GROUND AND EXCITED STATE CHEMISTRY OF SOME *N*-SUBSTITUTED PHTHALIMIDES

A thesis presented for the degree of Doctor of Philosophy

by

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at

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School of Chemical Sciences

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Declaration

I the undersigned hereby declare that this thesis, which I now submit for assessment on the programme of study leading to the award of Ph.D. represents the sole work of the author and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of the work.

Paul Mc Cormac

Paul B. McCormac

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Finally I wish to thank my parents for their assistance financial and otherwise without whom this endeavour would have been impossible.

"......books are fine enough in their own way, but they're a mighty bloodless substitute for life......"

Robert Louis Stephenson: **An Apology for Idlers**

Abstract

The synthesis and photochemistry of a number of *N*-(2-hydroxyethyl) phthalimides have been investigated. Irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide results in rapid photofragmentation to form *N*-methylphthalimide and benzaldehyde. This process is unusual as it involves intramolecular proton transfer from a hydroxyl group to an excited state phthalimido carbonyl as opposed to the expected γ-hydrogen abstraction processes. The mechanism has been investigated in regard to role of hydroxyl group and the nature of the excited state involved. The scope of the fragmentation has been investigated by synthesising and irradiating a series of *N*-(2-hydroxyethyl)phthalimides differing in the substituents located at the carbinyl carbon. Mono- and di- substitution led to products of fragmentation whereas the unsubstituted *N*-(2-hydroxyethyl)phthalimide affords no photoproducts even after prolonged irradiation. A mechanism involving an excited state intramolecular proton transfer mediated by hydrogen bonding between the hydroxyl group and the phthalimido carbonyl has been proposed.

The photochemistry of *N*-styrylphthalimide and *N*-styryltetrachlorophthalimide has also been investigated. Irradiation of *N*-styrylphthalimide in a range of solvents leads only to *E*-*Z* isomerisation whereas irradiation of *N*-styryltetrachlorophthalimide only gives rise to *E*-*Z* isomerisation in hydrocarbon solvents.

The reactions of phthaloyl-α-amino acid esters with alkyl magnesium halides has also been investigated. Treatment of phthaloyl α-amino acid methyl esters with Grignard reagents affords only products associated with addition to the phthalimido carbonyl as opposed to expected addition to the ester moiety. The structure and relative stereochemistry of these products has been confirmed by single crystal X-ray diffraction.

Abbrevations used in this thesis

NMP	*N*-methylphthalimide
P	Phthalimide
TMS	Trimethylsilyl-
TMSCl	Trimethylsilylchloride (Chlorotrimethylsilane)
TMSCN	Trimethylsilylcyanide
THF	Tetrahydrofuran
DMSO	Dimethylsulphoxide
DMF	Dimethylformamide

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Dedication

To My Parents and Family

Introduction

CHAPTER 1A:

The photochemistry of the carbonyl chromophore.

CHAPTER 1B:

The photochemistry of the phthalimide chromophore.

1.0 Introduction

The work contained in this thesis primarily concerns the photochemistry of *N*-substituted phthalimides. This introduction contains initially a brief discussion of the photochemistry of the carbonyl group. Included are some general photophysical aspects and the most important photochemical reactions. Many of these reactions are observed in the photoreactions of the phthalimide system and much of the mechanistic insight in this system comes from analogy with the photoreactions of simple carbonyl systems. This is followed by a comprehensive review of phthalimide photochemistry from the early 1970s to 1995. Both Kanaoka[1] in 1978 and Mazzochi[2] in 1982 have published reviews on the photochemistry of this system, however since much of the work published since complements earlier publications this review will include publications discussed by both Kanaoka and Mazzochi. Much of the review will concentrate on the variety of synthetic transformations possible

Photochemistry of the carbonyl group[3,4]

1.A.1 Structural aspects

Compounds containing the carbonyl chromophore are amongst the most widely studied in organic photochemistry. Aldehydes and ketones have received much more interest than carboxylic acid derivatives primarily due to experimental considerations as their longest wavelength absorptions are in a readily accessilble region of the electromagnetic spectrum (λ_{max} for ketones and aldehydes $\geq$ 280-300 nm, λ_{max} for carboxylic acids and derivatives $\geq$ 200-220 nm). For both classes of compound these absorptions correspond to the excitation of a non bonding (n) electron on oxygen to an antibonding orbital of the carbonyl group. Since these (n, π^*) transitions are quantum mechanically forbidden their intensities are weak, with extinction coefficients of the order 10-30 dm^3 mol^{-1} cm^{-1}. This excitation results in a considerable change in the electron density distribution around the carbonyl group. In the ground state the carbonyl bond is polarised which accounts for its susceptibility to nucleophilic

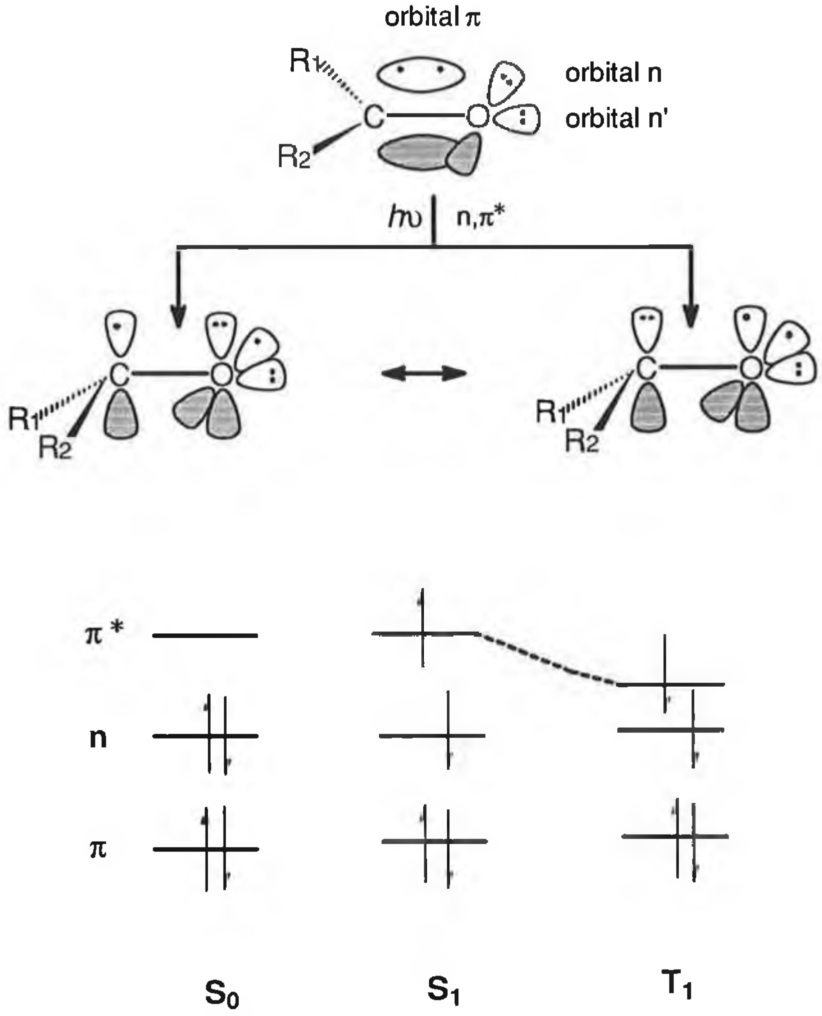


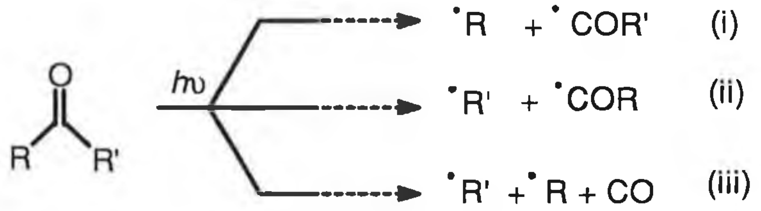
Fig .1: The (n, π) excitation of a carbonyl chromophore leading to formation of S_1 and formation of T_1 by intersystem crossing.*

attack at carbon. However in the first excited state (S_1) there is an unpaired electron in a π* antibonding orbital and another in a p type orbital on oxygen. The net result is that oxygen as well as its n orbital is electron deficient while the carbon atom becomes somewhat electron rich and can exhibit nucleophilic behaviour. In the (n, π*) triplet state (T_1) the electrons having parallel spins are as far removed from each other as possible, thus the (n, π*) triplet carbonyl chromophores have chemical and physical characteristics of a diradical and display similarities to alkoxy radicals with respect to α-cleavage reactions, their hydrogen abstraction abilities and attack at carbon-carbon multiple bonds. The energy difference between the singlet and triplet (n, π*) states of aliphatic ketones is small in comparison to for example, alkenes but in some cases the rate of intersystem crossing is slow enough ($k_{isc} \equiv 10^8 s^{-1}$) to allow chemical reactions of the (n, π*) singlet state to occur. Since however the energy of and electronic distribution in the two states are similar the same type of process may occur from singlet or triplet states or a mixture of the two. In conjugated systems (aryl ketones and enones) the (n, π*) and (π, π*) excited singlet states are lower in energy and hence the associated absorptions are at longer wavelengths compared to those in the isolated chromophores. From a photochemical viewpoint the major difference this causes is that for certain unsaturated compounds the (n, π*) states are not always the lowest in energy (due to delocalisation of the individual π and π* bonds). For some the lowest triplet state is definitely (π, π*) in nature (eg acyl naphthalenes) and for others the (n, π*) and (π, π*) triplet states are very close in energy (eg *p*-methoxyphenyl ketones) and because of differences in the reactions of (n, π*) and (π, π*) states this has a profound effect on the observed photochemistry.

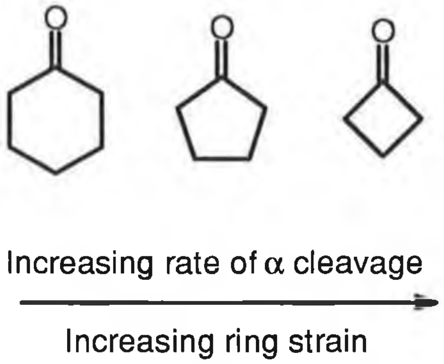
1.A.2. Photoreactions of the carbonyl group

1.A.2.1 α-Cleavage reactions(Norrish type I processes)

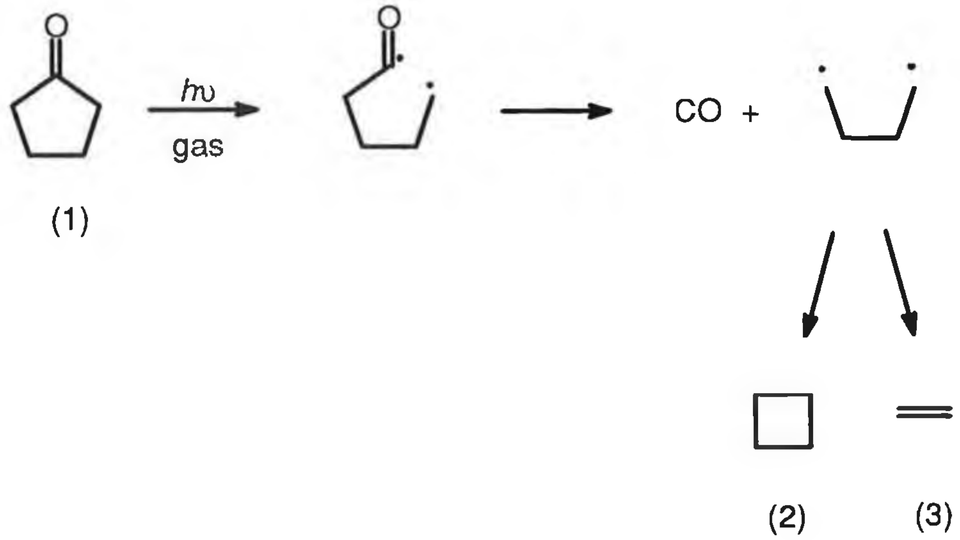
As was mentioned earlier the reactions of the (n, π*) excited states of carbonyl compounds can be likened to those of alkoxy radicals and in particular may undergo cleavage of the α bond. The occurrence of this process can be understood in terms of the weakening of the α bond by overlap with the vacant n orbital. When the two α bonds are not identical it is the weaker bond which cleaves preferentially forming the more stable radicals. As the energy of the absorbed quantum increases the selectivity between the two processes ((i) and (ii) (SCHEME 1.0), decreases markedly. Depending on the energy of the absorbed quantum various fractions of the acyl radicals (RCO & R'CO) may be also vibrationally excited (hot) and may decompose rapidly into an alkyl radical and carbon monoxide in an early vibration following the initial absorption of light (iii) (SCHEME 1.0). The dissociation of acyl radicals to alkyl radicals and carbon monoxide is very temperature dependent, acetyl radicals being virtually completely dissociated at temperatures above 120 ^{o}C. Other simple acyl radicals are less stable and are completely dissociated at correspondingly lower temperatures. The formation of products by the α-cleavage reaction is not a major reaction in solution at room temperature because the initially formed radicals are produced in a cage of solvent molecules and a major secondary process is recombination to reform ground state starting material. Indeed the reaction is only observed when the acyl group has an adjacent stabilising substituent present (eg R_3CCO and $PhCH_2CO$ radicals) to promote a second α cleavage. Cyclic ketones undergo α cleavage to give biradical species on photolysis in gas or solution phase. For these cyclic systems the reactivity pattern of ring opening follows that expected for relief of ring strain.



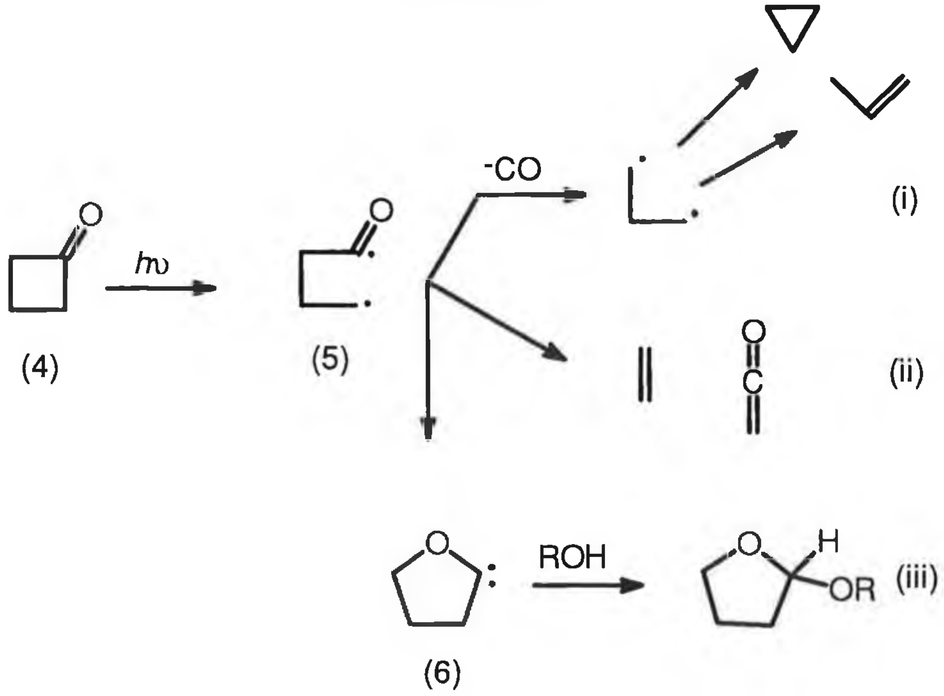
SCHEME 1.0



The biradical species produced on photolysis can recombine to give starting material or can fragment to lose carbon monoxide for example, cyclopentanone (1) leads to hydrocarbon products (2) and (3) (SCHEME 1.1).[5]



SCHEME 1.1

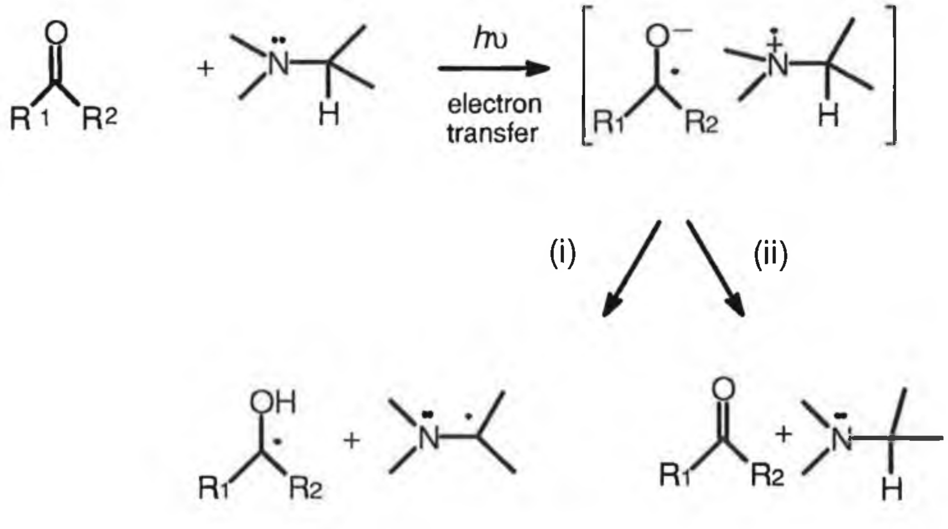


SCHEME 1.2

In contrast to other alkanones, cyclobutanones (4) undergo efficient α-cleavage from the (n, π*) singlet state to produce a singlet diradical (5). The reactions generally resulting from this diradical are (i) decarbonylation, (ii) cycloelimination and (iii) oxacarbene formation (SCHEME 1.2). The oxacarbene (6) has been trapped by alcohols.[6]

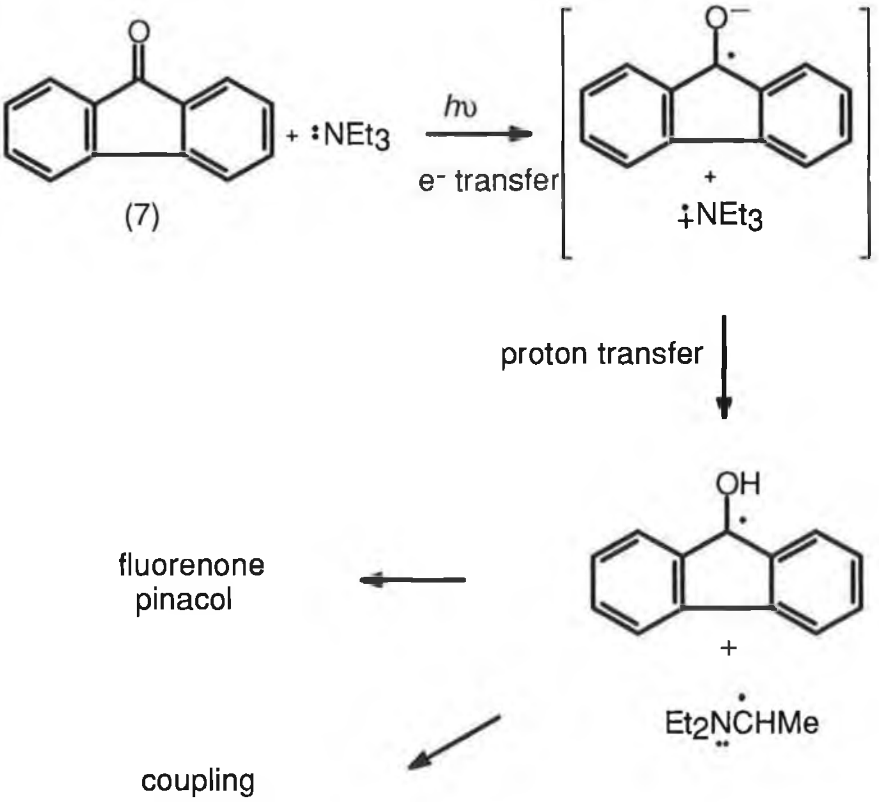
1.A.2.2 Hydrogen abstraction (Norrish type II photoreaction)

Abstraction of a hydrogen atom from a suitable donor by the electrophilic n orbital of an (n, π*) excited carbonyl group proceeds either intermolecularly or intramolecularly. The initial step of the mechanism involves either transfer of an electron or hydrogen atom to the oxygen atom of the carbonyl excited state from a donor molecule which may be solvent, an added reagent or a ground state molecule of reactant. For electron transfer to take place the donor molecule must have a low ionisation potential (approx. 9ev or less). For example electron transfer occurs to excited carbonyl compounds from amines or sulphides but not from alcohols. These reactions take place by initial electron transfer from the donor to the excited state carbonyl compound which forms a radical anion/radical cation pair (SCHEME 1.3). This is followed by transfer of a proton and formation of radicals (path (i)) or by back electron transfer to form starting materials (path (ii)). An example is the photoreduction of fluorenone (7)

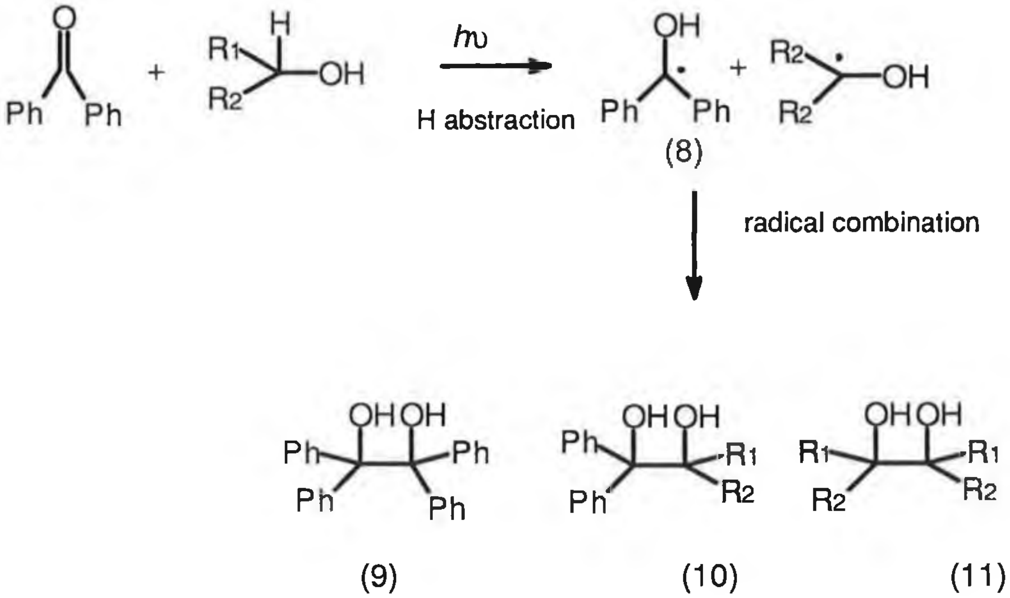


SCHEME 1.3

by triethylamine (SCHEME 1.4).[7] This process follows an electron transfer mechanism with both fluorenone pinacol and amine addition product being obtained as products. An example of a hydrogen abstraction reaction is the photopinacolisation of benzophenone which is one of the earliest known photoreactions(SCHEME 1.5).[8] Alcohols are commonly used as hydrogen donors as, are ethers and alkylbenzenes. Alkylbenzenes can also participate in the photoreduction of excited carbonyl species by way of an electron transfer mechanism. The initially formed ketyl radical (8) (SCHEME 1.5) can form products through a number of different routes and the favoured path depends on the structure of the radical species, the concentration of reagents, the hydrogen donor power of the reducing agent and on the temperature. The reaction is so efficient that under certain conditions benzopinacol (8) can be obtained from benzophenone in up to 80% yield.[9]



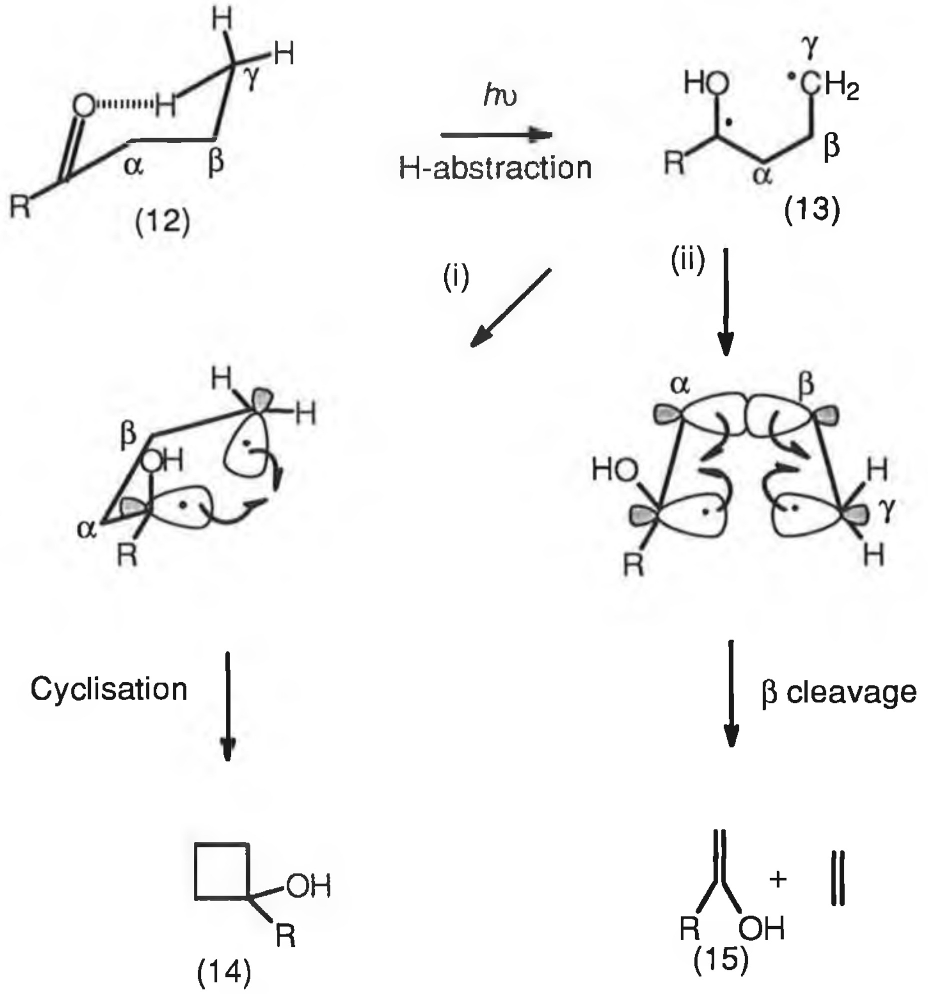
SCHEME 1.4



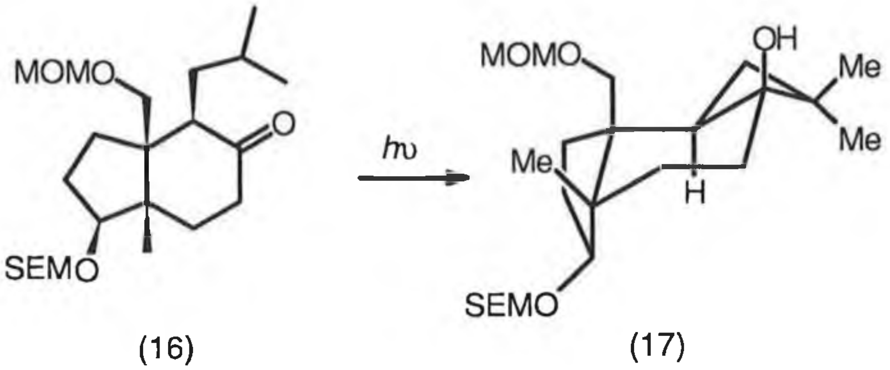
SCHEME 1.5

1.A.2.3 Intramolecular H-abstraction (Norrish type II photoreaction)

Molecules containing the carbonyl chromophore in which the molecular structure allows a close approach between the excited carbonyl group and a hydrogen atom attached to a sp^3 hybridised carbon atom undergo intramolecular H-abstraction. This process is favoured from the γ carbon since the two reacting centres can make a close approach in a "chair" like 6-membered transition state (12) (SCHEME 1.6). The subsequently formed biradical (13) can undergo cyclisation to form cyclobutanol derivatives (14) or a β-cleavage to form enol (15) and alkene. The process which is favoured depends on the conformation of the initially formed biradical (13). If only the sp-orbitals of the radical centres can overlap (path (i)) a cylobutanol is formed but if the sp orbitals of the radical centres are parallel to the β bond (path (ii)) they will participate in the formation of two double bonds.[10] The photocylisation has been used to great effect on a wide variety of ketonic systems one interesting example in the natural products field is its use to create the cyclobutane ring in *punctatin* by converting the ketone (16) to (17) in high yield (SCHEME 1.7).[11]



SCHEME 1.6

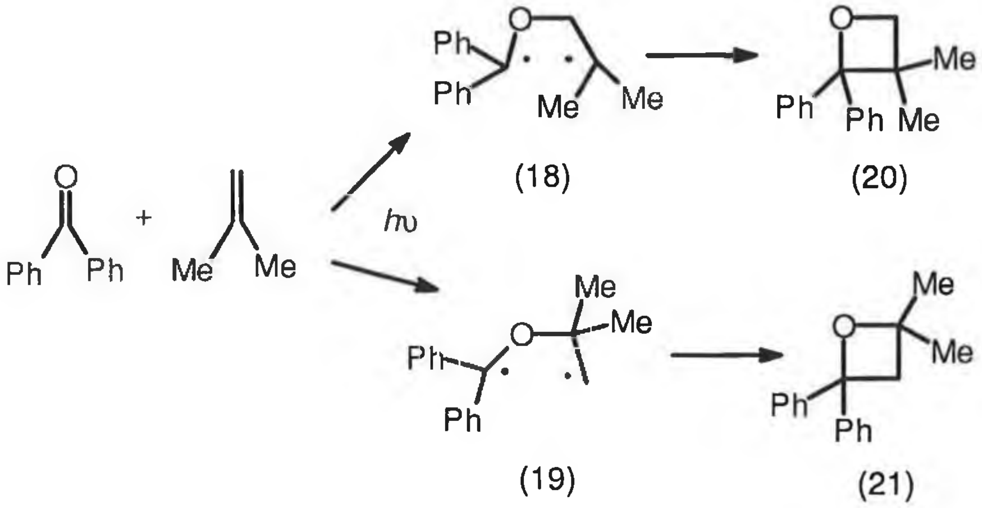


SCHEME 1.7

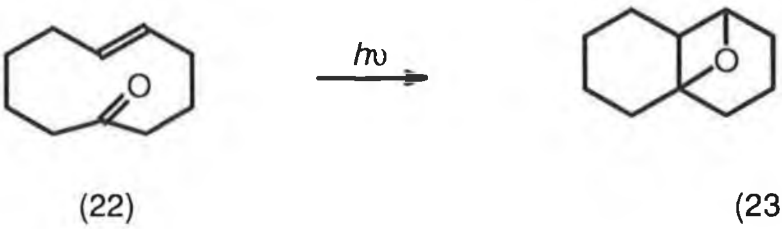
Intramolecular hydrogen abstraction will occur from other positions when there are no hydrogens availible at the γ position and the hydrogen atoms at the more remote site can come in close proximity to the excited carbonyl group.

1.A.2.4 Photocycloaddition (Oxetane formation)

On irradiation in the presence of alkenes, dienes, or alkynes carbonyl compounds undergo cycloaddition reactions to give 4-membered oxygen heterocycles. This reaction is commonly known as the *Paterno-Buchi* reaction.[12] An example of this is the reaction of benzophenone with *iso*-butene to give (20) and (21) in a ratio of 9:1(SCHEME 1.8).[13] The reactions are generally thought to proceed from an attack of a (n, π*) singlet or triplet state of the carbonyl compound on the ground state of the alkene to yield a 1,4-diradicals (18) & (19) which subsequently close to yield the observed products.



SCHEME 1.8



SCHEME 1.9

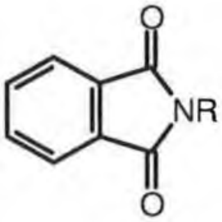
The presence of diradical intermediates has been confirmed by picosecond transient spectroscopy,[14] and with unsymmetrical alkenes the ratio of (20) to

(21) reflects the formation of the more stable biradical (18) as opposed to (19). The reaction can occur in a intramolecular manner if the functional groups are suitably orientated an example of which is the *Paterno-Buchi* reaction of (22) to form (23) (SCHEME 1.9).[15]

1.B Photochemistry of the Phthalimide system[1, 2]

1.B.1 Structural aspects

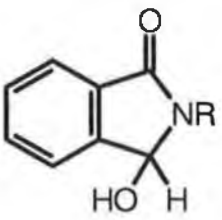
In *N*-substituted phthalimides (24) the carbonyl groups are part of a five membered heterocyclic ring. The rigid geometrical arrangment allows for effective intramolecular interaction between the carbonyl and certain *N*-side chain groups whereby the symmetrical structure and the presence of two equally reactive carbonyl groups increases the probability of such interactions by a factor of two. Phthalimides undergo virtually all of the major photochemical reactions known for the carbonyl chromophore and several unique reactions as well. The photoreactivity of the phthalimide system is nearly always associated with the carbonyl site. Phthalimide absorption spectra show a strong (π, π*) band at 220 nm and a shoulder at 295 nm attributed to a (n, π*) transition. The phthalimides also exhibit a strong phosphorescence emmision which is due to a (π, π*) transition of the triplet state. The lowest singlet excited state in phthalimides has been assigned as (n, π*) in character.[16] Coyle has suggested that the (n, π*) and (π, π*) states are very close energetically and there may be mixing of these states.



(24)

1.B.2 Photoreduction and addition

Compounds containing a carbonyl chromophore upon irradiation in solvents having readily abstractable hydrogens undergo photoreduction as one of the most common reactions. When *N*-alkyl phthalimides were photolysed in alcohols the reduced product (25) as well as the addition product (26) were obtained.[17] This type of photoreduction/addition is similar to that observed for



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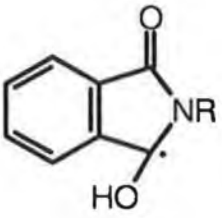
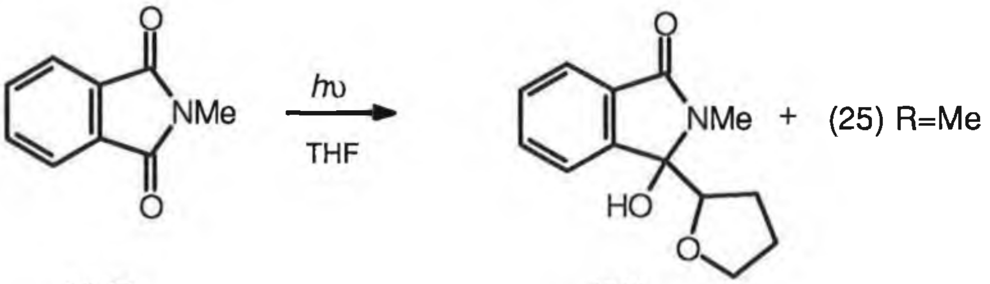


(27)

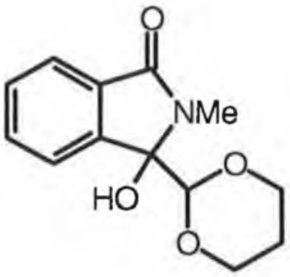
other carbonyl systems as discussed earlier. The authors suggest that the reaction proceeds via an initial hydrogen abstraction to form a semipinacol radical (27) followed by a second hydrogen abstraction to give (25) or reaction with a solvent derived radical to give the addition product (26). When THF was



NMP

(28)

SCHEME 1.10



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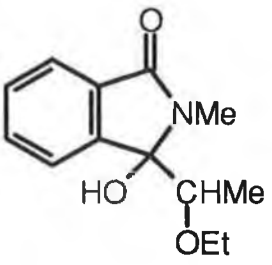

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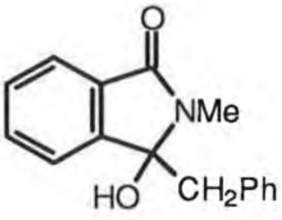
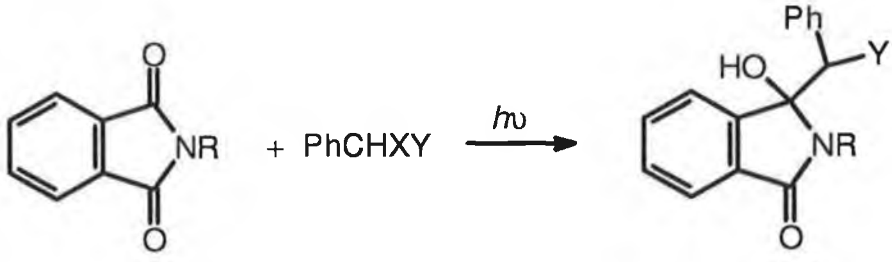


(31)

employed as solvent the photoreduced product (25) (11%) as well as the addition product (28) (20%) were obtained as the major products (SCHEME 1.10).[18] In a similar manner irradiation in dioxane, diethyl ether and toluene afforded the expected addition products (29), (30) and (31) respectively.[19] Albini and co-workers have examined[20] the photoreactivity of phthalimide (P) and *N*-methylphthalimide (NMP) and their 4,5 dicyano derivatives (35) with a series of alkyl benzenes (32). The only previously reported photoreaction of the phthalimide system with alkyl benzenes was the photoaddition of toluene to NMP to form the carbinol (31).[19] Irradiation of P and NMP gave the expected isoindolones (33) (SCHEME 1.11). The mechanism which is proposed is similar to that proposed for the reaction of alkyl benzenes with other electron acceptors,[21] involving electron transfer from arene to excited phthalimide to form arene radical cation/phthalimido radical anion pair (34), followed by transfer of X^+ to the phthalimido radical anion and subsequent radical combination to form the observed product (33) (SCHEME 1.12).



(32)

(33)

P: R=H

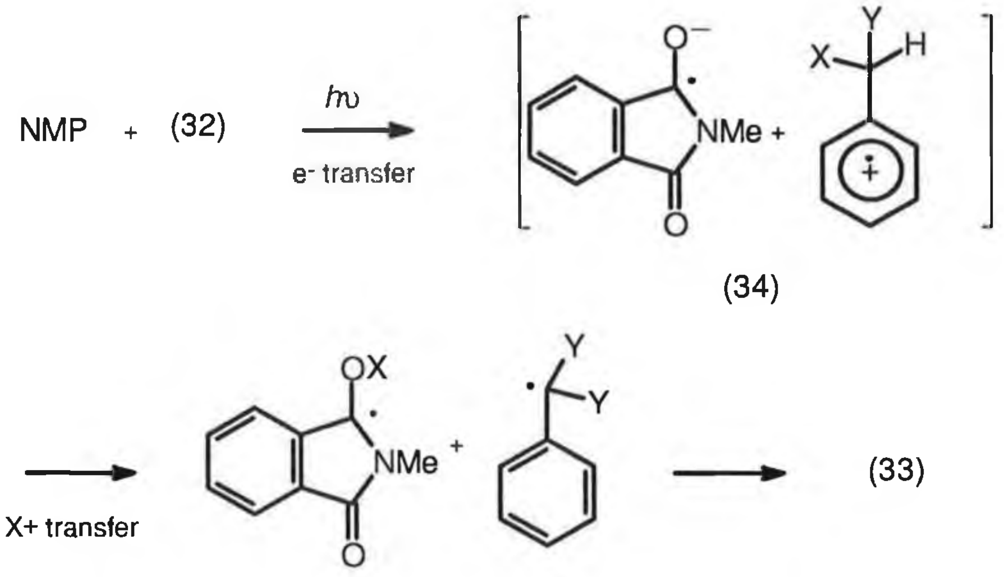
NMP: R=Me

(a): X=H, Y=H

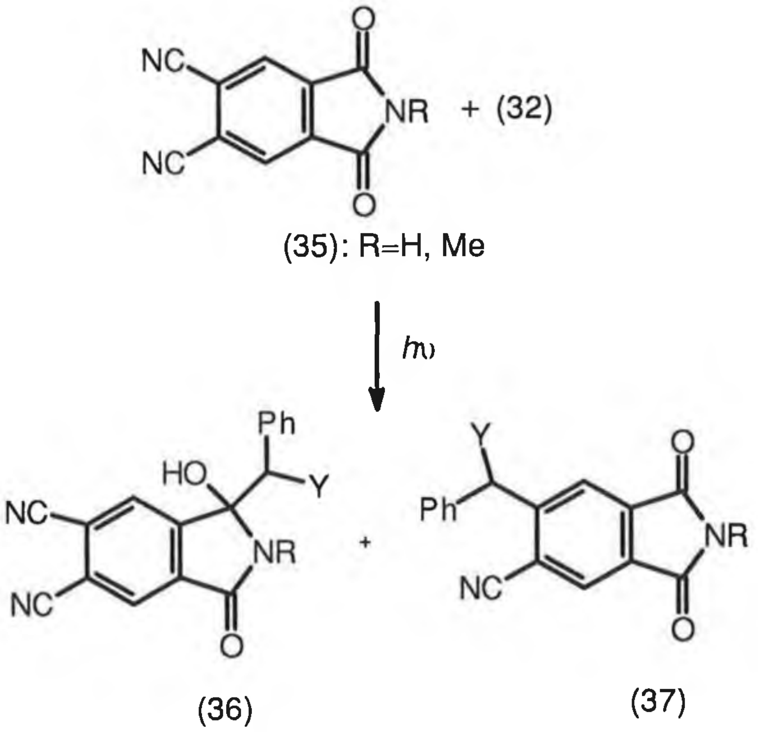
(b): X=SiMe$_3$, Y=H

(c): X=H, Y=Ph

SCHEME 1.11

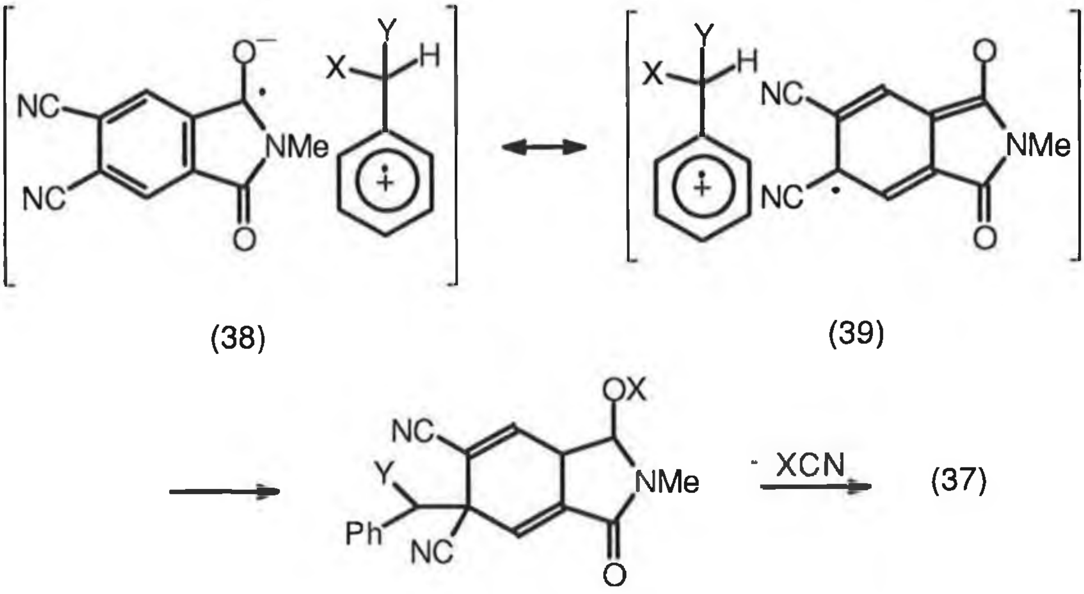


SCHEME 1.12



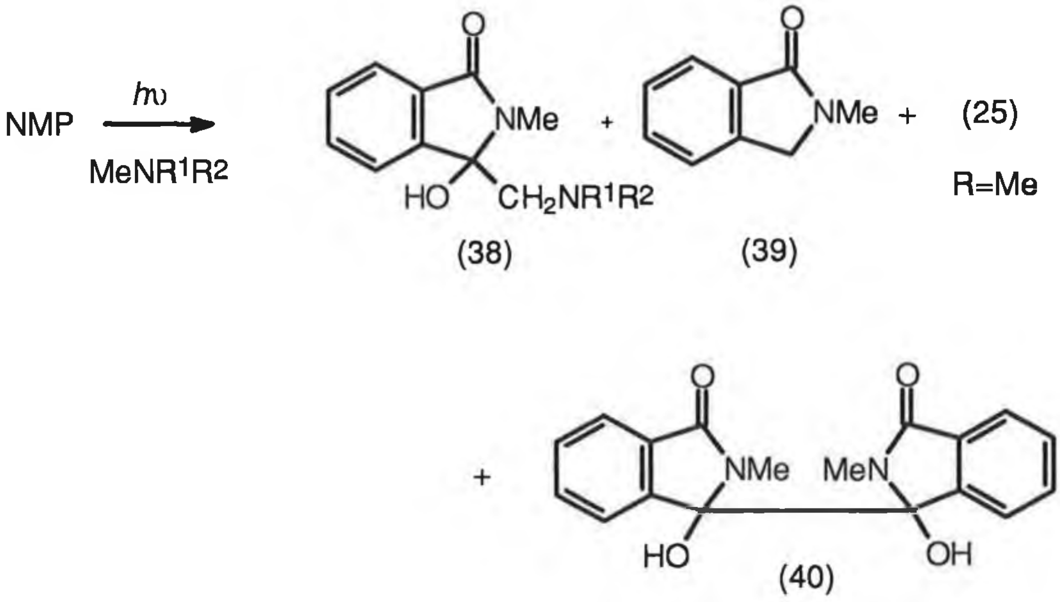
SCHEME 1.13

Irradiation of of the dicyano derivatives (35) however gave predominantly *ipso* substitution to give the benzyl cyanophthalimides (36) and varying yields of the dicyanoindolone (37) (SCHEME 1.13). The difference in reaction between the dicyanated phthalimides (34) and P, NMP has been explained in terms of charge localisation at the aromatic carbons bearing the cyano groups leading to efficient in-cage orientation of the donor and acceptor with the favoured process being *ipso* substitution of the cyano group rather than addition to the imide carbon (SCHEME 1.14)

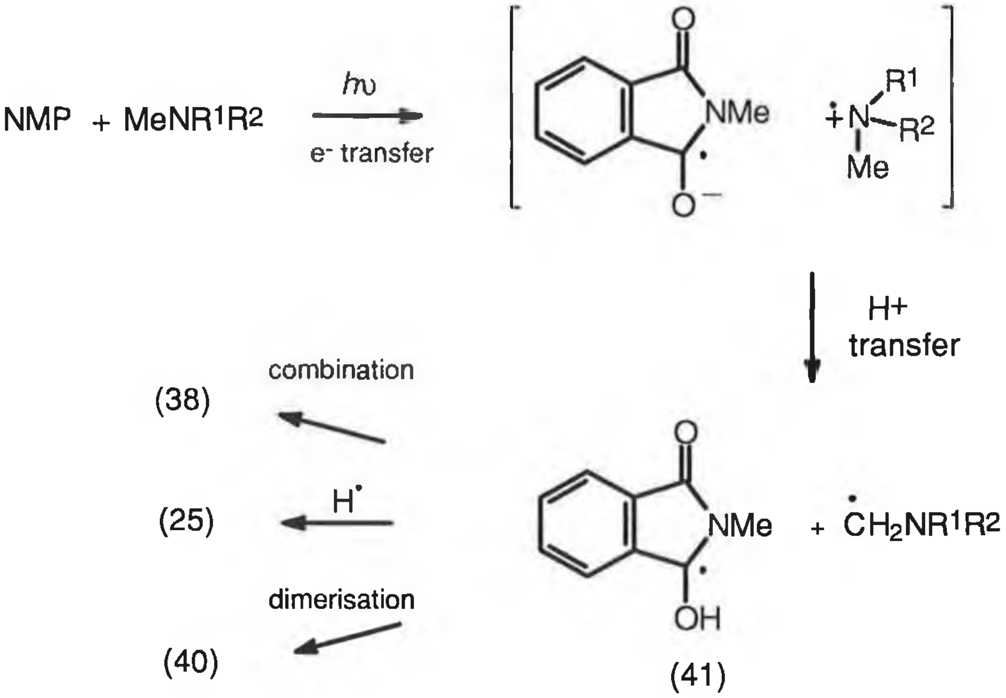


SCHEME 1.14

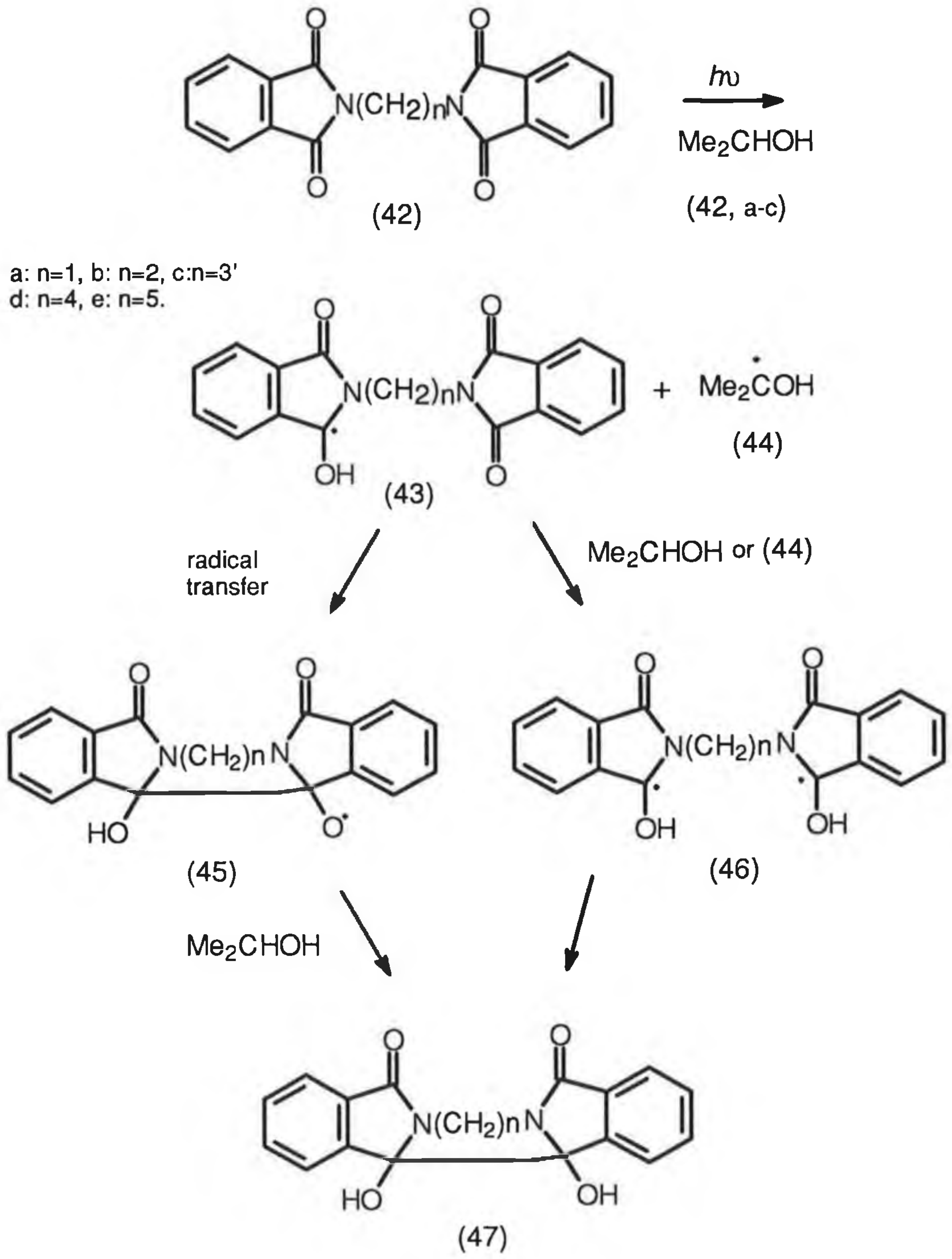
The photoreaction of *N*-methylphthalimide (NMP) with amines namely triethylamine, *N,N*-dimethylcyclohexylamine and *N,N*-dimethylaniline has also been reported.[19] Amines are known to be highly efficient reducing agents for aromatic ketones.[22] This efficiency was demonstrated by the fact that irradiation in the presence of triethylamine or *N,N*-dimethylcyclohexylamine of NMP led along with the expected addition product (38) and reduction product (25) to *N*-methylphthalimidine (39) a highly reduced species not seen in the photoreduction of *N*-alkylphthalimides by alcohols (SCHEME 1.15). The isolation of pinacol (40) is also worthy of note as pinacol formation is common in the photoreduction of ketone triplets (see 1.A.2.2) but also not observed in the photoreduction of NMP by alcohols. Photoreduction of ketone triplets by amines is generally known to proceed by way of electron transfer.[22] The authors suggest a similar mechanism for NMP ie initial electron transfer to excited NMP followed by subsequent proton transfer to yield a semipinacol radical (41) which then undergoes various additions (SCHEME 1.16).



SCHEME 1.15

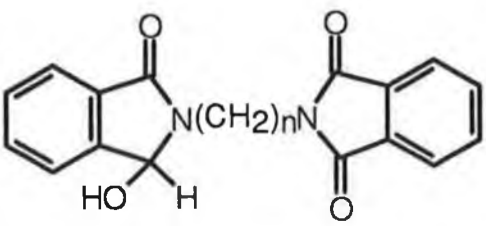


SCHEME 1.16



SCHEME 1.17

As was mentioned earlier photoreduction of NMP by alcohols did not lead to pinacol formation However intramolecular pinacol formation was observed with *N*-methylene bisphthalimides (42; a-c) when irradiated in an alcoholic solvent (SCHEME 1.17).[23] Compounds (42; d-e) in which the two phthalimido moieties are separated by more than three methylene groups did not afford the coupling product giving only the reduced product (48) and (49). The process of pinacol



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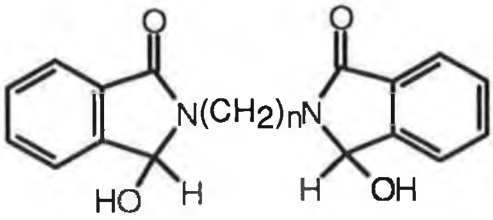


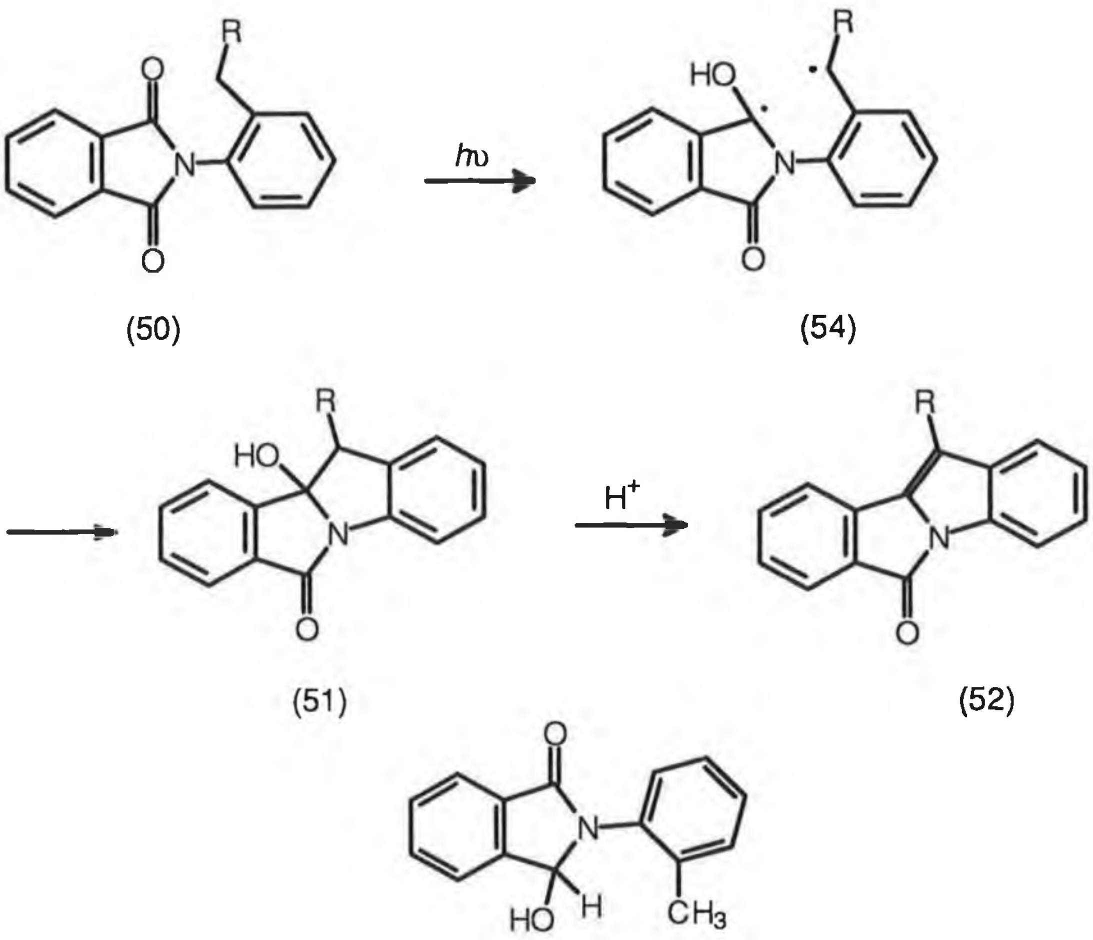
(49)

formation can be rationalised in terms of initial hydrogen abstraction by the imide carbonyl from *iso*-propyl alcohol giving two radicals (43) and (44) which are formed in a solvent cage and radical transfer occurs to give alkoxy radical (45) which can hydrogen abstract from another molecule of solvent to give the observed product (47). The authors also suggest an alternative pathway by which the second carbonyl of initially formed ketyl-radical (43) abstracts a hydrogen from *iso*-propyl alcohol or *iso*-propyl alcohol radical (44) to form diketyl radical (46) which can close to give (47). This however is unlikely as it involves excitation of a species (43) which is present in very low concentration.

