SOME ASPECTS OF QUINONOID CHEMISTRY

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DOCTOR OF PHILOSOPHY

by

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C O N T E N T S

SUMMARY

The first part of this thesis deals with the attempts made to synthesise 4 - hydroxypiloquinone.

The proposed synthesis involved the making of two correctly substituted aromatic moieties that could be joined together to give a stilbene, which on irradiation would give a phenanthrene, that could be further elaborated to give a suitable precursor to 4 - hydroxy-piloquinone.

All attempts to convert the precursor to the required quinone were unsuccessful.

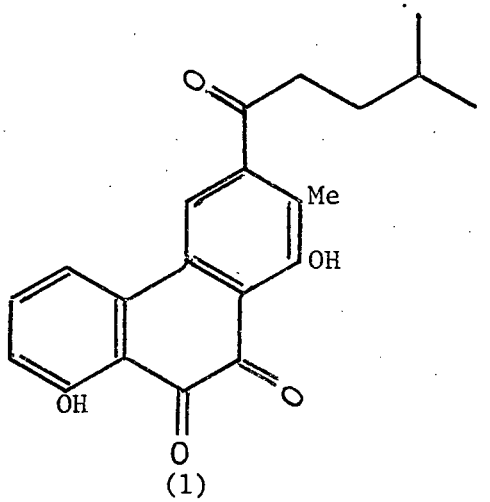
In the second part of this thesis, a number of 2 - acetyl - 3 - alkylamino - 6 - anilino - 1,4 - benzoquinones were prepared by the reaction of 2 - acetyl - 3,6 - dianilino - 1,4 - benzoquinone with alkylamines in chloroform. Irradiation of these alkylamino - p - benzoquinones with ultra-violet light gave benzoxazoles where an α - hydrogen atom was present in the alkylamino substituent, except for the cyclohexylamino - and s - butylamino - benzoquinones which gave an unstable photo-product. With t - butylamino - benzoquinone no photo-reaction was observed.

PART 1

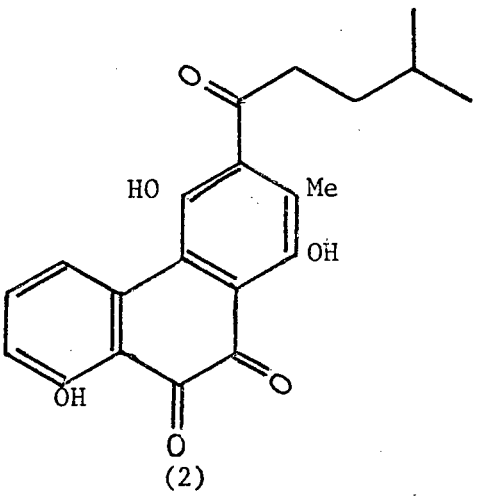
Attempted synthesis of 4 - hydroxy - piloquinone

1.1 Introduction

The occurrence of 9,10 - phenanthraquinones in Nature, unlike the isomeric 9,10 - anthraquinones, is extremely rare. Early reports[1] claiming to have isolated a dihydroxymethyl substituted compound were subsequently shown by synthesis to be incorrect.[2] In 1963 the isolation[3] of piloquinone from the mycelium of *Streptomyces pilosus* Ettlinger led to the structural assignment (1) for the compound, which was subsequently confirmed by synthesis.[4] In 1969, 4 - hydroxypiloquinone (2) was shown[5] to co-occur with piloquinone, and it seemed that an attempt to synthesise this congener of piloquinone would be a worthwhile exercise for two reasons; firstly to confirm the structural assignment, and secondly to verify the carbonyl stretching frequencies recorded by Lounasmaa and Zylber[5] for 4 - hydroxypiloquinone, these frequencies being significantly different from the values found for piloquinone.[3]



(1)

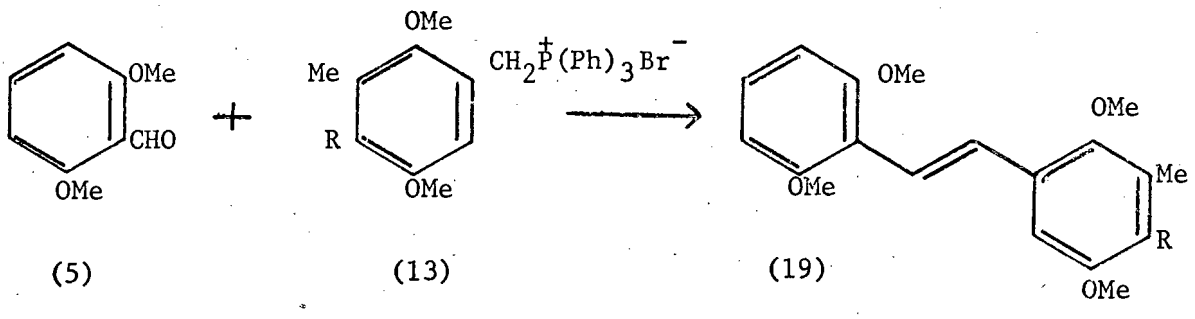


(2)

It was proposed to follow in broad outline the method successfully used in the previous synthesis of piloquinone[4], the main difference in approach being in the preparation of the two aromatic moieties which were to be coupled to give a stilbene suitable for photocyclisation to a phenanthrene which could subsequently be elaborated to give 4 - hydroxypiloquinone (2).

Thus the first part of this work describes the synthesis of *trans* - 4 - bromo - 2,2',5,6' - tetramethoxy - 3 - methylstilbene (19) shown in Scheme 1, and there is subsequently described the efforts to synthesise 4 - hydroxypiloquinone (2).

Scheme 1



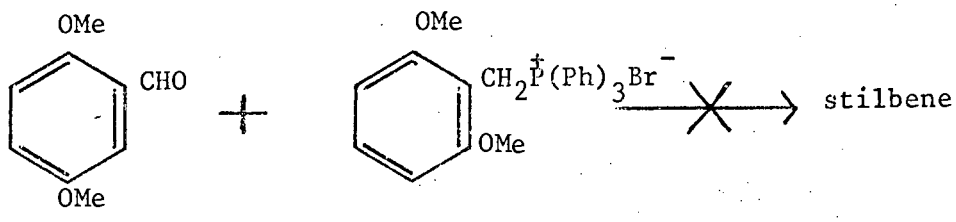
R = Br

The synthesis of the stilbene precursor (13) proved to be an intriguing exercise in aromatic substitution, the placing of the bromine atom in position 4 being much more difficult than was at first anticipated.

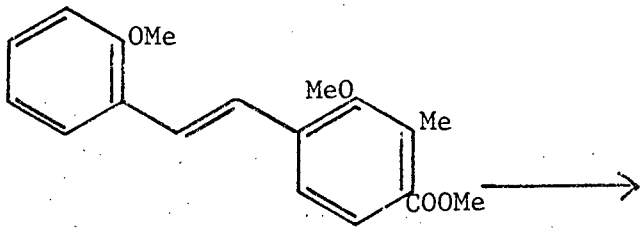
A possible alternative Wittig reaction using 2,6 - dimethoxybenzyltriphenylphosphonium bromide and a suitable

4 - substituted 2,5 - dimethoxy - 3 - methylbenzaldehyde was considered. However a trial reaction as shown in Scheme 2 did not succeed.

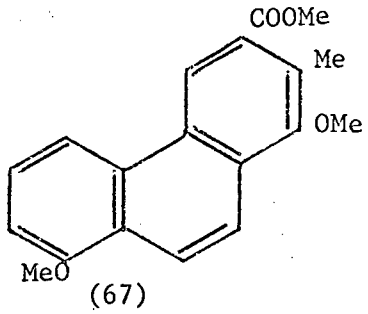
Scheme 2



Another reason for choosing to make a stilbene of the type (19) was because only one phenanthrene could arise on photo-cyclisation by loss of methanol. In the synthesis of piloquinone itself[4], irradiation of the stilbene (66) gave a mixture of products (67) and (68), this process being rather wasteful of starting material.

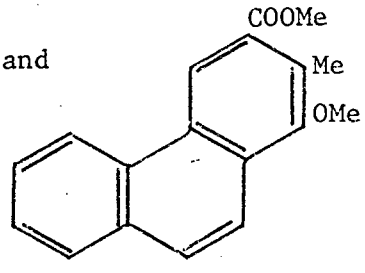


(66)



(67)

and



(68)

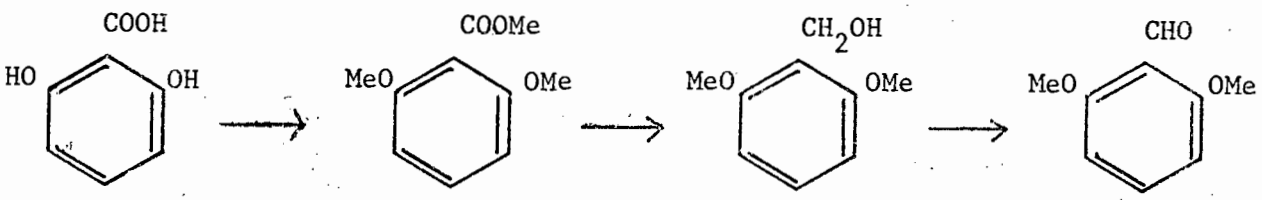
A trial irradiation of the stilbene (19) (R=Br) showed that a phenanthrene was not formed in this process, and because it had been previously reported that ring closure did not occur with acylstilbenes[9], a considerable amount of experimental work was performed in order to find a suitable way of converting the bromo -stilbene (19) into the stilbene ester (43) as shown in Scheme 15.

From this stage onwards the synthesis proceeded smoothly along the route used by Sargent et al[4] until the penultimate step when it was found that an acetyl group protecting the hydroxyl at the 4- position of 4 - hydroxypiloquinone could not be removed by conventional methods of hydrolysis.

Rather than using all the available material in attempts at hydrolysis of the acetoxy group which were not certain to bring success, another possible route to 4 - hydroxypiloquinone was investigated. This method also proved promising until the final step which gave products other than 4 - hydroxypiloquinone.

1.2 Synthesis of the stilbene precursors 2,6 - dimethoxybenzaldehyde (5) and 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyltriphenylphosphonium bromide (13).

The aldehyde (5) was prepared from 2,6 - dihydroxybenzoic acid by a literature process[6] as shown below.



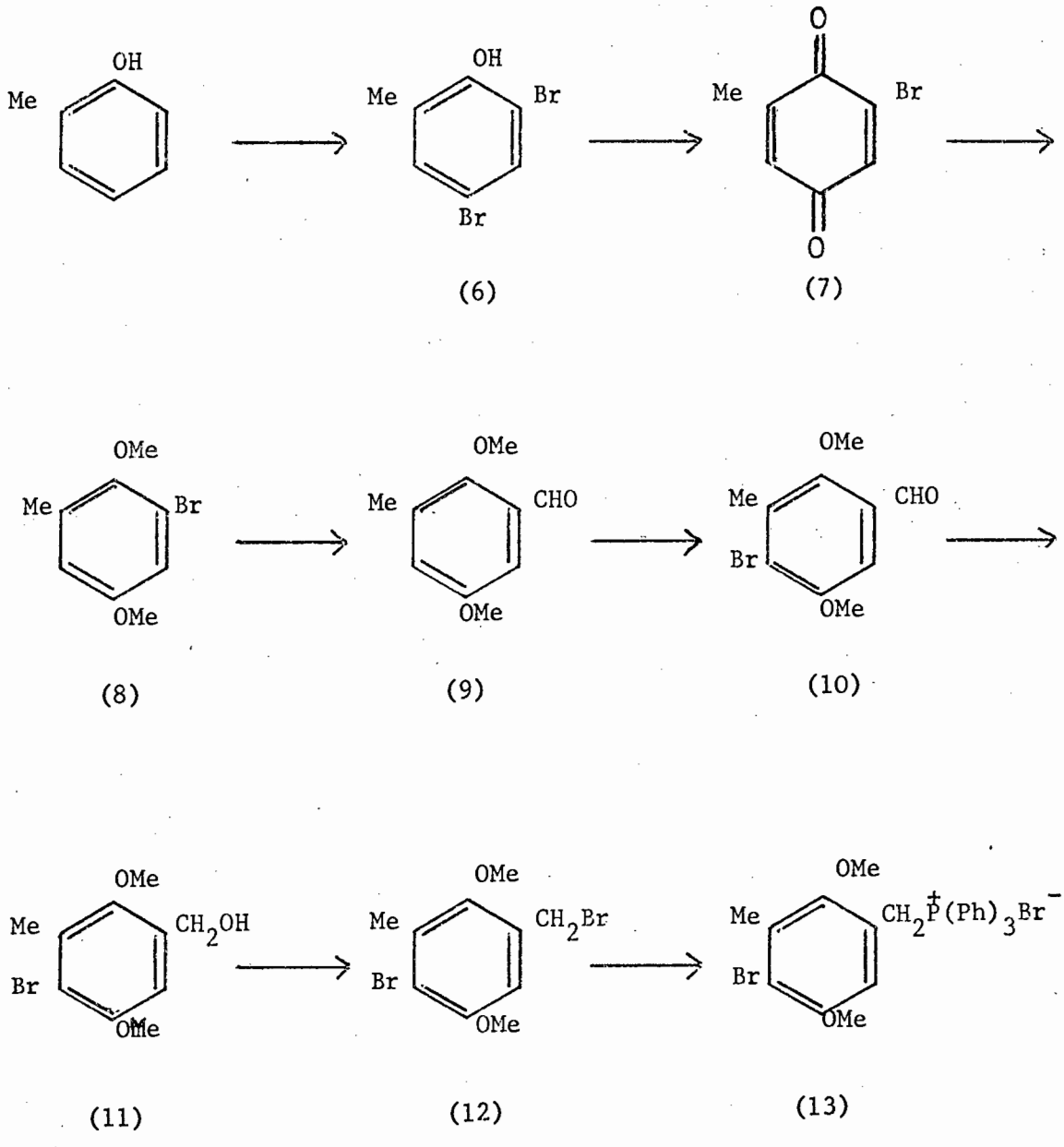
(3) (4) (5)

It is interesting to note that all the steps in the above reaction sequence were more difficult to perform than was the case for the conversion of 2,5 - dihydroxybenzoic acid to 2,5 - dimethoxybenzaldehyde, one of the reactants used in Scheme 2.

It seems likely that the difficulties encountered were either wholly steric in origin, or that for the first two steps in the sequence shown above, there was greater scope for intramolecular hydrogen bonding than was the case with the analagous reactions required to convert 2,5 - dihydroxybenzoic acid to 2,5 - dimethoxybenzyl alcohol.

The synthesis of the other key intermediate, the phosphonium salt (13) proved to be an interesting exercise in aromatic substitution. The method originally proposed for synthesising the compound (13) is shown in Scheme 3 overleaf.

Scheme 3

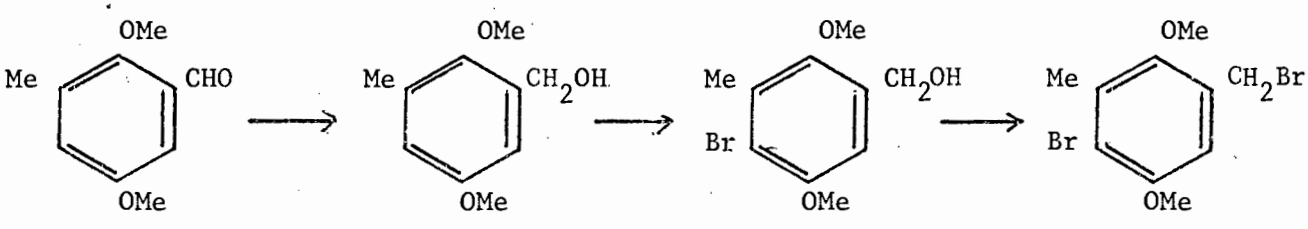

OH
Me
OH
Me
Br
Br
O
Me
Br
O
(6)
(7)
OMe
Me
Br
OMe
OMe
Me
CHO
OMe
OMe
Me
CHO
Br
OMe
(8)
(9)
(10)
OMe
Me
CH2OH
Br
OMe
OMe
Me
CH2Br
Br
OMe
OMe
Me
CH2P(Ph)3Br
Br
OMe
(11)
(12)
(13)

2,5 - Dimethoxy - 3 - methylbromobenzene (8) was prepared from o-cresol by first preparing 2 - bromo - 6 - methyl - 1,4 - benzoquinone by a literature process[7], reducing the quinone with sodium hydrosulphite to the quinol, followed by O-methylation using dimethyl sulphate and sodium hydroxide in ethanol[8]. Compound (8) was then converted using phenyl lithium and dimethyl formamide[9] to the aldehyde (9) in rather variable yields. The variation in yield was probably due to inexperience in the preparation and handling of phenyl lithium.

Bromination of 2,5 - dimethoxy - 3 - methylbenzaldehyde (9) with bromine in acetic acid gave a mixture of 4 - and 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzadehydes in approximately equal proportions as indicated by ^{1}Hn.m.r. spectroscopy. Bromination at this stage therefore did not appear to be an attractive method of obtaining the desired 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzaldehyde (10), and Scheme 3 was abandoned.

Consideration was then given to the possibility that compound (14) as shown in Scheme 4, would brominate and give a favourable ratio of the desired 4 - bromo substituted compound (11).

Scheme 4

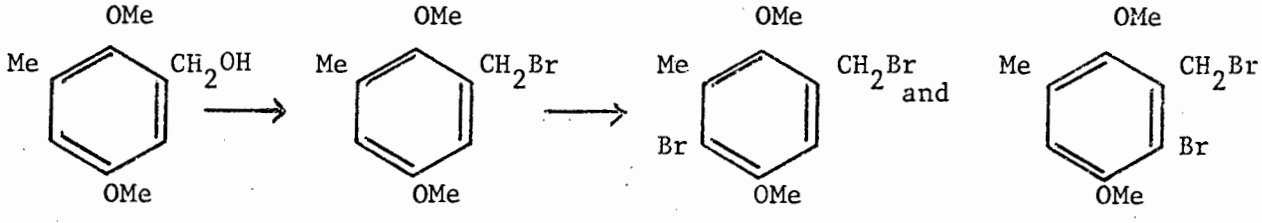


(9) (14) (11) (12)

The aldehyde (9) was reduced using lithium aluminium hydride in dry tetrahydrofuran to give 2,5 - dimethoxy - 3 - methylbenzyl alcohol (14) which was then treated with bromine in acetic acid to give directly a mixture of 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (12) and 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (16) in the ratio of 1 : 4. The two compounds were separated with extreme difficulty by column chromatography, and structures were assigned to them on the basis of their ^{1}Hn.m.r. spectral data.

It was apparent that the hydrogen bromide liberated in the electrophilic substitution at the ring positions 4 and 6, had in turn effected the substitution of the benzylic hydroxyl by bromine and it was therefore anticipated that the same two products (12) and (16) could be prepared as shown in Scheme 5.

Scheme 5



(14) (15) (12) (16)

It was hoped that prior introduction of the relatively large bromine atom at the benzylic position, as in Scheme 5, might favour electrophilic bromination at the 4 - position. In practice the bromine atom was not large enough to influence selectivity and on performing reaction (15) $\longrightarrow$ (12) plus (16) the ratio of the 4 - bromo to the 6 - bromo compounds obtained

proved to be the same as that for the previous attempt, namely about 1 : 4.

At this stage, therefore, the desired compound (12) was available in poor yield, but it had yet to be demonstrated by an unequivocal method that the structure assigned on the basis of ^{1}Hn.m.r. spectroscopy to compound (12) was in fact correct.

It is of interest to note the argument that was used to assign structures to compounds (12) and (16).

The ^{1}Hn.m.r. spectra (Figs. I,II and III) are those of (a) the mixture of dibromo compounds (12) and (16), (b) pure 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (12) and (c) pure 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (16).

Considering the methyl and methylene proton signals for (a), (b) and (c), it was argued that because of the positions of the ring bromine atoms relative to the above groups in each of the compounds (12) and (16), the methyl proton signal for (b) would be at lower field than for (c), and the methylene proton signal for (b) would be at higher field than for (c).

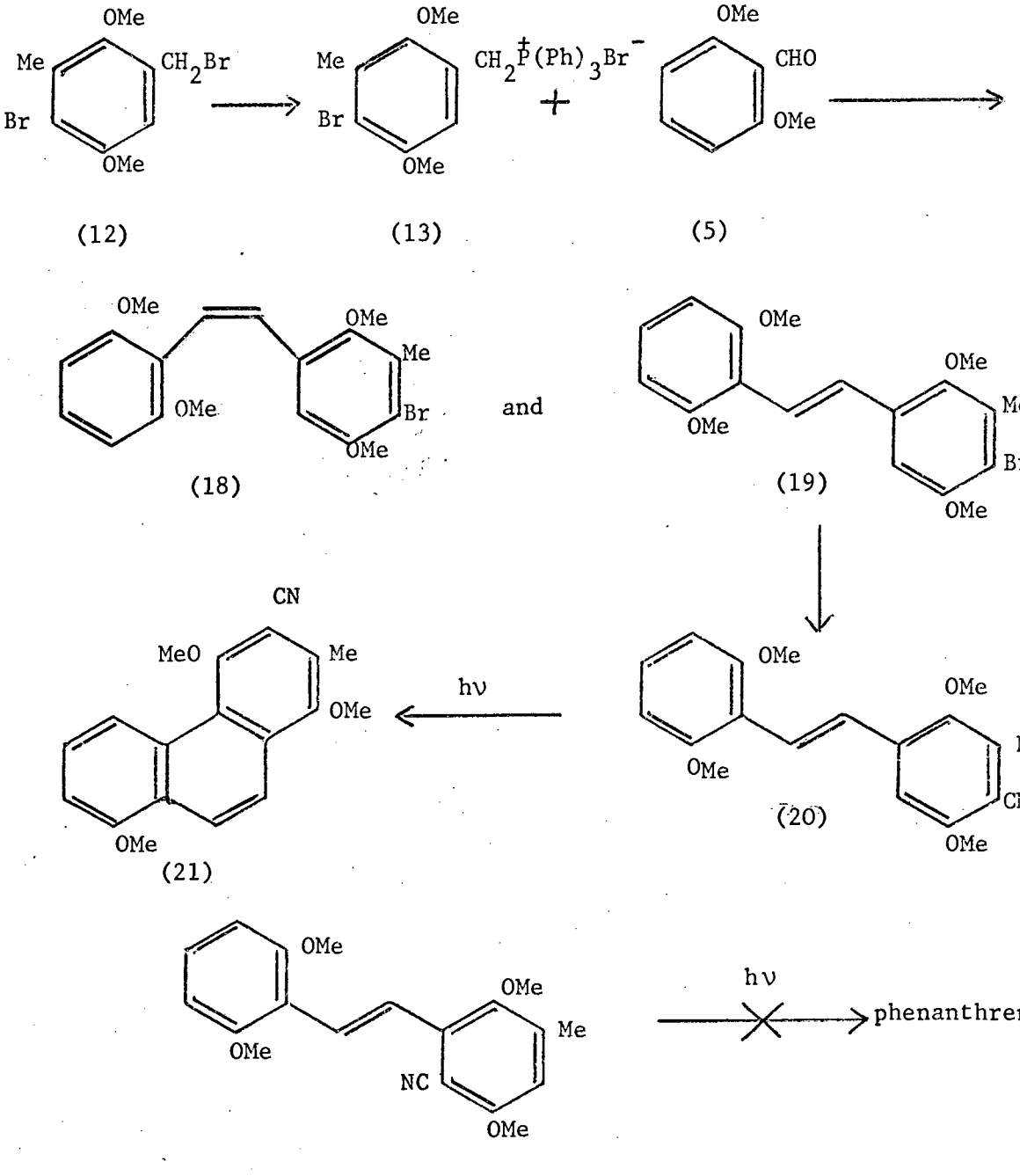
For the aromatic proton signals, it is possible that in (b) there is either a through space or an inductive effect by the benzylic bromine atom on the proton at position 6, thus making the aromatic proton signal in (b) appear at lower field than in (c). (See Appendix on Page 102 for ^{13}Cn.m.r. spectra of (12) and (16).

The structural assignments for (12) and (16) having been made on the basis of the foregoing arguments, it remained to demonstrate the correctness of the choice of isomer by making a suitable stilbene, and subjecting it to photolysis to give a

phenanthrene, cyclisation with loss of methanol would confirm the assignment. Failure to do so would be negative evidence against the assignment.

Pure compound (12) was reacted with triphenylphosphine to give the phosphonium salt (13) which was then treated as shown in Scheme 6.

Scheme 6



Addition of the calculated amount of lithium methoxide to a solution of the phosphonium salt (13) and the aldehyde (5) in methanol gave a mixture of the *cis* - and *trans* - bromostilbenes (18) and (19) in the ratio of 1 : 4. Recrystallisation from petroleum ether gave the pure *trans* - bromostilbene (19) [J16Hz for *trans* HC=CH].

The *trans* - bromostilbene (19) was then converted to the *trans* - cyanostilbene (20) by heating (~ 155°C) overnight with copper (I) cyanide in dimethyl formamide. The ^{1}Hn.m.r. spectrum showed that there had been no isomerisation despite the prolonged heating of the stilbene.

Finally photolysis of the *trans* - cyanostilbene (20) was carried out, by irradiating a cyclohexane solution of the above for 12 hours through quartz using a Vycor sleeve.

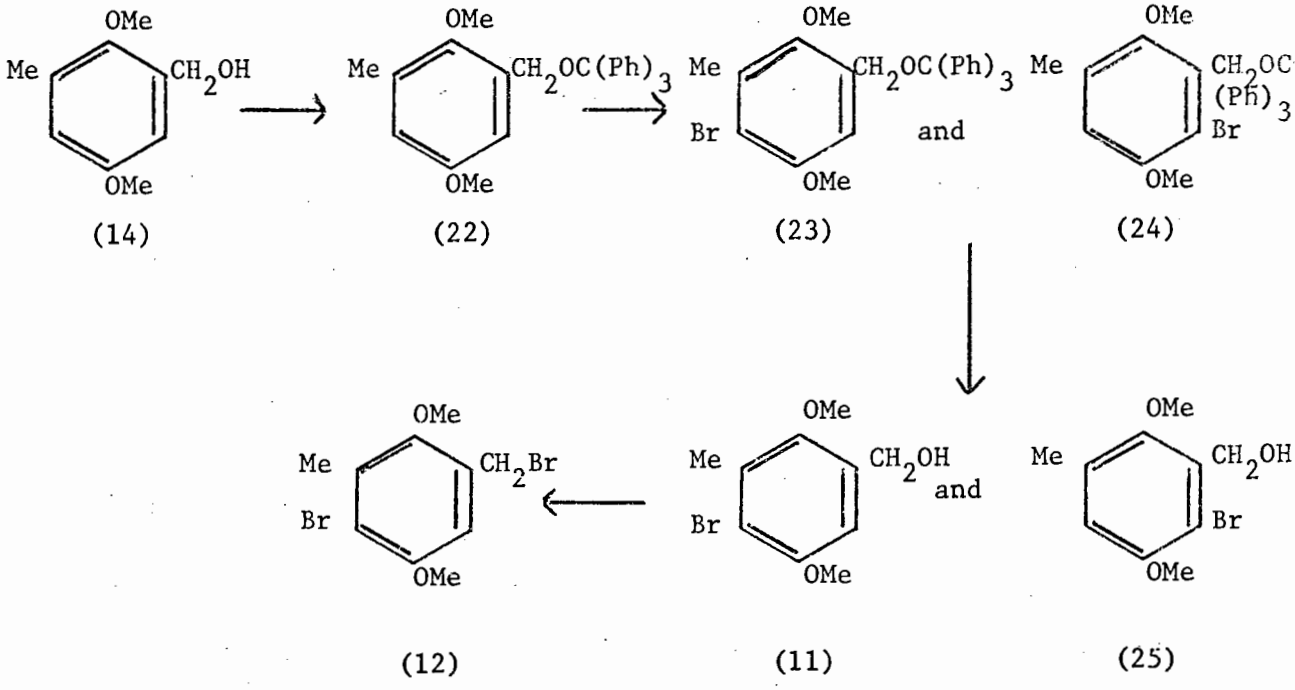
The cyanophenanthrene (21) was isolated in 40% yield by column chromatography from the photolysis reaction, thus indicating the structural assignment given to compound (12) from the ^{1}Hn.m.r. spectra.

The phenanthrene (21), and all the 4 - substituted phenanthrenes synthesised subsequently, displayed a low field doublet (approximately τ0,8 to τ1,5) in their ^{1}Hn.m.r. spectra. This signal was assigned to the proton at position 5, since it is known that the resonances from some of the protons in angularly condensed polycyclic compounds are abnormally deshielded.[10]

It is now clear that the yield of the desired dibromo compound (12) would have to be improved if the proposed method of synthesis of 4 - hydroxypiloquinone was to succeed, and efforts were accordingly concentrated on solving this problem.

Because the reaction of the substituted benzyl bromide (15) had failed to give a more favourable ratio of the desired isomer (12) to the unwanted isomer (16), it was considered necessary to introduce a very large group into the side chain at position 1 (the benzylic position), so that the relatively large bromine molecule would be forced to favour electrophilic substitution at position 4 of the benzene ring. Another consideration was that the large group in the side chain should be easy to remove, and bearing these requirements in mind, the trityl group was chosen for this purpose as shown in Scheme 7.

Scheme 7

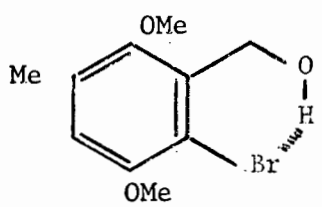


Tritylation of compound (14) using chlorotriphenylmethane in dry pyridine proceeded smoothly giving a product (22), which showed two relatively high field aromatic doublets at τ2,94 and 3,36.

On bromination of the trityl either (22) with one equivalent of bromine in dichloromethane, a mixture of two new brominated compounds (23) and (24) was obtained, each of which showed a high field aromatic singlet at τ2,96 and 3,31 respectively. While it was possible to separate the two compounds by column chromatography, it was found to be much easier to perform this operation on the alcohols (11) and (25) obtained by heating the mixture of ethers under reflux with 80% acetic acid for 10 minutes.

The desired product, 4 - bromo - 2,5 - dimethoxy - 3 methylbenzyl alcohol (11), was easily separated from its isomer (25), first by fractional crystallisation from light petroleum ether to afford the desired crystalline isomer (11), followed by column chromatography of the mother liquors.

A possible reason for the fact that isomer (11) crystallises preferentially from light petroleum ether and also has a lower R_f than isomer (25), is that intramolecular hydrogen bonding involving bromine may well exist in isomer (25) as shown, which is not possible for the desired isomer (11).

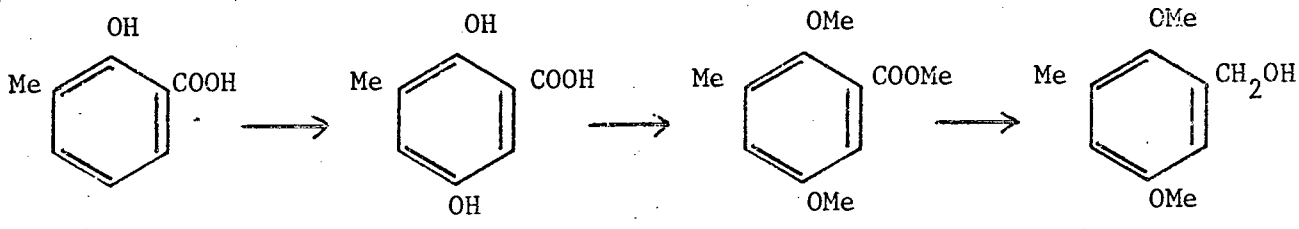


(25)

The method shown in Scheme 7 gave a mixture of alcohols in which the ratio of the desired alcohol (11) to the unwanted isomer (25) was 4 : 1, and treatment of the alcohol (11) with phosphorous tribromide in dry benzene gave 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (12) in workable quantity for the first time.

