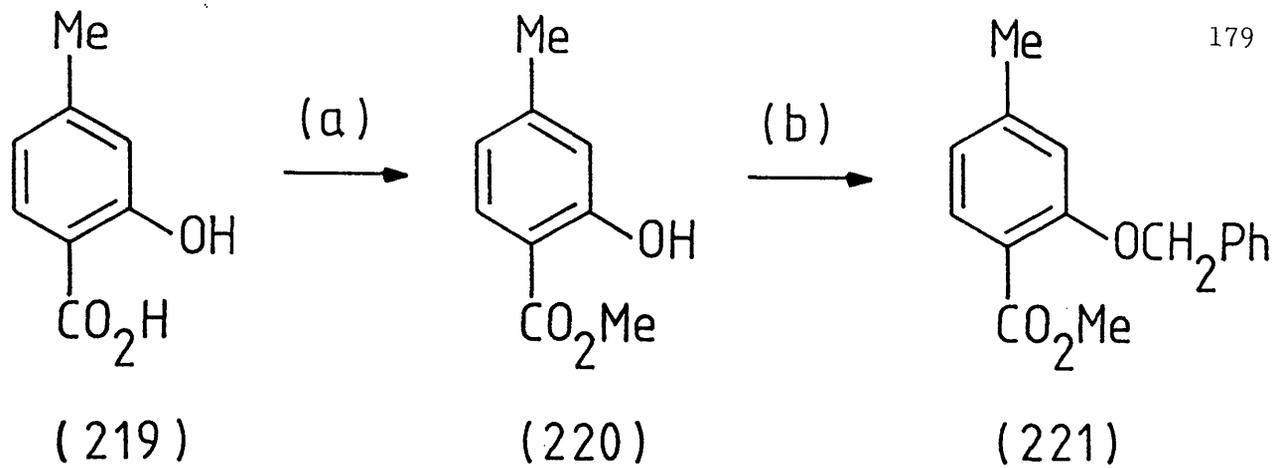
A simple nmr experiment demonstrated that sodium methoxide is a strong enough base to abstract the protons adjacent to the cyano group (CH_2CN) in the nitrile (217) while leaving the benzyloxy methylene protons (PhCH_2O) largely unchanged. The 90 MHz ^1H nmr spectrum of (217) was recorded in a mixture of d_1 -chloroform and d_4 -methanol. The spectrum displayed a 4H singlet at δ 4.92 ppm due to the two PhCH_2O groups and a 2H singlet at δ 3.60 ppm due to CH_2CN . A small piece of clean sodium was added to the nmr tube and the spectrum was re-recorded after 10 minutes. The peak at δ 3.60 ppm corresponding to CH_2CN was completely absent, suggesting that sodium methoxide generated in situ formed the dianion which was subsequently deuteriated by the solvent. The peak corresponding to PhCH_2O was essentially unchanged, even after adding more sodium and leaving for 20 minutes. The evidence from this experiment led to the initial thought that the failure of the reaction to produce the desired β -keto nitrile (211) in the presence of sodium methoxide might be due to steric hinderance on approach of the nitrile dianion and the benzoate ester (68). However, this is unlikely since sodium methoxide also failed to effect acylation of 3,5-dimethoxybenzyl cyanide (67) with methyl 2-methoxy-4-methylbenzoate (80). Thus it is not clear why sodium methoxide is an ineffective base in these reactions.

Owing to the failure of the route to the 5,7-dibenzyloxy phenanthrene (208) outlined in Scheme 66, a synthesis of the 2-benzyloxy-stilbene (223) was devised with the intention to photocyclise it to the

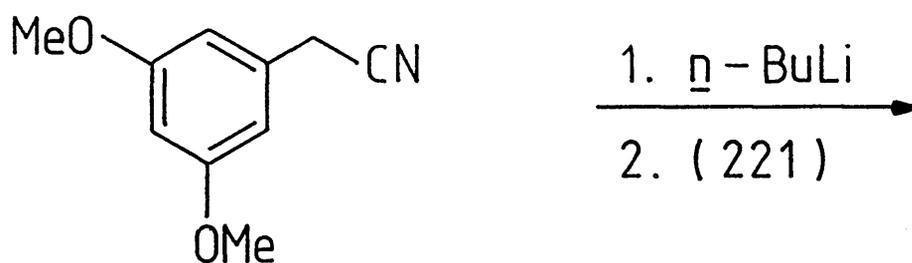
1-benzyloxyphenanthrene (218). TMSI would probably cleave the methoxyls at C-5 and C-7 in phenanthrene (218) since this reagent cleaves these methoxyls in the corresponding trimethoxyphenanthrene (73). The 1-benzyloxy substituent would probably also be cleaved upon treatment of phenanthrene (218) with TMSI.



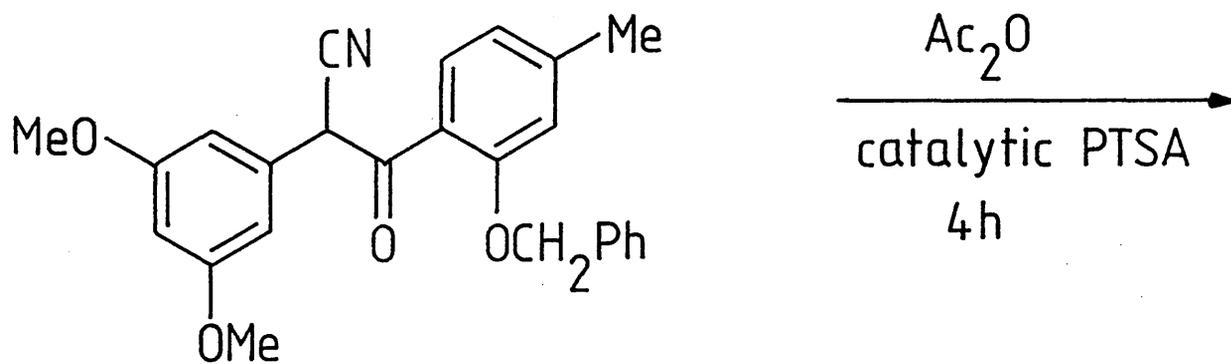
As shown in Scheme 68, the synthesis of the 2-benzyloxy-stilbene (223) involved acylation of 3,5-dimethoxybenzyl cyanide (67) with methyl 2-benzyloxy-4-methylbenzoate (221) using *n*-butyl lithium as the base. The crude product from this reaction was purified by column chromatography to afford a 58% yield of the β -keto nitrile (222) as a yellow gum. Reaction of (222) with acetic anhydride/catalytic *p*-toluenesulphonic acid for 4 hours afforded a stereoisomeric mixture of enol acetates (223) in 43% yield. This sample was obtained by preparative tlc after column chromatography of the crude reaction



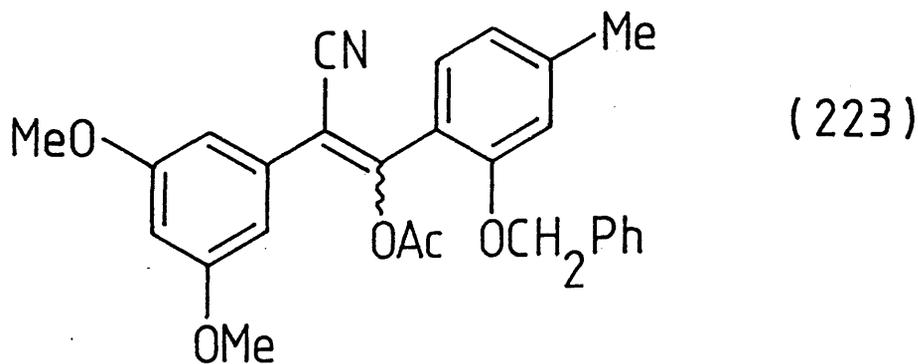
(a) MeOH / H⁺, (b) PhCH₂Cl / KI / K₂CO₃



(67)



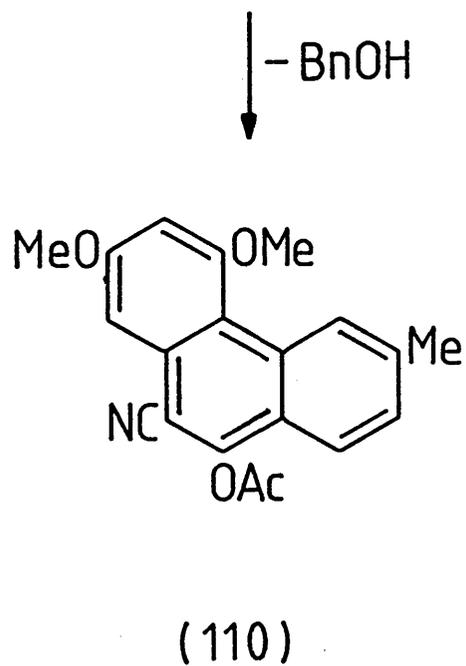
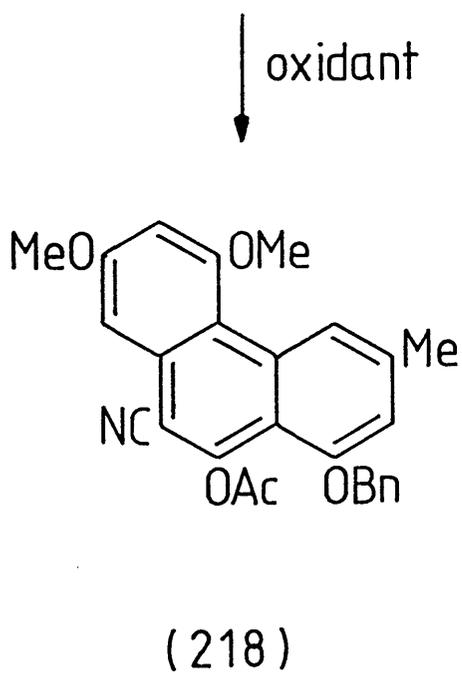
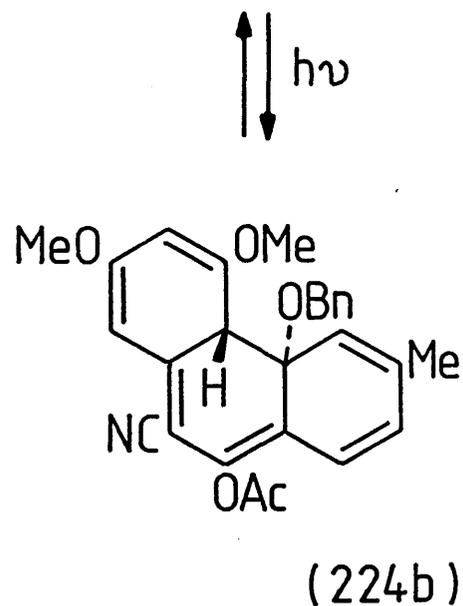
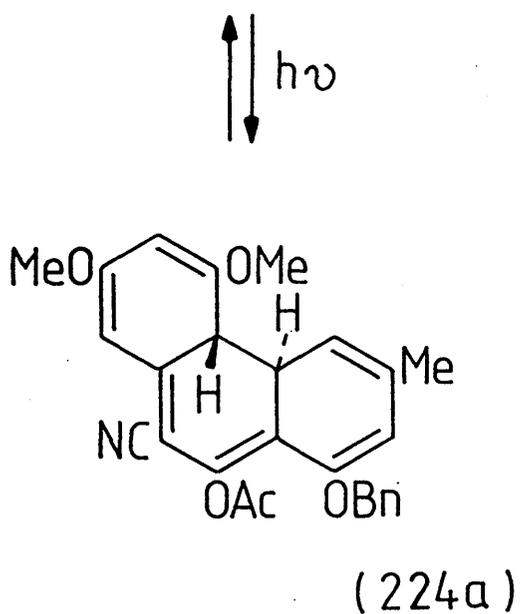
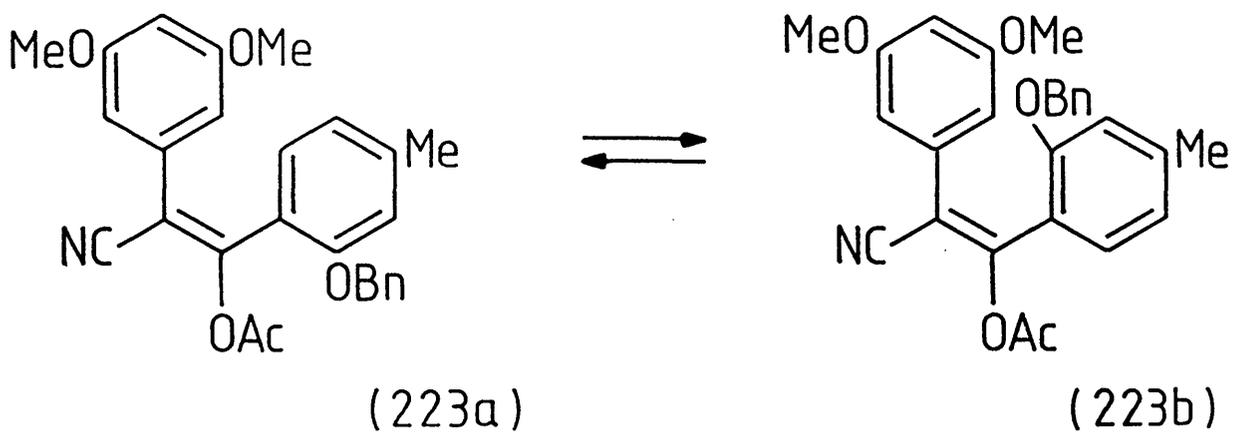
(222)



(223)

mixture. The ratio of stereoisomers was determined to be minor : major = 1.0 : 1.3 = isomer a : isomer b from the 200 MHz ^1H nmr integration of the PhCH_2O resonances at δ 5.08 and 4.82 ppm respectively. When a benzene solution of this mixture of stereoisomers and a trace of iodine was irradiated with visible light and heated at gentle reflux for 72 hours, the ratio changed to isomer a : isomer b = 1.4 : 1.0. These conditions equilibrate $\underline{\text{E}}$ - and $\underline{\text{Z}}$ - forms to give a mixture which is rich in the more thermodynamically stable isomer²⁵ (see Section 2.7). The uv spectrum of the 1.0 : 1.3 mixture of stereoisomers has the characteristic shape of a severely crowded stilbene and this implies that the $\underline{\text{E}}$ -isomer of (223) is more thermodynamically stable than the $\underline{\text{Z}}$ -isomer (see Sections 2.7 and 3.2). It follows that the $\underline{\text{E}}$ -isomer (isomer a) was the minor isomer in the stereoisomeric mixture isolated from the acetylation reaction. On the basis of this assignment, the ^1H nmr signal due to H-6' of the $\underline{\text{E}}$ -isomer occurs downfield from that of the $\underline{\text{Z}}$ -isomer and the acetoxy signal of the $\underline{\text{E}}$ -isomer occurs upfield from that of the $\underline{\text{Z}}$ -isomer. These relationships also exist in the other $\underline{\text{E}}/\underline{\text{Z}}$ pairs of α' -acetoxy- α -cyanostilbenes prepared during the course of this work (see Section 2.6.2). The observed 1.0 : 1.3 ratio of $\underline{\text{E}}$: $\underline{\text{Z}}$ isomers of the 2-benzyloxystilbene (223) is inconsistent with the greater thermodynamic stability of the $\underline{\text{E}}$ -isomer and may reflect losses of the $\underline{\text{E}}$ -isomer during the chromatographic purification steps.