1.B.3 Photocylisation reactions of the phthalimide system:

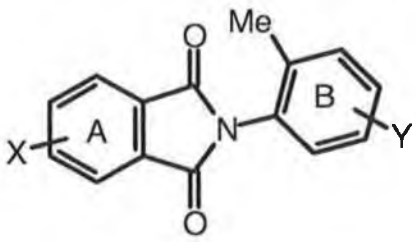
1.B.3.1 *N*-Arylphthalimides

The first reported photocylisation of *N*-substituted phthalimides was the cyclisation of (50; R= H) to (51) in ethanol.[17] Irradiation of (50) in addition to the reduced product (53) gave (51) which could be converted to (52) by treatment with acid (SCHEME 1.18). Similar results were obtained with (50; R= Me). The authors also noted significant quenching of the cyclisation of (50) in the presence of isoprene which suggests an excited triplet state intermediate. The reaction involves intramolecular hydrogen abstraction by the excited imide carbonyl to give the biradical (54) which subsequently closes to give (51). Irradiation of a series of *N*-*o*-tolylphthalimides (55) possessing various substituents on the A or B rings were examined in *t-butyl*-alcohol or acetone.[24]



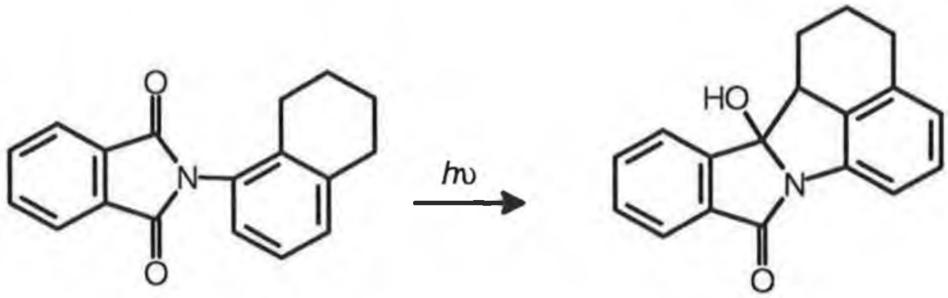
SCHEME 1.18

Whereas photolysis of the imides with an electron withdrawing group such as nitrile or methoxy-carbonyl on the A ring afforded the cyclised product the presence of electron donating substituents such as methoxyl and dimethylamino inhibited this cyclisation. By contrast imides possesing either an



(55)

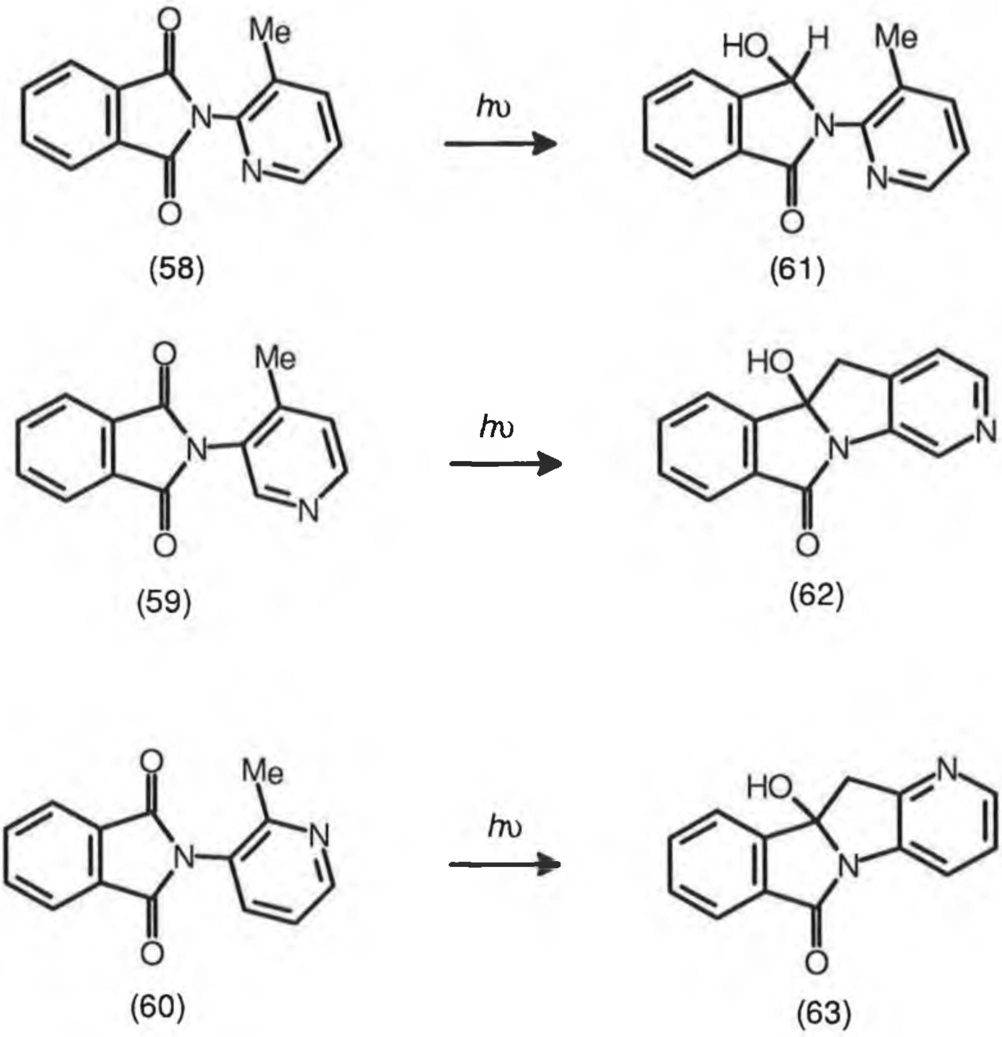
electron withdrawing or donating group on the B ring smoothly underwent cyclisation to the isoindoloindole derivatives analogous to (51). These results seem consistent with the postulated intermediacy of the biradical (54). While substituent Y influences the stability of the benzyl radical, substituent X must exhibit a direct effect on the reactivity of the excited carbonyl. Donor substitution is thought to result in an inversion of (n, π^*) and (π, π^*) excited state energies. Triplet (π, π^*) states are generally less reactive than their (n, π^*) counterparts in hydrogen abstraction reactions by ketones.[25] As an example of a variation of substrate structure, replacement of an alkyl of (50) by an alicyclic moiety led on irradiation of (56) to formation of a pentacyclic ring system (57) (SCHEME 1.19).[26]



(56) (57)

SCHEME 1.19

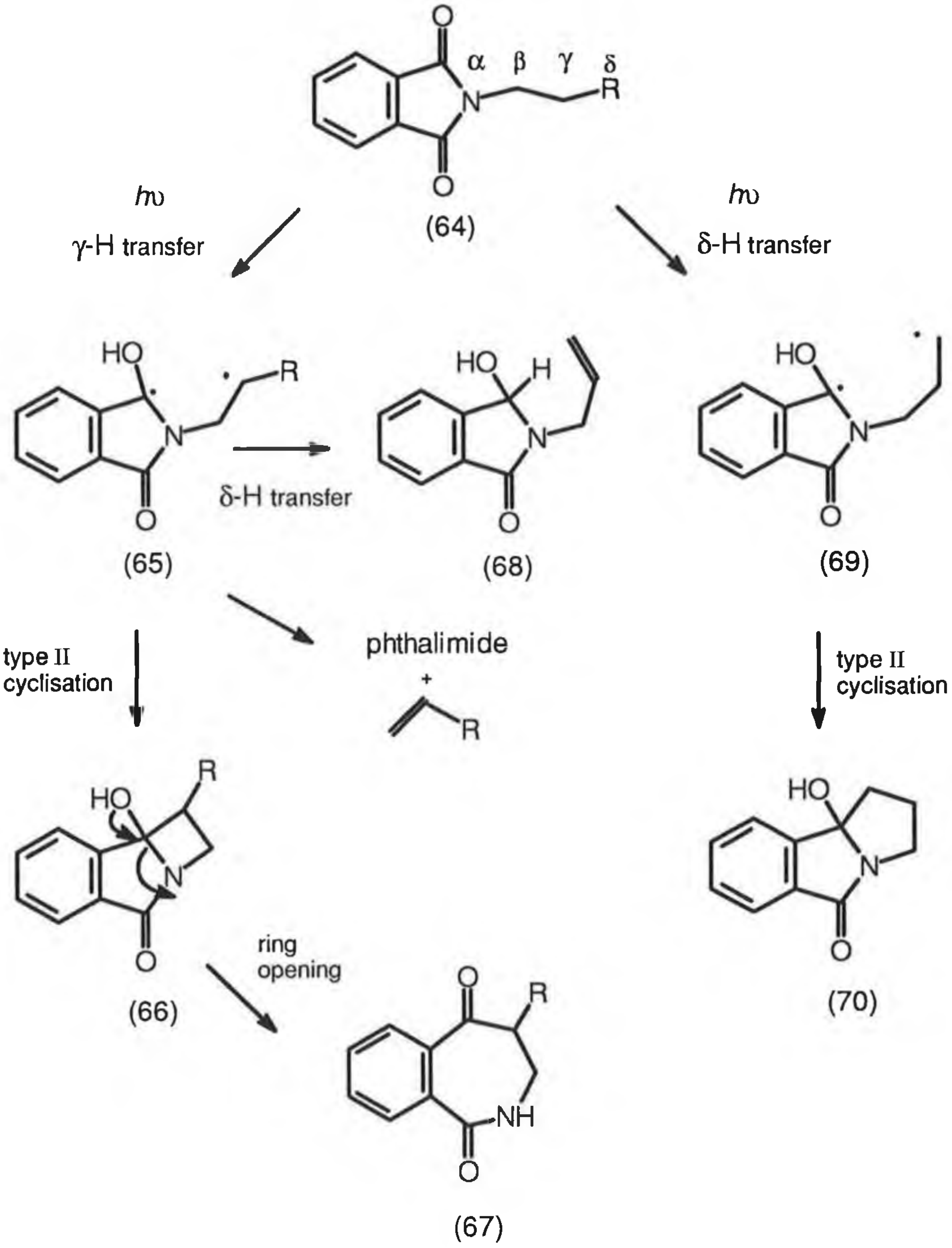
Photoreactions of *N*-arylphthalimides in which the B ring is heteroaromatic ring system have also been studied.[27] The prouducts isolated from the photolysis of three methyl substituted *N*-pyridyl phthalimides (58)-(60) are shown (SCHEME 2.9). The exact reason for the reluctance of (58) to cyclise is unknown but the authors suggest that interaction between the lone pair of the pyridyl nitrogen and the imide carbonyl would disturb the planarity of the molecule which is necessary for smooth cyclisation to occur.



SCHEME 1.20

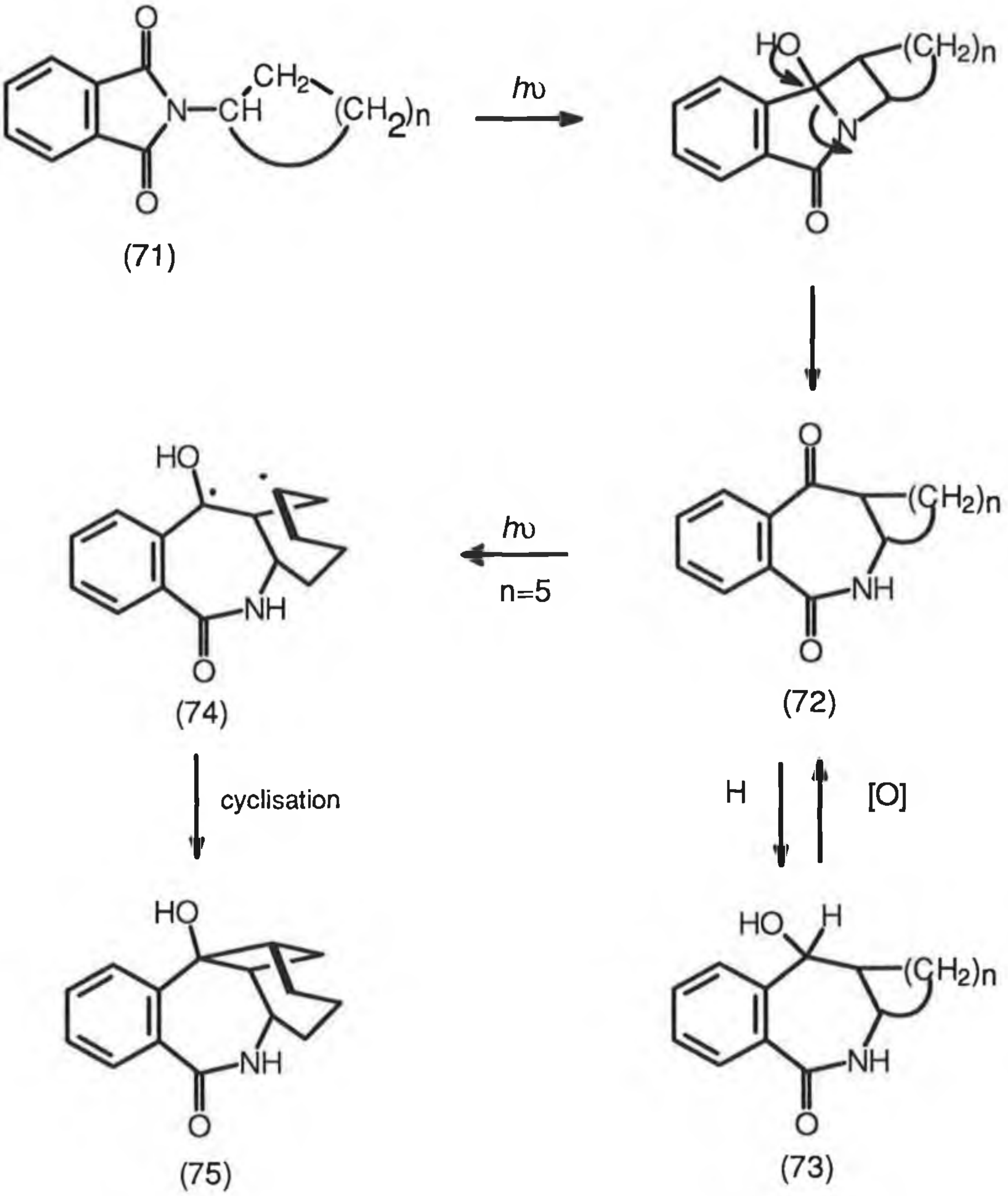
1.B.3.2 *N*-Alkyl phthalimides

The photochemical behaviour of a series of *N*-alkylphthalimides (64) which contain both γ and δ hydrogens were examined in several solvents.[28] The results are outlined (SCHEME 1.21) and are best rationalised by analogy with the Norrish type II hydrogen abstraction processes established in simple ketonic systems. The substrate (64) undergoes on photolysis initial γ-hydrogen abstraction to form a diradical (65) followed by either type II elimination to form phthalimide and alkene or type II cyclisation to an azacyclobutanol (66). This azacylobutanol presumably due to ring strain undergoes a retrotransannular ring opening to a benzazepinone lactam (67). Alternatively in some of the



SCHEME 1.21

diradicals (65) with δ-hydrogens a competing δ-hydrogen transfer can take place with formation of an unsaturated product (68). On irradiation of substrates containing a δ-hydrogen (64; R=Me) a competing δ-hydrogen abstraction process can take place to form diradical (69) which closes to azacyclopentanol (70) (SCHEME 1.21). This interpretation provides a rational basis for the

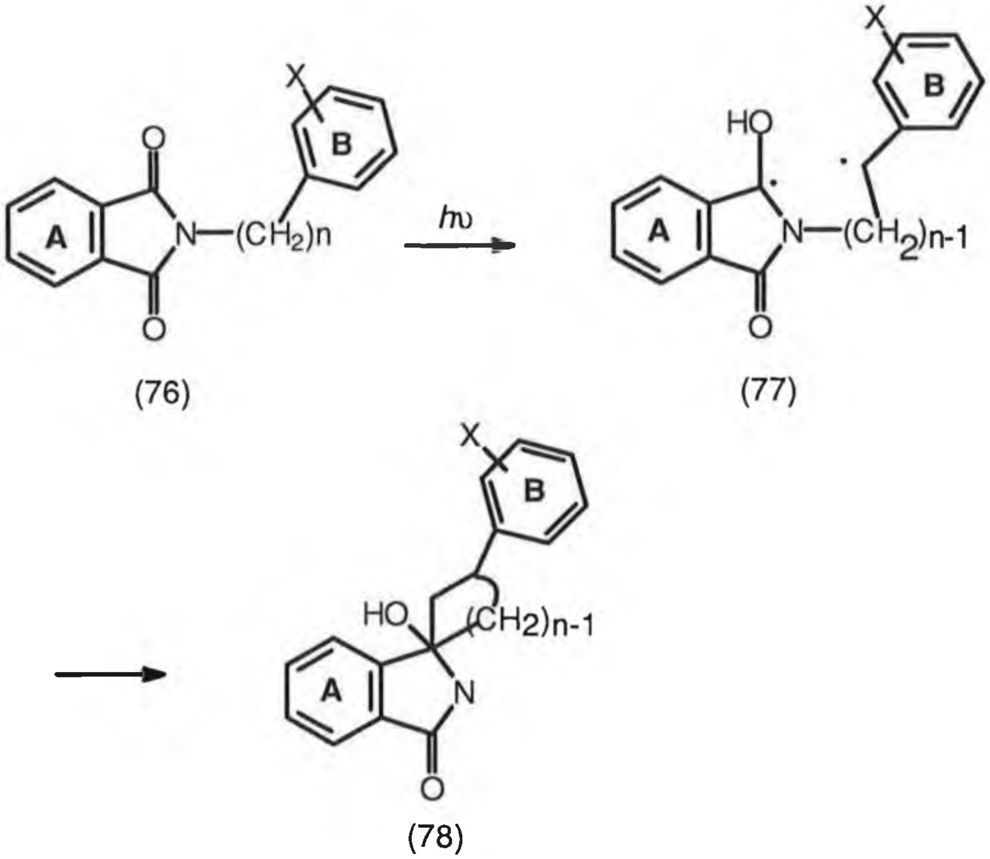


SCHEME 1.22

formation and ratio of almost all the products observed. Kanaoka and co-workers also observed an interesting cyclisation when investigating the photochemistry of *N*-alicyclic phthalimides (SCHEME 1.22).[29] Irradiation of *N*-cyclopentyl and *N*-cyclohexylphthalimides (71; n=3, 4) in ethanol gave mainly azepinones (72) accompanied by their reduced products (73). However the *N*-cycloheptyl compound (71; n=5) afforded a novel bridged cyclobutane system (75). The formation of (75) is perfectly consistent with the general pattern (SCHEME 1.21). At the benzazepinedione (72; n=5) a second γ-hydrogen abstraction leads to biradical (74) which closes to cyclobutanol (75).

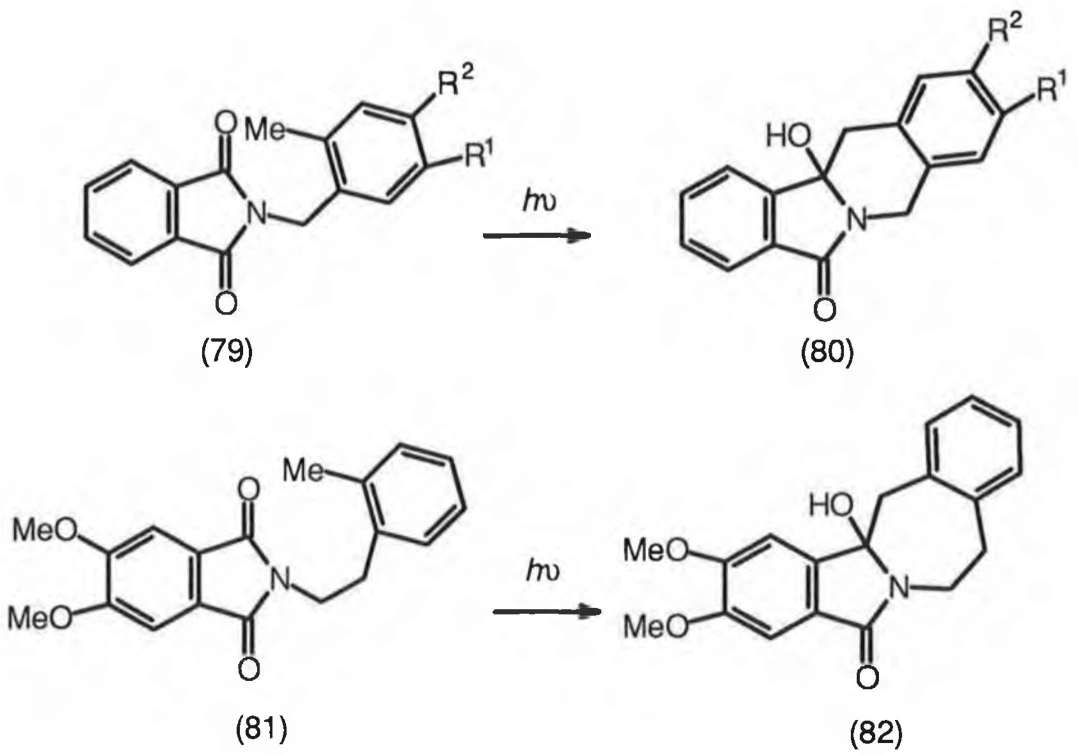
1.B.3.4 *N*-Aralkylphthalimides

Attempts to subject *N*-aralkylphthalimides (76) to cyclisation resulted in some interesting new aspects of bichromic systems.[30] On irradiation of (76)



SCHEME 1.22

(SCHEME 1.22) the yield of (78) was maximised at n=4 ie when the usually unfavourable eight-membered transition state (77; n=4) could be formed. Apparently the seven and six-membered analogues of (77) formed with relatively less ease. In addition electron-donating substituents X such as methoxyl and methyl distinctly promoted the reaction. Photolysis of *N*-aralkylphthalimides possessing substituents on both the phthalimido (A) aromatic ring and the aromatic ring (B) in the side chain has been reported.[31]

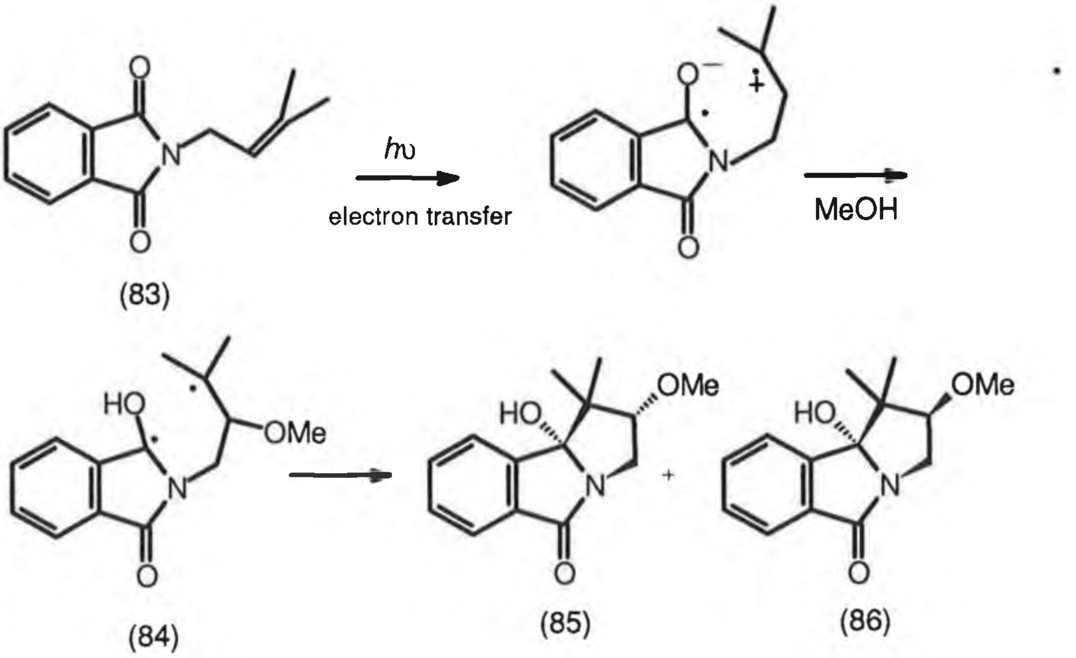


SCHEME 1.23

Irradiation of (79a; $R^1=R^2=H$) and (79b; $R^1=R^2=OMe$) in acetonitrile gave rise to the substituted isoindolones (80) in 18 and 52% yield respectively with the electron donating substituents on the B ring in (79b) distinctly promoting the cyclisation (SCHEME 1.23). Previous work had indicated that the presence of donor substitution on the A ring inhibits photocyclisation.[24] However (81), which has two methoxy groups underwent the photocyclisation to give (82) in 24% yield. The authors conclude that the photocyclisation of phthalimides possessing an *o*-methylphenyl group may provide a synthetic entry to tetracyclic systems related to berberine alkaloids.

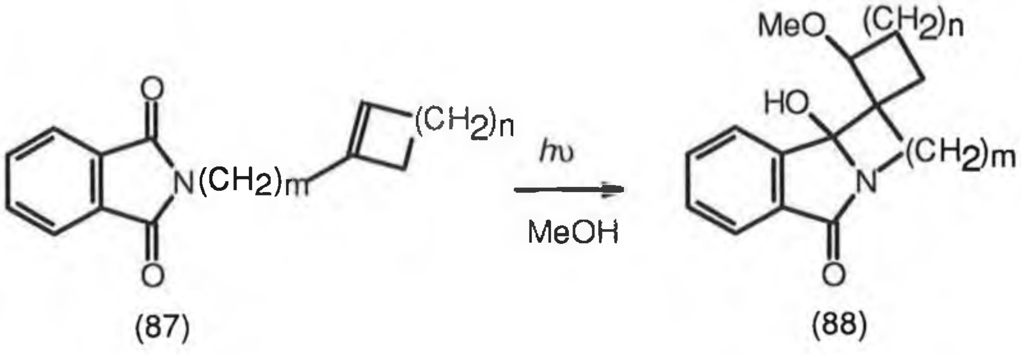
1.B.3.5 *N*-Alkenylphthalimides

Maruyama and Kubo have investigated the photochemistry of phthalimides possessing an alkenyl side chain.[32,33,34] The irradiation of the *N*-2alkenylphthalimides (83) in methanol affords two products (85) and (86) (SCHEME 1.24). The authors explain this cyclisation in terms of a mechanism involving initial single electron transfer from the double bond to the excited carbonyl followed by polar addition of the methanol to give a diradical (84)



SCHEME 1.24

which cyclises to give (85) and (86). This reaction was also found to proceed for *N*-3-alkenyl phthalimides to form solvent incorporated cylisation products.[35] The reaction has been extended to longer chain alkenyl compounds leading to medium sized cyclic and macrocyclic compounds.[36]

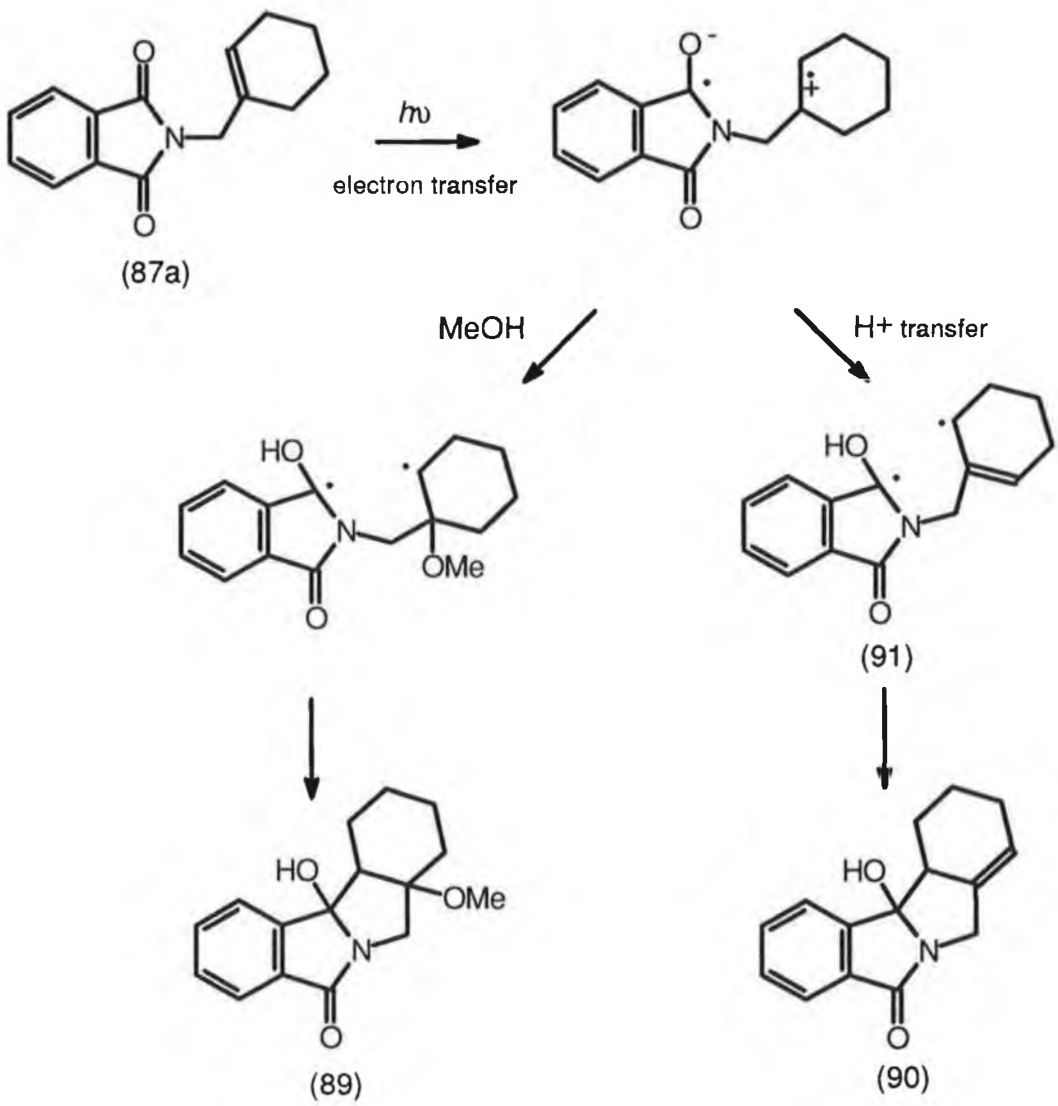


(a) $m=1$, $n=3$ (d) $m=3$, $n=2$

(b) $m=1$, $n=2$ (e) $m=n=3$

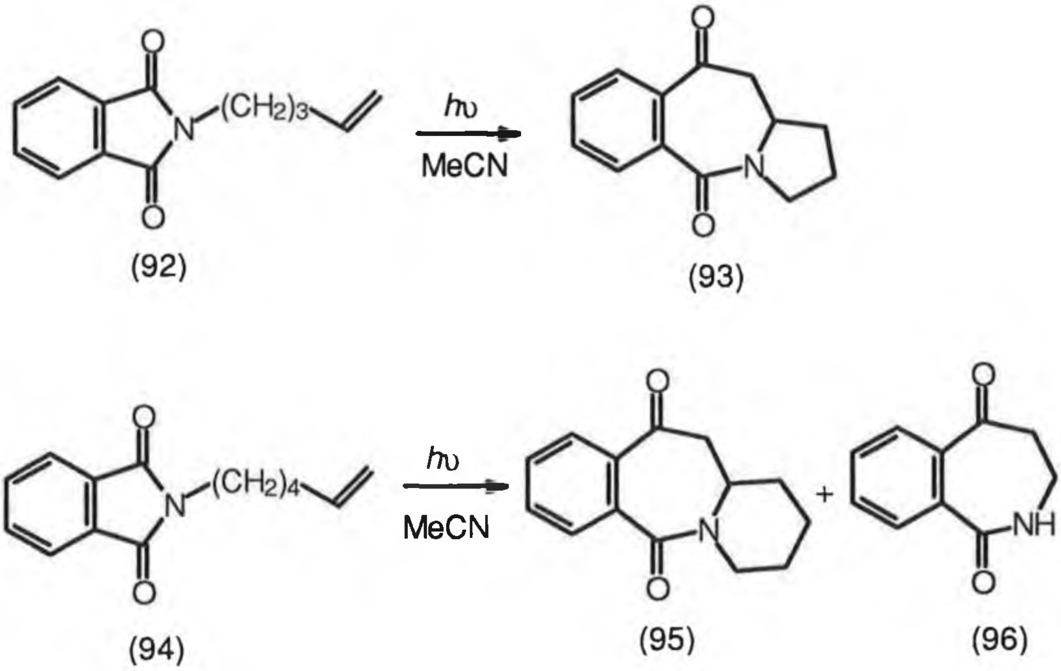
(c) $m=2$, $n=3$

SCHEME 1.25

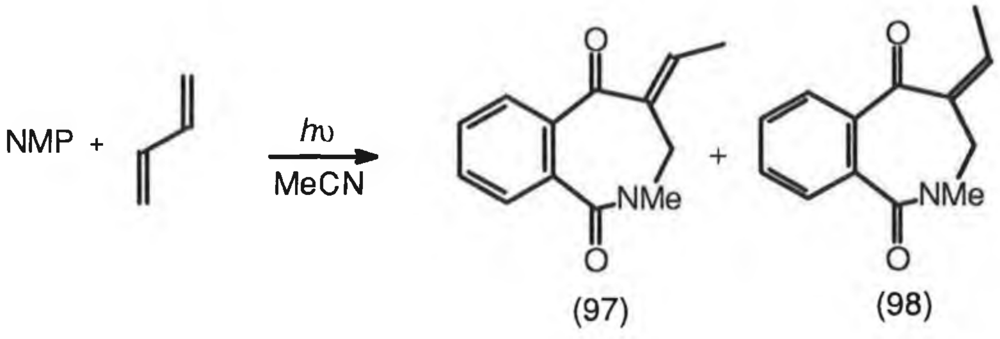


SCHEME 1.26

Kanaoka and co-workers have studied the photochemistry of *N*-cycloalkenyl phthalimides (87) in methanol.[37,38] Irradiation of (87; b-e) proceeded to give the cyclised spiro compounds (88; b-e), respectively (SCHEME 1.25). The mechanism proposed is as for straight chain alkenyl phthalimides involving electron transfer followed by addition of methanol forming the more stable biradical which cyclises to yield the observed product (88). Irradiation of (87a) in methanol afforded two products whose structures were assigned as (89) and (90) (SCHEME 1.26). The authors presume that for the substrate (87a), in which an allyic hydrogen is relatively close to the imide carbonyl a competing intramolecular proton transfer becomes possible leading to biradical (91) which closes to (90) (SCHEME 1.26). Maruyama and Kubo have also reported a different type of photocyclisation for certain alk-4 and 5-enyl phthalimides.[39,40] A series of *N*-4 and *N*-5-alkenylphthalimides was irradiatied in acetonitrile and a new type of cylisation product was observed, an example of which is conversion of (92) to (93) and (94) to (95) and (96) (SCHEME 1.27). The authors explain this as an intramolecular version of the reaction observed by Mazzochi and co-workers in which *N*-methylphthalimide (NMP) reacted with dienes to yield benzazepinediones (97) and (98) (SCHEME 1.28).[41] This reaction was not observed for *N*-alk-2-enylphthalimides in acetonitrile.

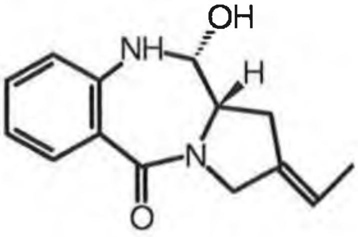


SCHEME 1.27

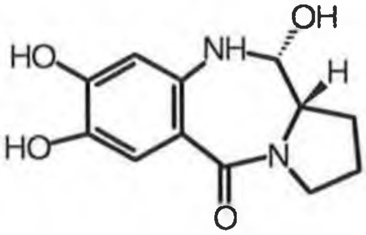


SCHEME 1.28

The authors also note that compounds of the type A-$(CH_2)_n$-D in which A and D are two different π-systems the efficiency of the intramolecular reaction is known to be a function of n, often for n=3 an optimum situation is attained as a result of steric factors.[42] Mazzochi and co-workers have utilised this formation of benzazepinediones intramolecularly from *N*-alk-4-enylphthalimides as a synthetic entry to the pyrrolo-1,4-benzodiazepine antibiotics, examples of which are Prothracarcin (99) and DC-81 (100).[43] The first step in the synthesis of



(99)



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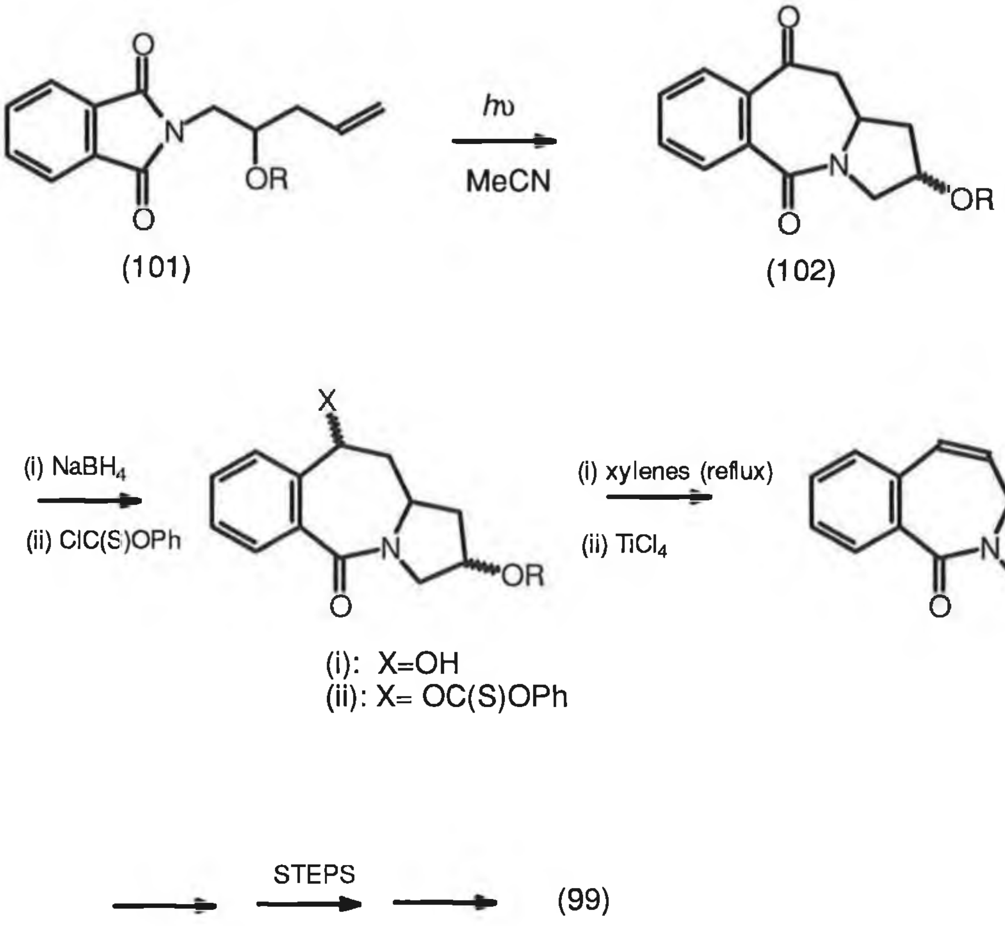
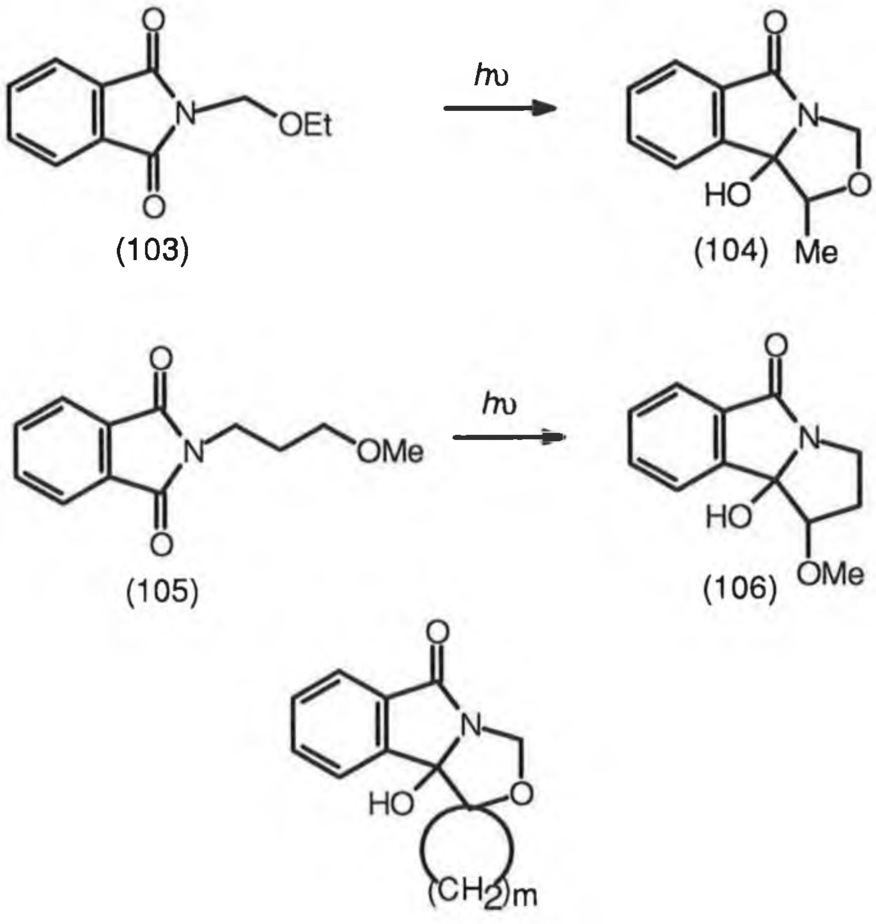


SCHEME 1.29

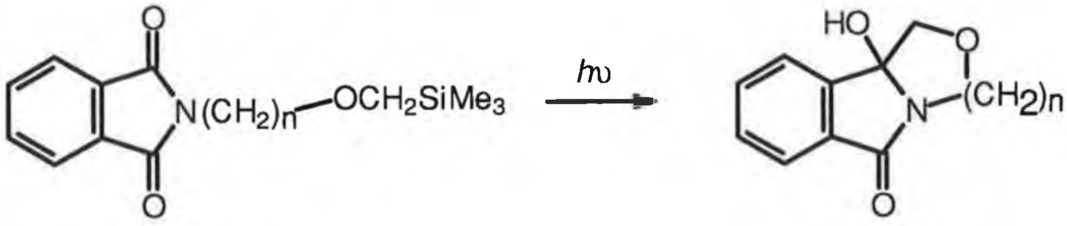
of Prothracarin (99) involved irradiation of a *N*-4-alkenylphthalimide (101) with an alkoxyl functionality at the C2 position to give the benzodiazepinedione (102) in 50% yield. This and some of the subsequent steps in the synthesis of (99) are outlined (SCHEME 1.29). The synthesis proved to be less efficient than one previously available but it demonstrated the possibility of incorporating an efficient photochemical step as a synthetic entry to desirable compounds. The nature and mechanism of the formation of benzazepinediones both intermolecularly and intramolecularly from phthalimide and alkene will be discussed in the section on reactions between phthalimide and alkenes.

1.B.3.6 Photocyclisation of *N*-substituted phthalimides containing alkyl-ether sidechains

Kanaoka and co-workers have reported a photocyclisation of phthalimides containing an ether linkage in the side chain (SCHEME 1.30).[44] The photoreactions of (103) and (105) were examined. On irradiation the products of δ-hydrogen abstraction (104) and (106) respectively were obtained. The mechanism for this reaction does not involve electron transfer as entropy factors do not favour a charge transfer complex between the carbonyl and alkoxy groups. However the authors suggest that the driving force for δ-hydrogen abstraction through a usually unfavourable seven membered transition state may be due to favourable geometry effects. The generation of spiro ring systems (107; m=4-7) in yields of 33-53% has also been described by Kanaoka's group.[45] Yoon and co-workers have reported[46] an efficient photocyclisation of the related *N*-(trimethylsilylmethoxyalkyl)phthalimide(108; n=2-6) in methanol. Irradiation of (108) in methanol gave cyclised product (109; n=2-6) in good to excellent yields (SCHEME 1.31).

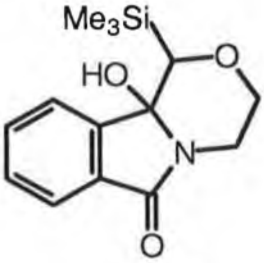


SCHEME 1.30



SCHEME 1.31

On irradiation in acetone (108; n=2) gave two additional cyclised products (110; 16%), (111; 19%) along with (109; 32%). The authors have rationalised the formation of the major cyclised product (109) in methanol as a result of electron transfer from alkoxy oxygen to singlet excited phthalimide to yield radical anion/radical cation species (112) which undergoes desilylation to generate biradical (113) which cyclises to generate the observed product (109) (SCHEME 1.32).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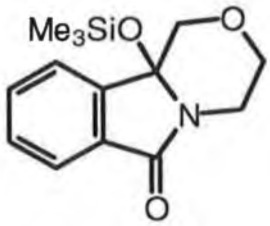
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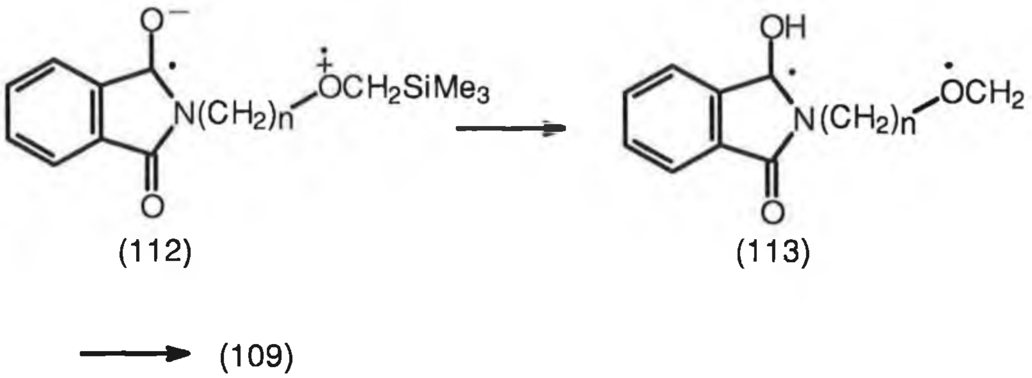
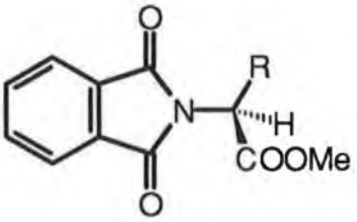


SCHEME 1.32

The formation of (110) and (111) in acetone has been ascribed to a competing proton or trimethylsilyl cation abstraction process by triplet state phthalimide to yield biradicals which cyclise to (110) and (111) respectively. The multiplicities of the excited states were assigned on the basis of oxygen quenching studies, the formation of (110) and (111) being quenched in the presence of oxygen while the formation of (109) was not. Kanaoka and co-workers have stated that entropy factors do not favour the formation of a charge transfer complex between excited state phthalimide and alkoxy side chains,[44] so whether an electron transfer process or some sort of oxygen mediated abstraction process is operating in this system is unclear.

1.B.3.7 Photocyclisation of phthaloyl-α-amino acids and derivatives

Griesbeck and co-workers have reported the photocyclisation of phthaloyl-α-amino acid esters (114) in a series of papers.[47,48,49] For the purposes of simplification they described the reactivity in terms of the abstractable hydrogens present.



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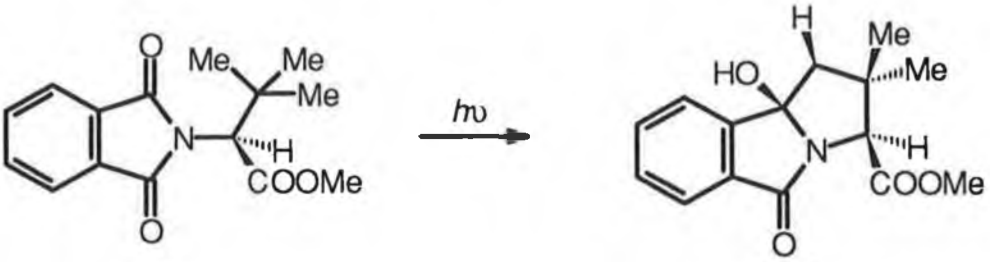
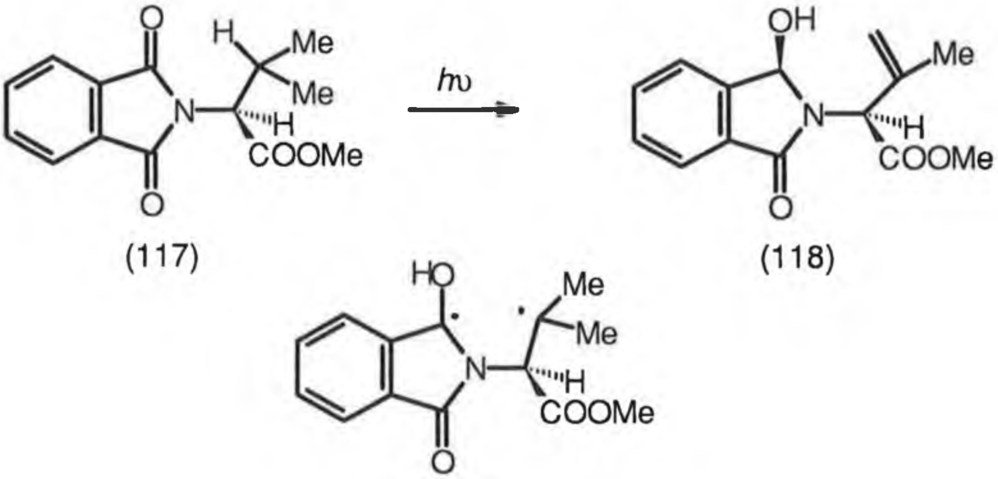


(115)   (116)

SCHEME 1.33

(a) δ-hydrogens: The *tert*-leucine derivative (115) contains only δ-hydrogens and on irradiation in benzene led to formation of the benzoannellated pyrrolidinone (116) in > 90% yield (SCHEME 1.33).The reaction is consistent



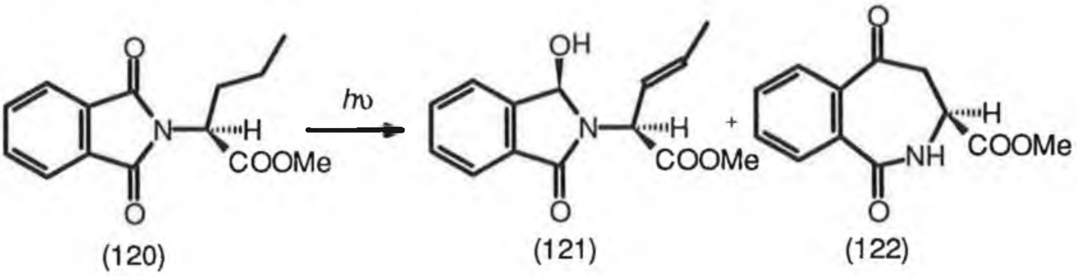
(117)   (118)

(119)

SCHEME 1.34

with δ-hydrogen abstraction by excited state phthalimide chromophore followed by radical combination. The reaction is also stereospecific with only one stereoisomer formed.

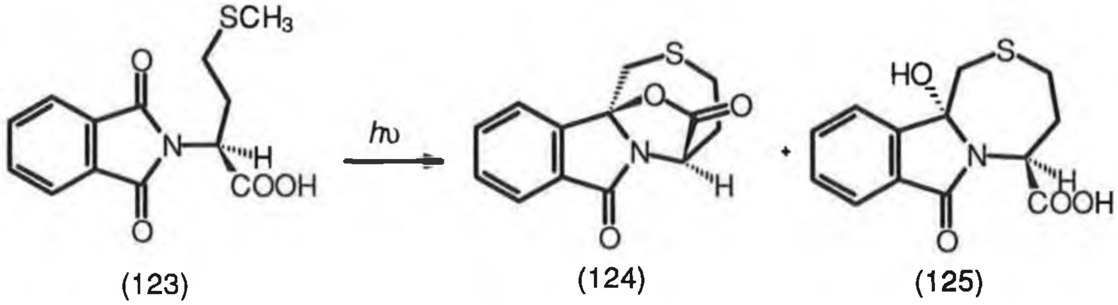
(b) γ- and δ-hydrogens: Irradiation of the valine derivative (117) gave rise to the substituted isoindolone (118) with high diastereoselectivity (SCHEME 1.34). The mode of reaction involves initial γ-hydrogen abstraction to give biradical (119) which undergoes a second hydrogen transfer stereoselectively to the Si face of the hydroxy radical to give (118) whose absolute stereochemistry was confirmed as (1'R, 2S).



SCHEME 1.35

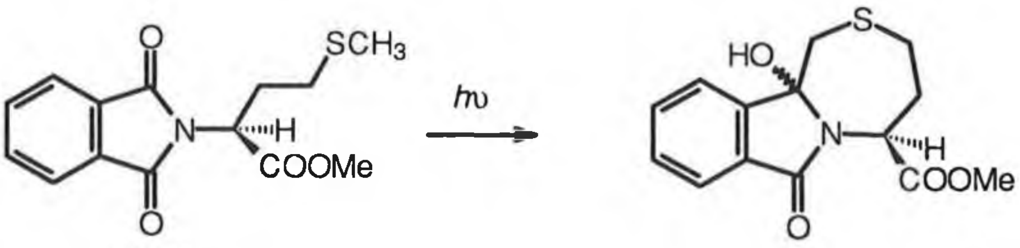
(c) γ-, δ-, ε-hydrogens: An example of a substrate containing three types of abstractable hydrogen is the norvaline derivative (120) which gave the isomerisation product (121) in 15% yield by a process equivalent to the isomerisation of (117) to give (118) (SCHEME 1.35). The major product isolated was the benzazepinedione (122) whose formation can be rationalised as a process analagous to the formation of benzazepinediones from photocyclisation followed by retrotransannular ring opening of *N*-alkyl phthalimides containing γ-hydrogens.[28] The initial benzazepinedione formed from (120) presumably undergoes a second hydrogen transfer followed by elimination of propene to give the observed product.

Griesbeck has also examined the photochemical behaviour of phthaloyl amino acids and their corresponding esters which contain electron donor functionality in their side chain.[49,50] An example of this type of substrate is phthaloyl methionine (123) and its methyl ester (126). The products obtained on irradiation in benzene of S-phthaloyl methionine (123) are lactone (124) and trans hydroxy acid (125) in 13% and 41% yield respectively (SCHEME 1.36).



SCHEME 1.36

Kanaoka and co-workers did not report formation of the lactone when they reported the photocyclisation of (123).[51] The photochemical process is thought to be as Kanaoka and co-workers suggested, single electron transfer from sulphur to excited state phthalimide followed by ζ-proton transfer and cyclisation to form cis/trans hydroxy acid. The cis hydroxy acid which is never detected in the reaction mixture immediately closes to lactone (124). A similar photoprocess occurs for the corresponding methyl ester of methionine (126) which closes on irradiation in benzene to a 1:1 mixture of cis and trans hydroxy esters (127) (SCHEME 1.37).