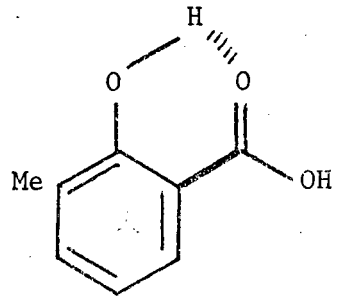
It had become necessary to make some more of the alcohol (14) and because of the rather variable results obtained in the method initially used to synthesise this compound, a new, shorter and more reliable route was used as shown in Scheme 8.

Scheme 8



(26) (27) (28) (14)

Hydroxylation of the starting material was carried out by Still's method[11], the yield being improved by the use of more ammonium peroxodisulphate than was used in the original method. Another modification was the use of light petroleum ether to remove the unchanged starting material (26) from the product (27). The greater solubility of the starting material (26) in petroleum ether is explained once again by the possibility of intramolecular hydrogen bonding in the starting material (26) making it less polar than the product (27).



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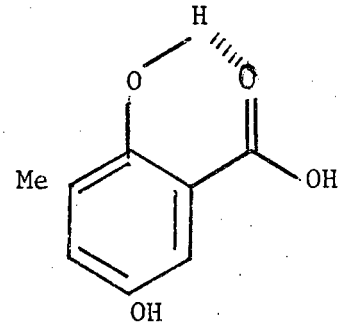


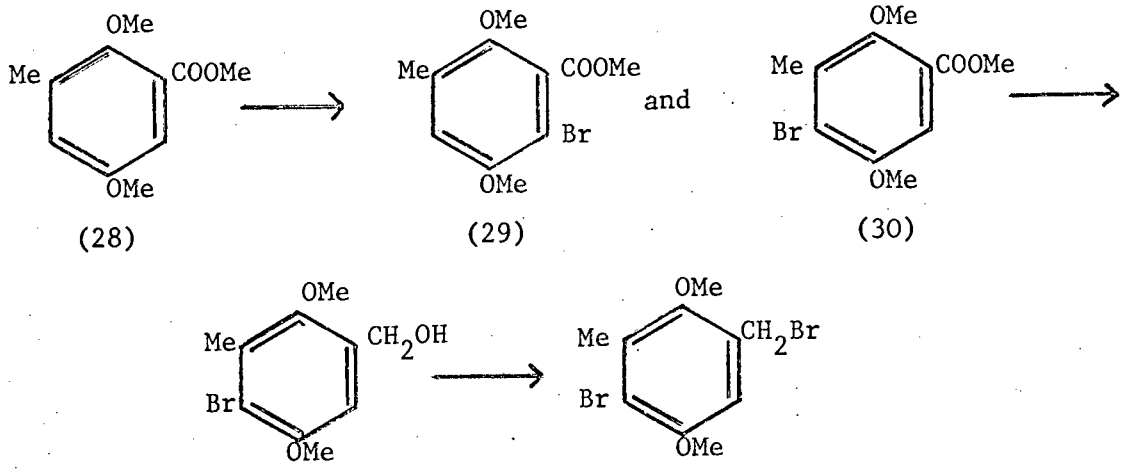
(27)

Methylation of the dihydroxy acid (27) using dimethyl sulphate and potassium carbonate in acetone had to be carried on for a prolonged period for the reaction to go to completion. The addition of a few millilitres of 10% methanolic potassium hydroxide[12] reduced reaction time from 20 hours to 5 hours.

In an early attempt at the methylation reaction some di-methylated material was obtained pure, and this was assigned the structure methyl - 2 - hydroxy - 5 - methoxy - 3 - methylbenzoate, by comparison with the reported ^{1}Hn.m.r. details of the authentic material.[13]

The compound methyl - 2,5 - dimethoxy - 3 - methylbenzoate (28) offered an alternative route to the dibromo compound (12) as shown in Scheme 9. It was hoped that the methyl ester group at position 1 might just be large enough to favourably influence the selectivity of the electrophile in the bromination reaction.

Scheme 9



Accordingly compound (28) was brominated using (a) bromine in acetic acid and (b) pyridinium hydrobromide perbromide in acetic acid. Both of these reagents gave a mixture of compounds (29) and (30) as indicated by ^{1}Hn.m.r. spectra, which showed, *inter alia*, two aromatic singlets at τ 3,24 and 3,07 in the ratio of 4 : 1 respectively. The proton with the lower chemical shift would be *ortho* to the ester function, and therefore could be assigned to the desired bromo ester (30).

In order to confirm the assignment of structures given to compounds (29) and (30), the more abundant isomer (29) was separated by chromatography, reduced using lithium aluminium hydride in dry tetrahydrofuran to give a benzyl alcohol, and this was then treated with phosphorous tribromide in dry benzene to give a product which had a ^{1}Hn.m.r. spectrum that was the same as that of 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (16). This showed that the method proposed in Scheme 9 was not suitable for synthesising compound (12).

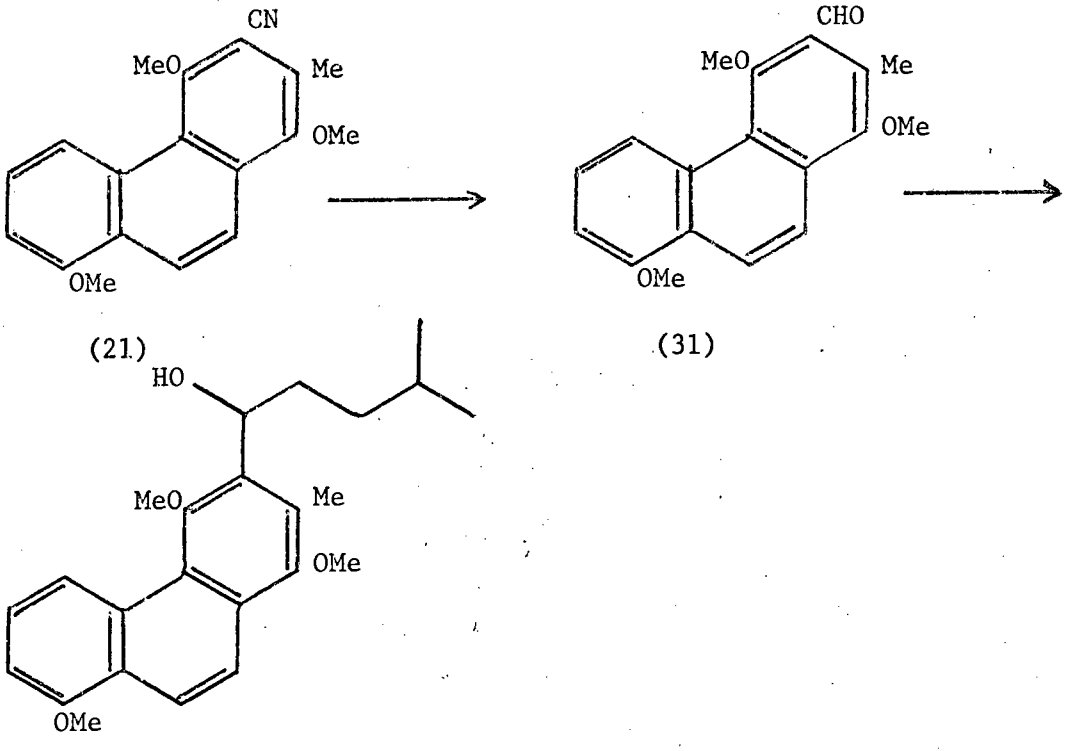
However by using the synthetic routes set out in Schemes 8 and 7 respectively, it had become possible to produce the phosphonium salt (13) fairly readily, in quantities sufficient to continue with the synthesis of 4 - hydroxypiloquinone (2).

1.3 Efforts to synthesise a phenanthrene to which the side chain of 4 - hydroxypiloquinone could be attached.

There appeared to be two possibilities. Either some suitable modification of 4 - bromo or 4 - cyano - 2,2′,5,6′ - tetramethoxy - 3 - methylstilbene (compounds (19) and 20)), followed by photocyclisation or simply modification of 3 - cyano - 1,4,8 - trimethoxy - 2 - methyl-phenanthrene (21) could be effected in order to facilitate attachment of a suitable side chain at position 3 of the phenanthrene molecule.

The latter possibility seemed more attractive because it involved fewer steps and consequently early efforts were concentrated on the possibility of converting the 3 - cyano group of the phenanthrene to either an aldehyde directly or to an ester which in turn could be converted to an aldehyde in order that the side chain could be attached as shown in Scheme 10; the direct conversion to an aldehyde, if this were possible, would have distinct advantages over the other method mentioned above.

Scheme 10



Ultimately suitable modification of the stilbene (19) was found to be the best approach to the problem of synthesising compound (31), but initially experiments were carried out to ascertain whether modification of the phenanthrene nitrile (21) would be a convenient way of achieving the synthetic goal.

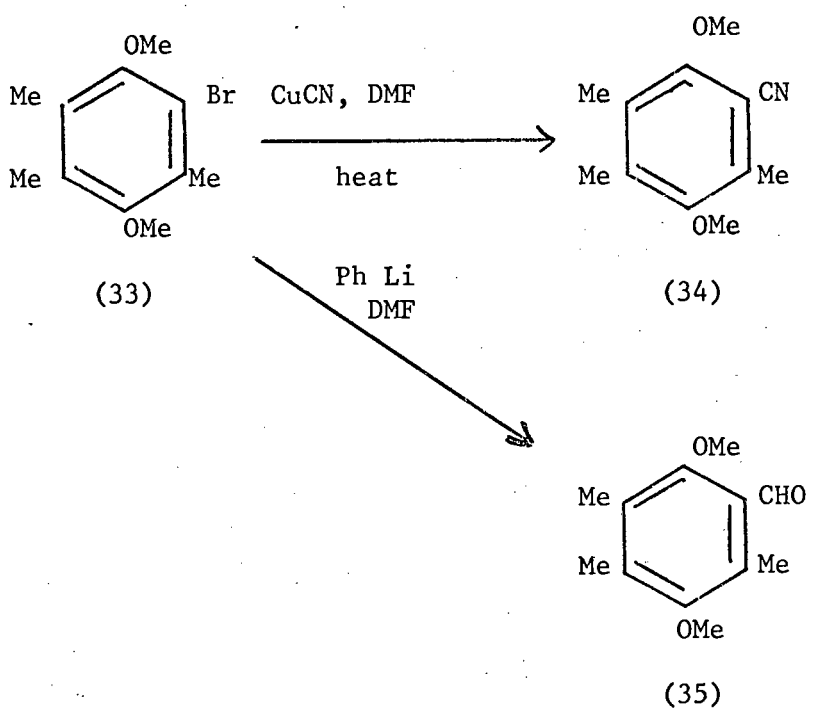
In order to conserve the small quantity of phenanthrene (21) that was available, a model compound, namely, 2,5 - dimethoxy - 3,4,6 - trimethylbromobenzene (33) was used in all the trial reactions carried out to see if it was possible to synthesise compound (31) from a phenanthrene precursor.

Compound (33) was obtained from 2,3,5 - trimethylhydroquinone in a two step process involving bromination of the hydroquinone with bromine in acetic acid followed by

O-methylation using dimethyl sulphate and potassium carbonate in acetone. At the bromination stage the product initially obtained was dark in colour. This dark material had to be reduced with dithionite to afford a white crystalline material before methylation was carried out to give the product (33).

To start off with two reactions were carried out on compound (33) as shown in Scheme 11.

Scheme 11



(33) (34) (35)

The benzonitrile (34) was readily prepared in good yield from the substituted bromobenzene (33), whilst on the other hand reaction of this compound with phenylithium and dimethylformamide gave only a poor yield of 2,5 - dimethoxy - 3,4,6 - trimethyl-benzaldehyde (35).

As a consequence of this finding, initial efforts were concentrated on compound (34), the idea being to convert the nitrile to an acid which could then be converted to an aldehyde by a series of reactions, or better still, to convert the nitrile directly to the aldehyde (35).

The nitrile (34) was boiled for three days with aqueous potassium hydroxide to which some ethanol had been added, and 2,5 - dimethoxy - 3,4,6 - trimethylbenzamide was obtained. All efforts at further hydrolysis using acid or base failed to give the desired substituted benzoic acid.

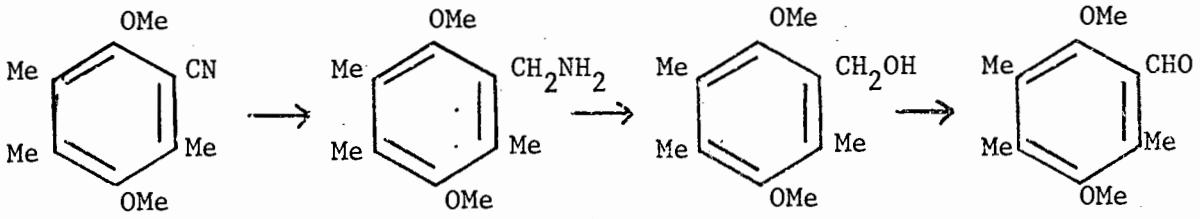
In an effort to overcome this difficulty the substituted benzamide was treated with sodium nitrite and sulphuric acid in the cold, and finally warmed at 60°C until gas evolution ceased. It was not clear what the product of this reaction was. The infra red spectrum had peaks at ν_{max} (Nujol) 3400 and 1670 cm^{-1} indicating that it might be an acid, whilst the ^{1}Hn.m.r. spectrum showed a very broad signal at τ1,5, and no signal below τ zero. This latter observation was not unequivocal evidence for the presence of an acid proton in the molecule. In order to resolve the dilemma the suspected acid was treated with diazomethane in dry ether to hopefully give the ester methyl-2,5 - dimethoxy - 3,4,6 - trimethylbenzoate. Yields were poor

and the method tedious so this approach to the problem was abandoned.

An attempt was made to convert the nitrile (34) directly to the aldehyde (35) using diisobutylaluminium hydride.[14] This reaction was a failure possibly because of the crowded nature of the nitrile (34).

Another indirect method of preparing the aldehyde (35) was tried as shown in Scheme 12.

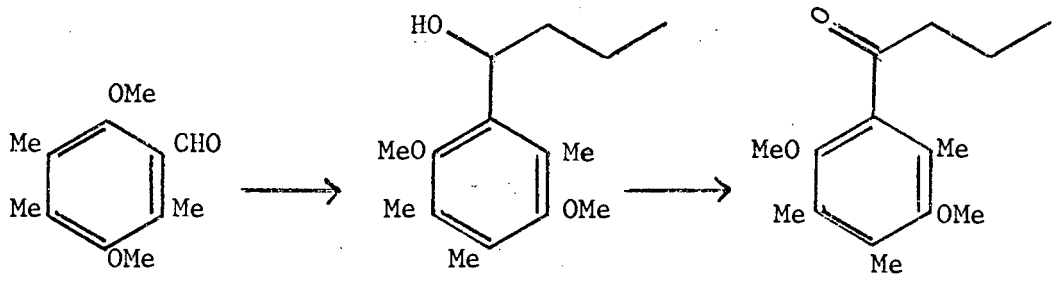
Scheme 12



Reduction of the nitrile (34) to the substituted benzylamine (36) took place readily giving about 60% yield. Likewise the diazotisation and subsequent decomposition of the diazonium salt was an easy reaction but after chromatography the yield of the benzyl alcohol (37) was less than 50%. Oxidation with manganese(IV)oxideproved difficult, heating for a prolonged period with a large excess of reagent was required to produce the required aldehyde (35) in about 70% yield. Thus with an overall yield of about 20%, this method was not considered to be a good way to produce the desired aldehyde (35).

The small quantities of the aldehyde (35) obtained by the methods shown in Schemes 11 and 12 were combined and a trial experiment (Scheme 13) was conducted to see if a side chain could be introduced on to the molecule.

Scheme 13.



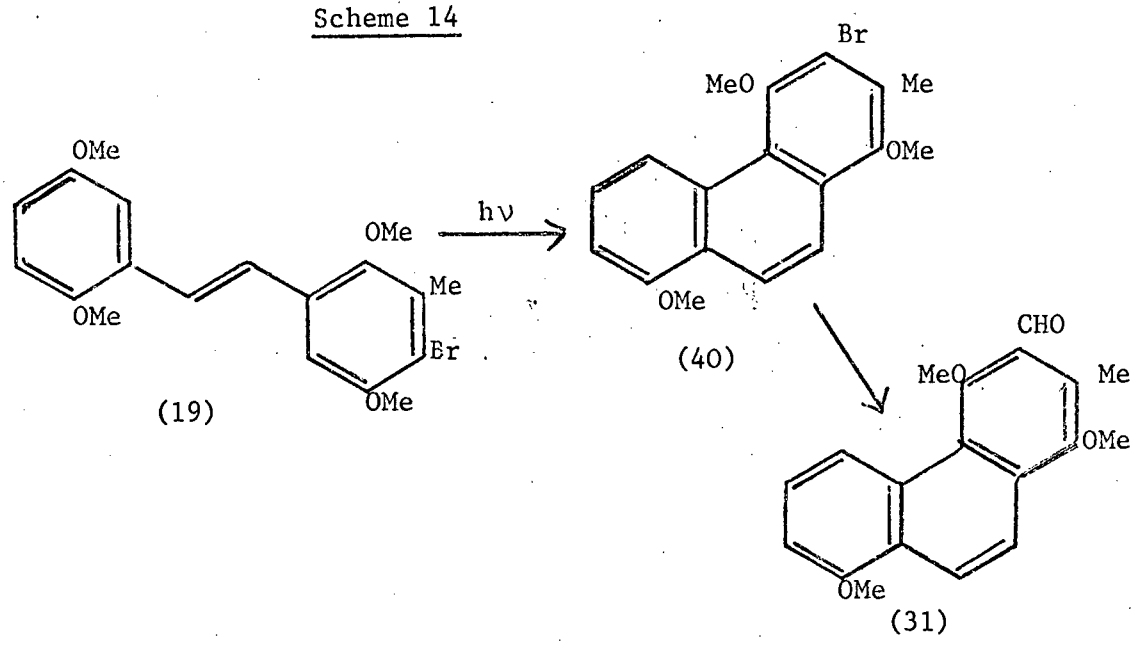
(35) (38) (39)

Both the Grignard reaction and the subsequent Jones oxidation proceeded smoothly showing that it would indeed be possible to attach a side chain to the phenanthrene aldehyde (31) and subsequently oxidise it to give a keto side chain.

Finally the aldehyde (35) was made easily and in excellent yield (97%), by treating the bromo compound (33) with butyl lithium in dry diethyl ether and then adding dimethylformamide. Butyl lithium had worked much better than phenyl lithium in this application to a substituted *ortho* - methoxy halobenzene.[15]

However, if this reaction was to be of synthetic value, it meant that the very elegant reaction sequence shown in Scheme 14 would have to be followed to obtain the phenanthrene aldehyde (31).

Scheme 14



(19) (40) (31)

Photolysis of the stilbene (19) was carried out and the crude product chromatographed to give two compounds neither of which was the desired bromophenanthrene (40). These compounds were not further investigated.

It therefore became clear that the problem of having a suitable group on the phenanthrene molecule to which the desired side chain could be attached, would have to be solved in some other way.

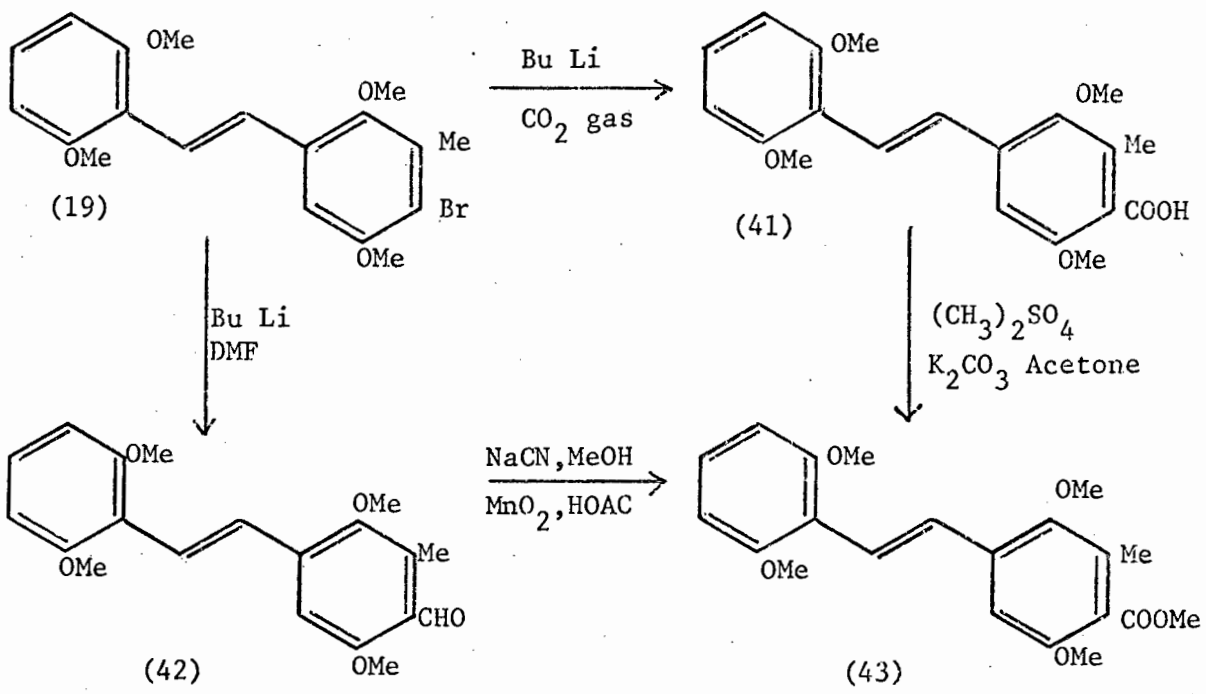
The search for a synthetic route that would successfully give the phenanthrene aldehyde (31) then reverted to the bromostilbene (19), and the quite considerable effort put into this part of the research project eventually led to the synthesis of methyl - 1,4,8 - trimethoxy - 2 - methylphenanthrene - 3 - carboxylate (46) from which the phenanthrene aldehyde (31) could be obtained.

In order to obtain the phenanthrene ester (46) it would be necessary to first prepare a stilbene ester (43) and then

photocyclise that compound. From the trial experiments with the nitrile (34) it was known that the crowded cyano group could not be hydrolysed to give an acid so obviously a new approach to the conversion of the bromostilbene (19) to a stilbene ester (43) was needed.

After an initial failure to synthesise the stilbene acid (41) using phenyl lithium and carbon dioxide gas with the bromostilbene (19) as starting material, the stilbene ester was successfully synthesised by both methods shown in Scheme 15.

Scheme 15



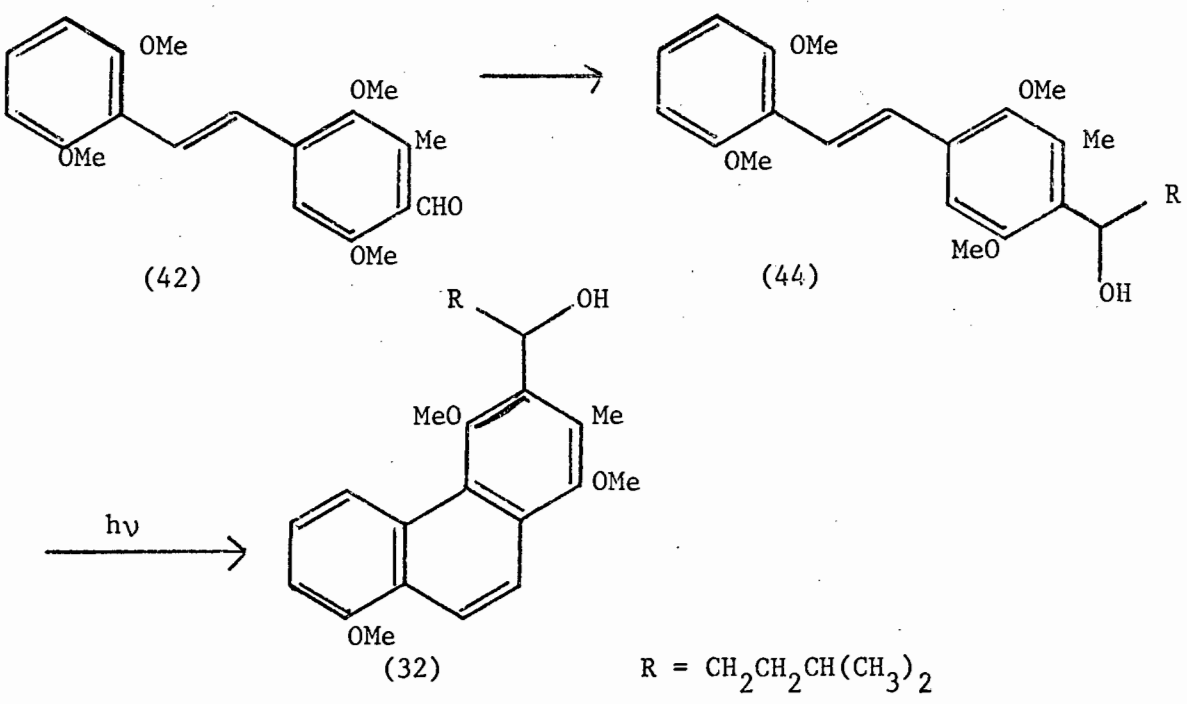
The reaction involving butyl lithium and carbon dioxide gas gave rather variable yields of the stilbene acid (41), and it was subsequently learnt that the use of solid carbon dioxide in place of the gas gives superior results.

A direct photocyclisation of the stilbene aldehyde (42) to give 3 - formyl - 1,4,8 - trimethoxy - 2 - methylphenanthrene (31) at this stage, was not attempted, because it had been previously reported that ring closure did not occur with acylstilbenes[9], but a subsequent report of the photocyclisation of formyl stilbenes to give the corresponding phenanthrenes[16], led to a reappraisal of this reaction, the results being shown in the appendix on Page 88.

In order to avoid wastage of the starting material (19) the alternative method shown in Scheme 15 was used to convert the bromostilbene (19), via the stilbene aldehyde (42) to the stilbene ester (43), both reactions going in good yield. The use of sodium cyanide and manganese (IV) oxide in the presence of methanol to convert the aldehyde (42) to the ester (43), is an adaption of the method of Corey[19] which he used to oxidise allylic and benzylic alcohols to the corresponding esters.

A possible short cut in the synthetic route was investigated at this juncture. If the reaction sequence shown in Scheme 16 was successful, two steps in the method eventually used would have been eliminated.

Scheme 16

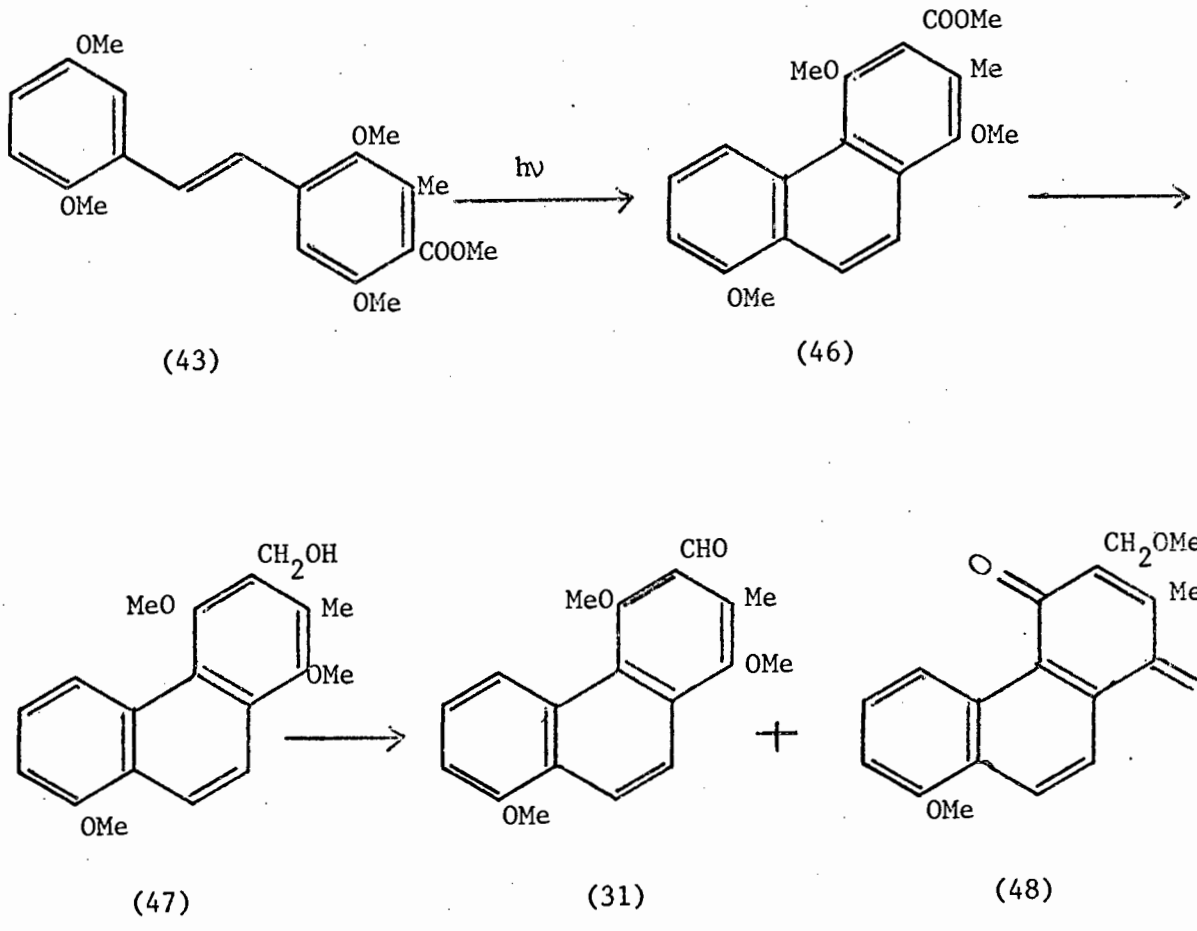


R = $CH_2CH_2CH(CH_3)_2$

The Grignard reaction worked well, 3 - methyl - 1 - bromobutane being used for the first time to give the correct side chain precursor in compound (44). However photolysis of this compound did not give the hoped for phenanthrene (32) so attention was turned to the stilbene ester (43).

The ester (43) dissolved in cyclohexane was irradiated with u.v. light through quartz with a Vycor sleeve for $2\frac{3}{4}$ hours. After removal of the solvent the phenanthrene ester (46) was obtained in 43% yield by column chromatography. This ester was reduced with lithium aluminium hydride in dry tetrahydrofuran to give the alcohol (47) which in turn was oxidised with manganese (IV) oxide in chloroform to the phenanthrene aldehyde (31) as shown in Scheme 17.