It was anticipated that uv irradiation of stilbene (223) in the presence of an oxidant (e.g. iodine) would lead to the 1-benzyloxyphenanthrene (218) in good yield [Scheme 69]. It was thought that



Bn = PhCH₂

Scheme 69

two factors would probably contribute to the strong preference for the formation of the 1-substituted phenanthrene (218) over the unsubstituted phenanthrene (110) under oxidising conditions:

- (i) stilbene conformer (223a) would predominate over the more crowded conformer (223b) such that relatively little of the dihydrophenanthrene (224b) would be generated photochemically;
- (ii) the more crowded dihydrophenanthrene (224b) would undergo an especially rapid ring opening reaction to regenerate stilbene (223b) and thus be more likely to escape eliminative trapping.

Irradiation of the 2-benzyloxystilbene (223) in air saturated cyclohexane containing iodine for 9 hours afforded a 23% yield of phenanthrene (110) and none of the expected phenanthrene (218). This result illustrates the unpredictable nature of stilbene photocyclisations and is currently unexplained.

The best strategy for future workers engaged in studying the biosynthesis of the fungal metabolite mollisin (1) would probably be to undertake a thorough investigation of demethylation of 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73). Preferably this should involve a single demethylating agent but the lower yields associated with more than one agent should be tolerated for the sake of generating a labelled substrate for feeding to the fungal medium.

General Experimental Procedures

Melting points (m.p.) were determined on a Kofler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 983 spectrophotometer. The following abbreviations are used: s - strong, m - medium, w - weak and br - broad. Ultra-violet spectra were recorded on a Pye Unicam SP8-100 or Perkin-Elmer 550 SE spectrophotometer. The units of ϵ are $1,000 \text{ cm}^2/\text{mol}$ and sh specifies a shoulder in the uv spectrum. Routine ^1H nmr spectra were determined on a Perkin-Elmer R32 (90 MHz) spectrometer using tetramethylsilane as internal standard. ^1H nmr spectra were also recorded at 200 MHz on a Bruker WP 200 SY instrument, employing a deuterium lock system, setting chloroform (CHCl_3) in CDCl_3 at $\delta 7.25$ ppm as internal standard. Proton noise-decoupled ^{13}C nmr spectra were recorded at 55 MHz on the Bruker WP 200 SY spectrometer, in CDCl_3 , setting the reference CDCl_3 signal at $\delta 77.0$ ppm. A Bruker WH-360 instrument was used to record the 360 MHz ^1H nmr spectrum given in Table 9, setting CHCl_3 at $\delta 7.25$ ppm as internal standard. This instrument was also used to record the ^{13}C (90.5 MHz) and ^2H (55 MHz) nmr spectra of mollisin acetate. Routine mass spectra were determined using a VG/Kratos MS 12 spectrometer. High resolution spectra were recorded on a VG/Kratos MS 902S spectrometer.

Organic solutions were dried over anhydrous magnesium sulphate and evaporated on a rotary evaporator under reduced pressure.

Column chromatography was performed using Fluka Kieselgel HF₂₅₄. Preparative thin layer chromatography (tlc) was performed using 20 x 20 cm glass plates coated with 1 mm of Fluka Kieselgel GF₂₅₄.

Photochemical experiments conducted in the absence of air involved deoxygenating the solution prior to irradiation and bubbling a slow flow of nitrogen gas through the solution during irradiation (unless otherwise stated). The initial deoxygenation step either involved purging the solution with nitrogen for 1-2h or refluxing the solution under nitrogen for $\frac{1}{2}$ - 1 $\frac{1}{2}$ h.

Solvents and reagents were dried and purified prior to use as follows: tetrahydrofuran was distilled from sodium/benzophenone and used immediately; ether was dried using sodium wire; benzene was distilled from calcium hydride and stored over sodium wire; methanol and tert-butanol were dried using magnesium activated with iodine and stored over 3A molecular sieves; butanone was dried over anhydrous magnesium sulphate, distilled and used immediately; pyridine, triethylamine, diisopropylamine and dicyclohexylamine were refluxed over sodium hydroxide pellets, distilled under nitrogen and stored over potassium hydroxide; thionyl chloride was distilled from iron and N-bromosuccinimide was recrystallised from water.

Crystal Structure Analysis of 3-(2,6-Dimethoxy-4-methylphenyl)-
2-(3,5-dimethoxyphenyl)-3-oxopropanenitrile (69)

Crystal Data

Colourless, cube-shaped crystals grown from acetone/heptane,

$C_{20}H_{21}NO_5$, $M = 355.4$, triclinic space group $P\bar{1}$, $a = 7.990(3)$,

$b = 8.206(1)$, $c = 14.473(2) \text{ \AA}$, $\alpha = 80.46(1)$, $\beta = 77.19(2)$,

$\gamma = 87.75^\circ$, $V = 912.5 \text{ \AA}^3$, $D_c = 1.23 \text{ g cm}^{-3}$, $Z = 2$, $F(000) = 360$,

$\mu(\text{Mo-K}\alpha) = 0.87 \text{ cm}^{-1}$, $T = 291\text{K}$.

Crystallographic Measurements

Cell dimensions were derived by least-squares treatment of the setting angles of 25 reflections ($\theta > 12^\circ$) measured on an Enraf-Nonius CAD4 diffractometer with $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$). 3565 independent observed reflections were collected in the range $\theta \leq 27^\circ$ and of these 1721 satisfied the criterion $I \geq 3.0\sigma(I)$.

Structure Analysis

The structure was solved using the direct phasing procedure MITHRIL.¹¹⁵ After preliminary least-squares adjustment of the co-ordinates of the C, N and O atoms, a subsequent difference Fourier synthesis enabled the locations of all the H atom co-ordinates to be determined. Refinement with anisotropic thermal parameters for the C, N and O atoms, with H atoms included but not refined, converged at $R = 0.048$, $R_w = 0.059$ with weights $w = 1/\sigma^2(F)$. Fourier, least-squares, geometry and ORTEP calculations were performed using the GX system of programs.¹¹⁶

Crystal Structure Analysis of 2-(2-Iodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanenitrile (138)

Crystal Data

Colourless, cube-shaped crystals grown from chloroform/hexane, $C_{19}H_{18}INO_4$, $M = 451.3$, monoclinic space group $P2_1/a$, $a = 9.220(2)$, $b = 18.969(5)$, $c = 10.602(6)$ Å, $\beta = 94.14(2)^\circ$, $V = 1849.4$ Å³, $D_c = 1.62$ g cm⁻³, $Z = 4$, $F(000) = 896$, $\mu(\text{Mo-K}\alpha) = 17.32$ cm⁻¹, $T = 291\text{K}$.

Crystallographic Measurements

As for compound (69) above except that 4023 reflections were collected and 3122 of these satisfied the criterion $I \gg 3.0\sigma(I)$.

Structure Analysis

As for compound (69) above except that least-squares adjustment and refinement of the C, N, O and I atoms were performed and $R = 0.029$, $R_w = 0.043$.

Culture of *Mollisia caesia*^{50,53}

M. caesia (CBS 220.56) was obtained from Centraalbureau voor Schimmelcultures, Baarn, The Netherlands. The organism was grown in culture tubes on slants of modified Blakeslee malt extract agar (plus sodium chloride) prepared from glucose (20g), Oxoid malt extract (20g), Bacto peptone (1g) and sodium chloride (0.5g) in de-ionised water (1L) containing 1.4% agar. The slant was inoculated by smearing the surface with a small piece of mycelium and allowed to grow at 21°C for 7-10 days.

Isolation⁵⁰ of Mollisin (1) and 2,7-Dimethylnaphthazarin (62)

The contents of the culture tubes were combined and continuously extracted with ethyl acetate overnight to afford a dark brown residue after evaporation of the solvent. This was passed through a short column of silica under suction using ethyl acetate as eluant to remove highly polar, resinous material. Further purification by preparative tlc on silica using 40:60 ether:hexane as eluant afforded mollisin (1) ($R_f = 0.5$) as orange needles (typical yield : 40 mg/ ℓ of medium) and 2,7-dimethylnaphthazarin (62) ($R_f = 0.6$) as a red oil which crystallised on standing (typical yield : 8 mg/ ℓ of medium). Mollisin (1) was recrystallised from methanol as yellow/orange flocculent needles, m.p. 203-204°C (lit.,⁵¹ 203-204°C). The naphthazarin (62) was recrystallised from 60-80° petroleum ether as needles, m.p. 130-132°C (lit.,⁵¹ 125-126°C).

Mollisin (1)^{50,51}

ν_{\max} . (KBr) 1720 s, 1650 s, and 1610 s cm^{-1} .

$\underline{m/z}$ 229 ($M^+ - \text{CHCl}_2$).

2,7-Dimethylnaphthazarin (62)^{50,51}

δ_{H} (90 MHz; CDCl_3): 2.25 (6H, s, ArCH_3) and 6.95 (2H, s, ArH).

ν_{\max} . (KBr) 1740 s, 1655 s, and 1610 s cm^{-1} .

$\underline{m/z}$ 218 (M^+).

Preparation of Mollisin Acetate (61)⁵³

To a mixture of mollisin (1) (104 mg) and acetic anhydride (1.0 ml) in a small test tube was added pyridine (0.8 ml). The test tube was shaken until solution occurred and then allowed to stand at room temperature for 5 min. During this period a precipitate of light yellow needles appeared. The mixture was poured into an excess of 2M hydrochloric acid and then extracted with chloroform. The organic extract was washed with brine, sodium bicarbonate solution, more brine, then dried. Evaporation of the solvent left a yellow solid which was recrystallised from methanol to give mollisin acetate (61) as bright yellow needles (116 mg, 98%), m.p. 210-212°C (lit.,⁵³ 211-213°C).

δ_{H} (200 MHz; CDCl_3): 2.13 (3H, d, J 1.5 Hz, 12- CH_3), 2.44 (3H, s, CH_3CO), 2.48 (3H, s, 11- CH_3), 6.38 (1H, s, H-14), 6.74 (1H, q, J 1.5 Hz, H-3), and 7.32 (1H, s, H-6).

δ_{C} (90.5 MHz; CDCl_3): 15.78 (C-12), 20.23 (C-11), 20.89 (C-16), 70.61 (C-14), 121.44 (C-10), 131.82 (C-6), 132.17 (C-9), 135.22 (C-8), 137.39 (C-3), 144.50 (C-7), 146.01 (C-2), 150.28 (C-5), 168.85 (C-15), 182.31 (C-4), 186.08 (C-1), and 191.74 (C-13).

ν_{max} . (KBr) 1770 s, 1710 s, 1650 s, and 1580 s cm^{-1} .

m/z 271 (M^+ - CHCl_2).

Feeding of Sodium [2-²H₃, 1-¹³C]acetate to *Mollisia caesia*

Sodium [2-²H₃, 1-¹³C]acetate (150 mg) was dissolved in the minimum amount of de-ionised water, mixed with modified Blakeslee malt extract agar (200 ml) and applied in equal portions as a thin surface layer to malt agar (150 ml) in 13 beakers. A smooth water suspension of the

above M. caesia culture was flooded over the agar surface in the beakers and the excess water drained off. Two control beakers lacking labelled acetate were set-up identically. The 15 beakers were incubated at 25°C for 21 days. The combined contents of the 13 fed beakers were continuously extracted with ethyl acetate overnight to afford a dark brown residue (0.84g) after evaporation of the solvent. Mollisin (1) was eluted in the first fraction upon silica gel column chromatography of this residue using chloroform. After recrystallisation the yield of mollisin (1) was 78 mg. The yield of recrystallised mollisin (1) from the two control beakers, obtained as above, was 10 mg. Each sample was acetylated to give mollisin acetate (61) and analysed by ^{13}C nmr spectroscopy. The sample of (61) from the labelled acetate feeding experiment was also examined by ^2H nmr (see Section 1.3).