(126)

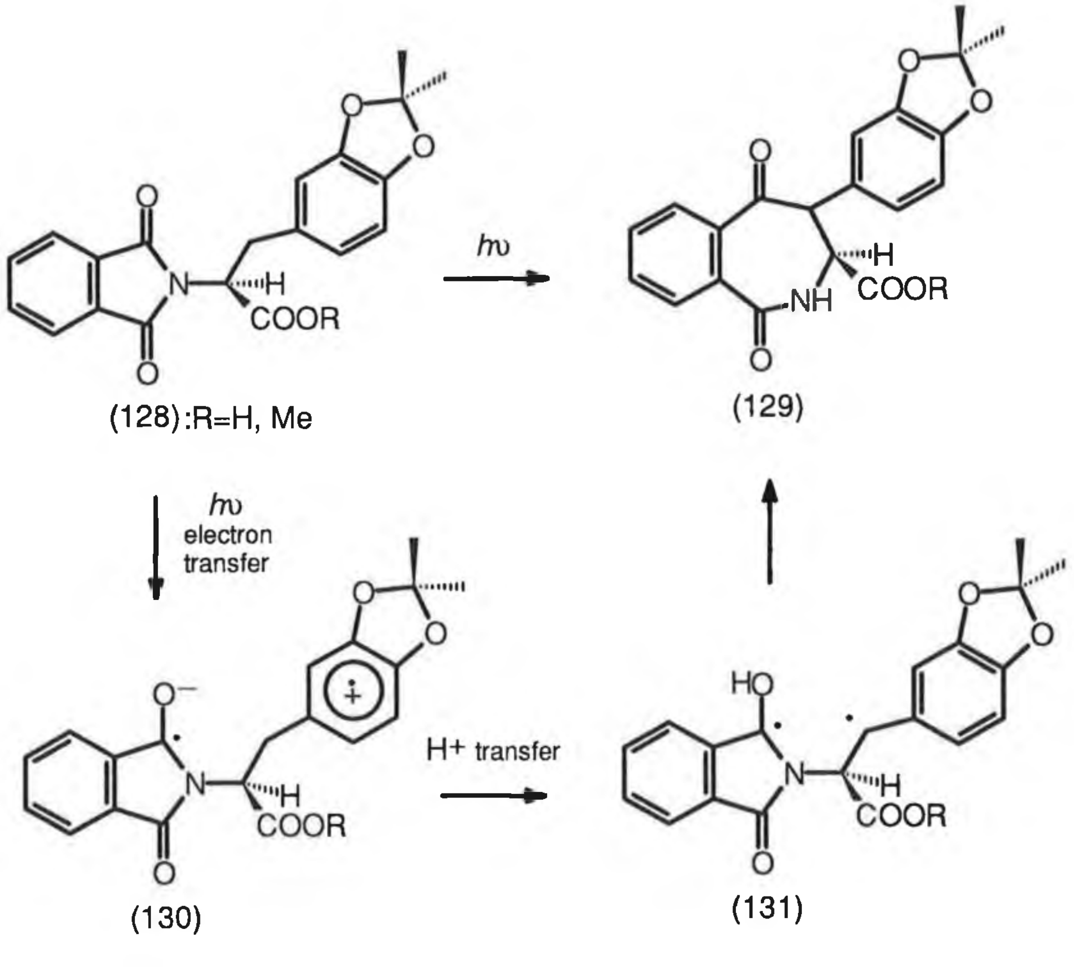
(127)

cis+trans

1:1

SCHEME 1.37

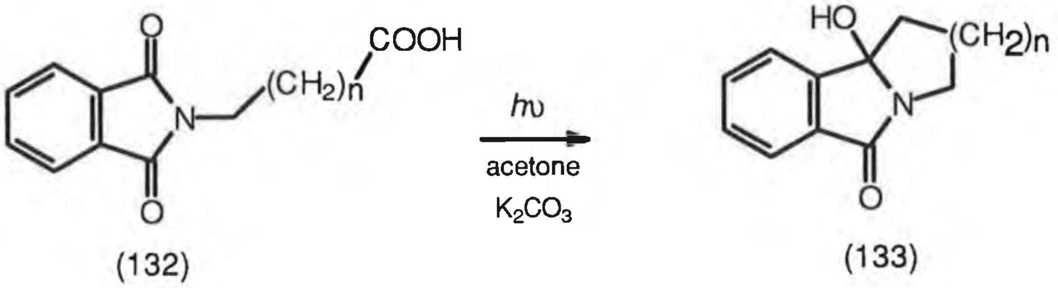
Grisebeck has also described the photocyclisation of phthaloyl derivatives of phthaloyl-*L*-dopa (SCHEME 1.38).[50] Irradiation of the acetone acetal of phthaloyl-*L*-dopa and its methyl ester (128; R=H, R=Me) gave rise to the benzazepinediones (129) in quantitative yield. The mechanism is suggested as single electron transfer from electron rich arene ring to excited state phthalimide chromophore to give radical cation/radical anion pair (130) followed by proton transfer from benzylic protons to generate radical pair (131). This species subsequently closes to give a hydroxyazetine which rapidly undergoes a retrotransannular ring opening to give observed product (129).



SCHEME 1.38

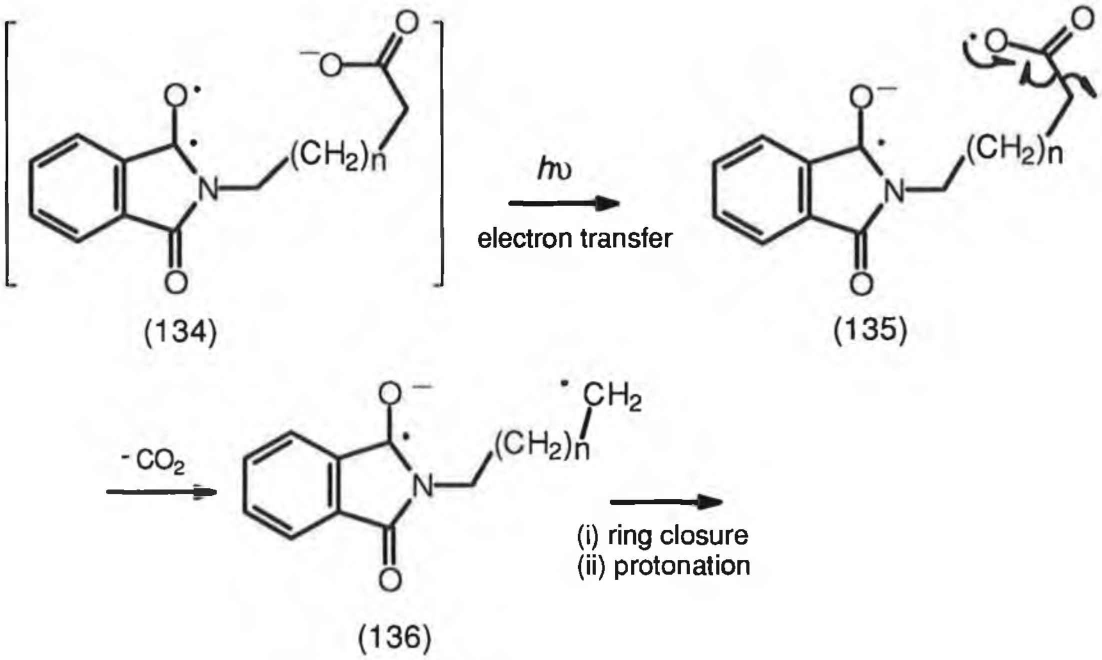
The authors note that photodecarboxylation, a well known photoprocess for phthaloyl-amino acids is not observed for the methionine (123) or the *L*-dopa

(128; R=H) derivatives. Obviously the rate of electron transfer from electron rich substituents is far greater than the rate of proton transfer from a γ-carboxylic position. Paleo and co-workers have also reported efficient formation of benzazepinediones from phthaloyl derivatives of *L*-dopa ethyl esters.[52, 53] Grisebeck and co-workers have very recently reported[54] that the photo-decarboxylation of phthaloyl amino acids can be exploited to form macrocyclic systems. Previous photochemical macrocyclic synthesis involving the phthalimide chromophore involved incorporation of the electron transfer moieties, principally thioether[55] and alkylamine[56] in the final product. Decarboxylation does not occur for phthaloyl derivatives of β– or γ-amino acids.[57] Grisebeck proposes that formation of an intramolecular hydrogen bond between phthalimide carbonyl and carboxyl proton is essential for the decarboxylation process and the electron donor species is carboxylate anion. In order to support this hypothesis a series of phthaloyl amino acids (132; n=2, 3, 9) with remote carboxyl groups was irradiated in acetone in the presence of potassium carbonate and cyclised carbinols (133) were obtained in yields of 80-90% (SCHEME 1.39). The mechanism (SCHEME 1.40) presumably involves

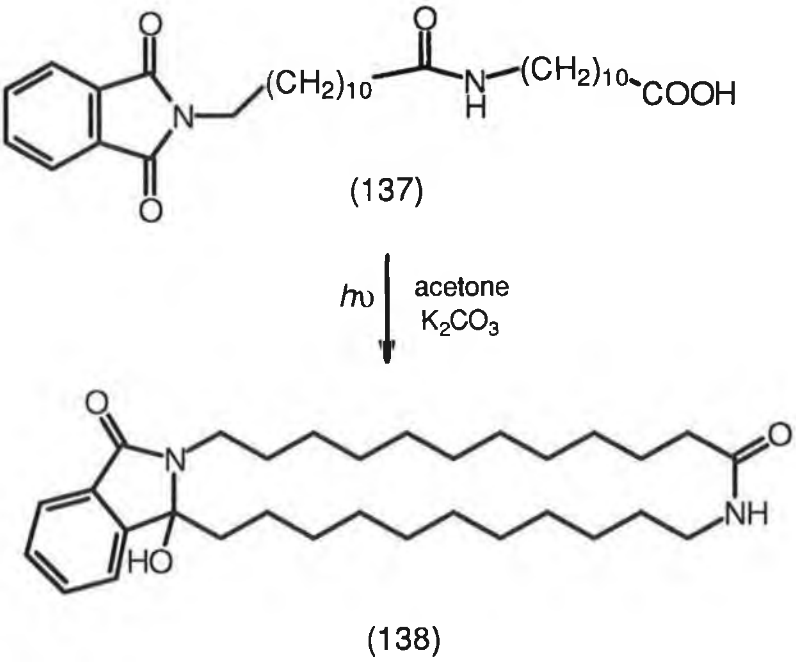


SCHEME 1.39

on generation of excited state deprotonated species (134) an intramolecular electron transfer from side chain carboxyl anion to excited state phthalimide chromophore, extrusion of carbon dioxide from (135) to form diradical (136) which subsequently closes. Extremely large macrocycles are possible by this route, an example of which is the formation of (138) on irradiation of (137) (SCHEME 1.41).[54] The authors suggest that this reaction could be extended to the synthesis of macrocyclic systems of use in host-guest applications.



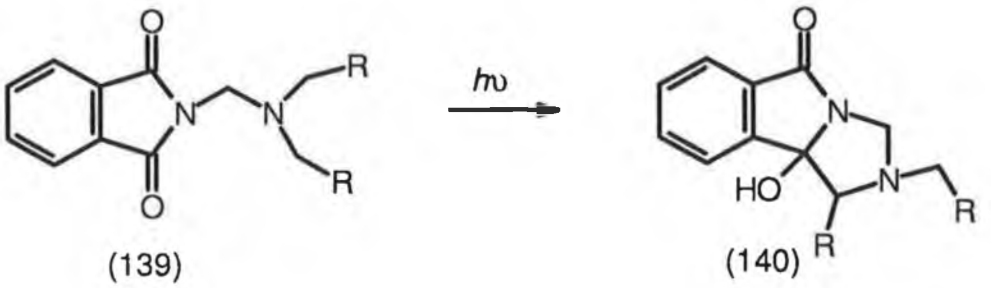
SCHEME 1.40



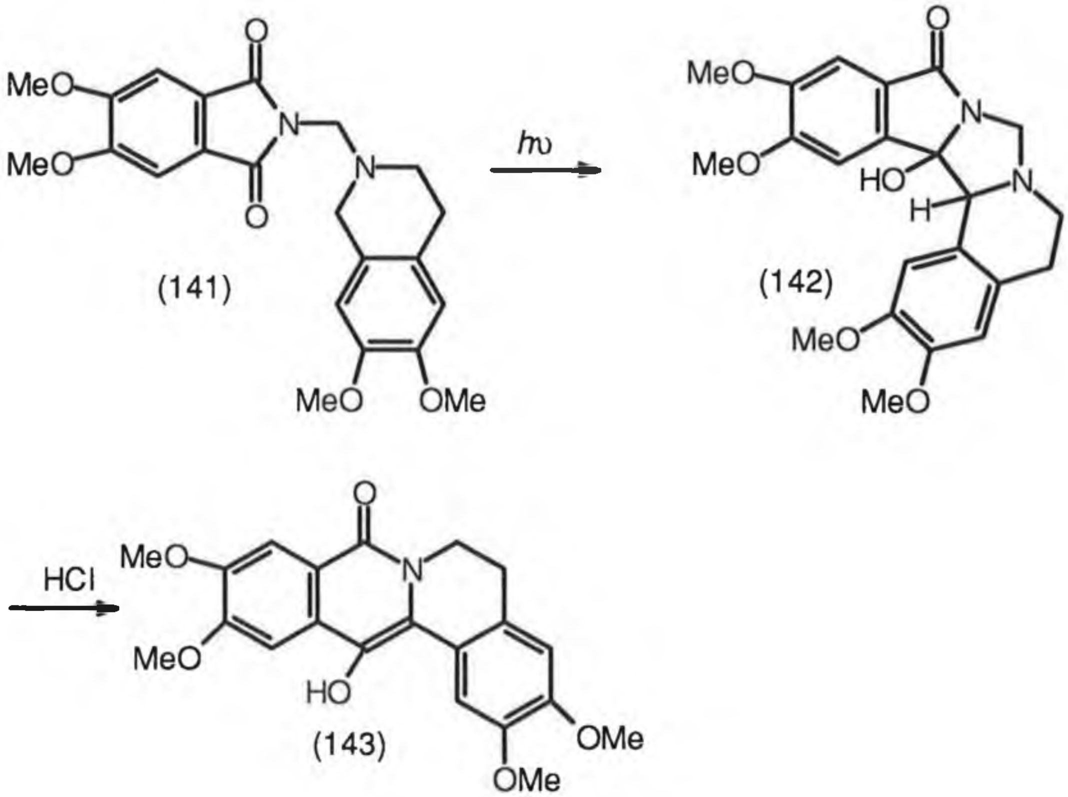
SCHEME 1.41

1.B.3.8 Photocyclisation of *N*-substituted phthalimides containing alkyl amine side chains

The photocyclisation of phthalimides containing nitrogen in the side chain has also been reported by a number of groups. Roth and co-workers reported[58, 59] the photocyclisation of a series of Mannich bases (139) to (140) as did Coyle and Newport (SCHEME 1.42).[60, 61, 62]

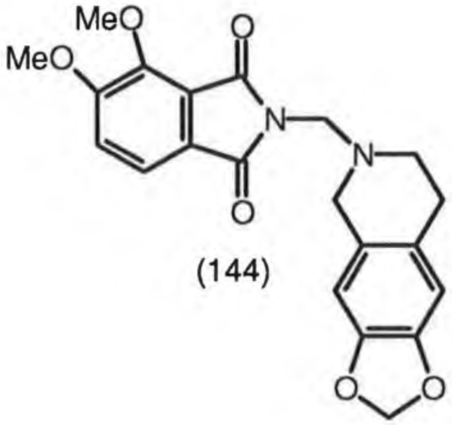


SCHEME 1.42



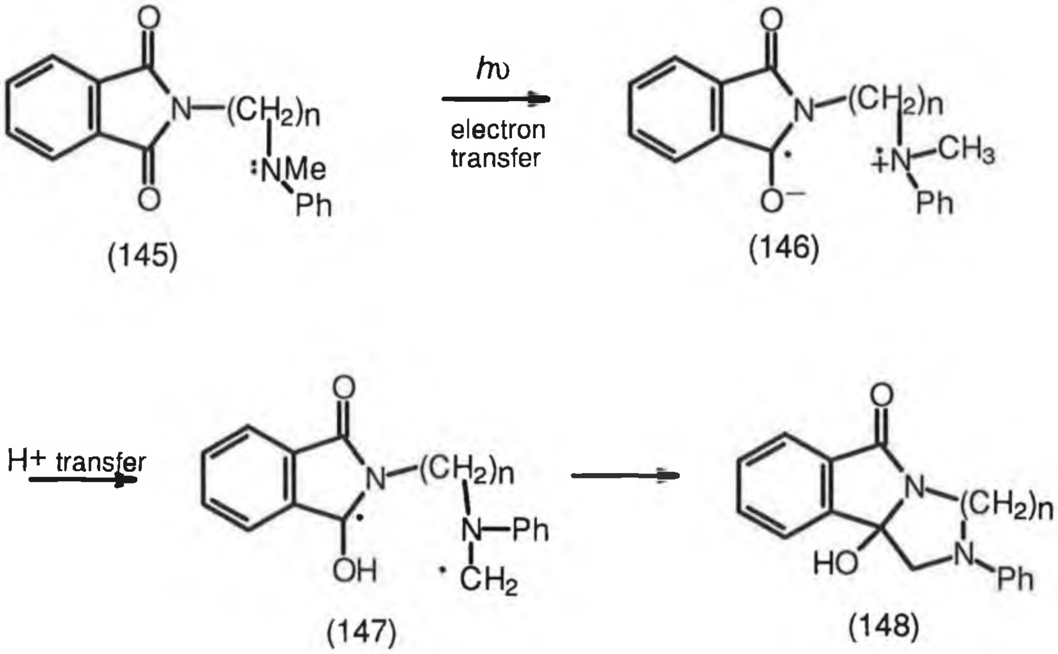
SCHEME 1.43

Coyle subsequently reported his attempts to extend this photocyclisation to the synthesis of alkaloids.[63] Irradiation of Mannich base (141) gave (142) in good



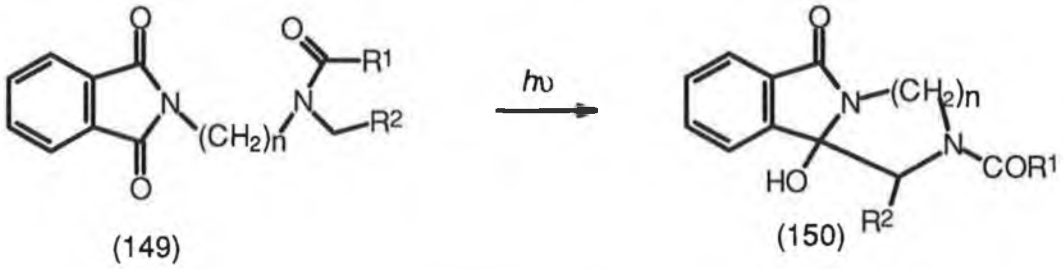
(144)

yield. Treatment of (142) with acid gave (143) which contains the tetracyclic system of the proterberine skeleton (SCHEME 1.43). Attempts to produce naturally occurring proterberine alkaloids proved unsuccessful as the unsymmetrical nature of the starting phthalimide mannich bases (144) gave rise to a number of photoproducts none of which could be isolated in good yield.

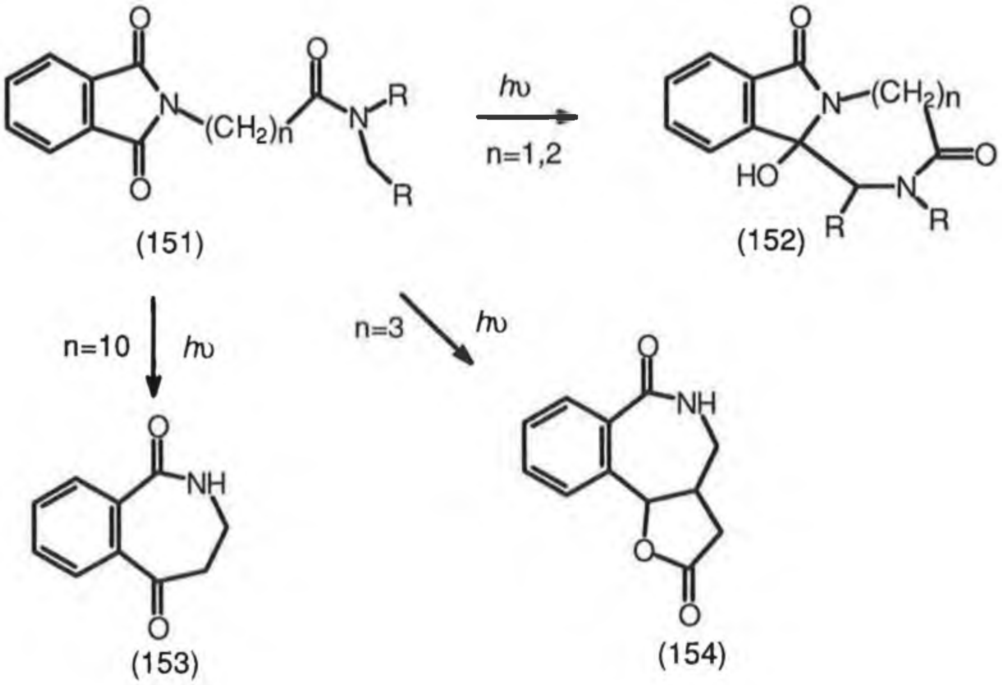


SCHEME 1.44

Kanaoka and co-workers reported the photocyclisation of a series of compounds (145; n= 1-12) resulting in the formation of new ring systems (148) containing between 5 and 16 members.[56] The authors suggest that the reaction proceeds through the intermediacy of the intramolecular electron transfer generated radical cation/radical anion (146) which transfers a proton to form a biradical (147) which subsequently closes to (148) (SCHEME 1.44).



SCHEME 1.45

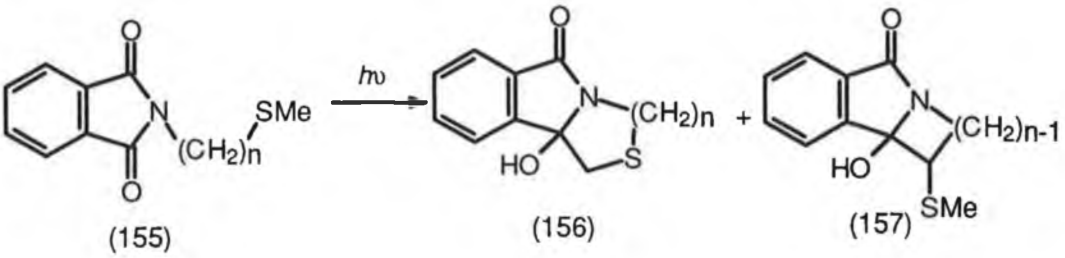


SCHEME 1.46

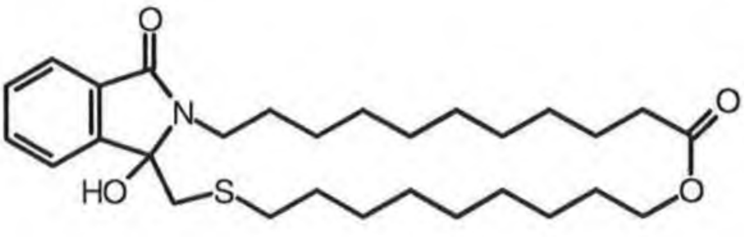
Kanaoka and co-workers subsequently reported[64] that on incorporation of an acyl group at the amino nitrogen in the *N*-alkyl side chain the efficiences of these reactions were highly improved. For example irradiation of (149; n=1-3) five,six or seven membered cyclised products (150; n=1-3) were obtained in good yield (SCHEME 1.45).[64] Also examined was the photochemistry of substrates (151).[65] The cyclisation occurred for phthalimides (151; n=1,2) to form (152; n=1,2) however for n ≥ 3 more conventional γ-hydrogen abstraction processes occurred to yield benzazepinediones such as (153) and (154) (SCHEME 1.46).

1.B.3.9 Photocyclisation of *N*-substituted phthalimides containing an alkyl sulphide side chain

As mentioned earlier Kanaoka's group reported the formation of (125), the ring closed derivative from phthaloyl methonine(123).[51,66] The reaction was subsequently developed by Kanaoka and co-workers[42,43] to include systems (155) which close to a pair of compounds (156) and (157) with (156) always the major product.[67,68] This reaction is remarkably efficient giving rings of up to 16 members in this series of compounds (SCHEME 1.47). The scope of this ring closure was extended to include substrates containing amide,[68, 69, 65] ester[69, 71] and ether[72] bonds. Some outstanding examples of the products from these reactions are (158)-(160). The mechanism as before involves formation of an electron transfer intermediate which affords following proton transfer two isomeric biradicals which close to yield (156) and (157). This reaction can be thought of as a pair system which consists of a phthalimide group as the acceptor and the methylthio group as the donor (SCHEME 1.48).[72] The authors

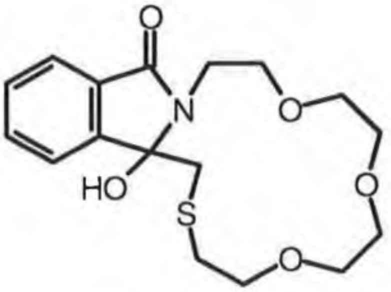


SCHEME 1.47

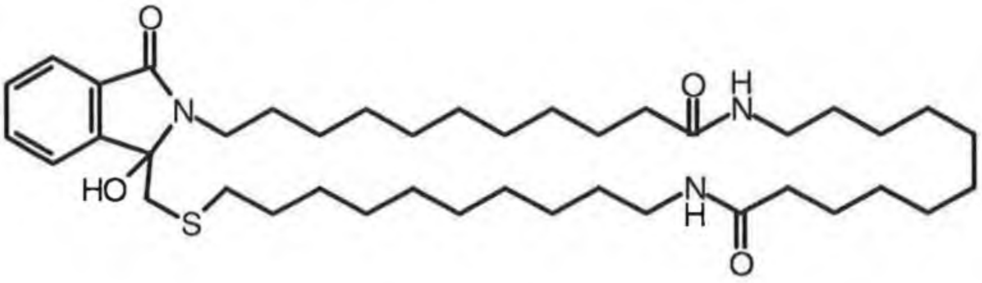


(158) ring size 27: yield 48%

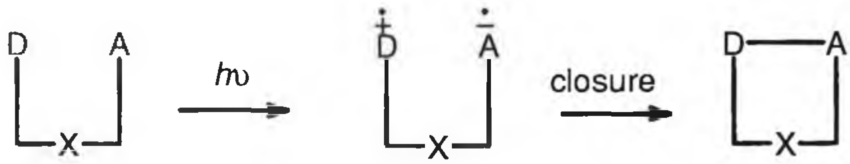
isomer ring size 25: yield 10%



(159) ring size 15: yield 35%
isomer ring size 13: yield 24%

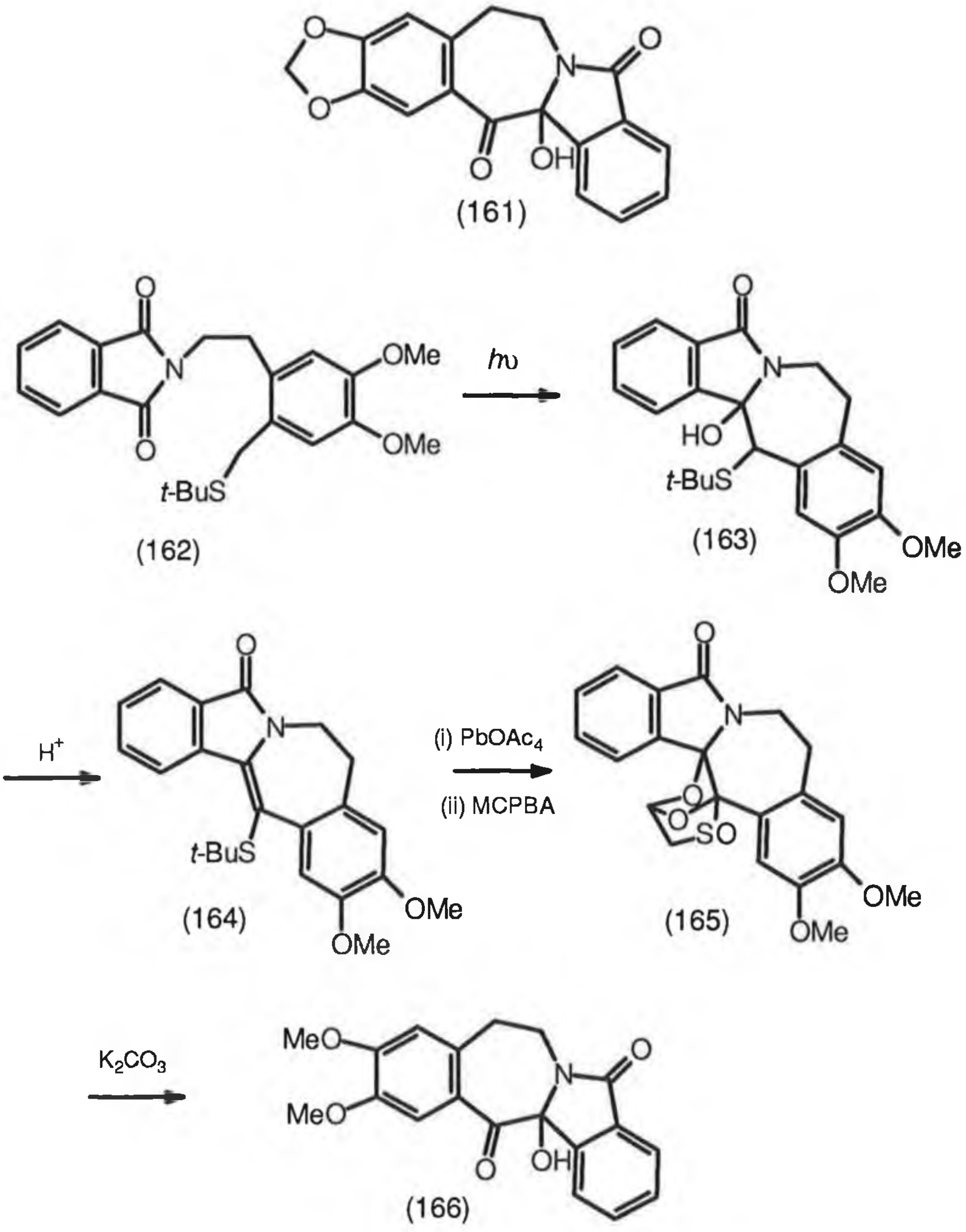


(160) ring size 38: yield 36%



SCHEME 1.48

note that they had reported earlier that phthalimides with an ether moiety would undergo facile δ-hydrogen abstraction,[44] so the polyether substrates used to produce (161) would have several potential reactive sites which the excited imide carbonyl could attack covalently. In view of this it is remarkable that the photocyclisation selectively occurs at the remote methylthio group. The authors suggest that this photocyclisation may be an attractive route for synthesis of crown type compounds with applications in host guest chemistry.[55] Mazzocchi and co workers have investigated the possibility of incorporating the photocyclisation of phthalimides containing a thioether linkage in the side chain as a photochemical approach to the synthesis of berberine alkaloids. such as chilinene (161).[73] Irradiation of (162) which contains a t-butyl thioether



SCHEME 1.49

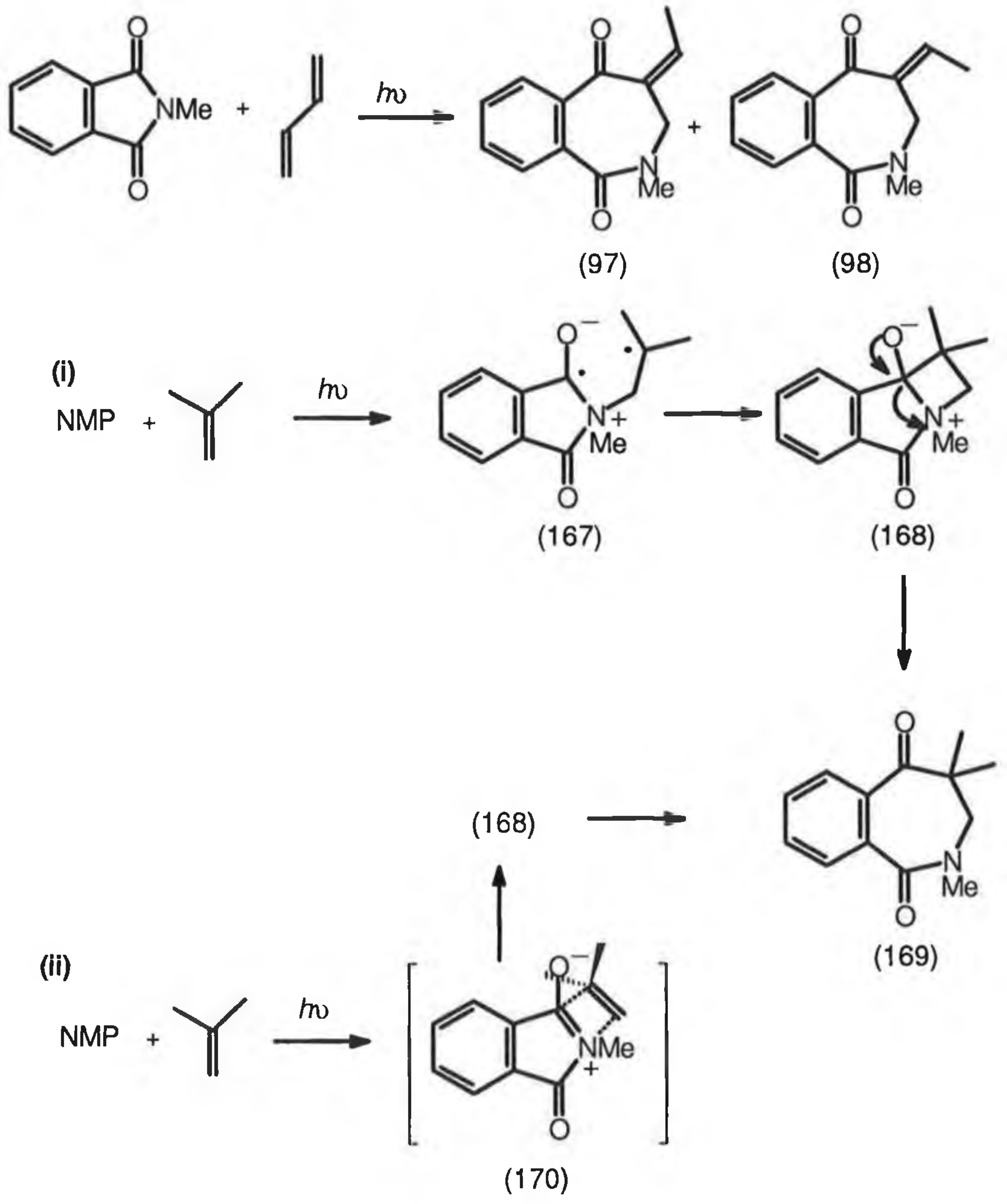
substituent photocyclised to (163) efficiently. Acid catalysed dehydration afforded (164) in 68% overall yield. Numerous attempts to hydrolyse (164) proved unsucessful, but treatment of (164) with lead tetraacetate, followed by oxidation with metachloroperbenzoic acid afforded the novel hexacyclic orthoester (165) in 26% yield. Its structure was confirmed by crystallographic analysis. Hydrolysis of (165) under basic conditions afforded (166) quantitatively the desired chilinene analogue (SCHEME 1.49). The authors conclude that the formation of (166) in 18% overall yield represents the best example to date of a synthesis of a functionalised chilinene system.[73]

1.B.3 Reaction of *N*-substituted phthalimides with alkenes

1.B.3.1 Benzazepinedione formation

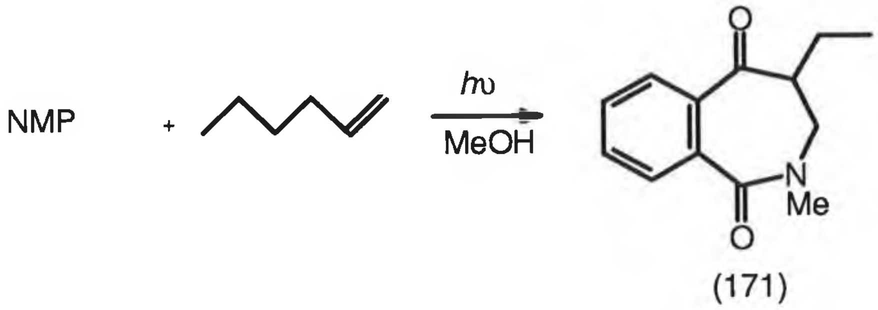
In the course of studying the quenching of type II processes of *N*-alkylphthalimides Mazzocchi and coworkers observed that the dienes used as quenchers also reacted with the phthalimides. Futher investigation led to the observation that an unprecedented addition of the alkene to the carbonyl nitrogen bond was occurring to afford benzazepinediones.[41] The reaction was synthetically efficient with conversion of *N*-methylphthalimide (NMP) to the benzazepinediones (97) & (98) in 93% yield. The reaction is general in that it takes place with dienes,[41] alkenes [74, 75, 39,] vinyl ethers and vinyl esters.[76] It has also been found to be regioselective with respect to the direction of addition of the alkene component, the more substituted carbon of the original alkene appearing adjacent to the carbonyl in the final product. Two mechanisms have been proposed to account for benzazepinedione formation (SCHEME 1.50).[77] The first involves addition the alkene (SCHEME 1.50, (i)) to afford zwitterionic biradical (167) which would close to give dipolar bicyclic intermediate (168) which subsequently reopens to give the observed benzazepinedione (169).

The second mechanism considered is a concerted addition of the alkene to the C(O)-N bond of NMP (which has considerable double bond character), possibly through an oriented exciplex (170) to give intermediate (168) directly (SCHEME 1.50, (ii)). If the reaction were taking place via a

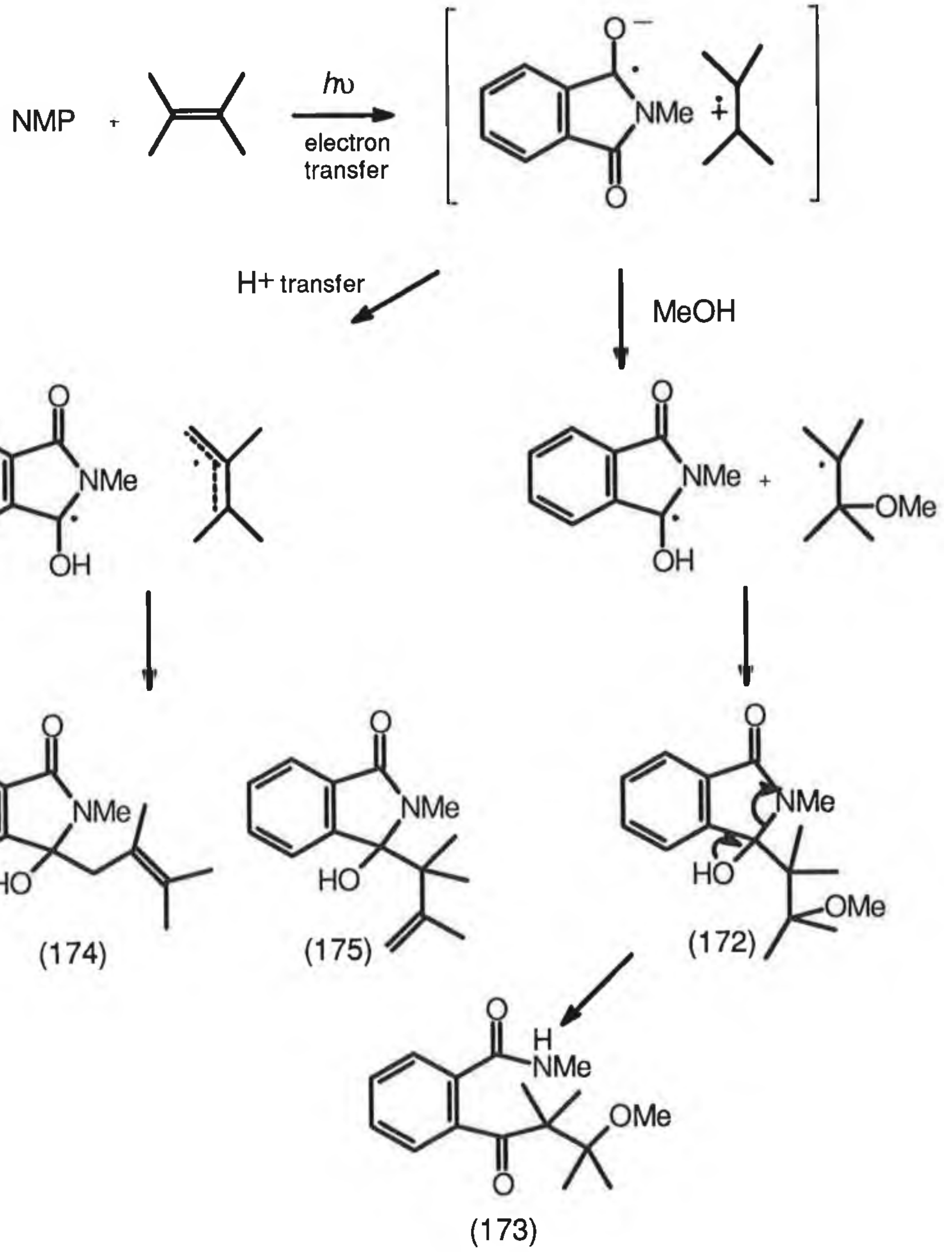


SCHEME 1.50

biradical intermadiate such as (167) and if the lifetime of the biradical is sufficiently long to permit rotation about the carbon carbon bond of the alkene the addition of *cis* but-2-ene to NMP would give both the *cis* and *trans* benzazepinediones. However if the reaction is taking place by the concerted mechanism addition of *cis* but-2-ene would give only the *cis* benzazepinedione. Experiments at low conversion and with excess alkene to ensure little *cis-trans* isomerisation of the alkene indicated that addition of *cis* but-2-ene gives only the *cis*-product.[77] Mazzocchi and co-workers concluded that the reaction is stereospecific in addition to being regiospecific and they are therefore in favour of the concerted process as the mode of addition. However a biradical mechanism in which ring closure is faster than bond rotation cannot be ruled out. Mazzocchi and co-workers[78, 79] observed that those alkenes with low ionisation potentials did not undergo benzazepinedione formation and they suggest that electron transfer may be a competing process. This suggestion was substantiated[80] by examination of the free energy values ΔG_{ET} for electron transfer between a variety of alkenes and NMP calculated using the Weller equation.[80] Weller's equation predicts that electron transfer to the NMP excited state will be exothermic and therefore efficient when the oxidation potential of the alkene is less than 2.1 volts. In this system benzazepinedione formation was only observed in those cases where ΔG_{ET} was positive, photoreduction products from an electron transfer mechanism being obtained from those alkenes for which ΔG_{ET} was negative. Evidence for this competing electron transfer process was obtained by studying[81] the photochemistry of *N*-methylphthalimide (NMP) and alkenes in methanol as solvent. Maruyama has shown[33] that the intramolecular radical anion/radical cation pair formed on irradiation of *N*-alkenyl phthalimides are very effectively trapped by alcohol solvents. It was

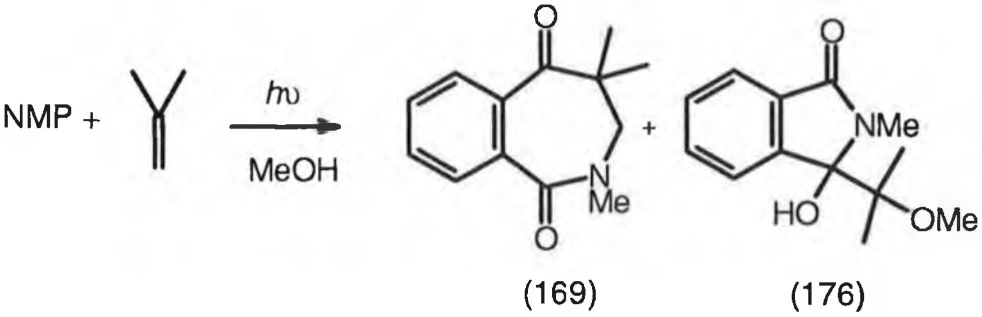


SCHEME 1.51



SCHEME 1.52

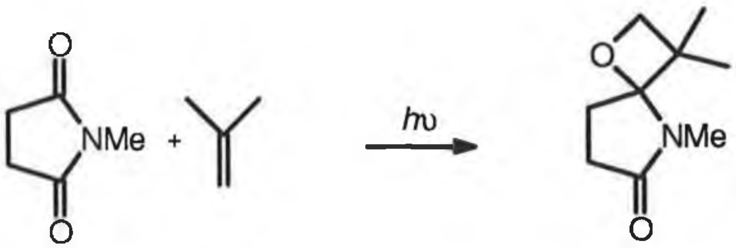
therefore expected that those alkenes which underwent efficient electron transfer to NMP (ΔG_{ET} negative) should afford only solvent trapped products. On the other hand those alkenes whose interaction with NMP resulted in positive ΔG_{ET} values should only afford benzazepinediones. The results obtained agreed with these observations. Irradiation of a solution of NMP and hex-1-ene in methanol gave only the benzazepinediones (171) consistent with the large positive calculated ΔG_{ET} value (SCHEME 1.51).[81] Under similar conditions 2,3-dimethylbut-2-ene afforded (173) which must arise from opening of the carbinolimide (172), along with the photoreduction products (174) and (175), no benzazepinediones were observed consistent with the large negative ΔG_{ET} value (SCHEME 1.52).[81] In cases where small positive ΔG_{ET} values are predicted for the alkene/NMP pairs both benzazepinediones and photoreduced products were observed. An example of this is that on irradiation of NMP with 2-methylpropene in methanol, both the benzazepinedione (169) and the photoreduction product (176) were obtained (SCHEME 1.53).[81]



SCHEME 1.53

1.B.3.2 Oxetane formation reactions

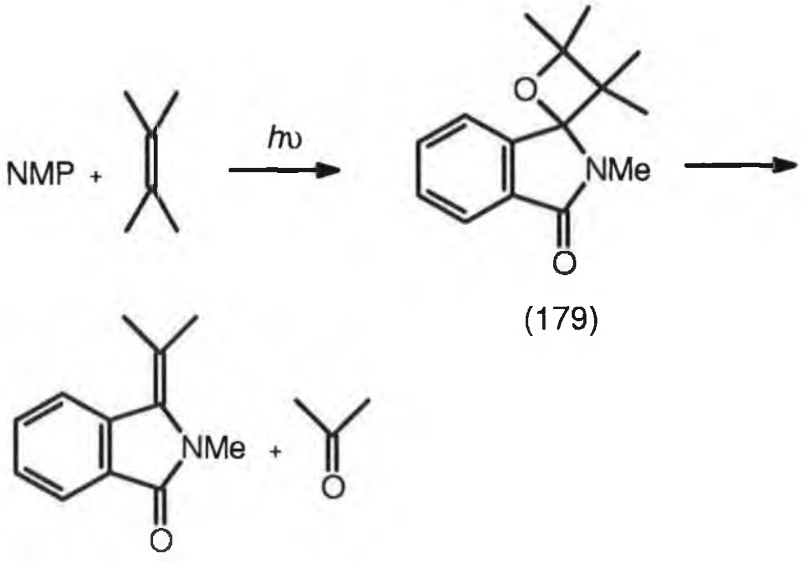
Irradiation of aliphatic cyclic imides in the presence of alkenes afforded the corresponding oxetanes in good yield both inter and intramolecularly.[39, 74, [82, 83] For example irradiation of *N*-methylsuccinimide (177) with 2-methyl prop-2-ene gives oxetane (178) (SCHEME 1.54).



(177) (178)

SCHEME 1.54

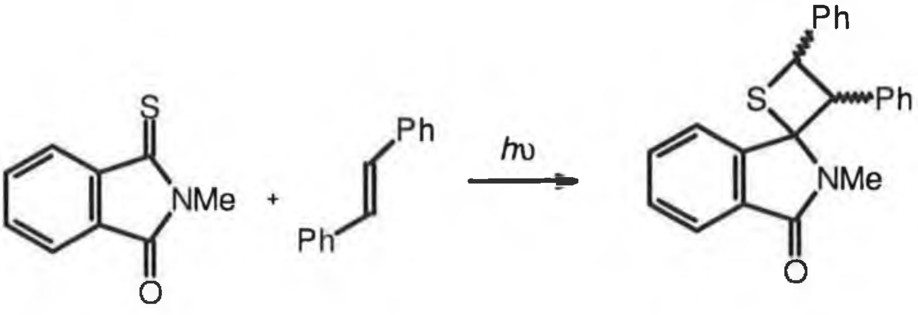
Oxetane formation has not been widely reported for the phthalimide system however in some cases the oxetane has been isolated.[75, 84, 85, 86] For example irradiation of NMP and 2,3 dimethylbut-2-ene resulted[84, 87] in the formation of a number of products including oxetane (179) and its degradation product 3-isopropylidene isoindolone (180) (SCHEME 1.55)



(180)

SCHEME 1.55

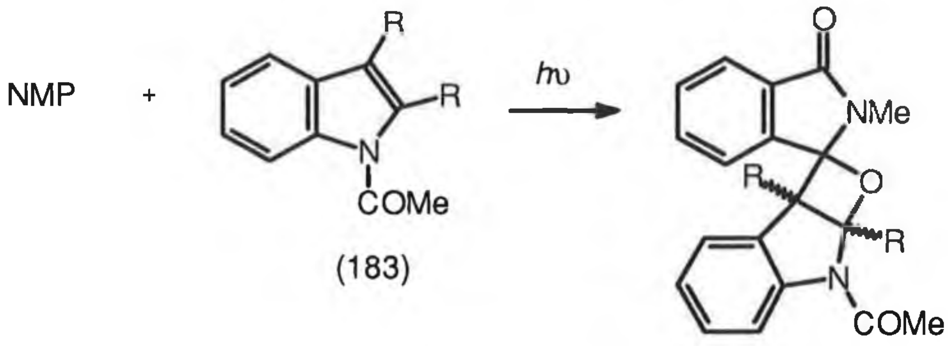
The low yield of oxetane products obtained is almost certainly due to the competing electron transfer reactions which occur in this system. Quenching studies indicate that oxetane products arise from the lowest triplet state while electron transfer products in this system arise from the lowest singlet state.[88] Coyle and co-workers have reported[89, 90] an efficient oxetane formation with *N*-methylthiophthalimide (181) to give spirothietane (182) (SCHEME 1.56).



(181) (182)

SCHEME 1.56

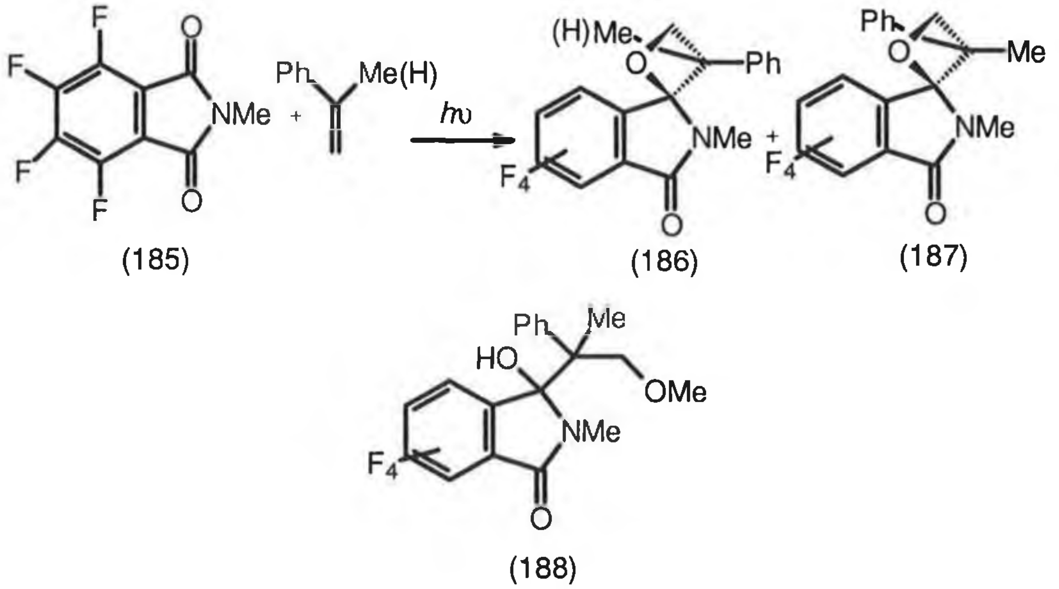
Kanaoka and co-workers have also reported efficient reaction between thiophthalimides and styrene derivatives to give thietanes. [91, 92] The authors explain the efficiency of oxetane formation in this system is due to the lower excited energy of thiocarbonyls which reduces the efficiency of electron transfer as compared with analogous carbonyl compounds.[90] Kanaoka and co-workers have however reported[93, 94] the first examples of efficient oxetane formation in a phthalimide system. NMP was irradiated with a series of *N*-acetylindole derivatives (183) to give the corresponding



(183) (184)

SCHEME 1.57

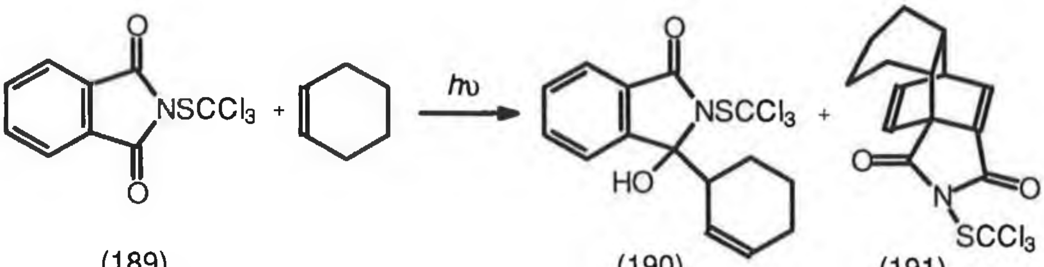
oxetanes (184) (SCHEME 1.57). This reaction has also been reported to occur intramolecularly.[95] Kubo and co-workers have reported[96] efficient oxetane formation on irradiation of alkenes and *N*-methyltetrafluoro phthalimide (185) in aprotic solvents (SCHEME 1.58). Typically irradiation of a benzene solution of (185) with styrene or α-methylstyrene affords oxetanes (186) and (187) in an approximately 1:1 ratio in a combined yield of greater than 80%. However irradiation in methanol affords exclusively the methanol incorporated adduct (188) as a pair of diastereomers. The formation of (188) is proposed to be analogous to the methanol incorporated adducts obtained on irradiation of NMP and alkenes with low ionisation potentials in methanol by Mazzocchi and Kubo,[33] ie electron transfer from alkene to excited state phthalimide followed by nucleophillic addition of methanol to generate a pair of radicals which combine to give the observed product (188). The authors propose that the exclusive formation of oxetanes (186) and (187) in aprotic solvents may be due to an inversion of (n, π*) and (π, π*) states which are energetically close.



SCHEME 1.58

1.B.3.3 Alkene addition to give photo-dearomatised products

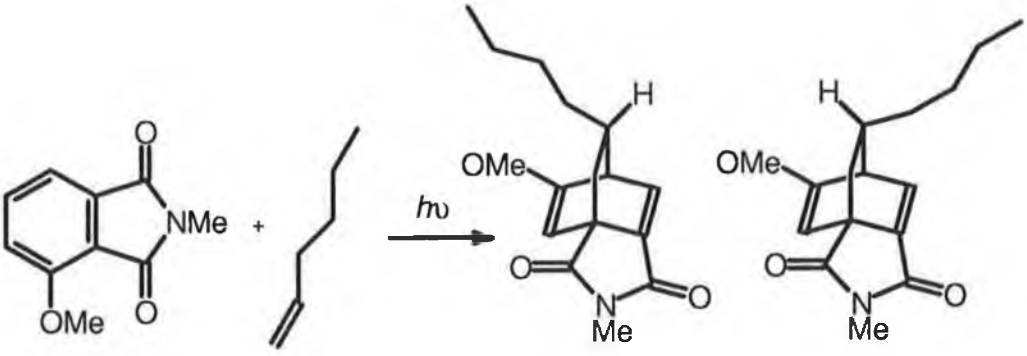
Schwack showed the major products from the irradiation of *N*-(trichloromethylthio)phthalimide (189) in cyclohexene to be the carbinol (190) but he also found the 1,4-cycloadduct (191) as a minor product (SCHEME 1.59).[97]



(189) (190) (191)

SCHEME 1.59

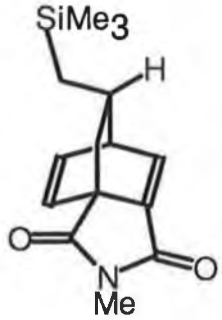
Suau and co-workers also observed the formation of 1,4-cycloadducts (193) and (194) on irradiation of 3-methoxy-*N*-methylphthalimide (192) in the presence of hex-1-ene (SCHEME 1.60).[98]



(192) (193) (194)

SCHEME 1.60

Kubo and co-workers isolated the 1,4-cycloadducts (195), (196) and the photoaddition product (197) on irradiation of NMP in the presence of allyltrimethylsilane.[100] On examination of the effect of alkene concentration on the yields of the photoproducts the authors show that the yields of (195), (196) decreased and that of (197) increased on increasing the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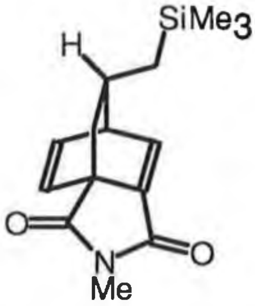
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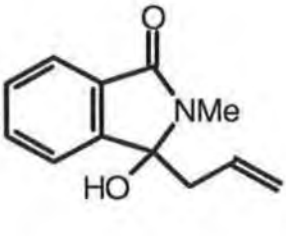
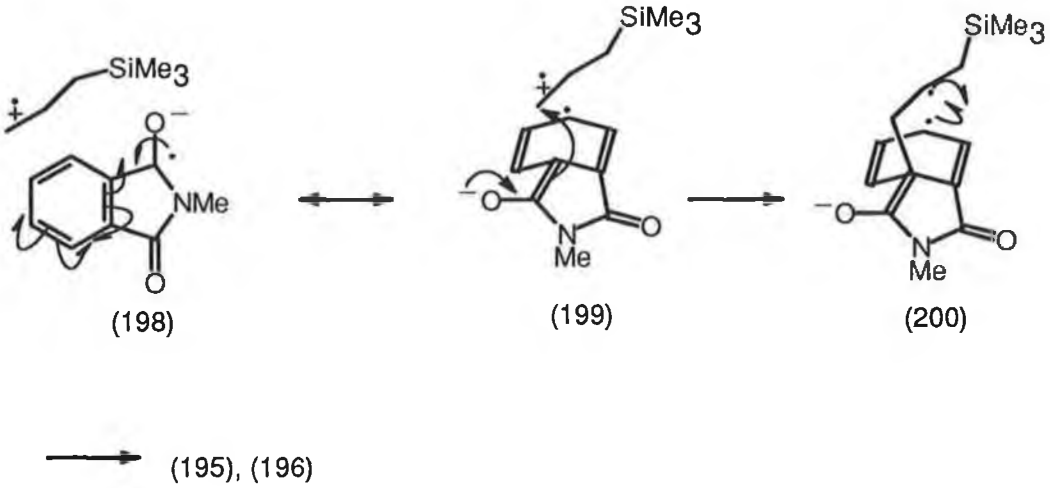

(197)

alkene concentration. The results indicate that the carbinol (197) arose from the relatively short lived singlet state and the 1,4-addition products (195) and (196) arise from the triplet excited state, since a marked decrease of yields of photoproducts from the triplet excited state of NMP have been reported with increasing concentration of alkene.[33] A mechanism to account for the formation of the 1,4-cycloadducts reported in these papers is outlined (SCHEME 1.61). It involves electron transfer



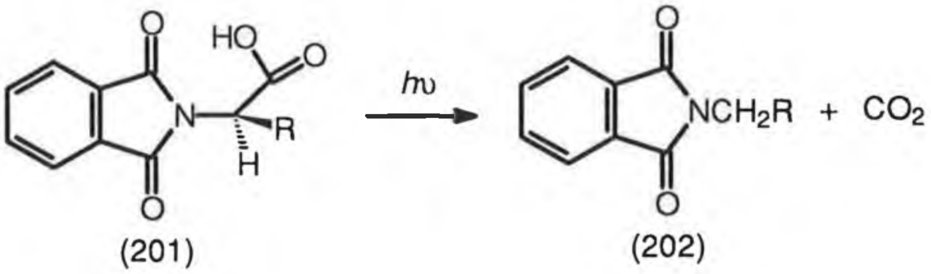
SCHEME 1.61

from alkene to excited state phthalimide to form radical cation/anion pair (198), isoelectronic with (199). From this species polar addition of alkene occurs to the phthalimide aromatic system to generate most stable diradical (200) which subsequently combines to generate the observed products (195) and (196).