Scheme 17



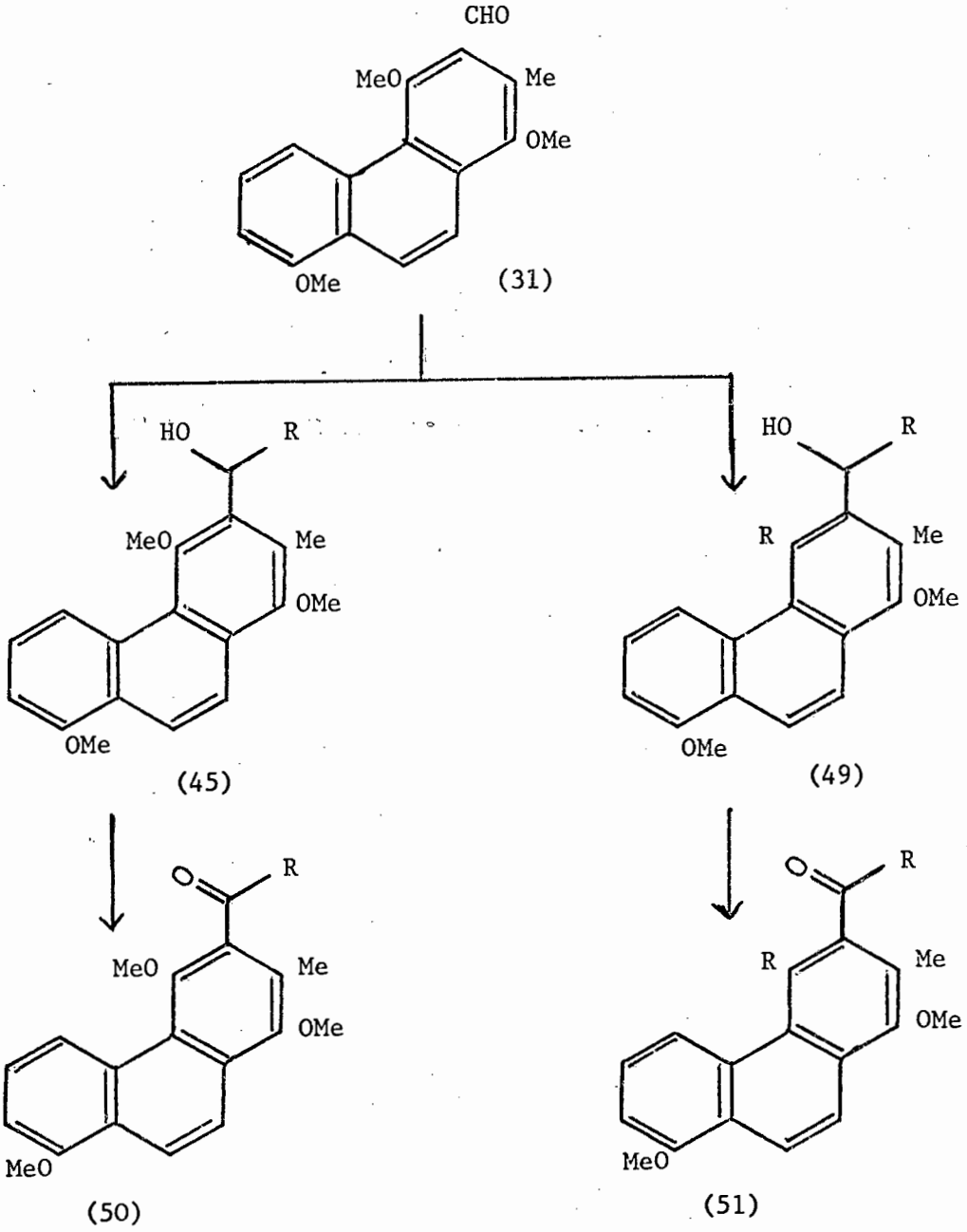
(43) (46) (47) (31) (48)

Oxidation of the phenanthrene alcohol (47) proved difficult, requiring prolonged heating under reflux with a large excess of manganese(IV)oxide. Column chromatography of the crude reaction product gave the red quinone (48) (2% yield) as well as the desired phenanthrene aldehyde (31). The origin of the quinone (48) was not investigated.

1.4 The proposed completion of the synthesis.

The key intermediate 1,4,8 - trimethoxy - 2 - methyl - 3 - (4 methylpentanoyl) phenanthrene (50) was then prepared from the aldehyde (31) as shown in Scheme 18.

Scheme 18



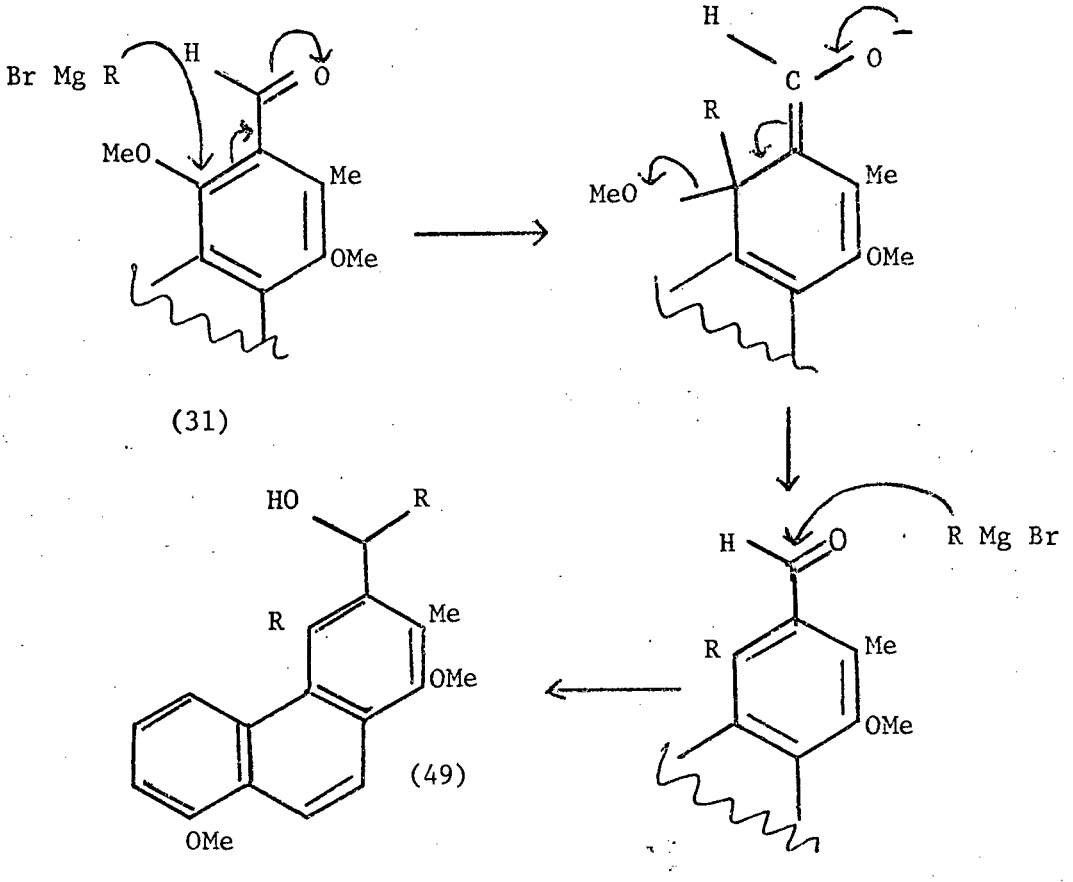
R = $CH_2CH_2CH(CH_3)_2$

The first time the ketophenanthrene (50) was prepared, the Jones oxidation (45) ⟶ (50) was performed on the crude product of the Grignard reaction and in addition to the desired product (50), the dialkylated species (51) was also collected when the crude was purified by column chromatography.

In a subsequent preparation, the two alcohols (45) and (49) were separated after being synthesised by the Grignard reaction in yields of 61% and 22% respectively. In this case the oxidation of the pure phenanthrene alcohol (45) went in 77% yield.

It is thought that the dialkylated by-product (49) was formed as follows :

Scheme 19

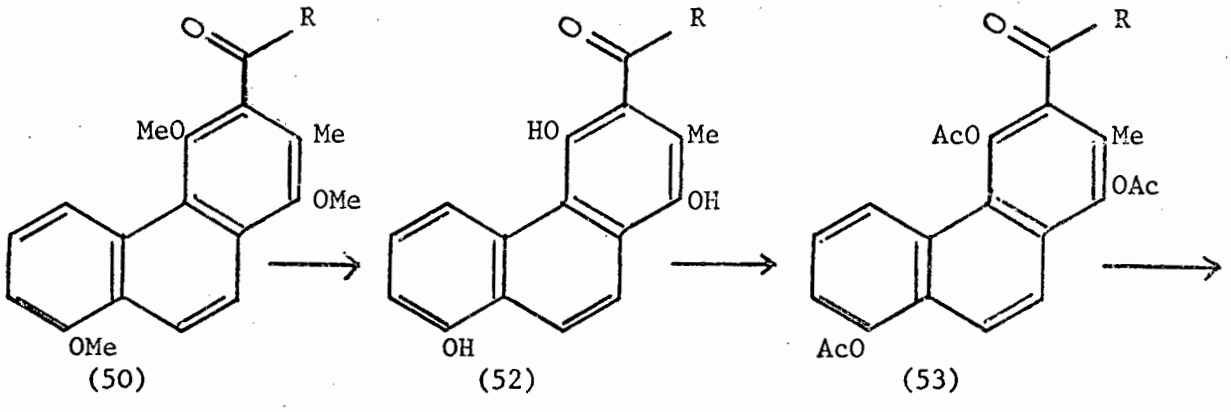


R = $CH_2CH_2CH(CH_3)_2$

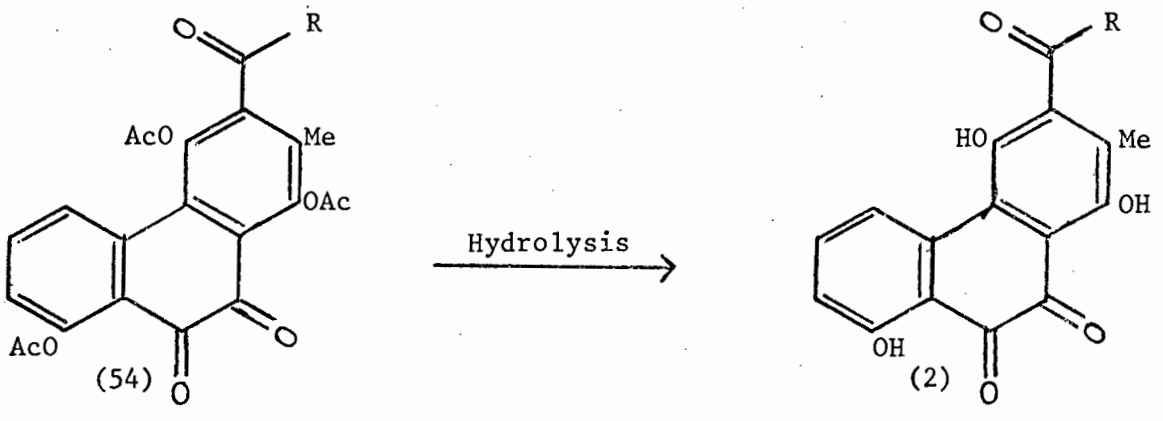
The reason for proposing this mechanism[17] is that if attack took place on the formyl group first, there would no longer be an *ortho* - formyl substituent present to facilitate nucleophilic displacement of the O-methyl at position 4 of the phenanthrene, and only a mono alkylated product could result.

When once the ketophenanthrene (50) had been synthesised, it seemed that in order to prepare 4 - hydroxypiloquinone all that remained was to follow a procedure related to that used by Sargent et al[4], in their synthesis of piloquinone (1). The method we proposed to follow is shown in Scheme 20.

Scheme 20

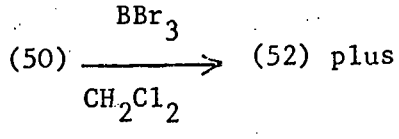


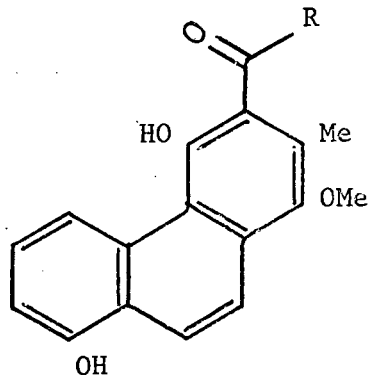
$R = CH_2CH_2CH(CH_3)_2$



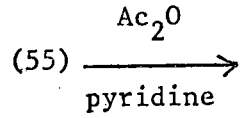
Treatment of compound (50) with three mole equivalents of boron tribromide gave a product (52) which was pure enough to be used in the next step of Scheme 20, provided the reaction was allowed to stir for a long enough period (about 2 hours) at room temperature. A shorter stirring time always gave some of the mono-methoxy derivative (55) which appeared as the mono-methoxy, diacetoxy compound (56) in the next step, shown in Scheme 21.

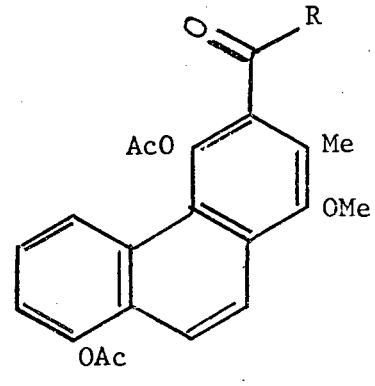
Scheme 21





(55)





(56)

R = $CH_2CH_2CH(CH_3)_2$

Since the presence of compounds (55) or (56) constituted a waste of valuable material, if compound (55) was detected by ^{1}Hn.m.r. spectroscopy when making the trihydroxy compound (52), all the material was re-treated with boron tribromide and stirred for a longer period to give a practically pure product (52) which could then be acetylated with acetic anhydride and pyridine to give the triacetoxy compound (53). The triacetoxy compound could easily be separated from the contaminant (56) by column chromatography, if need be.

The reasons for assigning the structure shown in Scheme 21 to compound (55) are as follows :

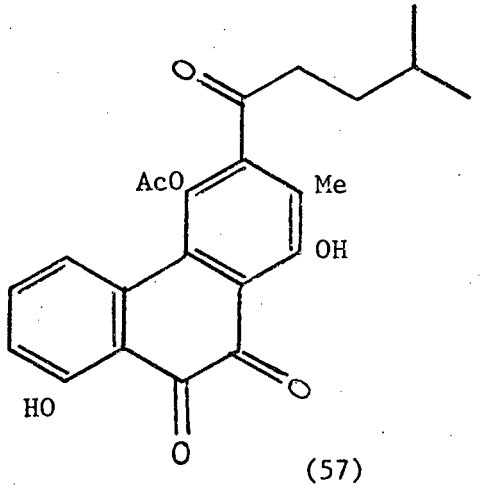
The presence in the ^{1}Hn.m.r. spectrum of the compound (55) of a low field signal (τ-2,99) suggests that there is a chelated hydroxyl proton (4-OH) present in the molecule, and hence that the O-methyl remaining is most probably present at position 1 on the basis that removal of a second O-methyl from the same ring (i.e. at position 1), is less likely than from the alternate, less crowded ring (i.e. position 8).

The next step in the proposed synthesis was to oxidise the triacetoxy compound (53) to give a 9,10 - quinone. Heating with chromium trioxide in acetic acid was used to effect the oxidation but this proved to be a poor method of obtaining the desired quinone (54).

Although reaction conditions were carefully controlled, the results were not repeatable and yields in all cases were low (30 - 40%) with the result that there never was much of the quinone (54) available for the last step in the synthesis of 4 - hydroxypiloquinone (2).

The crude product of oxidation of compound (54) gave a ^{1}Hn.m.r. spectrum in which the peaks were broadened, due probably to the presence of traces of chromium compounds in the unpurified material. In an effort to improve the ^{1}Hn.m.r. spectrum of compound (54) so that it could be compared with the published spectrum of 1,4,8 - triacetoxy - 2 - methyl - 3 - (4 - methylpentanoyl) - 9,10 - phenanthraquinone[5], the crude material was subjected to preparative t.l.c. in order to purify it. It soon became apparent that the compound (54) changed rapidly to some new material when in contact with the silica of the chromatography plate, because a maroon coloured band appeared on developing the plate in chloroform, whereas the compound had been originally applied to the plate as an orange coloured material.

This maroon band was recovered from the plate and ^{1}Hn.m.r. spectroscopy indicated that this material was 4 - acetoxypiloquinone (57), and it seemed that a more vigorous method of hydrolysis



(57)

was all that was required to remove the acetyl group at position 4 to give 4 - hydroxypiloquinone (2).

Accordingly experiments with 10 to 20 mg. of the compound (57) were carried out in an effort to remove the acetyl group at position 4 of the ring. These experiments included warming the starting material with dilute sodium carbonate solution, warming with dilute sodium hydroxide solution, treatment with boron trichloride[18], and heating under reflux with a small amount of concentrated sulphuric acid in ethyl acetate.[20] In all the above experiments the starting material appeared to decompose.

In another experiment compound (57) was stirred with neutral alumina in ethyl acetate[21] but on work up gave back starting material.

At this stage all of the available 4 - acetoxypiloquinone (57) had been used and a number of suggestions, namely dissolving the compound (57) in cold concentrated sulphuric acid and then pouring the solution into cold water or treatment with a non-protic super acid or treatment with lithium iodide in pyridine[25] or lithium iodide in dimethyl formamide[26] or with potassium tertiary butoxide in dimethyl sulphoxide[27] were not attempted.

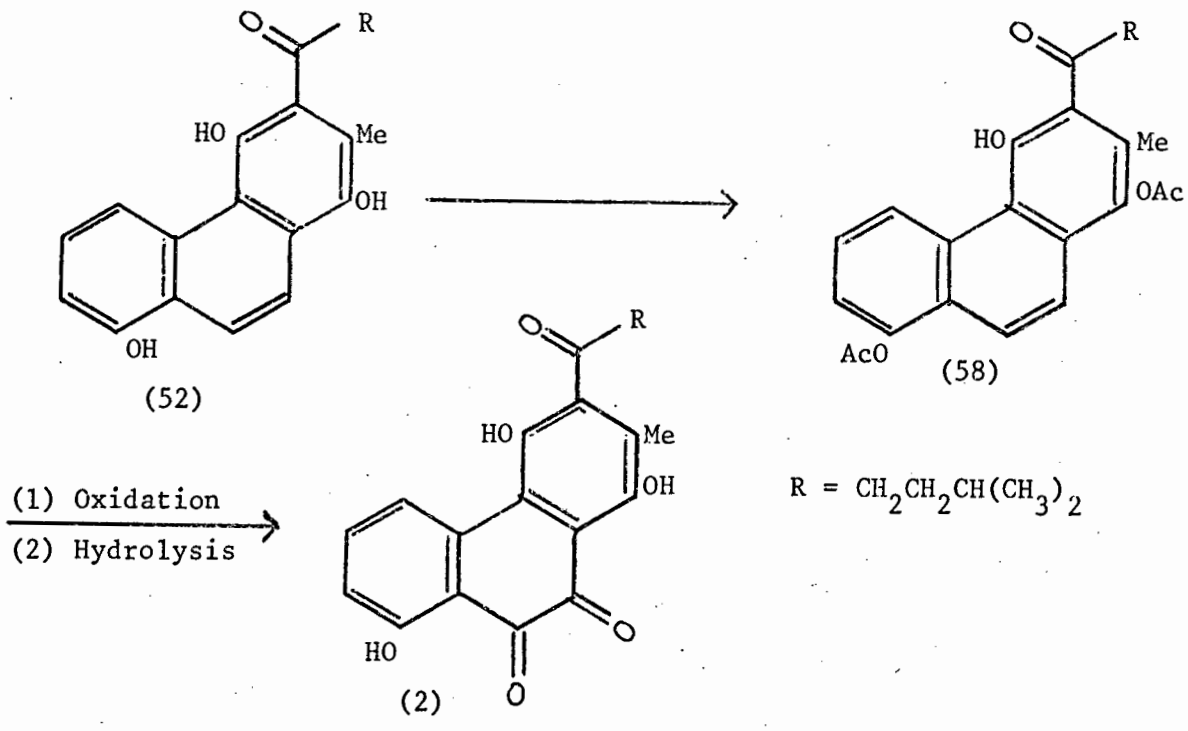
In further efforts to prepare some compounds, the physical properties of which could be directly compared with those reported by Lounasmaa and Zylber[5] for the triacetyl and leuco-acetate derivatives of 4 - hydroxypiloquinone the following two reactions were attempted.

A small quantity of 4 - acetoxypiloquinone (57) was treated with acetic anhydride and pyridine according to the method of Lounasmaa and Zylber[5] but work up of this reaction failed to afford the desired triacetate of 4 - hydroxypiloquinone (54). In fact the product isolated from this reaction had no ^{1}Hn.m.r. signals at all in the region where one might expect to find the acetyl methyl signals.

In the second experiment some impure triacetoxy quinone (54) was subjected to reductive acetylation. Preparative thin layer chromatography of the crude product gave starting material plus one other fraction which was not the required leucoacetate.

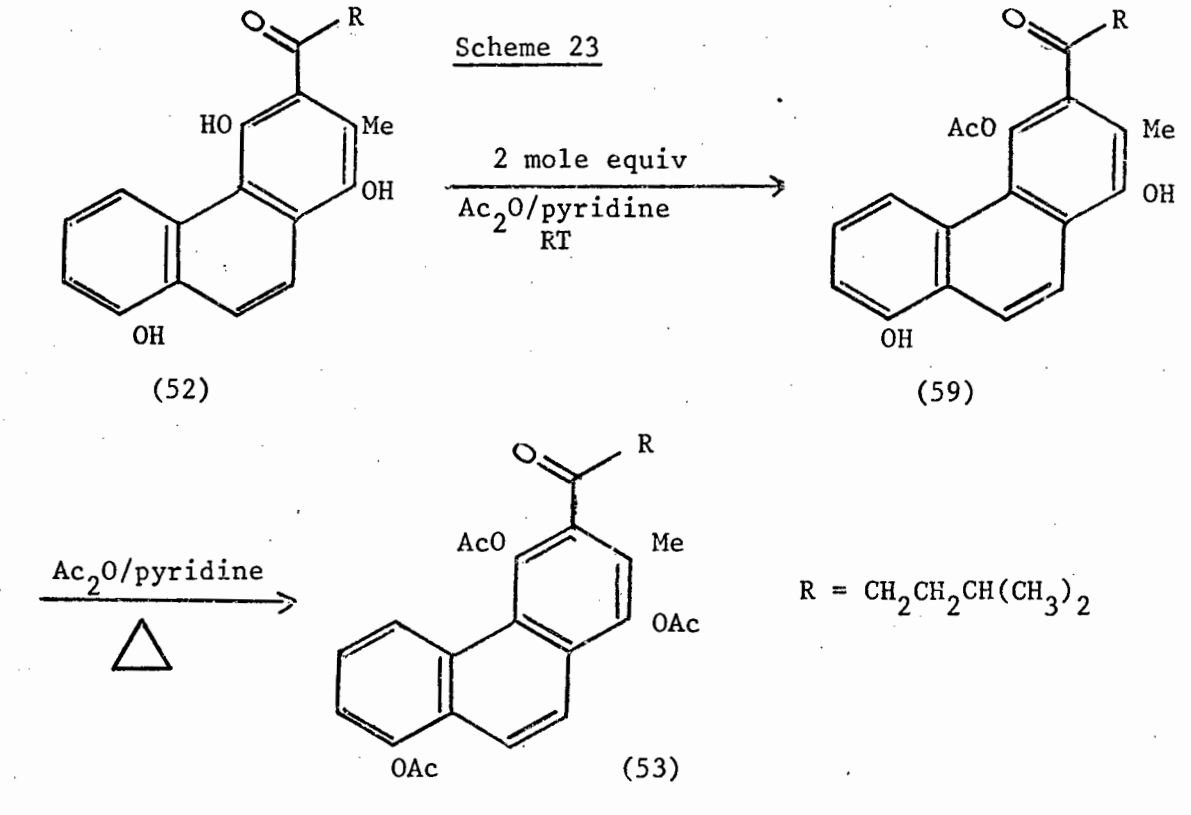
In another attempt at preparing 4 - hydroxypiloquinone the trihydroxyphenanthrene (52) was reacted overnight at room temperature with only two mole equivalents of acetic anhydride and pyridine. It was hoped that the diacetoxy derivative (58) might result, and that this could be oxidised at the 9,10 - positions and hydrolysed as in Scheme 22 to give the desired product (2).

Scheme 22

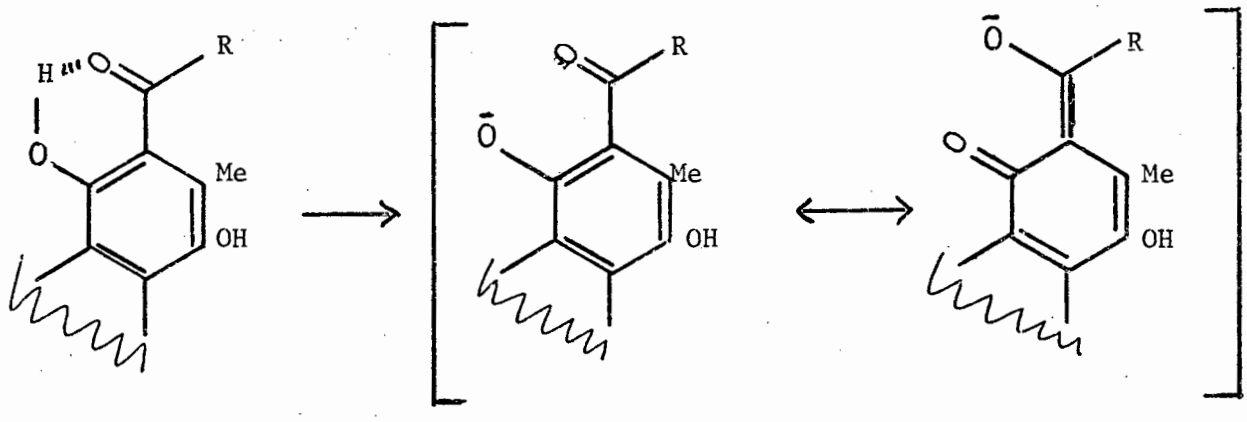


The actual product isolated from this reaction was 4 - acetoxy - 1,8 - dihydroxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (59) which was converted to the triacetate (53) as shown in Scheme 23.

Scheme 23



The reason for assigning the structure (59) to the product of the reaction of compound (52) with acetic anhydride/pyridine at room temperature was that the lowest field signal in the ^{1}Hn.m.r., previously assigned to the chelated 4-OH (see Page 33), was absent in the spectrum of compound (59), thus indicating that this was where the acetyl group had become attached to the molecule. Chelation of the hydroxyl proton at position 4 and presumably improved resonance stabilisation of the intermediate anion, must explain the relative ease with which acetylation occurred at this position.

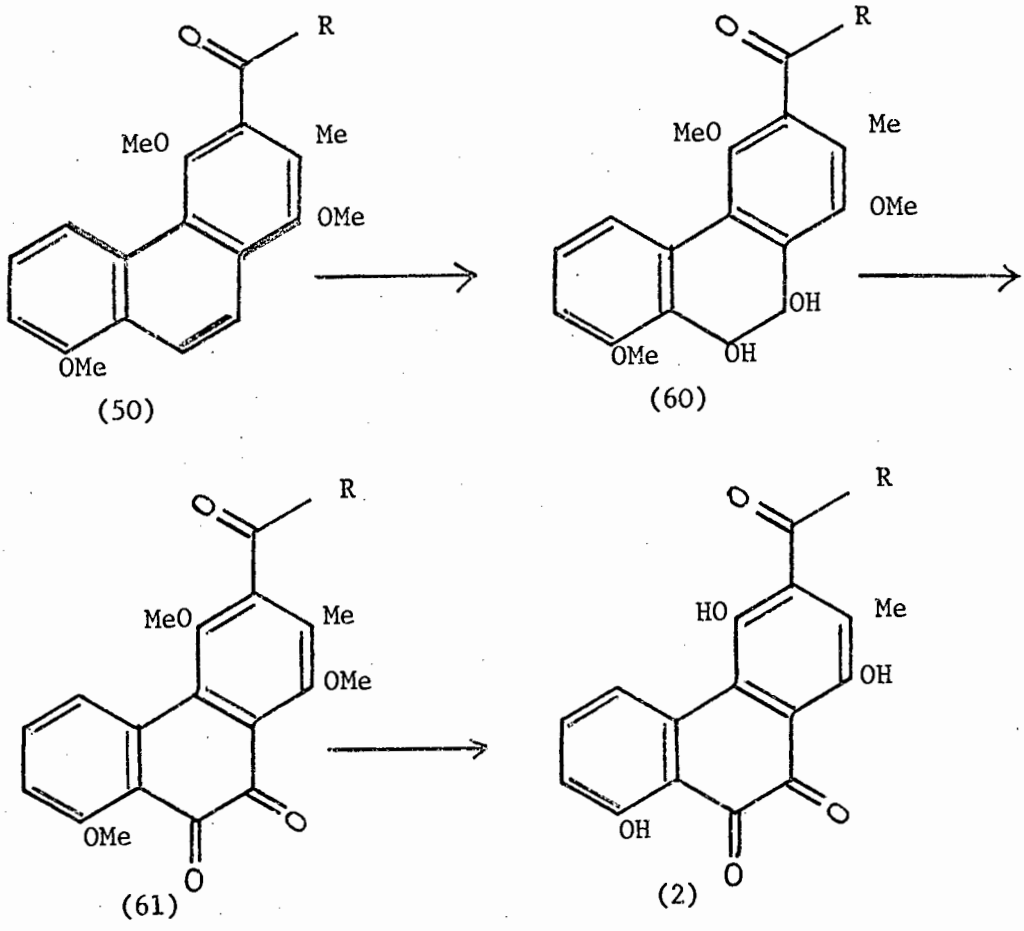


R = $CH_2CH_2CH(CH_3)_2$

1.5 An alternative approach to 4 - hydroxypiloquinone.

On taking stock of the situation at this stage, it was clear (a) that we had failed, with the methods tried, to remove the acetyl group from 4 - acetoxypiloquinone (57), (b) that the chances of ever having a large quantity of 4 - acetoxypiloquinone to experiment with were not good because of the poor yield encountered in converting the triacetoxyphenanthrene (53) to the triacetoxyquinone (54) and therefore further attempts to hydrolyse 4 - acetoxypiloquinone (57) did not appear attractive. Furthermore there was only a small quantity of the precursor, compound (50), available so an alternative route was devised. This is shown in Scheme 24, the ultimate success or failure of which depended on being able to remove the O-methyl groups after the 9,10 - quinone (61) had been formed.