Methyl 3,5-dimethoxybenzoate (64)⁶²

3,5-Dihydroxybenzoic acid (63) (30.0g) dissolved in Analar acetone (300 ml) with anhydrous potassium carbonate (130g) and dimethyl sulphate (60 ml) was heated at reflux for 7h with stirring. After cooling, the solution was filtered and the residue washed with acetone. The combined acetone solutions were evaporated and the golden brown residue dissolved in ether, washed with ammonia liquor, 10% sodium hydroxide solution, and water, then dried and evaporated. The residue solidified on cooling and was recrystallised from methanol as white needles (30.6g, 78%), m.p. 41-42°C (lit.,⁶² 42°C).

δ_{H} (90 MHz; CDCl_3): 3.82 (6H, s, CH_3O), 3.92 (3H, s, CO_2CH_3), 6.65 (1H, t, $\underline{\text{J}}$ 3Hz, H-4), and 7.19 (2H, d, $\underline{\text{J}}$ 3 Hz, H-2 and H-6).

ν_{max} . (KBr) 1720 s and 1600 s cm^{-1} .

3,5-Dimethoxybenzyl alcohol (65)⁶²

Methyl 3,5-dimethoxybenzoate (64) (25.0g) in dry tetrahydrofuran (200 ml) was added slowly to lithium aluminium hydride (6.0g) in THF (100 ml) and the mixture was stirred at reflux for 8h. After cooling, water (6.0 ml) was added cautiously, followed by 15% sodium hydroxide solution (6.0 ml) and more water (18.0 ml) with stirring. The granular aluminium hydroxide was filtered and washed with ether. The organic solutions were evaporated to dryness to give a white solid which was recrystallised from diisopropyl ether as needles (19.3g, 90%), m.p. 46-47°C (lit.,⁶² 47°C).

δ_{H} (90 MHz; CDCl_3): 2.06 (1H, br s, OH), 3.81 (6H, s, CH_3O), 4.64 (2H, s, CH_2), 6.41 (1H, t, $\underline{\text{J}}$ 2 Hz, H-4), and 6.54 (2H, d, $\underline{\text{J}}$ 2 Hz, H-2 and H-6).

ν_{max} . (KBr) 3400 br m and 1600 s cm^{-1} .

3,5-Dimethoxybenzyl chloride (66)⁶²

Thionyl chloride (10 ml) and pyridine (1 ml) in dry ether (150 ml) were added over 1h to 3,5-dimethoxybenzyl alcohol (65) (15.0g) in ether (100 ml) with stirring. More thionyl chloride (5 ml) was added in one portion and the reaction mixture gently heated until complete dissolution occurred. After a further 2h at room temperature the excess thionyl chloride was destroyed with water, and the ether layer washed with water, 10% sodium hydroxide solution and more water. The ether solution was dried and evaporated to afford a fawn coloured solid which was recrystallised from ether as fine white needles (11.6g, 70%), m.p. 47-48°C (lit.,⁶² 46°C).

δ_{H} (90 MHz; CDCl_3): 3.80 (6H, s, CH_3O), 4.51 (2H, s, CH_2), 6.41 (1H, t, J 2 Hz, H-4), and 6.53 (2H, d, J 2 Hz, H-2 and H-6).

ν_{max} . (KBr) 1600 s cm^{-1} .

3,5-Dimethoxybenzyl cyanide (67)⁶²

Potassium cyanide (13.5g) and 3,5-dimethoxybenzyl chloride (66) (12.5g) in ethanol (200 ml) and water (60 ml) were stirred at reflux for 4h then poured onto ice. The cream precipitate was allowed to stand for 2h then filtered, washed thoroughly with cold water and dried over phosphorus pentoxide in a vacuum desiccator. Recrystallisation from methanol yielded fine white needles (7.4g, 62%), m.p. 54°C (lit.,⁶² 53°C).

δ_{H} (90 MHz; CDCl_3): 3.66 (2H, s, CH_2), 3.78 (6H, s, CH_3O), and 6.44 (3H, m, ArH).

ν_{max} . (KBr) 2240 w and 1610 s cm^{-1} .

Methyl 2,6-dimethoxy-4-methylbenzoate (68)

Methyl 2,6-dihydroxy-4-methylbenzoate (50.0g) in Analar acetone (600 ml) containing dimethyl sulphate (60 ml) and anhydrous potassium carbonate (115g) was stirred at reflux for 9h. The reaction mixture was worked-up as outlined for the preparation of the ester (64). The crude product was recrystallised from methanol to yield the ester (68) as colourless plates (52.3g, 91%), m.p. 86°C (lit.,¹⁰² 86°C).

δ_{H} (90 MHz; CDCl_3): 2.32 (3H, s, ArCH_3), 3.79 (6H, s, CH_3O), 3.88 (3H, s, CO_2CH_3), and 6.36 (2H, s, ArH).

ν_{max} . (KBr) 1735 s, 1610 s, and 1585 s cm^{-1} .

$\underline{m/z}$ 210 (M^+).

3-(2,6-Dimethoxy-4-methylphenyl)-2-(3,5-dimethoxyphenyl)-3-oxopropanenitrile (69)⁶¹

3,5-Dimethoxybenzyl cyanide (67) (2.00g) in dry tetrahydrofuran (40 ml) was added over 15 min to n-butyl lithium (9.31 ml, 2.61M in hexane) in THF (20 ml) with stirring at 0°C and under nitrogen. The solution was stirred at 0°C for a further hour and then methyl 2,6-dimethoxy-4-methylbenzoate (68) (3.08g) in THF (40 ml) was introduced over 30 min. The reaction mixture was stirred and heated at reflux for 3½h. The cooled solution was added dropwise over 20 min to saturated aqueous ammonium chloride with rapid stirring. The THF was removed under reduced pressure and the resulting aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with brine and then dried. Evaporation of the solvent left a brown gum which produced compound (69) as white plates upon crystallisation from acetone/heptane and after washing with ether (2.41g, 60%), m.p. 165-167°C (lit.,⁶¹ 164-165°C).

δ_{H} (200 MHz; CDCl_3): 2.36 (3H, s, ArCH_3), 3.77 (6H, s, CH_3O), 3.83 (6H, s, CH_3O), 6.38 (1H, t, \underline{J} 2.3 Hz, H-4), 6.41 (2H, s, H-3' and H-5'), 6.47 (1H, s, CHCN or OH), and 7.00 (2H, d, \underline{J} 2.3 Hz, H-2 and H-6).

ν_{max} . (KBr) 3250 br m, 2210 m, 1635 s, 1610 s, and 1585 s cm^{-1} .

ν_{max} . (CHCl_3) 3550 br w, 2250 w, 2210 w, 1715 m, and 1610 s cm^{-1} .

λ_{max} . (MeOH) 246 sh (ϵ 7,900) and 286 nm (21,500).

m/z 355 (M^+) and 179 ($C_{10}H_{11}O_3$).

3-Acetoxy-3-(2,6-dimethoxy-4-methylphenyl)-2-(3,5-dimethoxy-phenyl)prop-2-enenitrile (70)⁶¹

A solution of the β -keto nitrile (69) (1.50g) in acetic anhydride (20 ml) containing a few crystals of *p*-toluenesulphonic acid was refluxed for 2h. The cooled solution was poured onto crushed ice, stirred for 20 min and then extracted with ethyl acetate. The combined organic extracts were washed with brine, saturated aqueous sodium bicarbonate, more brine, then dried and evaporated to give a brown gum. A light brown gum consisting of the E- and Z-isomers of the stilbene (70) was obtained by column chromatography over silica using ether as eluant (1.40g, 83%, E : Z = 1.0 : 1.1 from the ^1H nmr integration of the acetoxy resonances).

δ_{H} (200 MHz; CDCl_3): E-isomer, 2.07 (3H, s, CH_3CO), 2.29 (3H, d, J 0.5 Hz, ArCH_3), 3.79 (6H, s, CH_3O), 3.84 (6H, s, CH_3O), 6.40 (2H, d, J 0.5 Hz, H-3' and H-5'), 6.45 (1H, t, J 2.3 Hz, H-4), and 6.77 (2H, d, J 2.3 Hz, H-2 and H-6); Z-isomer, 2.22 (3H, s, CH_3CO), 2.35 (3H, d, J 0.5 Hz, ArCH_3), 3.57 (6H, s, CH_3O), 3.58 (6H, s, CH_3O), 6.26 (2H, d, J 0.5 Hz, H-3' and H-5'), 6.29 (1H, t, J 2.3 Hz, H-4), and 6.34 (2H, d, J 2.3 Hz, H-2 and H-6).

ν_{max} . (CHCl_3) 2940 m, 2210 w, 1750 s, and 1610 s cm^{-1} .

λ_{max} . (MeOH) 207 (ϵ 44,100) and 299 nm (10,400).

m/z 397 (M^+).

10-Acetoxy-9-cyano-1,5,7-trimethoxy-3-methylphenanthrene (71)⁶¹

Redistilled benzene (800 ml) was deoxygenated by refluxing for 1h while a stream of nitrogen was bubbled through the solution. The stilbene (70) (1.40g) was dissolved in deoxygenated benzene, added to the cooled solution in the photolysis flask, then stirred and irradiated under nitrogen for 20h. The solvent was evaporated and the residue crystallised from methanol. The crystals were collected and the mother liquors evaporated. This residue was dissolved in benzene and re-irradiated. This cycle was repeated twice to furnish the phenanthrene (71) as the sole product. Recrystallisation from chloroform/hexane gave plates (1.06g, 76%), m.p. 244-245°C (lit.,⁶¹ 244-245°C). δ_{H} (200 MHz; CDCl_3): 2.47 (3H, s, CH_3CO), 2.56 (3H, s, ArCH_3), 3.95 (3H, s, CH_3O), 3.98 (3H, s, CH_3O), 4.06 (3H, s, CH_3O), 6.76 (1H, d, J 2.4 Hz, ArH), 6.83 (1H, d, J 1.2 Hz, H-2), 7.18 (1H, d, J 2.4 Hz, ArH), and 9.05 (1H, m, H-4). ν_{max} . (CHCl_3) 3020 m, 2220 w, 1760 m, 1610 s, and 1575 m cm^{-1} . λ_{max} . (MeOH) 296 (ϵ 54,500) and 338 nm (34,000). m/z 365 (M^+).

9-Cyano-10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (72)⁶¹

A solution of the phenanthrene (71) (0.61g) in methanol (50 ml) and water (5 ml) containing sodium hydroxide (3g) was heated at reflux for 2h. After cooling, the mixture was poured into iced water (100 ml) and acidified with concentrated hydrochloric acid. The precipitate was collected, washed with water and dried in vacuo over phosphorus pentoxide. Recrystallisation from methanol gave the

phenanthrene (72) as needles (0.52g, 96%), m.p. 192-193°C (lit.,⁶¹ 192-193°C).

δ_{H} (200 MHz; CDCl_3): 2.53 (3H, s, ArCH_3), 3.95 (3H, s, CH_3O), 4.02 (3H, s, CH_3O), 4.08 (3H, s, CH_3O), 6.57 (1H, d, \underline{J} 2.5 Hz, ArH), 6.80 (1H, d, \underline{J} 1.3 Hz, H-2), 7.06 (1H, d, \underline{J} 2.5 Hz, ArH), 8.98 (1H, m, H-4), and 10.73 (1H, s, OH).

ν_{max} . (KBr) 3300 br m, 2210 m, 1610 s, and 1580 s cm^{-1} .

λ_{max} . (MeOH) 299 (ϵ 96,900), 337 (72,800), 354 (61,500), and 373 nm (55,200).

$\underline{m/z}$ 323 (M^+).

10-Hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73)⁶¹

Raney nickel alloy⁹⁵ (4.50g) was added as a water slurry to a suspension of the phenanthrene (72) (0.46g) in 75% formic acid solution (50 ml) and the mixture was stirred under nitrogen and heated at reflux for 12h. A further portion of Raney nickel (4.50g) was added and heating continued for a further 12h. After cooling, the mixture was filtered and the nickel washed with ethyl acetate (150 ml). The combined solutions were washed with water (50 ml), saturated aqueous sodium bicarbonate (4 x 60 ml) and water (50 ml). The organic solution was dried and evaporated to give a dark brown gum. Polar material was removed by passing through a short column of silica using chloroform as eluant. Further purification by preparative tlc on silica using chloroform as eluant gave the phenanthrene (73) as plates after recrystallisation from methylene chloride/hexane (0.13g, 31%), m.p. 177°C (lit.,⁶¹ 177-177.5°C).

δ_{H} (90 MHz; CDCl_3): 2.44 (3H, s, ArCH_3), 3.81 (3H, s, CH_3O), 3.93 (3H, s, CH_3O), 3.95 (3H, s, CH_3O), 6.46 (1H, d, J 2 Hz, ArH), 6.62 (1H, d, J 2 Hz, ArH), 6.70 (1H, s, ArH), 6.85 (1H, s, ArH), 9.00 (1H, s, H-4), and 9.58 (1H, s, OH).

ν_{max} . (KBr) 3310 br m and 1610 s cm^{-1} .

m/z 298 (M^+).

Methyl 2-methoxy-4-methylbenzoate (80)¹¹¹

4-Methylsalicylic acid (30.0g) in Analar acetone (300 ml) containing dimethyl sulphate (42 ml) and anhydrous potassium carbonate (120g) was heated at reflux with stirring for 8h. The reaction mixture was worked-up as outlined for the preparation of the ester (64). The golden brown oil thus obtained was purified by vacuum distillation to give the ester (80) as a colourless liquid (30.6g, 86%), b.p. 160°C/0.01 mm Hg.

δ_{H} (90 MHz; CDCl_3): 2.35 (3H, s, ArCH_3), 3.86 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 6.78 (2H, m, H-3 and H-5), and 7.71 (1H, d, J 8 Hz, H-6).

ν_{max} . (CHCl_3) 3020 m, 1715 s, and 1610 s cm^{-1} .