1.B.4 Photofragmentation reactions

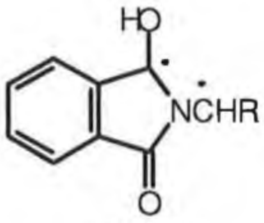
1.B.4.1 Photodecarboxylation

In one of the earliest papers describing the photochemistry of the phthalimide system Kanaoka and co-workers reported[51] the photochemical decarboxylation of phthaloyl α amino acids with the conversion of (201) to (202) (SCHEME 1.62). A number of amino acid derivatives were examined, all giving good yield of decarboxylated product (202). The role of solvent polarity seems important with yields lowest in protic solvents which suggests that hydrogen bonding between the carboxyl group and imide carbonyl may have an important role. Quenching experiments indicate an excited triplet state intermediate. Griesbeck and co-workers have also reported[49, 50] the photochemical decarboxylation of phthaloyl α-amino acids. They have also reported that phthaloyl amino acids containing remote carboxyl groups do not undergo this decarboxylation, except in the presence of added base when cyclised decarboxylated products are formed (see section 1.B.3.7). Griesbeck has proposed that the mechanism for the decarboxylation of phthaloyl α-amino acids involves an excited state

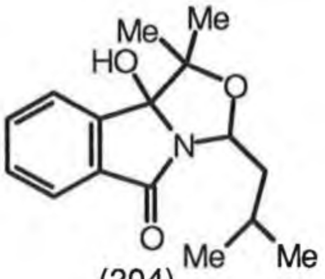


SCHEME 1.62

intramolecular proton transfer from hydrogen bonded hydroxyl group to excited phthalimide chromophore, subsequent intramolecular electron transfer from carboxylate and elimination of carbon dioxide forms diradical (203). Internal rearrangement generates the observed phthaloyl amine (202) (SCHEME 1.63).



(203)



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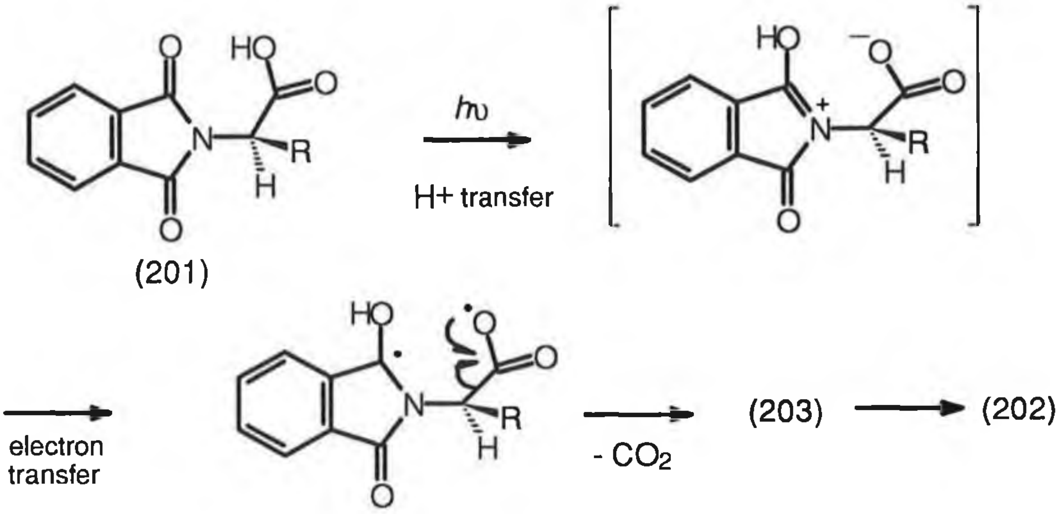
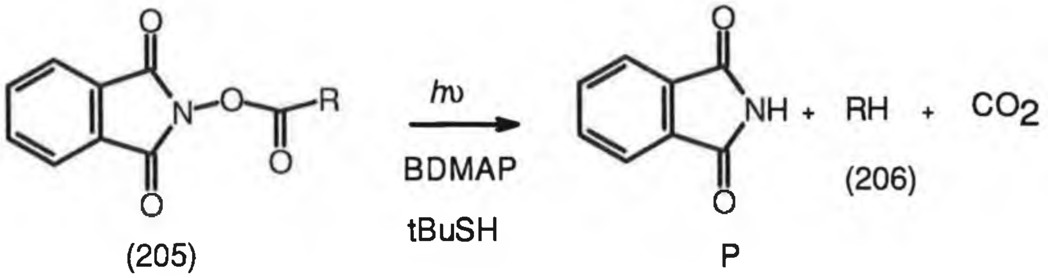


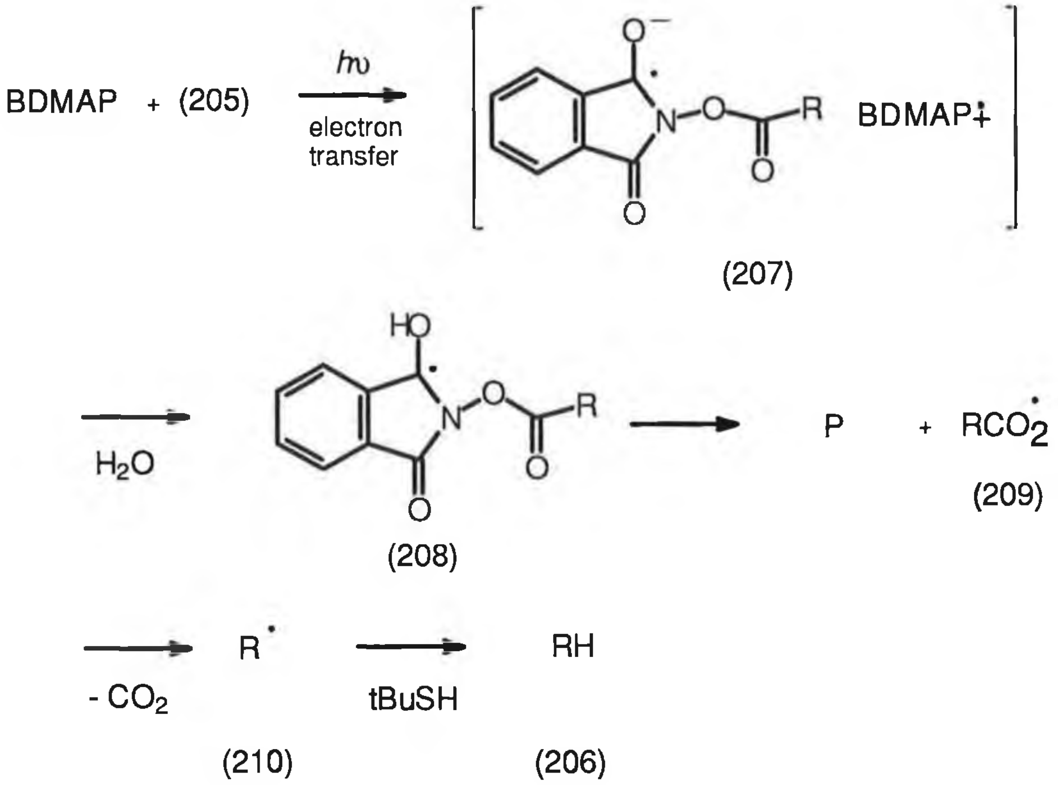
SCHEME 1.63

The intermediacy of (203) has been supported by its trapping in low yield by acetone to form (204).[51] Okada and Oda have reported[100] a photosensitised decarboxylation of *N*-acyloxyphthalimides (205) via an electron transfer mechanism. Irradiation of a solution of 1,6-bis(dimethylaminopyrene) (BDMAP), *N*-acyloxyphthalimide (205) and t-butyl thioalcohol (t-BuSH; 2%) gave (206) in excellent yield (SCHEME 1.64). A mechanism involving electron transfer from excited singlet state of



SCHEME 1.64

BDMAP to (205) is proposed. This generates the radical anion/cation pair (207) which is protonated in aqueous or protic solvents to give the radical (208). Ready cleavage of the weak nitrogen oxygen bond at the β-position of the radical (208) produces the carboxylate radical (209) which in turn undergoes decarboxylation to afford (210) and subsequent hydrogen abstraction from the thiol or from the solvent to afford the hydrocarbon (206). The same authors subsequently reported[102] an extension of this

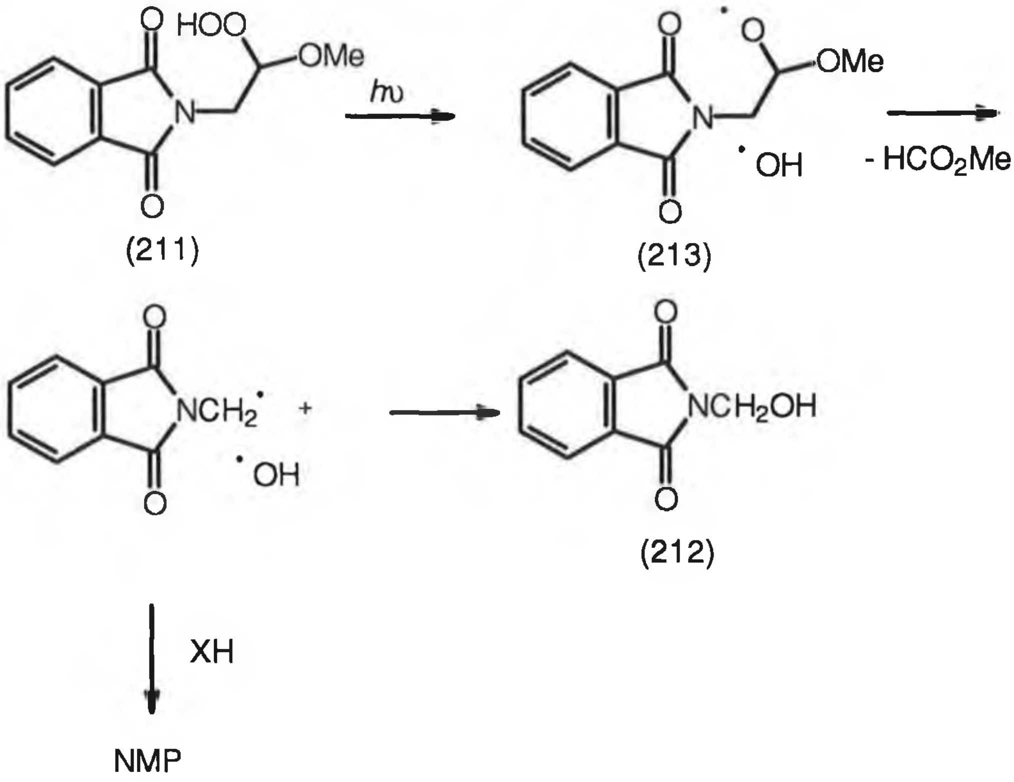


SCHEME 1.65

work in which the decarboxylation yields an alkyl chloride. The mechanism is assumed to be analogous with radical (210) abstracting chlorine from carbon tetrachloride to yield the alkyl chloride.

1.B.4.2 Cleavage of hydroperoxyalkylphthalimides

Matsugo and Saito have reported[102] an unusual type of selective photocleavage of *N*-(hydroperoxyalkyl)phthalimides initiated by intramolecular energy transfer. Irradiation of (211) in acetonitrile gave the cleavage products *N*-(hydroxymethyl)phthalimide (212) and methyl formate. The products were assumed to arise from cleavage of the radical (213). In contrast irradiation of (211) in a hydrogen donating solvent (THF) afforded NMP as the major product with a markedly diminished yield of (212) (SCHEME 1.66). The authors make the point that γ-cleavages with

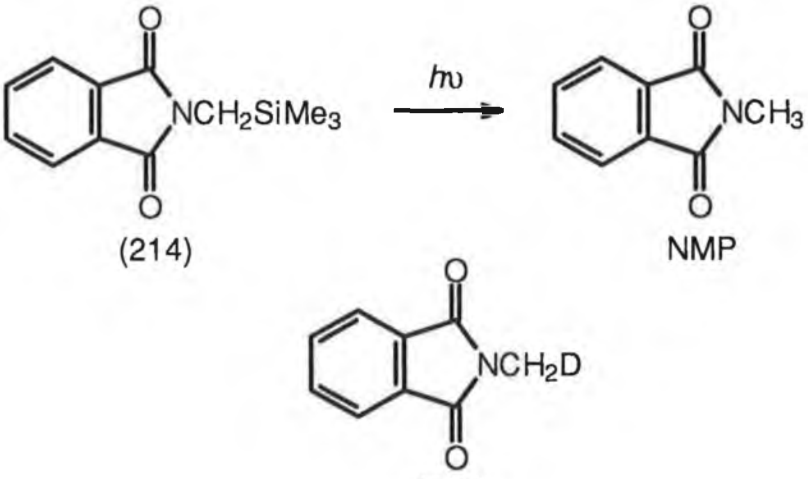


SCHEME 1.66

respect to the phthalimide chromophore are very rare in phthalimide photochemistry.

1.B.4.3 Photofragmentation of *N*-silylmethylimides

Yoon and co-workers have reported[103,104,105] an interesting photofragmentation of *N*-silylmethylphthalimides. Irradiation of (214) in acetonitrile gave rise to NMP in quantitative yield (SCHEME 1.67). Irradiation of (214) in acetonitrile containing deuterium oxide gave rise to the deuteriomethyl analogue of NMP (215). The authors proposed the photoreaction involves a carbon to oxygen trimethylsilyl cation migration to form diradical (218). This species is analogous to that reported by Kanaoka and co-workers as an intermediate in the photodecarboxylation of phthaloyl α amino acids.[51] Yoon and co-workers have shown that on irradiation of (214) in acetone gives rise to solvent incorporated adduct (216) in good yield (80%) SCHEME 1.68). The authors have also shown



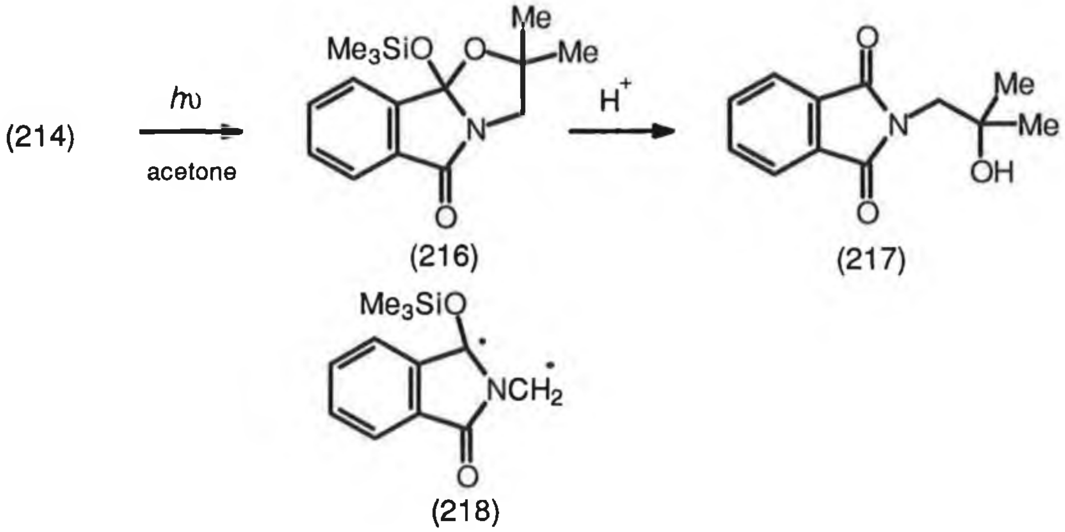
(214)

NMP

(215)

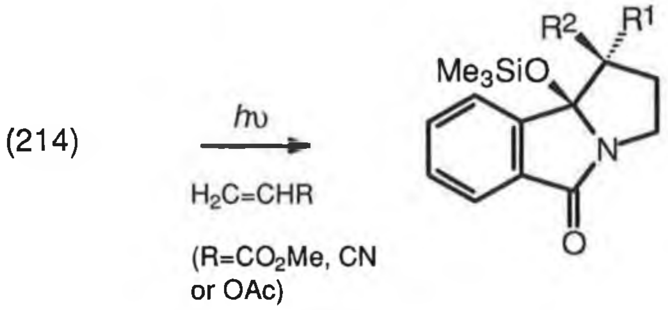
SCHEME 1.67

that the azomethine ylide formed from (214) can participate in 1,3 dipolar-cycloaddition reactions with a number of dipolarophiles to form solvent incorporated adducts such as (219) to (222) (SCHEME 1.69). A number of mechanisms were suggested but the authors favour a mechanism involving



SCHEME 1.68

electron transfer from the carbon-silicon σ bond to excited phthalimide to form radical anion/cation (223). Subsequent transfer of the trisilylmethyl cation from carbon to oxygen forms (218), isoelectronic with ylide (224), which undergoes 1,3-dipolar cycloaddition with added dipolarophile to form adduct (225) (SCHEME 1.70).



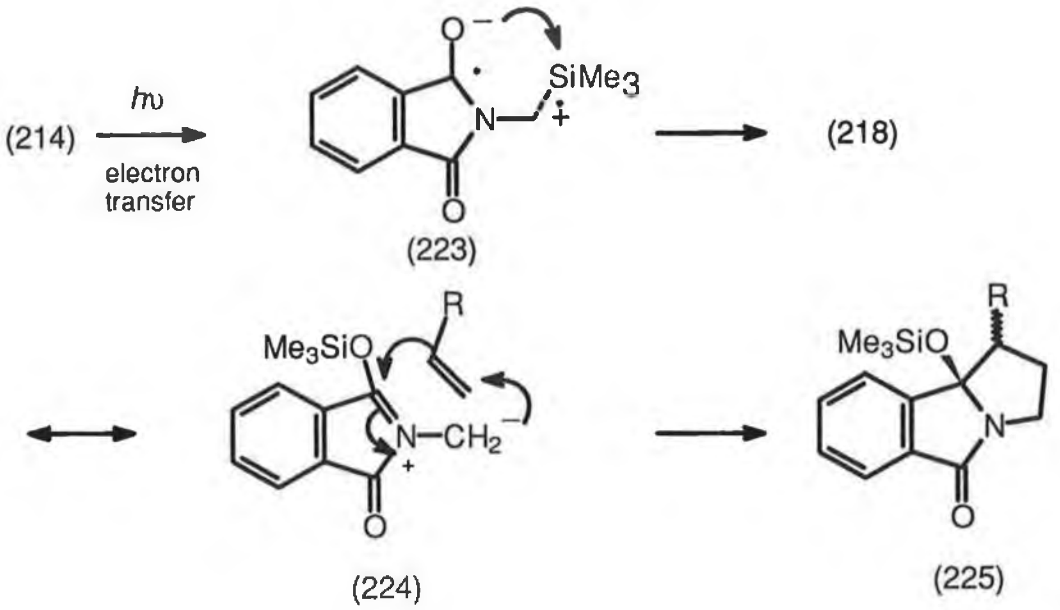
(219): R^1=CO_2Me, R^2=H

(220): R^1=H, R^2=CO_2Me

(221): R^1=CN, R^2=H

(222): R^1, R^2=OAc, H

SCHEME 1.69


(214)
hν
electron transfer
SiMe3
(223)
(218)
R
Me3SiO
N–CH2
(224)
R
Me3SiO
(225)

SCHEME 1.70

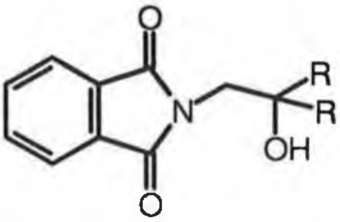
Results and Discussion

CHAPTER 2:

The photochemistry of some *N*-(2-hydroxyethyl) phthalimides.

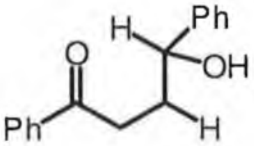
2.1 Introduction

The photochemistry of the phthalimide system as outlined in the previous chapter has attracted considerable interest to both synthetic and mechanistic aspects. At the outset of this work the photochemistry of phthaloyl-β-amino alcohols (226) R=alkyl, aryl or H had received virtually no attention.

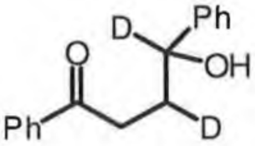


(226)

Being available, these compounds seemed attractive for a photochemical study as it would be of interest to examine whether the photochemistry observed mirrored the photochemistry of related ketonic systems in which the phthalimido group is replaced by an alkyl or aryl carbonyl. It has been shown that ketonic systems containing a hydroxy substituent on the γ-carbon are efficient sources of 1,4 biradicals via γ-H abstraction processes.[106] Lewis investigated[106] the photochemistry of γ-hydroxy-γ-phenylbutyrophenone (227) and its β,γ-dideuterio analogue (228). Irradiation of (227) in benzene led to quantitative

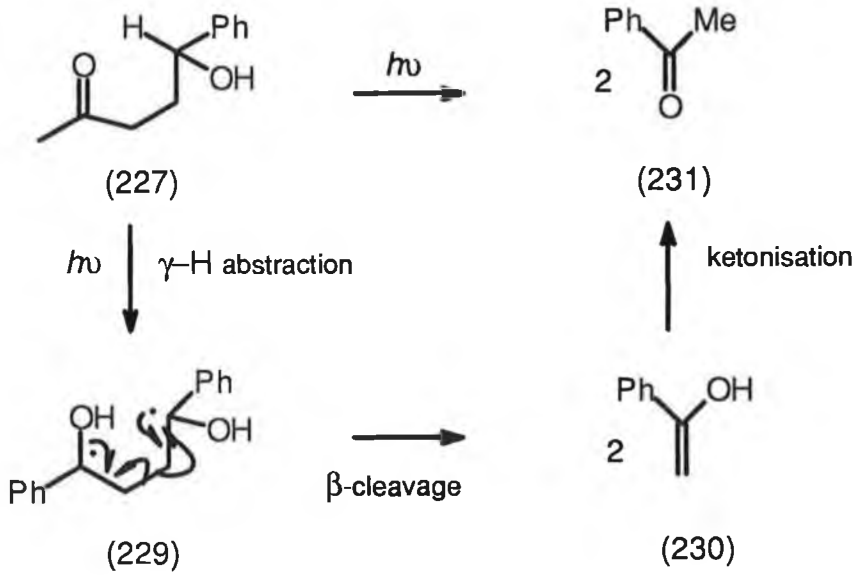


(227)



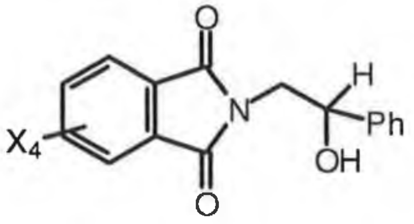
(228)

formation of two moles of acetophenone (231) (SCHEME 2.0). It was proposed that the reaction proceeds through conventional Norrish type II photochemistry for triplet excited ketones (see chapter 1) ie γ-H abstraction by triplet excited ketone to form a 1,4 diradical (229) which subsequently undergoes β cleavage to form enol (230) which ketonises to acetophenone (231). No evidence was found for formation of cyclised products in this system, a process which is



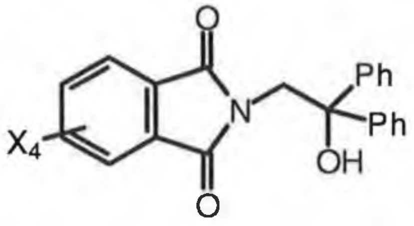
SCHEME 2.1

observed for ketonic systems without hydroxy substituents. Wirz[107] and Kregse[108,109] and co-workers have applied this Norrish type II fission of γ-hydroxy butyrophenones for flash photolytic generation of acetophenone enol (230) and measured rates of ketonisation in order to calculate the pK_a of acetophenone (231). We were interested in whether an analogous process might occur for phthalimido systems containing a hydroxyl group γ to the phthalimido carbonyl. We decided initially to study the photochemistry of four compounds (232) - (235).



(232): X=H

(234): X=Cl

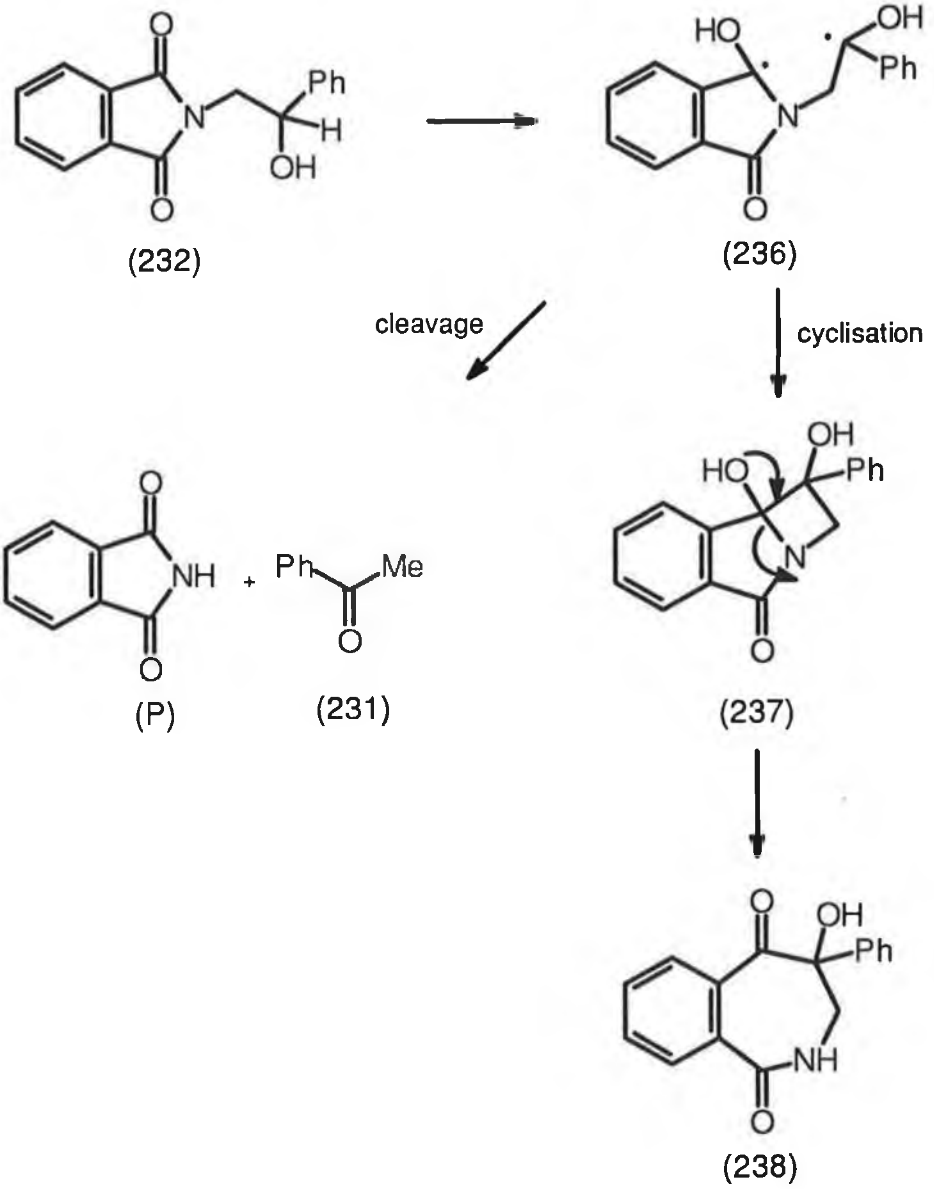


(233): X=H

(235): X=Cl

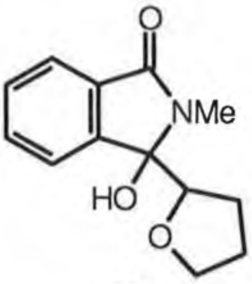
N-(2-Hydroxy-2-phenylethyl)phthalimide (232) is structurally analogous to the compounds studied by Lewis. It contains the same substituents γ to the imide carbonyl. The presence of a hydrogen at this point is also important as

N-alkyl phthalimides containing γ-hydrogens have been shown to undergo typical Norrish type II photochemistry to form both cyclised and elimination products.[28] By analogy irradiation of (232) might be expected to lead to formation of phthalimide (P) and acetophenone (231) as elimination products,

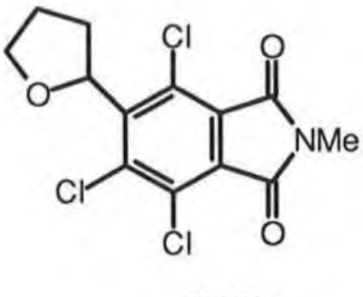


SCHEME 2.2

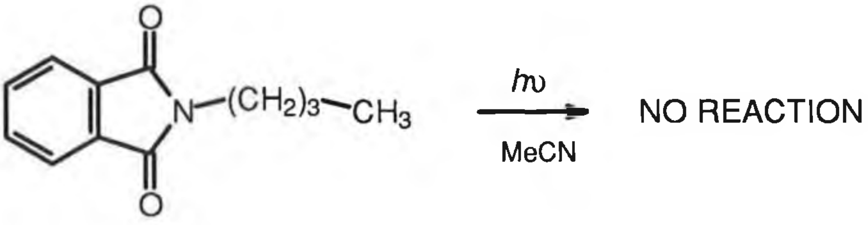
and/or cyclised products originating from initial closure of diradical (236) to form azetine (237) which would be expected to open retrotransannularly to form hydroxy benzazepine system (238) (SCHEME 2.2). The other compounds (233) to (235) proposed for the initial study are structural variants. Compounds (233) and (235) are fully substituted on the γ-carbon, blocking the possibility of γ-hydrogen abstraction processes taking place. We were also interested in studying some tetrachloro analogues such as (234) and (235). Previous work has indicated that the presence of chlorines on the phthalimido ring changes the observed photochemistry. For example irradiation of *N*-methylphthalimide (NMP) in THF has reported to afford carbinol (28).[18] Whereas irradiation of *N*-methyltetrachlorophthalimide in THF was shown to afford aromatic substituted product (239).[110] Also irradiation of *N*-alkyltetrachlorophthalimides containing both γ- and δ-hydrogens such as (240) has shown no products of abstraction[111] (SCHEME 2.3) whereas irradiation of analogous non-chlorinated *N*-alkylphthalimides has shown conventional Norrish type II photochemistry leading to products of cyclisation and/or elimination.[28] The reasons for this difference in reactivity are unclear, however work by Albini and co-workers on the photochemistry of *N*-methyldicyanophthalimide suggests that in the excited state charge localisation occurs on the aromatic ring rather than at the imide



(28)



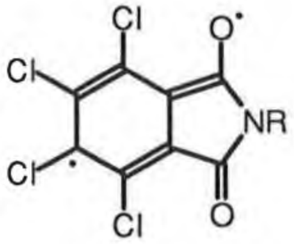
(239)



(240)

SCHEME 2.3

carbonyl,[20] so an intermediate like (241) may contribute considerably to the observed photochemistry of *N*-alkyltetrachlorophthalimides. The synthesis of

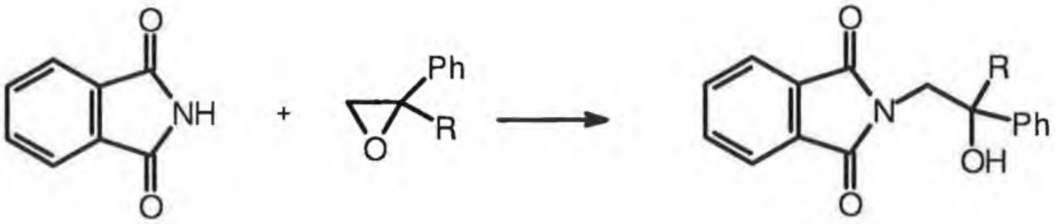


(241)

compounds (232)-(235) is outlined in the next section. The results obtained during the photochemical study of these compounds prompted an investigation of a wider range of *N*-(2-hydroxyethylphthalimides) to investigate the effect of structural variation on the observed photochemistry. The synthetic routes to these compounds are also outlined in the next section.

2.2 Synthesis of *N*-(2-hydroxy-2-phenylethyl)phthalimide (7) and *N*-(-2,2-diphenyl-2-hydroxyethyl)phthalimide (8)

An initial literature survey indicated that a convenient synthesis of (232) could be achieved by heating phthalimide (P) and styrene oxide (242) in the presence of a catalytic amount of base.[112] This was adopted as the initial synthetic approach to compounds (232) and (233) (SCHEME 2.4).



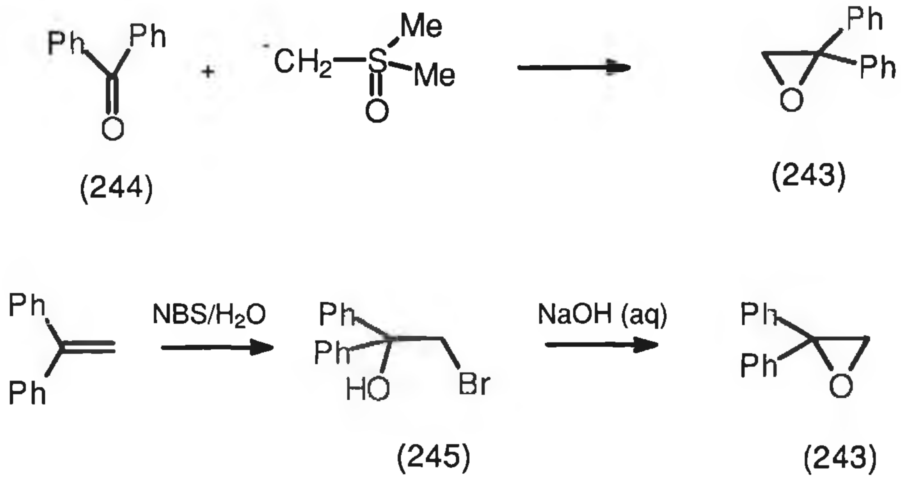
(P)

(242): R= H
(243): R= Ph

(232): R= H
(233): R= Ph

SCHEME 2.4

The usual procedure for alkylation of phthalimide involves treating potassium phthalimide with an alkyl halide in DMF. However it has been reported[113] that use of potassium phthalimide to ring open epoxides tends to give rise to complex mixtures. *N*-(2-Hydroxy-2-phenylethyl)phthalimide (232) was prepared by heating phthaiimide with a slight molar excess of styrene oxide and a catalytic amount of potassium phthalimide. The proton and carbon NMR spectra were consistent with this known compound.[104] The synthesis of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) had not been previously reported in the literature however it was synthesised by the reaction of phthaiimide (P) with 1,1-diphenylethylene oxide (243) which was synthesised from either 2-bromo-1,1-diphenylethanol (245)[115] or benzophenone (244)[114] (SCHEME 2.5).

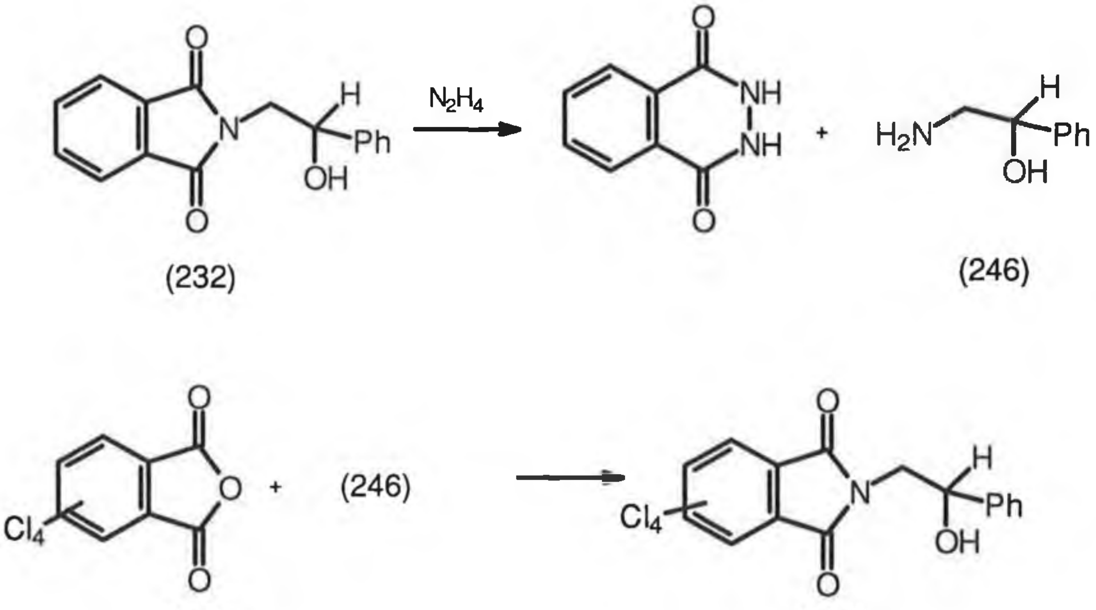


SCHEME 2.5

Phthaiimide was heated with 1,1-diphenylethyleneoxide (243) in DMSO to afford *N*-(2,2-Diphenyl-2-hydroxyethyl)phthalimide (233) as white crystals (SCHEME 2.4). The infrared spectrum contained many spectral characteristics common to the monophenyl compound (232). The proton NMR spectrum displayed a singlet at 4.50 ppm (methylene protons), a singlet at 5.10 ppm (hydroxyl proton), an aromatic multiplet between 7.12 and 7.50 ppm (two monophenyl substituted systems) and a symmetrical phthalimido multiplet between 7.61 and 7.80 ppm.

2.3 Synthesis of *N*-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (234) and *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235)

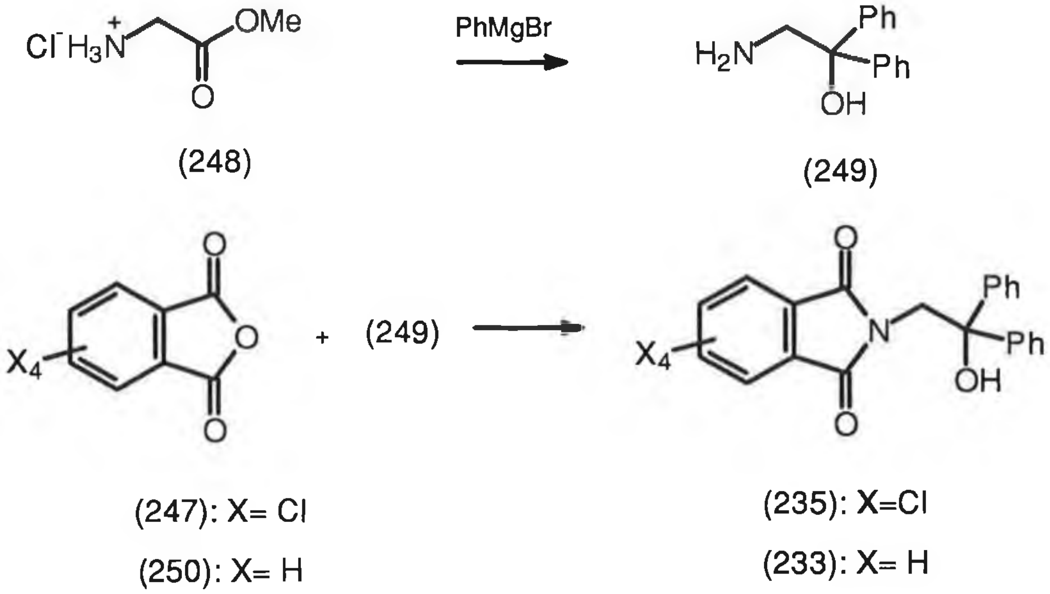
These compounds had not previously been reported. Initially a route similar to that used for synthesis of the unchlorinated analogue (232) was attempted for the synthesis of (234). This involved heating tetrachlorophthalimide in the presence of styrene oxide in DMF as solvent. However the product obtained was impure even after repeated recrystallisation. The reason for the low yield of product obtained for this reaction may be the low nucleophilicity of the imide NH towards electrophiles caused by the electron withdrawing effect of the chlorine substitution. This lack of reactivity of tetrachlorophthalimide with electrophiles, as compared with phthalimide has also been observed for the reactions of tetrachlorophthalimide with acyl chlorides.[116]



SCHEME 2.6

An attractive alternative to the synthesis of (234) seemed to be the reaction of tetrachlorophthalic anhydride with the β-amino alcohol 1-amino-2-phenylethanol (246), easily obtainable by dephthaloylation of (232) using either strong alkali or hydrazine hydrate.[117] *N*-(2-Hydroxy-2-phenylethyl)phthalimide

(232) was treated with excess of hydrazine hydrate in ethanol to yield 1-amino-2-phenylethanol (246) as an oily solid (SCHEME 2.6). The crude β-amino alcohol (246) was heated with tetrachlorophthalic anhydride (247) in acetic acid to afford *N*-(2-hydroxyethyl)tetrachlorophthalimide (234). The NMR spectra for (234) corresponded to those expected and were very similar to that obtained for (232), the unchlorinated analogue, except for the absence of any phthalimido aromatic protons in the proton spectrum.

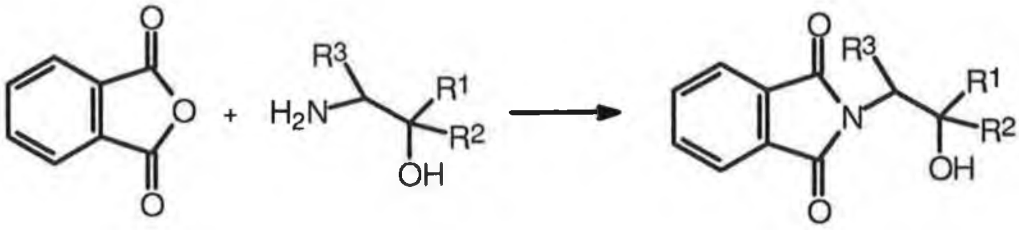


SCHEME 2.7

N-(2,2-Diphenyl-2-hydroxy)tetrachlorophthalimide (235) was similarly synthesised via the tetrachlorophthaloylation of 1-amino-2,2-diphenylethanol (249), obtained by the treatment of glycine methyl ester hydrochloride (248) with phenylmagnesium bromide, following the method of Itsuno and co-workers[118,119].(SCHEME 2.7). Treatment of 1-amino-2,2-diphenylethanol (249) with phthalic anhydride (250) or tetrachlorophthalic anhydride (247) under reflux in glacial acetic acid afforded afforded the diphenyl substituted compounds (233) and (235) in good yield (SCHEME 2.7).

2.4 Synthesis of *N*-(2-hydroxyethyl)phthalimide (254), *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) and *N*-(2-hydroxy-2-methylethyl) phthalimide (256)

The reaction of suitable β-aminoalcohols with phthalic anhydride was adopted as a general route. Ethanolamine (251): $R^1=R^2=R^3=H$, phenylalanol (252): R^3=benzyl, $R^1=R^2=H$ and isopropanolamine (253): $R^1=R^3=H$, $R^2=Me$ were readily available so *N*-(2-hydroxyethyl)phthalimide (254), *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) and *N*-(2-hydroxy-2-methylethyl)phthalimide (256) were readily synthesised according to the procedure outlined previously (SCHEME 2.8) and all spectral details were consistent with the assigned structure for these compounds.



(250) (251) (254): $R^1=R^2=R^3=H$

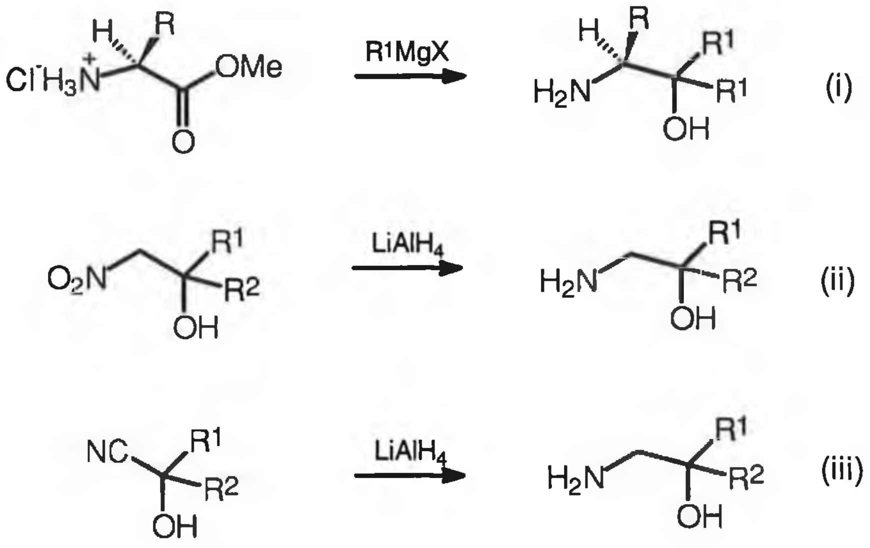
(252) (255): $R^1=R^2=H$, $R^3=CH_2P$

(253) (256): $R^1=R^3=H$, $R^2=Me$

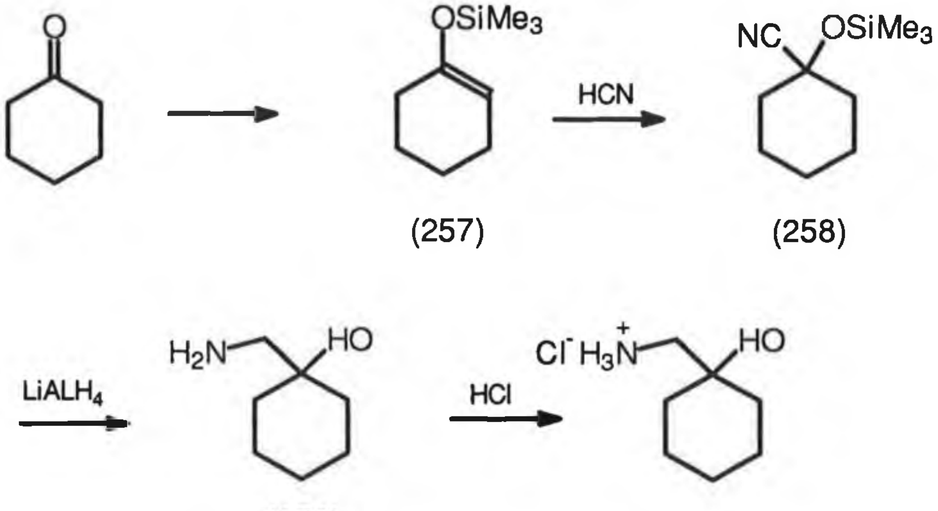
SCHEME 2.8

2.5 Synthesis of *N*-(2-hydroxy-2-*p*-methoxyphenylethyl)phthalimide (275) *N*-(2-hydroxy-2-*p*-bromophenylethyl)phthalimide (276), *N*-(2-hydroxy-2-styrylethyl)phthalimide (277) and *N*-(2-hydroxy-2-methylpropyl) phthalimide (278)

As not all the β-amino alcohols required were commercially available it seemed prudent to investigate a general synthesis of these compounds. A number of general routes to these synthetically important compounds included among these are (i) addition of Grignard reagents to α-amino acid esters, (ii) reduction of β-nitromethyl alcohols and (iii) reduction of aldehyde/ketone cyanohydrins (SCHEME 2.9). The addition of Grignard reagents to α-amino acid esters (SCHEME 2.9, (i)) was the route used to synthesise 1-amino-2,2-diphenylethanol (249). However it has been reported that extension to alkyl Grignard reagents proved unsuccessful.[120] The reduction of β-nitromethylalcohols (SCHEME 2.9, (ii)) has been reported to be problematic in terms of yields and generality.[121] The synthesis of nitromethyl alcohols via the addition of nitromethane anion to aldehydes and ketones (Henry reaction) is not efficient with hindered ketones.[122] The reduction of aldehyde/ketone cyanohydrins (SCHEME 2.9, (iii)) also suffers from lack of generality and low yields for both production of the initial cyanohydrin and the reduction step.[123] However Parham and co-workers have shown that cyanohydrin *O*-TMS ethers can be prepared easily from hindered ketones and subsequent reduction affords the β-amino alcohols in good yield.[124] The ketone cyanohydrin *O*-TMS ether of cyclohexanone (258) was synthesised by first preparing the *O*-TMS enol ether (257) and subsequent addition of hydrogen cyanide. The cyanohydrin *O*-TMS ether (258) is readily reduced to afford the β-amino alcohol (259) (SCHEME 2.10).



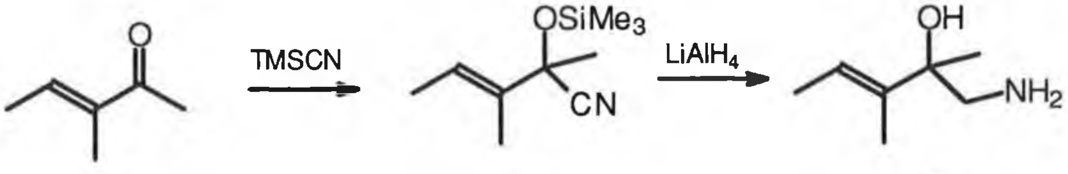
SCHEME 2.9



(257) (258) (259)

SCHEME 2.10

Evans and co-workers reported that cyanohydrin-*O*-TMS ethers could be prepared by the addition of trimethylsilylcyanide (TMSCN) to aldehydes or ketones[125,126] which could be readily reduced to afford β-amino alcohols in good yield.[127] They noted that the addition of TMSCN afforded cyanohydrin *O*-TMS ethers even for hindered ketones. They also noted[127] that treatment of α,β–unsaturated aldehydes or ketones with TMSCN afforded exclusively the carbonyl addition product as opposed to products arising from Michael



(260) (261) (262)

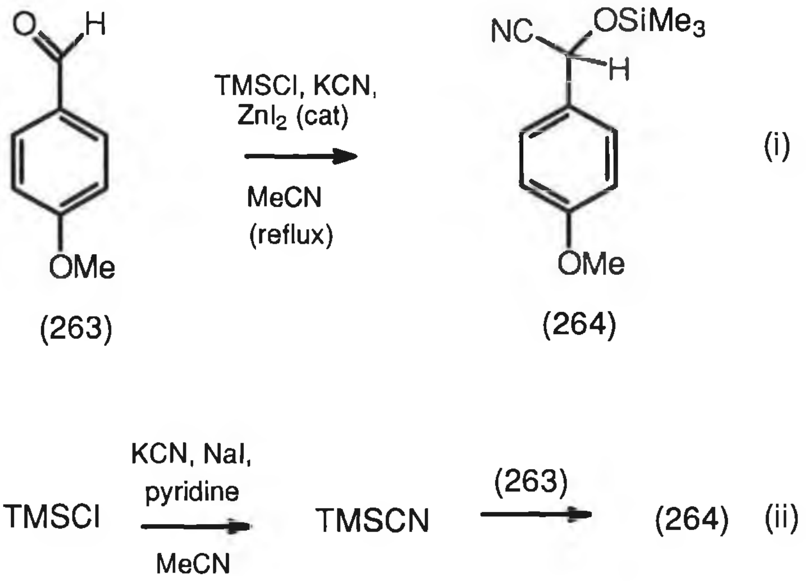
SCHEME 2.11

addition. This is of importance as it enables synthesis of β-amino alcohols containing vinylic substitution. An example is the addition of TMSCN to 3-methyl-3-penten-2-one (260) to afford the cyanohydrin *O*-TMS ether (261) which when reduced afforded β-amino alcohol (262) (SCHEME 2.11). TMSCN seemed to be a general reagent for addition to a wide variety of aldehydes and ketones to afford cyanohydrin *O*-TMS ethers which can be readily reduced, so it was decided to adopt this approach to the synthesis of β-amino alcohols. TMSCN is commercially available but its expense and air-sensitivity prompted an investigation of a reliable synthesis. Evans and co-workers described[127] two synthetic approaches ((i) and (ii) SCHEME 2.12). Route (i) involves the use of very expensive silver cyanide and route (ii) involves condensation of large amounts of hydrogen cyanide. Neither route was particularly attractive.

$$\mathrm{AgCN + TMSCl \longrightarrow TMSCN + AgCl} \qquad \text{(i)}$$

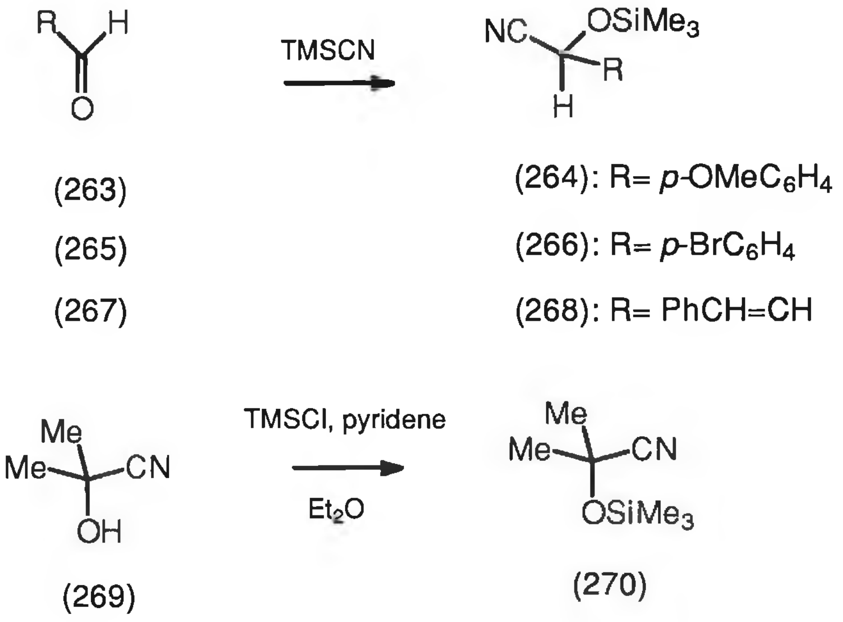
$$\left.\begin{array}{l}\mathrm{HCN + LiH \longrightarrow LiCN} \\ \mathrm{LiCN + TMSCl \longrightarrow TMSCN + LiCl}\end{array}\right\} \quad \text{(ii)}$$

SCHEME 2.12



SCHEME 2.13

An examination of the literature indicated that several researchers have developed more convenient and less expensive routes to TMSCN. It has been reported that TMSCN can be generated insitu to cyanosilylate non-enolisable aldehydes[128] and TMSCN can be synthesised using potassium cyanide and TMSCl in the presence of sodium iodide and pyridine and used without isolation.[129,130,131] These routes were both investigated as a synthetic route to *p*-anisaldehyde *O*-TMS ether (264) ((i) and (ii) SCHEME 2.13). The required *p*-anisaldehyde cyanohydrin *O*-TMS ether (264) was isolated in excellent yield from both procedures however the method involving pre-preparation was the method of choice as it was deemed to be more convenient. The cyanohydrin *O*-TMS ethers of *p*-bromobenzaldehyde (265) and *trans* cinnamaldehyde (267) in addition to *p*-anisaldehyde (263) were prepared using the second procedure to afford the crude cyanohydrin *O*-TMS ethers (264), (266), and (268) as brown oils. (SCHEME 2.14). The reactions were clean and high yielding in all cases.



(263)
(265)
(267)

(264): R= *p*-$OMeC_6H_4$
(266): R= *p*-BrC_6H_4
(268): R= PhCH=CH

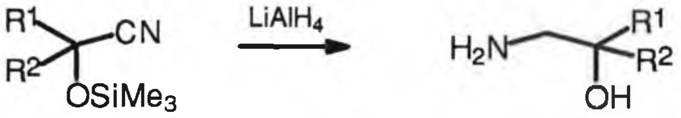
(269)

(270)

SCHEME 2.14

The proton and carbon NMR spectra of the crude cyanohydrin *O*-TMS ethers isolated were consistent with the assigned structure. Acetone cyanohydrin (269) was obtained commercially and converted to the cyanohydrin *O*-TMS ether (270) (SCHEME 2.14).

The cyanohydrin *O*-TMS ethers were reduced according to the method reported by Evans and co-workers.[127] The reactions were quenched using aqueous sodium hydroxide solution work up and afforded the β-amino alcohols (275)-(278) (SCHEME 2.15) in good yield. Evans reported[127] that almost



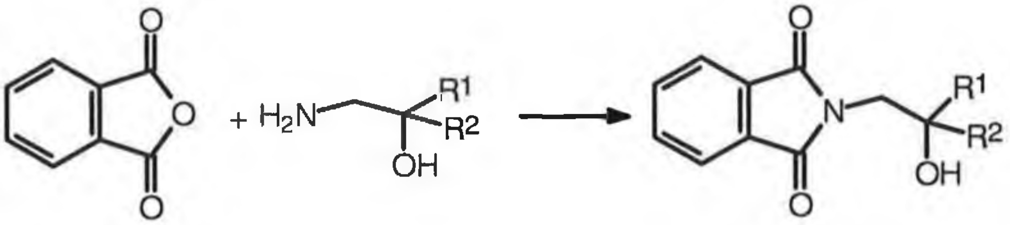
(264) (271): R^1= H, R^2= p-OMeC_6H_4

(266) (272): R^1= H, R^2= p-BrC_6H_4

(268) (273): R^1= H, R^2= PhCH=CH

(270) (274): R^1= R^2= Me

SCHEME 2.15



(271) (275): R^1= H, R^2= p-OMeC_6H_4

(272) (276): R^1= H, R^2= p-BrC_6H_4

(273) (277): R^1= H, R^2= PhCH=CH

(274) (278): R^1= R^2= Me

SCHEME 2.16

quantitative yield of β-amino alcohol were obtained on reduction of a wide variety of cyanohydrin O-TMS derivatives and crude yields by us indicated this to be so. It was decided that since the β-amino alcohols were quite hygroscopic and found to be difficult to recrystallise direct phthaloylation of the crude amino-alcohols would produce the desired product in a more manageable form.