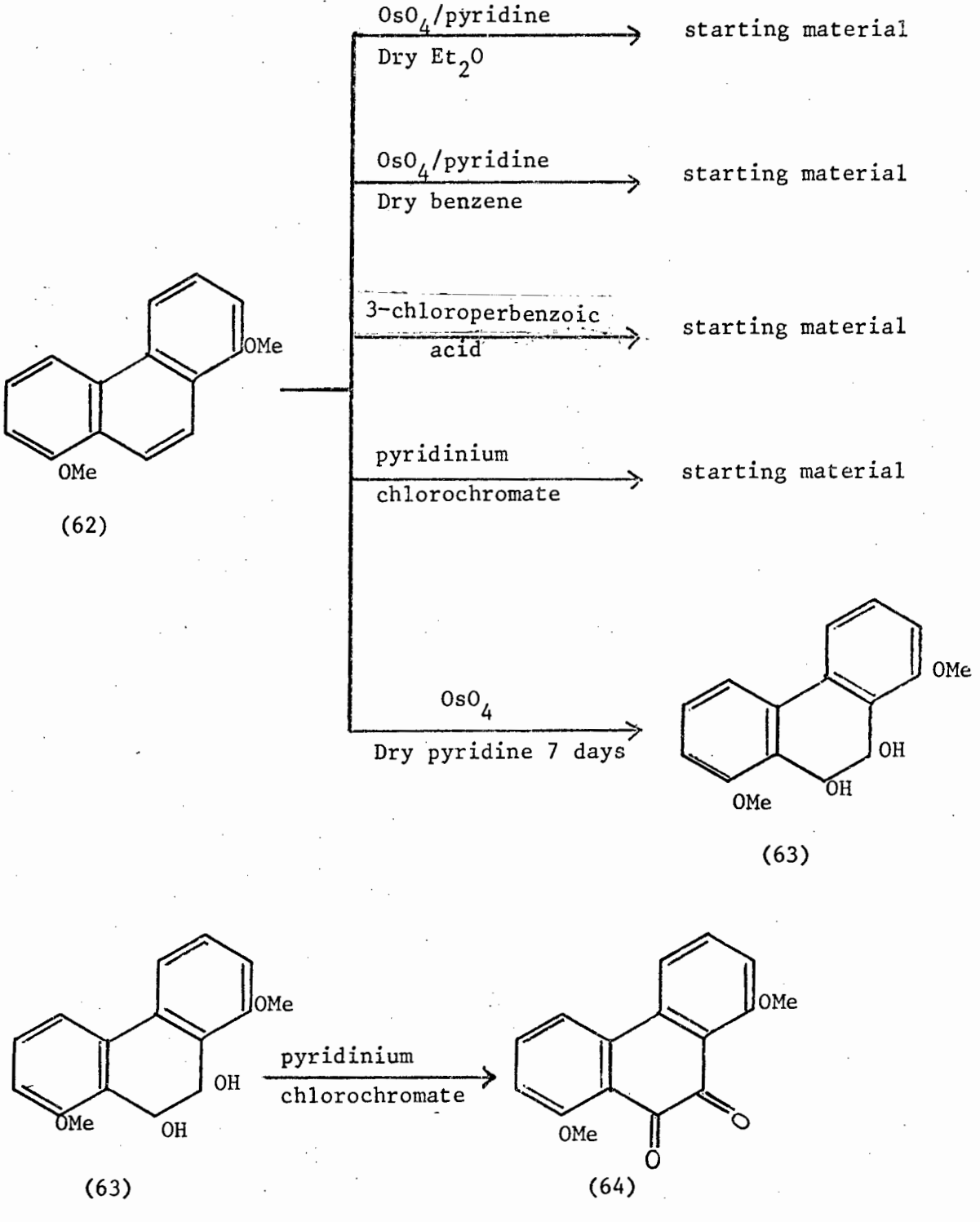
Scheme 24



R = $CH_2CH_2CH(CH_3)_2$

In order to conserve the small amount of starting material (compound 50) that was available, preliminary experiments were carried out on 1,8 - dimethoxyphenanthrene (62). The results obtained from these experiments are summarised in Scheme 25.

Scheme 25



It is interesting to note that some 1,8 - dimethoxy - 9,10 - phenanthraquinone (64) was also formed during the prolonged treatment of compound (62) with osmium VIII oxide[22], and that the quinone present as a mixture with the *cis* - dihydroxy compound (63) was unaffected when oxidation of compound (63) was carried out using pyridinium chlorochromate.[23] It was therefore not necessary to remove any quinone formed during the *cis* - hydroxylation reaction.

Furthermore, unreacted starting material could easily be separated from the products of the hydroxylation reaction and re-used in further reactions.

After the correct conditions for this reaction were established, 1,4,8 - trimethoxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (50) was subjected to the same treatment and the quinone (61) was obtained in reasonable yield (56%, based on unrecovered starting material).

Treatment of 1,4,8 - trimethoxy - 2 - methyl - 3 - (4 - methylpentanoyl) - 9,10 - phenanthraquinone (61) with boron tribromide at -80° in three different experiments with the stirring time at room temperature being varied from 2 hours to 10 minutes, all led to decomposition of the quinone, so boron trichloride (room temperature stirring for 0,5 hours) was used in an attempt to de-O-methylate the quinone (61). This reaction led to the removal of only one O-methyl group probably at position 4, and it was rather surprising that the ^{1}Hn.m.r. spectrum of this compound showed no low field hydroxyl proton signal as is found in 4 - hydroxypiloquinone. It can only be

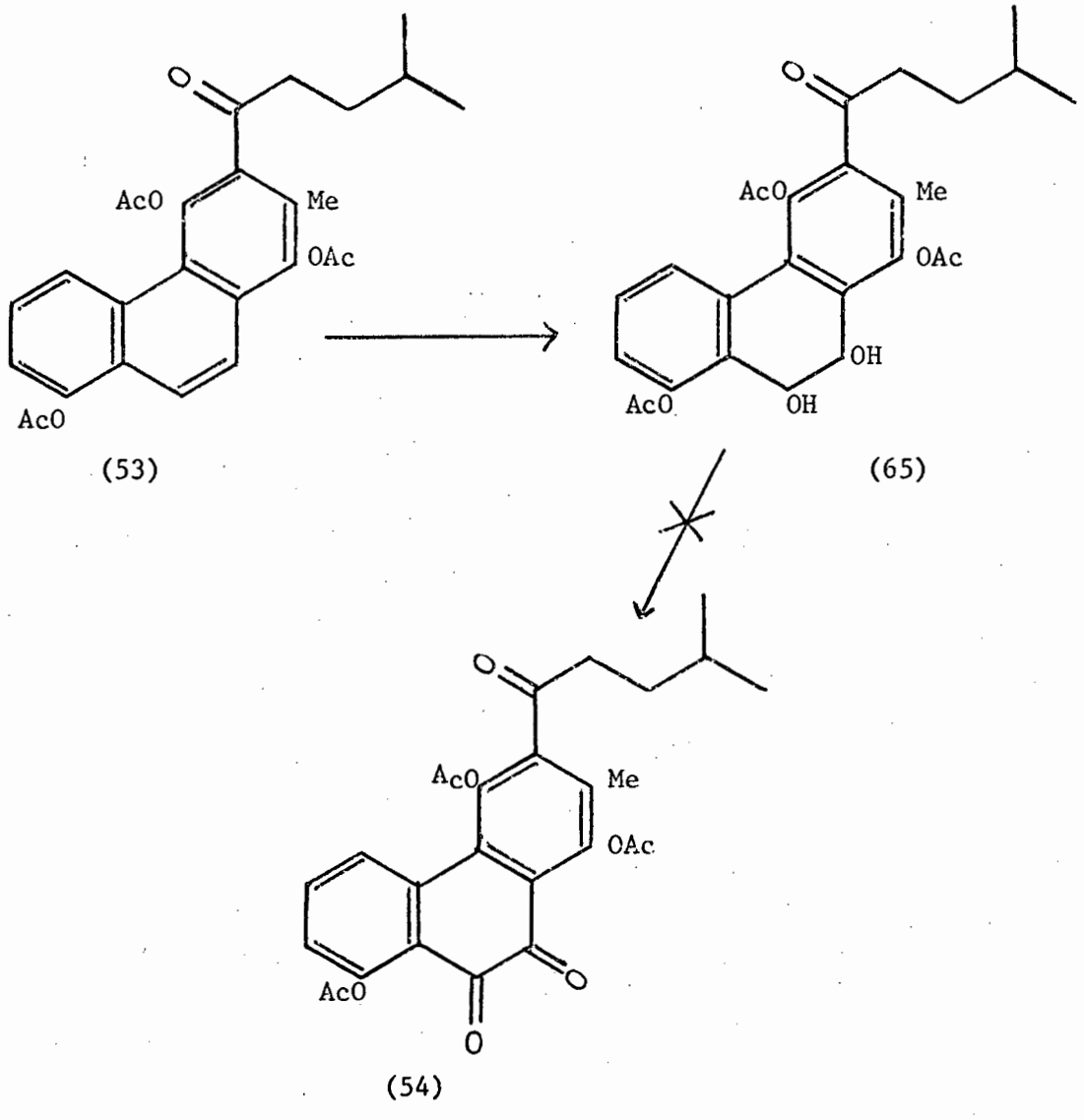
inferred that the hydroxyl proton was not strongly hydrogen bonded. Prolonged treatment (72 hours stirring at room temperature) of the quinone (61) with boron trichloride led to decomposition of the compound.

Removal of the O-methyl groups of compound (61) was also attempted using anhydrous lithium iodide in dry hexamethyl-phosphoric triamide[28] at 100° under dry nitrogen. Thin layer chromatography of the reaction products gave among others a pinkish red band but ^{1}Hn.m.r. spectroscopy indicated that this was not the hoped for 4 - hydroxypiloquinone (2).

Two further reactions involving the use of osmium VIII oxide were attempted. In the first experiment 1,4,8 - trihydroxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (52) was stirred with osmium VIII oxide at room temperature for about 24 hours. A large number of products plus some starting material were isolated but none of these proved to be hydroxylated at the 9,10 - position.

Secondly the starting material recovered from the above reaction was acetylated to give the tri-acetoxy compound (53) and this was stirred with osmium VIII oxide for seven days to give a reaction product which showed encouraging signs of being the *cis* - 9,10 - dihydroxy - 9,10 - dihydrophenanthrene (65) which was then reacted with pyridinium chlorochromate that apparently failed to oxidise the molecule at the 9,10 - position. Scheme 26 shows the proposed reaction sequence.

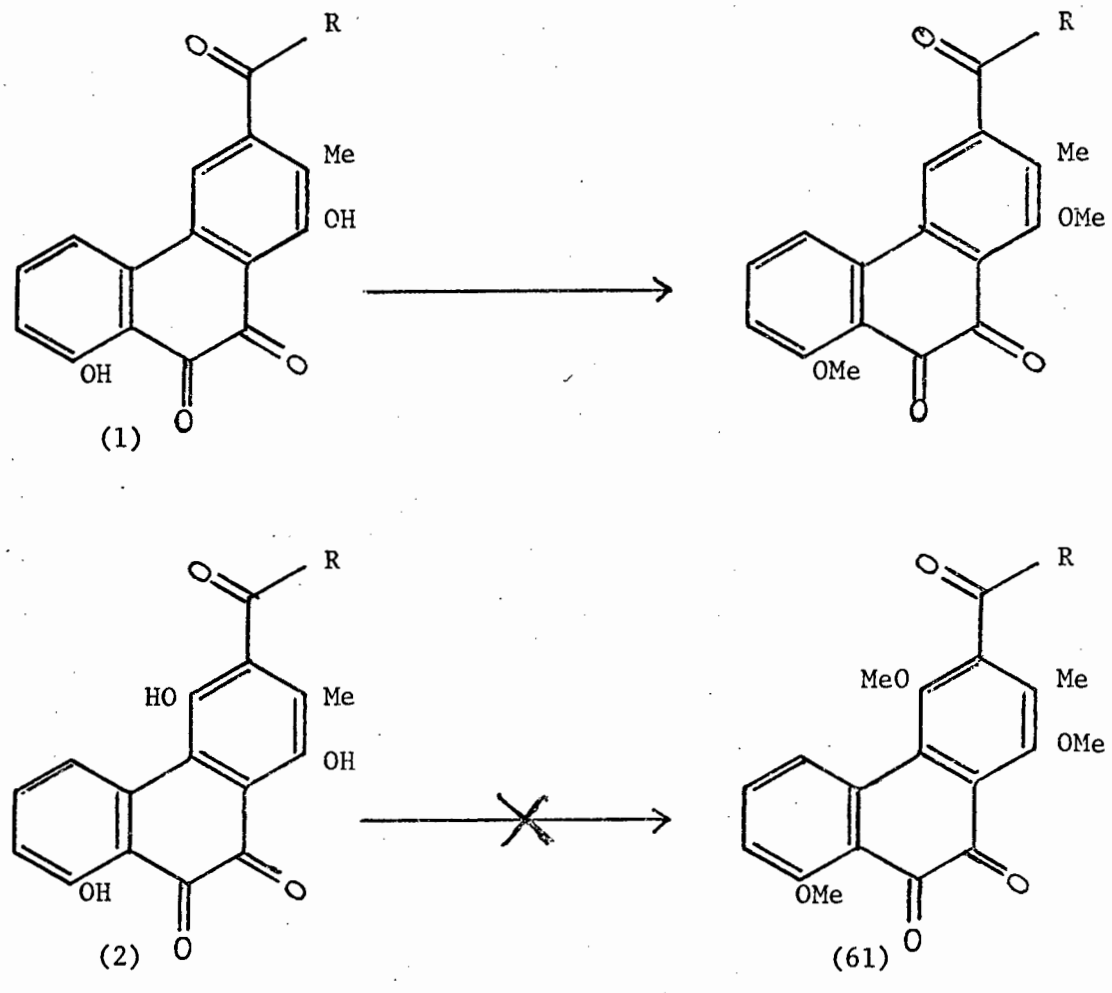
Scheme 26



Finally in a trial experiment it was shown that piloquinone (1) could be successfully di-O-methylated using iodomethane in the presence of silver (I) oxide and magnesium sulphate in chloroform.[24] (Scheme 27)

When a similar reaction was carried out on some 4 - hydroxy-piloquinone (2) supplied by Mme. Polonsky of the CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE, none of the desired product 1,4,8, - trimethoxy - 2 - methyl - 3 - (4 - methylpentanoyl) - 9,10 - phenanthraquinone (61) was obtained from the reaction mixture.

Scheme 27



R = $CH_2CH_2CH(CH_3)_2$

EXPERIMENTAL

EXPERIMENTAL

Unless otherwise stated, the following conditions apply to all experimental sections in this thesis.

Infrared spectra were measured either as nujol mulls or solutions in solvents as shown, on a Perkin Elmer 237 spectrometer, while ultraviolet spectra were measured in chloroform on a Beckman D.B. spectrophotometer. Nuclear magnetic resonance (^{1}Hn.m.r.) spectra were recorded in [^{2}H]chloroform with tetramethylsilane as internal reference on a 100 MHz Varian XL 100 spectrometer or on a 90 MHz Bruker WH-90 spectrometer. Light petroleum refers to the fraction having b.p. between 60 and 80. All melting points are quoted uncorrected as determined on a Fisher-Johns m.p. apparatus. Thin layer chromatography (t.l.c.) was carried out on Merck aluminium foil plates of Kieselgel 60 F 254, while preparative layer chromatography (p.l.c.) was performed on Merck glass plates of the same Kieselgel. Column chromatography was carried out with Merck Kieselgel 60 (70 - 230 mesh) in dry columns, unless wet columns are indicated, in which cases Merck Kieselgel 60 (30 - 70 mesh) was used.

Irradiation of samples was performed either through a quartz or a Pyrex immersion well, using an Hanovia 450 Watt high pressure mercury-vapour lamp. A suitable filter sleeve was used where applicable.

2,6 - Dimethoxybenzaldehyde (5)

Dimethyl sulphate (33 ml) in acetone (50 ml) was added dropwise to a stirred suspension of dry potassium carbonate (100g) and 2,6 - dihydroxybenzoic acid (52,8g) in acetone (300 ml). After the addition of the dimethyl sulphate was complete, the mixture was stirred at reflux for 23 hours. The potassium carbonate was filtered off and washed with acetone (200 ml). After removal of the solvent the resulting solid was taken up in diethyl ether (150 ml) and washed with concentrated ammonia solution until free of acid. The ethereal solution was then washed with dilute hydrochloric acid and finally with water, dried with sodium sulphate and the solvent removed to give crude 2,6 - dimethoxymethylbenzoate (3).

The crude ester was dissolved in dry tetrahydrofuran (50 ml) and added over a period of 15 minutes to a stirred slurry of lithium aluminium hydride (1,6g) in dry tetrahydrofuran (50 ml). The mixture was then heated under reflux and stirred for 1 hour, cooled, and saturated ammonium chloride added until coagulation occurred. The solid was filtered and washed with ethyl acetate. The filtrate and washings were dried with sodium sulphate and the solvent removed to give 2,6 - dimethoxybenzyl alcohol (4). Crude yield 9,5g.

τ 2,79 (1H,t, J8Hz, 4-H), 3,25 (2H,d, J8Hz, 3 and 5-H), 5,21 (2H,s,CH_2), 6,16 (6H,s,2 x OCH_3) and 7,50 br (1H,s, OH).

2,6 - Dimethoxybenzyl alcohol (2,33g) and activated manganese (1V) oxide (23,3g) were stirred and heated under reflux in chloroform (100 ml) for 6 hours. The manganese oxides were filtered off and washed with further chloroform (100 ml). The solvent was removed to give 2,6 - dimethoxybenzaldehyde (5) as white platelets (2,16g, 94%) m.p. 96 - 97° (dichloromethane/light petroleum), (lit.,[29] 98 - 99°, ν_{max} (Nujol) 1680, 1595, 1588, 1485, 1420, 1306, 1260, 1195, 1115, 819, 779 cm^{-1}, τ -0,45 (1H,s, CHO), 2,55 (1H,t, J8Hz, 4-H), 3,43 (2H,d, J8Hz, 3 and 5-H), and 6,12 (6H,s, 2 x OCH_3).

3,5 - Dibromo - 2 - hydroxytoluene (6)

Bromine (162g) in carbontetrachloride (150 ml) was added at room temperature to a stirred solution of 2 - hydroxytoluene (54g) in carbontetrachloride (250 ml). The mixture was stirred for a further 1 hour and then most of the solvent was removed. The remaining solution was washed with dilute hydrochloric acid, dried with sodium sulphate and the solvent completely removed to give crude product (130g). Some of the material was recrystallised from dilute ethanol to give white needles m.p.56 - 57° (lit.,[30] 57 - 58°) ν_{max} (Nujol) 3545, 1609, 1585, 1185 cm^{-1}, τ2,58 (1H, d, J2Hz, 4-H) 2,79 (1H,d, J2Hz, 6-H), 4,44 (1H,s,OH), and 7,72 (3H,s, CH_3).

2 - Bromo - 6 - methyl - 1,4 - benzoquinone (7)

3,5 - Dibromo - 2 - hydroxytoluene (6) (13,3g) was dissolved in acetic acid (25 ml) by warming slightly and to this solution was added dropwise with stirring a solution of chromium (Vl) oxide (10g) in water (35 ml) and acetic acid (25 ml). The resulting solution was stirred at room temperature for 1 hour and finally heated to 55 - 60° for 15 minutes. Water (250 ml) was added to the oxidation mixture and the quinone extracted with chloroform.

The chloroform extract was dried with sodium sulphate and the solvent removed to give the quinone which was recrystallised from light petroleum to give yellow platelets. Yield (6,36g, 63%) m.p. 94° (lit.,[7] 95°). ν_{max} (Nujol) 1679, 1660 cm^{-1}.

2 - Bromo - 6 - methyl - 1,4 - dimethoxybenzene (8)

2 - Bromo - 6 - methyl - 1,4 - benzoquinone (6,36g) in diethyl ether (60 ml) was shaken up with sodium hydrosulphite (11g) in water (30 ml). As soon as the orange colour in the organic layer was discharged, the aqueous layer was run off, and the organic layer was washed with water, dried with sodium sulphate and the solvent removed to give crude quinol (6,4g).

The crude quinol (6,4g) was dissolved in ethanol (60 ml) and heated to 50°. To the stirred solution was added alternately 10 M sodium hydroxide (6,4 ml) and dimethylsulphate (6 ml). Finally an excess (2 ml) of 10 M NaOH was added and the solution was heated under reflux for 1,5 hours in a hot water bath. The solvent was removed

to give a semi-solid residue which was taken up in water (200 ml) and extracted with chloroform (4 x 30 ml). The extract was washed with water, dried with sodium sulphate, and the solvent removed to yield a brown oil (5g). The oil was distilled b.p. 81 - 82° at 0,3 mm Hg. ν_{max} (neat) 3010, 2940, 2840, 1600, 1570, 1486, 1430, 1230, 1058 cm^{-1}, τ3,08 (1H, d, J3Hz, 5-H), 3,33 (1H, d, J3Hz, 5-H), 6,23 (3H, s, OCH_3), 6,25 (3H, s, OCH_3), and 7,69 (3H, s, CCH_3).

2,5 - Dimethoxy - 3 - methylbenzaldehyde (9)

2 - Bromo - 6 - methyl - 1,4 - dimethoxybenzene (8) (3g) in dry diethyl ether (25 ml) was added over a period of 10 minutes to a stirred solution of phenyllithium made by reacting lithium (0,27g) and bromobenzene (2 ml) in dry diethyl ether (60 ml).

The mixture was stirred for 4 hours and then dimethylformamide (1,2g) in dry diethyl ether (25 ml) was added over a period of 10 minutes, the solution being stirred for a further 2 hours. Saturated ammonium chloride solution was added and the precipitated lithium salt filtered off and washed with diethyl ether. The combined filtrate and washings were then washed with water, dried with sodium sulphate and the solvent removed to give a brown oil (4,5g).

The oil was chromatographed on a column packed with silica using 10% ethyl acetate/light petroleum as eluant. A fraction was collected containing the aldehyde (9) (1,73g 74%). m.p. 39 - 40° (lit.,[31] 42°) ν_{max} (Nujol) 1695, 1235, 1068 cm^{-1}, τ -0,38 (1H, s, CHO), 2,81 (1H, d, J3Hz, 6-H), 2,96 (1H, d, J3Hz, 4-H), 6,12 (3H,s, OCH_3), 6,16 (3H, s, OCH_3), and 7,65 (3H, s, CCH_3).

Bromination of 2,5 - dimethoxy - 3 - methylbenzaldehyde (9)

The aldehyde (9) (0,25g) was dissolved in acetic acid (10 ml) and bromine (0,23g) in acetic acid (5 ml) was added. The mixture was heated under reflux for 0,5 hours, cooled slightly and the solvent removed. The resulting brown liquid was taken up in diethyl ether and washed successively with sodium bicarbonate solution and water, dried with sodium sulphate and the solvent removed to give a yellow solid. ^{1}Hn.m.r. showed this solid to be a mixture of 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzaldehyde and 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzaldehyde (10) in the ratio of 1 : 1.

Methyl 2,5 - dimethoxy - 3 - methylbenzoate (28)

(a) From *ortho* - cresotic acid

Crude 2,5 - dihydroxy - 3 - methylbenzoic acid (27) was obtained by a modification of Still's method[11] in which *ortho* - cresotic acid (40g) was oxidised using a saturated solution of potassium peroxodisulphate (about 100g) in water (1700 ml). After removal of most of the excess starting material as described by Still, the crude 2,5 - dihydroxy - 3 - methylbenzoic acid was further purified by heating under reflux with light petroleum. The hot solution was filtered to remove residual *ortho* - cresotic acid in solution. The solid remaining in the filter afforded pure 2,5 - dihydroxy - 3 - methylbenzoic acid (27) (24,7g, 56%). This material was dissolved in dry acetone

(225 ml) and methylated by adding anhydrous potassium carbonate (96g) and dimethyl sulphate (75 ml) in more acetone (225 ml). The stirred mixture was heated under reflux overnight. The solids were removed by filtration, and washed with more acetone (250 ml). The solvent was evaporated off, and the solid product dissolved in ether. The ethereal solution was washed successively with concentrated ammonia, water and then dilute hydrochloric acid and finally again with water and dried with sodium sulphate. The ether was removed and the resultant dark oil chromatographed on a silica column using 10% ethyl acetate/light petroleum as eluant. The resulting colourless oil (27g, 91%) could be distilled at 100° (bath/0,4 mm Hg)to afford methyl 2,5 - dimethoxy - 3 - methylbenzoate (28) which slowly crystallised. m.p. 81 - 82°

(Found : C, 62,6; H, 6,5. $C_{11}H_{14}O_4$ requires C, 62,8; H, 6,7%), ν_{max} (neat) 3020, 2950, 2840, 1740, 1610, 1500, 1340, 1250, 1215, 1130, 1060, 1010, 790, 750 cm^{-1}, τ 2,89 (1H,d, J3Hz, 6-H), 3,15 (1H, d, J3Hz, 4-H), 6,12 (3H, s, OCH_3), 6,24 (6H, s, 2 x OCH_3), and 8,72 (3H, s, CCH_3).

(b) From 2 - bromo - 6 - methyl - 1,4 - dimethoxybenzene (8)

The above compound (8)(5g) in dry diethyl ether (25 ml) was added dropwise over a period of 10 minutes to a solution prepared from lithium (0,45g) and dry bromobenzene (3,3 ml) in dry diethyl ether (60 ml). The reaction mixture was stirred at room temperature for 3 hours and then carbon dioxide gas

was passed into the mixture for 1 hour.

The reaction mixture was exhaustively extracted with aqueous 10% sodium carbonate solution and the extract rendered acid with concentrated hydrochloric acid and then re-extracted with diethyl ether (4 x 50 ml), washed with water and dried with sodium sulphate. The ether was evaporated to give crude 2,5 - dimethoxy - 3 - methylbenzoic acid (1,0g). τ 0,27 br (1H,s,OH), 2,61 (1H, d, J3Hz, 6-H), 3,05 (1H, d, J3Hz, 4-H), 6,14 (3H,s, OCH_3), 6,20 (3H, s, OCH_3), and 7,66 (3H, s, CCH_3).

The crude acid (1g) was heated under reflux overnight with methanol (25 ml) and concentrated sulphuric acid (0,2 ml).

The methanol was evaporated and the brown oily residue taken up in diethyl ether (20 ml) and washed successively with saturated aqueous sodium bicarbonate solution and water, dried with sodium sulphate and the solvent evaporated to give crude methyl 2,5 - dimethoxy - 3 - methylbenzoate (28) (0,84g).

2,5 - Dimethoxy - 3 - methylbenzyl alcohol (14)

The ester (28) (23,6g) in dry diethyl ether (300 ml) was added dropwise to lithium aluminium hydride (5,5g) in diethyl ether (200 ml) and the mixture heated under reflux for 3 hours. Saturated ammonium chloride solution was added to the cooled ether slurry until coagulation occurred. The solid was filtered off and washed with more diethyl ether. The filtrate and washings were dried with sodium sulphate and evaporated to give the alcohol (14) (19,5g, 95%). ν_{max} (neat) 3400, 2940, 2840, 1610, 1595, 1220, 1060, 1010, 860, 755 cm^{-1}, τ 3,28 (1H, d, J3Hz, 6-H), 3,42 (1H, d, J3Hz, 4-H), 5,39 (2H, d, J6Hz, CH_2),

6,31 (3H, s, OCH_3), 6,35 (3H, s, OCH_3), 7,41 (1H, t, J6Hz, OH), and 7,77 (3H, s, CCH_3).

2,5 - Dimethoxy - 3 - methylbenzyl triphenylmethyl ether (22)

The alcohol (14) (18,2g) in dry pyridine (100 ml) was stirred overnight with an excess of chlorotriphenylmethane (47,9g). Most of the solvent was removed under reduced pressure and dry diethyl ether (100 ml) added to the residue. The precipitate was removed by filtration and washed with further dry diethyl ether. The filtrate and washings were evaporated to yield the crude ether (22) as an oil (38,0g). A small portion was chromatographed (chloroform) for analysis. (Found : C, 82,5; H, 6,8. $C_{29}H_{28}O_3$ requires C, 82,05; H6, 65%), τ 2,30 - 2,95 (15H, m, Ph_3C), 2,94 (1H, d, J3Hz, 6-H), 3,35 (1H, d, J3Hz, 4-H), 5,78 (2H, s, CH_2), 6,22 (3H, s, OCH_3), 6,52 (3H, s, OCH_3), and 7,77 (3H, s, CCH_3).

4 - Bromo - 2,5 - dimethoxy - 3 - methylbenzyl triphenylmethyl ether (23)

The crude ether (22) (45,3g) (containing about 32g ether contaminated with triphenylcarbinol, as estimated by ^{1}Hn.m.r.) in dry chloroform (120 ml) containing pyridine (7 ml) was treated dropwise with a solution of bromine (48 ml of a solution containing bromine (66,98g) in chloroform (250 ml)). The solution was stirred at room temperature for 4 hours, and then the solvent and pyridine were evaporated off. The residue was dissolved in dichloromethane and washed with water, dried with sodium sulphate and the solvent removed to yield a mixture of (23) and (24) as an oil (56g). A small portion was

chromatographed on silica with 20% ethyl acetate/light petroleum as eluant to give the product (23) as white needles. m.p. 225° (from chloroform/light petroleum). (Found : C, 69,6; H, 5,4. $C_{29}H_{27}BrO_3$ requires C, 69,2; H, 5,4%), τ 2,35 - 2,9 (15H, m, Ph_3C), 2,96 (1H, s, 6H), 5,76 (2H, s, CH_2), 6,10 (3H, s, OCH_3), 6,52 (3H, s, OCH_3), and 7,66 (3H, s, CCH_3).

4 - Bromo - 2,5 - dimethoxy - 3 - methylbenzyl alcohol (11) and 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl alcohol (25).

The above crude mixture of bromoethers (55g) was heated under reflux in glacial acetic acid/water (4 : 1, 100 ml) for 10 minutes. The solution was cooled in ice and the precipitated triphenyl-carbinol was removed by filtration. This was washed with a little cold 80% acetic acid. The filtrate and washings were evaporated and the residue was rapidly chromatographed on silica with chloroform as eluant to separate residual triphenylcarbinol from the mixture of slower running bromoalcohols (11) and (25). This latter mixture was recrystallised from dichloromethane/light petroleum to afford 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl alcohol (11) (11g) as white needles m.p. 87 - 88°, (Found : C, 46,05; H, 5,05. $C_{10}H_{13}BrO_3$ requires C, 46,0; H 5,0%), τ 3,20 (1H, s, 6-H), 5,34 (2H, s, CH_2), 6,15 (3H, s, OCH_3), 6,31 (3H, s, OCH_3), 7,44 br (1H, s, OH), and 7,64 (3H, s, CCH_3). The mother liquors from the above recrystallisation were evaporated and chromatographed on silica using 20% ethyl acetate/light petroleum as eluant. Early fractions afforded 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl alcohol (25) (3,5g) as white needles m.p. 69 - 70° (from light petroleum). (Found : C, 46, 1;

H, 4,85. $C_{10}H_{13}BrO_3$ requires C, 46,0; H, 5,0%), ν_{max} (Nujol) 3390, 1580, 1235, 1090, 1005 cm^{-1}, τ 3,10 (1H, s, 4-H), 5,16 (2H, d, J7Hz, CH_2), 6,15 (3H, s, OCH_3), 6,23 (3H, s, OCH_3), 7,58 (1H, t, J7Hz, OH), and 7,72 (3H, s, CCH_3). Later fractions afforded more of the alcohol (11) (3g).