2-(3,5-Dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanenitrile (81)⁶¹

3,5-Dimethoxybenzyl cyanide (67) (2.00g) in dry tetrahydrofuran (40 ml) was added over 15 min to *n*-butyl lithium (9.31 ml, 2.61M in hexane) in THF (20 ml) with stirring at 0°C and under nitrogen. The solution was stirred at 0°C for a further hour and then methyl

2-methoxy-4-methylbenzoate (80) (2.64g) in THF (40 ml) was introduced over 30 min. The reaction mixture was stirred and heated at reflux for 3½h. The cooled solution was added dropwise over 20 min to saturated aqueous ammonium chloride with rapid stirring. The THF was removed in vacuo and the resulting aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with brine and then dried. Evaporation of the solvent left a light brown solid which produced white plates upon recrystallisation from acetone/hexane (2.13g, 58%), m.p. 144-145°C (lit.,⁶¹ 144-145°C).

δ_{H} (90 MHz; CDCl_3): 2.37 (3H, s, ArCH_3), 3.76 (6H, s, CH_3O), 3.96 (3H, s, CH_3O), 5.85 (1H, s, CHCN), 6.41 (1H, t, J 2 Hz, H-4), 6.50 (2H, d, J 2 Hz, H-2 and H-6), 6.82 (2H, m, H-3' and H-5'), and 7.60 (1H, d, J 8 Hz, H-6').

ν_{max} . (KBr) 2240 w, 1680 s, and 1610 s cm^{-1} .

m/z 325 (M^+).

2-(2-Bromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanenitrile (82)

Recrystallised N-bromosuccinimide (1.10g) was added in small portions over 1½h to a refluxing solution of the β -keto nitrile (81) (2.01g) in carbon tetrachloride (75 ml) with stirring. After a further 1½h the hot solution was filtered and the filtrate washed with water. Drying and evaporation of the organic phase afforded a yellow gum which crystallised on adding ether. Recrystallisation from methylene chloride/hexane gave the desired bromo compound (82) (1.62g, 73%), m.p. 140-141°C.

δ_{H} (90 MHz; CDCl_3): 2.39 (3H, s, ArCH_3), 3.79 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 3.96 (3H, s, CH_3O), 6.33 (1H, s, CHCN), 6.48 (1H, d, J 3 Hz, ArH), 6.65 (1H, d, J 3 Hz, ArH), 6.83 (2H, m, H-3' and H-5'), and 7.71 (1H, d, J 8 Hz, H-6').

ν_{max} . (KBr) 2250 w, 1670 s, 1610 s, and 1580 s cm^{-1} .

m/z 405, 403 (M^+) and 324 ($\text{M}^+ - \text{Br}$).

Found: C, 56.40; H, 4.51; N, 3.37; Br, 19.79. $\text{C}_{19}\text{H}_{18}\text{BrNO}_4$ requires C, 56.45; H, 4.49; N, 3.46; Br, 19.76%.

3-Acetoxy-2-(2-bromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enenitrile (83)

A solution of the β -keto nitrile (82) (1.58g) in acetic anhydride (40 ml) containing a few crystals of *p*-toluenesulphonic acid was heated at reflux for 2h. The reaction mixture was worked-up as outlined for the preparation of the enol acetate (70) to give a brown gum.

Chromatography over silica using 30:70 ethyl acetate:hexane as eluant afforded a mixture of E- and Z-isomers of the stilbene (83) as a yellow gum (1.70g, 98%, E : Z = 1.0 : 1.3 from the ^1H nmr integration of the H-6' doublets). Most of the E-isomer could be separated by adding ether/hexane. White plates were obtained upon recrystallisation from acetone/hexane, m.p. 162-163°C.

E-isomer

δ_{H} (200 MHz; CDCl_3): 1.95 (3H, s, CH_3CO), 2.39 (3H, s, ArCH_3), 3.80 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 3.89 (3H, s, CH_3O), 6.50 (1H, d, J 2.7 Hz, ArH), 6.56 (1H, d, J 2.7 Hz, ArH), 6.79 (1H, s, H-3'), 6.85 (1H, dq, J 0.7 and 7.8 Hz, H-5'), and 7.53 (1H, d, J 7.8 Hz, H-6').

$\nu_{\max.}$ (CHCl₃) 3020 m, 2210 w, 1770 s, 1610 s, and 1585 s cm⁻¹.

$\lambda_{\max.}$ (EtOH) 204 (ϵ 45,800), 232 (15,300), 283 (10,800), and 303 nm (10,800).

m/z 447, 445 (M⁺) and 405, 403 (M⁺-ketene).

Found: C, 56.54; H, 4.50; N, 3.00; Br, 18.30. C₂₁H₂₀BrNO₅ requires C, 56.52; H, 4.52; N, 3.14; Br, 17.90%.

Z-isomer + 21% E-isomer (yellow gum)

δ_{H} (200 MHz; CDCl₃): Z-isomer, 2.25 (3H, s, ArCH₃), 2.28 (3H, s, CH₃CO), 3.56 (3H, s, CH₃O), 3.63 (3H, s, CH₃O), 3.82 (3H, s, CH₃O), 6.21 (1H, d, J 2.7 Hz, ArH), 6.36 (1H, d, J 2.7 Hz, ArH), 6.57 (2H, m, H-3' and H-5'), and 7.02 (1H, d, J 7.7 Hz, H-6').

$\nu_{\max.}$ (CHCl₃) 3020 m, 2220 w, 1770 s, 1610 s, and 1585 s cm⁻¹.

$\lambda_{\max.}$ (EtOH) 204 (ϵ 32,400), 232 (12,300), and 299 nm (8,100).

Found: M⁺, 447.0518 and 445.0545. C₂₁H₂₀BrNO₅ requires M⁺, 447.0505 and 445.0525.

Photochemistry of the 2-bromostilbene (83)

(a) $h\nu/N_2/t\text{-BuOK}/t\text{-BuOH}/C_6H_6$

A mixture of the 2-bromostilbene (83) (0.51g) and potassium tert-butoxide (0.54g) in dry benzene (250 ml) and tert-butanol (150 ml) was purged with nitrogen for 1½h. The solution was stirred and irradiated under nitrogen for 17½h, then concentrated to dryness under reduced pressure to give a brown residue. Chloroform was added, the resultant mixture filtered to remove the insoluble material and the filtrate evaporated to give a brown gum (0.37g). Polar material was removed by passing through a short column of silica using 40:60

chloroform:hexane as eluant. Evaporation of the combined fractions gave a light brown residue (0.33g). This was purified by preparative tlc on silica using two developments in chloroform to give two main products, namely the β -keto nitrile (82) (0.12g, 26%) and the dimer (91) (0.20g, 27%), m.p. 171-173°C (from chloroform/hexane).

Dimer (91)

δ_{H} (200 MHz; CDCl_3): 2.41 (6H, s, 2 x ArCH_3), 3.86 (6H, s, 2 x CH_3O), 3.97 (6H, s, 2 x CH_3O), 3.98 (6H, s, 2 x CH_3O), 6.47 (2H, d, \underline{J} 2.2 Hz, 2 x ArH), 6.70 (2H, d, \underline{J} 2.2 Hz, 2 x ArH), 6.83 (2H, s, 2 x ArH), 6.86 (2H, dq, \underline{J} 0.7 and 7.9 Hz, 2 x ArH), and 7.74 (2H, d, \underline{J} 7.9 Hz, 2 x ArH).

δ_{C} (55 MHz; CDCl_3): 21.93 (ArCH_3), 54.52 (CH_3O), 55.93 (CH_3O), 56.12 (CH_3O), 91.70 ($^{\dagger}\text{Cq}$), 92.52 ($\underline{\text{CH}}$), 98.57 ($\underline{\text{CH}}$), 112.06 ($\underline{\text{CH}}$), 114.24 (Cq), 114.52 (Cq), 121.48 ($\underline{\text{CH}}$), 129.37 ($\underline{\text{CH}}$), 129.72 (Cq), 137.63 (Cq), 143.30 (Cq), 145.54 (Cq), 157.14 (Cq), 157.93 (Cq), and 158.93 (Cq).

† a quaternary carbon atom

ν_{max} . (KBr) 2220 m, 1630 m, and 1610 s cm^{-1} .

$\underline{m/z}$ 323 ($\frac{1}{2} \text{M}^+$).

Found: C, 70.46; H, 5.42; N, 4.47. $\text{C}_{38}\text{H}_{34}\text{N}_2\text{O}_8$ requires C, 70.58; H, 5.30; N, 4.33%.

(b) $\text{hv/N}_2/\text{Et}_3\text{N/CH}_3\text{CN}$

A solution of the 2-bromostilbene (83) (0.63g) in acetonitrile (350 ml) was deoxygenated by refluxing for 1½h while nitrogen gas was bubbled through the solution. Redistilled triethylamine (1.3 ml) was added via syringe to the cooled solution and then the solution was

stirred and irradiated under nitrogen for 20h. The reaction mixture was evaporated to dryness by heating at 60°C in vacuo and the dark brown residue dissolved in chloroform and washed with 5% hydrochloric acid followed by brine. Drying and evaporation yielded a dark brown semi-solid mass (0.59g). The ^1H nmr spectrum of this suggested the presence of starting material, the β -keto nitrile (82) and a phenanthrene type compound. Addition of methanol caused crystallisation of a fawn coloured solid which was identified as the phenanthrene (72) (0.04g, 9%).

(c) $\frac{h\nu/\text{N}_2/\text{C}_6\text{H}_6}$

Dry benzene (140 ml) was deoxygenated by heating at reflux for $\frac{1}{2}$ h while nitrogen gas was bubbled through the solution. A solution of the 2-bromostilbene (83) (160 mg) in benzene (10 ml) was purged with nitrogen for $\frac{1}{2}$ h and then transferred via syringe to the cooled solution in the photolysis flask. The solution was irradiated under nitrogen for 16h. Evaporation of the solvent left a dark brown semi-solid mass which was shown by tlc and 90 MHz ^1H nmr to be a mixture of several compounds. The nmr spectrum suggested that four phenanthrenes were present in the ratio of 1 : 2.5 : 2 : 2 from the integration of the singlets at δ 9.24, 9.05, 8.90 and 8.68 ppm respectively. Preparative tlc of this residue on silica using methylene chloride as eluant gave three major bands. Extraction of the least polar band with chloroform gave the phenanthrene (110) after crystallisation from methanol. Recrystallisation from methylene chloride/hexane gave fine white needles (13 mg, 11%), m.p. 200-202°C. Extraction of the most polar band with chloroform gave the phenanthrene (112) after crystall-

isation from methanol. Recrystallisation from methylene chloride/hexane gave yellow needles (28 mg, 18%), m.p. 258-260°C. The remaining band was further purified by preparative tlc on silica using 20:80 ethyl acetate:benzene as eluant. This yielded the phenanthrene (71) which was recrystallised from methylene chloride/hexane to give white needles (27 mg, 21%), m.p. 244-245°C (lit.,⁶¹ 244-245°C). It also yielded the phenanthrene (111) which was recrystallised from methylene chloride/hexane to give yellow needles (35 mg, 24%), m.p. 197-198°C.

10-Acetoxy-9-cyano-1,5,7-trimethoxy-3-methylphenanthrene (71)⁶¹

The 200 MHz ¹H nmr, ir, uv and ms data for this compound are given on p.194.

9-Acetoxy-10-cyano-2,4-dimethoxy-6-methylphenanthrene (110)

δ_{H} (200 MHz; CDCl₃): 2.58 (3H, s, CH₃CO), 2.60 (3H, s, ArCH₃), 3.99 (3H, s, CH₃O), 4.10 (3H, s, CH₃O), 6.81 (1H, d, \underline{J} 2.4 Hz, ArH), 7.24 (1H, d, \underline{J} 2.4 Hz, ArH), 7.42 (1H, dd, \underline{J} 1.2 and 8.4 Hz, H-7), 7.82 (1H, d, \underline{J} 8.4 Hz, H-8), and 9.39 (1H, m, H-5).

ν_{max} . (CHCl₃) 3030 m, 2220 m, 1775 s, and 1610 s cm⁻¹.

λ_{max} . (MeOH) 206 (ϵ 23,700), 244 (32,700), 266 (33,700), 290 (31,400), 316 (9,000), and 330 nm (8,400).

m/z 335 (M⁺) and 293 (M⁺-ketene).

Found: C, 71.88; H, 5.11; N, 3.95. C₂₀H₁₇NO₄ requires C, 71.63; H, 5.11; N, 4.18%.

9-Acetoxy-1-bromo-10-cyano-2,4-dimethoxy-6-methylphenanthrene (111)

δ_{H} (200 MHz; CDCl₃): 2.59 (6H, s, CH₃CO and ArCH₃), 4.03 (3H, s, CH₃O), 4.12 (3H, s, CH₃O), 6.86 (1H, s, H-3), 7.43 (1H, dd, \underline{J} 1.6 and 8.4 Hz, H-7), 7.82 (1H, d, \underline{J} 8.4 Hz, H-8), and 9.29 (1H, m, H-5).

ν_{\max} . (CHCl_3) 3020 m, 2220 w, 1780 s, and 1600 s cm^{-1} .

λ_{\max} . (MeOH) 206 (ϵ 23,100), 242 (30,000), 260 (23,700), 296 (34,800), 328 (4,500), and 342 nm (3,300).

m/z 415, 413 (M^+) and 373, 371 (M^+ -ketene).

Found: C, 57.92; H, 3.88; N, 3.33; Br, 19.39. $\text{C}_{20}\text{H}_{16}\text{BrNO}_4$ requires C, 57.99; H, 3.89; N, 3.38; Br, 19.29%.