The crude amino alcohols were directly phthaloylated to afford the phthaloyl derivatives (275) - (278) in good yield (SCHEME 2.16).

2.6 Photochemical reactions of *N*-(2-hydroxyethyl)phthalimides (232) to (235)

As was mentioned in the introduction we were initially interested in probing the photochemical reactivity of the phenyl substituted compounds (232) and (233) and their tetrachloro analogues (234) and (235). This discussion will initially address the results obtained for these compounds and subsequently the results observed for the range of *N*-(2-hydroxyethyl)phthalimides as a whole will be discussed. The chromophore in these compounds is essentially an *N*-alkylphthalimide or *N*-alkyltetrachlorophthalimide. The absorption spectra recorded in dichloromethane for compounds (232) and (233) were consistent with that reported by Coyle for other *N*-alkyl phthalimides.[16] They showed a strong absorption at λ_{max} 220 nm attributed to a (π, π^*) transition and a weaker shoulder at 295 nm attributed to a (n, π^*) transition. The tetrachloro analogues (234) and (235) showed a similar absorption profile to the *N*-alkyltetrachlorophthalimides with a (π, π^*) absorption at λ_{max} 242 nm and a shoulder (n, π^*) at 330 nm. The photochemical reactions of these compounds were investigated by irradiating solutions in degassed dichloromethane using a preparative immersion well photolysis system consisting of a medium pressure mercury lamp fitted with a Pyrex filter to ensure excitation wavelengths above 300 nm. Dichloromethane was chosen as solvent as it is photochemically inert to wavelengths above 300 nm and the compounds showed good solubility.

2.6.1 Irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in dichloromethane:

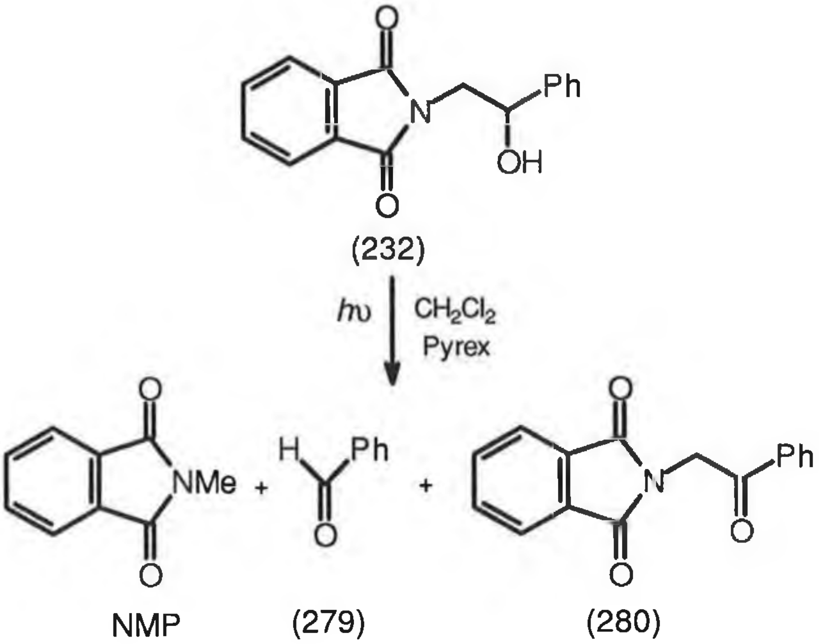
N-(2-Hydroxy-2-phenylethyl)phthalimide (232) was irradiated through Pyrex in dichloromethane as solvent. Reaction progress was followed using TLC (Thin Layer Chromatography) and rapid formation of three products was observed. Irradiation was discontinued after one hour at which point the starting material

(232) had been almost completely consumed. One of the major photoproducts was volatile, evaporating from TLC plates left in an oven (80°C) for twenty minutes. The product mixture was separated by preparitive TLC using a Chromatotron to give, in order of recovery (i) an oil (279) (ii) a white solid (NMP), (iii) a white solid (280) which was obtained in trace amounts and (iv) unreacted (232). The products were readily identified from their NMR and infra red spectra.

The proton NMR spectrum of (279) contained an aromatic multiplet between 7.4 and 7.6 ppm and a sharp singlet at 10.1 ppm with an integration ratio 5:1. The infra-red spectrum contained a strong carbonyl at 1712 cm^{-1} and a distinctive C-H stretching frequency at 2780 cm^{-1}. That the product was benzaldehyde (279) was confirmed by comparison of its infra red spectrum with that of an authentic sample.

The proton NMR spectrum of (NMP) contained a sharp singlet at 3.2 ppm and a symmetrical aromatic multiplet between 7.65 and 7.85 ppm, the integration ratio of these signals being 3:4 respectively. The Infra red spectrum contained carbonyl bands at 1768 and 1705 cm^{-1}. The spectra suggested the product was *N*-methylphthalimide (NMP) and this was confirmed by comparison of its infra red spectrum with an authentic sample.

Photoproduct (280) was isolated in trace amounts and the proton NMR spectrum contained a singlet at 5.2 ppm, an aromatic multiplet between 7.4 and 7.7 ppm a symmetrical aromatic multiplet between 7.8 and 8.0 ppm and an aromatic doublet at 8.1 ppm. The integration ratio of these signals being 2:3:4:2. The mass spectrum showed a molecular ion at m/z 265 and the most intense fragment was at m/z 105 ($^{+}$COPh). The product was identified on the basis of this data as phenacylphthalimide (280), confirmed by independent synthesis. Thus manganese dioxide oxidation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232), a standard procedure for oxidation of benzylic alcohols[132] afforded phenacylphthalimide (280) in good yield.



SCHEME 2.17

HPLC was used to follow the reaction quantitatively since the volatility of benzaldehyde led to losses during solvent removal and an accurate estimate of final composition was therefore not possible after chromatographic isolation of the photoproducts. It was also necessary to elucidate whether formation of phenacylphthalimide was a primary photochemical process. A HPLC method seemed suitable in which the photolysis solution could be diluted with mobile phase and injected directly onto the column without prior solvent removal. Standard stock solutions of *N*-(2-hydroxy-2-phenylethyl) phthalimide (232) and each of the photoproducts isolated were prepared and, from these, mixed standards of varying concentrations from 0-4 mM were prepared. The best separation was achieved with a reverse phase C18 column using acetonitrile/water 50:50 as the mobile phase. A linear response for the concentration range of interest was established, and an external standardisation method was used in which a standard containing all constituents was injected prior to photolysis samples. The presence of dichloromethane in the analysis samples caused band broadening and poor resolution compared to the standard analyses. Chloroform was chosen as an alternative solvent and standards prepared using chloroform which had been

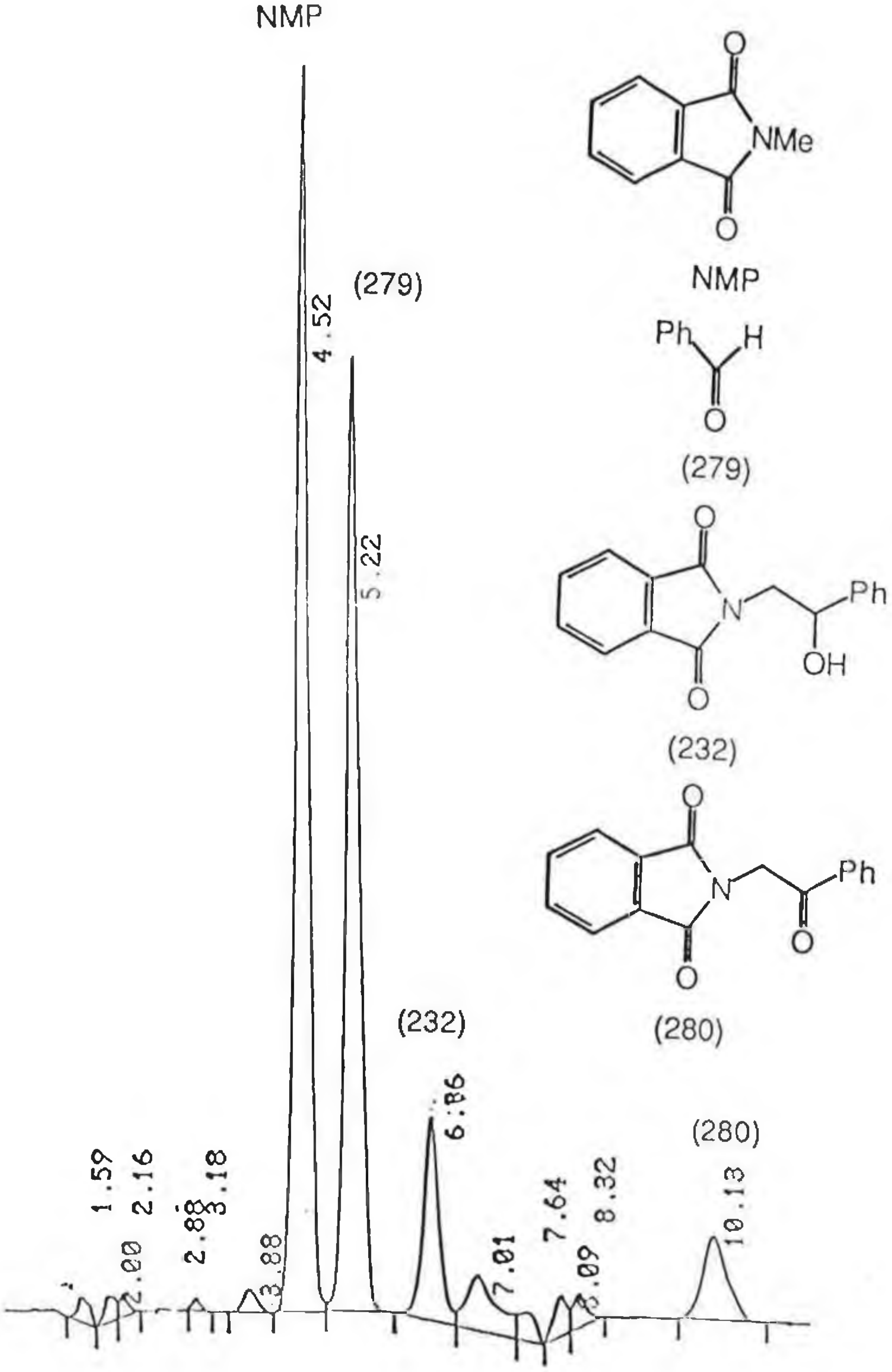
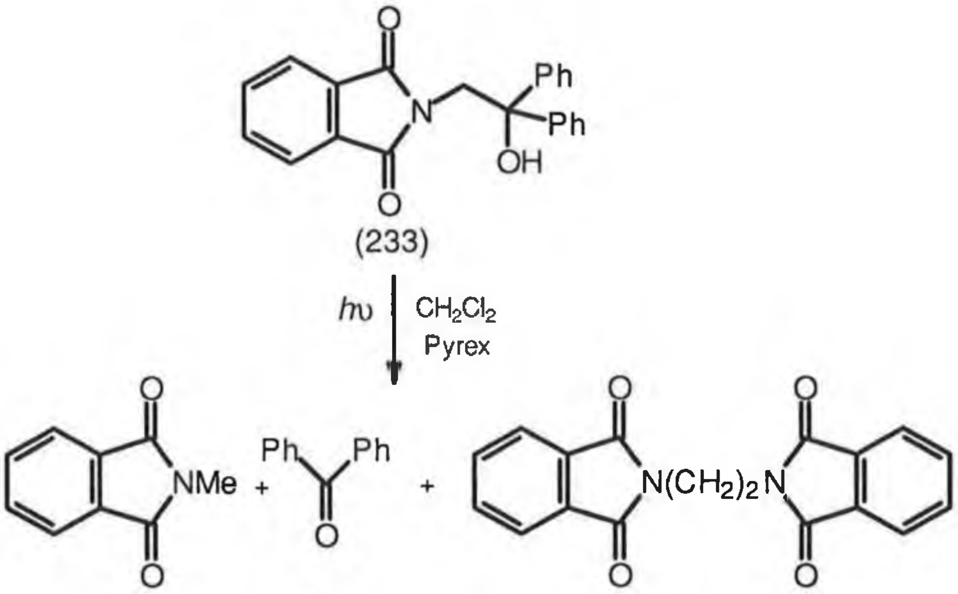


Fig 2.1: HPLC chromatogram for irradiation of (232) in chloroform at high conversion.

acid washed and distilled to remove stabiliser showed good resolution. A 2.5 mM solution of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in chloroform was irradiated using a medium pressure lamp and samples were periodically withdrawn and analysed by HPLC. At low conversion the formation of *N*-methylphthalimide (NMP) and benzaldehyde (279) in almost equimolar amounts was observed. The formation of phenacylphthalimide (280), though in much lower yield was also observed suggesting that it is formed as a result of a primary photochemical process. The chromatogram in *Fig 2.1* shows photolysis of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in chloroform at high conversion, the major products *N*-methylphthalimide (NMP) at 4.5 mins and benzaldehyde (279) at 5.2 mins were calculated to be present in approximately 80 and 90% yield respectively. Phenacylphthalimide (280) at 10.1 mins was calculated to be present in 8% yield. The other peaks present are thought to be due to secondary photoproducts. The HPLC analysis does show that the fragmentation of (232) to form NMP and benzaldehyde (279) is the major process operating in this system (SCHEME 3.17), with a minor photochemical process being the oxidation of (232) to phenacylphthalimide (280).

2.6.2 Irradiation of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) in dichloromethane

N-(2,2-Diphenyl-2-hydroxyethyl)phthalimide (233) was irradiated through Pyrex in dichloromethane as solvent. Reaction progress was followed using TLC analysis and rapid formation of two major products and one minor product was observed. Irradiation was discontinued after approximately 45 mins at which time the starting material (233) had been completely consumed. The solvent was removed and proton NMR and comparative TLC analysis of the crude photolysis mixture suggested that the major products were *N*-methylphthalimide (NMP) and benzophenone (244) (SCHEME 2.18). The mixture was separated using a Chromatotron to give, benzophenone (244), *N*-Methylphthalimide (NMP), and bisphthalimidoethane (281) which was isolated in trace amounts and identified from its characteristic NMR signals. The proton NMR of (281) displayed a singlet at 4.01 ppm and a symmetrical phthalimido aromatic multiplet between 7.68 and 7.79 ppm, integration ration 4:8. The carbon NMR spectrum displayed a methylene absorption at 36.8 ppm, three aromatic absorptions and a carbonyl absorption at 168.2 ppm.

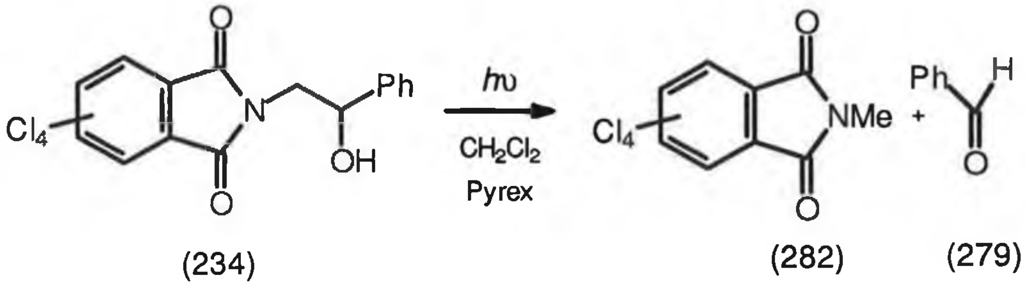


SCHEME 2.18

This identification was confirmed by an independent synthesis of bisphthalimidoethane (281) by the reaction of phthalic anhydride and ethylene diamine.[23] The product obtained from this reaction was identical in all respects to the product assigned as bisphthalimidoethane (281) obtained on irradiation of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) in dichloromethane.

2.6.3 Irradiation of *N*-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (234) in dichloromethane

N-(2-Hydroxy-2-phenylethyl)tetrachlorophthalimide (234) was irradiated in dichloromethane through Pyrex. Reaction progress was followed by TLC analysis and rapid formation of two products was observed. Irradiation was discontinued after approximately 20 mins at which point the starting material (233) had been completely consumed. The solvent was removed and the proton NMR and comparative TLC analysis of the crude reaction mixture suggested that the major photoproducts in this system were benzaldehyde (279) and *N*-methyltetrachlorophthalimide (282) (SCHEME 2.19).

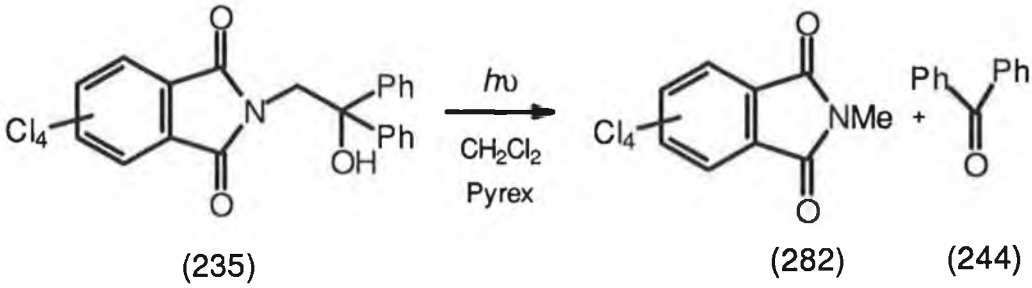


SCHEME 2.19

The solid residue from the photolysis was recrystallised to afford *N*-methyltetrachlorophthalimide (282) as white crystals. The resulting mother liquor was separated on a Chromatotron to give benzaldehyde (279) and *N*-methyltetrachlorophthalimide (282), identified by comparison of spectra to authentic samples, no other products were isolated.

2.6.4 Irradiation of *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachloro phthalimide (235) in dichlormethane:

The final compound in the initial series investigated was *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235). This compound was irradiated in dichloromethane through Pyrex. Reaction progress was followed by TLC analysis and extremely rapid formation of two photoproducts was observed by TLC. The reaction was so rapid that within ten mins the starting material had been completely consumed. On discontinuation of irradiation and removal of

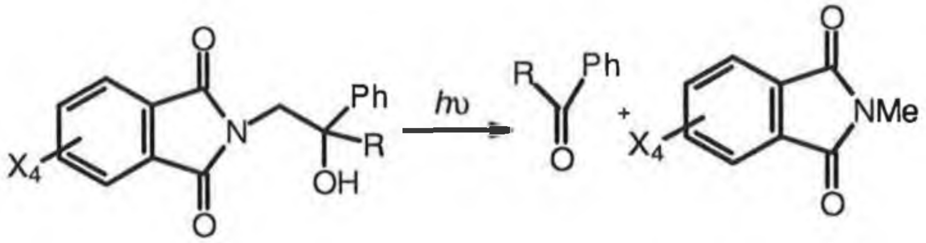


SCHEME 2.20

solvent, proton NMR and comparative TLC analysis suggested that the major products were *N*-methyltetrachlorophthalimide (282) and benzophenone (244) (SCHEME 2.20). Chromatographic isolation of both compounds and comparison with authentic samples confirmed this identification.

2.7 Discussion: The photofragmentation of phenyl substituted *N*-(2-hydroxyethyl)phthalimides (232) & (233) and phenyl substituted *N*-(2-hydroxyethyl)tetrachlorophthalimides (234) & (235)

The major photochemical process observed for the series of compounds (232) to (235) on irradiation through Pyrex using dichloromethane as solvent can be thought of as a proton or hydrogen transfer to excited state phthalimido carbonyl and subsequent cleavage of the β,γ-carbon-carbon bond of the *N*-alkyl side chain. The results are summarised in SCHEME 2.21 and *Table 1*. The yields of fragmentation product presented represent chromatographically isolated yields. Proton NMR analysis of crude reaction mixtures indicate that these products represent approximately 90% of overall photoproduct obtained on irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimides (232) to (235). Although the products are unremarkable from a synthetic point of view, the mechanism of formation is intriguing. As was discussed earlier, Lewis has shown[106] that on irradiation of γ-hydroxy-γ-phenylbutyrophenone (227) the products observed are consistent with cleavage of the α,β-carbon-carbon bond with respect to the carbonyl chromophore. This process can be rationalised in terms of conventional γ-H abstraction by excited state carbonyl to form a 1,4-diradical and subsequent cleavage to form two molecules of acetophenone (231) (SCHEME 2.22). Compounds (232) and (234) are structurally analogous to (227), both containing a hydrogen atom in the γ-position. Photofragmentation via a similar process would be expected to yield phthalimide (P) and acetophenone (231) from *N*-(2-hydroxy-2-phenylethyl)phthalimide (232), and tetrachlorophthalimide (283) and acetophenone (231) from *N*-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (234) (SCHEME 2.22). These products were not detected, so an alternate photoprocess must be operative, one which is different from the conventional Norrish type II photoprocesses.



(232): X= R= H	(279): R= H	NMP: X= H
(233): X= H, R= Ph	(244): R= Ph	NMP
(234): X= Cl, R= H	(279)	(282): X= Cl
(235): X= Cl, R= Ph	(244)	(282)

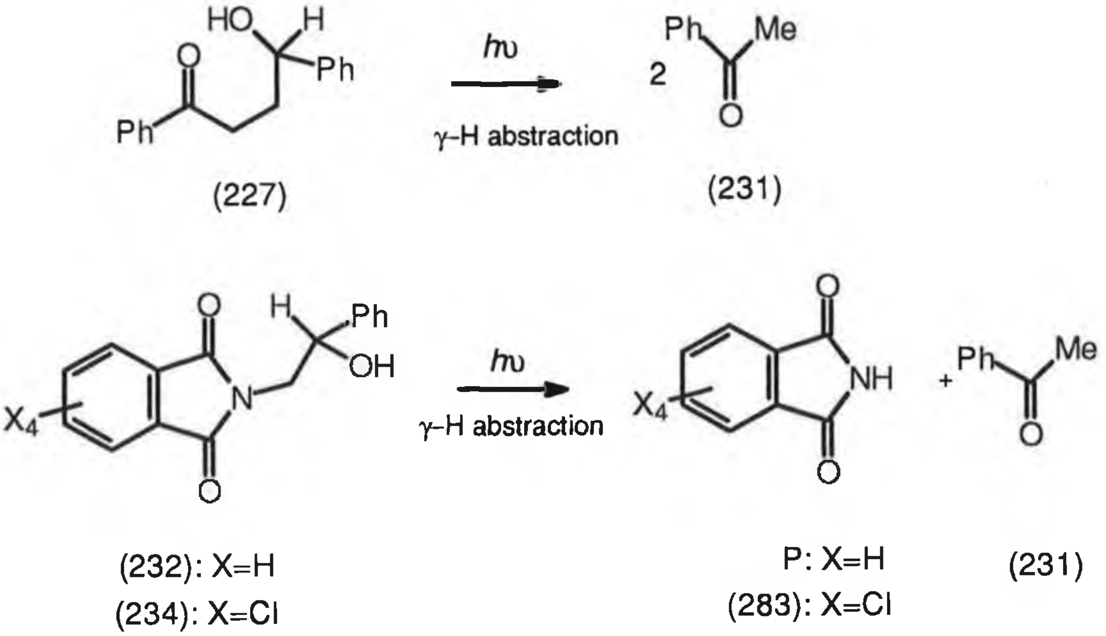
SCHEME 2.21

Table 1: Results for irradiation of (232) to (235) in dichloromethane through Pyrex

SUBSTRATE	IRRADIATION TIME (MINS)	% CONVERSION	PRODUCTS (%YIELDS)[a]
(232)	90	60	NMP (60) 279 (38)
(233)	45	100	NMP (59) 244 (55)
(234)	20	100	282 (67) 279 (8)[b]
(235)	15	100	282 (74) 244 (64)

[a] Isolated yields based on consumed starting material.

[b] ^{1}H NMR analysis yield of benzaldehyde >90 %.



(227)

(231)

(232): X=H
(234): X=Cl

P: X=H
(283): X=Cl

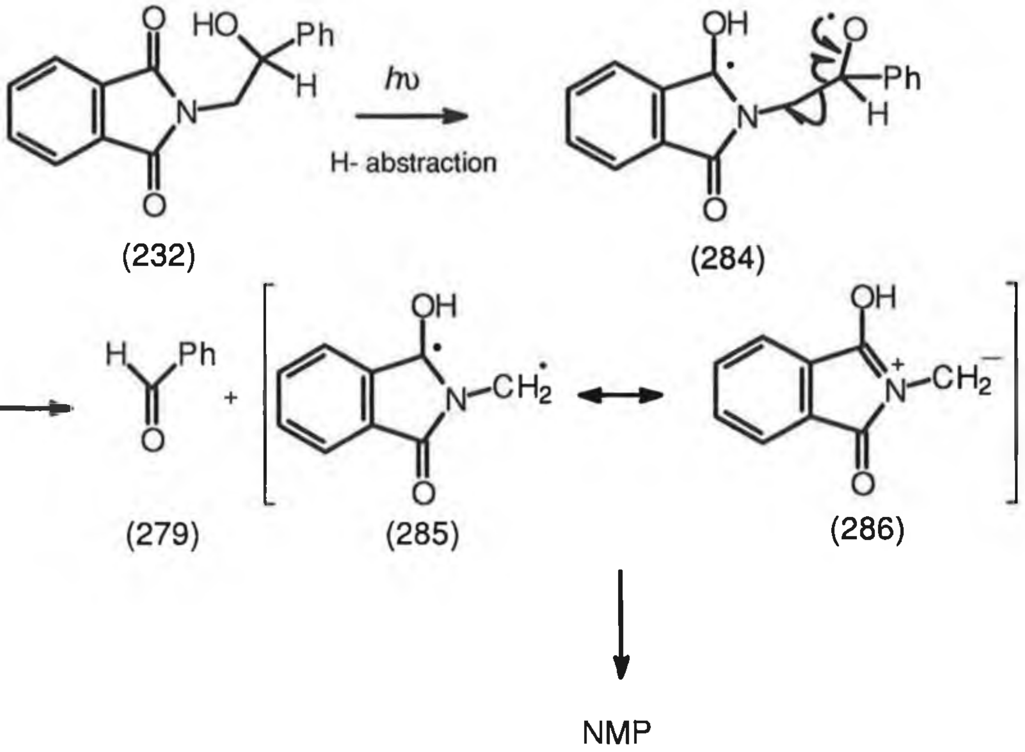
(231)

SCHEME 2.22

Two minor products were isolated on irradiation of unchlorinated analogues (232) and (233). Thus phenacylphthalimide (280) was obtained from *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) and bisphthalimidoethane (281) from *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233). In the introduction the point was made that previous experiments had shown that the photochemistry of *N*-alkyltetrachloro phthalimides did differ considerably from that of nonchlorinated analogues (see 2.1) however in this case a common product profile was observed for both chlorinated and nonchlorinated analogues. A number of possible mechanisms have been considered for these photofragmentations and are introduced for *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in the following sections. They apply equally to structural analogues (233), (234) and (235).

2.7.1 Hydrogen transfer from hydroxyl group

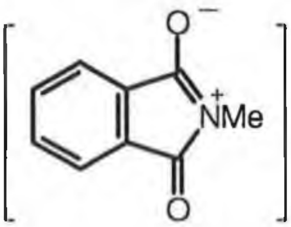
One mechanism considered to account for the product profile observed on irradiation of (232) involves a hydrogen abstraction from the hydroxyl group by alkoxy-radical-like excited carbonyl to produce diradical (284) which cleaves to produce benzaldehyde (279) and diradical (285) which is isoelectronic with azomethine ylide (286), the latter rapidly rearranges to produce NMP (SCHEME 2.23).



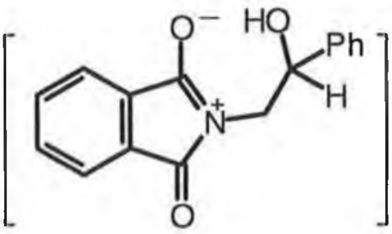
SCHEME 2.23

2.7.2 Proton transfer to zwitterionic excited state

Mazzochi and co-workers have suggested[77] the intermediacy of a zwitterionic singlet excited state (287) to account for the addition of alkenes with high oxidation potentials to *N*-methylphthalimide (NMP). A similar intermediate



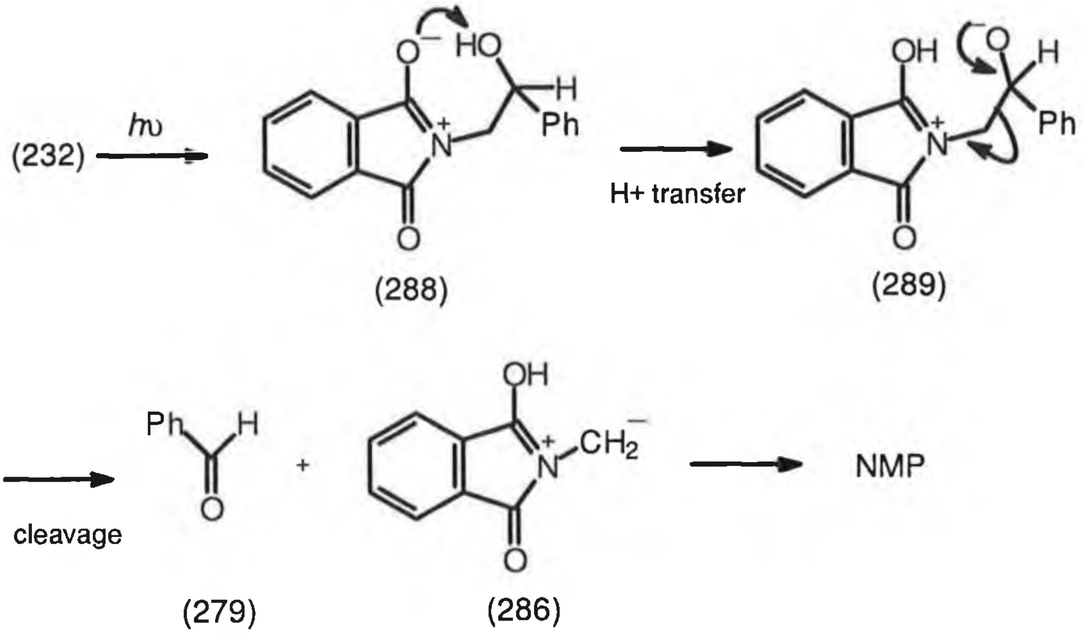
(287)



(288)

(288) could be proposed to account for the photoreaction of (232). An intramolecular proton transfer from the hydroxyl group to the anionic oxygen in zwitterion (288) generating zwitterionic species (289) and subsequent γ-β-

carbon-carbon bond scission would generate azomethine ylide (286) and benzaldehyde (279) (SCHEME 2.24).



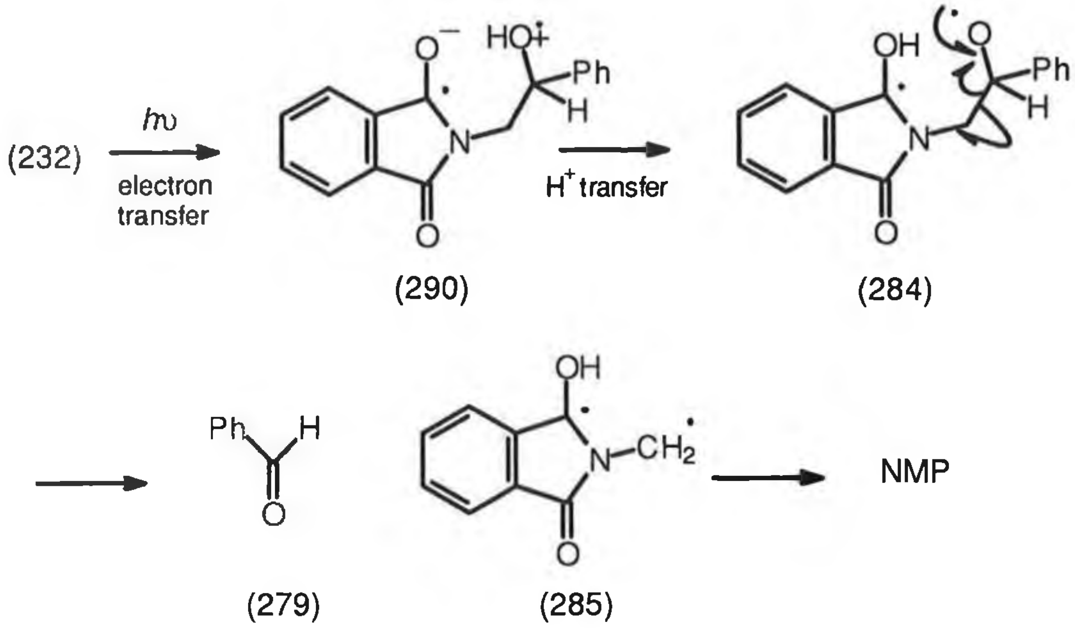
SCHEME 2.24

2.7.3 Electron transfer from hydroxyl group

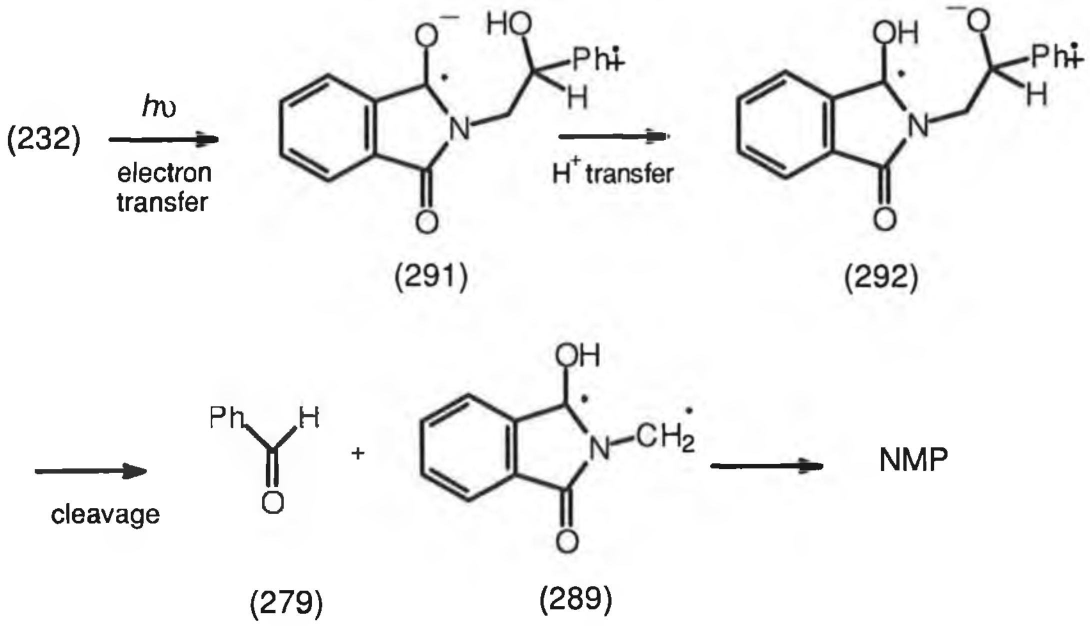
This mechanism can be considered analogous to the intramolecular photoreaction of *N*-substituted phthalimides containing alkyl amine or alkyl sulfide side chains.[56] The mechanism would involve electron transfer from hydroxyl oxygen to excited phthalimide to generate radical cation/radical anion species (290). Intramolecular proton transfer would generate diradical species (284) which subsequently could fragment to generate diradical (285), leading to *N*-methylphthalimide (NMP),and benzaldehyde (279) (SCHEME 2.25).

2.7.4 Intramolecular electron transfer from side chain aryl groups:

Albini[20] and Kanaoka[19] have shown that toluene and other electron rich aryl systems can participate in intermolecular electron transfer reactions with *N*-alkylphthalimides. A similar intramolecular mechanism could be proposed for *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) involving intramolecular electron transfer from the aryl group to generate radical cation/anion (291) subsequent proton transfer from hydroxyl group to yield biradical (292), which could then cleave to form the observed products.



SCHEME 2.25

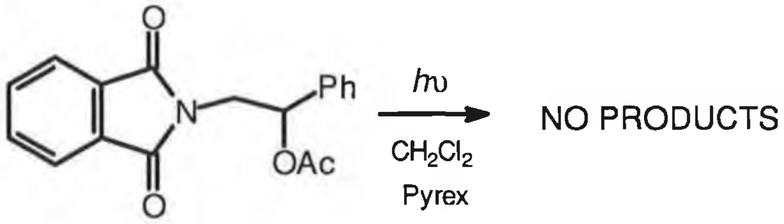


SCHEME 2.26

The four mechanisms outlined above could in principle lead to the observed product profile and a broader study was required to ascertain which mechanism was operative. The most obvious course of action was to examine the photofragmentation in terms of the effect substrate changes would have on the observed photochemistry. Of primary interest was whether the reaction was general for all *N*-(2-hydroxyethyl)phthalimides or would changes in side chain substituent enhance or hinder the reaction. We were also interested in the role of the hydroxyl group, particularly the changes which might be observed on irradiating a substrate protected at the hydroxyl group, and also whether it might be possible to directly relate the origins of one of the methyl protons of photoproduct *N*-methylphthalimide to the hydroxyl group of the substrate. The final area of interest was whether the excited state responsible was singlet or triplet in nature.

2.8 Role of hydroxyl group photochemistry of *N*-(2-acetoxy-2-phenylethyl) phthalimide (293) and deuterium exchange studies

It was decided that an acetyl group would be a convenient protecting group and, *N*-(2-hydroxyl-2-phenylethyl)phthalimide (293) was acetylated by heating in acetic anhydride to produce the known[112] *N*-(2-acetoxy-2-phenylethyl)phthalimide (70) in good yield. No product formation was observed even after prolonged irradiation of (70) in dichloromethane through Pyrex (SCHEME 2.27).

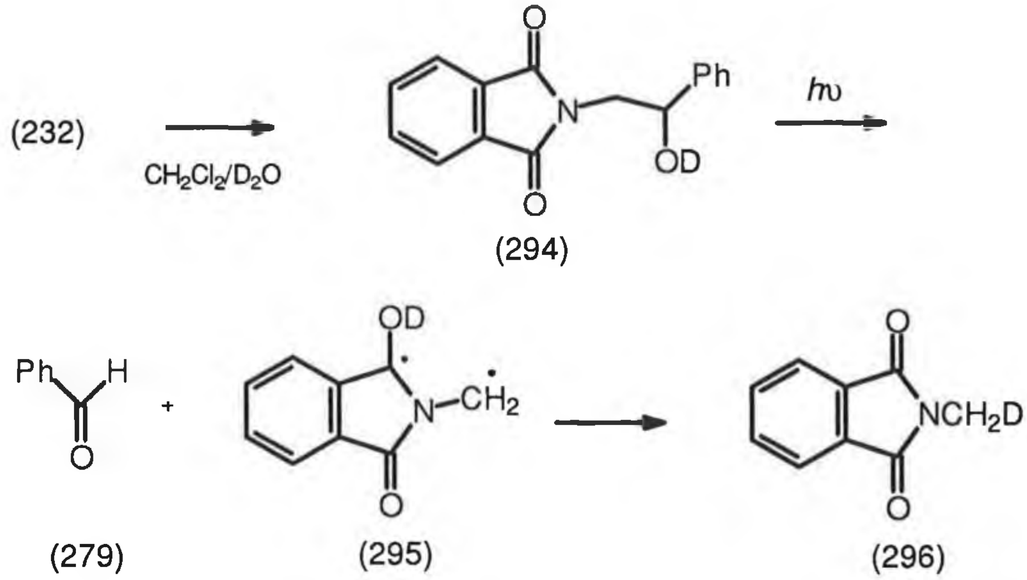


(293)

SCHEME 2.27

Additional information was obtained concerning the mechanistic course of the photofragmentation of (232) by carrying out reactions in the presence of deuterium oxide. An initial proton NMR experiment indicated that irradiation of a deuterated chloroform solution of *N*-(2-Hydroxy-2-phenylethyl)phthalimide

(232) which had been shaken with a drop of deuterium oxide and complete hydroxyl exchange had been observed, produced *N*-(monodeuteriomethyl) phthalimide (296) and benzaldehyde (279) as the major products. This was confirmed by chromatographic separation of the products obtained from a preparative irradiation of (232) in dichloromethane shaken with deuterium oxide. This reaction yielded *N*-(monodeuteriomethyl)phthalimide (296) (SCHEME 2.28) with an R_f identical to *N*-methylphthalimide (NMP) and was



SCHEME 2.28

identified from its characteristic proton NMR signals which displayed a triplet at 3.2 ppm and a symmetrical aromatic multiplet between 7.6 and 7.8 ppm, the integration ratio of these signals being 2:4 respectively. The lack of photochemical reaction observed on irradiation of the acetylated compound (293) and the isolation *N*-(monodeuteriomethyl)phthalimide (296) on irradiation of *N*-(2-deuteroxy-2-phenylethyl)phthalimide (294) demonstrate the importance of a proton transfer from hydroxyl group to phthalimide carbonyl in the photofragmentation of (232). As was discussed earlier the product profile is inconsistent with a γ-hydrogen abstraction process, so one must assume that in the deuteration experiment that the species transferred is a deuterium ion or a deuterium atom to produce diradical (295) which can then rearrange to (296).

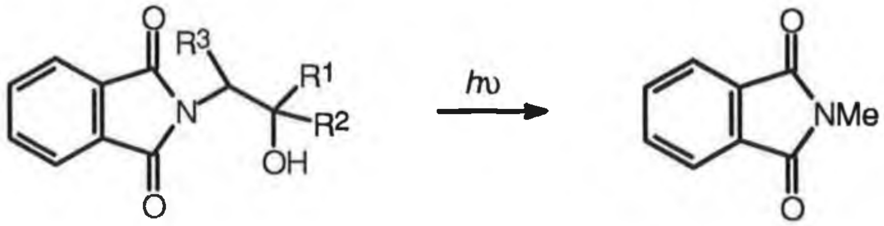
2.9 Scope of photofragmentation of-*N*-(2-hydroxyethyl)phthalimides

The role of proton/hydrogen transfer had been established both with the acetylation and deuteration studies but the nature of the photochemical process occurring prior to the proton/hydrogen transfer was still unclear. The mechanistic nature of the process was further probed by examining the photochemistry of a series of *N*-(2-hydroxyethylphthalimides with different substituents at the the second carbon of the alkyl side chain.

2.9.1 Irradiation of *N*-(2-hydroxyethyl)phthalimide (254), *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255), *N*-(2-hydroxypropyl)phthalimide (256) and *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) in dichloromethane

These compounds were irradiated as before in dichloromethane through Pyrex. Reaction progress was monitored by TLC. On ceasing irradiation and removal of solvent the crude reaction mixtures were analysed by proton NMR. The product of the γ-fragmentation reaction namely *N*-methylphthalimide (NMP) was identified if present by virtue of its characteristic proton NMR signals. Where possible the photoproducts were isolated by column chromatography and their identity confirmed by comparison of infra red and proton NMR spectra to authentic samples. The carbonyl fragments expected for these compounds were not individually isolated due to their volatility. The results are summarised in *Table 2* and SCHEME 2.29.

Neither of the compounds unsubstituted at the second carbon of the alkyl side chain (254) and (255) showed evidence of the γ-fragmentation reaction even after prolonged irradiation. These compounds did show some photodegradation on TLC but no evidence of a clean photochemical process, and examination of the proton NMR spectra of the crude reaction mixtures indicated greater than 90% recovery of starting material. However



(254): $R^1 = R^2 = R^3 = H$

(255): $R^1 = R^2 = H$, $R^3 = CH_2Ph$

(256): $R^1 = R^3 = H$, $R^2 = Me$

(278): $R^1 = R^2 = Me$, $R^3 = H$

NMP

SCHEME 2.29

Table 2: Results for irradiation of (254) to (256) and (278) in dichloromethane through Pyrex.

SUBSTRATE	**IRRADIATION TIME (HOURS)**	**% CONVERSION**	**PRODUCT (% YIELD)**[a]
(254)	40	< 10	NPI
(255)	18	< 10	NPI
(256)	29	38	NMP (63)
(278)	10	65	NMP (67)

[a]: isolated product based on consummed starting material

NPI: no products isolated.

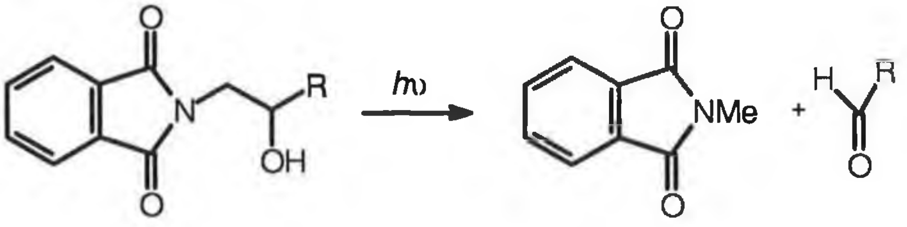
compounds (256) and (278) did form *N*-methylphthalimide (NMP) indicative that the γ-fragmentation process occurs for these substrates. Analysis of the proton NMR spectra of the crude reaction mixtures indicated that for the dimethyl compound (278) the sole photoprocess observed was formation of NMP. For the mono methyl substituted compound (256) the formation of NMP was the major process. Analysis of the TLC prior to separation did show the presence of a two small fast running spots which were present in insufficient quantities for positive identification. The Irradiation times were considerably longer than the phenyl substituted compounds (232) and (233) particularly for *N*-(2-hydroxypropyl)phthalimide (256) which required an irradiation period of 29 hours for approximately 40% conversion. The dimethyl substituted analogue (278) was considerably more photolabile but still required an irradiation period 30 times that required for complete reaction of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) to achieve 60% conversion of (278) to NMP.

2.9.3 Irradiation of *N*-(2-hydroxy-2-*p*-methoxyphenylethyl)phthalimide (275), *N*-(2-hydroxy-2-*p*-bromophenylethyl)phthalimide (276) and *N*-(2-hydroxy-2-styrylethyl)phthalimide (277) in dichloromethane

These compounds were irradiated as before, the results for the fragmentation reaction if observed being summarised in *Table 3* and SCHEME 2.30.

The *p*-methoxyphenyl substituted compound (275) showed clean fragmentation to form *N*-methylphthalimide (NMP) and *p*-anisaldehyde (297). These products were calculated to be present in (84%) and (71%) from integration of the characteristic signals in the proton NMR spectrum. The low yield of the isolated aldehyde (297) in *Table 3* is a result of loses due to its volatility on purification. Analysis of the proton NMR spectrum identified the oxidised product *p*-methoxyphenacylphthalimide (298) as a minor product

(12%) on the basis of its characteristic methylene signal at 5.2 ppm it was not isolated individually.



(275): R= *p*-OMeC$_6$H$_4$ NMP (297)

(276): R= *p*-BrC$_6$H$_4$

(277): R= PhCH=CH

SCHEME 2.30

Table 3: Results for irradiation of (275) to (278) in dichloromethane through Pyrex.

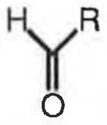
SUBSTRATE	IRRADIATION TIME	% CONVERSION	PRODUCTS (% YIELDS)^a
(275)	35 mins	100	NMP (70) 297 (7)^b
(276)	1 hour	100	NPI
(277)	18 hours	<10	NPI

a: isolated product based on consumed starting material.

b: ^{1}H NMR analysis yield 71%.

NPI: no products isolated.

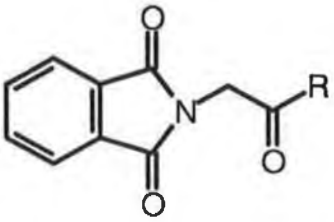
On irradiation of the *p*-bromophenyl substituted compound (276) formation of *N*-methylphthalimide (NMP), *p*-bromobenzaldehyde (299) and *p*-bromophenacylphthalimide (300) was observed which were identified by comparitive TLC and examination of the proton NMR spectrum of the crude reaction mixture. However increasing irradiation time led to formation of an increasing number of photoproducts and individual isolation of these products proved impossible.



(297): R= *p*-OMeC_6H_4

(299): R= *p*-BrC_6H_4

(301): R= PhCH=CH



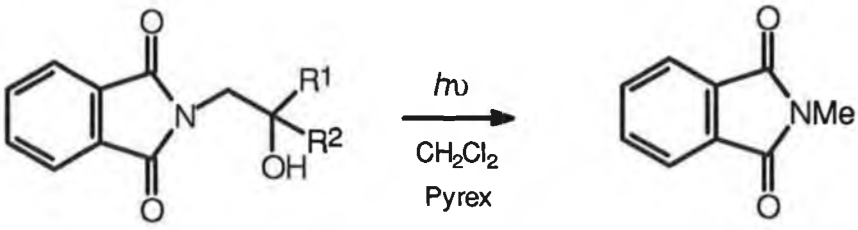
(298): R= *p*-OMeC_6H_4

(300): R= *p*-BrC_6H_4

The final compound to be irradiated in this series was the styryl substituted compound (277) which after prolonged irradiation showed no evidence of formation of *N*-methylphthalimide (NMP) or cinnamaldehyde (301). Slow formation of a number of photoproducts were observed by TLC, however these were present in insufficient quantities to be individually isolated, and identification from examination of the proton NMR spectrum of the crude reaction mixture was inconclusive.

2.10 Sensitised irradiation of *N*-(2-hydroxy-2-methylpropyl)phthalimide and *N*-(2-hydroxyethyl)phthalimide in dichloromethane through Pyrex

The nature of the excited state responsible for the γ-fragmentation of the *N*-(2-hydroxyethyl)phthalimides was investigated using benzophenone as sensitiser. Benzophenone is widely used in organic photochemistry as a triplet sensitiser due to its high efficiency of intersystem crossing from single to triplet (n, π*) excited state and ability to transfer this triplet energy to molecules with less efficient intersystem crossing.[133] As was mentioned before the chromophore in the *N*-(2-hydroxyethyl)phthalimides can be regarded as a simple *N*-alkylphthalimide and they show a (n, π^*) λ_{max} at 296 nm (ε=1100 dm^3 mol^{-1} cm^{-1}) which tails off at 330nm. The uv spectrum of benzophenone in dichloromethane shows a broad (n, π^*) absorption from 305 to 380 nm (λ_{max} 336 nm, ε=125 dm^3 mol^{-1} cm^{-1}). A medium pressure mercury lamp with pyrex filter allows two main 30 nm regions of light to pass between 300 and 400 nm.[134] These are the 300-330nm region which correspond to the output lines of the lamp at 302 and 313 nm with a spectral output of approximately 0.04 Einsteins hour^{-1} and the 360-390 nm region corresponding to the output line at 365.5 nm with an output of approximately 0.06 Einsteins hour^{-1}. Both the *N*-(2-hydroxyethyl)phthalimides and benzophenone absorb in the first spectral region showing similar extinction coefficients, whereas only benzophenone absorbs in the second 360-390 nm region. Taking this into account two solutions of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) one containing three equivalents of benzophenone as added sensitiser were irradiated for a short period of time. A similar experiment was performed for *N*-(2-hydroxy-2-phenylethyl) phthalimide (232) and the unsubstituted compound *N*-(2-hydroxyethyl) phthalimide (254) was irradiated in the presence of sensitiser for a longer period of time to establish whether it would photofragment under sensitised conditions. The results are outlined in *Table 4*, the formation of *N*-methyl phthalimide (NMP) was indicative of the γ-fragmentation process. The % conversion and % yield of product were calculated by integration of the characteristic signals for NMP and the substrate in the proton NMR spectra of the crude reaction mixtures. The results obtained for both the dimethyl substituted compound (278) and the mono-phenyl substituted compound (232) show much more efficient conversion to product in the sensitised reaction compared to the unsensitised case. The lack of reaction observed



(278): R^1=R^2=Me

(232): R^1=H, R^2=Ph

(278): R^1=R^2=H

NMP

SCHEME 2.31

Table 4: Results for the irradiation of (278) and (232) in the presence and absence of benzophenone as sensitiser and the irradiation of (254) in the presence of added sensitiser.

SUBSTRATE	**IRRADIATION TIME (MINS)**	**% CONVERSION**	**PRODUCT (% YIELD)**[a]
(278)*	45	100%	NMP (>90%)
(278)	45	15%	NMP (100%)
(232)*	40	65%	NMP (100%)
(232)	40	1%	NMP (100%)
(254)*	360	NR	NI

*: sensitised irradiation

a: ^{1}H NMR analysis

NR: no reaction observed

NI: no products identified

for the unsubstituted compound (254) on prolonged irradiation under sensitising conditions indicates that its lack of reaction must be due to structural considerations rather than attainment of a sufficient triplet state population. It is likely that the fragmentation of the phenyl substituted series of compounds to form aromatic carbonyl fragment and NMP would lead to a "self sensitisation" process as the carbonyl fragment produce would compete with the substrate for light and subsequently transfer triplet energy to the substrate thus enhancing the rate of fragmentation. Although these experiments indicate that the excited state responsible for this fragmentation for both the phenyl substituted compounds and methyl substituted compounds is most likely triplet in nature, the reaction may also occur from the singlet state. A monochromatic source of radiation was not used for these experiments so it is diffucult to calculate what proportion of the incident light is absorbed by the benzophenone, however the points made above regarding the absorption spectra of the substrate and benzophenone and the output of a medium pressure lamp above 300 nm and the clear difference in product yield between sensitised and unsensitised reactions suggest that efficient triplet energy transfer was occurring.

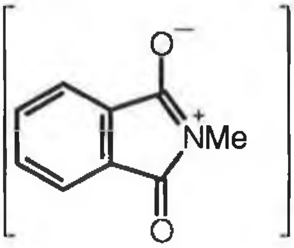
2.11 Discussion: The mechanism of the γ-fragmentation process observed for γ- substituted *N*-(2-hydroxyethyl)phthalimides

The product profile attained for the photoreaction of these compounds cannot as was discussed earlier be attributed to conventional Norrish type II photoprocess. A number of mechanisms were initially proposed to account for the observed photofragmentation (2.7.1 to 2.7.4).

Hydrogen abstraction from hydroxy group by excited state phthalimide carbonyl is unlikely as the very polar nature of the hydroxyl bond would make a homolytic cleavage energetically unfavourable which is demonstrated in the difference of 50 KJ mol^{-1} in the bond dissociation energies for a carbon hydrogen versus oxygen hydrogen bond.[135]

Another mechanism proposed was that of electron transfer from side chain aryl group to excited state phthalimide chromophore. The compound containing an electron rich aromatic ring *N*-(2-hydroxy-2-*p*-methoxyphenyl ethyl)phthalimide (275) required considerably less irradiation time for complete conversion to products of fragmentation than the monophenyl substituted compound. This could be as a result of increased efficiency of electron transfer however since the compounds containing alkyl substitution at the second carbon of the side chain (256) and (278) both engaged in the photofragmentation reaction, it is unlikely that two different mechanistic pathways are in operation leading to a similar product profile. Also the lower irradiation time required for the *p*-methoxyphenyl compound may be a result of enhanced efficiency of fragmentation rather than enhanced rates of electron transfer.

The next mechanism proposed was that of proton transfer to zwitterionic excited state (288). A similar zwitterionic excited state (287) was proposed by Mazzochi[77] to account for the addition of alkenes with high oxidation potentials to NMP. These reactions have been shown to arise from the singlet excited state whereas the triplet excited state has been reported to be more oxy-radical in nature. [104] The results obtained by us indicate that



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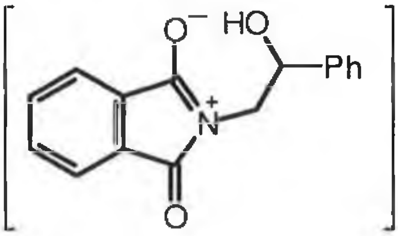
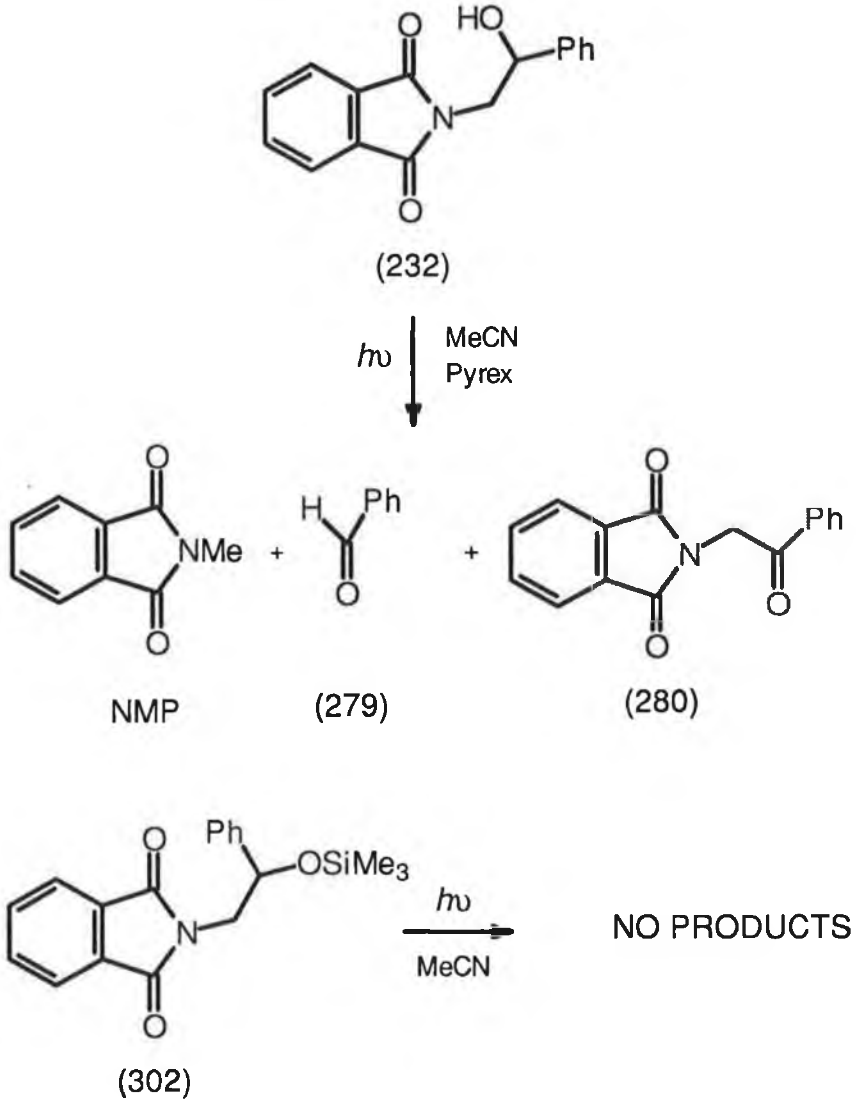


(288)

the excited state operative in the fragmentation reaction is triplet in nature, although a similar reaction from the singlet state cannot be totally ruled out. The sensitisation experiments show that in the presence of a triplet sensitiser the irradiation times are considerably reduced for complete conversion indicating a reactive triplet state, which would preclude the participation of a species analogous to (288) in the photoreaction.