4 - Bromo - 2,5 - dimethoxy - 3 - methylbenzylbromide (12)

The alcohol (11) (8,2g) in dry benzene (50 ml) was stirred at room temperature for 5 hours with phosphorous tribromide (3,3g). The solution was washed with water, 10% aqueous sodium bicarbonate solution, and finally with water. The solution was dried with sodium sulphate and evaporated to afford the product (12) as white needles (8,2g, 80%) m.p. 85 - 86°(ethanol). (Found : C, 37,2; H, 3,6. $C_{10}H_{12}Br_2O_2$ requires C, 37,0; H, 3,7%), ν_{max} (Nujol) 3020, 1330, 1233, 1075, 1010 cm^{-1}, τ 3,22 (1H, s, 6-H), 5,44 (2H, s, CH_2), 6,11 (3H, s, OCH_3), 6,18 (3H, s, OCH_3), and 7,61 (3H, s, CCH_3).

6 - Bromo - 2,5 - dimethoxy - 3 - methylbenzylbromide (16)

2,5 - Dimethoxy - 3 - methylbenzyl alcohol (14) (0,55g) in acetic acid (10 ml) was treated with bromine (0,55g) in acetic acid (10 ml) and then stirred at 55 - 60° for 3 hours. The solvent was evaporated and the residual brown oil taken up in diethyl ether and washed with 10% aqueous sodium bicarbonate solution and then with water. The ethereal solution was dried with sodium sulphate and the solvent evaporated. Chromatography of the resulting brown oil on silica with 10% ethyl acetate/light petroleum as eluant gave 4 - bromo - 2,5 -

dimethoxy - 3 - methylbenzyl bromide (12) (0,13g) in the early fractions and the product (16) (0,24g, 25%) in the later fractions. m.p. 102 - 103° (ethanol) (Found : C, 37,2; H, 3,6. $C_{10}H_{12}Br_2O_2$ requires C, 37,0; H, 3,7%), τ 3,27 (1H, s, 4-H), 5,25 (2H, s, CH_2), 6,12 (6H, s, 2 x OCH_3), and 7,70 (3H, s, CCH_3).

4 - Bromo - 2,5 - dimethoxy - 3 - methylbenzyltriphenylphosphonium bromide (13)

To the bromide (12) (21,77g) in dry benzene (75 ml) was added triphenylphosphine (21,25g). The solution was stirred and heated under reflux overnight, during which time precipitation of the product occurred. The mixture was cooled in ice, filtered, and the precipitate was washed with cold dry diethyl ether. Recrystallisation afforded the phosphonium salt (13) as a white powder (36,4g, 97%) m.p. 212 - 213° (dichloromethane/diethyl ether). (Found : C, 56,8; H, 5,1. $C_{28}H_{27}Br_2O_2P$ requires C, 57,3; H, 4,6%), ν_{max} (Nujol) 1600, 1585, 1250, 1111, 1078, 1000, 846, 754, 688 cm^{-1}, τ 2,05 - 2,55 (15H, m, Ph_3C), 3,17 (1H, d, J2Hz, 6-H), 4,80 (2H, d, J14Hz, CH_2), 6,47 (6H, s, 2 x OCH_3), and 7,82 (3H, s, CCH_3).

2,5 - Dimethoxy - 3 - methylbenzyl bromide (15)

2,5 - Dimethoxy - 3 - methylbenzyl alcohol (14) (2,18g) and phosphorous tribromide (1,26g) in dry benzene (30 ml) were stirred overnight at room temperature and then the solution was washed successively with water, 10% aqueous sodium bicarbonate solution and then finally with water. The benzene solution was dried with sodium sulphate, and the solvent evaporated to the crude bromide (15) (2,86g, 97%). τ 3,24 (1H, d, J3Hz, 6-H), 3,31 (1H, d, J3Hz, 4-H), 5,45 (2H, s, CH_2), 6,17 (3H, s, OCH_3), 6,23 (3H, s, OCH_3), and 7,69 (3H, s, CCH_3).

Bromination of 2,5 - dimethoxy - 3 - methylbenzyl bromide (15)

The bromide (15) (2,85g) in acetic acid (50 ml) was treated with bromine (1,9g) in acetic acid (20 ml) and stirred at room temperature for 5 hours. The acetic acid was evaporated under reduced pressure and the resulting solid was taken up in diethyl ether and washed with 10% aqueous sodium bicarbonate solution and water. The ethereal solution was dried with sodium sulphate and the solvent removed to give a mixture of dibromo compounds in the ratio of 1 : 4 as shown by ^{1}Hn.m.r.

The above compounds were separated by preparative t.l.c. and shown to be the identical to compounds (12) and (16).

trans - 4 - Bromo - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene (19)

The phosphonium salt (13) (18,3g) and 2,6 - dimethoxybenzaldehyde (5) (5,2g) were dissolved by warming slightly in dry methanol (250 ml) under nitrogen. Lithium methoxide (35 ml of a solution containing lithium (0,31g) in methanol (50 ml)) was added dropwise with stirring at room temperature. The solution became pale yellow and was then heated under reflux for 2 hours. The solution was cooled slightly and then evaporated, and the residue was chromatographed on silica (eluant 10% ethyl acetate/light petroleum) to afford the product (11,3g, 92%), as a mixture of the *cis* isomer (18) and the *trans* isomer (19). the latter predominating. Recrystallisation from dichloromethane/ light petroleum afforded the pure *trans* product (19)as white needles m.p. 94 - 95°. (Found : C, 58,0; H, 5,35. $C_{19}H_{21}BrO_4$ requires C, 58,0; H, 5,4%), ν_{max} (Nujol) 1600, 1245, 1112, 1095, 975, 762 cm^{-1}, τ 2,21 and 2,63 (2H, ABq, J16Hz, *trans* CH=CH), 2,83 (1H, t, J8Hz, 4′-H), 2,95 (1H, s, 6-H), 3,41 (2H, d, J8Hz, 3′ - and 5′ -H), 6,07 (3H, s, OCH_3), 6,10 (6H, s, 2 x OCH_3), 6,28 (3H, s, OCH_3), and 7,60 (3H, s, CCH_3).

trans - 4 - Cyano - 2, 2′, 5, 6′- tetramethoxy - 3 - methylstilbene (20)

The bromostilbene (19) (0,42g) and copper (I) cyanide (0,39g) in dry dimethyl formamide (75 ml) were heated under reflux for 20 hours. Work up as for nitrile (34) afforded crude material (0,4g) which was recrystallised from dichloromethane/methanol to give the product (20) as white needles m.p. 167 - 168°. (Found : C, 70,6; H, 6,4; N, 4,0.

$C_{20}H_{21}NO_4$ requires C, 70,8; H, 6,2; N, 4,15%), ν_{max} (Nujol) 2220, 1593, 1250, 1105, 1095, 975, 777 cm^{-1}, τ 2,19 and 2,53 (2H, ABq, J16Hz, *trans* CH=CH), 2,79 (1H, t, J8Hz, 4-H), 2,98 (1H, s, 6-H), 3,41 (2H, d, J8Hz, 3′ - and 5′-H), 6,04 (3H, s, OCH_3), 6,09 (6H, s, 2 x OCH_3), 6,27 (3H, s, OCH_3), and 7,54 (3H, s, CCH_3).

3 - Cyano - 1,4,8 - trimethoxy - 2 - methylphenanthrene (21)

The cyanostilbene (20) (0,31g) in cyclohexane (800 ml) was irradiated through quartz, using a Vycor sleeve, for 12 hours. The solvent was evaporated and the residue chromatographed on silica (eluant 5% ethyl acetate/light petroleum) to afford the nitrile (21) (0,12g, 43%) as white needles m.p. 168 - 169° (methanol). (Found : C, 74,0; H, 5,45; N, 4,8. $C_{19}H_{17}NO_3$ requires C, 74,25; H, 5,55; N, 4,55%), τ 1,00 (1H, d, J9Hz, 5-H), 1,58 and 2,01 (2H, ABq. J9Hz, 9- and 10-H), 2,40 (1H, d, J9Hz, 6-H), 2,94 (1H, d, J9Hz, 7-H), 5,96 (6H, s, 2 x OCH_3), 6,11 (3H, s, OCH_3), and 7,36 (3H, s, CCH_3).

Bromination of methyl 2,5 - dimethoxy - 3 - methylbenzoate (28)

(a) With bromine in acetic acid

Bromine (0,65g) in acetic acid (10 ml) was added dropwise to a stirred solution of the above ester (28) (0,84g) and sodium acetate (0,4g) in acetic acid (10 ml). The mixture was heated under reflux for 1,25 hours, cooled slightly and the solvent removed in vacuo. The resulting brown oil was dissolved in chloroform and washed with aqueous 10% sodium bicarbonate

solution and then water. The organic layer was dried with sodium sulphate and the solvent evaporated to give a brown oil (1,06g).

^{1}Hn.m.r. indicated that the brown oil was a mixture of methyl 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzoate (29) and methyl 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzoate (30) in the ratio of 4 : 1.

Column chromatography (Silica gel) (25% ethyl acetate in light petroleum) failed to separate the two isomers.

(b) With pyridinium hydrobromide perbromide

The ester (28) (0,21g) and pyridinium hydrobromide perbromide (0,32g) in glacial acetic acid (15 ml) were stirred overnight at 50 - 60°. The colour of the perbromide having been discharged the mixture was worked up as in part (a) to give a brown oil (0,24g). ν_{max} (neat) 3020, 2960, 2860, 1730, 1608, 1581, 1230, 1073, 1010 cm^{-1}.

^{1}Hn.m.r. indicated that the brown oil was a mixture of the same two products as in part (a), the ratio of these two products being almost identical to that in (a).

3 - Formyl - 1,4,8 - trimethoxy - 2 - methylphenanthrene (31)

The alcohol (47) (1,55g) in chloroform (150 ml) was stirred and heated at reflux with activated manganese (IV) oxide (32g) for 30 hours. The solution was cooled, filtered, and evaporated, and the residue was chromatographed on silica (eluant 2,5% ethyl acetate/ light petroleum). Early fractions afforded the aldehyde (31) (1,19g, 77%) m.p. 138 - 139° (methanol). (Found : C, 73,35; H,6,0. $C_{19}H_{18}O_4$ requires C, 73,55; H, 5,85%), ν_{max} (Nujol) 1679, 1606, 1255, 768 cm^{-1}, τ -0,79 (1H, s, CHO), 0,97 (1H, d, J9Hz, 5-H), 1,56 and 1,97 (2H, ABq, J9, 5Hz, 9- and 10-H), 2,40 (1H, t, J9Hz, 6-H), 2,95 (1H, d, J9Hz, 7-H), 5,95 (3H, s, OCH_3), 6,12 (6H, s, 2 x OCH_3), and 7,31 (3H, s, CCH_3). Later fractions afforded 8- methoxy - 3 - methoxymethyl - 2 - methyl - 1,4 - phenanthraquinone (48) (40 mg, 2%) as red needles, m.p. 150 - 151° (dichloromethane/light petroleum). (Found : M^+ 296. $C_{18}H_{16}O_4$ requires M.M. 296), ν_{max} (CH Cl_3) 1660, 1595, 1580, 1465, 1240 cm^{-1}, τ 0,97 (1H, d, J9Hz, 5-H), 1,38 and 1,90 (2H, ABq, J9Hz, 9- and 10-H), 2,42 (1H, t, J9Hz, 6-H), 3,06 (1H, d, J9Hz, 7-H), 5,46 (2H, s, CH_2), 5,98 (3H, s, Ar OCH_3), 6,54 (3H, s, CH_2 OCH_3), and 7,72 (3H, s, CCH_3).

1,4,8-Trimethoxy-2-methyl-3-(4-methyl-1-hydroxypentyl)phenanthrene (32)

The phenanthrene aldehyde (31) (1,58g) in dry tetrahydrofuran (20 ml) was added to the Grignard reagent prepared from magnesium (0,125g) and 3 - methylbromobutane (0,78g) in dry diethyl ether (30 ml). The mixture was heated at reflux for 0,5 hours, and worked up by adding saturated ammonium chloride and filtering off the precipitated

inorganic salts, drying the organic filtrate with sodium sulphate and evaporating the solvent to give a solid residue. The residue was chromatographed on silica using 2½%ethyl acetate/light petroleum as eluant. Early fractions afforded 1,8 - dimethoxy - 2 - methyl - 3-(4 - methyl - 1 - hydroxypentyl - 4 - (4 - methylpentyl) phenanthrene (49) (0,51g) as an oil. Later fractions afforded 1,4,8 - trimethoxy - 3 - (4 - methyl - 1 - hydroxypentyl) phenanthrene (32) (1,20g, 62%) as an oil. τ 1,11 (1H, d, J9Hz, 5-H), 1,74 and 2,02 (2H, ABq, J8Hz, 9- and 10-H), 2,50 (1H, t, J8Hz, 6H), 3,04 (1H, d, J8Hz, 7-H), 4,84 br (1H, s, OH), 6,00 (3H, s, OCH_3), 6,15 (3H, s, OCH_3), 6,24 (3H, s, OCH_3), 7,50 (3H, s, CCH_3), 8,29 (6H, m, $\underline{CH\ CH_2\ CH_2\ CH}\ (CH_3)_2$), and 9,08 (6H, d, side chain CH_3).

1,4,8 - Trimethoxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (50)

The crude product from a Grignard reaction using the aldehyde (31) (1,08g), 3 - methylbromobutane (3,10g) and magnesium (0,50g) was dissolved in acetone (15 ml) and Jones reagent (4,3 ml) added dropwise to the solution at room temperature. The solution was stirred for 0,5 hours, and then partitioned between water and chloroform. Work up of the organic layer afforded a crude product (1,57g) which showed on t.l.c. that it was composed of two components. The reaction mixture was separated by preparative t.l.c. (1% ethyl acetate/light petroleum). A front band afforded 1,8 - dimethoxy - 2 - methyl - 3 - (4 - methylpenantoyl) - 4 - (4 - methylpentyl) phenanthrene (51) (0,09 g, 6%) as a clear oil. (Found : C, 80,05; H, 8,55. $C_{28}\ H_{36}\ O_3$ requires C, 79,95; H, 8,65%), τ 1,72 (2H, d, J9Hz, 5- and 9- or 10-H), 1,97

(1H, d, J9Hz, 9- or 10-H), 2,55 (1H, t, J9Hz, 6-H), 3,02 (1H, d, J9Hz, 7-H), 5,99 (3H, s, OCH_3), 6,14 (3H, s, OCH_3), 6,8 br (2H, s, Ar CH_2), 7,22 (2H, deformed t, J7Hz, CO CH_2 CH_2 CH $(CH_3)_2$), 7,68 (3H, s, Ar CH_3), 8,3 (6H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ (CH_{32}) and Ar CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,03 (12H, apparent triplet, side chain CH_3).

A second band gave the required ketone (50) as white needles (0,66g, 50%) m.p. 76 - 77° (from methanol). (Found : C, 75,8; H,7,6. C_{24} H_{28} O_4 requires C, 75,75; H, 7,4%), ν_{max} (Nujol) 1692, 1605, 1304, 1240, 960 cm^{-1}, τ 1,03 (1H, d, J9Hz, 5-H), 1,70 and 2,01 (2H, ABq, J9, 5Hz, 9- and 10-H), 2,48 (1H, t, J9Hz, 6H), 3,02 (1H, d, J9Hz, 7-H), 6,00, 6,13, and 6,26 (3H each, s, OCH_3), 7,05 (2H, deformed t, J7Hz,CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,66 (3H, s, Ar CH_3), 8,31 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,05 (6H, d, J6Hz, side chain CH_3).

trans - 4 - Formyl - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene (42)

The bromostilbene (19) (2,0g) in dry diethyl ether (60 ml) was treated dropwise with butyl lithium (1,6 ml of a 15,5% solution in hexane) under dry nitrogen. The mixture was stirred for 0,5 hours, and then dimethyl formamide (0,3 ml) was added, and stirring was continued for a further hour, after which time saturated ammonium chloride was added and the ethereal layer was separated, dried with sodium sulphate and evaporated to give crude material which was chromatographed on silica using 5% ethyl acetate/light petroleum as eluant. The yellow fraction was collected to afford aldehyde (42) as yellow needles (1,34g, 77%), m.p. 125 - 126° (from ethanol).

(Found : C, 70,15; H, 6,55. $C_{20}H_{22}O_5$ requires C, 70,2; H6,4%), ν_{max} (Nujol) 1668, 1592, 1250, 1108, 1095, 1042, 971, 770 718 cm^{-1}, τ -0,56 (1H, s, CHO), 2,13 and 2,51 (2H, ABq, J16Hz, *trans* CH=CH), 2,80 (1H, t, J8Hz, 4′-H), 2,91 (1H, s, 6-H), 3,41 (2H, d, J8Hz, 3′- and 5′-H), 6,06 (3H, s, OCH_3), 6,10 (6H, s, 2 x OCH_3), 6,39 (3H, s, OCH_3), and 7,45 (3H, s, CCH_3).

trans - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene - 4 - carboxylic acid (41)

The bromostilbene (19) (0,5g) in dry diethyl ether (50 ml) was treated dropwise with butyl lithium (0,55 ml of a 15,5% solution in hexane) under dry nitrogen. The mixture was stirred at room temperature for 0,5 hours, and then gaseous carbon dioxide was passed through for 1 hour. The solution was extracted with sodium hydroxide (5%) solution, and the basic solution acidified with dilute hydrochloric acid and re-extracted with chloroform. Evaporation of the chloroform solution gave crude acid (41) (0,44g, 97%). τ 0,20 br (1H, s, CO OH), 2,16 and 2,59 (2H, ABq, J16Hz, *trans* CH=CH), 2,72 (1H, t, J8Hz, 4′-H), 2,91 (1H, s, 6-H), 3,42 (2H, d, J8Hz, 3′- and 5′-H), 6,06 (3H, s, OCH_3), 6,10 (6H, s, 2 x OCH_3), 6,29 (3H, s, OCH_3), and 7,58 (3H, s, CCH_3).

On repeating the above reaction the yields were variable.

Methyl 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene - 4 - carboxylate (43)

(a) from the acid

The acid (41) (0,44g) was methylated with dimethyl sulphate (0,16g) and anhydrous potassium carbonate (0,5g) in dimethyl formamide (10 ml) by stirring overnight at room temperature. Work up as for the ester (28) afforded the product (43) as an oil. A sample was purified for analysis by preparative t.l.c. (5% ethyl acetate/light petroleum). (Found : C, 67,3; H, 6,8. $C_{21}H_{24}O_6$ requires C, 67,7; H, 6,5%), ν_{max} (neat) 3010, 2960, 2850, 1725, 1590, 1408, 1340, 1260, 1110, 1058, 777, 750 cm^{-1}, τ 2,18 and 2,62 (2H, ABq, J16Hz, *trans* CH=CH), 2,82 (1H, t, J8Hz, 4′-H), 2,96 (1H, s, 6-H), 3,41 (2H, d, J8Hz, 3′- and 5′-H), 6,09 (9H, s, 3 x OCH_3), 6,13 (3H, s, OCH_3), 6,28 (3H, s, OCH_3), and 7,76 (3H, s, CCH_3).

(b) from the aldehyde (42)

The aldehyde (42) (2,35g) in methanol (150 ml) was treated with sodium cyanide (7,1g) and acetic acid (2,3 ml). Activated manganese IV oxide(70g) was added and the whole stirred for 48 hours. The solution was filtered, the solvent evaporated off, and the residue partitioned between dilute aqueous sodium carbonate and ethyl acetate. The organic layer was washed with water, dried with sodium sulphate, and evaporated to yield an oil (2,56g, 100%) which was identical (R_f and ^{1}Hn.m.r.) with that obtained in (a) above. No further purification was required.

Methyl 1,4,8 - trimethoxy - 2 - methylphenanthrene - 3 - carboxylate (46)

The stilbene ester (43) (2,94g) was irradiated in cyclohexane (800 ml) through quartz (Vycor sleeve) for 3 hours. The crude product obtained by removing the solvent, was chromatographed on silica using 10% ethyl acetate/light petroleum as eluant, to afford the phenanthrene ester (46) (1,16g, 43%) as white needles, m.p. 121 - 122° (methanol). (Found : C, 70,9; H, 6,3. $C_{20}H_{20}O_5$ requires C, 70,6; H, 5,9%), ν_{max} (Nujol) 3010, 1728, 1609, 1596, 1312, 1260, 1245, 778, τ 1,04 (1H, d, J9Hz, 5-H), 1,68 and 2,00 (2H, ABq, J9, 5Hz, 9- and 10-H), 2,48 (1H, t, J9Hz, 6-H), 3,01 (1H, d, J9Hz, 7-H), 5,98 (6H, s, 2 x OCH_3), 6,13 (3H, s, OCH_3), 6,16 (3H, s, OCH_3), and 7,59 (3H, s, CCH_3).

1,4,8 - Trimethoxy - 2 - methylphenanthrene - 3 - ylmethanol (47)

The ester (46) (1,04g) in dry tetrahydrofuran (30 ml) was added dropwise at room temperature to a suspension of lithium aluminium hydride (0,6g) in dry tetrahydrofuran (70 ml), and the mixture was stirred for 4 hours. Work up as for compound (14) afforded the phenanthrene alcohol (47) (0,90g, 95%) as white needles, m.p. 144 - 145° (methanol). (Found : C, 72,8; H, 6,5. $C_{19}H_{20}O_4$ requires C, 73,1; H, 6,4%), ν_{max} (Nujol) 3330, 1618, 1592, 1295, 1260, 1070, 778 cm^{-1}, τ 0,98 (1H, d, J9Hz, 5-H), 1,73 and 2,02 (2H, ABq, J9, 5Hz, 9- and 10-H), 2,49 (1H, t, J9Hz, 6-H), 3,02 (1H, d, J9Hz, 7-H), 5,02 (2H, s, CH_2), 5,98 (3H, s, OCH_3), 6,14 (3H, s, OCH_3), 6,20 (3H, s, OCH_3), 7,46 (3H, s, CCH_3), and 7,56 br (1H, s, OH).

2,5 - Dimethoxy - 3,4,6 - trimethylbromobenzene (33)

2,3,5 - Trimethylhydroquinone (10g) was dissolved in acetic acid (100 ml) by warming gently. Bromine (3,4 ml) in acetic acid (25 ml) was added dropwise, and the mixture was stirred overnight at room temperature. The acetic acid was evaporated off under reduced pressure to give a silvery grey solid (probably a quinhydrone) which was taken up in diethyl ether and shaken with a solution of sodium hydrosulphite (5g) in water (100 ml). The organic layer was dried with sodium sulphate, the solvent evaporated off to afford 6 - bromo - 2,3,5 - trimethylhydroquinone (7,75g,51%) m.p. 183 - 184° (ethanol) (lit.,[32] 185°).

The bromo trimethyl hydroquinone (7,75g) together with dry potassium carbonate (14,7g) and dimethyl sulphate (6,35 ml) in dry acetone (150 ml) was stirred at reflux for 16 hours. The potassium salts were filtered off, washed with further acetone (150 ml) and the solvent evaporated off to yield 2,5 - dimethoxy - 3,4,6 - trimethyl-bromobenzene (33) (8,4g, 98%). A small portion was recrystallised from methanol to give colourless needles m.p. 72 - 73° (Lit.[33], 71 -72°), ν_{max} (Nujol) 1230, 1090, 1040 cm^{-1}, τ 6,26 (3H, s, OCH_3), 6,36 (3H, s, OCH_3), 7,65 (3H, s, CCH_3), 7,77 (3H, s, CCH_3) and 8,23 (3H, s, CCH_3).

2,5 - Dimethoxy - 3,4,6 - trimethylbenzonitrile (34)

The bromo compound (33) (1g) and copper (I) cyanide (1,04g) were heated under reflux in dry dimethyl formamide (100 ml) for 14 hours. The hot solution was poured into hydrochloric acid solution (2M, 250 ml) containing iron (III) chloride hexahydrate (3,4g). The mixture was stirred at 60 -75° for 0,5 hours, cooled and extracted with dichloromethane. This extract was washed with dilute hydrochloric acid, then with water, dried with sodium sulphate and the solvent evaporated. The residue (0,92g) was recrystallised from light petroleum to afford the product (34), m.p. 104 - 105°. (Found : C, 69,95; H, 7,1; N, 6,9. $C_{12}H_{15}NO_2$ requires C, 70,2; H, 7,35; N, 6,85%, ν_{max} (Nujol) 2235, 1600, 1263, 1087 cm^{-1}, τ 6,11 (3H, s, OCH_3), 6,32 (3H, s, OCH_3), 7,57, 7,75, and 7,81 (3H each, s, CCH_3).

2,5 - Dimethoxy - 3,4,6 - trimethylbenzaldehyde (35)

(a) by treatment of the bromo compound (33) with phenyl lithium and dimethylformamide

A solution of the bromo compound (33) (2,0g) in dry diethyl ether (20 ml) was added dropwise to a stirred solution of phenyl lithium [lithium (0,11g) and bromobenzene (1,22g) in dry diethyl ether (20 ml)] over a period of 10 minutes. The stirring was continued for 3 hours and then dimethylformamide (0,71g) in dry diethyl ether (20 ml) was added in 10 minutes. The mixture was stirred for a further 2 hours, and worked up by adding saturated

aqueous ammonium chloride solution, separating the organic layer, washing this layer with water, drying with sodium sulphate and evaporating the solvent to give a crude product. This product was chromatographed on silica using 5% ethyl acetate/light petroleum as eluant. Early fractions were unreacted starting material (1,50g) and later fractions afforded the aldehyde (35) (0,2g, 13%) m.p. 85°. (Found : C, 69,4; H, 7,8. $C_{12}H_{16}O_3$ requires C, 69,2; H, 7,8%), ν_{max} (Nujol) 1690, 1590, 1565, 1257, 1079 cm^{-1}, τ -0,44 (1H, s, CHO), 6,22 (3H, s, OCH_3), 6,34 (3H, s, OCH_3), 7,50, 7,72, and 7,78 (3H each, s, CCH_3).

(b) <u>by treatment of the bromo compound (33) with butyl lithium and dimethylformamide</u>

The bromo compound (33) (1g) in dry diethyl ether (30 ml) was treated dropwise with butyl lithium (1,9 ml of a 13,2% solution in hexane) under dry nitrogen. The mixture was stirred for 0,5 hours during which time a white precipitate formed, then dimethylformamide (0,3 ml) was added and the mixture stirred at room temperature for a further 1 hour. The reaction was worked up by adding saturated aqueous ammonium chloride solution, separating the organic layer, drying with sodium sulphate and evaporating off the solvent to afford the product (35) (0,78g, 97%) which was identical (R_f and ^{1}Hn.m.r.) with that obtained in (a) above.

(c) from 2,5 - dimethoxy - 3,4,6 - trimethylbenzylamine (36)

The substituted benzylamine (36) (0,3g) was dissolved in a small volume of concentrated hydrochloric acid and diluted with water to about four times the original volume and cooled to 0^{o}. Some solid sodium nitrite was added and after 10 minutes the diazonium salt was decomposed by heating in a boiling water bath for 0,5 hours. The organic material was extracted with dichloromethane, the organic layer washed with water, dried with sodium sulphate and the solvent evaporated off to give crude product which was chromatographed on silica using chloroform as eluant. The fractions collected were a mixture of 2,5 - dimethoxy - 3,4,6 - trimethylbenzylamine (36) and 2,5 - dimethoxy - 3,4,6 - trimethylbenzyl alcohol (37) in the ratio of 3 : 4 (0,16g).

The mixture so obtained (0,16g) was stirred at reflux for 90 hours with activated manganese (1V) oxide (3g) in chloroform (30 ml). The solid material was filtered off, washed with further quantities of chloroform and the combined filtrate and washings evaporated off to give a mixture (0,11g) of the benzylamine (36) and 2,5 - dimethoxy - 3,4,6-trimethylbenzaldehyde (35) as indicated by ^{1}H n.m.r. (Signal at τ -0.44 for CHO) in the ratio of 3:4.

1 - Phenylpentan - 1 - ol

Benzaldehyde (4,38g) in dry diethyl ether (5 ml) was added dropwise over a period of 10 minutes to a refluxing Grignard solution made from 1 - bromobutane (5,65g) and magnesium turnings (1,0g) in dry diethyl ether (15 ml). The mixture heated at reflux overnight, cooled and worked up by adding saturated aqueous ammonium chloride solution, and filtering off the precipitated salts. The filtrate was dried with sodium sulphate and the solvent evaporated off to give the alcohol (6,5g, 87%) τ 2,77 (5H, s, Ar-H), 5,48 (1H, deformed t, HO $\underline{CH}$ CH_2 CH_2 CH_2 CH_3), 7,08 br (1H, s, OH), 8,32 (2H, m, HO CH $\underline{CH_2}$ CH_2 CH_2 CH_3), 8,72 (4H, m, HO CH CH_2 $\underline{CH_2}$ $\underline{CH_2}$ CH_3), and 9,14 (3H, deformed t, side chain CH_3).

1 - (2,5 - Dimethoxy - 3,4,6 - trimethyl)phenyl - 1 - pentanone (39)

The aldehyde (35) (0,3g) in dry diethyl ether (10 ml) was added dropwise to a Grignard solution prepared from 1 - bromobutane (1,42g) and magnesium turnings (0,25g) in 15 ml dry diethyl ether. The mixture was heated under reflux for 6 hours and then stirred at room temperature overnight. Work up of the reaction afforded the crude alcohol (38) (0,41g). The crude alcohol was dissolved in A.R. acetone (10 ml) and Jones reagent was added until the solution showed a persistent light orange colour. The mixture was stirred at room temperature for 0,5 hours, water (100 ml) was added. The aqueous solution was extracted with diethyl ether, the extract washed with water, dried with sodium sulphate and the solvent evaporated to afford the crude product (39) (0,34g).

Irradiation of *trans* - 4 - bromo - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene (19)

The above stilbene (19) (0,30g) in Merck Uvasol cyclohexane (800 ml) was irradiated through quartz using a Vycor sleeve for 2,5 hours. The crude yield (0,3g) from the irradiation was chromatographed on silica using 10% ethyl acetate/light petroleum as eluant. Fractions containing two different products were collected neither of which was the desired phenanthrene (40).

2, 2′, 5, 6′ - Tetramethoxy - 4 - (1 - hydroxy - 4 - methylpentyl) - 3 - methylstilbene (44).

4 - Formyl - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene (42) (1,3g) in dry diethyl ether (15 ml) was added to the Grignard solution prepared from bromo - 4 - methylpentane (0,7g) and magnesium turnings (0,113g) in dry diethyl ether (15 ml). The mixture was stirred and heated under reflux for 2 hours and then worked up by adding saturated aqueous ammonium chloride solution, separating the organic layer, drying with sodium sulphate and evaporating off the diethyl ether to give a crude orange oil. The oil was purified by preparative t.l.c. (eluant 15% ethyl acetate/light petroleum) to afford the compound (44) (0,13g, 8%). ν_{max} (neat) 3540, 1675, 1582, 1460, 1400, 1335, 1250, 1100, 1010, 970 cm^{-1}, τ 2,17 and 2,69 (2H, ABq, J17Hz, *trans* CH=CH), 2,77 (1H, t, J6Hz, 4′-H), 2,92 (1H, s, 6-H), 3,41 (2H, d, J8H, 3′- and 5′-H), 5,20 (1H, dxd, J6Hz, CH OH CH_2 CH_2 CH $(CH_3)_2$), 6,06 (3H, s, OCH_3), 6,10 (3H, s, OCH_3), 7,73 (3H, s, OCH_3), 8,50 (5H, m, CH OH CH_2 CH_2 CH $(CH_3)_2$), and 9,11 (6H, d, J6Hz, side chain CH_3).