9-Acetoxy-1-bromo-10-cyano-2,4,8-trimethoxy-6-methyl-phenanthrene (112)

δ_{H} (200 MHz; CDCl_3): 2.47 (3H, s, CH_3CO), 2.53 (3H, s, ArCH_3), 3.94 (3H, s, CH_3O), 4.00 (3H, s, CH_3O), 4.05 (3H, s, CH_3O), 6.79 (1H, s, H-3), 6.82 (1H, d, J 1.2 Hz, H-7), and 8.86 (1H, m, H-5).

ν_{\max} . (CHCl_3) 3020 m, 2220 w, 1765 m, and 1595 s cm^{-1} .

λ_{\max} . (MeOH) 260 (ϵ 79,500), 310 (77,100), and 358 nm (33,900).

m/z 445, 443 (M^+).

Found: C, 56.79; H, 4.07; N, 3.18; Br, 18.10. $\text{C}_{21}\text{H}_{18}\text{BrNO}_5$ requires C, 56.77; H, 4.08; N, 3.15; Br, 17.98%.

(E)-2-(3,5-Dimethoxyphenyl)-3-methoxy-3-(2-methoxy-4-methylphenyl)prop-2-enitrile (103)⁵⁰

The β -keto nitrile (81) (0.30g) was dissolved in trimethyl orthoformate (5 ml) and the solution distilled via a short fractionating column until the temperature of the distillate rose to 90°C. The reaction mixture was stirred at reflux for 1h and then concentrated to dryness under reduced pressure. The resulting red gum was crystallised from methanol, filtered and washed with a little methanol to afford white plates (0.28g, 90%), m.p. 145-146°C (lit.,⁵⁰ 146°C).

δ_{H} (90 MHz; CDCl_3): 2.40 (3H, s, ArCH_3), 3.67 (3H, s, CH_3O), 3.87 (6H, s, CH_3O), 3.92 (3H, s, CH_3O), 6.40 (1H, s, H-4), 6.47 (1H, d, \underline{J} 2 Hz, ArH), 6.67 (1H, d, \underline{J} 2 Hz, ArH), 6.86 (2H, m, H-3' and H-5'), and 7.37 (1H, d, \underline{J} 8 Hz, H-6').

ν_{max} . (KBr) 2205 m, 1610 s, and 1585 s cm^{-1} .

2-(2,6-Dibromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanenitrile (134)

A solution of bromine (0.63 ml) in acetic acid (100 ml) was added over 3h to a solution of the β -keto nitrile (81) (2.00g) in acetic acid (80 ml) with stirring and heating. (The temperature of the acetic acid solution was 70-80°C). After a further 4h, the cooled solution was filtered and the white solid washed thoroughly with cold water. It was then dried over phosphorus pentoxide in a vacuum desiccator to give the desired dibromo compound (134) as white plates, m.p. 268-269°C (2.15g). A further quantity (0.15g) of compound (134) was obtained by keeping the filtrate in the fridge for a few days (m.p. 266-270°C, total yield 77%). Owing to a lack of solubility in all common solvents (except dimethyl sulphoxide and tetrahydrofuran) compound (134), shown by nmr to be sufficiently clean, was used in the next step without purification.

δ_{H} (90 MHz; d_6 -dmsO): 2.37 (3H, s, ArCH_3), 3.84 (3H, s, CH_3O), 3.94 (6H, s, CH_3O), 6.95 (3H, m, ArH), and 7.38 (1H, d, \underline{J} 8 Hz, H-6')

ν_{max} . (KBr) 3250 br m, 2210 m, 1640 m, 1610 m, and 1570 s cm^{-1} .

λ_{max} . (THF) 258 (ϵ 9,100) and 290 nm (9,600).

m/z 485, 483, 481 (M^+) and 404, 402 (M^+-Br).

3-Acetoxy-2-(2,6-dibromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enenitrile (135)

An acetic anhydride solution (10 ml) of the dibromo derivative (134) (0.74g) was refluxed for 8h. The hot solution was filtered and allowed to stand overnight whereupon the E-isomer crystallised out. Recrystallisation from chloroform/hexane afforded white plates (0.48g, 59%), m.p. 239-241°C. The solution was concentrated to dryness by removing the acetic anhydride as an azeotrope with toluene. The remaining white solid was recrystallised from chloroform/hexane to yield the Z-isomer as white plates (0.21g, 26%), m.p. 221-223°C.

E-isomer

δ_{H} (200 MHz; CDCl_3): 1.95 (3H, s, CH_3CO), 2.39 (3H, s, ArCH_3), 3.90 (3H, s, CH_3O), 3.94 (6H, s, CH_3O), 6.56 (1H, s, H-4), 6.78 (1H, s, H-3'), 6.87 (1H, dq, J 0.7 and 7.8 Hz, H-5'), and 7.59 (1H, d, J 7.8 Hz, H-6').

ν_{max} . (KBr) 2220 m, 1775 s, 1625 s, 1610 s, and 1570 s cm^{-1} .

λ_{max} . (CH_2Cl_2) 242 (ϵ 16,100), 279 (15,100), and 304 nm (14,000).

m/z 525 (M^+) and 482, 480 ($\text{M}^+ - \text{CH}_3\text{CO}$).

Found: C, 48.11; H, 3.69; N, 2.55; Br, 30.46. $\text{C}_{21}\text{H}_{19}\text{Br}_2\text{NO}_5$ requires C, 48.03; H, 3.65; N, 2.67; Br, 30.43%.

Z-isomer

δ_{H} (200 MHz; CDCl_3): 2.24 (3H, s, ArCH_3), 2.29 (3H, s, CH_3CO), 3.74 (3H, s, CH_3O), 3.87 (6H, s, CH_3O), 6.46 (1H, s, H-4), 6.50 (1H, dq, J 0.7 and 7.8 Hz, H-5'), 6.59 (1H, s, H-3'), and 7.00 (1H, d, J 7.8 Hz, H-6').

ν_{max} . (KBr) 2210 m, 1780 s, 1610 s, and 1570 s cm^{-1} .

$\lambda_{\text{max.}}$ (CH_2Cl_2) 241 (ϵ 10,500), 282 (8,900), and 306 nm (9,500).
 m/z 525, 523 (M^+) and 482, 480 ($\text{M}^+-\text{CH}_3\text{CO}$).

2-(2-Iodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-
 3-oxopropanenitrile (138)

N-Iodosuccinimide (0.85g) was added in small portions over 1½h to a solution of the β -keto nitrile (81) (1.21g) in chloroform (60 ml) at room temperature. The solution was stirred for a further 9h and then washed with water and dried. Removal of the solvent yielded an amber gum which crystallised on adding ether. Recrystallisation from chloroform/hexane gave white plates (0.99g, 84%), m.p. 153-155°C.

δ_{H} (90 MHz; CDCl_3): 2.39 (3H, s, ArCH_3), 3.80 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 3.97 (3H, s, CH_3O), 6.34 (1H, s, CHCN), 6.42 (1H, d, J 2 Hz, ArH), 6.68 (1H, d, J 2 Hz, ArH), 6.84 (2H, m, H-3' and H-5'), and 7.72 (1H, d, J 8 Hz, H-6').

$\nu_{\text{max.}}$ (KBr) 2240 w, 1680 s, 1610 s, and 1585 s cm^{-1} .

$\lambda_{\text{max.}}$ (EtOH) 280 nm (ϵ 3,400).

m/z 451 (M^+).

Found: C, 50.54; H, 4.06; N, 3.10; I, 28.48. $\text{C}_{19}\text{H}_{18}\text{INO}_4$ requires C, 50.57; H, 4.02; N, 3.10; I, 28.12%.

Photolysis of the 2-iodo β -keto nitrile (138)

A deaerated acetonitrile solution (360 ml) of the β -keto nitrile (138) (0.51g) and iodine (0.60g) was stirred and irradiated for 22h. The solvent was evaporated off and the residue dissolved in ethyl acetate and then washed with 10% sodium thiosulphate solution. Drying and evaporation gave a brown/black oil which was shown by tlc

and nmr to be a complex mixture of components which could not be resolved by chromatography. The 90 MHz ^1H nmr spectrum contained a singlet at $\delta 8.90$ ppm which probably corresponded to H-4 of the phenanthrene (72).

3-Acetoxy-2-(2-iodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enenitrile (139)

A solution of the β -keto nitrile (138) (0.46g) in acetic anhydride (10 ml) containing a few crystals of *p*-toluenesulphonic acid was heated at reflux for 2h. The reaction mixture was worked-up as outlined for the preparation of the stilbene (70) to give a dark brown gum. Silica gel column chromatography using 30:70 ethyl acetate:hexane as eluant afforded a yellow gum which was shown by ^1H nmr to consist mainly of the E- and Z-stilbenes (139) (0.31g, 62%, E : Z = 1.0 : 1.0 from the ^1H nmr integration of the H-6' doublets). Further purification by preparative tlc on silica using several developments in 40:60 hexane:chloroform provided a pure sample. The ^1H nmr spectrum of the E- and Z-2-iodostilbenes (139) was assigned by comparison with the spectra of the E- and Z-isomers of the 2-bromostilbene (83).

E : Z = 1.0 : 2.1

δ_{H} (200 MHz; CDCl_3): E-isomer, 1.92 (3H, s, CH_3CO), 2.38 (3H, s, ArCH_3), 3.80 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 3.90 (3H, s, CH_3O), 6.42 (1H, d, J 2.6 Hz, ArH), 6.58 (1H, d, J 2.6 Hz, ArH), 6.78 (1H, s, H-3'), 6.86 (1H, dq, J 0.7 and 7.8 Hz, H-5'), and 7.56 (1H, d, J 7.8 Hz, H-6'); Z-isomer, 2.25 (3H, s, ArCH_3), 2.28 (3H, s, CH_3CO), 3.58 (3H, s, CH_3O), 3.66 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 6.27

(2H, m, H-4 and H-6), 6.58 (2H, m, H-3' and H-5'), and 7.04 (1H, d, J 7.9 Hz, H-6').

ν_{max} . (CHCl₃) 3000 m, 2200 w, 1760 s, 1600 s, and 1575 s cm⁻¹.

λ_{max} . (MeOH) 203 (ϵ 32,000) and 283 nm (7,400).

Found: M⁺, 493.0369. C₂₁H₂₀INO₅ requires M⁺, 493.0385.

Photolysis of the 2-iodostilbene (139)

A solution of the 2-iodostilbene (139) (0.20g) in redistilled benzene (150 ml) was refluxed for 30 min under nitrogen and then cooled. The solution was stirred and irradiated while a slow flow of nitrogen was bubbled through the solution. After 14h the dark brown solution was washed with 20% aqueous sodium thiosulphate followed by brine and then dried. Removal of the solvent left a dark brown residue which was purified by column chromatography over silica using 20:80 ethyl acetate:hexane as eluant to afford the phenanthrenes (71) and (110) in 50% and 15% yields respectively. The spectral characteristics of these compounds are recorded on pages 194 and 202.

2-(2,6-Diiodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanenitrile (152)

N-Iodosuccinimide (1.38g) was added in small portions to the β -keto nitrile (81) (1.00g) in chloroform (50 ml) over a period of 2h. The reaction mixture was stirred at room temperature overnight. Most of the desired diiodo compound (152) precipitated out during the reaction. It was collected by filtration, washed with ether and dried (0.54g). The filtrate was washed with water, dried and evaporated to

give an orange/brown foam which afforded a further quantity of (152) (0.24g) upon crystallisation from chloroform/hexane (total weight 0.78g, yield 44%). Owing to a lack of solubility in all common solvents (except dimethyl sulphoxide and tetrahydrofuran) compound (152), shown by nmr to be sufficiently clean, was used in the next step without purification. A sample for microanalysis (white plates, m.p. 228-229°C [decomp.]) was obtained by recrystallisation from a very dilute solution of acetone containing a small amount of hexane.

δ_{H} (200 MHz; d_6 -dmsO): 2.37 (3H, s, ArCH₃), 3.82 (3H, s, CH₃O), 3.90 (6H, s, CH₃O), 6.67 (1H, s, H-4), 6.90 (1H, d, J 7.6 Hz, H-5'), 6.98 (1H, s, H-3'), 7.44 (1H, d, J 7.6 Hz, H-6'), and 10.00 (1H, br s, OH).

ν_{max} . (KBr) 3210 br s, 2205 s, 1630 s, 1610 s, and 1560 s cm^{-1} .

λ_{max} . (THF) 294 nm (ϵ 3,300).

m/z 577 (M^+), 450 (M^+-I), and 323 (M^+-2I).

Found: C, 39.54; H, 2.91; N, 2.35; I, 44.27. $C_{19}H_{17}I_2NO_4$ requires C, 39.54; H, 2.97; N, 2.43; I, 43.98%.

Photolysis of the 2,6-diiodo enolic compound (152)

Compound (152) (1.13g) was dissolved in dry tetrahydrofuran (400 ml) and then purged with nitrogen for 1h. The solution was stirred and irradiated under a nitrogen balloon for 20h. Upon removal of the solvent a dark brown oil remained which was purified by silica gel chromatography using 40:60 chloroform:hexane as eluant to afford the phenanthrene (72) (0.13g, 20%) and the phenanthrene (151) (0.06g, 10%). The former phenanthrene was identical to that produced by base

hydrolysis of the phenanthrene (71) (see p.195). A sample of the phenanthrene (151) for microanalysis (white needles, m.p. 249-251°C) was obtained upon recrystallisation from methylene chloride/hexane.

10-Cyano-9-hydroxy-2,4-dimethoxy-6-methylphenanthrene (151)

δ_{H} (200 MHz; d_6 -acetone): 2.57 (3H, s, ArCH₃), 3.97 (3H, s, CH₃O), 4.13 (3H, s, CH₃O), 6.79 (1H, d, J 2.5 Hz, ArH), 7.10 (1H, d, J 2.5 Hz, ArH), 7.47 (1H, dd, J 1.6 and 8.4 Hz, H-7), 8.33 (1H, d, J 8.4 Hz, H-8), and 9.39 (1H, m, H-5).