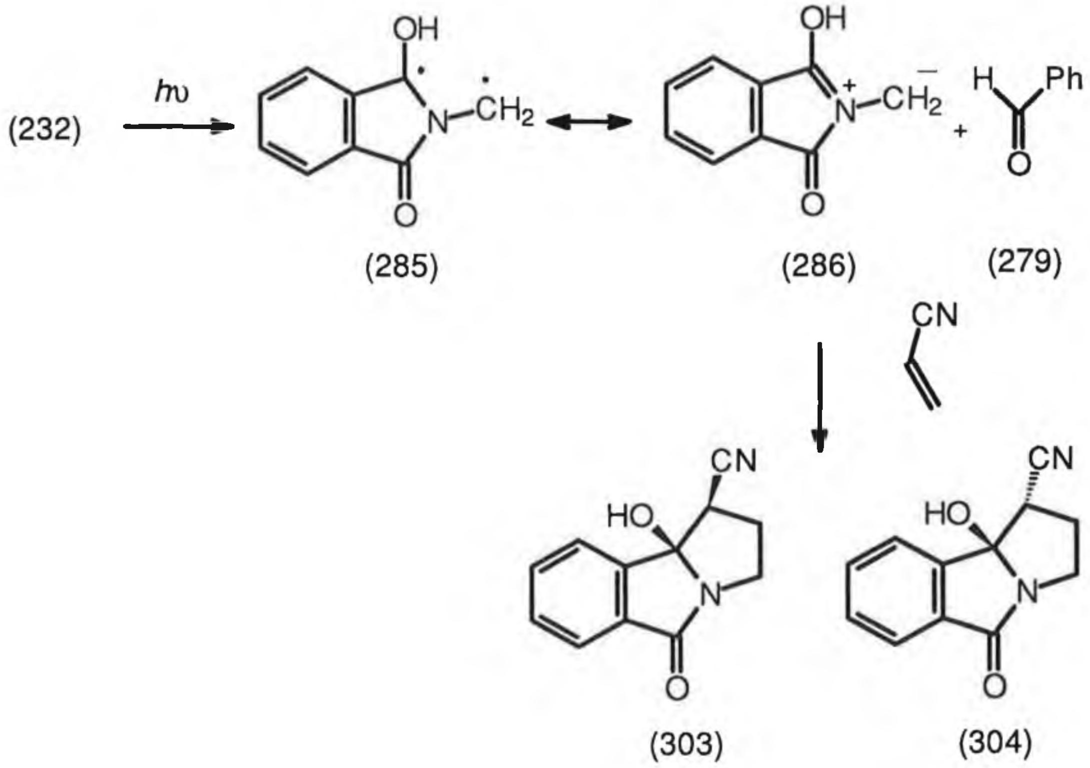
At the outset of this work there were no reports of the photofragmentation of *N*-(2-hydroxyethyl)phthalimides (226) in the literature, however recently two



SCHEME 2.32

groups have reported results similar to ours. Mariano and co-workers have reported[104] that irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in acetonitrile produces *N*-methylphthalimide (NMP) and benzaldehyde (279) as the major products with phenacylphthalimide (280) as a minor product

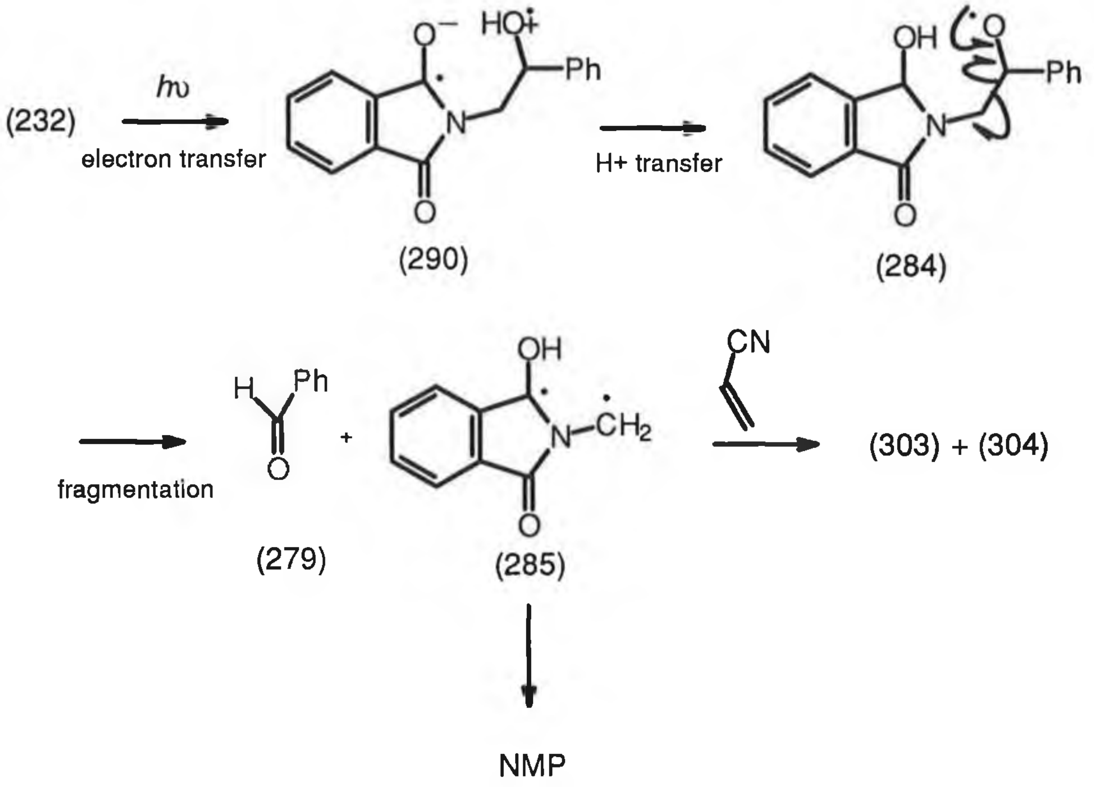
(SCHEME 2.32). They have also investigated the photochemistry of the *O*-trimethylsilyl derivative (302) and found it to be photochemically inert over comparable irradiation periods (SCHEME 2.32). Both these results are comparable to the results obtained by us for this compound. Interestingly Mariano and co-workers confirmed[104] the existence of azomethine ylide (286) by trapping with dipolarophiles to form adducts (303) and (304) (SCHEME 2.33).



SCHEME 2.33

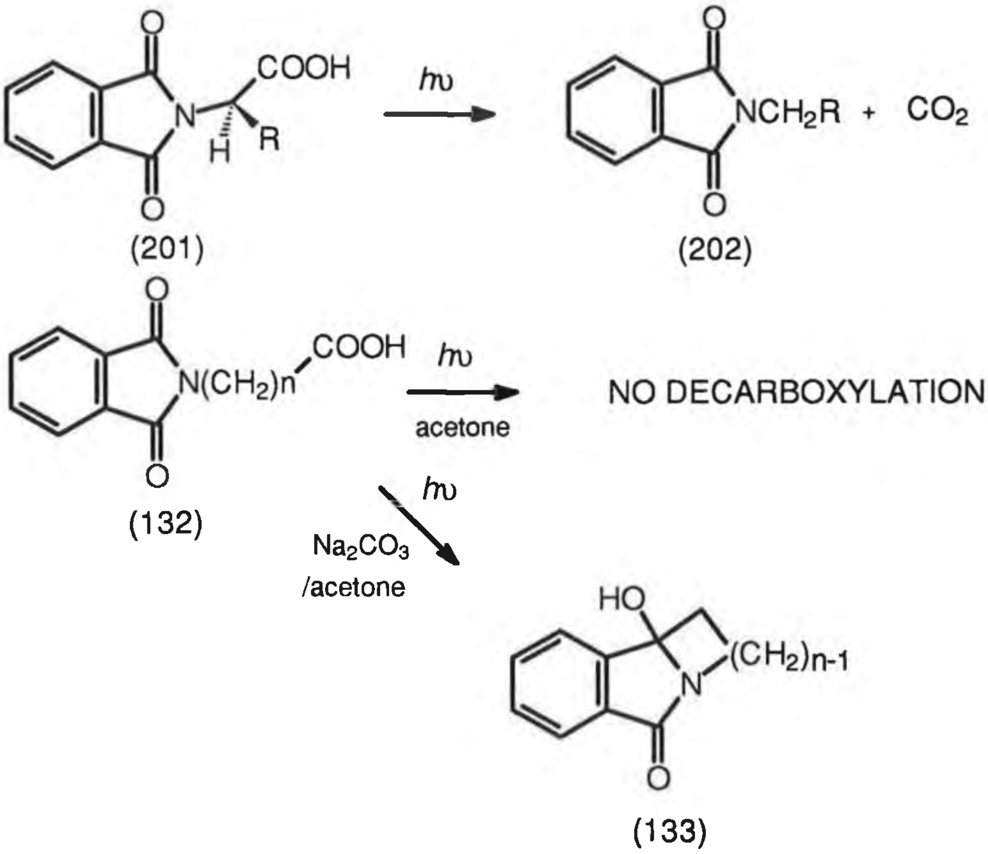
They report that irradiation of (232) in acetone (triplet sensitiser) produces complete conversion to products of fragmentation in less than half the time required for a comparable irradiation in acetonitrile. They also report that irradiation times in the presence of added dipolarophile were ten times longer that than in the absence of dipolarophile. The triplet state of *N*-substituted phthalimides has been reported to be quenched in the presence of added alkene[88] and this coupled with the observation of lower reaction times in acetone is further evidence that the excited state operative in this photofragmentation has considerable triplet character.

The mechanism proposed involving electron transfer from hydroxyl group to excited state phthalimide chromophore seems the most likely and Mariano and co-workers proposed[104] such a mechanism to account for the photofragmentation of (232) the monophenyl compound (SCHEME 2.34).



SCHEME 2.34

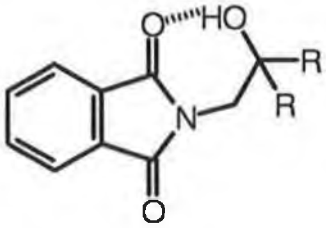
The suggested mechanism involves electron transfer from hydroxyl group to triplet excited phthalimide carbonyl to produce radical cation/anion (290) subsequent intramolecular proton transfer from hydroxyl radical cation to alkoxy radical anion generates biradical (284) which rapidly cleaves to produce species (285) which is isoelectronic with azomethine ylide (286) and benzaldehyde (279). The azomethine ylide (286) can be trapped to form cycloadducts (303) and (304) or internally rearrange to form NMP. The authors make the point that it is a suggested mechanism and it needs further study to clarify. Alcohols are not recognised as efficient electron donors in the excited state SET (single electron transfer) reactions with carbonyl compounds and Kanaoka and co-workers[44] have suggested that formation of intramolecular charge transfer complexes between the phthalimide chromophore and oxygen containing substrates is unlikely because of entropy factors ie the oxidation potentials of alcohols and ethers are not sufficiently low enough to make such an interaction energetically favourable.



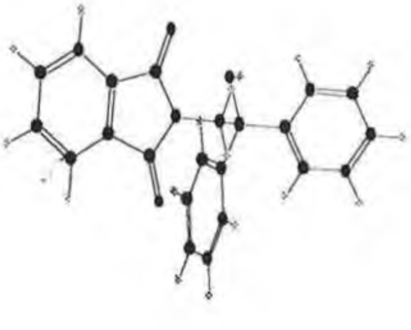
SCHEME 2.35

As was discussed earlier Grisebeck and co-workers have shown[57,54] that whereas phthaloyl α-amino acids (201) undergo a rapid photodecarboxylation phthaloyl amino acids (132) containing carboxylate groups at more remote sites did not show this reactivity. However irradiation of (132, n=3,4,11) in the presence of added base gave rise to cyclised decarboxylated products (133). Both Grisebeck[57] and Kanaoka[51] proposed that the formation of an intramolecular hydrogen bond between carboxylate proton and phthalimide chromophore aids the decarboxylation of phthaloyl α-amino acids (201). Grisebeck proposes that on excitation a primary proton transfer takes place followed by electron transfer from carboylate anion and subsequent decarboxylation yields the observed product (202) (see 1.B.3.7). Such an intramolecular hydrogen bonded complex is not formed with phthaloyl amino acids containing more remote carboxylate groups but if the carboxylate anion is generated with added base then electron transfer can take place and decarboxylation products are found. Whether an actual proton transfer to form carboylate anion is the initial process is unclear but the role of intramolecular hydrogen bonding for the phthaloyl α-amino acids is important.

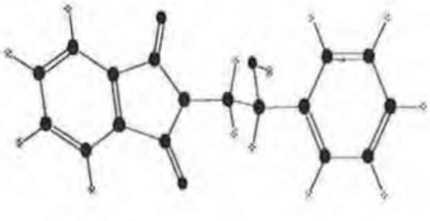
This evidence seemed to indicate that perhaps a hydrogen bonding interaction between hydroxyl group and phthalimido carbonyl may explain the participation of the side chain hydroxyl group in electron transfer initiated fragmentation of the *N*-(2-hydroxyethyl)phthalimides studied. It seems reasonable to assume that formation of a similar intramolecular hydrogen bonded complex could occur for the *N*-phthaloyl β-amino alcohol system (226). To check this hypothesis monophenyl compound (232), diphenyl compound (233) and the γ-carbon unsubstituted compound (254) were examined using a molecular modeling package. The package used was Chem-x^{136} and the minimum energy conformation calculated using simple molecular mechanics minimisation. The results for the three compounds



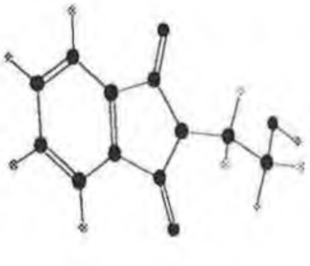
(226)



(233): Energy = 12.311, O-H to C=O distance 2.5 A

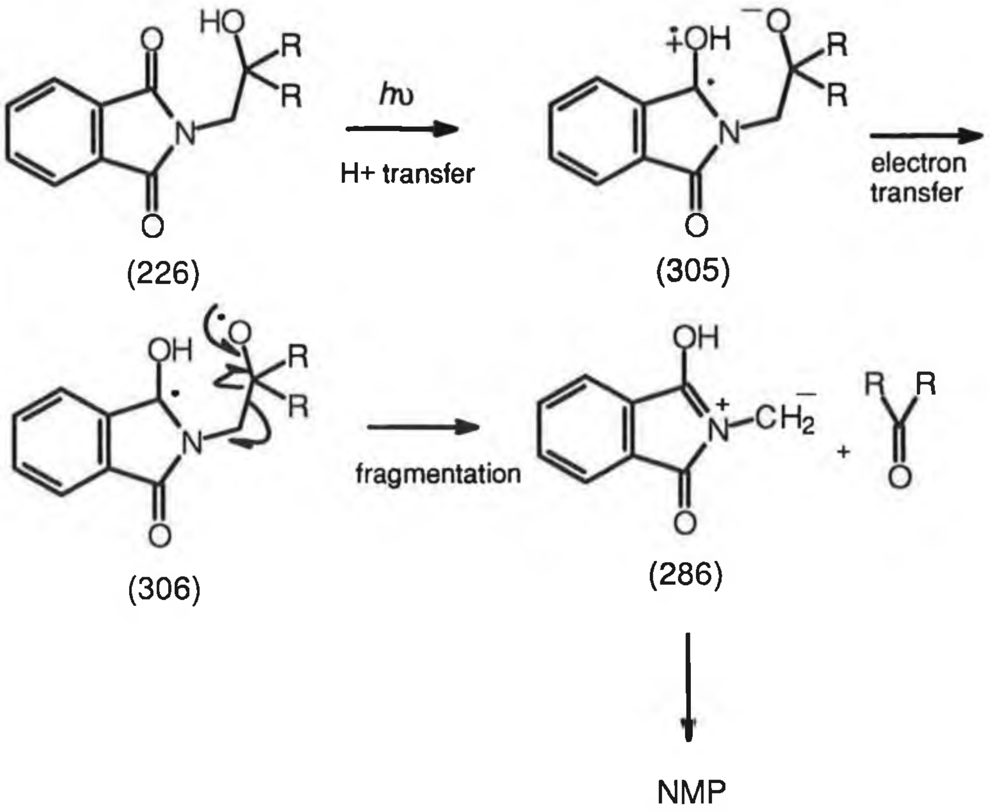


(232): Energy = 3.747, O-H to C=O distance 3.1 A



(254): Energy 1.601, O-H to C=O distance 4.1 A

Fig 2.2: Chem-x minimisations for (233), (232) and (254) showing the lowest energy conformation are shown in *Fig 2.2*. Interestingly *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) showed the shortest hydroxyl to carbonyl distance of 2.5 Angstroms with the unsubstituted compound *N*-(2-hydroxyethyl)phthalimide (254) showing the greatest distance of 4.1 Angstroms, *N*-(2-Hydroxy-2-phenylethyl)phthalimide showed a distance of 3.1 Angstroms. These results are reflected in the relative ease of photofragmentation for the three compounds with the unsubstituted compound (254) unreactive towards γ-fragmentation. The presence of the two phenyl substituents on the γ-carbon seems to orient the hydroxyl group towards the imide carbonyl, the relative energy value of 12.3 for (233) reflects the crowding effect of the two phenyl groups, whereas this value is reduced for to 3.7 for the monophenyl compound (232) and finally the value of 1.6 for the unsubstituted compound reflects a very low energy conformation with the hydroxyl group pointing away from the carbonyl group. The conformations observed here are only crude approximations of the situation in dichloromethane solution where one would expect the use of a non polar solvent to result in an increase in intramolecular interaction between the hydroxyl group and the carbonyl group. However the trend observed here does seem to reflect for the phenyl substituted systems (232) and particularly (233) increased interaction between carbonyl and hydroxyl group. So an analogous mechanism to that proposed for decarboxylation of phthaloyl-α-amino acids could be considered for this system. On irradiation transfer of hydrogen bonded hydroxyl proton to excited phthalimide chromophore generates species (305), subsequent electron transfer from alkoxide generating biradical (306) which cleaves to generate azomethine ylide (286) and carbonyl compound as the observed products (SCHEME 2.36). The total lack of fragmentation associated with the compounds



SCHEME 2.36

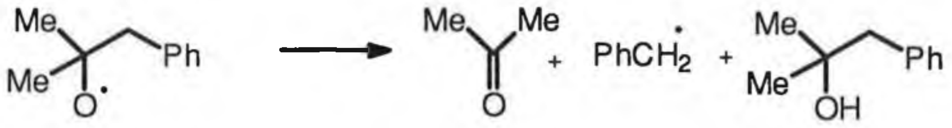
unsubstituted at the γ-carbon of the alkyl side chain *N*-(2-hydroxyethyl) phthalimide (254) and *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) which on prolonged irradiation showed no products of fragmentation and even in the case of (254) under sensitising conditions may be in part due to the inability to form a hydrogen bonded complex.

The radical species (306) proposed as the intermediate leading to the cleavage contains in essence a terminal alkoxy radical. The two competitive unimolecular and bimolecular routes by which alkoxy radicals react in solution are (i) hydrogen abstraction to form alcohol and (ii) fragmentation to form carbonyl compound and alkyl radicals[137] (SCHEME 2.37). The efficiency of the fragmentation reaction (ii) can increase on changing the nature of the substituent R. For example α,α-dimethylphenylethoxy radical (307) cleaves so rapidly to benzyl radical and acetone that only 5% of the tertiary alcohol (308) is detected in the reaction mixture (SCHEME 2.38).[138]

$$R_3C\text{—}O^{\bullet} + RH \longrightarrow R_3C\text{—}OH + R^{\bullet} \quad \text{(i)}$$

$$R_3C\text{—}O^{\bullet} \longrightarrow R_2CO + R^{\bullet} \quad \text{(ii)}$$

SCHEME 2.37

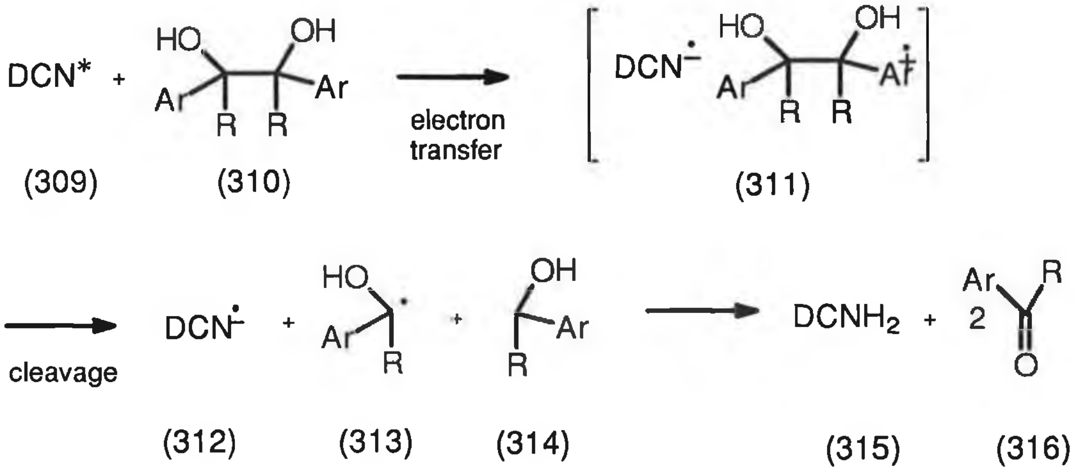


(307) (308)

SCHEME 2.38

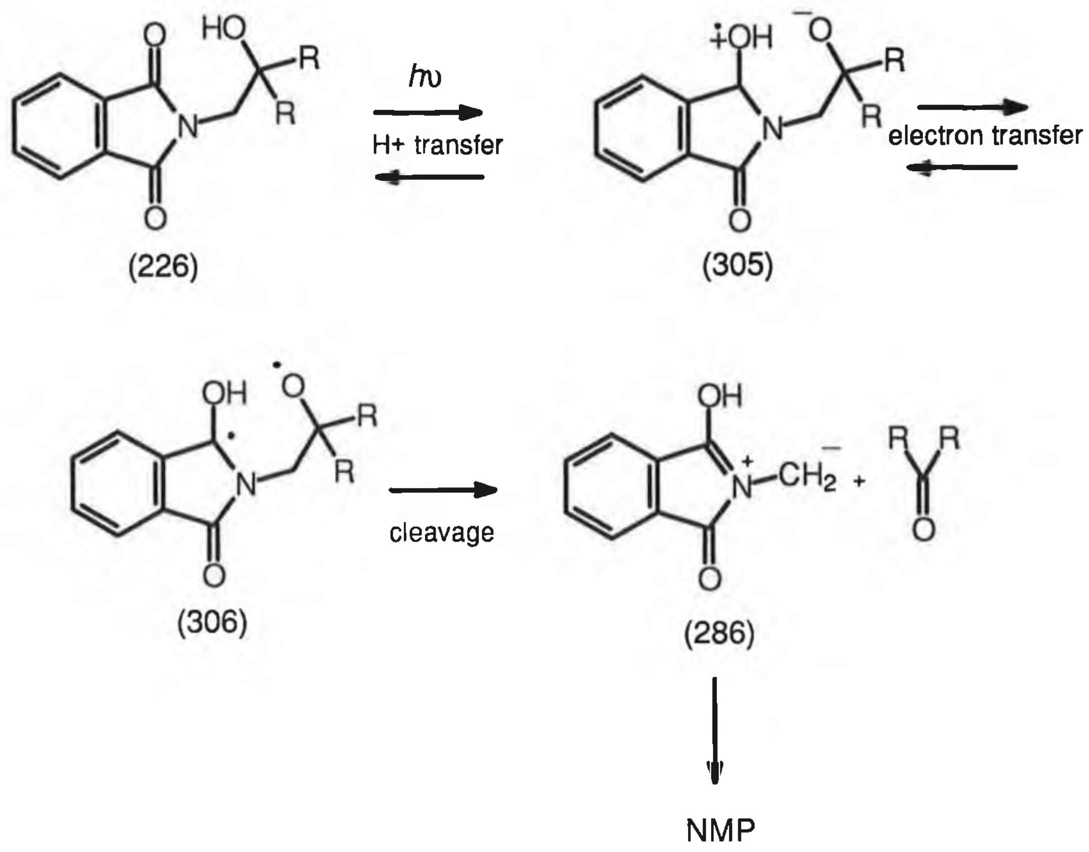
The free energy of activation of the cleavage would be expected to be lowered as the stability of the leaving radical increases with ease of cleavage in the order $C_6H_5CH_2$ >> C_2H_5 > > CH_3. The photochemical fragmentation of the *N*-(2-hydroxyethyl)phthalimides studied can be thought of as a similar cleavage of an alkoxy radical to generate the most stable radical and carbonyl compound. The azomethine ylide (286) generated in the reaction contains a delocalised π system so its formation would be the most thermodynamically favoured. However formation of the azomethine ylide (286) does not explain the role of substituents observed in the reactivity of the *N*-(2-hydroxyethyl)phthalimides.

Oxidative carbon-carbon bond cleavage effected by electron transfer to excited state cyanoaromatics is well known process and has been studied by a number of groups.[139,140,141] Das and co-workers have studied the 1,4 dicyanonaphthalene sensitised irradiation of several systems containing carbon-carbon bonds flanked by aryl substituents and they have shown[142] that cleavage to afford aldehyde and ketone products is very efficient. Among the the systems studued[142] were the aryl pinacols (310) which on irradiation afford two moles of ketone (316) and reduced acceptor (315) (SCHEME 2.39). The mechanism involves electron transfer from pinacol aryl group to excited state dicyanonapthalene (309) to generate radical anion/cation pair (311). Rapid carbon-carbon bond cleavage generates aryl hydroxyl radical (313) and aryl hydroxyl carbocation (314) which reduce



SCHEME 2.39

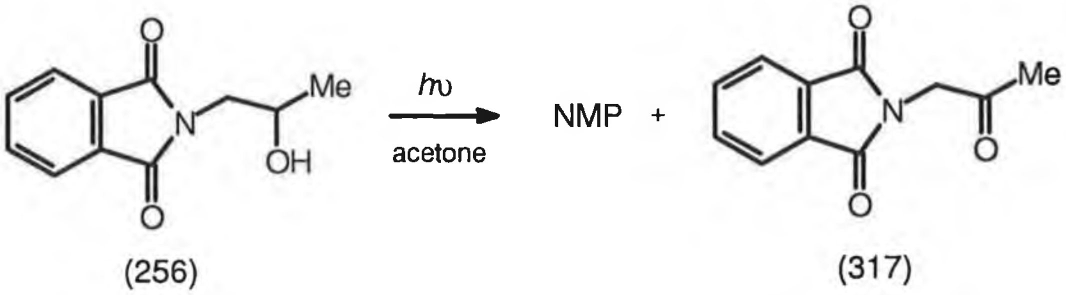
dicyanonaphthalene radical anion (312) to generate carbonyl compound (316) and reduced dicyanonaphthalene (315). Flash photolysis studies[142] indicate that rate of cleavage is higher for aryl pinacols (310) R=Ph over the acetophenone analogue (310) R=Me. This is attributed to larger steric effects in the diaryl substituted radical pairs (311) which lower the carbon-carbon bond energy and lead to greater stabilisation of the radical (313) and carbocation fragments (314). Although mechanistically different from the photofragmentation of *N*-(2-hydroxyethyl)phthalimides (226) both processes involve cleavage of a carbon-carbon bond with a noticeble increase in cleavage efficiency with increased aryl substitution. It seems reasonable to assume that the steric effects of aryl substitution reduce the β–γ bond energy and concomitant stabilisation of the alkoxy radical (306) make cleavage to carbonyl compound and azomethine ylide (286) a thermodynamically favoured process in competition with back electron transfer (SCHEME 2.40).



SCHEME 2.40

However *N*-(2-hydroxyethyl)phthalimide (254) does not have the necessary stabilisation of either an alkyl group or an aryl group at the γ-carbon of the side chain, so cleavage is not competitive with back electron transfer and the products of fragmentation are not observed. In conclusion the results obtained by us indicate that the major photochemical process observed on irradiation of *N*-(2-hydroxyethyl)phthalimides containing either alkyl or aryl substituents on the second carbon of the alkyl side chain is photofragmentation to form *N*-methylphthalimide and carbonyl fragment. The most likely mechanism involves an initial proton transfer from hydrogen bonded side chain hydroxyl group to excited state phthalimide chromophore to generate species (305), followed by intramolecular electron transfer from side chain alkoxide anion to hydroxy radical cation to generate diradical (306) which cleaves to generate azomethine ylide (286) and carbonyl fragment. Azomethine ylide (286) can be trapped by dipolarophiles as was observed by Mariano or rearrange to form *N*-methylphthalimide. The molecular modelling studies and coupled to the observations by Griesbeck concerning photodecarboxylation of phthaloyl α-amino acids[54] indicate that formation of an intramolecular hydrogen bond plays an Important role in the fragmentation, it seems that aryl substitution on the γ-carbon aids formation of such a complex. Also aryl and alkyl substitution on the γ-carbon aid the fragmentation of the radical species (306) via stabilisation and steric effects.

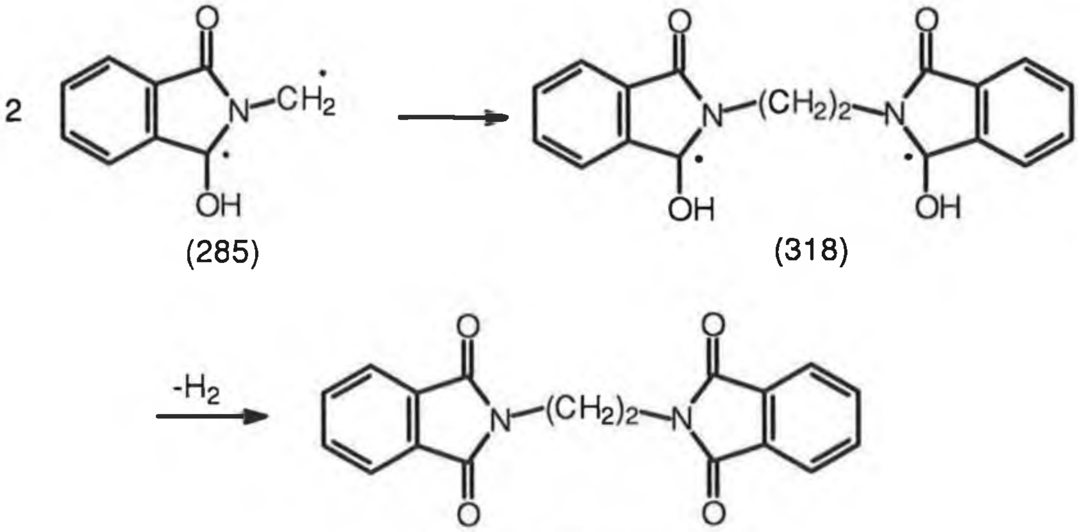
Irradiation of *N*-(2-hydroxy-2-phenyl)phthalimide afforded phenacyl phthalimide (280) the oxidation product in low yield as well as the fragmentation products. The mechanism of its formation is unclear but HPLC studies at low conversion have shown its presence indicating that it is the result of a primary photochemical process. Grisebeck has recently reported[50] the photochemistry of *N*-(2-hydroxypropyl)phthalimide (256) in acetone and reports the formation of *N*-methylphthalimide and the oxidation product 1-phthalimidoacetone (317) after irradiation for four days (SCHEME 2.41).



SCHEME 2.41

Although the oxidised product (317) was not identified by us when the photochemistry of *N*-(2-hydroxypropyl)phthalimide (256) in dichloromethane was examined, the possibilty is that it may have been amongst the minor products observed but since the reaction was very inefficient they were not present in sufficient quantity to be isolated individually. Grisebeck attributes its formation to dehydrogenation of secondary alcohols via hydrogen transfer to solvent molecule.[50] Mariano and co-workers also observed[104] the formation of phenacylphthalimide (280) in low yield on irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in acetonitrile, no explanation for its formation was given. It seems likely that the proposal of hydrogen transfer to solvent or solvent impurities is the most likely explanation.

Bisphthalimidoethane (281) was obtained as a minor product on irradiation of *N*-(2,2-diphenylethyl)phthalimide (233). This product was not isolated or detected in the product mixtures of any of the other compounds studied. A proposed mechanism for its formation might involve a dimerisation of the diradical (285) formed on fragmentation of (233) to give diradical species (318) which subsequently loses hydrogen to solvent to generate bisphthalimidoethane (281) (SCHEME 2.42).



(285)

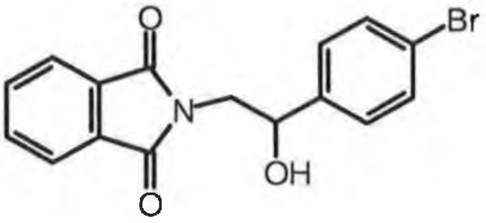
(318)

(281)

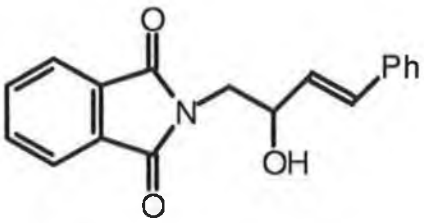
SCHEME 2.42

N-(2-Hydroxy-2-*p*-bromophenylethyl)phthalimide (276) gave rise to a complex mixture on irradiation in dichloromethane. Both *N*-methylphthalimide (NMP) and and *p*-bromobenzaldehyde were identified as products from examination of the proton NMR spectrum of the crude reaction mixture.

However isolation proved impossible. It is thought that the formation of a large number of products is due to photochemical debromination of both the substrate (276) and products which is a well known process for aryl bromine systems.[143] Also *N*-(2-hydroxy-2-styrylethyl)phthalimide (277) gave rise to no appreciable formation of γ-fragmentation products even after prolonged irradiation. It is thought that this may be due to intramolecular quenching of the excited state of the phthalimide chromophore by interaction with the styryl moiety.



(276)



(277)

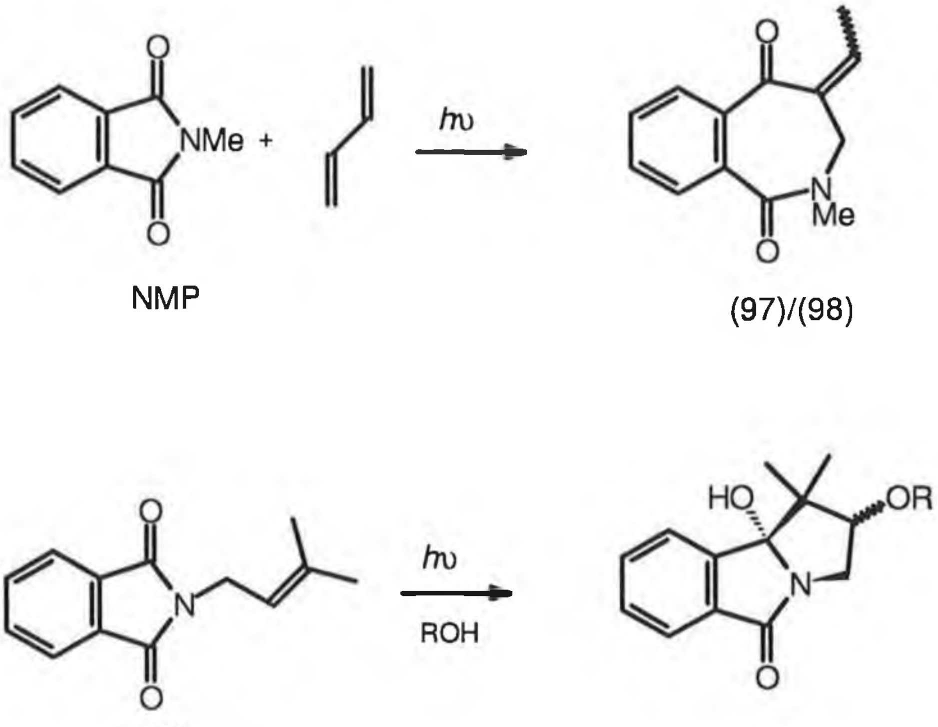
Results and Discussion

CHAPTER 3:

The Photochemistry of some *N*-styrylphthalimides.

3.1 Introduction

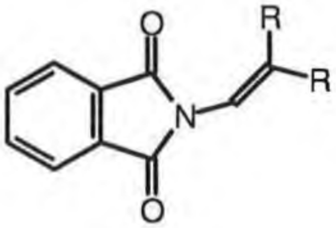
The photochemistry of *N*-substituted phthalimides with alkenes has been studied in detail by a number of groups (see Chapter 2). Mazzochi and co-workers have extensively examined the intermolecular photoreactions of *N*-methylphthalimide (NMP) with alkenes and found that on irradiation of NMP with alkenes with high ionisation potentials an intermolecular addition occurs to afford benzazepinedione systems (97)/(98) (SCHEME 3.1).[41] Maruyama and Kubo have investigated[32] the intramolecular reactions of *N*-(alkenyl) phthalimides and they observed an interesting photocyclisation to give solvent incorporated adducts. An example of this is the formation of solvent incorporated adducts (85)/(86) on irradiation of *N*-(2-alkenyl) phthalimide (83) in alcohols (ROH) (SCHEME 3.1).[32] At the outset of this work there had been no literature reports of the photochemistry of phthalimides conjugated to a vinyl system an "eneimide" such as (319) R=Aryl or H. The photochemistry of the



NMP (97)/(98)

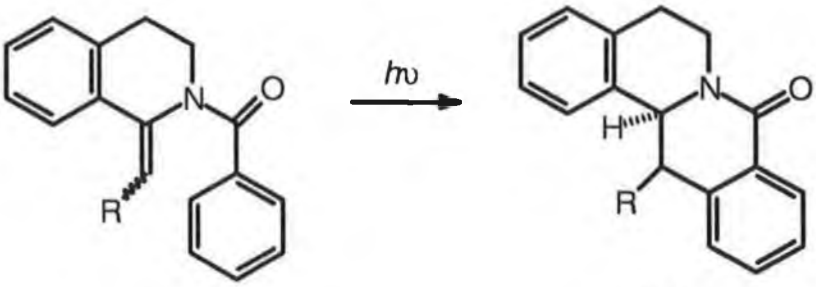
(83) (85)/(86)

SCHEME 3.1



(319)

the structurally related enamides has been extensively studied and they have been shown to produce some interesting synthetic products. Ninomiya, Naito and co-workers reported[150] that irradiation of eneamide (320) afforded the



(320)

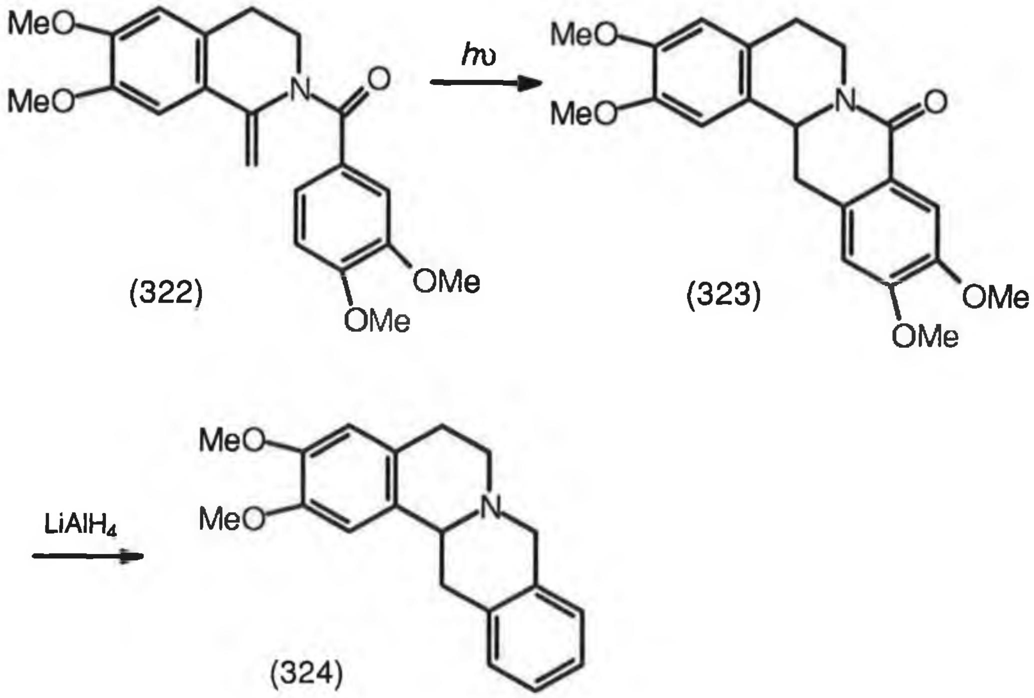
(321)

a: R=Me

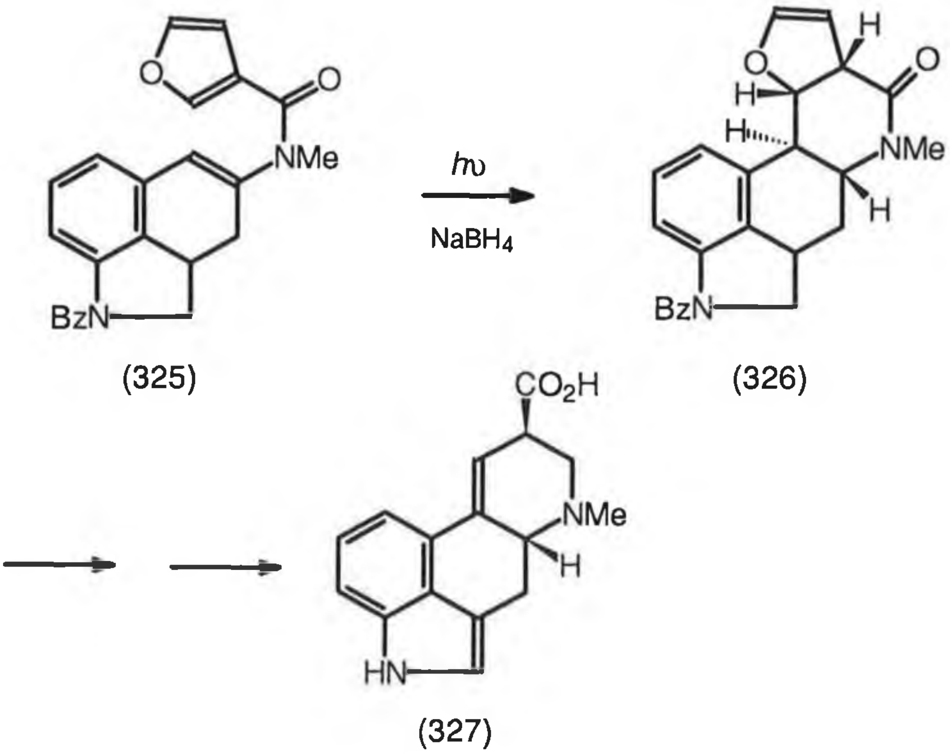
b: R=H

SCHEME 3.2

the fused ring system (321) in good yield (SCHEME 3.2). This photocyclisation was shown to be a useful method for synthesis of proterberine alkaloids such as xylophine (324).[151] Irradiation of eneamide (322) affords cyclised product (323) which on reduction affords (+/-) xylophine (324) (SCHEME 3.3). This photocyclisation of eneamides has also been extended to a reductive photocyclisation procedure which involves reduction in the presence of a complex hydride. [152] A synthetically interesting example of this is irradiation of eneamide (325) in acetonitrile containing sodium borohydride afforded the lactam (326) in good yield.[153] This intermediate was used as a precursor to ergot alkaloids such as lysergic acid (327) (SCHEME 3.4).

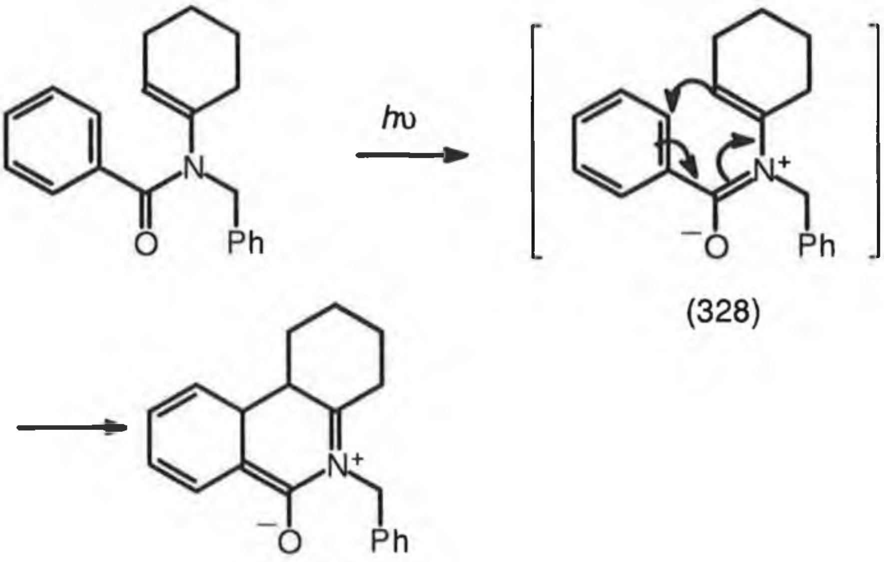


SCHEME 3.3



SCHEME 3.4

The mechanism proposed[152] for these excited state cyclisations is a 6π conrotatory cyclisation of intermediates such as (328) to afford cyclised

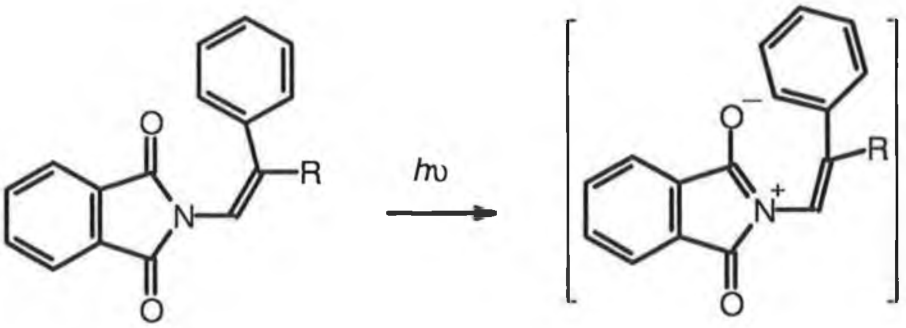


(328)

(329)

SCHEME 3.5

intermediate (329) which on reduction affords the observed products (SCHEME 3.5). We were interested whether on irradiation of a styryl substituted phthalimide such as (330) formation of an analogous intermediate (331) would lead to interesting products.

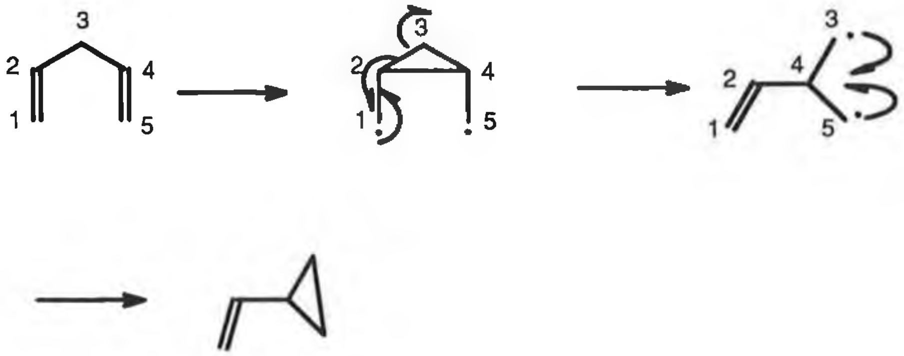


(330)

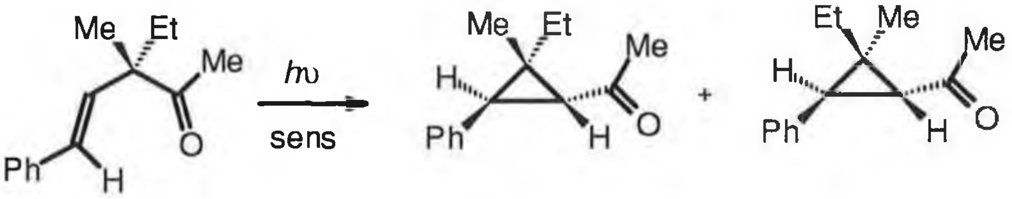
(331)

SCHEME 3.6

Another possible photochemical pathway for the "eneimide" could be in a "di-π-methane" fashion. The "di-π-methane" or Zimmermann rearrangment[154] of dienes having two π systems separated by a sp^3 hybridised carbon atom. It involves a 1,2 shift of one of the π units to the other π group followed by ring closure to a cyclopropane ring between the methylene group and the other end of the nonmigrating π group (SCHEME 3.7). A similar photochemical process occurs for β–γ enones under triplet sensitised conditions and is referred to as the "oxa-di-π-methane" rearrangment.[155] An example of this is the formation of diastereomeric acylcylopropanes (333) and (334) on irradiation of β-γ enone (332) (SCHEME 3.8). Vinyl substituted phthalimides such as (319) can be considered a di π system separated by an sp^3 hybridised nitrogen so a possible route of reaction could be via an oxa-di-π mechanism (SCHEME 3.9). The two possible routes of reaction on irradiation of (319) and formation of cyclopropane intermediate (335) are 1,2 carbon nitrogen bond cleavage and subsequent closure to generate fused aziridine system (336) or 2,3 carbon nitrogen bond cleavage and subsequent ring closure to afford oxaziridine system (337). It was decided to synthesise two compounds *N*-styrylphthalimide

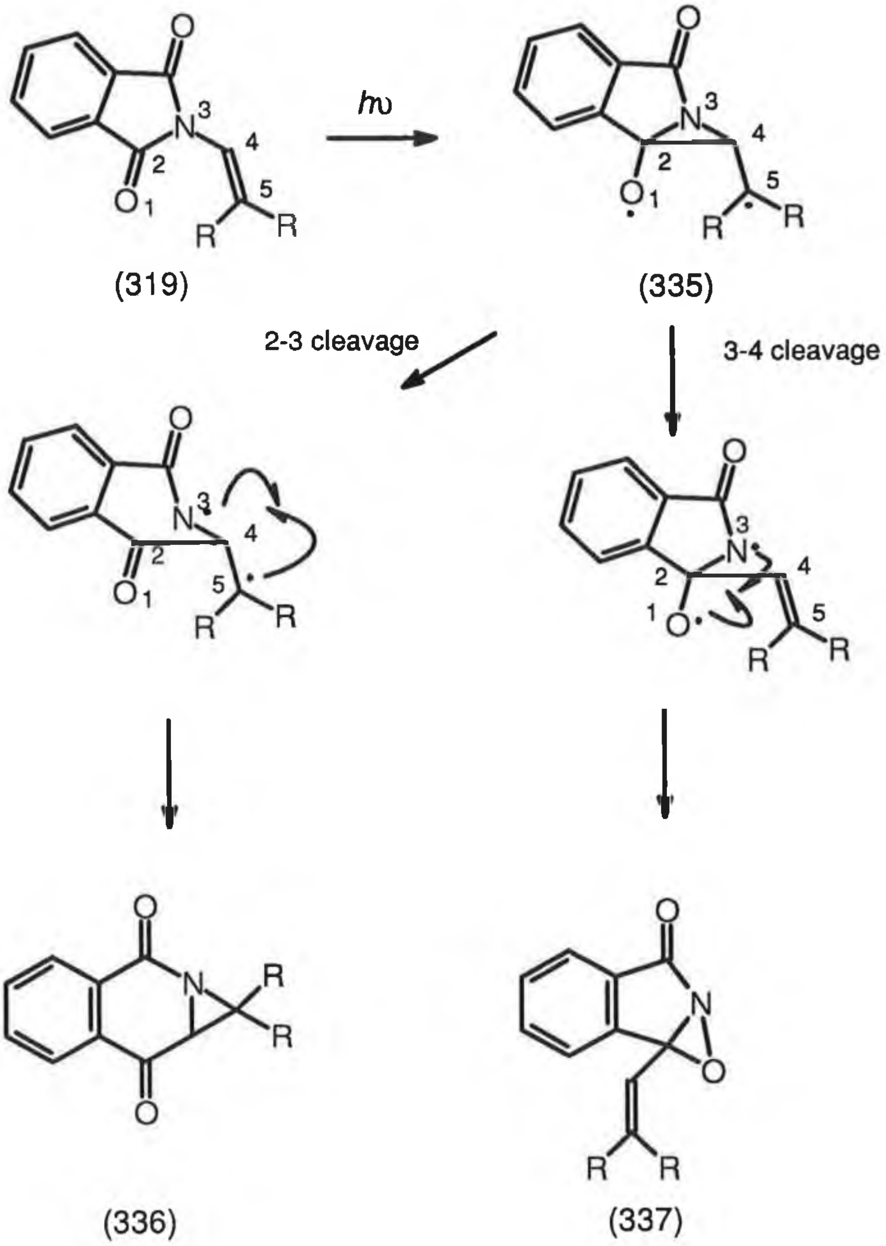


SCHEME 3.7



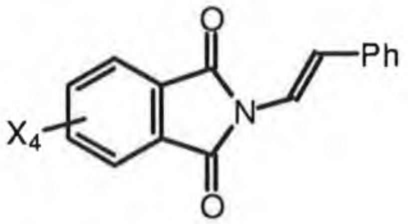
(332) (333) (334)

SCHEME 3.8



SCHEME 3.9

(338) and its tetrachloro analogue (339) and examine the photochemical behaviour of each.

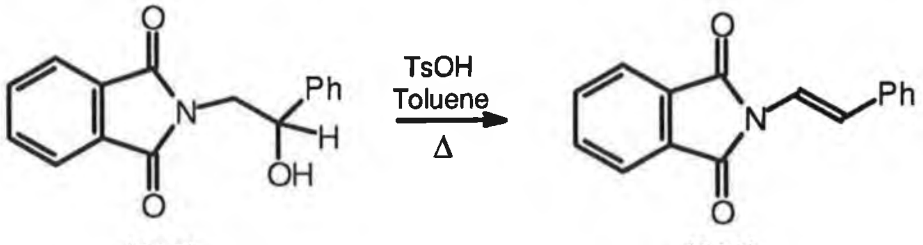


(338): X= H

(339): X= Cl

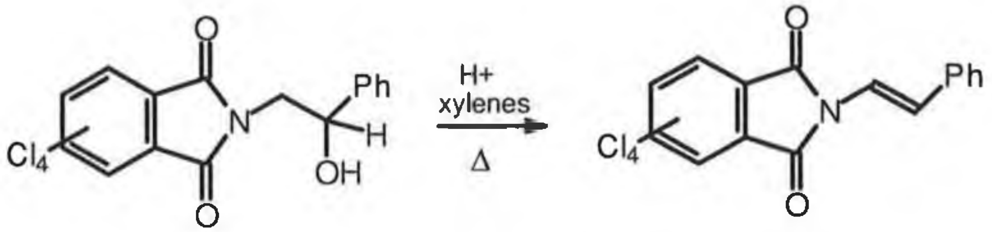
3.2 Synthesis of *N*-styrylphthalimide (338) and *N*-styryltetrachloro phthalimide (339)

It has been reported[112] that (338) could be prepared by heating *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in a furnace at 450°C. It was decided to employ less drastic conditions and the proposed synthesis involved an acid catalysed dehydration of (232). Conventional acid catalysed dehydrations involve use of concentrated mineral acid usually hydrochloric or sulphuric acid however due to possible problems associated with acid lability of the phthalimido group the procedure chosen involved heating a toluene solution of (232) containing a catalytic amount of toluene sulphonic acid under reflux using a Dean and Stark condenser. The progress of the reaction was monitored by TLC and slow formation of a fast running yellow spot was observed, this increased in intensity as the reaction progressed. The reaction times were slow and typically took between 24-30 hours for complete consumption of starting alcohol (232). A TLC observation during the course of the reaction indicated the formation of an intermediate which built up in intensity and subsequently diminished as the reaction approached completion. The identity of this intermediate is unknown but it has been suggested that it is the tosylate ester. Further evidence for this is that increasing the amount of catalyst tended to reduce reaction times. When the reaction was perceived to be complete the toluene solution was washed with water to remove the catalyst, dried and subsequent removal of the solvent afforded *N*-styrylphthalimide (338) as yellow needles (SCHEME 3.10). The infra red spectrum of (338) showed the


(232) (338)

SCHEME 3.10

absence of a hydroxyl absorption and a strong carbonyl absorption. All the signals in the proton NMR spectrum were between 7.24 and 7.93 ppm indicating the absence of aliphatic protons. These were assigned as a symmetrical four proton aromatic phthalimido multiplet between 7.74 and 7.94 ppm, a one proton vinylic doublet (J=15.2 Hz) 7.66 ppm and a six proton multiplet between 7.25 and 7.46 ppm. Expansion of this last region showed a two proton aromatic doublet at 7.48 ppm, a two proton aromatic triplet superimposed upon a one proton aromatic doublet (J=15.2 Hz) between 7.32 and 7.89 ppm and a one proton aromatic triplet between 7.24 and 7.29 ppm which was superimposed by the residual chloroform signal in the NMR solvent. The second vinylic proton although superimposed by the absorptions from the meta aromatic protons could be assigned on the basis of its coupling constant of 15.2 Hz. This vinylic absorption was only observed in dilute solutions on increasing concentration its signal became totally superimposed by that of the aromatic protons. The carbon NMR spectrum contained two vinylic absorptions at 117.5 and 120.0 ppm, seven aromatic absorptions between 123.6 and 135.6 and a carbonyl absorption at 166.3. Both the proton and carbon NMR data was consistent with a dehydration process and the vinylic coupling constant of 15.2 Hz was consistent with the expected *E* geometry for the molecule. A similar procedure was employed for the dehydration of *N*-(2-hydroxy-2-phenylethyl) tetrachlorophthalimide (234). This reaction was found to be even slower and yields considerably lower than was found for the dehydration of the unchlorinated analogue (232). It was found that the best yield of product was obtained using xylene as solvent with a catalytic amount of toluene sulphonic acid and a drop of concentrated sulphuric acid. The reaction mixture was refluxed using a Dean and Stark condenser for two hours followed by work-up as for (338) to afford a brownish solid. The formation of a fast running yellow spot by TLC was indicative of formation of the dehydrated product, however if reaction times were any longer than approximately two hours the reaction mixture turned brown in colour and the formation of other products was observed by TLC. The brownish solid obtained after work-up was purified by chromatography and recrystallisation to afford *N*-styryltetrachlorophthalimide (339) in poor yield (SCHEME 3.11). The infrared spectrum contained no hydroxyl absorption and was very similar to the unchlorinated analogue (338). Both the proton and carbon NMR spectra were similar to (338) with the absence of phthalimido aromatic proton signals. Only one of the vinylic proton doublets could be distinguished from the aromatic signals and its coupling constant of 14.6 Hz was consistent with an *E*-geometry around the vinylic double bond.