Irradiation of 2, 2′, 5, 5′ - tetramethoxy - 4 - (4 - methyl - 1 - hydroxypentyl) - 3- methylstilbene (44)

The above stilbene (44) (0,13g) in Merck Uvasol cyclohexane (800 ml) was irradiated through quartz using a Vycor sleeve for 5,5 hours. At this stage t.l.c. indicated that all the starting material had disappeared but that a very large number of products had been formed, indicating that this was not a satisfactory method of obtaining a phenanthrene.

1,4,8 - Trihydroxy - 2 - methyl - 3-(4 - methylpentanoyl) phenanthrene (52)

The ketone (50) (0,6g) in dry dichloromethane was added dropwise to a stirred solution of boron tribromide (1,43g) in dry dichloromethane (15 ml) at -75°. Stirring at this temperature was continued for 1 hour and then for 2 hours at room temperature. This mixture was worked up by cautiously adding water, and finally shaking vigorously with water in a separating funnel. The organic layer was separated, dried with sodium sulphate and evaporated to afford the product (52) (0,45g, 84%), τ -2,90 (1H, s, 4-OH), 0,72 (1H, d, J9Hz, 5-H), 1,73 and 2,12 (2H, ABq, J9Hz, 9- and 10-H), 2,6 (1H, t, J9Hz, 6-H), 3,06 (1H, d, J9Hz, 7-H), 4,25 br (1H, s, OH), 5,15 br (1H, s, OH), 7,12 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,55 (3H, s, CCH_3), 8,34 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,12 (6H, d, J6Hz, side chain CH_3).

1,4,8 - Triacetoxy - 2 - methyl - 3-(4 - methylpentanoyl) phenanthrene (53)

Crude trihydroxy compound (52) (0,5g) was heated on a steam bath for 2 hours with a mixture of dry pyridine (4 ml) and acetic anhydride (4 ml), cooled and allowed to stand at room temperature overnight. The acetylating mixture was removed by evaporation firstly on a Buchi rotary evaporator and finally by high vacuum. The crude product was purified by preparative t.l.c. using dichloromethane as eluant. Two bands were removed from the plate. The first band proved to be the monomethoxy diacetoxy compound (56) (0,2g, 31%) as white needles, m.p. 194 - 195° (methanol/dichloromethane). (Found : C, 71,50; H, 6,47. $C_{26}H_{28}O_6$ requires C, 71,54; H, 6,47%), τ 1,51 (1H, d, J5Hz, 5H), 1,70 and 2,35 (2H, ABq, J9Hz, 9- and 10-H), 2,45 (1H, t, J5Hz, 6-H), 3,02 (1H, d, J5Hz, 7-H), 6,02 (3H, s, OCH_3), 7,12 (2H, deformed t, J8Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,51 (3H, s, CO CH_3), 7,63 (3H, s, CO CH_3), 7,78 (3H, s, CCH_3), 8,33 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,06 (6H, d, J5Hz, side chain CH_3).

A second band afforded the desired triacetoxy compound (53) (0,25g, 36%) as white needles, m.p. 205 - 206° (methanol/dichloromethane). (Found : C, 69,7; H, 6,25. $C_{27}H_{28}O_7$ requires C, 69,81; H, 6,08%). ν_{max} (Nujol) 1756, 1694, 1230, 1205, 1164 cm^{-1}, τ 1,18 (1H, d, J8Hz, 5-H), 2,11 and 2,32 (2H, ABq, J9Hz, 9- and 10-H), 2,40 (1H, t, J9Hz, 6-H), 2,64 (1H, d, J8Hz, 7-H), 7,10 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,50 (3H, s, CO CH_3), 7,54 (3H, s, CO CH_3), 7,61 (3H, s, CO CH_3), 7,76 (3H, s, CCH_3), 8,32 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,04 (6H, d, J6Hz, side chain CH_3).

4 - Acetoxypiloquinone (57)

Chromium VI oxide (55 mg) in 96% acetic acid (0,5 ml) and water (0,3 ml) was added dropwise to the triacetoxy compound (53) (50 mg) in 96% acetic acid (2,5 ml). The reaction mixture was stirred and heated at 65 - 67° for 0,75 hours, poured into water (50 ml) and extracted with dichloromethane until the organic layer showed no more orange colour. The dichloromethane extract was washed successively with 10% aqueous sodium bicarbonate solution and water, dried with sodium sulphate and evaporated to give crude triacetoxy quinone (54) (37 mg) m.p. 215 - 220°.

The impure compound (54) was loaded on to a preparative t.l.c. and developed with 20% ethyl acetate/light petroleum and a maroon band was removed from the plate. ^{1}Hn.m.r. indicated that this band was 4 - acetoxypiloquinone (57) (10 mg, 23%) as maroon needles, m.p. 180 - 182°. (Found : C, 67,15; H, 5,70. $C_{23}H_{22}O_7$ requires C, 67,31; H, 5,40%), ν_{max} ($CHCl_3$) 3630, 3450, 1780, 1710, 1632 cm^{-1}, τ -3,06 (H, s, OH), -2,40 (1H, s, OH), 2,20 (1H, d, J8Hz, 5-H), 2,46 (1H, t, J8Hz, 6-H), 3,00 (1H, d, J8Hz, 7-H), 7,26 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$) 8,36 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,05 (6H, d, J6Hz, side chain CH_3).

Attempted acetylation of 4 - acetoxypiloquinone (57)

4 - Acetoxypiloquinone (57) (9,9 mg) was stirred for 3 hours at room temperature with dry pyridine (0,5 ml) and acetic anhydride (0,5ml). The solvent was evaporated off under reduced pressure to give crude compound (54) (10,4 mg), τ 1,95 (1H, d, J8Hz, 5-H), 2,35 (1H, t, J8Hz, 6-H), 2,90 (1H, d, J8Hz, 7-H), 7,26 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,60 (3H, s, CO CH_3), 7,64 (3H, s, CO CH_3), 7,78 (3H, s, CO CH_3), 7,88 (3H, s, CCH_3), 8,35 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,05 (6H, d, J6Hz, side chain CH_3). All efforts to recrystallise the crude material failed, and this crude material was subjected to further treatment as above, the stirring being carried on overnight. This treatment destroyed the compound.

Attempted diacetylation of 1,4,8 - trihydroxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (52)

The above triol (52) (0,3g) in dry tetrahydrofuran (20 ml) was stirred overnight at room temperature with acetic anhydride (0,2 g) and dry pyridine (0,2 ml). ^{1}Hn.m.r. indicated that the product of this reaction was 4 - acetoxy - 1,8 - dihydroxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (59). τ 0,64 (1H, d, J9Hz, 5-H), 1,70 and 1,83 (2H, ABq, J8Hz, 9- and 10-H), 2,28 (1H, t, J8Hz, 6-H), 2,59 (1H, d, J8Hz, 7-H), 3,68 br (2H, s, 2 x OH), 7,19 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,48 (3H, s, CO CH_3), 7,87 (3H, s, CCH_3), 8,29 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), 9,02 (6H, d, J5Hz, side chain CH_3).

Reaction of 1,8 - dimethoxyphenanthrene

(a) With 3 - chloroperbenzoic acid

3 - chloroperbenzoic acid (0,15g) was added portionwise to a cooled, stirred solution of 1,8 - dimethoxyphenanthrene (0,16g) in dichloromethane (15 ml). After stirring for 0,5 hours, t.l.c. showed only starting materials so more 3 - chloroperbenzoic acid (0,1g) was added and stirring continued for a further 0,25 hours. Once more t.l.c. showed only starting materials. The experiment was abandoned.

(b) With osmium VIII oxide and pyridine in diethyl ether

(i)

1,8 - Dimethoxyphenanthrene (0,2g), osmium VIII oxide (0,24g) in a mixture of dry pyridine (10 ml) and dry diethyl ether (12 ml) were stirred at room temperature for 0,75 hours. Sodium bisulphite (0,8 g) in water (16 ml) and pyridine (16 ml) was added and the mixture stirred for 0,5 hours, further diluted with water (150 ml) and extracted with chloroform. The extract was dried with sodium sulphate and the solvent removed to give back starting material as indicated by t.l.c. and ^{1}Hn.m.r.

(ii)

The above experiment was repeated using the starting material from (1), osmium V111 oxide (0,26g), pyridine (0,3g) in dry benzene (15 ml). The reaction was stirred at room temperature for 7 days and then worked up as in (i) to give back starting material as indicated by t.l.c.

(c) With osmium V111 oxide in dry pyridine

1,8 - Dimethoxyphenanthrene (0,2g) together with osmium V111 oxide (0,26g) in dry pyridine (15 ml) was stirred at room temperature for 5 days and worked up as in (b) (i) to give a 50/50 mixture of 1,8 - dimethoxyphenanthrene and 1,8 - dimethoxy - 9,10 - dihydroxy - 9,10 - dihydrophenanthrene (63) as indicated in the ^{1}Hn.m.r. spectrum of the mixture by a signal at τ 4,80 for the 9,10 - methine protons.

1,4,8 - Trimethoxy - 2 - methyl - 3(4 - methylpentanoyl) - 9,10 - dihydroxy - 9,10 - dihydrophenanthrene (60)

The phenanthrene (50) (51,2 mg) and osmium V111 oxide (100 mg) in dry pyridine (15 ml) was stirred at room temperature for 7 days. The pyridine was evaporated off and the crude product purified by chromatography on silica the eluant being progressively change from 10% ethyl acetate/light petroleum to 20% ethyl acetate/light petroleum. Three fractions were separated and were shown to be respectively

starting material (50) (13 mg), the quinone (61) (3 mg) and the product (60) (17 mg). ν_{max} ($CHCl_3$) 3440, 1700, 1600, 1470, 1390, 1240, 1090, 1013, 969 cm^{-1}, τ 2,00 (1H, d, J8Hz, 5-H), 2,68 (1H, t, J8Hz, 6-H), 3,10 (1H, d, J8Hz, 7-H), 4,84 and 4,94 (2H, ABq, J4Hz, 9- and 10-H), 5,98 br (2H, s, 2 x OH), 6,06 (3H, s, OCH_3), 6,12 (3H, s, OCH_3), 6,56 (3H, s, OCH_3), 7,18 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,82 (3H, s, CCH_3), 8,36 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,05 (6H, d, side chain CH_3).

Oxidation of 1,4,8 - trimethoxy - 2 - methyl - 3-(4 - methylpentanoyl) - 9,10 - dihydroxy - 9,10 - dihydrophenanthrene (60)

(a) With silver 1 oxide

The phenanthrene (60) (17 mg), silver 1 oxide (100 mg) and dry magnesium sulphate (100 mg) in dry benzene (15 ml) was stirred at room temperature for 1 hour. t.l.c. showed that only starting material was present.

(b) With 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ)

The phenanthrene (60) (17 mg) together with DDQ (20 mg) in dry benzene (10 ml) was stirred at room temperature for 20 hours. t.l.c. showed that only starting material was present.

(c) With pyridinium chlorochromate

The phenanthrene (60) (22,3mg) and pyridinium chlorochromate (36,5 mg) in dry dichloromethane (5 ml) were stirred at room temperature for 20 hours. No visible black precipitate formed but the orange colour of the pyridinium chlorochromate had been discharged so dry diethyl ether (25 ml) was added to the mixture and the brown precipitate filtered off. The solvent was evaporated off and the resulting oil chromatographed on silica using chloroform as eluant to afford the quinone (61) (19,3 mg, 87%) as an oil which later crystallised to give yellow platelets, m.p. 139 - 140°. (Found : C, 69,85; H, 6,3. $C_{24}H_{26}O_6$ requires C, 70,2; H, 6,4%), ν_{max} ($CHCl_3$) 1685, 1585, 1470, 1390, 1240, 1090, 1013, 969 cm^{-1}, τ 1,87 (1H, d, J8Hz, 5-H), 2,38 (1H, t, J8Hz, 6-H), 3,00 (1H, d, J8Hz, 7-H), 6,05 (3H, s, OCH_3), 6,13 (3H, s, OCH_3), 6,45 (3H, s, OCH_3), 7,19 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 $CH(CH_3)_2$), 7,85 (3H, s, CCH_3), 8,34 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,04 (6H, d, side chain CH_3).

Bromination of 2,5 - dimethoxy - 3 - methylbenzaldehyde (9)

The aldehyde (9) (0,25g) was dissolved in acetic acid (10 ml) and bromine (0,23g) in acetic acid (5 ml) was added. The mixture was heated under reflux for 0,5 hours, cooled slightly, and the acetic acid evaporated off. The resulting brown oil was taken up in diethyl ether (20 ml) and washed with 10% aqueous sodium carbonate solution, and then with water. The ethereal solution was dried with sodium sulphate and the solvent evaporated to afford a yellow solid (0,29g).

^{1}Hn.m.r. showed that this was a mixture of 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzaldehyde (10) and the 6 - bromo - isomer in roughly equal proportions.

Reaction of 2,5 - dimethoxy - 3,4,6 - trimethylbenzonitrile (34)

(a) With lithium aluminium hydride (LAH)

The nitrile (34) (0,5g) in dry diethyl ether (20 ml) was added dropwise to a stirred slurry of LAH (0,25g) in dry diethyl ether (20 ml). The mixture was heated under reflux for 2 hours, cooled, and 5M sulphuric acid (50 ml) was added. The aqueous phase was washed with dichloromethane (2 x 25 ml) and then rendered alkaline by adding solid sodium hydroxide. The basified aqueous solution was extracted with dichloromethane, the extract was washed with water, dried with sodium sulphate and the solvent removed to give crude 2,5 - dimethoxy - 3,4,6 - trimethylbenzylamine (36) (0,49g). τ 6,18 (2H, s, CH_2), 6,30 (3H, s, OCH_3), 6,38 (3H, s, OCH_3), 7,72 (3H, s, CCH_3), 7,84 (6H, s, CCH_3), and 8,33 (2H, s, NH_2).

(b) With potassium hydroxide

The nitrile (34) (0,7g) and potassium hydroxide (7,0g) in a mixture of ethanol (5 ml) and water (15 ml) were heated under reflux for 72 hours. Most of the ethanol was removed by distillation and a further quantity of water (80 ml) was added to the reaction mixture, which was then extracted with diethyl ether.

The extract was washed with water, dried with sodium sulphate and the solvent evaporated off to afford crude 2,5 - dimethoxy - 3,4,6 - trimethylbenzamide (0,59g, 82%). ν_{max} (Nujol) 3370, 3195, 1656, 1246, 1076 cm^{-1}, τ 3,61 br (1H, s, NH), 3,78 br (1H, s, NH), 6,29 (3H, s, OCH_3), 6,36 (3H, s, OCH_3), 7,72 (3H, s, CCH_3), 7,82 (3H, s, CCH_3), and 7,88 (3H, s, CCH_3).

1 - (2,5 - Dimethoxy - 3,4,6 - trimethylphenyl) - 1 - pentanol (38)

The aldehyde (35) (0,3g) in dry diethyl ether (10 ml) was added to the Grignard solution prepared from 1 - bromobutane (1,42g) and magnesium turnings (0,25g) in dry diethyl ether (30 ml). The mixture was heated under reflux for 6 hours, and then stirred overnight at room temperature. Saturated aqueous ammonium chloride solution was added and the ethereal layer separated, washed with water, dried with sodium sulphate and evaporated off to give the crude product (38) (0,38g). τ 5,01 (1H, m, $\underline{CH}$ OH CH_2 CH_2 CH_2 CH_3), 6,25 (3H, s, OCH_3), 6,38 3H, s, OCH_3), 7,75 (3H, s, CCH_3), 7,82 (6H, s, 2 x CCH_3), 8,73 (6H, m, CH OH $\underline{CH_2\ CH_2\ CH_2}$ CH_3), and 9,08 (3H, deformed t, side chain CH_3).

Attempted demethylation of 1,4,8 - trimethoxy - 2 - methyl - 3-(4 - methylpentanoyl) - 9,10 - phenanthraquinone (61)

(a) With boron tribromide

The quinone (61) (0,2g) in dry dichloromethane (10 ml) was added dropwise to a cooled (-75^{o}) solution of boron tribromide (0,53g) in dry dichloromethane (10 ml). After stirring at -75^{o} for 0,75 hours the mixture was stirred at room temperature for a further 2 hours, and then worked up by pouring it into water (150 ml), separating the organic layer, drying with sodium sulphate and evaporating off the solvent. Preparative t.l.c. using chloroform as eluant showed that a large number of products had been formed in the reaction. A red band was removed from the plate but ^{1}Hn.m.r. indicated that this was not the hoped for 4 - hydroxypiloquinone (2).

(b) With boron trichloride

The quinone (61) (10 mg) in dry dichloromethane (10 ml) was added dropwise to a cooled (-10^{o}) solution of boron trichloride (20 mg) in dry dichloromethane (2 ml). After 1 minute the freezing mixture was removed and the reaction mixture was stirred at room temperature for a further 0,5 hours and then worked up as in (a) above.

A reddish/orange band (7 mg) plus starting material (1 mg) was obtained by preparative t.l.c. (eluant chloroform). From the

^{1}Hn.m.r. spectrum of the reddish/orange band it appeared that boron trichloride had removed only one O - methyl group. τ 1,93 (1H, d, J8Hz, 5-H), 2,44 (1H, t, J8Hz, 6-H), 3,09 (1H, d, J8Hz, 7-H), 6,08 (3H, s, OCH_3), 6,16 (3H, s, OCH_3), 7,09 (2H, deformed t, J6Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,60 (3H, s, CCH_3), 8,34 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$), and 9,08 (6H, d, side chain CH_3). No signal for the hydroxyl proton could be identified. A mass spectrum of this compound gave the molecular ion $^M/_e$ as 396.

Reaction of 1,4,8 - trihydroxy - 2 - methyl - 3-(4 - methylpentanoyl) phenanthrene (52) with osmium V111 oxide

The phenanthrene (52) (39 mg) and osmium V111 oxide (100 mg) in dry pyridine (30 ml) were stirred at room temperature for 21 hours. The reaction mixture was worked up by adding sodium bisulphite (0,5g) in water (50 ml) and stirring for a further 0,5 hours. After dilution to 400 ml with water, the organic material was extracted with chloroform. The extract was dried with sodium sulphate and the solvent evaporated off to give a crude product which was chromatographed on preparative t.l.c. using chloroform as eluant.

A number of bands were removed from the plate but none gave any indication by ^{1}Hn.m.r. of the presence of a 9,10 - dihydroxy - 9,10 - dihydro compound.

Attempted oxidation of 1,4,8 - trimethoxy - 2 - methyl - 3 - (4 - methylpentanoyl) phenanthrene (50) at the 9,10 - position using chromium (Vl) oxide in acetic acid

The phenanthrene (50) (50 mg) was dissolved in 96% acetic acid (2,5 ml) by heating to 70°. A solution of chromium (Vl) oxide (55 mg) in 96% acetic acid (0,5 ml) and water (0,3 ml) was added dropwise and the reaction mixture was stirred and heated at 65 - 67° for 0,75 hours. The reaction mixture was poured into water (100 ml) and extracted with chloroform until no more orange colour showed. The chloroform extract was washed successively with 10% aqueous sodium carbonate solution and water. The organic layer was dried with sodium sulphate and evaporated off to afford 8 - methoxy - 2 - methyl - 3 - (4 - methylpentanoyl) - 1,4 - phenanthraquinone (45) (13 mg, 28%) as red needles, m.p. 135 - 137°. (Found : M^+ 350. $C_{22}H_{22}O_4$ requires M.M. 350), ν_{max} ($CHCl_3$), 1704, 1664, 1600, 1584, 1458, 1230 cm^{-1}, τ 0,96 (1H, d, J9Hz, 5-H), 1,32 and 1,87 (2H, ABq, J9Hz, 9- and 10-H), 2,37 (1H, t, J8Hz, 6-H), 3,02 (1H, d, J8Hz, 7-H), 5,96 (3H, s, OCH_3), 7,21 (2H, deformed t, J7Hz, CO $\underline{CH_2}$ CH_2 CH $(CH_3)_2$), 7,90 (3H, s, CCH_3), 8,36 (3H, m, CO CH_2 $\underline{CH_2}$ $\underline{CH}$ $(CH_3)_2$, and 9,04 (6H, d, J6Hz, side chain CH_3).

Di - O - methylpiloquinone

Piloquinone (1) (30 mg) in chloroform (10 ml) with silver 1 oxide (150 mg), magnesium sulphate (100 mg) and iodomethane (2 ml) were stirred at room temperature until t.l.c. showed that all the starting material had reacted. The solid materials were filtered off, and the solvent removed to give 35 mg of crude di - O - methylpiloquinone. ^{1}Hn.m.r. τ 2,31 (1H, s, 4-H), 2,43 (2H, m, 5- and 6-H), 2,96 (1H, d, J7Hz, 7-H), 6,03 (3H, s, OCH_3), 6,10 (3H, s, OCH_3), 7,08 (2H, deformed t, J7Hz, $CO\underline{CH_2}CH_2CH(CH_3)_2$), 7,67 (3H, s, CCH_3), 8,34 (3H, m, $CH_2\underline{CH_2}\underline{CH}(CH_3)_2$), 9,04 (6H, d, J6Hz, side chain CH_3).

Attempted tri - O - methylation of 4 - hydroxypiloquinone

4 - Hydroxypiloquinone (2) (10 mg) in chloroform (10 ml) with silver 1 oxide (100 mg), magnesium sulphate (100 mg) and iodomethane (2 ml) were stirred at room temperature until t.l.c. showed that all the starting material had reacted. The solid materials were filtered off, and the solvent removed to give a crude product which was subjected to preparative t.l.c. using 10% ethyl acetate/petroleum ether as eluant. None of the bands removed from the plate proved to be the desired 1,4,8 - trimethoxy - 2 - methyl - 3-(4 - methylpentanoyl) - 9,10 - phenanthraquinone (61).

APPENDIX

1. Irradiation of formyl stilbenes

Irradiation of the *trans*-formyl stilbene (42) was carried out under a variety of conditions as indicated below. None of the experiments gave a good yield of the formyl phenanthrene (31), and it is noteworthy that, in every case where irradiation was carried on until the starting material had been completely consumed (as indicated by t.l.c.), negligible yields of the formyl phenanthrene (31) were obtained.

(a) Two experiments were carried out in which a cyclohexane solution of the formyl stilbene was irradiated through quartz using a Vycor sleeve. In the first experiment irradiation of a mixture of *cis*- and *trans*-formyl stilbenes (1 : 1) was carried out for 0,75 hours, and in the second experiment, pure *trans*-formyl stilbene (42) was irradiated for 3 hours. In neither case could the presence of a formyl phenanthrene be detected by either t.l.c. or ^{1}Hn.m.r.

In all the following experiments pure *trans*-formyl stilbene (42) was used as the starting material.

(b) In a further set of two experiments, the conditions used were the same as in (a) above, except that irradiation was carried out in an atmosphere of high purity nitrogen.

In the first experiment samples were taken at irregular intervals, and when it became apparent that no further formyl phenanthrene was being formed, the irradiation was stopped and the reaction mixture worked up to give an 8% yield of formyl phenanthrene (31), based on unrecovered starting material.

In the second experiment, irradiation was continued until all the starting material had reacted. In this case no formyl phenanthrene was detectable amongst the many reaction products formed.

(c) In a single experiment, the procedure used by Sargent[6] to produce methyl 1 - methoxy - 2 - methyl - phenanthrene - 3 - carboxylate from its stilbene precursor were followed (Cyclohexane solution with a Pyrex inner tube and no filter). At no stage of the irradiation could the presence of a phenanthrene be detected by t.l.c.

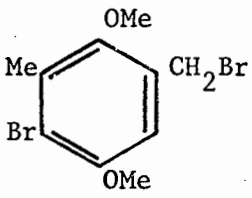
(d) A further two irradiations were carried out under conditions described by Leznoff[34] (Benzene solution with a Pyrex inner tube and no filter in the presence of iodine). After only 40 minutes, the starting formyl stilbene had all reacted and only a trace of formyl phenanthrene (31) was detected by t.l.c. Further irradiation (up to 5,5 hours) did not afford further formyl phenanthrene (31).

(e) A further two irradiations were carried out under similar conditions to (d) above except that no iodine was added. In the first experiment irradiation was carried on for a total period of two hours by which time it was apparent that no more formyl phenanthrene was being formed. On work up, a 13% yield (based on unrecovered starting material) of formyl phenanthrene (31) was obtained.

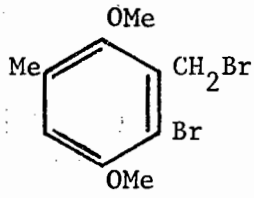
In a second experiment irradiation was carried out for 5,25 hours, by which time all the starting material had disappeared, and only traces of formyl phenanthrene were detected by t.l.c.

On the basis of these experiments, it appears that irradiation of the *trans*-formyl stilbene (42) to give the phenanthrene aldehyde (31) directly, does not give superior results to those obtained by the indirect method originally employed to effect this part of the synthesis. (See pages 26 to 28)

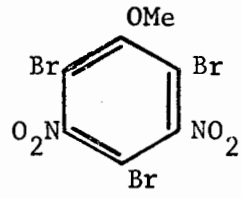
2. ^{13}Cn.m.r. spectroscopy of 4 - bromo - 2,5 - dimethoxy - 3 - methyl-benzylbromide (12) and 6 - bromo - 2,5 - dimethoxy - 3 - methyl-benzylbromide (16).



(12)



(16)



(69)

The ^{13}Cn.m.r. spectra of the compounds (12), (16) and (69) are shown in figures 1V, V and V1 on pages 102 to 104. Initially the spectra of compounds (12) and (16) were examined to see if these proton coupled spectra would provide a facile method of assigning the correct structure to the two isomers. In each case the C4 (or C6) H, C3 - CH_3, and C1 - CH_2Br resonances can be unambiguously assigned.

From a report[35] of the proton coupled spectrum of toluene, a ^3J value of 4,5 - 5,0Hz for CH_2X - CH and CH_2X - CH (where X = H or Br) might be expected. The observed ^3J coupling constants (see table on page93) of 5,0 - 6,5 Hz are, however, somewhat larger than those found in toluene. Thus, for one of the compounds, the signal due to the ring carbon atom carrying only a proton (C-4 in this case) is split into a large doublet (^{1}JC - H), each resonance of which is further split into a quartet (^3J = 5,0 Hz); this must arise from coupling to the adjacent C - CH_3 protons. Similarly, the methyl carbon resonance has a doublet fine structure (^3J = 5,9 Hz). The carbon resonance of the - CH_2Br group is a triplet with no additional splitting, this confirming that the species is in fact compound (16).

In the other species (compound 12) the resonance of the ring carbon atom at position 6 has a triplet fine structure, (^3J = 5,8 Hz) and the - CH_2Br resonance a doublet fine structure, (^3J = 6,5 Hz), and the methyl carbon resonance is a quartet with no additional splitting. This confirms the species as being compound (12).

Thus the isomers (12) and (16) could readily be distinguished by ^{13}Cn.m.r. spectroscopy, but it was immediately clear from an examination of the proton coupled spectra that an almost comple te,

(OCH_3 at position 2 and 5 can not be distinguished from one another), assignment of the resonances would be possible if the coupling of the methoxy protons to the ring carbons was known.

Since the proton coupled spectrum of anisole has not been reported, 3,5 - dinitro - 2,4,6 - tribromoanisole (69) was synthesised; a proton coupled spectrum of this compound showed that only C - 1 had any fine structure (^3J = 4,1 Hz).

Thus, in compound (12) the resonance at δ 150,20 is a large multiplet and must be C-2, showing coupling to the protons of the methoxyl, methyl and bromomethyl groups. The resonance at δ 151,68 is broad with a non-resolvable structure and is assigned to C - 5. The resonance at δ 114,96 in the spectrum of compound (12) is a double quartet, rather poorly resolved with coupling constant of about 6 or 7 Hz, is assigned to C - 4. The resonance at δ 129,24 shows a small triplet structure, is assigned to C - 1, whilst the resonance at δ 132,72 shows a well resolved quartet, and is assigned to C - 3 (^3J = 5,9 Hz).

The assignment of the resonances of the compound (16) follows from a similar examination of the resonance structures in its ^{13}C n.m.r. spectrum.

	C1	C2	C3	C4	C5	C6	C2-O<u>C</u>H$_3$ or C5-O<u>C</u>H$_3$	C3-<u>C</u>H$_3$	C1-<u>C</u>H$_2$Br
Compound (12)	129,24	150,20	132,72	114,96	151,68	109,80	55,86 / 60,72	16,48	27,60

^{3}JC1-<u>C</u>H$_2$Br-C6-<u>H</u> = 6,5Hz

^{3}J<u>C</u>6-C1-<u>C</u>H$_2$Br = 5,8Hz

Compound (16)	132,54	151,67	131,40	114,96	152,96	112,31	56,68 / 61,32	14,23	28,81

^{3}JC3-<u>C</u>H$_3$-C4-H = 5,9Hz

^{3}J<u>C</u>4-C3-<u>C</u>H$_3$ = 5,0Hz

Compound (69)	156,84	112,84	152,20	101,44	152,20	112,84	C1-O<u>C</u>H$_3$ δ = 61,50		

^{3}JO<u>C</u>H$_3$-<u>C</u>1 = 4,1Hz

^{4}J = 0

EXPERIMENTAL

1. Irradiation of 4 - formyl - 2, 2′, 5, 6′ - tetramethoxy - 3 - methylstilbene (42)

(a) In cyclohexane solution through quartz with a Vycor sleeve.

(i) 0,21 g of the pure *trans*-formyl stilbene (42) was irradiated for 3 hours by which time t.l.c. indicated that all the starting material had reacted but no phenanthrene had been formed. A ^{1}Hn.m.r. spectrum of the product of the reaction showed no peaks in the range 0 to 4τ.

(ii) 0,17g of a 1 : 1 mixture of *cis*- and *trans*-formyl stilbenes was irradiated for 0,75 hours. All the starting material had reacted but no phenanthrene was detectable by either t.l.c. or ^{1}Hn.m.r. spectroscopy.

(b) The conditions used were the same as in (a), but the irradiations were carried out in an atmosphere of dry nitrogen.

(i) 0,16g of pure *trans*-formyl stilbene (42) was irradiated for consecutive periods of 30, 20, 35, 35, 50 and 35 minutes. A new product formed after about 1,5 hours of irradiation, but the relative amount of this product

in the reaction mixture (as indicated by t.l.c.), did not appear to increase on further irradiation; the solvent was removed and the products of reaction separated by column chromatography using 5 - 10% ethyl acetate/ petroleum ether as eluant. The product (31) (65 mg, 8% yield calculated on unrecovered starting material) was eluted from the column first, and had an ^{1}Hn.m.r. spectrum identical with that of the authentic material. A later fraction afforded 73 mg of the starting material.

(ii) 50 mg of the pure *trans*-formyl stilbene (42) was irradiated as in (b) (i) for 5,5 hours by which time all of the starting material had reacted, but no traces of phenanthrene could be detected by t.l.c.

(c) In cyclohexane solution through a Pyrex inner tube with no sleeve.

(i) 73 mg of pure *trans*-formyl stilbene was irradiated for 6,75 hours by which time no starting material or phenanthrene product could be detected by t.l.c.

(d) In dry benzene through a Pyrex inner tube with no sleeve.