ν_{max} . (CHCl₃) 3250 br m, 3020 m, 2210 w, and 1610 s cm⁻¹.

m/z 293 (M⁺).

Found: C, 73.74; H, 5.13; N, 4.82. C₁₈H₁₅NO₃ requires C, 73.71; H, 5.15; N, 4.78%.

3-Acetoxy-2-(3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enenitrile (156)⁶¹

A solution of the β -keto nitrile (81) (0.30g) and a few crystals of p-toluenesulphonic acid in acetic anhydride (10 ml) was refluxed for 2h. The reaction mixture was worked-up as outlined for the preparation of the stilbene (70). Column chromatography of the crude product over silica using ether as eluant gave a mixture of the E- and Z-stilbenes (156) as a light brown gum (0.27g, 80%, E : Z = 1.0 : 1.4 from the ¹H nmr integration of the H-6' doublets).

δ_{H} (200 MHz; CDCl₃): 2.09 (3H, s, E-CH₃CO), 2.26 (3H, s, Z-CH₃CO), 2.31 (3H, s, Z-ArCH₃), 2.38 (3H, s, E-ArCH₃), 3.54 (3H, s, E-CH₃O), 3.59 (6H, s, Z-CH₃O), 3.79 (6H, s, E-CH₃O), 3.88 (3H, s, Z-CH₃O), 6.33 (3H, m, ArH), 6.45 (1H, t, J 2.3 Hz, ArH), 6.62 (1H,

s, ArH), 6.69 (3H, m, ArH), 6.78 (1H, s, ArH), 6.83 (1H, dq, J 0.7 and 7.8 Hz, ArH), 7.11 (1H, d, J 7.8 Hz, $Z\text{-H}_{6t}$), and 7.43 (1H, d, J 7.8 Hz, $E\text{-H}_{6t}$).

2-Bromo-3,5-dimethoxybenzyl alcohol (175)⁹⁶

3,5-Dimethoxybenzyl alcohol (65) (1.00g) was dissolved in carbon tetrachloride (35 ml) and recrystallised N-bromosuccinimide (1.06g) was added in small portions over 10 min with stirring. The mixture was heated at 70-80°C (bath temperature) for 40 min and then filtered hot. The filtrate was diluted with ether (50 ml) and then washed with water (2 x 30 ml) and saturated brine (2 x 30 ml).

Drying and evaporation yielded a cream solid which was recrystallised from acetone/hexane as fine white needles (1.08g, 73%), m.p. 95-96°C (lit.,⁹⁶ 96°C).

δ_{H} (90 MHz; CDCl_3): 3.82 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.72 (2H, s, CH_2), 6.44 (1H, d, J 3 Hz, ArH), and 6.70 (1H, d, J 3 Hz, ArH).

ν_{max} . (KBr) 3280 br m and 1590 s cm^{-1} .

2-Bromo-3,5-dimethoxybenzyl chloride (176)

The method of preparation of the benzyl chloride (66) was followed using a dry ether solution (60 ml) of thionyl chloride (2.6 ml) and pyridine (0.15 ml) and the bromo alcohol (175) (2.5g) in ether (40 ml). The crude product was recrystallised from methanol to give white needles (2.4g, 89%), m.p. 112-113°C.

δ_{H} (90 MHz; CDCl_3): 3.82 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.69 (2H, s, CH_2), 6.45 (1H, d, J 2 Hz, ArH), and 6.66 (1H, d, J 2 Hz, ArH).

ν_{max} . (KBr) 1585 m and 1330 s cm^{-1} .

m/z 268, 266, 264 (M^+) and 231, 229 ($\text{M}^+ - \text{Cl}$).

Found: C, 40.67; H, 3.66; Br, 30.05; Cl, 13.57. $\text{C}_9\text{H}_{10}\text{BrClO}_2$ requires C, 40.71; H, 3.80; Br, 30.09; Cl, 13.35%.

2-Bromo-3,5-dimethoxybenzyl cyanide (177)

A mixture of the benzyl chloride (176) (1.00g), potassium cyanide (1.30g), ethanol (20 ml) and water (5 ml) was stirred at reflux for 4h. The hot solution was poured onto crushed ice and left to stand for 2h. The cream precipitate was collected by filtration, washed thoroughly with water and dried over phosphorus pentoxide in a vacuum desiccator. Fine white needles were obtained upon recrystallisation from methanol (0.77g, 80%), m.p. 114-115°C.

δ_{H} (90 MHz; CDCl_3): 3.84 (5H, s, CH_3O and CH_2), 3.89 (3H, s, CH_3O), 6.47 (1H, d, J 2 Hz, ArH), and 6.72 (1H, d, J 2 Hz, ArH).

ν_{max} . (KBr) 2240 w and 1610 s cm^{-1} .

m/z 257, 255 (M^+).

Found: C, 46.91; H, 3.87; N, 5.32; Br, 31.23. $\text{C}_{10}\text{H}_{10}\text{BrNO}_2$ requires C, 46.90; H, 3.94; N, 5.47; Br, 31.20%.

Methyl 2-bromo-3,5-dimethoxyphenylacetate (178)

The nitrile (177) (0.50g) was dissolved in methanol (45 ml) and water (5 ml) and concentrated sulphuric acid (10 ml) was cautiously added. The solution was refluxed for 16h and then poured onto crushed

ice while still hot. The white precipitate was filtered off after 2h, washed with water and dried over phosphorus pentoxide in vacuo. The crude product was recrystallised from ether as white needles (0.39g, 70%), m.p. 104-105°C.

δ_{H} (90 MHz; CDCl_3): 3.72 (3H, s, CH_3O), 3.80 (5H, s, CH_3O and CH_2), 3.87 (3H, s, CH_3O), 6.42 (1H, d, J 2 Hz, ArH), and 6.48 (1H, d, J 2 Hz, ArH).

ν_{max} . (KBr) 1725 s and 1590 s cm^{-1} .

m/z 290, 288 (M^+), 231, 229 ($\text{M}^+ - \text{CO}_2\text{CH}_3$), and 209 ($\text{M}^+ - \text{Br}$).

Found: C, 45.72; H, 4.52; Br, 27.67. $\text{C}_{11}\text{H}_{13}\text{BrO}_4$ requires C, 45.70; H, 4.53; Br, 27.64%.

Methyl 2-(2-bromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanoate (179)

n-Butyl lithium (1.48 ml, 1.40M in hexane) was added rapidly to dry diisopropylamine (0.29 ml) in dry tetrahydrofuran (10 ml) with stirring at 0°C and under nitrogen. After 10 min the solution was cooled to -78°C and methyl 2-bromo-3,5-dimethoxyphenylacetate (178) (0.30g) in THF (15 ml) was introduced over 10 min. The cooling bath was removed and the solution stirred at room temperature for 1h. Methyl 2-methoxy-4-methylbenzoate (80) (0.28g) in THF (15 ml) was added over 10 min and the reaction mixture heated at 40°C for 4h. After cooling, 2M hydrochloric acid (25 ml) was added and the THF evaporated off. The acidic solution was extracted with ethyl acetate and the organic layer washed with saturated aqueous sodium bicarbonate followed by brine. Drying and evaporation yielded a gum which was

purified by column chromatography over silica using 45:55 cyclohexane:chloroform as eluant. Further purification by preparative tlc on silica using chloroform as eluant gave the β -keto ester (179) as white plates after recrystallisation from chloroform/hexane (0.10g, 22%), m.p. 142-143°C.

δ_{H} (90 MHz; CDCl_3): 2.30 (3H, s, ArCH_3), 3.66 (3H, s, CH_3O), 3.73 (3H, s, CH_3O), 3.77 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 6.21 (1H, s, CHCO_2CH_3), 6.38 (2H, s, H-4 and H-6), 6.67 (1H, s, H-3'), 6.77 (1H, d, J 8 Hz, H-5'), and 7.75 (1H, d, J 8 Hz, H-6').

ν_{max} . (KBr) 1740 s, 1680 s, 1610 s, and 1580 s cm^{-1} .

m/z 438, 436 (M^+) and 357 ($\text{M}^+ - \text{Br}$).

Found: C, 54.99; H, 4.82; Br, 18.42. $\text{C}_{20}\text{H}_{21}\text{BrO}_6$ requires C, 54.93; H, 4.84; Br, 18.27%.

Methyl 3,5-dimethoxyphenylacetate (180)

Concentrated sulphuric acid (45 ml) was carefully added to a solution of the nitrile (67) (1.50g) in methanol (170 ml) and water (10 ml) and the solution heated at reflux for 16h. Upon cooling, the methanol was removed under reduced pressure and the acidic solution extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate followed by brine and then dried. Evaporation of the solvent afforded a brown oil which was distilled in vacuo to give the ester (180) as a colourless liquid (1.21g, 68%), b.p. 125°C/0.06 mm Hg (lit.,¹¹² 94°C/0.04 mm Hg).

δ_{H} (90 MHz; CDCl_3): 3.52 (2H, s, CH_2), 3.65 (3H, s, CO_2CH_3), 3.74 (6H, s, CH_3O), and 6.40 (3H, m, ArH).

ν_{\max} . (CHCl_3) 3020 m, 1730 s, and 1600 s cm^{-1} .

$\underline{m/z}$ 210 (M^+) and 151 ($\text{M}^+ - \text{CO}_2\text{CH}_3$).

Methyl 2-(3,5-dimethoxyphenyl)-3-(2-methoxy-4-methyl-phenyl)-3-oxopropanoate (181)

n-Butyl lithium (6.90 ml, 2.61M in hexane) and dry dicyclohexylamine (3.26g) in dry tetrahydrofuran (20 ml) were stirred at 0°C under nitrogen for 30 min. The solution was cooled to -78°C and methyl 3,5-dimethoxyphenylacetate (180) (1.80g) in THF (40 ml) was added over 15 min. The cooling bath was removed after a further 40 min at -78°C. After 20 min the solution was again cooled to 0°C and 2-methoxy-4-methylbenzoyl chloride (183) (2.13g) in THF (50 ml) was introduced over 30 min. The reaction mixture was maintained at room temperature for a further 2h and then added dropwise over 15 min to a saturated solution of ammonium chloride with efficient stirring. The THF was removed under reduced pressure and the remaining aqueous phase extracted with ethyl acetate. The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate and brine, then dried and evaporated to leave an amber gum. Purification by silica gel chromatography using 20:80 ethyl acetate:hexane as eluant yielded the β -keto ester (181) as a yellow gum (2.58g, 84%).

δ_{H} (90 MHz; CDCl_3): 2.35 (3H, s, ArCH_3), 3.76 (9H, s, CH_3O), 3.88 (3H, s, CH_3O), 5.62 (1H, s, CHCO_2CH_3), 6.40 (1H, t, \underline{J} 2 Hz, H-4), 6.50 (2H, d, \underline{J} 2 Hz, H-2 and H-6), 6.81 (2H, m, H-3' and H-5'), and 7.72 (1H, d, \underline{J} 8 Hz, H-6').

ν_{\max} . (CHCl_3) 3020 m, 1735 s, 1675 s, and 1610 s cm^{-1} .

Found: M^+ , 358.1416. $C_{20}H_{22}O_6$ requires M^+ , 358.1416.

2-Methoxy-4-methylbenzoic acid (182)

A solution of the ester (80) (10.0g) in methanol (20 ml) and 30% aqueous sodium hydroxide (80 ml) was refluxed for 16h. Upon cooling, the methanol was removed under reduced pressure and the basic solution washed with ether and then acidified with concentrated hydrochloric acid. The acidic solution was extracted with ethyl acetate and the organic layer washed with water and then dried. A white solid remained upon removal of the solvent which was recrystallised from chloroform as white plates (7.8g, 85%), m.p. 105-106°C (lit.,¹¹¹ 103-104°C).

δ_H (90 MHz; d_6 -acetone): 2.40 (3H, s, $ArCH_3$), 4.04 (3H, s, CH_3O), 6.93 (1H, d, J 8 Hz, H-5), 7.08 (1H, s, H-3), and 7.85 (1H, d, J 8 Hz, H-6).

ν_{max} . (KBr) 2950 br m, 1670 s, and 1610 s cm^{-1} .

m/z 166 (M^+).

2-Methoxy-4-methylbenzoyl chloride (183)

2-Methoxy-4-methylbenzoic acid (182) (2.50g) in thionyl chloride (10 ml) was stirred at room temperature for 2h. The excess thionyl chloride was removed under reduced pressure and the residue purified by bulb-tube distillation (106°/0.03 mm Hg) to afford the acid chloride (183) as a colourless oil (2.40g, 86%) (lit.,¹¹³ b.p. 148-149°C/12.5 mm Hg). The product was used immediately.

δ_{H} (90 MHz; CDCl_3): 2.42 (3H, s, ArCH_3), 3.90 (3H, s, CH_3O), 6.84 (2H, m, H-3 and H-5), and 7.96 (1H, d, J 8 Hz, H-6).

ν_{max} . (CHCl_3) 3020 m, 1770 s, 1755 s, and 1610 s cm^{-1} .

Methyl 2-(2-iodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanoate (184)

N-Iodosuccinimide (0.852g) was added in small portions over 2h to a solution of the β -keto ester (181) (1.356g) in chloroform (55 ml). After stirring at room temperature for a further 7h the deep red solution was washed with water and then dried. A brown semi-solid mass remained upon removal of the solvent which produced a fawn coloured solid upon addition of ether. Recrystallisation from chloroform/hexane gave the β -keto ester (184) as white plates (1.260g, 69%), m.p. 144-145°C.

δ_{H} (90 MHz; CDCl_3): 2.35 (3H, s, ArCH_3), 3.73 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 3.84 (6H, s, CH_3O), 6.24 (1H, s, CHCO_2CH_3), 6.48 (1H, d, J 2 Hz, ArH), 6.54 (1H, d, J 2 Hz, ArH), 6.71 (1H, s, H-3'), 6.82 (1H, d, J 8 Hz, H-5'), and 7.81 (1H, d, J 8 Hz, H-6').