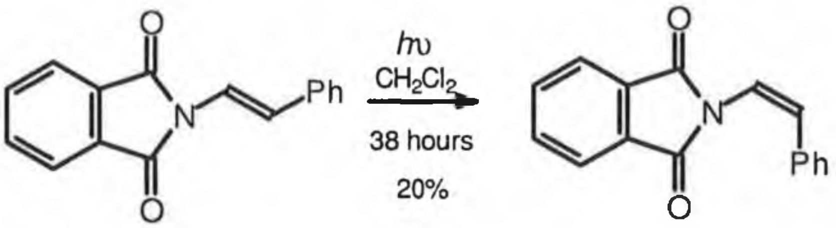
(234)

(339)

SCHEME 3.11

3.3 Irradiation of *E*-*N*-styrylphthalimide (338) in dichloromethane

The photochemistry of this compound was investigated by irradiating solutions in degassed dichloromethane. A preparative photolysis system was used equipped with a medium pressure lamp and Pyrex filter to ensure excitation wavelengths above 300 nm. Dichloromethane was chosen as the solvent as it is photochemically inert above 300 nm and the compound showed reasonable solubility. *E*-*N*-styrylphthalimide (338) was irradiated through Pyrex using dichloromethane as solvent. The reaction was followed by TLC and slow formation of one product was observed. This product was seen to slowly increase in intensity. Prolonged irradiation led to the formation of no other products. On ceasing irradiation after 36 hours the solvent was removed under reduced pressure to afford a yellow solid. Proton NMR analysis of the crude reaction mixture indicated a complex aromatic region and a pair of doublets at 6.25 and 6.63 ppm with identical coupling constants of 8.8 Hz. The crude reaction mixture was separated using a Chromatotron to afford as well as *E*-*N*-styrylphthalimide (338), the observed photoproduct as a light yellow crystalline solid. The infra red spectrum of the isolated photoproduct was almost identical to that of the starting material (338). All the signals in the proton NMR occured between 6.26 and 7.81 ppm. These were assigned as a symmetrical four proton aromatic phthalimido multiplet between 7.65 and 7.81 ppm, a five proton aromatic multiple between 7.12 and 7.22 ppm, a one proton vinylic doublet (J=8.8 Hz) at 6.63 ppm and a second one proton vinylic doublet (J=8.8 Hz) at 6.26 ppm. The carbon NMR spectrum contained two vinylic carbon absorptions at 116.3 and 123.8 ppm, seven aromatic absorptions between 128.0 and 135.0 and a carbonyl absorption at 156.4 ppm. On the basis of this data the sole photoproduct was identified as *Z*-*N*-styrylphthalimide (340). The vinylic coupling constant of 8.8 Hz is consistent with a *Z* geometry around the vinylic bond. The microanalytical data was also consistent with the product being



(338) (340)

SCHEME 3.12

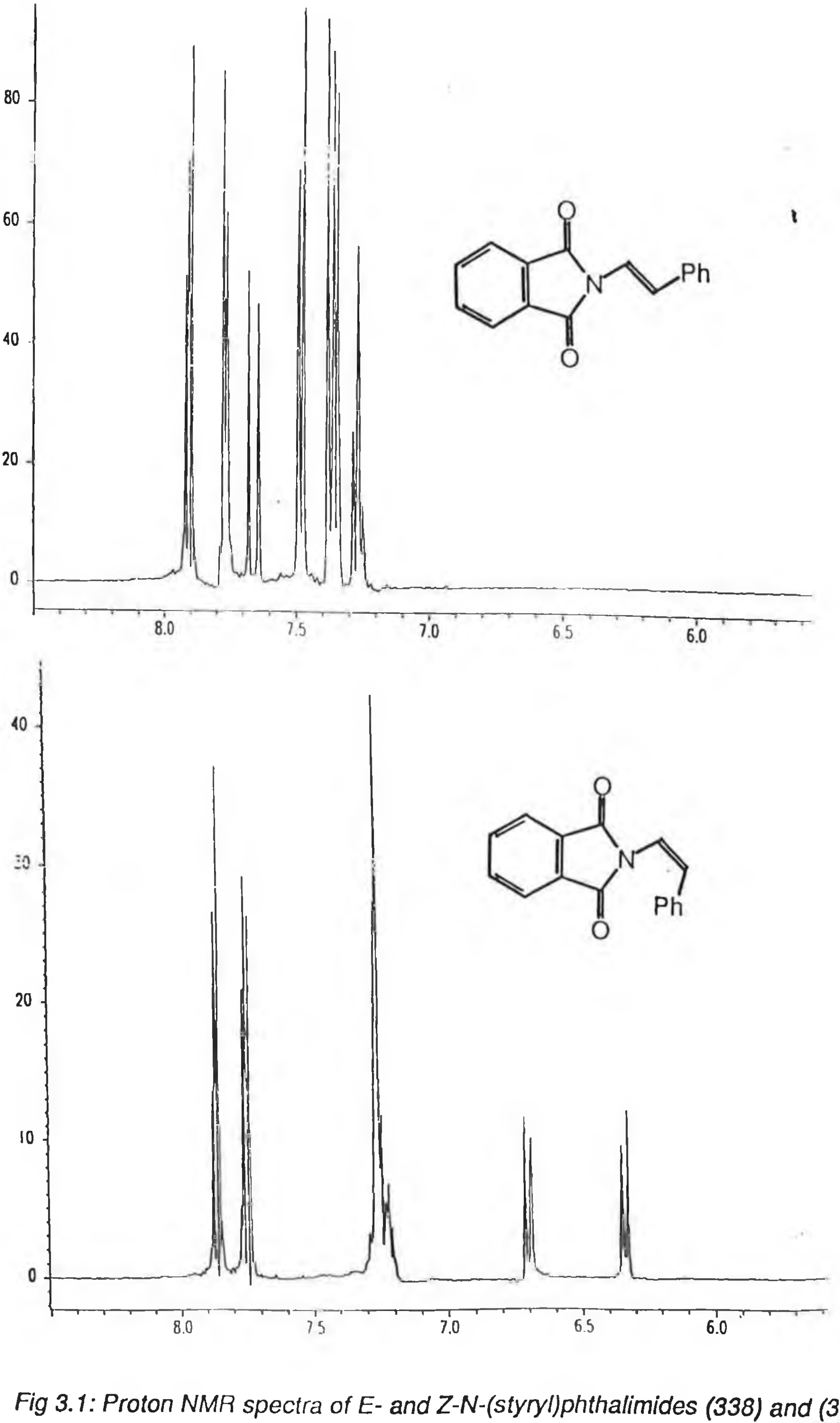
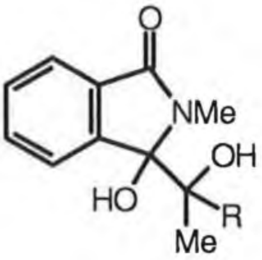


Fig 3.1: Proton NMR spectra of E- and Z-N-(styryl)phthalimides (338) and (340)

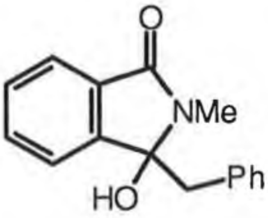
isomeric with the starting material. The sole photoprocess observed on irradiation of *E-N*-styrylphthalimide (338) in dichloromethane is *E-Z* isomerisation (SCHEME 3.12). The proton NMR spectra of both isomers (338) and (340) are shown in *Fig 3.1* demonstrating the difference both in chemical shift and coupling constant for the vinylic protons in each isomer.

3.3.1 Irradiation of *E-N*-styrylphthalimide (338) in active solvents

Dichloromethane does not normally react with excited state species or itself become excited above 300 nm. It was decided to investigate the photochemistry of (338) in active solvents to investigate whether an excited state interaction with solvent would occur. *N*-methylphthalimide (NMP) has been shown to undergo photoaddition reactions with isopropanol[17], toluene[19] and cyclohexene[18] to afford solvent incorporated adducts (26): R= Me, (31)



(26)



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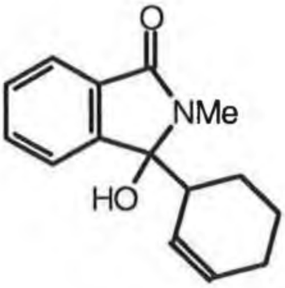
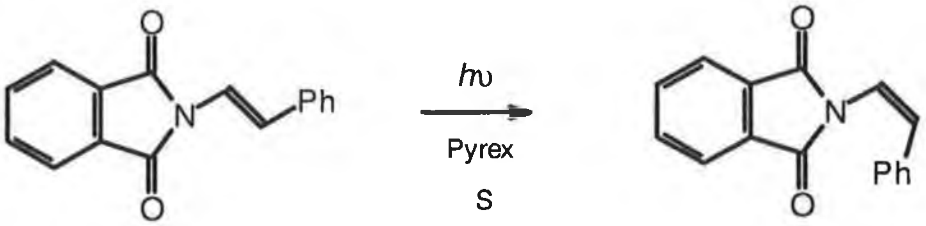


(341)

and (341) respectively. It was of interest to investigate whether a similar process would be observed on irradiation of *E-N*-styrylphthalimide (338) in



(338) (340)

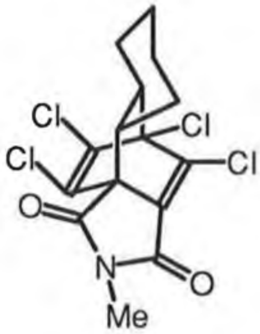
S= dichloromethane/isopropanol, toluene, dichloromethane/cyclohexene

SCHEME 3.13

active solvents. *E*-*N*-Styrylphthalimide (338) was irradiated through Pyrex in isopropanol/dichloromethane, toluene and cyclohexene/dichloromethane (50:50) for prolonged periods. The only process observed was formation of the *Z*-isomer (340) (SCHEME 3.13). In each case the *Z* isomer (340) was isolated and identified by comparison of its infra red and proton NMR spectra with an authentic sample.

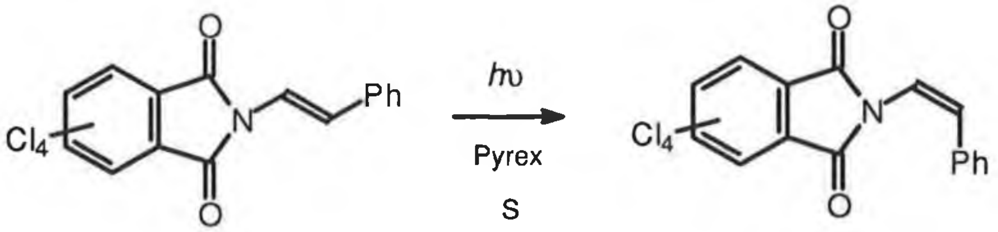
3.4 Irradiation of *E*-*N*-styryltetrachlorophthalimide (339) in dichloromethane

The tetrachloro compound (339) was irradiated in dichloromethane through Pyrex and the reaction was followed by TLC. Slow formation of a number of photoproducts was observed. Irradiation was ceased after 28 hours at which point seven minor products were observable by TLC. The solvent was removed under diminished pressure and proton NMR analysis of the crude reaction mixture indicated a complex mixture containing mainly unreacted starting material. Attempts to isolate individually by chromatography the photoproducts proved unsuccessful. Careful examination of the proton NMR for the crude reaction mixture was inconclusive as to whether *E*-*Z* isomerisation was one of the processes occuring on direct irradiation in dichloromethane. Previous work had indicated[156] that *N*-methyltetrachlorophthalimides on irradiation in the presence of cyclohexene undergo addition to the phthalimido aromatic system



(342)

to afford adduct (342). The tetrachloro compound (339) was irradiated in dichloromethane/cyclohexene (50:50) through Pyrex and the reaction was followed by TLC. The slow formation of one product was observed which after prolonged irradiation showed formation of no other products. The solvent was removed under reduced pressure and the crude reaction mixture was separated by flash chromatography to afford the sole photoproduct as a white crystalline solid. The infra-red spectrum of the product was almost identical to that of the starting material. The proton NMR spectrum contained all absorptions between 6.26 and 7.26 ppm. These signals were assigned as a five proton aromatic multiplet between 7.19 and 7.26 ppm, a one proton vinylic doublet (J=9.24 Hz) at 6.76 ppm and a one proton vinylic doublet (J=9.24 Hz) at 6.27 ppm. The carbon NMR spectrum contained two vinylic absorptions at 115.5 ppm and 127.5 ppm, seven aromatic absorptions between 128.0 and 140.5 ppm and a carbonyl absorption at 161.5 ppm. The photoproduct was identified by virtue of this data as *Z*-*N*-styryl tetrachlorophthalimide (343). The microanalytical data was also consistent with the product being isomeric with the starting material. The clean formation of the *Z* isomer (343) on irradiation of (339) in dichloromethane/cyclohexene (SCHEME 3.14) as opposed to straight dichloromethane prompted an investigation as to whether the photoreaction observed was as a result of an electronic interaction between cyclohexene and the phthalimido excited state or as a result of the considerable reduction in polarity on irradiation in cyclohexene. The tetrachloro compound (339) was irradiated through Pyrex in light petroleum/dichloromethane (3:1), the reaction



(339) (343)

S= dichloromethane/cyclohexene, dichloromethane/light petroleum

SCHEME 3.14

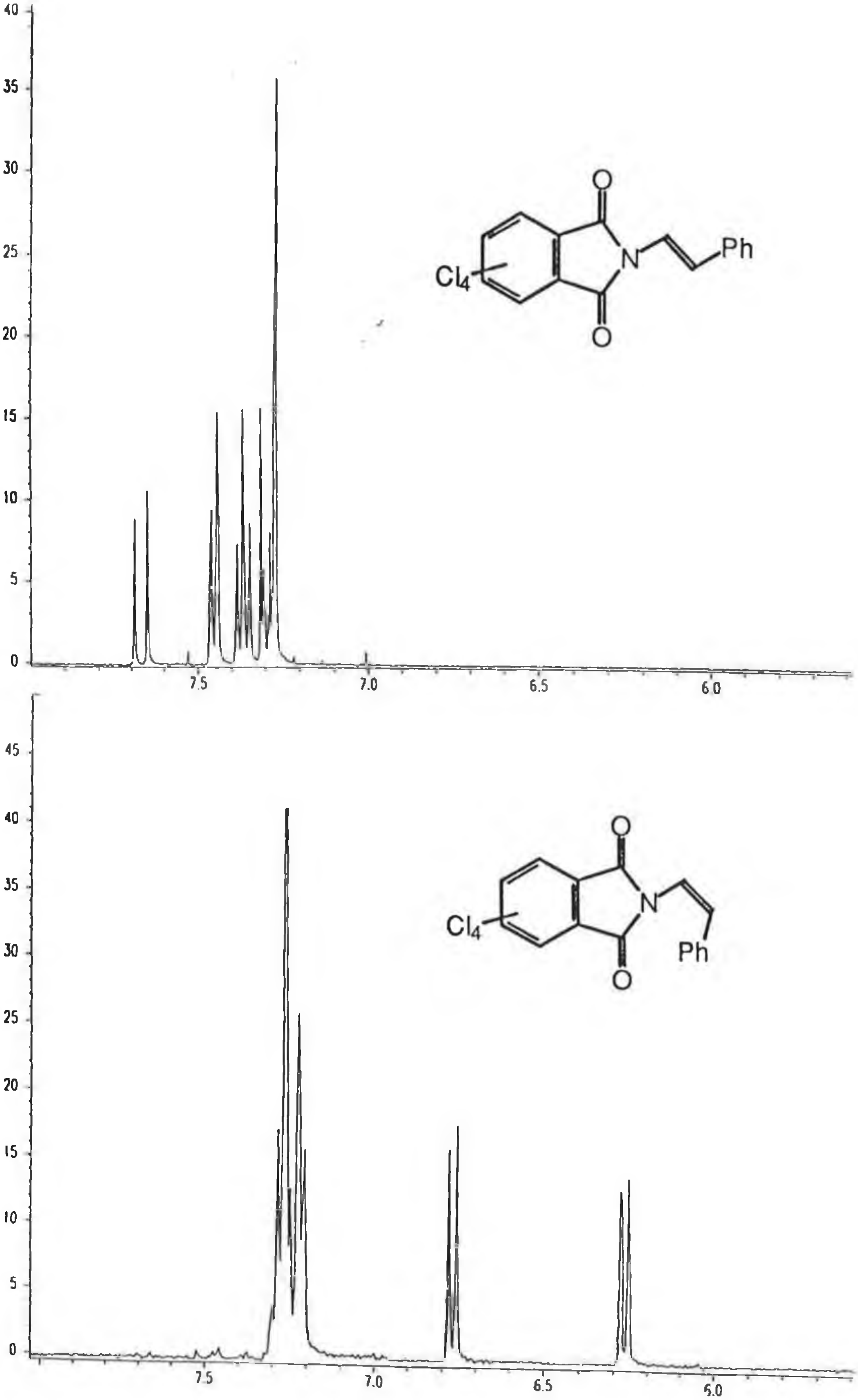


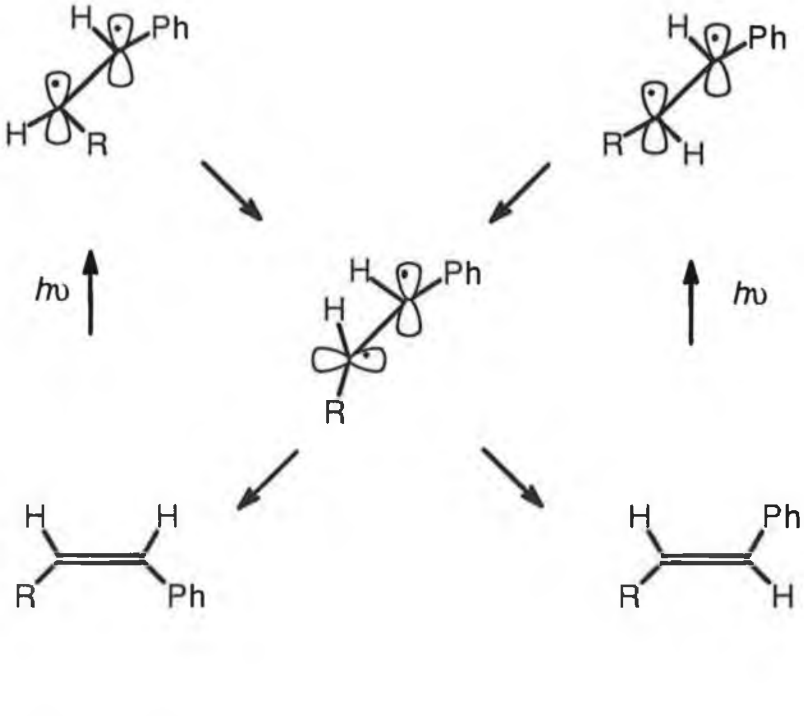
Fig 3.2: Proton NMR spectra of E- and Z-N-(styryl)tetrachlorophthalimides (339) and (343).

was followed by TLC and slow formation of one product was observed. On ceasing irradiation the solvent was removed and the reaction mixture was separated by chromatography to afford *Z-N*-styryltetrachlorophthalimide (343) as the sole photoproduct (SCHEME 3.14). The proton NMR spectra of both isomers (339) and (343) are shown in *Fig 3.2.*

3.5 Discussion

3.5.1 Irradiation of *E-N*-styrylphthalimide

The only product observed on irradiation of *E-N*-styrylphthalimide (338) in dichloromethane was the formation of the corresponding *Z* isomer (340). The formation of photoreduced or photoaddition products was not observed on irradiation in the presence of isopropyl alcohol, toluene and cyclohexene in contrast to what was observed for *N*-alkylphthalimides. This lack of reaction is perhaps not too surprising since geometrical isomerisation is the most facile photochemical process for disubstituted alkenes. On initial excitation of *E* and



R= phthalimido

SCHEME 3.15

Z ethenes the first excited state retains the same geometry as that of the corresponding ground state. In these states there is effectively no π bond so the central bond may rotate to give the lowest energy conformation where there is a 90^{o} angle of twist from the initially formed excited state or "vertical" state so that the adjacent p orbitals are orthogonal to each other. This so called "non-vertical" state can then via radiationless decay lead to either geometrical isomer (SCHEME 3.15). The vinyl imides studied here contain a conjugated π system so on excitation there may be a large number of possible contributions to the excited state which would make even the process of *E-Z* isomerisation diffucult to totally rationalise. The isolated yield of *Z-N*-styrylphthalimide (340) obtained for direct irradiation of (338) through Pyrex in a number of solvent systems studied was approximately 20%-30%. It seems likely that a true photostationary state was not attained for these compounds even after 38 hours irradiation. Since one would expect that in an analogous manner[157] to stilbene systems the photostationary state for these compounds would contain a greater proportion of the Z isomer (340), taking into account the wavelength of the incident radiation which is above 300nm with the most intense line being at 313nm and the relative extinction coefficients for each isomer at 310nm being 3,650 $dm^3\ mol^{-1}\ cm^{-1}$and 19,500 $dm^3\ mol^{-1}cm^{-1}$ for the *Z* and *E* isomers respectively. However it seems that the irradiation times required to attain such a state would be extremely long. This also suggests that alternative processes both radiaitive and non-radiative may also be involved in deactivation of the excited state. As was mentioned the excited state of these systems is quite complicated and direct comparison to stilbene systems is not very appilicable in the sense that the chromophore contains both phthalimido and styryl contribution. Isopropyl alcohol in particular is known as a very efficient hydrogen donor solvent in the excited state reactions of carbonyl compounds and the lack of intermolecular photoreaction with *E/Z-N*-styrylphthalimide indicates efficient deactivation through formation of a non-vertical state which can then relax to form either isomer, or other photophysical processes which were not investigated.

3.5.2 Irradiation of *E-N*-styryltetrachlorophthalimide (339)

On irradiation of this compound in dichloromethane slow photodegradation to form at least seven products was observed by TLC. The nature of these products is unknown due to the difficulty of isolating them individually, however on irradiation in cyclohexene/dichloromethane 50:50 formation of one product was observed which was identified as the Z isomer (343). It was thought that the observed *E/Z* isomerisation may be due to an electronic interaction between excited state tetrachlorophthalimide species and cyclohexene or a result of the considerable reduction in polarity on changing from neat dichloromethane to a solution containg 50% cyclohexene. This hypothesis was checked by irradiating *E-N*-styryltetrachlorophthalimide in a solution of light petroleum/dichloromethane (3:1) and it was found that *E/Z* isomerisation was the only photoprocess observed indicating that the reduction in polarity was the most probable cause of the observed *E/Z* isomerisation. Coyle has suggested[16] that that the (n, π^*) and (π, π^*) excited states of *N*-substituted phthalimides are quite close energetically, a change in solvent polarity may well lead to an inversion of these states and a change in the observed photochemistry. A similar process may be occurring here or the change in polarity may be leading to quenching of the excited state responsible for the photodegradation observed on direct irradiation in dichloromethane.

In conclusion the principle aim of studying the photochemistry of the vinyl imides (338) and (339) was to investigate whether interaction of the vinyl group with the phthalimide group would lead to interesting synthetic products. However the only photochemical reaction observed was *E-Z* isomerisation for both compounds.

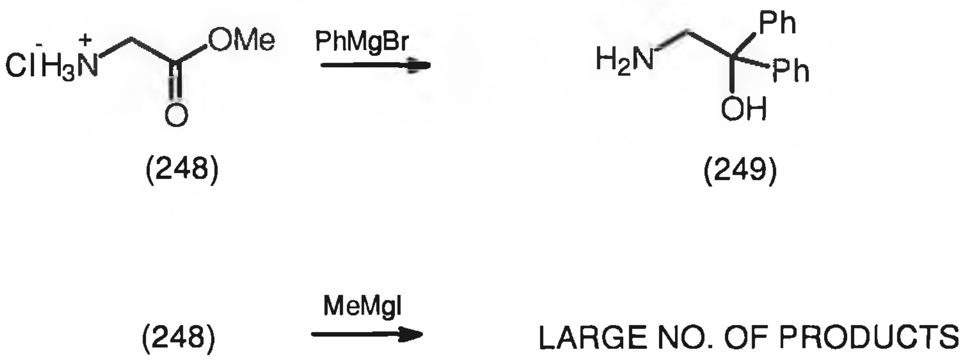
Results and Discussion

CHAPTER 4:

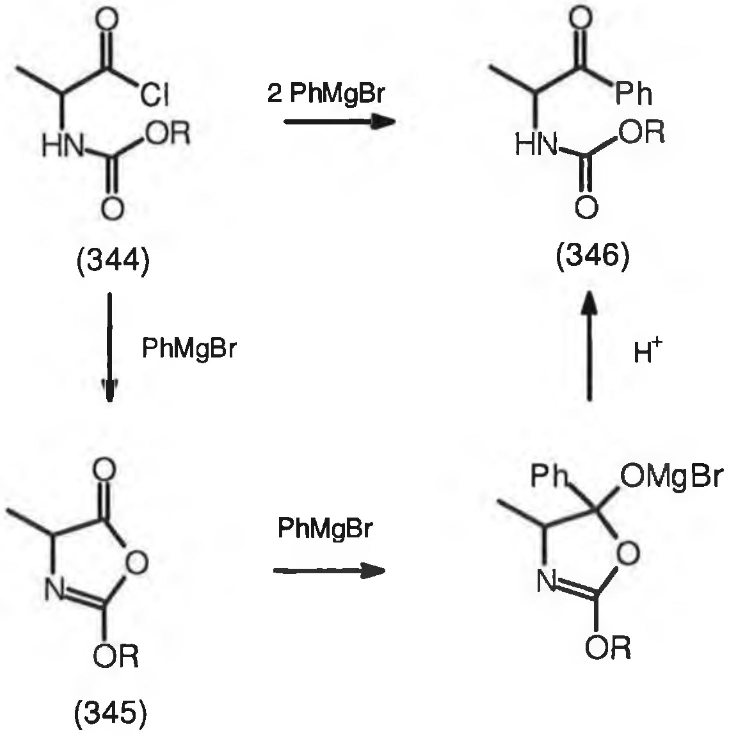
The addition of Alkyl Grignard Reagents to some *N*-phthaloyl-α-amino acid methyl esters.

4.1 Intoduction

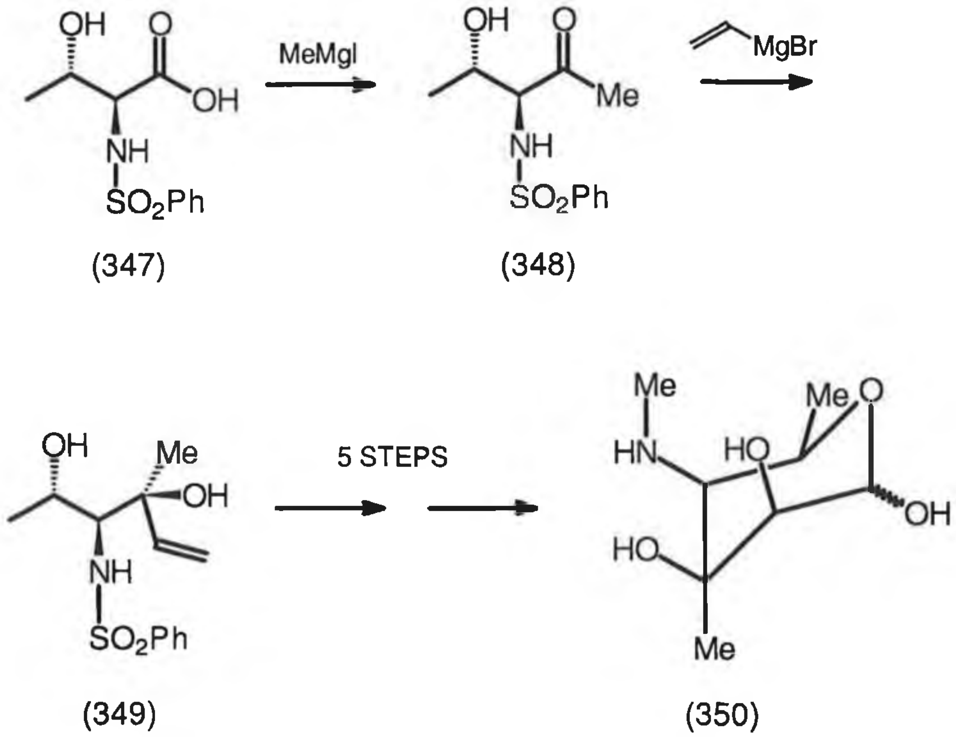
The addition of excess phenyl magnesium bromide to glycine methyl ester hydrochloride (248) has been shown to afford 1-amino-2,2-diphenyl ethanol (249) in reasonable yield (see section 2.3) (SCHEME 4.1). It was of interest to investigate whether this reaction could be extended to the synthesis of 2,2-dialkyl substituted amino ethanols. However treatment of glycine methyl ester hydrochloride (248) with an excess of methyl magnesium iodide afforded a large mixture of products (SCHEME 4.1). Einhorn and co-workers[120] have also reported the formation of useless mixtures on addition of alkyl Grignard reagents to α-amino ester hydrochlorides. A number of workers have investigated the addition of Grignard reagents to *N*-protected α-amino acids and their derivatives in both the synthesis of *N*-protected amino ketones or *N*-protected dialkyl or diaryl substituted amino alcohols. Rappoport and co-workers have shown[158] that treatment of *N*-ethoxycarbonyl alanine acid chloride (344) with two equivalents of Grignard reagent affords the *N*-protected amino ketone (346) in good yield (SCHEME 4.2). The requirement of two equivalents of Grignard reagent suggest that the first equivalent is involved in formation of oxazoline (345) and the second equivalent of Grignard reagent attacks the oxazoline carbonyl leaving the ring system intact until aqueous hydrolysis liberates the aryl ketone (346). The use of other *N*-protecting groups such as acetyl, benzoyl and phenyl as well as alkyl and vinyl Grignard reagents



SCHEME 4.1



SCHEME 4.2

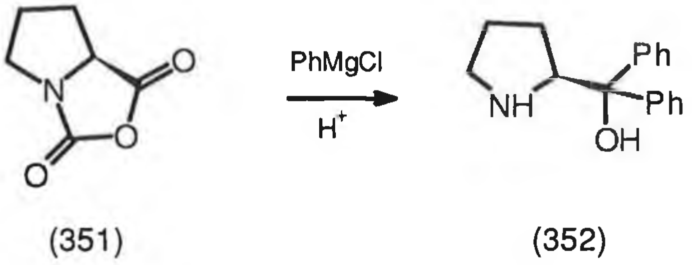


SCHEME 4.3

have also been examined[159] and shown to afford the alkyl or aryl substituted amino ketone as the major product. Rappoport and co-workers used this methodology towards the synthesis of the amino sugar methyl-*L*-sibirosaminide

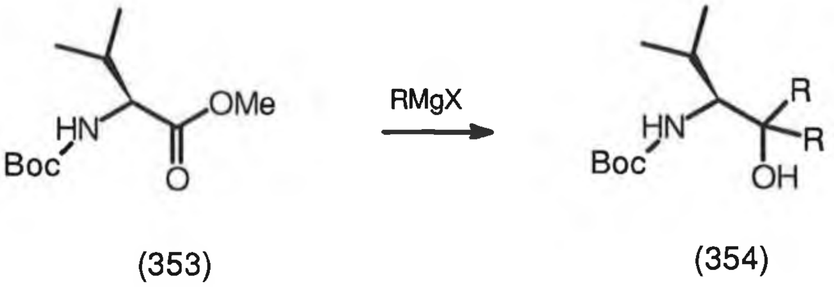
(350) (SCHEME 4.3).[160] The initial steps involved conversion of the *N*-phenylsulfonyl allo theronine (347) to its methyl ketone (348). Subsequent addition of vinyl magnesium bromide affords diol (349) which is converted in subsequent steps to amino sugar (350).

The formation of amino alcohols by addition of Grignard reagents to amino acid derivatives has been less extensively studied. Mathre and co-workers showed[161] that diaryl-2-pyrolidine methanol (352) could be synthesised in



SCHEME 4.4

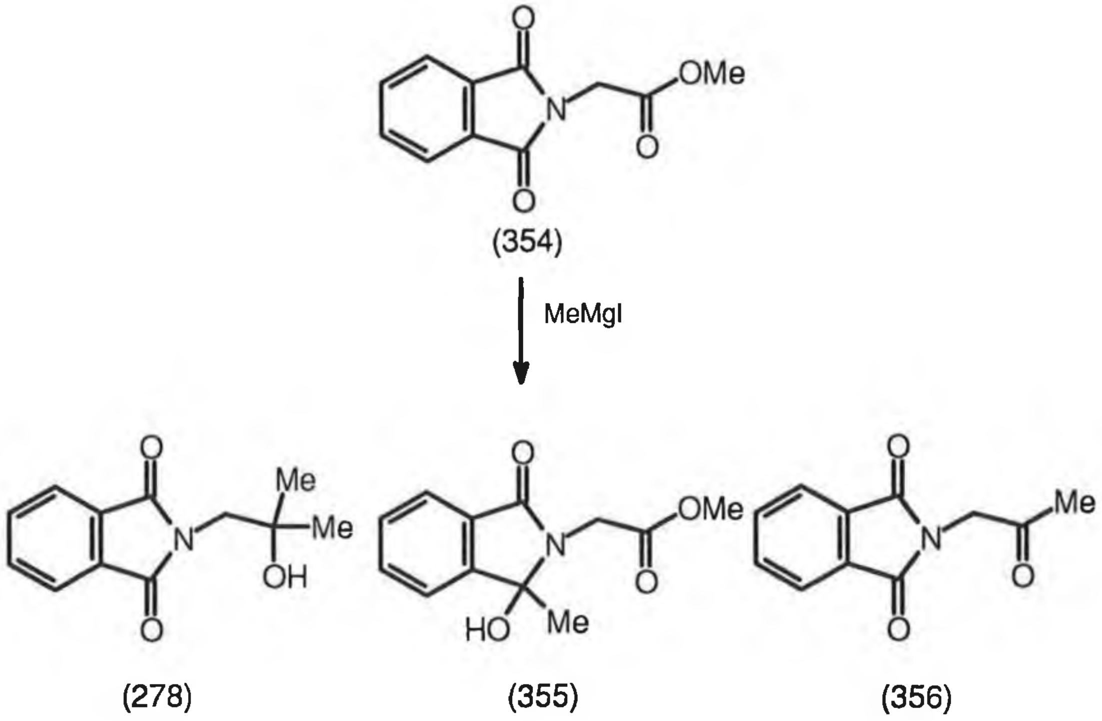
good yield by treatment of proline *N*-carboxyanhydride (351) with phenyl magnesium chloride with almost no racemisation (SCHEME 4.4). Einhorn and Luche suggest[120] that for efficient synthesis of 2,2-dialkylsubstituted 1-amino ethanols from α-amino acid alkyl esters the amino group should be mono protected with an electron withdrawing group. These workers found that treatment of *N*-boc protected amino acid esters (352) with alkyl magnesium



R= Me, nBu, nDec

SCHEME 4.5

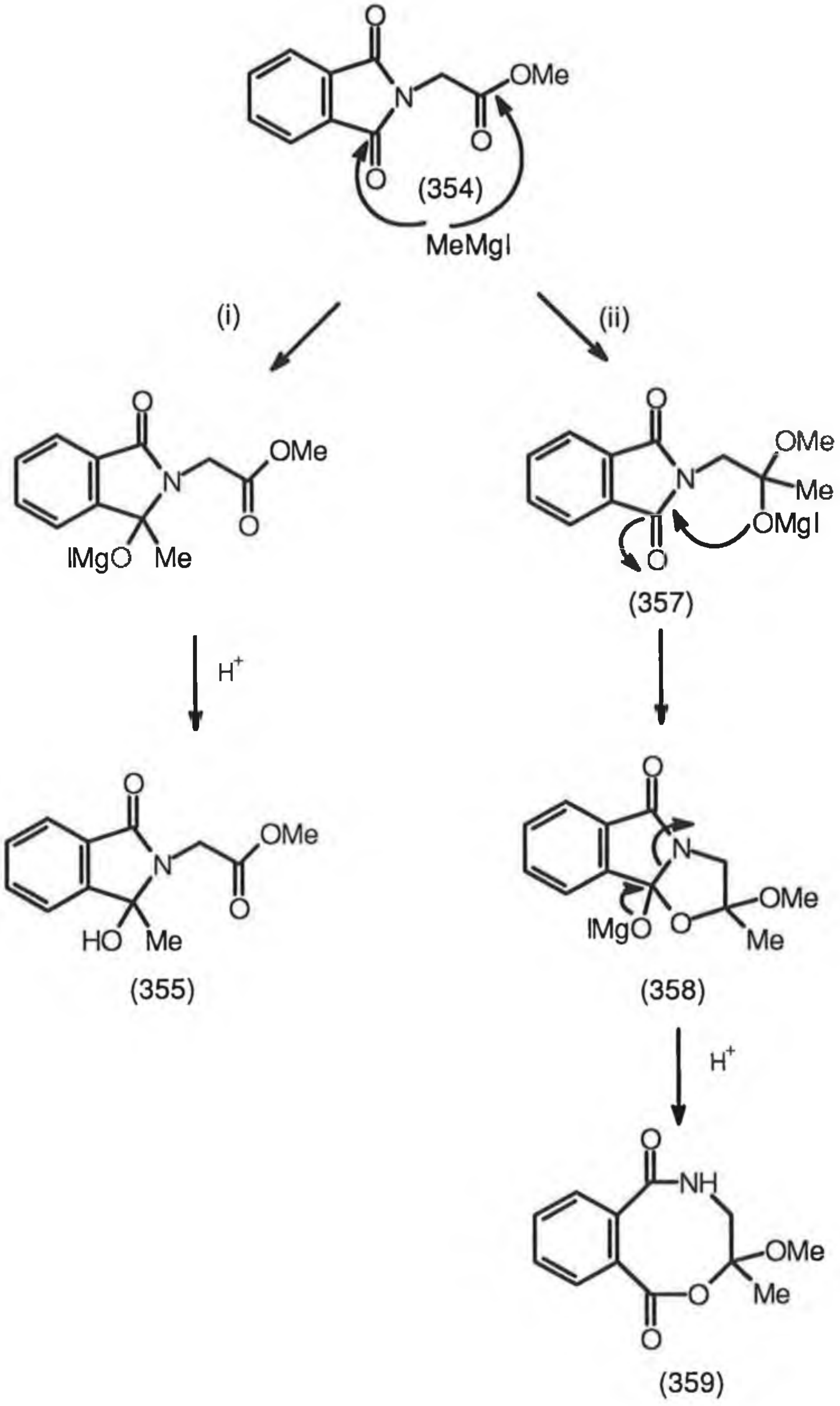
reagents affords the dialkyl substituted amino alcohols (353) in good yield with little or no racemisation (SCHEME 4.5). It was thought since a protecting group seems to be required for efficient addition of alkyl Grignard reagents to α-amino acid esters, that treatment of phthaloyl protected amino acid ester with alkyl Grignard reagent may furnish the desired phthaloyl protected 2,2-dialkyl substituted amino ethanol directly. A comprehensive literature search indicated that there are no reports of addition of Grignard reagents to phthaloyl protected α-amino acid esters. Literature reports of addition of Grignard reagents to simple *N*-alkyl phthalimides indicate that addition to imide carbonyl is sluggish.[162] The product profile expected on addition of an excess of methyl magnesium bromide to phthaloyl glycine methyl ester (354) was expected to afford the phthaloyl-2,2-dimethylamino ethanol (278) as the major product with the methyl carbinol (355) and the methyl ketone (356) as minor products (SCHEME 4.6)



SCHEME 4.6

4.2 Addition of methylmagnesium iodide to phthaloyl glycine methyl ester.

Phthaloyl glycine methyl ester (354) was treated with an excess of methyl magnesium iodide to afford after work up a purple oily solid. TLC analysis of this solid indicated that it consisted of one major product. Purification by flash chromatography yielded the major product as a white crystalline solid. The proton NMR spectrum contained a three proton singlet at 1.61 ppm, a three proton singlet at 3.67 ppm, a one proton doublet at at 3.81 ppm (J= 17.7 Hz) a one proton singlet at 4.00 ppm, a one proton doublet at 4.20 ppm (J= 17.7 Hz) and a four proton non symmetrical aromatic multiplet between 7.53 and 7.70 ppm. The number of distinct signals and the non-symmetrical nature of the aromatic multiplet indicated that this was not the expected phthaloyl-2,2-dimethyl amino ethanol (278). The carbon NMR spectrum confirmed this with aliphatic signals at 23.2 ppm, 38.9 ppm, 52.1 ppm, a quaternary signal at 91.8 ppm, six aromatic carbon signals between 121.4 and 146.9 ppm and two carbonyl signals at 168.0 and 171.2 ppm. The Dept 135 spectrum showed seven carbons bearing hydrogen and combined with the C-H correlation spectrum confirmed the proton singlet at 1.61 ppm to be a methyl group. The singlet at 3.67 ppm was assigned as a methoxy group, the doublets at 3.81 ppm and 4.20 ppm were assigned as a diastereotopic methylene protons and the singlet at 4.0 ppm was assigned as a hydroxy or amide proton. This was confirmed by its disappearance from the proton NMR spectrum on shaking with deuterium oxide. The NMR data indicated that the addition of only one methyl group had occurred, the methoxy group had been retained and the non-symmetrical nature of the aromatic protons indicated that the phthalimide group was no longer intact. Examination of the infra-red spectrum showed a strong absorption at 3318 cm^{-1}, two carbonyl absorptions at 1746 and 1677 cm^{-1}. The microanalytical data was also consistent with addition of one methyl group and retention of the methoxy group. On the basis of these data two possible structures were considered possible for the major product observed in this system. The two possible modes of reaction considered for this system are (SCHEME 4.7, (i)), attack at imide carbonyl which would yield after acidic quenching carbinol (355). The other being (SCHEME 4.8, (ii)), attack at ester

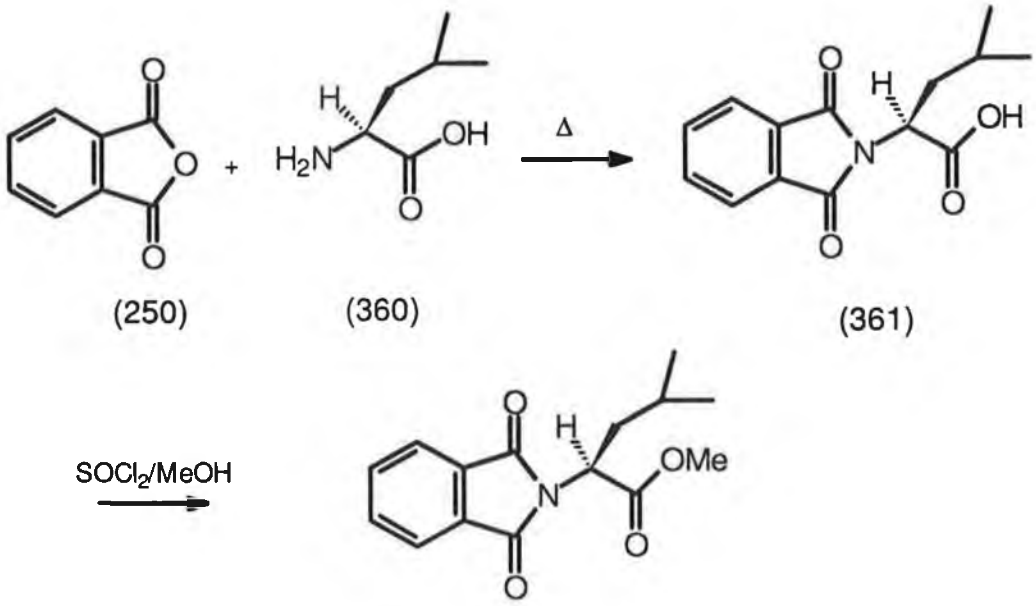


SCHEME 4.8

carbonyl to yield alkoxy magnesium species (357) which intramolecularly attacks imide carbonyl to yield ring closed species (358), which subsequently reopens to form benzoxazocine (359). Both products are consistent with the addition of one equivalent of Grignard reagent and retention of the methoxy group. The diastereotopic nature of the methylene protons in the proton NMR spectrum indicates the presence of a chiral centre in the product. Diastereotopicity of methylene protons is usually as a result of the methylene protons being α to the chiral centre as they are in benzoxazocine (359), however the methylene protons in the carbinol (355) may also be non equivalent due to restricted rotation around the nitrogen-carbon bond of the side chain. The infrared spectrum contains a strong sharp absorption at 3318 cm^{-1}, this may be due to either an amide stretch or a hydrogen bonded hydroxy stretch. It was thought that the ester carbonyl of the side chain would be more reactive towards nucleophillic attack by Grignard reagent compared to imide carbonyl and previous literature reports suggest[162] the imide carbonyl was sluggishly reactive towards Grignard reagents and generally heating was required. The reaction was repeated with this in mind at low temperature with addition of methyl Grignard to etheral solution of phthaloyl-glycine methyl ester maintained at approximately -80 ^{o}C using a toluene/liquid nitrogen slush bath. The reaction afforded a white crystalline solid. TLC analysis indicated that complete conversion to one product had occurred which had an identical R_f to the product isolated from the room temperature reaction. This was confirmed when spectral analysis indicated that the product was identical. Slow crystalisation of the product gave rise to crystals which were deemed suitable for X-ray analysis however these crystals were unstable in the diffractometer. It was decided to examine the addition of Grignard reagent to another phthaloyl amino acid ester in the hope that it would produce suitable crystals.

4.3 Addition of methylmagnesium iodide to phthaloyl-*L*-leucine methyl ester

Phthaloyl-*L*-leucine methyl ester (362) was synthesised according to modifications of methods reported by Sheehan[163] and Grisebeck.[48] All spectral details were consistent with the assigned structure (SCHEME 4.9).



(250) (360) (361)

(362)

SCHEME 4.9

Treatment of this phthaloyl α-amino acid ester with methyl magnesium iodide at low temperature afforded a crude product as a colourless oil. Examination of the proton NMR spectrum indicated that the product was a mixture of diastereomeric Grignard addition products equivalent to the product obtained from addition of methyl magnesium iodide to phthaloyl glycine methyl ester (354). The diastereomeric Grignard addition products were present in a ratio of 65:35 major to minor based on integration of characteristic signals in the proton NMR spectrum. TLC analysis indicated an R_f difference of approximately 0.1 between the diastereomers. The diastereomers were separated by repeated flash chromatography to yield two crystalline solids which could be individually charecterised. Suitable crystals for X-ray diffraction were grown of the minor diastereomer and the structure is shown (*Fig 4.1*). This clearly shows the product to arise from addition of the Grignard reagent to the imide carbonyl, the carbinol (364). The stereochemistry of the minor diastereomer can be assigned using the atomic numbering in *Fig 4.1* as C8 R, C10 S. The major diastereomer (364) can be therefore be assigned as C8 S, C10 S (SCHEME 4.10).

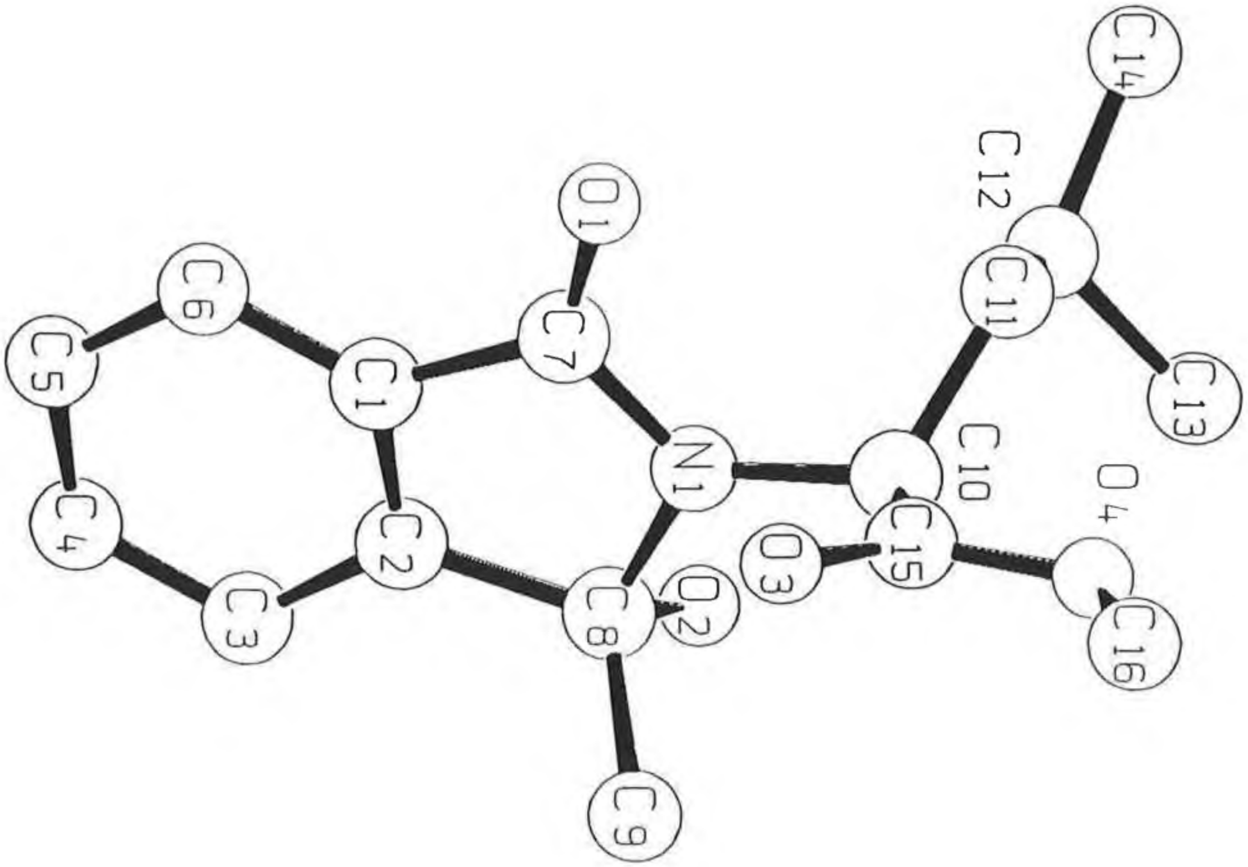
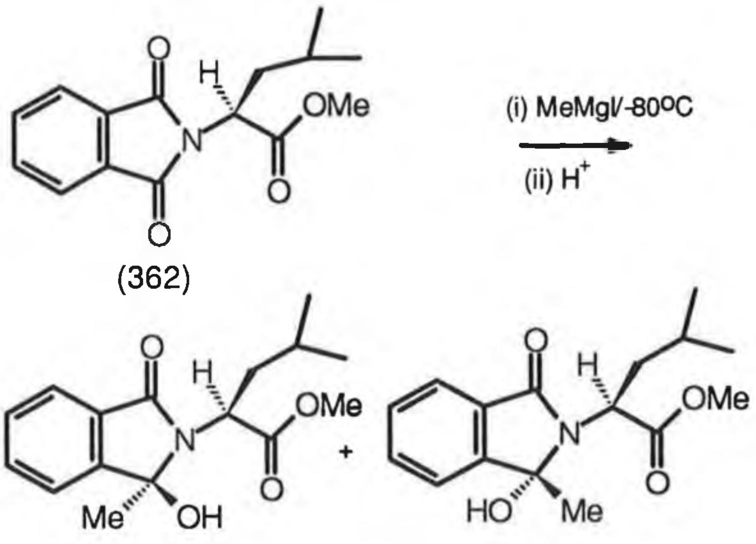


Fig 4.1: Schakal representation of X-ray crystal structure of minor diastereomer (364)

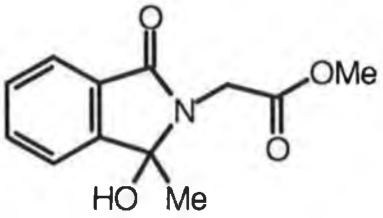


(362)

(363) (364)

SCHEME 4.10

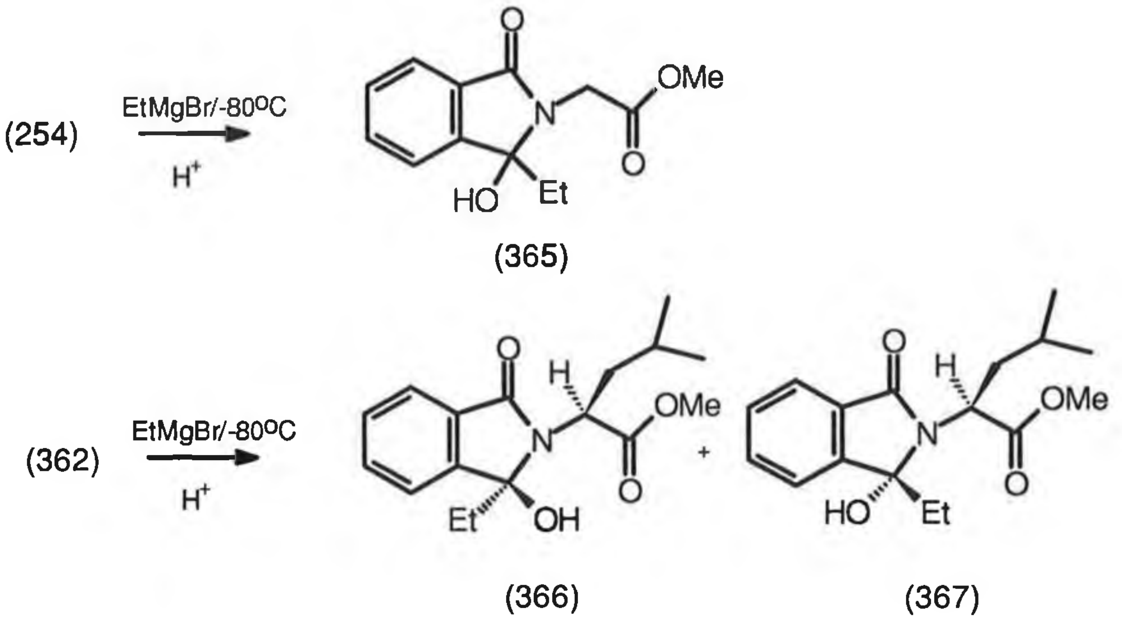
This confirms the product obtained on addition of methyl Grignard to phthaloyl glycine methyl ester (354) to be the carbinol (355).



(355)

4.4 Addition of ethyl magnesium bromide to phthaloyl-glycine and phthaloyl-*L*-leucine methyl esters

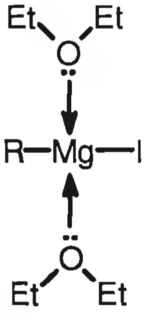
Both phthaloyl-*L*-leucine methyl ester (362) and phthaloyl glycine methyl ester (354) were treated with ethyl magnesium bromide to afford the ethyl adducts (SCHEME 4.11) quantitatively. The reaction of ethyl magnesium bromide with phthaloyl-*L*-leucine methyl ester also as expected afforded adducts as a pair of diastereomers (366) and (367) with a major (366) to minor (367) ratio of 70:30 which were separated by repeated flash chromatography. The proton NMR and carbon NMR spectra of these diastereomeric adducts were as expected very similar to those obtained for the methyl addition products (363) and (364) and could be used to assign the relative stereochemistry for each diastereomer.