(i) 100 mg of pure *trans*-formyl stilbene, together with 126 mg iodine, was irradiated in an atmosphere of dry nitrogen for 0,65 hours. Thin layer chromatography of

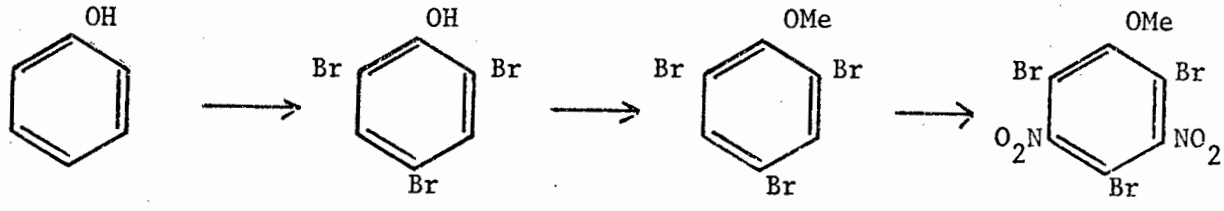
the reaction mixture showed that the starting material had all reacted and that a trace amount of the phenanthrene (31) had been formed.

(ii) 106 mg of pure *trans*-formyl stilbene (42) was irradiated in an atmosphere of dry nitrogen for consecutive periods of 15, 20, 30, 55 and 30 minutes. A new product formed rapidly (after 35 minutes of irradiation), but the relative amount of this product in the reaction mixture, (as indicated by t.l.c.), did not appear to increase on further irradiation. The solvent was removed and the reaction mixture separated into its components as in (b) (i).

59 mg of starting material was recovered and 5,3 mg of the product (31) isolated; the yield calculated on unrecovered starting material was 13%.

(iii) 82 mg pure *trans*-formyl stilbene (42) was irradiated in an atmosphere of dry nitrogen for 5,25 hours by which time t.l.c. indicated that all the starting material had reacted and that no trace of the phenanthrene (31) was present.

2. Synthesis of 3,5 - dinitro - 2,4,6 - tribromoanisole (69)



(69)

The required compound (69) was prepared in threee steps.

Step one involved treating phenol (9,4g) in acetic acid (120 ml) with bromine (30 ml). The reaction mixture was poured into cold water (1 litre) and the precipitate was filtered off and washed with a further amount of water (800 ml). The crude yield of 2,4,6 - tribromophenol was 32,5g. ^{1}Hn.m.r. τ 2,40 (s, 2H, 3- and 5-H), 4,13 (s, OH).

10g of 2,4,6 - tribromophenol was dissolved in 96% ethanol (75 ml) and warmed to 50^{o}C. Dimethyl sulphate (3 ml) and 10 M sodium hydroxide (3,4 ml) were added to the stirred solution over a period of ten minutes.

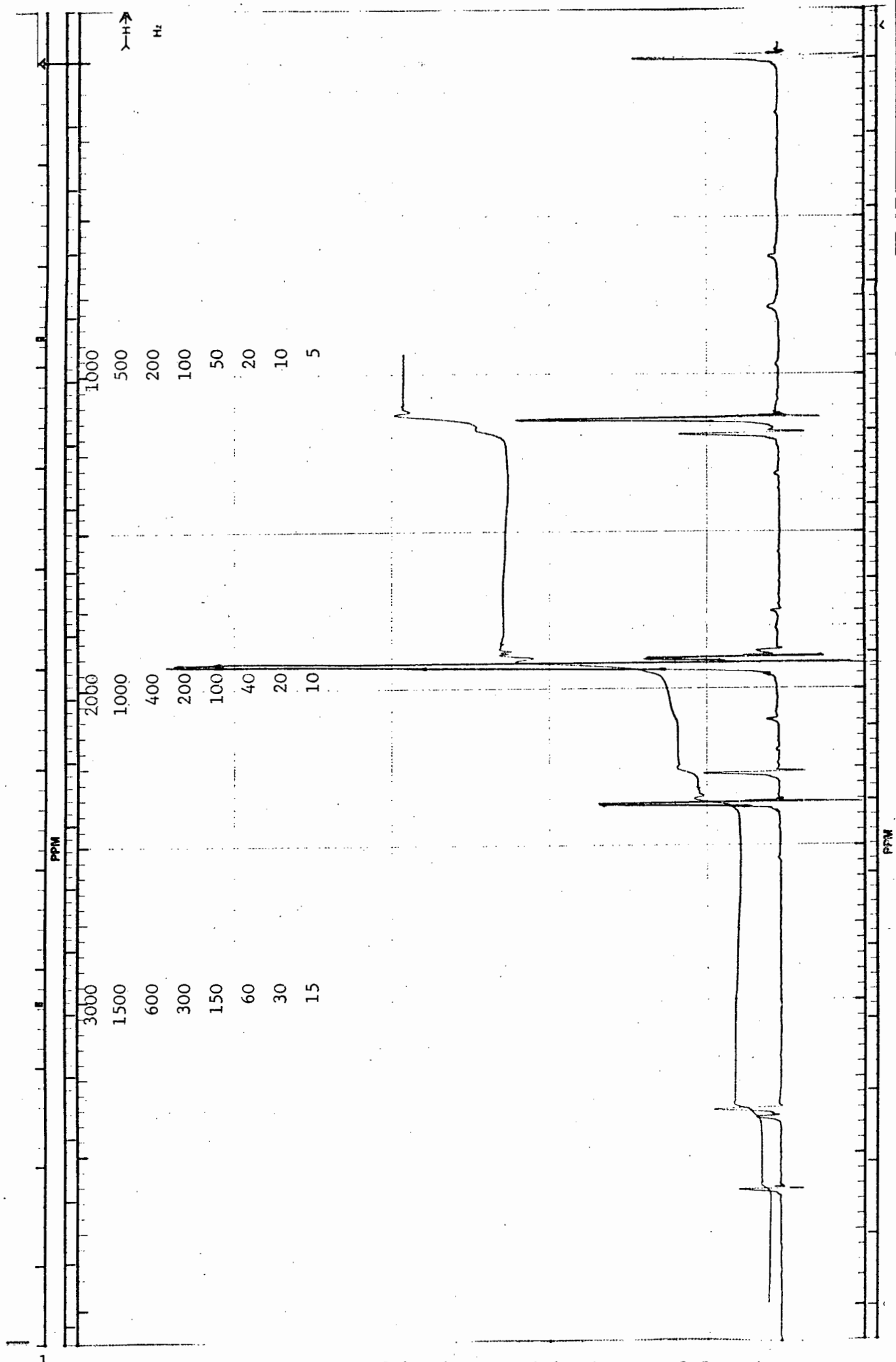
Finally 10 M sodium hydroxide (1,6 ml) was added and the reaction mixture was heated under reflux of 1,5 hours. After cooling, the solvent was removed and the resulting semi-solid was partitioned between water and chloroform. The chloroform extract was dried over sodium sulphate and the solvent removed to give crude 2,4,6 - tribromoanisole in a yield of 7,4g. Some of the material was recrystallised from

ethanol to give colourless needles m.p. 87°. Lit[36]., 87 - 88°. ^{1}Hn.m.r. τ 2,34 (s, 2H, 3- and 5-H), 6,12 (s, 3H, $-OCH_3$).

2,4,6 - Tribromoanisole (2g) was dissolved in a cold nitrating mixture [Conc. nitric acid (d = 1,5) (2 ml) and conc. sulphuric acid (6 ml)] and the mixture was then placed in a boiling water bath for 0,5 hours. After cooling to room temperature the mixture was poured into cold water (100 ml) and the solid filtered off and washed with further cold water (100 ml). Recrystallisation from dilute ethanol gave the product (69) (1,4 g) m.p. 149 - 150°. Lit.[37], 148°.

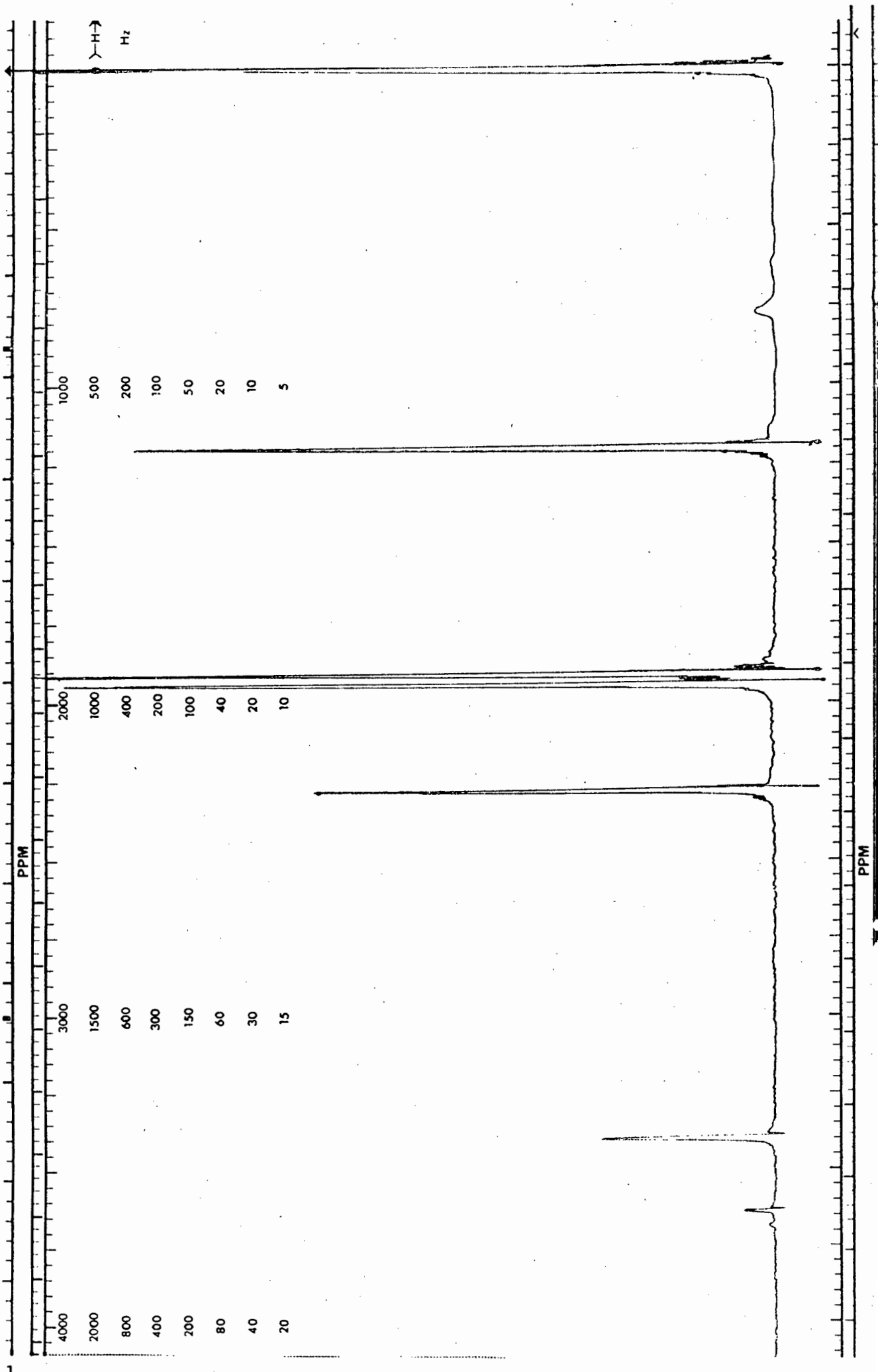
^{13}Cn.m.r. spectra were recorded on a Bruker WH - 90DS spectrometer operating at 22, 634 MHz. Saturated solutions of the samples were run in deuterio-chloroform at 28°C. Typically, 50 000 transients were needed with a cycle time of 0,5 seconds and using a 45° pulse.

FIGURE I



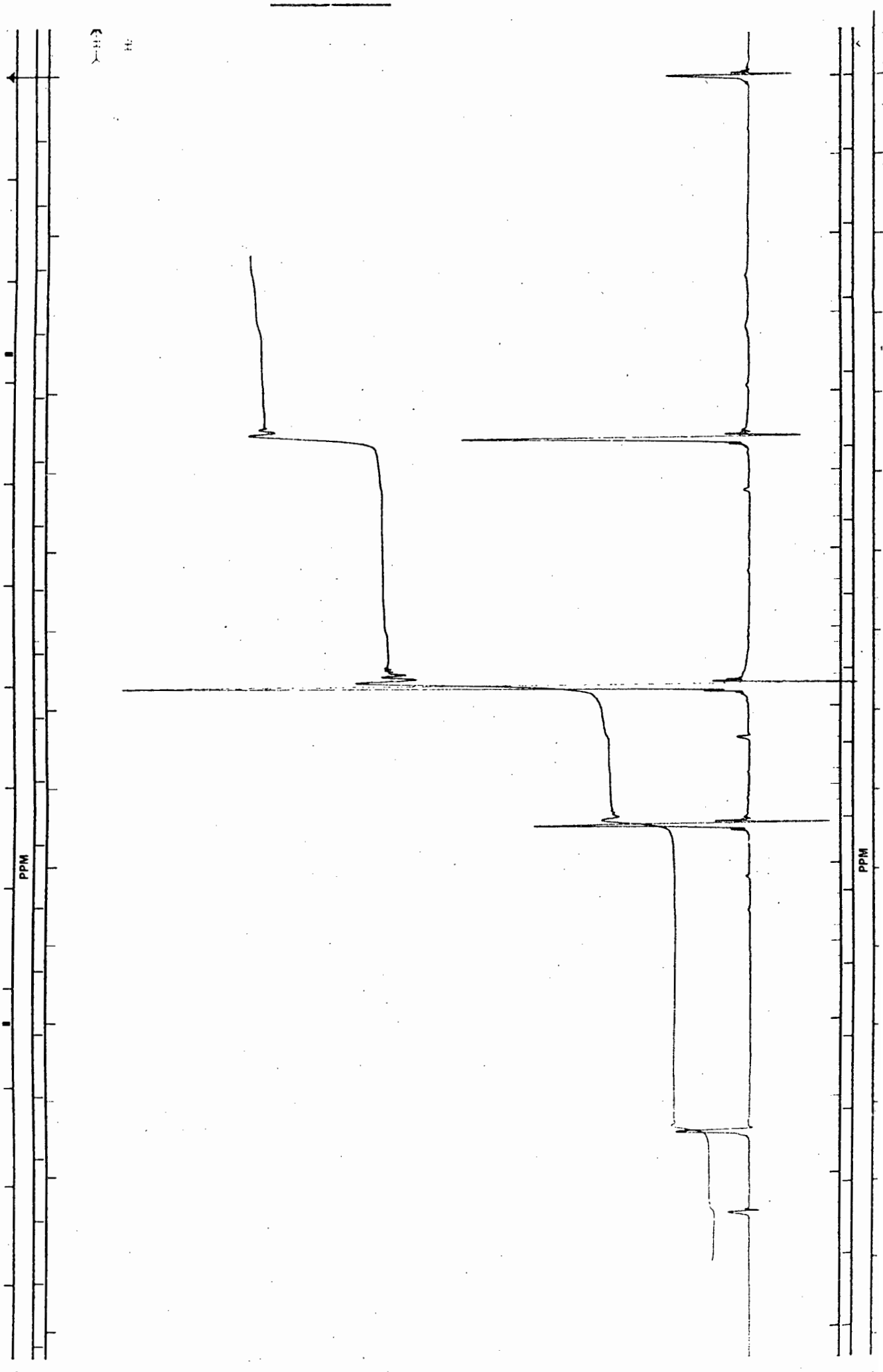
^{1}Hn.m.r. spectrum of a mixture of 4 - bromo and 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzylbromide.

FIGURE II



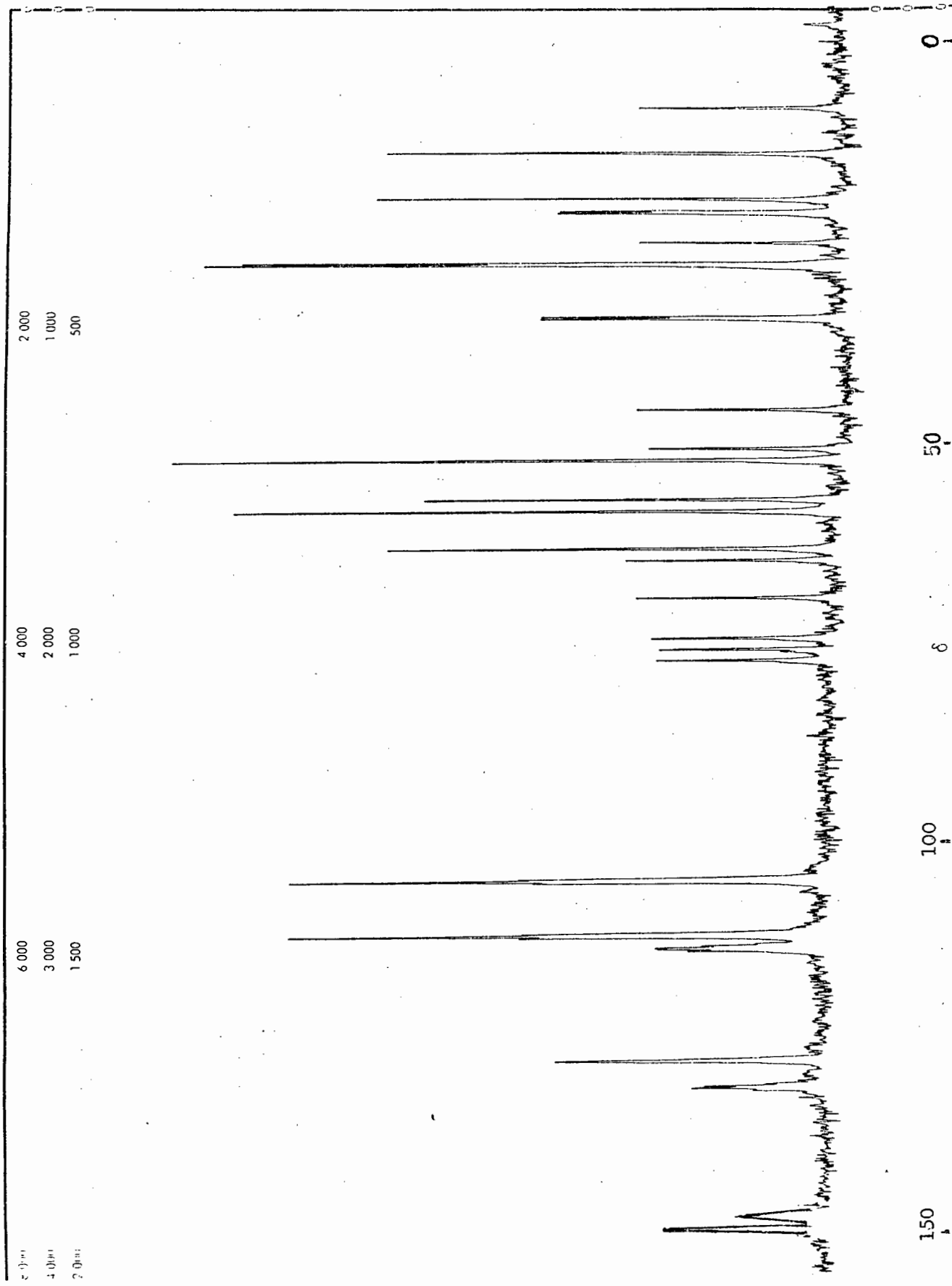
^{1}Hn.m.r. spectrum of pure 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl-bromide (12).

FIGURE III



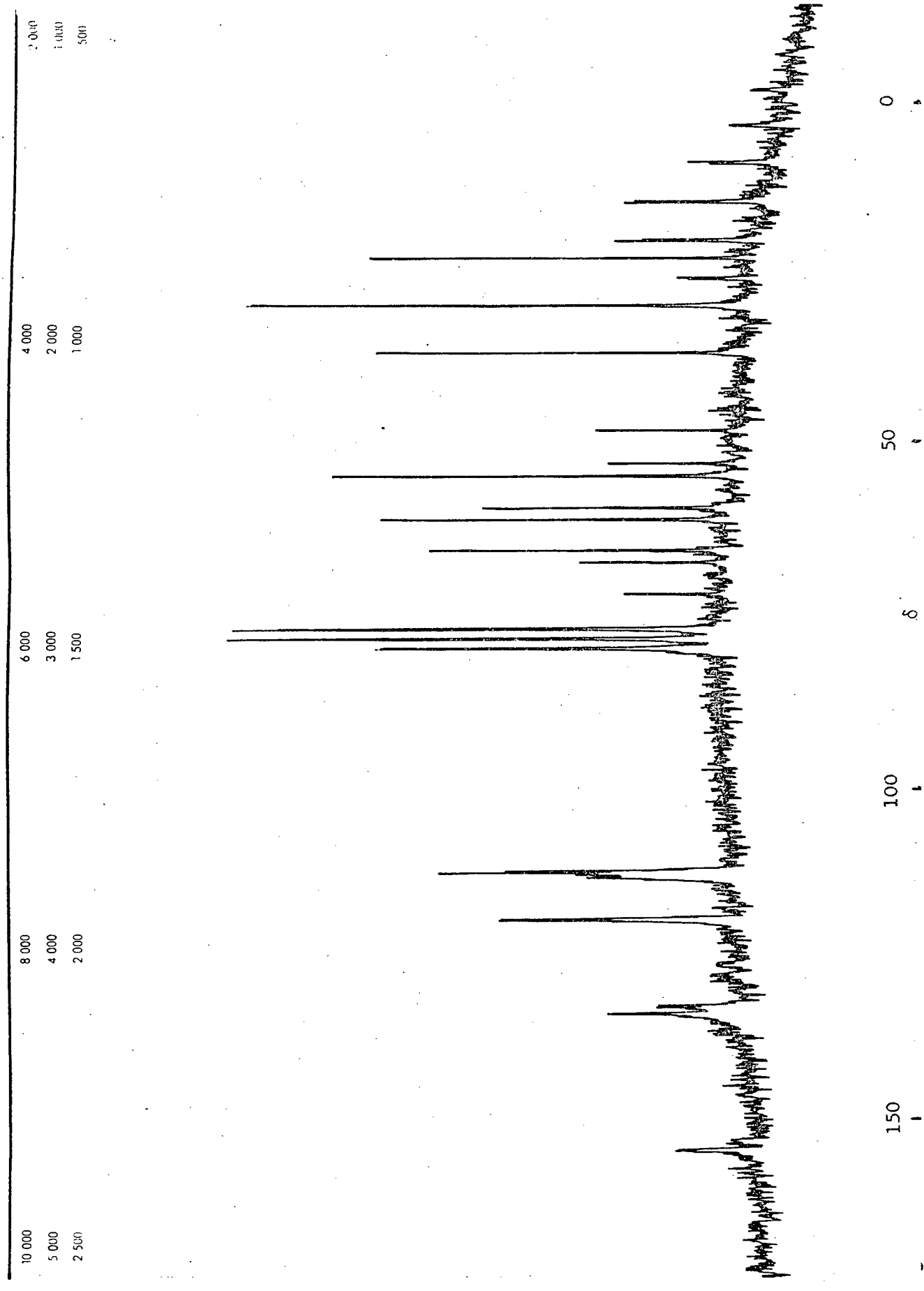
^{1}Hn.m.r. spectrum of pure 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl bromide (16).

FIGURE IV



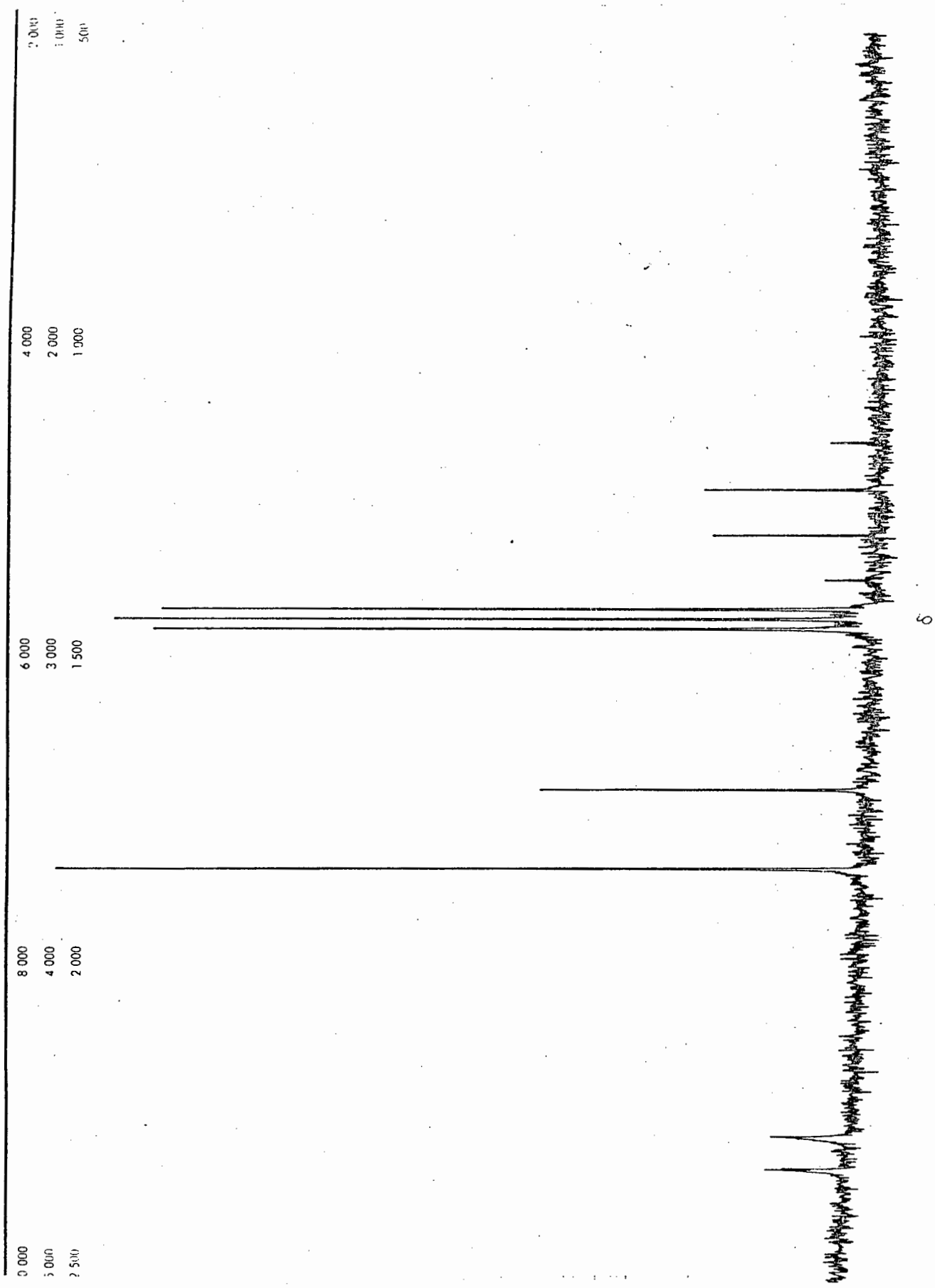
^{13}Cn.m.r. spectrum of pure 4 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl-bromide (12).

FIGURE V



^{13}Cn.m.r. spectrum of pure 6 - bromo - 2,5 - dimethoxy - 3 - methylbenzyl-bromide (16).

FIGURE VI



^{13}Cn.m.r. spectrum of pure 3,5 - dinitro - 2,4,6 - tribromoanisole (69).

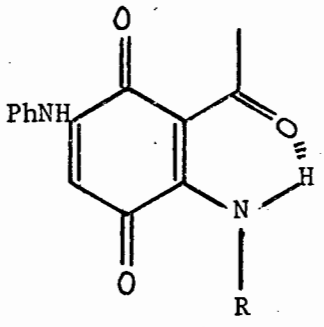
PART 11

A photochemical reaction of 2 - acetyl - 3 - alkylamino - 1,4 - benzoquinones : Formation of benzoxazoles.

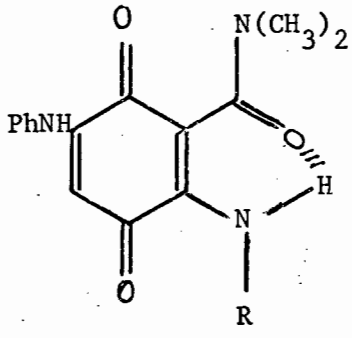
1. Introduction

Photoisomerisation of 3,6 - bisdialkylamino - p - xyloquinones in benzene solution is known to give rise to benzoxazolines[38]. However related 3,6 - bismonoalkylamino - p - xyloquinones fail to undergo photoisomerisation to benzoxazolines[39], presumably because of the unfavourable spatial relationship between the N - alkyl group and the quinone carbonyl group thus preventing abstraction of a hydrogen radical. It was therefore decided to synthesise quinones of the type (70) in which the N - alkyl group is held near to the quinone carbonyl group by means of a hydrogen bond between the NH group and the carbonyl of an acetyl group in the molecule.

If these types of quinone failed to give benzoxazolines it was proposed to synthesise a series of quinones of the type (71) in which it was felt there would be even more chance of the N - alkyl group being held in the correct position for hydrogen radical abstraction during photolysis.



(70)



(71)

Due to the success of the project using quinones of the type (70) the only compound of the type (71) prepared was 3,6 - bisanilino - 2 - N,N - dimethylamido - 1,4 - benzoquinone (R = Ph).

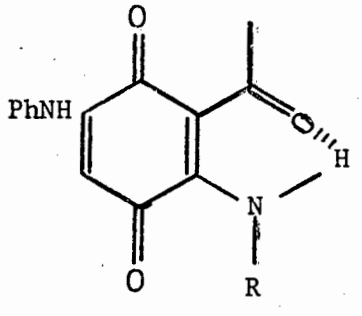
An improved method of generating quinones of the type (70) is also described.

2.1 Preparation of the starting material

2 - Acetyl - 1,4 - benzoquinone was prepared by oxidation of the corresponding quinol with silver (I) oxide in benzene solution. The crude quinone was purified by sublimation and then treated with aniline as in the method of Vorozhtsov and Marmaev[40] to give crude 2 - acetyl - 3,6 - dianilino - 1,4 - benzoquinone which could be purified by column chromatography. A second method for preparing this compound was developed in which 2 , 5 - dihydroxyacetophenone was treated with aniline and an excess of silver (I) carbonate in dry benzene. Filtration and removal of the solvent gave a product which could easily be purified by recrystallisation either from benzene/light petroleum to give orange coloured crystals or from ethanol to give purple crystals, both types of crystal having the same melting point, and infrared and ^{1}Hn.m.r. spectra.

2.2 The 2 - acetyl - 3 - alkylamino - 1,4 - benzoquinones

Compounds (70 b-j) were conveniently prepared from 2 - acetyl - 3,6 - dianilino - 1,4 - benzoquinone (70a) by amine exchange in chloroform solution.



(70)

a; R = Ph
b; R = Me
c; R = H
d; R = Pr^n
e; R = CH_2CH_2Ph
f; R = cyclohexyl
g; R = CHMe Et
h; R = Bu^t
i; R = Bu^n
j; R = CH_2Ph

The reactions were essentially complete after a few minutes except in the case of t - butylamine which required a long reaction period, presumably because of increased steric hindrance.

Attempts to replace the second anilino-residue by using a large excess of alkylamine and extended reaction times on both the dianilino - compound (70a) and the monoalkylamino - derivatives failed, but treatment of the methylamino - quinone (70b) with neat n - butylamine gave the quinone (70i) by alkylamine exchange.