ν_{max} . (KBr) 1740 s, 1680 s, 1610 s, and 1575 s cm^{-1} .

m/z 484 (M^+) and 357 (M^+-I).

Found: C, 49.60; H, 4.34; I, 26.36. $\text{C}_{20}\text{H}_{21}\text{IO}_6$ requires C, 49.58; H, 4.37; I, 26.22%.

(Z)-Methyl 3-acetoxy-2-(2-iodo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enoate (185)

A solution of the β -keto ester (184) (0.25g) in acetic anhydride (10 ml) containing a few crystals of *p*-toluenesulphonic acid was heated at reflux for 1½h. The reaction mixture was worked-up as outlined for the preparation of the stilbene (70) to give a brown oil. The Z-2-iodostilbene (185) was isolated by preparative tlc on silica using two developments in 20:80 ethyl acetate:hexane and recrystallised from acetone/hexane to yield white needles (0.19g, 68%), m.p. 153-155°C.

δ_{H} (200 MHz; CDCl_3): 2.23 (6H, s, CH_3CO and ArCH_3), 3.52 (3H, s, CH_3O), 3.70 (6H, s, CH_3O), 3.80 (3H, s, CH_3O), 6.20 (1H, d, $\underline{\text{J}}$ 2.7 Hz, ArH), 6.27 (1H, d, $\underline{\text{J}}$ 2.7 Hz, ArH), 6.53 (2H, m, H-3' and H-5'), and 7.06 (1H, d, $\underline{\text{J}}$ 8.0 Hz, H-6').

ν_{max} . (KBr) 1760 s, 1720 s, 1635 m, 1610 s, and 1570 s cm^{-1} .

λ_{max} . (MeOH) 202 (ϵ 27,200) and 280 nm (3,700).

m/z 526 (M^+) and 399 (M^+-I).

Found: C, 50.13; H, 4.27; I, 24.38. $\text{C}_{22}\text{H}_{23}\text{IO}_7$ requires C, 50.20; H, 4.40; I, 24.11%.

Photochemistry of the Z-2-iodostilbene (185)

(a) $\underline{h\nu/N_2/C_6H_6}$

A solution of the Z-stilbene (185) (141 mg) in redistilled benzene (150 ml) was deoxygenated by heating at reflux for 1h while nitrogen gas was bubbled through the solution. The cooled solution was irradiated for 22h and then evaporated to leave a dark green semi-solid mass. Purification by column chromatography over silica using chloroform as

eluant yielded the phenanthrenes (173) and (188). The phenanthrene (173) was recrystallised from methylene chloride/hexane as white plates (25 mg, 23%), m.p. 200-202°C. The phenanthrene (188) was also recrystallised from methylene chloride/hexane as white plates (6 mg, 6%), m.p. 150-152°C.

10-Acetoxy-9-carbomethoxy-1,5,7-trimethoxy-3-methylphenanthrene

(173)

δ_{H} (200 MHz; CDCl_3): 2.33 (3H, s, CH_3CO), 2.54 (3H, s, ArCH_3), 3.89 (3H, s, CH_3O), 3.91 (3H, s, CH_3O), 4.01 (3H, s, CH_3O), 4.04 (3H, s, CH_3O), 6.72 (1H, d, J 2.5 Hz, ArH), 6.76 (1H, d, J 2.5 Hz, ArH), 6.82 (1H, d, J 1.2 Hz, H-2), and 9.05 (1H, m, H-4).

ν_{max} . (CHCl_3) 3010 m, 1765 s, 1730 s, 1610 s, and 1575 s cm^{-1} .

m/z 398 (M^+), 356 (M^+ -ketene), and 324 (M^+ -ketene-MeOH).

Found: C, 66.30; H, 5.55. $\text{C}_{22}\text{H}_{22}\text{O}_7$ requires C, 66.32; H, 5.56%.

9-Acetoxy-10-carbomethoxy-2,4-dimethoxy-6-methylphenanthrene

(188)

δ_{H} (200 MHz; CDCl_3): 2.44 (3H, s, CH_3CO), 2.58 (3H, s, ArCH_3), 3.91 (3H, s, CH_3O), 4.03 (3H, s, CH_3O), 4.06 (3H, s, CH_3O), 6.76 (1H, d, J 2.4 Hz, ArH), 6.98 (1H, d, J 2.4 Hz, ArH), 7.38 (1H, dd, J 1.2 and 8.4 Hz, H-7), 7.76 (1H, d, J 8.4 Hz, H-8), and 9.37 (1H, m, H-5).

ν_{max} . (CHCl_3) 3010 m, 1765 s, 1730 s, and 1610 s cm^{-1} .

m/z 368 (M^+), 326 (M^+ -ketene), and 294 (M^+ -ketene-MeOH).

Found: C, 68.50; H, 5.49. $\text{C}_{21}\text{H}_{20}\text{O}_6$ requires C, 68.47; H, 5.47%.

(b) $h\nu/\text{N}_2/\text{Et}_3\text{N}/\text{C}_6\text{H}_6/20\text{h}$

A solution of the Z-stilbene (185) (0.21g) in dry benzene (400 ml) containing dry triethylamine (0.8 ml) was purged with nitrogen

for 2h and then stirred and irradiated for 20h while a slow flow of nitrogen was bubbled through the solution. After washing with 5% hydrochloric acid followed by water, the solution was dried and evaporated to yield a brown gum (0.17g). The phenanthrenes (173) and (188) were isolated in 10% and 3% yields respectively upon preparative tlc on silica using 50:50 chloroform:hexane as eluant.

(c) $\frac{h\nu/N_2/Et_3N/C_6H_6}{4h}$

The foregoing procedure was repeated using the Z-stilbene (185) (0.35g) and dry triethylamine (1.4 ml) and an irradiation time of 4h. This produced a yellow foam comprising of the E- and Z-isomers of the starting stilbene. Addition of ether/hexane caused crystallisation of some of the E-stilbene (185a) which was recrystallised from methylene chloride/hexane as white plates, m.p. 167-168°C.

δ_H (200 MHz; $CDCl_3$): 1.85 (3H, s, CH_3CO), 2.37 (3H, s, $ArCH_3$), 3.57 (3H, s, CH_3O), 3.79 (3H, s, CH_3O), 3.84 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 6.40 (1H, d, J 2.7 Hz, ArH), 6.60 (1H, d, J 2.7 Hz, ArH), 6.74 (1H, s, H-3'), 6.80 (1H, dq, J 0.7 and 7.7 Hz, H-5'), and 7.31 (1H, d, J 7.7 Hz, H-6').

ν_{max} . (KBr) 1760 s, 1720 s, 1620 m, 1610 m, and 1580 cm^{-1} .

λ_{max} . (MeOH) 206 (ϵ 43,300) and 280 nm (5,300).

m/z 526 (M^+) and 399 (M^+-I).

(Z)-Methyl 3-acetoxy-2-(3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)prop-2-enoate (186)

A solution of the β -keto ester (181) (0.48g) and p-toluenesulphonic acid (0.10g) in isopropenyl acetate (15 ml) was slowly distilled for 3h using a 15 cm fractionating column. More isopropenyl acetate

was added occasionally to keep the volume above 5 ml and then the solution was refluxed for 8h. After cooling, sodium bicarbonate (0.50g) was added and the solution concentrated to dryness under reduced pressure. The residue was dissolved in methylene chloride, washed with brine, dried and evaporated to give a brown semi-crystalline residue. The Z-stilbene (186) was obtained as white plates upon recrystallisation of this residue from methylene chloride/hexane and after washing with ether (0.51g, 95%), m.p. 146°C.

δ_{H} (200 MHz; CDCl_3): 2.17 (3H, s, CH_3CO), 2.26 (3H, s, ArCH_3), 3.59 (6H, s, CH_3O), 3.62 (3H, s, CH_3O), 3.76 (3H, s, CH_3O), 6.25 (3H, s, ArH), 6.58 (2H, m, H-3' and H-5'), and 7.05 (1H, d, J 7.6 Hz, H-6').

ν_{max} . (KBr) 1760 s, 1720 s, 1640 s, 1610 s, and 1590 s cm^{-1} .

λ_{max} . (MeOH) 204 (ϵ 38,800) and 280 nm (7,900).

m/z 400 (M^+), 358 (M^+ -ketene), and 326 (M^+ -ketene-MeOH).

Found: C, 65.96; H, 6.02. $\text{C}_{22}\text{H}_{24}\text{O}_7$ requires C, 65.99; H, 6.04%.

Photocyclisation of the Z-stilbene (186)

A solution of the Z-stilbene (186) (0.33g) and iodine (0.44g) in cyclohexane (400 ml) was stirred and irradiated for 20h, then washed with 20% aqueous sodium thiosulphate and dried. Evaporation of the solvent gave a brown gum which was purified by column chromatography over silica using methylene chloride as eluant to afford the pure phenanthrene (188) and a mixture of the phenanthrenes (188) and (173). This mixture was resolved by preparative tlc on silica using two developments in 30:70 ethyl acetate:hexane. Both phenanthrenes were

identical in all respects to those obtained upon photocyclisation of the corresponding Z-2-iodostilbene (185) (see p.219). The yields of the phenanthrenes (173) and (188) were 21% (0.07g) and 56% (0.17g) respectively.

Methyl 2-(2,6-dibromo-3,5-dimethoxyphenyl)-3-(2-methoxy-4-methylphenyl)-3-oxopropanoate (187)

A solution of bromine (0.12 ml) in acetic acid (15 ml) was added over 1h to a solution of the β -keto ester (181) (0.42g) in acetic acid (15 ml) with stirring and heating. (The temperature of the acetic acid solution was maintained at 70-80°C). After a further 3h, the hot solution was poured onto crushed ice and extracted with ethyl acetate. The combined organic extracts were washed with brine, saturated aqueous sodium bicarbonate, more brine, then dried and evaporated to give a fawn coloured solid. Recrystallisation from chloroform/hexane afforded the dibromo derivative (187) as white plates (0.51g, 84%), m.p. 68-70°C.

δ_{H} (200 MHz; d_6 -dmsO): 2.43 (3H, s, ArCH₃), 3.37 (6H, s, CH₃O), 3.93 (6H, s, CH₃O), 6.90 (1H, s, H-4), 7.21 (1H, d, J 8.0 Hz, H-5'), 7.25 (1H, s, H-3'), and 7.83 (1H, d, J 8.0 Hz, H-6').

ν_{max} . (KBr) 3400 br m, 2940 m, 1740 m, and 1590 s cm^{-1} .

m/z 518, 516, 514 (M^+).

Found: C, 46.49; H, 3.86; Br, 30.82. $\text{C}_{20}\text{H}_{20}\text{Br}_2\text{O}_6$ requires

C, 46.54; H, 3.90; Br, 30.96%.

2,6-Dimethoxy-4-methylbenzoic acid (192)

A solution of the ester (68) (5.1g) in 30% aqueous sodium hydroxide (50 ml) was refluxed for 17h. The cooled solution was washed with ether and then acidified to pH 2 with concentrated hydrochloric acid. The resulting precipitate was filtered off, washed thoroughly with water and then dried over phosphorus pentoxide in vacuo to give the acid (192) as a white solid (3.8g, 80%), m.p. 200-202°C (lit.,¹⁰² 180-182°C [decomp.]). The product was sufficiently pure to use without purification.

δ_{H} (90 MHz; CD_3OD): 2.32 (3H, s, ArCH_3), 3.80 (6H, s, CH_3O), and 6.52 (2H, s, ArH).

ν_{max} . (KBr) 3000 br m, 1690 s, 1610 s, and 1585 s cm^{-1} .

$\underline{m/z}$ 196 (M^+) and 179 (M^+-OH).

Decarbomethoxylation of the 9-carbomethoxyphenanthrene (173)

A solution of the phenanthrene (173) (0.10g) in 15% aqueous sodium hydroxide (15 ml) and the minimum amount of methanol (2-3 ml) was refluxed for 6h under a nitrogen balloon. Concentrated hydrochloric acid was added to the cooled reaction mixture until pH 2 and the resulting white precipitate was collected by filtration and washed thoroughly with cold water. The crude product was dried over phosphorus pentoxide in a vacuum desiccator and identified as the required compound 10-hydroxy-1,5,7-trimethoxy-3-methylphenanthrene (73) (0.067g, 90%) by 90 MHz ^1H nmr. The spectrum showed that the phenanthrene (73) was very pure, but on attempted recrystallisation the product developed a purple colouration due to partial oxidation to the 9,10-quinone (193).

Conversion of the β -keto ester (181) to the desoxybenzoin (201)

using HCl

A solution of the β -keto ester (181) (0.47g) in 5M hydrochloric acid (40 ml) was refluxed for 18h. The cooled solution was extracted with ether and the combined ether layers washed with brine, saturated aqueous sodium bicarbonate and more brine. Drying and evaporation of the organic phase gave a brown oil which afforded the desoxybenzoin (201)⁶¹ as an amber gum upon silica gel column chromatography using 10:90 hexane:methylene chloride as eluant (0.28g, 71%).

δ_{H} (90 MHz; CDCl_3): 2.25 (3H, s, ArCH_3), 3.64 (6H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.18 (2H, s, CH_2), 6.27 (1H, t, J 2 Hz, H-4), 6.35 (2H, d, J 2 Hz, H-2 and H-6), 6.70 (2H, m, H-3' and H-5'), and 7.54 (1H, d, J 8 Hz, H-6').

ν_{max} . (CHCl_3) 1670 m and 1610 s cm^{-1} .

Found: M^+ , 300.1361. $\text{C}_{18}\text{H}_{20}\text{O}_4$ requires M^+ , 300.1342.

Conversion of the β -keto ester (181) to the carboxylic acids (182)

and (202) using NaOH

A solution of the β -keto ester (181) (0.64g) in methanol (10 ml) and 10% aqueous sodium hydroxide (10 ml) was refluxed for 16h. The cooled solution was washed with ether, acidified with concentrated hydrochloric acid, then extracted with ethyl acetate. The combined organic extracts were washed with water and dried. Removal of the solvent yielded an off-white solid (0.48g) which was shown to be a mixture of 2-methoxy-4-methylbenzoic acid (182)¹¹¹ and 3,5-dimethoxyphenylacetic acid (202).¹¹⁰

δ_{H} (90 MHz; CDCl_3): acid (182), 2.36 (3H, s, ArCH_3), 3.98 (3H, s, CH_3O), 6.88 (2H, m, H-3 and H-5), and 7.95 (1H, d, J 8 Hz, H-6); acid (202), 3.55 (2H, s, CH_2), 3.74 (6H, s, CH_3O), 6.34 (1H, t, J 2 Hz, H-4), and 6.42 (2H, d, J 2 Hz, H-2 and H-6).
 m/z 196 (M^+ , acid (202)) and 166 (M^+ , acid (182)).

Methyl 3,5-dihydroxybenzoate (212)¹¹⁰

A solution of 3,5-dihydroxybenzoic acid (63) (10.0g) in dry methanol (50 ml) was saturated with dry hydrogen chloride gas and heated at reflux for 2h. The solution was cooled and evaporated to give a residue which was recrystallised as slightly coloured needles from ethanol (9.0g, 82%), m.p. 167-168°C (lit.,¹¹⁰ 164-165°C).

δ_{H} (90 MHz; d_6 -acetone): 3.83 (3H, s, CO_2CH_3), 6.58 (1H, t, J 2 Hz, H-4), 6.99 (2H, d, J 2 Hz, H-2 and H-6), and 8.44 (2H, s, OH).

ν_{max} . (KBr) 3250 br s, 1695 s, and 1600 s cm^{-1} .

3,5-Dibenzyloxybenzoic acid (214)¹¹⁰

A mixture of methyl 3,5-dihydroxybenzoate (212) (10.0g), benzyl chloride (30 ml), anhydrous potassium carbonate (50g) and potassium iodide (11g) in dry butanone (400 ml) was stirred at reflux for 8h. After cooling, water (150 ml) and ether (100 ml) were added and the organic layer separated and washed with 10% sodium hydroxide solution (2 x 50 ml). The solvents were evaporated and the residue mixed with 30% sodium hydroxide solution (60 ml) and ethanol (30 ml). This was heated at reflux for 2½h, cooled and diluted with water (60 ml). The solution was extracted with ether and the ether layer washed with

water (2 x 60 ml). The combined aqueous solutions gave a cream solid on acidification. The product was recrystallised from ethanol as colourless needles (16.2g, 81%), m.p. 210-212°C (lit.,¹¹⁰ 211-212°C).

δ_{H} (90 MHz; d_6 -acetone): 5.12 (4H, s, PhCH₂), 6.87 (1H, t, J 2 Hz, H-4), 7.13 (2H, d, J 2 Hz, H-2 and H-6), and 7.35 (10H, m, C₆H₅).

ν_{max} . (KBr) 2880 br m, 1690 s, 1595 s, and 1165 s cm⁻¹.

3,5-Dibenzyloxybenzyl alcohol (215)¹¹⁰

A solution of 3,5-dibenzyloxybenzoic acid (214) (10.0g) in dry tetrahydrofuran (100 ml) was added dropwise to a slurry of lithium aluminium hydride (1.0g) in THF (30 ml) with stirring and the mixture was refluxed for 5h. After cooling, water (1.0 ml) was added cautiously, followed by 15% sodium hydroxide solution (1.0 ml) and more water (3.0 ml). The precipitate was removed by filtration and washed with ether (100 ml). The organic solvents were evaporated and the product recrystallised from ether/hexane as colourless needles (6.5g, 68%), m.p. 78°C (lit.,¹¹⁰ 77-78°C).

δ_{H} (90 MHz; CDCl₃): 2.41 (1H, s, OH), 4.44 (2H, s, CH₂OH), 4.89 (4H, s, PhCH₂), 6.50 (3H, m, ArH), and 7.28 (10H, s, C₆H₅).

ν_{max} . (KBr) 3350 br m, 1590 s, and 1160 s cm⁻¹.

3,5-Dibenzyloxybenzyl chloride (216)¹¹⁰

The method of preparation of the benzyl chloride (66) was followed using a dry ether solution (70 ml) of thionyl chloride (5 ml) and pyridine (0.2 ml) and 3,5-dibenzyloxybenzyl alcohol (215) (5.0g) in ether (70 ml). The crude product was recrystallised from ether as colourless needles (4.0g, 76%), m.p. 74-76°C (lit.,¹¹⁰ 75-76°C).

δ_{H} (90 MHz; CDCl_3): 4.44 (2H, s, CH_2Cl), 4.97 (4H, s, PhCH_2), 6.59 (3H, m, ArH), and 7.35 (10H, s, C_6H_5).

$\nu_{\text{max.}}$ (KBr) 1600 s cm^{-1} .

3,5-Dibenzyloxybenzyl cyanide (217)¹¹⁰

A mixture of 3,5-dibenzyloxybenzyl chloride (216) (5.0g), potassium cyanide (2.5g), ethanol (50 ml) and water (25 ml) was heated at reflux for 3h. The hot solution was poured onto ice (60g) and extracted with chloroform (3 x 70 ml). The chloroform was dried and evaporated and the residue recrystallised from ethyl acetate/hexane as needles (3.5g, 72%), m.p. 84-85°C (lit.,¹¹⁰ 85-86°C).

δ_{H} (90 MHz; CDCl_3): 3.59 (2H, s, CH_2CN), 4.92 (4H, s, PhCH_2), 6.48 (3H, s, ArH), and 7.28 (10H, s, C_6H_5).

$\nu_{\text{max.}}$ (KBr) 2250 w, 1590 s, and 1160 s cm^{-1} .

Methyl 4-methylsalicylate (220)

4-Methylsalicylic acid (219) (5.0g) in dry methanol (30 ml) was saturated with dry hydrogen chloride gas and the solution refluxed overnight. Upon cooling, the methanol was evaporated off and the semi-solid residue dissolved in ethyl acetate and washed successively with saturated aqueous sodium bicarbonate and brine. The organic solution was dried and evaporated to leave an amber oil which crystallised on standing. This was sublimed in vacuo (160°C/1mm Hg) to afford the ester (220) as white crystals (4.1g, 75%), m.p. 25-26°C (lit.,¹¹⁴ 27-28°C).

δ_{H} (90 MHz; CDCl_3): 2.29 (3H, s, ArCH_3), 3.90 (3H, s, CH_3O), 6.65 (1H, d, \underline{J} 8 Hz, H-5), 6.76 (1H, s, H-3), 7.67 (1H, d, \underline{J} 8 Hz,

H-6), and 10.63 (1H, s, OH).

ν_{\max} . (CHCl₃) 3180 br w, 1670 s, and 1620 m cm⁻¹.

Methyl 2-benzyloxy-4-methylbenzoate (221)

A mixture of methyl 4-methylsalicylate (220) (5.6g), benzyl bromide (4.5 ml), dry potassium iodide (6.2g) and dry potassium carbonate (7.8g) in dry butanone (150 ml) was stirred at reflux overnight. The cooled solution was filtered and the residue washed with ether. The combined organic solutions were evaporated to dryness and the residue dissolved in ether, then washed with 30% sodium hydroxide followed by water. Drying and evaporation yielded an amber oil which afforded the ester (221) as a light yellow oil upon distillation (6.2g, 72%), b.p. 175°C/0.005 mm Hg.

δ_{H} (90 MHz; CDCl₃): 2.27 (3H, s, ArCH₃), 3.82 (3H, s, CH₃O), 5.09 (2H, s, PhCH₂), 6.73 (2H, m, H-3 and H-5), 7.20-7.56 (5H, m, C₆H₅), and 7.70 (1H, d, J 8 Hz, H-6).

ν_{\max} . (CHCl₃) 3025 m, 1720 s, and 1610 s cm⁻¹.

Found: M⁺, 256.1110. C₁₆H₁₆O₃ requires M⁺, 256.1099.

3-(2-Benzyloxy-4-methylphenyl)-2-(3,5-dimethoxyphenyl)-3-oxopropanenitrile (222)

3,5-Dimethoxybenzyl cyanide (67) (1.40g) in dry tetrahydrofuran (30 ml) was added over 10 min to n-butyl lithium (6.40 ml, 2.61M in hexane) in THF (15 ml) at 0°C and under nitrogen. After stirring at 0°C for a further 50 min, methyl 2-benzyloxy-4-methylbenzoate (221) (2.63g) in THF (50 ml) was introduced over 30 min and the solution stirred at reflux for 5h. The cooled solution was added dropwise over

20 min to a saturated solution of ammonium chloride with efficient stirring. The THF was removed in vacuo and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and evaporated to give a brown gum. The β -keto nitrile (222) was obtained as a yellow gum upon column chromatography over silica using 30:70 ethyl acetate:hexane as eluant (1.83g, 58%).

δ_{H} (90 MHz; CDCl_3): 2.30 (3H, s, ArCH_3), 3.66 (6H, s, CH_3O), 5.16 (2H, s, PhCH_2), 5.85 (1H, s, CHCN), 6.34 (3H, s, ArH), 6.79 (2H, m, H-3' and H-5'), 7.39 (5H, br s, C_6H_5), and 7.58 (1H, d, $\underline{\text{J}}$ 8 Hz, H-6').

ν_{max} . (CHCl_3) 3010 m, 2210 w, 1680 m, and 1610 s cm^{-1} .

Found: M^+ , 401.1612. $\text{C}_{25}\text{H}_{23}\text{NO}_4$ requires M^+ , 401.4664.

3-Acetoxy-3-(2-benzyloxy-4-methylphenyl)-2-(3,5-dimethoxyphenyl)-prop-2-enitrile (223)

A solution of the β -keto nitrile (222) (0.51g) in acetic anhydride (10 ml) containing a few crystals of p-toluenesulphonic acid was refluxed for 4h. The reaction mixture was worked-up as outlined for the preparation of the stilbene (70). The crude product was initially purified by column chromatography over silica using 25:75 chloroform:hexane as eluant. Further purification by preparative tlc on silica employing two developments in chloroform afforded a light brown gum consisting of the E- and Z- isomers of the stilbene (223) (0.24g, 43%, E : Z = 1.0 : 1.3 from the ^1H nmr integration of the PhCH_2 resonances).

δ_{H} (200 MHz; CDCl_3): 1.87 (3H, s, $\underline{\text{E}}\text{-CH}_3\text{CO}$), 2.15 (3H, s, $\underline{\text{Z}}\text{-CH}_3\text{CO}$), 2.24 (3H, s, $\underline{\text{Z}}\text{-ArCH}_3$), 2.31 (3H, s, $\underline{\text{E}}\text{-ArCH}_3$), 3.44 (6H, s, $\underline{\text{Z}}\text{-CH}_3\text{O}$), 3.72 (6H, s, $\underline{\text{E}}\text{-CH}_3\text{O}$), 4.82 (2H, s, $\underline{\text{Z}}\text{-PhCH}_2$), 5.08 (2H, s, $\underline{\text{E}}\text{-PhCH}_2$), 6.23 (3H, m, ArH), 6.39 (1H, t, $\underline{\text{J}}$ 2.3 Hz, $\underline{\text{E}}\text{-H}_4$), 6.65 (4H, m, ArH), 6.83 (2H, m, $\underline{\text{E}}\text{-H}_3$, and $\underline{\text{E}}\text{-H}_{5'}$), 7.09 (1H, d, $\underline{\text{J}}$ 7.7 Hz, $\underline{\text{Z}}\text{-H}_{6'}$), 7.18-7.42 (10H, m, C_6H_5), and 7.46 (1H, d, $\underline{\text{J}}$ 7.6 Hz, $\underline{\text{E}}\text{-H}_{6'}$).

ν_{max} . (CHCl_3) 2220 w, 1775 s, and 1600 s cm^{-1} .

λ_{max} . (MeOH) 242 (ϵ 9,000) and 286 nm (10,300).

Found: M^+ , 443.3955. $\text{C}_{27}\text{H}_{25}\text{NO}_5$ requires M^+ , 443.1733.

Equilibration of the E- and Z-isomers of the 2-benzyloxystilbene (223)

A solution of the above stereoisomeric mixture ($\underline{\text{E}} : \underline{\text{Z}} = 1.0 : 1.3$) of the 2-benzyloxystilbene (223) (50 mg) in benzene (3 ml) containing a trace of iodine was irradiated with visible light and heated at gentle reflux for 3 days. Upon cooling, the solution was washed with 20% aqueous sodium thiosulphate, dried and evaporated to afford a brown gum (50 mg). The integration of the PhCH_2O resonances in the 200 MHz ^1H nmr spectrum of this residue showed that the ratio of isomers had changed to $\underline{\text{E}} : \underline{\text{Z}} = 1.4 : 1.0$.

Photocyclisation of the 2-benzyloxystilbene (223)

A solution of the stilbene (223) (0.17g) in redistilled cyclohexane (400 ml) containing iodine (0.11g) was stirred and irradiated for 9h. Washing with 10% aqueous sodium thiosulphate, drying and evaporation of the cyclohexane solution afforded a brown semi-solid residue. Addition of methanol caused crystallisation of a yellow solid which was

identified as the phenanthrene (110) (0.03g, 23%). The spectral characteristics of this phenanthrene are recorded on p.202. ^1H nmr of the residue showed that none of the desired oxidative photocyclisation product (218) was present.

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