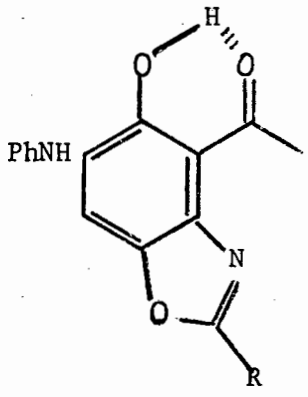
The ^{1}Hn.m.r. spectrum of compound (70b) confirmed the gross structure and indicated the presence of a strongly hydrogen-bonded NH proton (τ -3,42). That it is the alkylamino NH which is strongly hydrogen-bonded was confirmed by the observation that spin-decoupling of this low-field signal caused the doublet at τ 6,44, assigned to the N - methyl group, to collapse to a singlet.

The use of i.r. spectroscopy to obtain evidence for hydrogen bonding to the acetyl group rather than with the quinone carbonyl group is limited because of uncertainties concerning the assignment of peaks in the 1650 - 1600 cm^{-1} region. Compounds of type (70), with the exception of (70c), show a medium intensity absorption in the 1656 - 1640 cm^{-1} region which could be assigned to the acetyl carbonyl group, the frequency being lowered by hydrogen bonding and/or conjugation with the amino substituent. However, it is known that there are considerable contributions by quadrupolar species to the structures of aminated benzoquinones which in this case could involve the acetyl group and thus lead to a lowering of the frequency of the carbonyl absorption[41,42].

Support for the supposition that the NH hydrogen bond is with the acetyl rather than with the quinone carbonyl group may be inferred from the course of the photo-reactions discussed below.

2.3 Photoreactions of some 2 - acetyl - 3 - alkylamino - 1,4 - benzoquinones.

Ultraviolet irradiation of a solution of the quinone (70b) in benzene through a Pyrex filter for 1 hour gave the quinone (70c) and the benzoxazole (72a) in 20 and 80% yields respectively.



(72)

a; R = H
b; R = Et
c; R = CH_2Ph

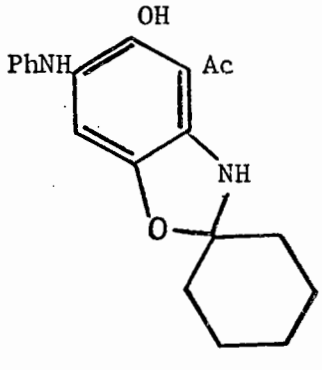
The structure of the quinone (70c) was deduced from spectral data and confirmed by synthesis from the quinone (70a) and ammonia. On the other hand the structure of benzoxazole (72a) was supported by its i.r. spectrum ν_{max} 3410 (NH), 3115 (oxazole CH), and 1630 cm^{-1} (H - bonded CO) and its ^{1}Hn.m.r. spectrum τ 2,42 (7-H), 2,06 (2-H), and -3,67 (H - bonded OH) .

Catalytic reduction of the quinone (70c) to the quinol followed

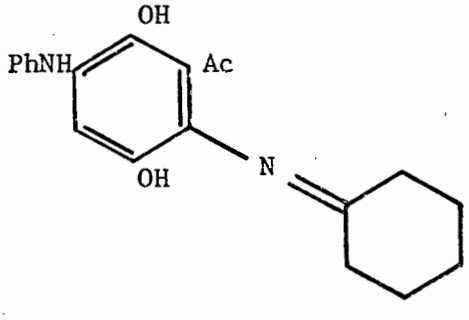
by reaction with formalin yielded the benzoxazole (72a), thus confirming its structure. Irradiation of the quinones (70d and 70e) gave the benzoxazoles (72b and 72c) respectively, as well as the quinone (70c).

Photolysis of the cyclohexylamino - compound (70f) gave a product which was too unstable for characterisation but which decomposed to yield the quinone (70c) and cyclohexanone which could be trapped as its 2,4 - dinitrophenylhydrazone and compared with the 2,4 - DNP of authentic cyclohexanone. In an attempt to trap the photo-product as a dihydrochloride, the irradiation was carried out in dry diethyl ether for 0,5 hours and then dry hydrogen chloride gas was passed through the solution for 3 hours. On removal of the solvent a brown solid was obtained which rapidly went black on exposure to the atmosphere.

The formation of the products (cyclohexanone and the quinone (70c)) is consistent with the photoproduct being either the benzoxazoline[39] (73) or the imine (74). Photolysis of the s - butylamino - quinone (70g) also gave an unstable photoproduct.

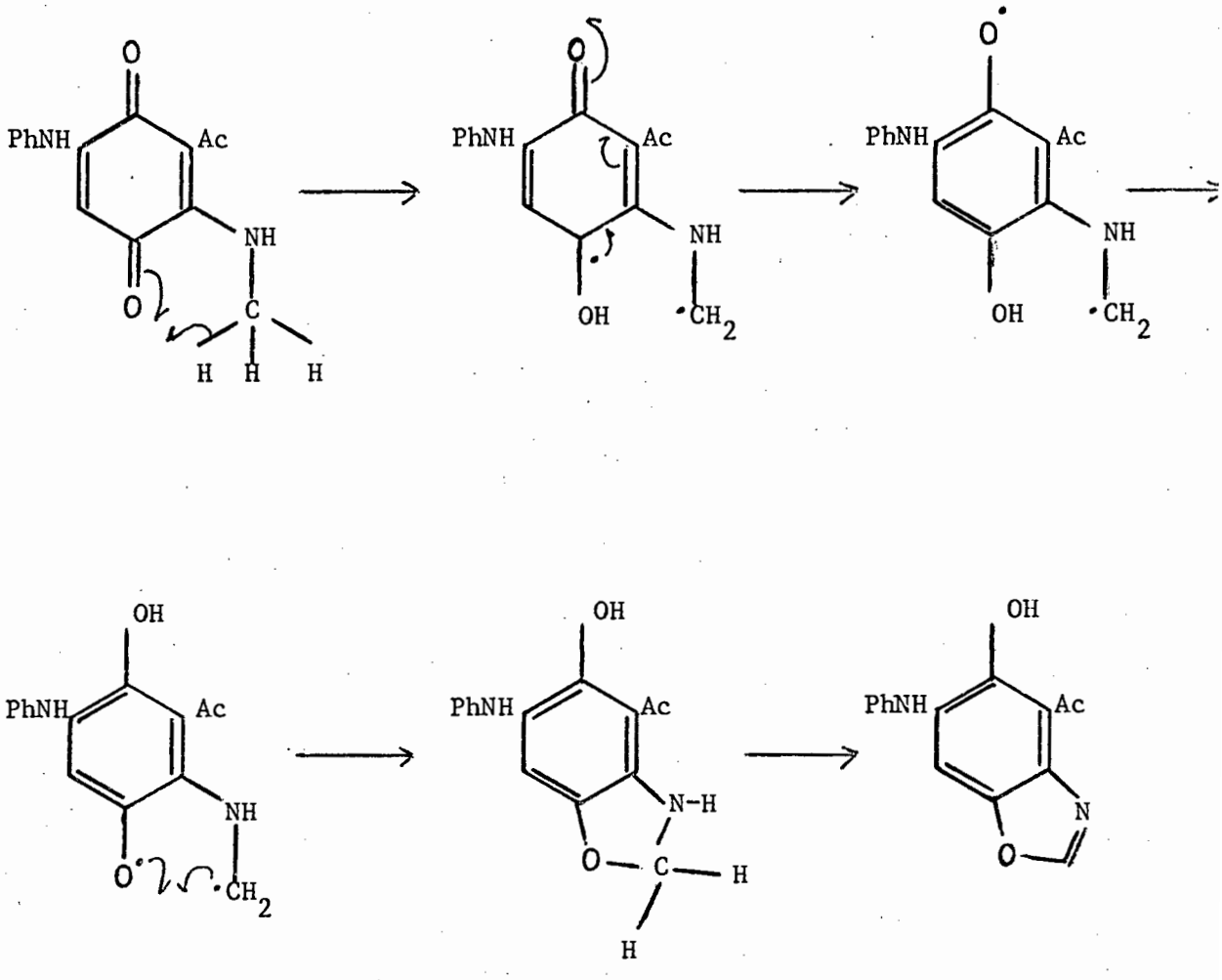


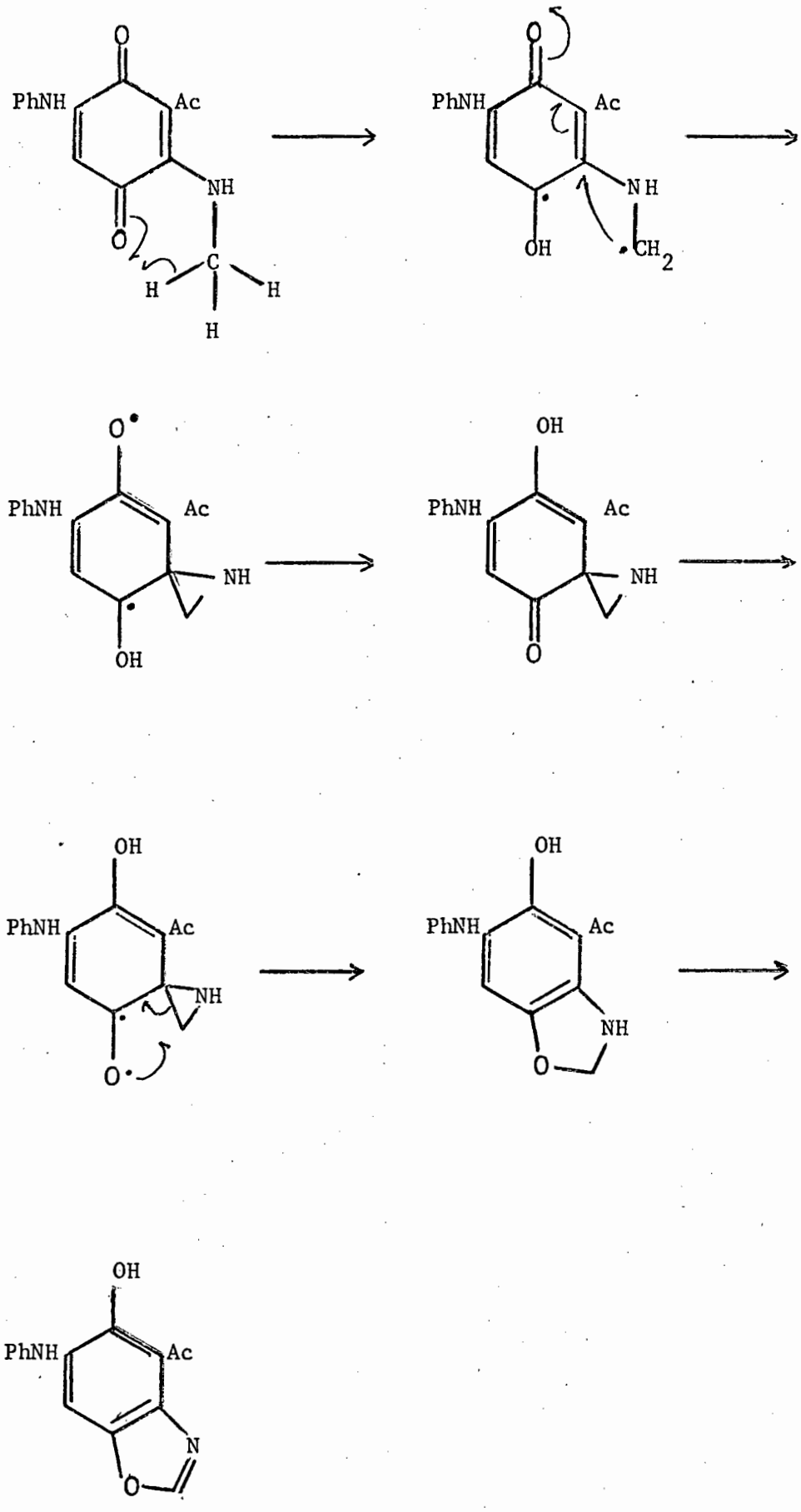
(73)

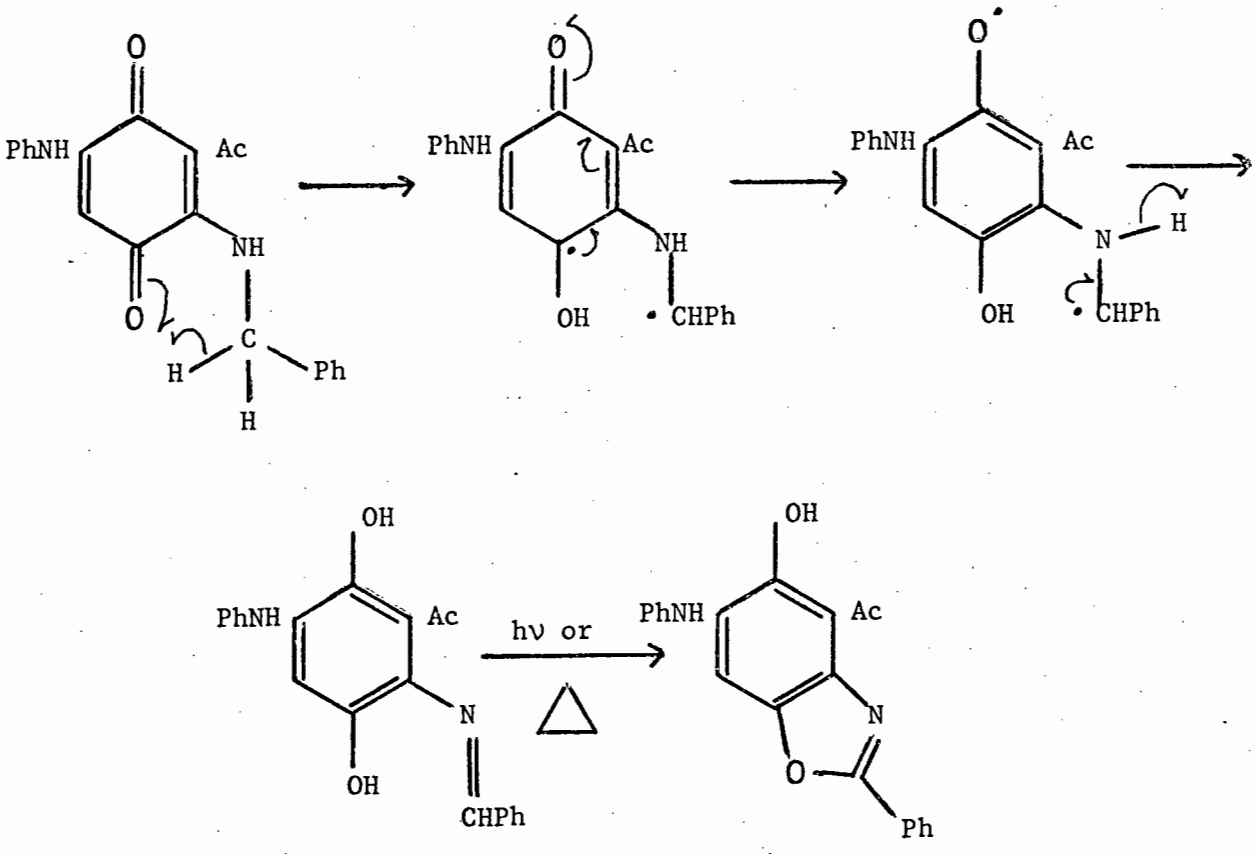


(74)

The photochemical formation of the benzoxazoles presumably involves intra molecular hydrogen abstraction by the excited quinone as the first step since if there are no α - hydrogen atoms in the alkylamino side chain [as in (70h)] no photoreaction is observed. Subsequently the diradical could lead to the benzoxazole either by hydrogen transfer, ring closure, and aromatization, or via a spiroaziridine species[43] or loss of a hydrogen radical and formation of an imine, which may then cyclise either photochemically[44] or thermally[45] to yield benzoxazoles.




PhNH
Ac
NH
O
H
H
H
OH
CH2
N
O



The formation of the aminoquinone (70c) may be due to hydrolysis of an intermediate by traces of water in the organic solvents. Consistent with this view, photolysis of the quinone (70b), when performed in benzene to which a small quantity of water had been added, gave the quinone (70c) and the benzoxazole (72a); the yield of the former (78%) being significantly increased at the expense of that of the latter (22%).

EXPERIMENTAL

EXPERIMENTAL

2 - Acetyl - 3,6 - dianilino - 1,4 - benzoquinone (70a)

The above compound was prepared in the first instance by a literature method[40] but at a later stage as follows. A mixture 2 , 5 - dihydroxy-acetophenone (50 mg), aniline (130 mg), and silver carbonate (970 mg) in dry benzene (25 ml) was heated under reflux for 2 minutes and the solid filtered off. The solvent was evaporated off and the resulting solid recrystallised from ethanol to give the quinone (70a) (60 mg, 55%) m.p. 200° (lit.[40], 189,5 - 190°) (with darkening), ν_{max} (Nujol) 3305, 1652, 1631 cm^{-1}, τ -3,75 br (1H, s, NH), 1,82 (1H, s, NH), 2,6 - 3,0 (10H,m, ArH), 3,98 (1H, s, CH = C), and 7,38 (3H, s, $COCH_3$).

2 - Acetyl - 3 - amino - 6 - anilino - 1,4 -benzoquinone (70c)

5M - aqueous ammonia solution (0,2 ml) was added to a stirred mixture of the quinone (70a) (190 mg) in a mixture of chloroform (15 ml) and ethanol (10 ml). After stirring for 0,5 hours the resulting precipitate was filtered off and recrystallised from benzene to give the quinone (70c) (55 mg , 37,5%) m.p. about 280° (lit.[46], 282°). (Found : C, 65,8; H, 4,9; N, 10,8. $C_{14}H_{12}N_2O_3$ requires C, 65,6; H, 4,7; N, 10,9%), ν_{max} (Nujol) 3300, 3240, 1645, 1610, 1590 cm^{-1}, λ_{max}(EtOH) 247, 285, 317, and 437 nm (log ε 3,91, 3,92, 3,98, and 3,10).

2 - Acetyl - 6 - anilino - 3 - methylamino - 1,4 - benzoquinone (70b)

A mixture of the quinone (70a) (0,5g), aqueous methylamine (33% W/W; 0,2 ml) and chloroform (30 ml) was stirred at room temperature for 5 minutes, washed with dilute hydrochloric acid, then water and dried with sodium sulphate. The solvent was evaporated off and the resulting solid recrystallised from ethanol to give the quinone (70b) (0,4 g, 98,5%) m.p. 137° (lit.[46], 138°). (Found : C, 66,6; H, 5,4; N, 10,3. $C_{15}H_{14}N_2O_3$ requires C, 66,6; H, 5,2; N, 10,4%), ν_{max} (Nujol) 3280, 1648, 1630, 1585, 1510 cm^{-1}, λ_{max} (EtOH) 243, 295, 348, and 487 nm (log ε 3,95, 3,90, 4,01, and 2,96), τ -3,42 br (1H, s, NH), 1,58 br (1H, s, NH), 2,4 - 2,7 (5H, m, ArH) 3,82 (1H, s, CH = C), 6,44 (3H, d, J6Hz, NHMe), and 7,32 (3H, s, $COCH_3$).

2 - Acetyl - 6 - anilino - 3 - (1 - propylamino) - 1,4 - benzoquinone (70d)

A mixture of the quinone (70a) (0,66 g) and 1 - propylamine (0,12 g) in chloroform (20 ml) was stirred at room temperature for 5 minutes, washed with dilute hydrochloric acid, then with water and dried with sodium sulphate. The solvent was evaporated off, and the resulting solid was recrystallised from ethanol to give the quinone (70d) (0,52 g, 87,5%) m.p. 145 - 146°. (Found : C, 68,8; H, 6,2; N, 9,4. $C_{17}H_{18}N_2O_3$ requires C, 68,4; H, 6,0; N, 9,4%), ν_{max} (Nujol) 3258, 1643, and 1620 cm^{-1}, τ 1,78 br (1H, s, NH), 2,6 - 2,9 (5H, m, ArH), 3,94 (1H, s, CH = C), 6,08 (2H, m, $CH_3CH_2\underline{CH_2}NH$), 7,38 (3H, s, $COCH_3$), 8,3 (2H, m, $CH_3\underline{CH_2}CH_2NH$), and 8,9 (3H, t, J9Hz, $\underline{CH_3}CH_2CH_2NH$).

2 - Acetyl - 6 - anilino - 3 - (2 - pheneythylamino) - 1,4 - benzoquinone (70e)

A mixture of the quinone (70a) (0,45 g) and 2 - phenylethylamine (0,33 g) in chloroform (20 ml) was stirred at room temperature for 5 minutes, washed with dilute hydrochloric acid, then with water and dried with sodium sulphate. The solvent was evaporated off, and the resulting solid recrystallised from ethanol to give the quinone (70e) (0,46 g, 94,3%) m.p. 138°. (Found : C, 73,7; H, 5,2; N, 7,5. $C_{22}H_{20}N_2O_3$ requires C, 73,5; H, 5,6; N, 7,8%), τ 1,78 br (1H, s, NH), 2,4 - 3,0 (10H, m, ArH), 3,96 (1H, s, CH = C), 5,8 (2H, m, $PhCh_2\underline{CH_2}NH$), 7,02 (2H, t, J7Hz, $Ph\underline{CH_2}CH_2NH$), 7,40 (3H, s, $COCH_3$).

2 - Acetyl - 6 - anilino - 3 - cyclohexylamino - 1,4 - benzoquinone (70f)

A mixture of the quinone (70a) (0,2 g) and cyclohexylamine (0,11 g) in chloroform (20 ml) was stirred at room temperature for 5 minutes, washed with dilute hydrochloric acid, and then with water and dried with sodium sulphate. The solvent was evaporated off, and the resulting solid was recrystallised from ethanol to give the quinone (70f) (0,16 g, 78,5%) m.p. 137 - 138°. (Found : C, 70,7; H, 6,5; N, 8,4. $C_{20}H_{22}N_2O_3$ requires C, 71,0; H, 6,5; N8,3%), ν_{max} (Nujol) 3300, 1635, and 1620 cm^{-1}, τ 1,74 br (1H, s, NH), 2,5 - 2,9 (5H, m, ArH), 6,20 (1H, m, CH.N), 7,38 (3H, s, $COCH_3$), and 8,0 - 8,8 (10H, m, cyclohexyl CH_2).

2 - Acetyl - 6 - anilino - 3-(2 - methylpropylamino) - 1,4 - benzoquinone (70g)

A mixture of the quinone (70a) (0,75 g) and 2 - methylpropylamine (0,2 g) in chloroform (20 ml) was stirred at room temperature for 7 minutes, washed with dilute hydrochloric acid, and then with water and dried with sodium sulphate. The solvent was evaporated off and the resulting solid was recrystallised from ethanol to give the quinone (70 g) (0,64 g, 91%) m.p. 120 - 121°. (Found : C, 69,4; H, 6,6; N, 9,0. $C_{18}H_{20}N_2O_3$ requires C, 69,3; H, 6,4; N, 9,0%).

2 - Acetyl - 6 - anilino - 3 - (1,1 - dimethylethylamino) - 1,4 - benzoquinone (70h)

A mixture of the quinone (70a) (0,72 g) and 1,1 - dimethylethylamine (0,2g) in chloroform was kept in the dark for 1 week and then it was washed successively with dilute hydrochloric acid and water, dried with sodium sulphate and the solvent evaporated off to give the quinone (70h) (0,51 g, 74,5%) m.p. 151 - 152° (from ethanol). (Found : C, 69,2; H, 6,1; N, 9,1. $C_{18}H_{20}N_2O_3$ requires C, 69,3; H, 6,4; N, 9,0%), ν_{max} (Nujol) 3310, 1656, and 1621 cm^{-1}, τ -3,75 br (1H, s, NH), 1,80 br (1H, s, NH), 2,5 - 2,9 (5H, m, ArH), 3,92 (1H, s, CH = C), 7,37 (3H, s, $COCH_3$), and 8,44 (9H, s, $C(CH_3)_3$).

2 - Acetyl - 6 - analino - 3 - (1 - butylamino) - 1,4 - benzoquinone (70i)

(i) A mixture of the quinone (70a) (0,6 g) and 1 - butylamine (0,135 g) in chloroform (20 ml) was stirred at room temperature for 5 minutes, washed with dilute hydrochloric acid, and then with water and dried with sodium sulphate. The solvent was evaporated to give the quinone (70i) (0,48 g, 85%) m.p. 113 - 114° (from ethanol). (Found : C, 69,4; H, 6,5; N, 8,9. $C_{18}H_{20}N_2O_3$ requires C, 69,3; H, 6,4; N, 9,0%), ν_{max} (Nujol) 3287, 1643, and 1622 cm^{-1}, τ -3,30 br (1H, s, NH), 1,72 br (1H, s, NH), 2,74 (5H, m, ArH), 3,95 (1H, s, CH = C), 6,02 (2H, q, J6Hz, $\underline{CH_2}CH_2CH_2CH_3$), 7,35 (3H, s, $COCH_3$), 8,36 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), and 9,02 (3H, deformed t, J6Hz, $CH_2CH_2CH_2\underline{CH_3}$).

(ii) A solution of the quinone (70b) (40 mg) in freshly distilled 1 - butylamine (0,5 ml) was kept for 1 hour and then evaporated to dryness. Recrystallisation of the residue gave the quinone (70i) (30 mg, 80%) m.p. 113 - 114° (from ethanol).

2 - Acetyl - 6 - anilino - 3 - benzylamino - 1,4 - benzoquinone (70j)

A mixture of the quinone (70a) (0,4 g) and benzylamine (0,25 g) was stirred at room temperature for 7 minutes, washed with dilute hydrochloric acid, and then with water and then dried with sodium sulphate. The solvent was evaporated off to give the quinone (70j) (0,39 g , 96,5%) m.p. 136 - 137°(from ethanol). (Found : C, 72,5; H, 5,5; N, 8,3. $C_{21}H_{18}N_2O_3$ requires C, 72,7; H, 5,2; N, 8,1%), ν_{max} (Nujol) 3285, 1642, and 1616 cm^{-1}, τ 1,76 br (1H, s, NH), 2,6 - 2,9 (10H, m, ArH), 3,93 (1H, s, CH = C), 4,86 (2H, d, J6Hz, CH_2NH), and 7,40 (3H, s, $COCH_3$).

Photolysis of quinone (70b)

A solution of the quinone (0,120 g) in benzene (800 ml) was irradiated for 1 hour through a Pyrex filter. The solvent was evaporated off and the residue chromatographed on a silica gel column. Elution with benzene gave 4 - acetyl - 6 - anilino - benzoxazol - 5 - ol (72a) (0,096 g, 80,5%) m.p. 132 - 133° (from ethanol). (Found : C, 66,9; H, 4,5; N, 10,1. $C_{15}H_{12}N_2O_3$ requires C, 67,2; H, 4,5; N, 10,4%), ν_{max} (Nujol) 3410, 3115 and 1630 cm^{-1}, λ_{max} (EtOH) 276 and 410 nm (log ε 4,14 and 2,61), τ -3,67 (1H, s, OH), 2,06 (1H, s, CH = N), 2,42 (1H, s, ArH), 2,5 - 3,1 (5H, m, PhN), 3,5 br (1H, s, NH), and 6,92 (3H, s, $COCH_3$). Elution with chloroform gave 2 - acetyl - 3 - amino - 6 - anilino - 1,4 - benzoquinone (70c) (0,022 g, 19,1%) m.p. 284 - 286°, identical with the product obtained earlier.

Repetition of this photo-reaction with the quinone (70b) (0,083 g) in benzene (800 ml) containing water (0,5 ml) and 2 drops of hydrochloric acid gave, as before, the benzoxazole (72a) (0,018 g, 21,8%) and the quinone (70c) (0,061 g, 77,5%).

Irradiation of quinone (70d)

A suspension of the quinone (0,43 g) in cyclohexane (800 ml) was irradiated from 0,75 hours through a Pyrex filter, the solvent evaporated off, and the residue chromatographed on a silica gel column. Elution with benzene gave 4 - acetyl - 6 - anilino - 2 - ethylbenzoxazol - 5 - ol (72b) (0,19 g, 44,5%) m.p. 143 - 144° (from ethanol). (Found : C, 68,8; H, 5,7; N, 9,4. $C_{17}H_{16}N_2O_3$ requires C, 68,9; H, 5,4; N, 9,4%), ν_{max}

(Nujol) 3420, 1628, and 1603 cm^{-1}, τ -3,45 (1H, s, OH), 2,44 (1H, s, ArH), 2,6 - 3,0 (5H, m, PhN), 3,75 br (1H, s, NH), 6,92 (3H, s, $COCH_3$), 7,06 (2H, q, J7Hz, $\underline{CH_2}CH_3$), and 8,57 (3H, t, J7Hz, $CH_2\underline{CH_3}$).

Irradiation of quinone (70e)

A solution of the quinone (0,35 g) in benzene (800 ml) was irradiated for 0,75 hours through a Pyrex filter, the solvent evaporated off, and the residue chromatographed on a silica gel column. Elution with benzene gave 4 - acetyl - 6 - anilino - 2 - benzylbenzoxazol - 5 - ol (72c) (0,13 g, 37,7%) m.p. 131 - 132° (from ethanol). (Found : C, 73,6; H, 5,1; N, 8,1. $C_{22}H_{18}N_2O_3$ requires C, 73,8; H, 5,0; N, 7,8%), ν_{max} (Nujol) 3405, 1630 and 1604 cm^{-1}, τ -3,50 (1H, s, OH), 2,49 (1H, s, ArH), 2,6 - 3,1 (10H, m, ArH and PhN), 3,68 br (1H, s, NH), 4,78 (2H, s, CH_2Ph), and 6,95 (3H, s, $COCH_3$). Further elution with chloroform gave 2 - acetyl - 3 - amino - 6 - anilino - 1,4 - benzoquinone (70c) (0,07 g, 38%).

Irradiation of quinone (70f)

A solution of the quinone (0,35 g) in cyclohexane (800 ml) was irradiated for 0,75 hours through Pyrex and the solvent evaporated off to give a maroon residue.

The photolysis was repeated with the same amount of quinone in benzene (800 ml) but the product decomposed to a dark maroon coloured substance before the initial yellow coloured material could be purified by column chromatography.

In a third photolysis the quinone (0,35 g) in dry diethyl ether was irradiated for 35 minutes through Pyrex. The solution was concentrated under reduced pressure and the last traces of solvent were removed in a stream of dry nitrogen. Aqueous 10% sulphuric acid (140 ml) was added, and the resulting solution distilled at constant volume into a saturated solution of 2,4 - dinitrophenylhydrazine in dilute hydrochloric acid.

When 80 ml of distillate had been collected, the precipitate (0,15 g) was removed and recrystallised from ethanol to give cyclohexanone 2,4 - dinitrophenylhydrazone (0,115 g) m.p. 157 - 158°, identical with an authentic sample. No product was isolated from the aqueous residue of the distillation.

From another reaction in which the irradiated solution was kept in air for several days, 2 - acetyl - 3 - amino - 6 - anilino - 1,4 - benzoquinone (0,09 g) was obtained by filtration.

4 - Acetyl - 6 - anilinobenzoxazol - 5 - ol (72a)

A solution of 2 - acetyl - 3 - amino - 6 - anilino - 1,4 - benzoquinone (70c) (0,424 g) in benzene (70 ml) was stirred with pre-reduced Adams catalyst in hydrogen until one equivalent of hydrogen had been absorbed. A solution of aqueous formaldehyde (40%; 4 ml) in ethanol (10 ml) was added and the mixture was stirred overnight, filtered, and evaporated to dryness. Chromatography of the residue on silica gel using benzene as eluant afforded the benzoxazole (0,165 g) m.p. 128 - 129°, identical with the material obtained earlier.

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