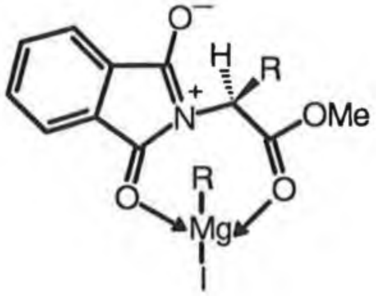
SCHEME 4.11

4.5 Discussion

Addition of an excess of alkyl Grignard reagents to phthaloyl-α-amino acid methyl esters did not afford as expected phthaloyl-β-amino alcohols but instead afforded a product resulting from addition to the imide carbonyl. These reactions were quantitative and no evidence of addition to the ester carbonyl was found. Previous reports had indicated that addition of Grignard reagents to simple *N*-alkyl phthalimides afforded imide addition products but in low yield and heating was required, so it was initially expected that some reaction would be observed at the ester carbonyl. A likely explanation for the observed reaction may be explained in terms of the structure of Grignard reagents. The sturucture of Grignard reagents has been the subject of much controversy whether they are dimeric or monomeric however it is known[164] that in etheral solutions the magnesium can coordinate two molecules of ether in addition to its two covalent bonds in structures such as (368). It seems likely that co-ordination of the Grignard reagent by both ester carbonyl and imide carbonyl would lead to an intermediate analogous to (369) which would be in equilibrium with solvated Grignard reagent (368). This coupled with both the relief of strain in a five membered ring containing in essence four sp^2 carbons and the contribution of delocalisation of the nitrogen lone pair in an intermediate such



(368)

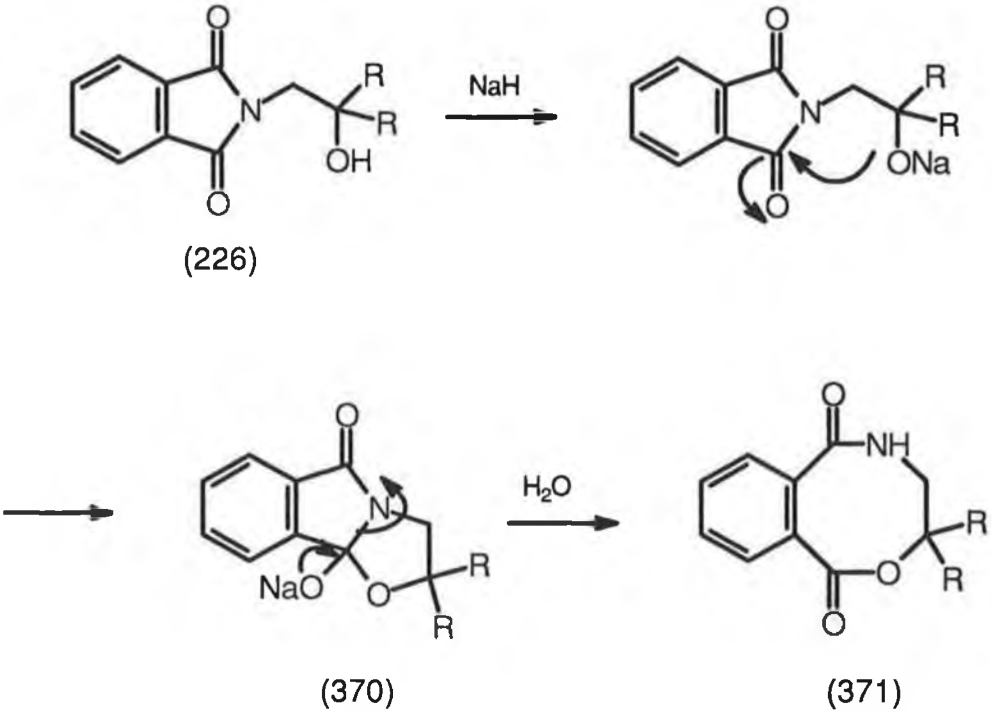


(369)

as (369) would make one carbonyl more electron deficient and more succeptible to nucleophillic attack. This combination of steric and electronic effects contributes towards converting what is normally regarded as a protecting group into quite a reactive electrophile. Griesbeck[48] and Sheehan[163] have both reported synthesis of phthaloyl-α-amino acids and their methyl esters without racemisation of the stereogenic centres. The stereochemical assignments for the diastereomeric adducts formed on addition of ethyl and methyl Grignard to phthaloyl-*L*-leucine methyl ester (362) have been made on the assumption that scrambling of the stereogenic centre does not occur during the addition. Since quantitative yields of Grignard adduct were obtained when using a 1.3 molar (approx.) excess of Grignard reagent and the observed optical activity for (363) it is likely that such scrambling is a minor process at the reaction temperatures used. However a enantio-descriminating technique would be required to confirm this.

4.6 Attempted cyclisation of *N*-(2-hydroxyethyl)phthalimides

The benzoxazocine lactam (359) was initially considered as a possible structure for the product isolated from the reaction of phthaloyl glycine methyl ester (254) with methyl Grignard. There has been no substantiated reports of synthesis of this interesting heterocyclic system. We were interested whether generation of a side chain alkoxide in a phthaloyl β-amino alcohol (226) would result in intramolecular nucleophillic attack by the alkoxide on the imide carbonyl to generate intermediate (370) which would ring open to form the benzoxazocine system (371) (SCHEME 4.12). Both *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) and *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) were treated with a slight excess of sodium hydride in THF and allowed to stir for a number of hours and subsequently quenched with water. However the only products isolated from these reactions were the acid-amide products (372) and (373) (SCHEME 4.13). These products are presumably formed via hydrolysis of the imide group during aqueous quenching. The structure was confirmed with an X-ray crystal structure of the hydrolysis product (373) from *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) shown in *Fig 4.2.*

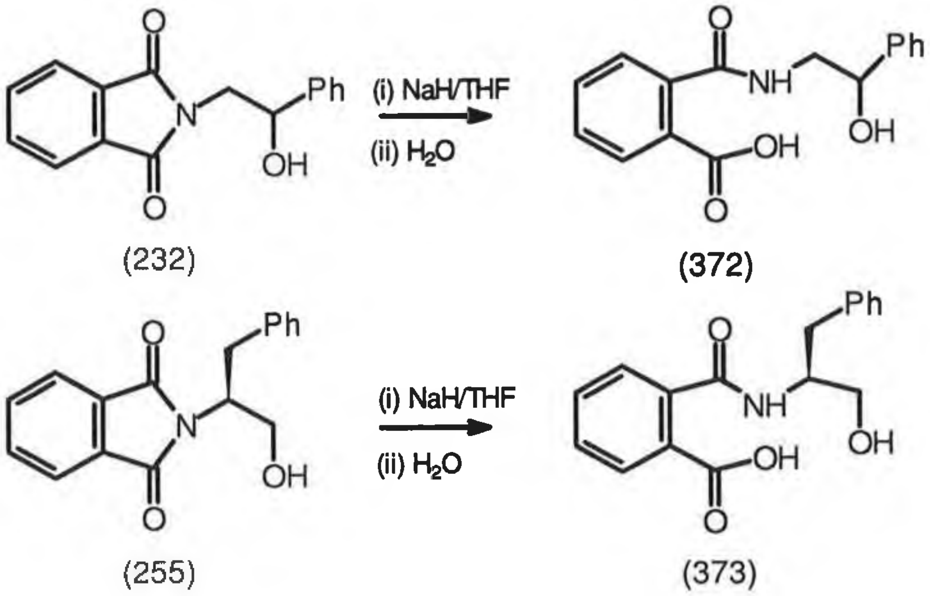


(226)

(370)

(371)

SCHEME 4.12



SCHEME 4.13

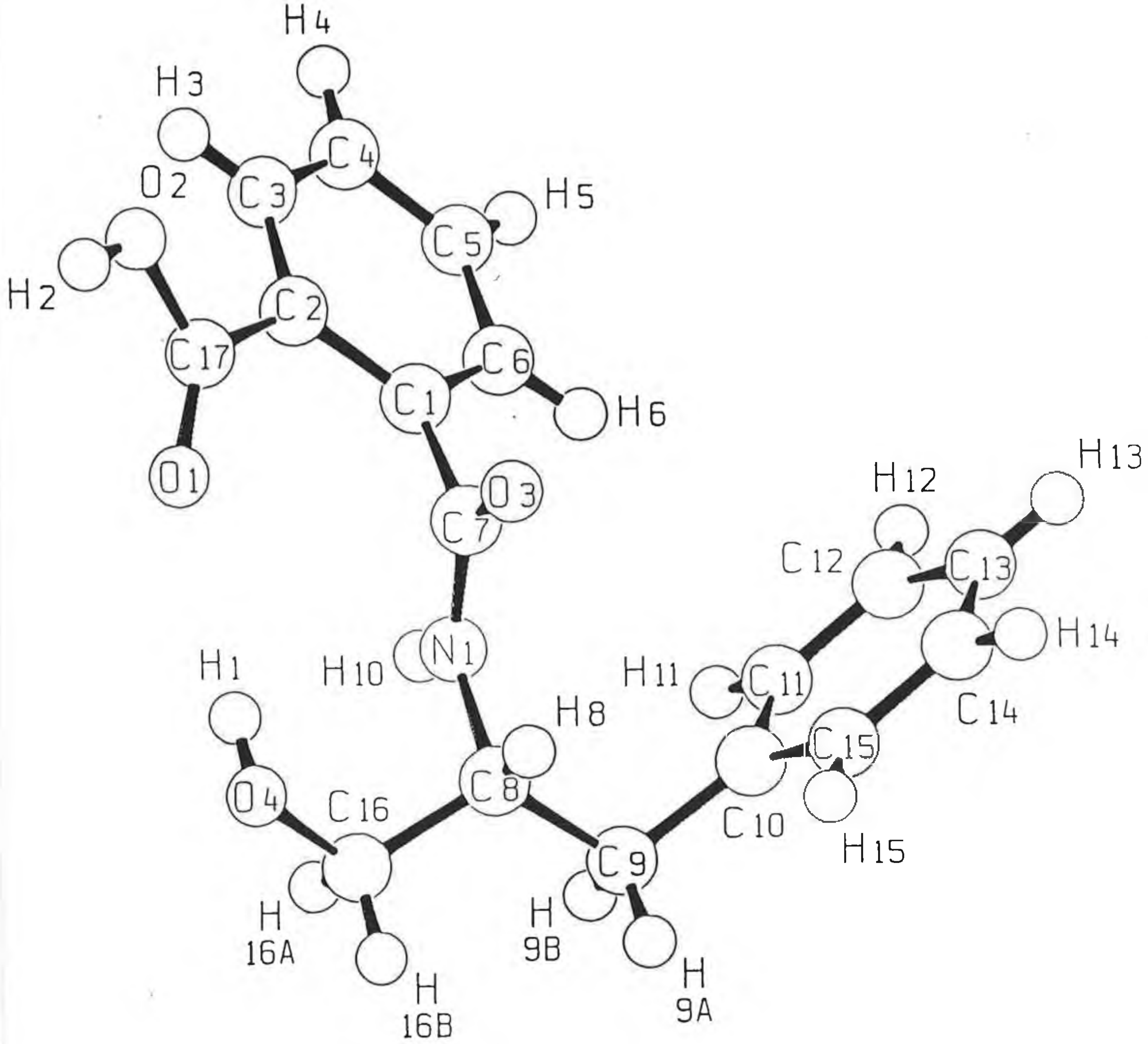


Fig 4.2: Schakal representation of X-ray crystal structure of acid-amide (373).

General Techniques

Nuclear magnetic resonance spectra were recorded on a Bruker AC-400 instrument operating at 400 MHz for ^{1}H NMR (δ_H) and 100 MHz for ^{13}C NMR (δ_C). All spectra were recorded using deuterated chloroform as solvent unless otherwise stated (d= doublet, t= triplet, q= quartet, m= multiplet).

Infrared spectra (υ_{max}) were recorded on either a Perkin Elmer 983G infrared spectrophotometer or a Nicolet 205 FT-IR spectrophotometer.

Ultraviolet spectra (λ_{max}) were recorded on a Hewlett Packard 8452 A diode array UV-Vis. spectrophotometer. Units for extinction coefficient (ε) are dm^3 mol^{-1} cm^{-1}.

Melting points (m.p.) were recorded using a Gallenkamp melting point apparatus.

Elemental analyses were carried out by the Microanalytical Laboratory at University College Dublin.

High resolution Mass Spectra were caried out at the University of Dundee.

Thin layer chromatography (TLC) was carried out on pieces of aluminum coated with silica gel containing a fluorescent indicator (Riedel-de-Haen, D.C. Karten Si F, layer thickness 0.2 mm). After development, plates were examined using an ultra-violet lamp operating at 254 nm.

Optical rotations were carried out using a Optical Activity -AA-10 automatic digital polarimeter, equipped with a 0.5 dm cell .

Radial centrifugal thin layer chromatography was carried out using a Chromatotron (Model 7924T, Harrison Research, Palo Alto, California). Circular glass plates (24 cm in diameter) were covered in silica gel (Merck No 7749, silica gel 60 PF 254 containing calcium sulphate as binder) of layer thickness 1 or 2 mm). The crude reaction mixture and solvent were then applied to the centre of the plate which was spinning at a constant rate. The polarity of the solvent was increased slowly over approximately an hour and movement of the resulting concentric bands which formed on the silica was followed using an ultraviolet lamp operating at 254 nm. The separated bands were collected as they reached the edge of the plate.

Conventional flash column chromatography was caried out using silica gel (Riedel de Haen, Kiesel gel S, 0.032-0.063 mm).

High performance liquid chromatography (HPLC) was carried out using a Waters 510 HPLC pump and Waters μbonbpack C_{18} RCM cartridges with 15μm packing (RCM 8 x 10 cartridge).

Preparative photochemical reactions were carried out in a cylindrical vessel approximately 30 cm in length and 8 cm in diameter. The vessel was fitted with a water-cooled quartz immersion well containing a 400 w medium pressure mercury vapour lamp fitted with a pyrex filter. Sensitisation and analytical scale photochemical reactions were carried out in sealed quartz tubes fitted to a merry go round apparatus surrounding the immersion well. All solutions were first degassed by vigorous bubbling with nitrogen. A slow stream of the gas was employed throughout the reaction period for the preparative photochemical reactions. All solvents used for photochemical reactions were of high purity grade.

Synthesis of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232)

Phthalimide (20.0 g ,136 mmol) was placed in a 500 cm^3 round bottomed flask, styrene oxide (19.7 g, 150 mmol) and potassium phthalimide (20 mg) were added. The flask was fitted with a reflux condenser and heated with stirring at 150 ^oC on an oil bath for six hours. The reaction mixture was allowed to cool below 100 ^oC and 150 cm^3 of toluene was added and the mixture was then brought to reflux for 20 mins. On cooling a white powdery product precipitated. The solid was filtered off and further recrystallised from ethanol containing 10% chloroform to give *N*-(2-hydroxy-2-phenylethyl)phthalimide (232), (24.6g, 68%), m.p. 162-163 ^oC, (lit.[112] 163-164 ^oC); λ_{max}: 223 (ε=22,000) and 298nm (1150); υ_{max}: 3465 (OH), 1771 and 1768 cm^{-1} (C=O); δ_H: 2.90 (br. s, 1H, OH), 3.91 (dd, 1H, J=14.3 and 3.6 Hz, $C\underline{H}_ACH_B$), 4.00 (dd, 1H, J=14.3 and 8.6 Hz, $CH_AC\underline{H}_B$), 5.05 (dd, 1H, J=8.6 and 3.6 Hz, CH), 7.25-7.47 (m, 5H, aromatic) and 7.66-7.88 ppm (m, 4H, aromatic); δ_C (DMSO): 45.5 (CH_2), 68.9 (CH), 123.0, 125.9, 127.7, 128.2, 131.6, 134.4, 143.7 (aromatic C) and 167.2 ppm (C=O).

Synthesis of trimethylsulfoxonium iodide

Dry dimethyl sulfoxide (24.0 g, 308 mmol) and methyl iodide (45 cm^3, 720 mmol) were placed in a dry 250 cm^3 round bottomed flask and the flask was fitted with a reflux condenser, a magnetic follower and a drying tube. The reaction mixture was heated with stirring under reflux for three days during which time a solid precipitated. The solid was filtered off, washed with chloroform, recrystallised from water and dried under vacuum to afford trimethylsulfoxonium iodide (18.1 g, 20%) as white plates, m.p. 169-171 ^oC (dec.) (lit[144] 170-171 ^oC (dec.)).

Synthesis of 1.1 Diphenylethyleneoxide (243) from benzophenone

Sodium hydride (0.93 g, 31mmol) as an 80% oil dispersion was placed in a dry three necked 250 cm^3 round bottomed flask and washed three times with light petroleum by swirling and removal of solvent with a pasteur pipette. The flask was fitted immediately with a reflux condenser, a stirring bar, a pressure compensated dropping funnel and a nitrogen inlet. The nitrogen inlet was turned on and a slow flow of nitrogen was allowed through the system to ensure the last traces of petroleum were removed. Trimethylsulfoxonium iodide (6.6 g, 30 mmol) was added to the flask, dry dimethyl sulphoxide (40 cm^3) was then added slowly via the dropping funnel, leading to the evolution of hydrogen. When gas evolution ceased benzophenone (4.4 g, 24 mmol) in dimethyl sulphoxide (10cm^3) was added via the dropping funnel. The reaction mixture was maintained under nitrogen and stirred at 50 ^oC for 1 hour at which time water (60 cm^3) was added slowly. The reaction mixture was then extracted three times with diethyl ether. The etheral fractions were then combined washed with water and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to give 1,1 diphenylethylene oxide (243) (3.8 g, 80%) as a white crystalline solid, m.p. 51-53^{o}C, (lit[114] 55-56 ^{o}C); υ_{max}: 3055, 2988 (CH) 1446, 758 and 698 cm^{-1}; δ_H: 3.30 (s, 2H, CH_2) and 7.21-7.40 ppm (m, 10H, aromatic); δ_C: 56.9 (CH_2), 61.9 (quaternary), 127.5, 128.0, 128.4 and 139.15 ppm (aromatic).

Synthesis of 1.1-diphenylethylene oxide (243) from 2-bromo-1.1-diphenylethanol (245)

1,1 diphenylethylene (9.2 g, 51 mmol) was added to dry dimethyl sulphoxide (25 cm^3) in a 250 cm^3 flask fitted with a nitrogen inlet. Two equivalents of water (1.8 cm^3) was added and the reaction mixture was stirred on an ice bath under an inert atmosphere. *N*-Bromosuccinimide (18.7 g, 105 mmol) was added in two portions. After an initial induction period the reaction vessel became hot. The bright orange solution was left to stir for a further ten minutes. The reaction was quenched by addition of of water (100 cm^3) and solid sodium bicarbonate until effervescence ceased. The reaction mixture was extracted three times with diethyl ether, the organic extracts were combined, washed twice with water and dried over anhydrous magnesium sulphate. The ether was removed under reduced pressure to yield a yellow oil which solidified on addition of light petroleum recrystallisation from petroleum (b.p. 100-110 ^oC) yielded 2-bromo-1,1-diphenylethanol (245) (9.7 g, 72%) as white crystals, m.p. 70-71 ^oC (lit[115] 71-72 ^oC); υ_{max}: 3048, 2938 (CH), 1228, 1164, 754 and 699 cm^{-1}; δ_H: 3.12 (s, 1H, OH), 4.15 (s, 2H, CH_2), and 7.22-7.45 ppm (m, 10H, aromatic); δ_C: 43.8 (CH_2), 77.1 (quaternary), 126.2, 127.6, 128.2, 143.1 (aromatic).

2-Bromo-1,1-diphenylethanol (245) (7.0 g, 25 mmol) was placed in a 250 cm^3 round bottomed flask and sodium hydroxide solution (100 cm^3 , 20% (w/v)) was added, the flask was fitted with a reflux condenser and the suspension stirred for 45 minutes on a water bath at 60 ^oC. The reaction mixture was cooled and extracted twice with diethyl ether. The extracts were combined washed with water and dried over anhydrous magnesium sulphate. Removal of solvent under reduced pressure yielded 1,1-diphenylethylene oxide (243) (4.1 g, 82%) as a yellow oil which solidified on standing, m.p. 51-52 ^oC. The epoxide (243) was identical in all respects to the epoxide (243) prepared by the reaction of benzophenone with the methylene transfer ylide.

Synthesis of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233)

Phthalimide (P) (1.1 g, 7.5 mmol) was dissolved in dry dimethyl sulphoxide (8 cm^3) in a 25 cm^3 round bottomed flask, potassium phthalimide (20 mg) and 1,1-diphenylethylene oxide (243) (1.5 g, 7.5 mmol) were added. The flask was fitted with a stirring bar and reflux condenser and the mixture was heated with stirring at 150 ^{o}C for three hours. On cooling water (30 cm^3) was added and the mixture extracted three times with dichloromethane. The combined extracts were washed three times with water and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to afford a white solid which on recrystallisation from ethanol afforded *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233) (0.8 g, 31%) as white needles, m.p. 182-184 ^{o}C; λ_{max}: 225 (ε= 22,000) and 298 nm (1180); υ_{max}: 3484 (OH), 1772 (C=O) and 1708 cm^{-1} (C=O); δ_H: 4.5 (s, 2H, CH_2), 5.12 (br s ,1H, OH), 7.11-7.45 (m, 10H, aromatic) and 7.55-7.70 ppm (m, 4H , aromatic); δ_C: 49.5 (CH_2), 78.2 (quaternary), 124.0, 126.1, 127.1, 128.0, 131.2, 134.1, 144.0 (aromatic) and 169.1 ppm (C=O); (Found: C, 76.96; H, 5.08; N, 4.03. $C_{22}H_{17}NO_3$ requires C, 76.96; H, 4.99; N, 4.10%).

Synthesis of *N*-(2-hydroxy-2-phenylethyl) tetrachlorophthalimide (234) via 1-amino-2-phenylethanol (246)

N-(2-Hydroxy-2-phenylethyl) phthalimide (232) (20.0 g, 79 mmol) was placed in a 500 cm^3 round bottomed flask and 100 cm^3 of ethanol was added, to this solution. Hydrazine hydrate (4.5 g, 90 mmol) was added slowly. A reflux condenser was fitted to the flask and the reaction mixture was heated slowly with stirring on a steam bath. The solution turned clear and a pasty solid started to precipitate. After 45 mins approximately concentrated hydrochloric acid (50 cm^3) was added to the solution and the volume was reduced on a rotary evaporator. The resulting solution was filtered and the filitered solid (phthalalhydrazide) was then washed with a small volume of water. The filtrates were combined and rendered basic using concentrated sodium hydroxide solution (40% w/v), and were subsequently extracted five times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield 1-amino-2-

phenylethanol (246), (8.1 g, 80%) as an oily yellow solid. The crude β-amino alcohol (246) was authenticated by comparison of its ^{1}H NMR spectrum with a purchased sample.

Tetrachlorophthalic anhydride (247) (13.0 g, 45 mmol) and glacial acetic acid (100 cm^3) were added to the crude β-amino alcohol (246) (8.1 g, 59 mmol). The reaction mixture was heated under reflux for one hour (heating mantle) and on cooling a white crystalline solid precipitated. This was filtered off and washed with a large volume of light petroleum to remove residual acetic acid and recrystallised from ethanol/chloroform 50:50 to yield *N*-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (234) (11.8 g, 65%) as white crystals, m.p. 208-210 $^{\circ}$C; λ_{max}: 242 (ε=46,800) and 330 nm (2700); υ_{max}: 3514 (OH), 1778 and 1705 cm^{-1} (C=O); δ_H: 2.45 (br. s, 1H, OH), 3.85 (dd, 1H, J=3.6 and 14.2 Hz, C$\underline{H}_A$CH$_B$), 4.05 (dd ,1H, J=9.4 and 14.2 Hz, CH$_A$C$\underline{H}_B$), 5.10 (d, 1H, J= 8.8 Hz, CH), and 7.26-7.41 ppm (m, 5H, aromatic); δ_C (DMSO): 46.2 (CH_2), 69.2 (CH), 126.1, 127.7, 128.2, 128.3, 128.5, 138.5, 142.0 (aromatic C) and 167.2 ppm (C=O); (Found: C, 47.56; H, 2.23; N, 3.40. $C_{14}H_9NO_3Cl_4$ requires C, 47.45; H, 2.24; N; 3.45 %).

Synthesis of 1-amino-2,2-diphenylethanol (249)

Dry magnesium turnings (16.0 g, 660 mmol) were placed in a dry 1 litre three necked round bottomed flask. The flask was fitted with a nitrogen inlet, a reflux condenser, a magnetic follower and a pressure compensated dropping funnel. Bromobenzene (20.0 g, 127 mmol) in anhydrous diethyl ether (40 cm^3) was added slowly via the dropping funnel under a nitrogen atmosphere. The reaction was heated gently on a warm water bath until reflux began. At this point additional bromobenzene (86.0 g, 546 mmol) in diethyl ether (200 cm^3) was added at such a rate to maintain vigorous reflux. When the addition was complete (approximately 45 mins) glycine methyl ester hydrochloride (248)

(10.0 g, 80mmol) was added portion wise to the mixture, further diethyl ether (100 cm^3) was added and the reaction was stirred at room temperature for six hours. At this point the flask was placed in an ice bath and ice water (100 cm^3) was added slowly followed by 50% (w/v) aqueous ammonium chloride (100 cm^3). The reaction mixture was rendered basic by the addition of concentrated ammonia solution (approx. 50 cm^3). The ether layer was removed and the remaining aqueous suspension was extracted four times with ethyl acetate. The combined organic extracts were washed with water and and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the resultant yellow solid was recrystallised from ethanol-water (50:50) to give 1-amino-2,2-diphenylethanol (249) (8.6 g, 51%) as white neeedles, m.p. 109-110 $^{\circ}$C (lit[145] m.p. 110-111 $^{\circ}$C); δ_H: (acetone): 2.71 (s, 1H, OH), 3.6 (s, 2H, CH$_2$) and 7.05-7.42 (m, 10H, aromatic); δ_C(acetone): 58.4 (CH$_2$), 86.6 (quaternary), 125.9, 126.4, 127.9 and 147.3 ppm (aromatic C).

Synthesis of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233)

Phthalic anhydride (250) (4.0 g, 27 mmol) was placed in a 100 cm^3 round bottomed flask, 1-amino-2,2-diphenylethanol (249) (7.5 g, 35 mmol) and glacial acetic acid (40 cm^3) were added. The mixture was heated under reflux for 30 mins and a white crystalline material precipitated on cooling. The precipitate was filtered off and washed with light petroleum. Recrystallisation from ethanol yielded *N*-(2,2-diphenyl-2-hydroxyethyl) phthalimide (232) (6.1 g, 61%) as white needles , m.p. 182-184 $^{\circ}$C which was identical in all respects to (233) which was prepared via the epoxide route.

Synthesis of *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235)

Tetrachlorophthalic anhydride (247) (1.5 g, 5.2 mmol) was heated under reflux with 1-amino-2,2-diphenylethanol (249) (1.3g , 5.8 mmol) in glacial acetic acid (10 cm^3) for 30 mins. On cooling, a white crystalline precipitate formed which on recrystallisation from chloroform/ethanol yielded *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235) (1.3 g, 52%) as white crystals, m.p. 202-204 ^0C; λ_{max}: 242(ε =56,300), and 330 nm (6246); υ_{max}: 3353 (OH), 1778 and 1704 cm^{-1} (C=O); δ_H: 4.38 (s, 1H, OH), 4.58 (s, 2H, CH_2) and 7.24-7.30 ppm (m, 10H, aromatic); δ_C: 50.2 (CH_2), 78.0 (quaternary), 125.7, 126.7, 127.3, 128.0, 129.5, 140.1, 143.4 (aromatic) and 164.0 ppm (C=O); (Found: C, 54.19; H, 2.72; N, 2.90. $C_{22}H_{13}NO_3Cl_4$ requires C, 54.92; H, 2.72; N, 2.91%).

Synthesis of *N*-(2-hydroxypropyl)phthalimide (256)

Isopropanolamine (253) (2.8 g, 37 mmol) was heated under reflux in glacial acetic acid (10 cm^3) with phthalic anhydride (250) (5.0 g, 33 mmol) for 30 mins. On cooling water (100 cm^3) was added and the resulting milky suspension was extracted twice with ethyl acetate. The organic extracts were combined and washed twice with saturated sodium bicarbonate solution. The organic extract was dried over anhydrous magnesium sulphate, the solvent was was removed under reduced pressure to yield a colourless oil which solidified on standing. Recrystallisation from ethyl acetate/light petroleum yielded *N*-(2-hydroxypropyl)phthalimide (256) (4.2 g, 61%) as white crystals, m.p. 92-94 ^0C (lit[146] 93-94 ^0C); λ_{max}: 234 (ε=11512) and 296nm (1680); υ_{max}: 3450 (OH), 1763 and 1711 cm^{-1} (C=O); δ_H: 1.22 (d, 3H, J= 6.11 Hz, CH_3), 2.79 (br s, 1H, OH), 3.67 (d, 2H, J = 5.7 Hz, CH_2), 4.04-4.10 (m, 1H, CH) and 7.66-7.87 ppm (m, 4H, aromatic); δ_C: 20.9 (CH_3), 45.4 (CH_2), 66.3 (CH), 123.2, 131.8, 134.0 (aromatic) and 168.8 ppm (C=O).

Synthesis of *N*-(2-hydroxyethyl)phthalimide (254)

N-(2-Hydroxyethyl)phthalimide (254) previously prepared[147] was recrystallised from ethanol to afford white plates m.p. 128-129°C (lit[147] 128-129 °C); λ_{max}:234 (ε=13350) and 296nm (1950); υ_{max}: 3495 (OH) , 1786 and 1711 cm^{-1} (C=O); δ_H: 2.37 (br s, 1H, OH), 3.87 (m, 4H, CH_2) and 7.70-7.88 ppm (m, 4H, aromatic); δ_C: 41.1 (N-CH_2), 61.3 (CH_2-OH), 123.7, 132.2 ,134.4 (aromatic) and 169.1 ppm (C=O).

Synthesis of *N*-(1-benzyl-2-hydroxyethyl) phthalimide (255)

Phthalic anhydride (250) (2.0 g, 13.5 mmol) was placed in a 100 cm^3 round bottomed flask equipped with a magnetic follower. The flask was sealed and heated to 145-150 °C on an oil bath, when the phthalic anhydride had melted completely phenylalanol (252) (2.0 g, 13.5 mmol) was added and the flask was sealed and vigorous stirring was continued. After five mins the seal was removed to allow the water generated to evaporate and stirring was continued for a further ten mins. On cooling a crystalline residue formed which was recrystallised from ethyl acetate/light petroleum which yielded *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255), (2.6 g, 69%) as white crystals, m.p. 103-104 °C, λ_{max}: 234 (ε=12250) and 296 nm (ε=1430); υ_{max}: 3482 (OH), 1773 and 1712 cm^{-1} (C=O); δ_H: 3.20 (d, 2H J=8.4 Hz, PhC$\underline{H}_2$), 3.95 (dd ,1H J=3.44 and 11.82 Hz, C$\underline{H}_A$CH_B) 4.05 (dd, 1H J=7.4 and 12.81 Hz, CH_AC$\underline{H}_B$), 4.65 (m, 1H, CH), 7.1-7.25 (m, 5H, aromatic) and 7.65-7.80 ppm (m, 4H, aromatic); δ_C: 34.7 (Ph$\underline{C}H_2$), 55.2 (CH_2), 62.76 (CH), 123.3, 126.6, 128.5, 129.0, 131.5, 134.1, 137.3 (aromatic) and 168.9 ppm (C=O); (Found: C, 72.14; H, 5.41; N, 4.91. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

Synthesis of acetone cyanohydrin-*O*-TMS ether (270)

Acetone cyanohydrin (269) (10.0 g, 117 mmol) and pyridine (9.2 g, 117 mmol) were placed in a dry 2-necked 250cm^3 round bottomed flask. Diethyl ether (20 cm^3) was added, the flask was fitted with a reflux condenser, a quick fit dropping funnel, a magnetic follower and calcium chloride guard tubes. Stirring was begun and the temperature was maintained between 0-5 ^oC (ice bath). Chlorotrimethylsilane (13.2 g, 117 mmol) was added slowly via the dropping funnel over a period of 15 mins, a white precipitate was formed rapidly during the addition. Stirring was maintained at room temperature for twenty hours. The solution was filtered to remove the precipitated pyridine hydrochloride. The solvent was removed under reduced pressure and the subsequent residue was dissolved in pentane and washed twice with cold dilute sodium metabisulphate solution. The solvent was removed under reduced pressure to yield acetone cyanohydrin- *O*-TMS ether (270) (17.2 g, 93%) as a clear oil which was sufficiently pure to use for the next stage, υ_{max} (film): 2995, 2965, 1460, 920 and 850 cm-1; δ_H: 0.15 (s, 9H, Si-CH$_3$), and 1.27 ppm (s, 6H, CH$_3$); δ_C -0.2 (Si-CH$_3$), 26.3 (CH$_3$), 78.3 (quaternary) and 118.2 ppm (CN); (lit[148] τ_H 8.44 (s, 6H, CH$_3$), 9.78 (s, 9H, Si-CH$_3$).

General procedure for reduction of cyanohydrin-*O*-TMS ethers

Synthesis of 1-amino-2-methylpropanol (274)

To a dry 3-necked 250 cm^3 round bottomed flask anhydrous diethyl ether (60 cm^3) and lithium aluminium hydride (5.5 g, 136 mmol) was added. The flask was fitted with a reflux condenser, a nitrogen inlet, a magnetic follower and a quick fit dropping funnel. Acetone cyanohydrin-*O*-TMS ether (270) (17.2 g, 110 mmol) in anhydrous diethyl ether (20 cm^3) was added via the dropping funnel at such a rate that gentle reflux of the reaction mixture was maintained. Stirring was continued for 1hour after the addition was complete. Slow dropwise addition of water (2 cm^3) followed by addition of sodium hydroxide solution (15% w/v) (2 cm^3) and subsequent addition of water (5cm^3) lead to the destruction of excess lithium aluminium hydride. Stirring was continued until a granular white precipitate formed. The solution was filtered and the filtrate was dried over anhydrous magnesium sulphate. The solvent was removed under reduced presure to yield 1-amino-2-methylpropanol (274) (8.8 g, 90%) as a colourless oil. The crude β-amino alcohol (274) was used without further purification, δ_H: 1.23 (s, 6H, CH_3), 1.98 (s, 6H, CH_2); δ_C 27.1 (CH_3), 50.3 (CH_2), 70.6 (quaternary).

Synthesis of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278)

1-Amino-2-methylpropanol (274) (6.2 g, 76 mmol) and phthalic anhydride (250) (9.1 g, 61 mmol) were heated under reflux in glacial acetic acid (10 cm^3) for 30 mins. On cooling a white crystalline precipitate formed which was filtered and washed with light petroleum to remove residual glacial acetic acid. Recrystallisation from ethyl acetate/light petroleum yielded *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) (7.8 g, 60%) as white crystals, m.p. 108-110^{o}C; λ_{max} 234 (ε=12,200) and 296nm (1863); υ_{max}:3456 (OH), 1774 and 1697 cm^{-1} (C=O); δ_H: 1.28 (s, 6H, CH_3), 2.80 (br s, 1H, OH), 3.75 (s, 2H, CH_2), and 7.74-7.89 ppm (m, 4H, aromatic); δ_C: 27.7 (CH_3), 49.5 (CH_2), 71.8 (quaternary), 123.8, 132.2, 134.5 (aromatic) and 169.6 ppm (C=O); (Found: C, 65.67; H, 6.08; N, 6.42; $C_{12}H_{13}NO_3$ requires C, 65.74: H, 5.98: N, 6.39%).

General procedure for preparation of cyanohydrin *O*-TMS ethers

(i) In situ cyanosilylation of *p*-anisaldehyde:

Dry potassium cyanide (9.7 g, 150 mmol) was placed in a dried 250 cm^3 2-necked round bottomed flask, chlorotrimethyl silane (9.5 g, 75 mmol), *p*-anisaldehyde (263) (6.5 g, 48 mmol), zinc iodide (100 mg) and dry acetonitrile (20 cm^3) were added. The flask was fitted with a reflux condenser, a nitrogen inlet, a magnetic follower and a rubber septum. The reaction mixture was blanketed with dry nitrogen and the system was closed to maintain an inert atmosphere, stirring was begun and the flask was heated to gentle reflux on an oil bath. The reaction mixture was left to stir under reflux over night (16 hours) at this point a small sample was withdrawn via syringe and IR spectroscopy indicated absence of starting aldehyde (no carbonyl absorption). The reaction mixture was allowed to cool and was filtered, the filtercake was washed twice with dry acetonitrile and the filtrates were combined. The solvent was removed under reduced pressure to afford a brown oily residue. The residue obtained was dissolved in pentane and washed twice with cold dilute sodium bisulphite solution and washed with water. The pentane layer was dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield *p*-anisaldehyde cyanohydrin-*O*-TMS ether (264) (10.4 g, 92%) as a brown oil which could be used without further purification, υ_{max} (film): 2941, 1613, 1513 , 1465 and 850 cm^{-1}; δ_H: 0.15 (s, 9H, CH_3), 3.6 (s, 3H, OCH_3), 5.35 (s, 1H, CH), 6.81 (d, 2H J=8.8 Hz, aromatic) and 7.34 ppm (d, 2H J=8.4 Hz, aromatic); δ_C; -0.1 (CH_3), 55.3 (OCH_3), 63.3(CH) , 114.5, 128.3, 128.8, 160.9 (aromatic) and 119.7 ppm (CN); (lit[131] δ_H: 0.2 (CH_3), 3.8 (OCH_3). 5.4 (CH); δ_C: -0.2 (CH_3), 55.3 (OCH_3), 63.4 (CH), 119.2 (CN), 128.6 (*i*-C), 160.4 (*p*-C), 114.3 (*o*-C) , 127.8(*m*-C).

(ii)pre preparation of trimethylsilylcyanide prior to cyanosilylation of *p*-anisaldehyde (263)

In a 100cm^3 Erlenmeyer flask oven dried prior to use was placed sodium iodide (1.0 g) (dried at 120^{o}C for 24 hours), dry acetonitrile (20 cm^3) and a stirring bar. The flask was fitted with a rubber septum and stirring was begun. After stirring for 5 mins under an inert atmosphere the septum was removed and potassium cyanide (2.7 g, 40 mmol)) (dried at 100^{o}C under vacuum for 24 hours) was added portionwise. The septum was refitted and distilled chlorotrimethylsilane (4.40 g, 40 mmol) and dry pyridine (1 cm^3) were added via syringe. The reaction flask was purged with nitrogen and was was allowed to stir at room temperature for 24 hours. At this point *p*-anisaldehyde (263) (3.8 g, 28 mmol) was added via syringe and stirring was continued for a further three hours. After this period a small sample was withdrawn by syringe and analysis by infrared spectroscopy indicated complete absence of starting aldehyde (no carbonyl absorption). The crude reaction mixture was added to ice water (100 cm^3) and extracted with pentane twice, the organic layers were combined washed with cold dilute sodium bisulphite solution and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to yield *p*-anisaldehyde cyanohydrin-*O*-TMS ether (264) (5.3 g, 88%) as a brownish oil which was identical spectroscopically to that prepared by the alternative method above and was suitable for use without further purification.

Synthesis of 1-amino-2-*p*-methoxyphenylethanol (271)

p-Anisaldehyde cyanohydrin-*O*-TMS ether (264) (4.0 g, 19 mmol) was reduced with lithium aluminium hydride (0.82 g, 22 mmol) in diethyl ether to yield 1-amino-2-*p*-methoxyphenylethanol (271) (2.5 g, 82%) as a yellowish oily solid. The crude ethanolamine was phathaloylated without further purification, δ_H: 2.45 (br. s, 1H, OH), 2.72 (dd, 1H, J=8.3 and 13.3 Hz, $C\underline{H}_ACH_B$), 2.85 (dd, 1H, J=5.2 and 13.3 Hz, $CH_AC\underline{H}_B$), 3.82 (s, 1H, OCH3), 4.52, (dd, 1H, J=8.3 and 5.2 Hz, CH), 6.85 (d, 1H, J=7.5 Hz, aromatic), and 7.25 ppm (d, 1H, J= 7.6 Hz, aromatic).

Synthesis of *N*-(2-hydroxy-2-*p*-methoxyphenylethyl)phthalimide (275)

1-Amino-2-*p*-methoxyphenylethanol (271) (2.2 g, 15 mmol) and phthalic anhydride (250) (1.6 g, 11 mmol) in glacial acetic acid (10 cm^3) were heated under reflux for 30 mins. On cooling a light brown solid precipitated which was filtered off and washed with light petroleum to remove residual acetic acid . The solid was recrystallised from ethylacetate/light petroleum to yield *N*-(2-hydroxy-2-*p*-methoxyphenylethyl)phthalimide (275) (1.9 g, 55%) as light yellow crystals, m.p. 163-164 ^{o}C, λ_{max}: 234 (ε =16230) 282 (2390) and 294 nm (1925); υ_{max}: 3473 (OH), 1742 and 1698 cm^{-1} (C=O); δ_H: 2.83 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.90 (dd, 1H J=3.7 and 14.5 Hz, $C\underline{H}_ACH_B$) 4.05 (dd, 1H J=9.2 and 14.5 Hz, $CH_AC\underline{H}_B$) 5.03 (d, 1H, J=5.6 Hz, CH), 6.86 (d, 2H J=9.2 Hz, aromatic), 7.35 (d, 2H J=9.3 Hz, aromatic) and 7.81- 7.95 ppm (m, 4H, aromatic); δ_C: 45.0 (OCH_3), 54.6(CH_2), 71.5 (CH), 113.3, 122.8, 126.5, 131.2, 132.5, 133.5, 158.7 (aromatic) and 168.1 (C=O); (Found: C, 68.55; H, 5.09; N, 4.72; $C_{17}H_{15}NO_4$ requires C, 68.68; H, 5.09; N, 4.71%).

Synthesis of *p*-bromobenzaldehyde cyanohydrin *O*-TMS ether (266)

p-bromobenzaldehyde (3.7 g, 20 mmol) was cyanosilylated in acetonitrile to yield after workup *p*-bromobenzaldehyde cyanohydrin-*O*-TMS ether (266) (5.6 g, 95%) as a brown oil which was sufficiently pure to use without further purification, υ_{max} (film): 2960; δ_H: 0.15 (s, 9H, CH_3), 5.35 (s, 1H, CH), 7.30 (d, 2H J=7.5 Hz, aromatic) and 7.52 ppm (d, 2H J= 7.6 Hz, aromatic); δ_C: 0.7 (CH_3), 62.6 (CH_2), 118.3(CN), 123.0, 127.5, 131.7 and 134.9 ppm (aromatic).

Synthesis of 1-amino-2-*p*-bromophenylethanol (272)

p-bromobenzaldehyde cyanohydrin-*O*-TMS ether (266) (5.0 g, 18 mmol) was reduced with lithium aluminium hydride (0.80 g, 21 mmol) in anhydrous diethyl ether to yield 1-amino-2-*p*-bromophenylethanol (272) (3.3 g, 85%) as a light yellow powder. The crude ethanolamine was used without further purification,

δ_H: 2.73 (dd, 1H, J=7.4 and 12.9 Hz, C$\underline{H}_A$CH$_B$), 2.92 (dd, 1H, J=3.7 and 12.9 Hz, CH$_A$C$\underline{H}_B$), 4.56 (dd, 1H, J=3.7 and 7.4 Hz, CH), 7.19 (d, 2H, J=9.25 Hz, aromatic), and 7.46 ppm (d, 2H, J=7.4 Hz, aromatic); δ_C: 49.0 (CH$_2$), 73.4 (CH), 121.3, 127.5, 131.4 and 141.5 ppm (aromatic).

Synthesis of *N*-(2-hydroxy-2-*p*-bromophenylethyl) phthalimide (276)

Phthalic anhydride (250) (1.7 g, 11.5 mmol) and 2-amino-2-*p*-bromophenyl ethanol (272) (2.8 g, 13 mmol) were heated under reflux in glacial acetic acid (10 cm^3) for 30 mins to afford a white crystalline solid which crystallised on cooling. Recrystallisation from ethanol/chloroform yielded *N*-(2-hydroxy-2-*p*-bromophenylethyl)phthalimide (276) (2.6 g, 65%) as white crystals, m.p. 193-195 ^{0}C, λ_{max}: 234 (ε =14,700) and 296 nm (932); υ_{max}: 3433 (OH), 1778 and 1697 cm-1 (C=O); δ_H: 3.12 (s, 1H, OH), 3.85 (dd, 1H J= 3.4 and 14.0 Hz, C$\underline{H}_A$CH$_B$), 3.95 (dd, 1H J=8.4 and 14.1 Hz, CH$_A$C$\underline{H}_B$) 5.0 (dd, 1H , J=8.4 and 3.4 Hz, CH) , 7.30 (d, 2H J=8.4 Hz, aromatic), 7.45(d, 2H J= 3.4 Hz, aromatic) and 7.70-7.85 ppm (m, 4H, aromatic); δ_C: 45.1 (CH2), 71.7 (CH), 121.5, 123.1 , 127.1, 131.2, 131.3, 133.8 , 139.5, (aromatic) and 168.3 ppm (C=O); (Found: C, 55.27; H, 3.46; N, 4.02; $C_{16}H_{12}NO_3Br$ requires C, 55.51; H, 3.49; N, 4.05%).

Synthesis of *trans*-cinnamaldehyde cyanohydrin *O*-TMS ether(268)

trans-Cinnamaldehyde (8.1 g, 60 mmol) was cyanosilylated in acetonitrile to yield after work-up *trans*-cinnamaldehyde cyanohydrin *O*-TMS ether (268) (12.9 g, 91%) as a yellow oil which was used without further purification, υ_{max}(film): 2960, 1450 and 1256 cm^{-1}; δ_H: 0.2 (s, 9H, CH$_3$), 5.05 (d, 1H, J = 7.3 Hz, CH), 6.12 (dd, 1H J = 7.3 and J = 14.5 Hz CH-C$\underline{H}$=CHPh), 6.70 (d, 1H J = 14.5 Hz, CH=C$\underline{H}$Ph) and 7.20-7.35 ppm (m, 5H, aromatic); δ_C: -0.5 (CH$_3$), 61.8 (CH), 117.0 (CN), 123.1, 126.5, 128.3, 128.4, 133.5 and 136.4 ppm (aromatic and vinylic).

Synthesis of 2-amino-2-styrylethanol (273)

Reduction of *trans*-cinnamaldehyde *O*-TMS ether (268) (11.2 g, 48 mmol) in diethyl ether with lithium aluminium hydride (2.2 g, 58 mmol) gave 1-amino-2-styrylethanol (273) (5.5 g, 70%) as an orange powder which was phthaloylated without further purification, δ_H (acetone d_6): 2.85 (dd, 1H, J=6.4 and 11.8 Hz, $C\underline{H}_ACH_B$), 3.35 (dd, J=6.9 and 11.8 Hz, $CH_AC\underline{H}_B$), 4.43 (m, 1H, CH), 6.25 (dd, 1H, J=6.9 and 15.8 Hz, CH-C$\underline{H}$=CHPh), 6.57 (d, 1H, J=15.8 Hz CH=C$\underline{H}$Ph), and 7.19-7.48 ppm (m, 5H, aromatic); δ_C (acetone d_6): 52.3 (CH_2), 78.03 (CH), 126.5, 126.6, 127.6, 128.8, 130.1, and 131.5 ppm (aromatic and vinylic).

Synthesis of *N*-(2-hydroxy-2-styrylethyl) phthalimide (277)

2-Hydroxy-2-styrylethylamine (273) (4.0g, 24.5 mmol) was heated under reflux with phthalic anhydride (250) (3.0 g, 20 mmol) in glacial acetic acid (10 cm^3) for 30 mins to afford a brown powder which crystallised on cooling. Recrystallisation from chloroform/light petroleum afforded *N*-(2-hydroxy-2-styrylethyl) phthalimide (277) (3.6 g, 62%) as a light brown crystalline solid, m.p. 187-188^{o}C, λ_{max}:242 (ε =22,520), 284 (3,270) and 292 nm (3020); υ_{max}: 3451 (OH), 1772 and 1699 cm-1 (C=O); δ_H: 2.55 (s, 1H, OH), 3.85 (m, 2H, $C\underline{H}_AC\underline{H}_B$), 4.62 (m, 1H, CH), 6.25 (dd, 1H J=5.2 and 16.6 Hz, CH-C$\underline{H}$=CHPh) 6.70 (d, 1H, J=16.6Hz, CH=C$\underline{H}$Ph), 7.15-7.35 (m, 5H, aromatic), and 7.70-7.85 ppm (m, 4H, aromatic); δ_C: 43.5 (CH_2), 70.7 (CH), 123.0, 126.2, 127.4, 128.0, 128.1, 131.4, 131.6, 133.7, 135.8 (aromatic and vinylic) and 167.8 ppm (C=O); (Found: C, 73.42; H, 5.28; N, 4.78; $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.28; N, 4.81%).

Irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232)

N-(2-Hydroxy-2-phenylethyl)phthalimide (232) (1.0 g, 3.7 mmol) was irradiated through Pyrex for 90 mins. TLC showed formation of three products. The solvent was removed under reduced pressure to yield a light brown solid. The mixture was separated with a 4 mm Chromatotron plate using 70:30 light petroleum/dichloromethane as eluent increased stepwise to 100% dichloromethane. This gave in order of recovery from plate:

(i) benzaldehyde (279) (98 mg) which was identical (IR and ^{1}H NMR spectra) with an authentic sample;

(ii) *N*-methylphthalimide (NMP) (228 mg) which was identical (IR and ^{1}H NMR spectra) with an authentic sample;

(iii) phenacylphthalimide (280) (12 mg) which was identical (IR and ^{1}H NMR spectra) with an authentic sample;

(iv) *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) (370 mg) which was identical (IR and ^{1}H NMR spectra) with an authentic sample.

Synthesis of phenacylphthalimide (232)

N-(2-Hydroxy-2-phenylethyl) phthalimide (232) (2.0 g, 7.5 mmol) was placed in a 250cm^3 round bottomed flask. Manganese dioxide (6.5 g, 75 mmol) and toluene (100 cm$^{3)}$ were added. The flask was fitted with a Dean and Stark condenser and the mixture heated under reflux for 1hr, by which time TLC indicated complete conversion to one product. The flask was allowed cool and the manganese dioxide filtered off. The resulting black solution was passed through a plug of sillica gel to remove residual oxidising agent. The solvent was removed under reduced pressure to afford an off-white solid which was subsequently recrystallised from chloroform/light petroleum to afford phenacylphthalimide (280) as white crystals (1.2 g, 58%), m.p. 168-70 $^{\circ}$C (lit^{149} 168-70 $^{\circ}$C); υ_{max}: 1773 and 1699 cm-1 (C=O); δ_H: 5.21 (s, 2H, CH_2), 7.40-7.54

(m, 3H, aromatic), 7.65-7.85 (m, 4H, phthalimido), and 8.10 ppm (m, 2H, aromatic); δ_C: 44.1 (CH_2), 123.4, 128.0, 128.8, 132.1, 133.9, 134.0, 134.2 (aromatic), 167.8 (C=O) and 190.9 ppm (C=O).

Irradiation of *N*-(2,2-diphenyl-2-hydroxyethyl)phthalimide (233)

N-(2,2-Diphenyl-2-hydroxyethyl)phthalimide (233) (800 mg, 2.3 mmol) in dichloromethane (300 cm^3)was irradiated through pyrex for 45 mins. At which point TLC showed complete consumption of starting material and formation of three products. The solvent was removed under reduced pressure to yield a brown oily solid. The mixture was separated with a 2 mm Chromatotron plate using 70:30 light petroleum/dichloromethane as eluent increased stepwise to 100% dichloromethane which gave in order of recovery from the plate:

(i) Benzophenone (244) (230 mgs) which was identical (IR and ^1H NMR spectra) with an authentic sample;

(ii) *N*-methylphthalimide (NMP) (220 mgs) which was identical (IR and ^1H NMR spectra) with an authentic sample;

(iii) bisphthalimidoethane (281) (18 mgs) which was identical (IR and ^1H NMR spectra) with an authentic sample.

Synthesis of bisphthalimidoethane (281)

Ethylene diamine (0.4 g, 7 mmol) and phthalic anhydride (2.0 g, 13.5 mmol) were heated under reflux in glacial acetic acid (15 cm^3) for 20 mins during which time a yellowish solid precipitated. On cooling, the solid was filtered off and washed with light petroleum and was recrystallised from ethanol/chloroform to afford bisphthalimidoethane (281) (1.2 g, 58%) as white crystals, m.p. 234-236^oC (lit[23] 234-236 ^oC); υ_{max}: 1772 and 1712 cm^{-1} (C=O); δ_H: 4.01 (s, 4H,

CH_2), and 7.68-7.79 ppm (m, 8H, aromatic); δ_C: 36.8 (CH_2), 123.3, 131.9, 134.0 (aromatic) and 168.2 ppm (C=O).

Irradiation of *N*-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (234) in dichloromethane

N-(2-hydroxy-2-phenylethyl)tetrachlorophthalimide (233) (1.0 g, 2.5 mmol) in dichloromethane (300 cm^3) was irradiated through Pyrex for 20 mins. TLC indicated complete reaction of (234) and formation of two products. The solvent was removed under reduced pressure to yield a white oily solid. Examination of the ^1H NMR of the crude photolysis mixture suggested *N*-methyltetrachloro phthalimide (282) and benzaldehyde (279) as the sole products. Recrystallisation of the crude photolysis mixture using chloroform/light petroleum yielded *N*-methyltetrachlorophthalimide (282) (320 mgs) which was identical (IR and ^1H NMR spectra) with an authentic sample. The mother liquors were evaporated to dryness under reduced pressure and the residual products separated with a 1 mm Chromatotron plate using 70/30 light petroleum/dichloromethane as eluent increased stepwise to 100% dichloromethane to give, in order of recovery from the plate:

(i) Benzaldehyde (279) (20 mgs) which was identical (^1H NMR and IR spectra) with an authentic sample;

(ii) *N*-methyltetrachlorphthalimide (282) (190 mgs) which was identical (^1H NMR and IR spectra) with an authentic sample.

Irradiation of *N*-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235) in dichloromethane

N-(2,2-diphenyl-2-hydroxyethyl)tetrachlorophthalimide (235) (500 mgs, 1.0 mmol) in dichloromethane (300 cm^3) was irradiated through Pyrex for 15 mins.

TLC indicated complete reaction of (234) and formation of two products. The solvent was removed under reduced pressure to yield a yellowish oily solid. Examination of the ^{1}H NMR of the crude reaction mixture suggested *N*-methyltetrachlorophthalimide (282) and benzophenone (244) as the sole products. Recrystallisation of the crude photolysis mixture from chloroform/light petroleum yielded *N*-methyltetrachlorophthalimide (282) (140 mgs) which was identical (^{1}H NMR and IR spectra) with an authentic sample. The mother liquors were evapourated to dryness under reduced pressure and the residual products separated on a 1 mm Chromatotron plate using 70:30 light petroleum/ dichloromethane as eluent increased stepwise to 100% dichloromethane to give in order of recovery

(i) Benzophenone (244) (120 mgs) which was identical (^{1}H NMR and IR spectra) with an authentic sample.

(ii) *N*-methyltetrachlorophthalimide (282) (110 mgs) which was identical (^{1}H NMR and IR spectra) with an authentic sample.

Synthesis of *N*-(2-*O*-acetyl-2-phenylethyl)phthalimide (293)

N-(2-Hydroxy-2-phenylethyl)phthalimide (232) (4.8 g, 18 mmol) was placed in a 250 cm^3 round bottomed flask, acetic anhydride (80 cm^3) was added and the mixture was heated under reflux for five hours. The reaction was allowed to cool and water (80 cm^3) was added. The reaction mixture was heated for a further 30 mins to ensure conversion of excess acetic anhydride to acetic acid. The mixture was extracted three times dichloromethane. The organic extracts were combined and washed three times with a sodium hydroxide solution (1% w/v) and then dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to give a white solid which an recrystallisation from ethanol/light petrol gave *N*-(*O*-acetyl-2-phenylethyl) phthalimide (293) (2.8 g, 48%) as white crystals, m.p. 102-104 ^{o}C (lit^{112} 103-104 ^{o}C); υ_{max}: 1772, 1742 and 1714 cm^{-1} (C=O); δ_H: 1.91 (s, 1H, CH_3), 3.85 (dd, 1H, J=14.7 and 3.5 Hz, $C\underline{H}_AH_B$) , 4.1 (dd, 1H, J= 14.7 and 8.7 Hz, $CH_A\underline{H}_B$), 6.05(dd, 1H , J= 8.7 and 3.5 Hz, CH), 7.21-7.43 (m, 5H, aromatic) and 7.62-7.83 ppm (m, 4H, aromatic); δ_C: 21.0 (CH_3), 42.9 (CH_2), 73.3 (CH), 123.4, 126.6, 128.6, 128.7, 131.8 , 134.1, 137.1 (aromatic), 167.9 and 170.2 ppm (C=O).

Irradiation of *N*-(2-*O*-acetyl-2-phenyl)ethylphthalimide (293) in dichloromethane

N-(2-*O*-Acetyl-2-phenyl)ethylphthalimide (293) (1.0 g, 3.2 mmol) in dichloromethane (300 cm^3) was irradiated through Pyrex for 23 hours. TLC indicated no significant product formation. The solvent was removed under reduced pressure to yield *N*-(2-*O*-acetyl-2-phenyl)ethylphthalimide (293) (950 mgs) as a white solid which was identical (^1H NMR and IR spectra) with an authentic sample.

Irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in dichloromethane/ deuterium oxide

N-(2-Hydroxy-2-phenylethyl)phthalimide (232) (20 mg, 0.07 mmol) was dissolved in dichloromethane (10 cm^3) and placed in a Pyrex tube. After degassing (stream of nitrogen gas) deuterium oxide (1cm^3) was added. The tube was sealed and vigourously shaken for ten mins to ensure complete isotopic exchange. The solution was irradiated for 20 mins through Pyrex, on ceasing irradiation the aqueous layer was removed and the photolysis solution was dried over anhydrous magnesium sulphate. TLC indicated a similar product profile to that obtained with unexchanged (232). The solvent was removed under reduced pressure and the resulting brown oily solid was separated on a 1mm chromatotron plate using 50:50 light petroleum/dichloromethane as the eluent to give in order of elution.

(i) Benzaldehyde (trace) which was identical (TLC R_f)with an authentic sample.

(ii) N-(monodeuteriomethyl)phthalimide (296) (6mg) identified by comparison of its ^{1}H NMR spectrum with that reported in the literature, δ_H: 3.15 (t, 2H , J=2.1 Hz, CH_2-D) and 7.64-7.75 ppm (m,4H,aromatic) (lit[104] δ_H 3.15 (t, 2H, J= 2 Hz, CH_2-D)).

Irradiation of *N*-(2-hydroxyethyl)phthalimide (254) in dichloromethane

N-(2-Hydroxyethyl)phthalimide (254) (600 mg, 3.2 mmol) in dichloromethane (500 cm3) was irradiated through Pyrex for 40 hours. Reaction progress was monitored by TLC with no significant product formation observed, some slow photodegradation was observed (TLC). The solvent was removed under reduced pressure to yield a light brown crystaline solid (530 mgs) whose IR spectrum was identical in all respects to that of an authentic sample of *N*-(2-hydroxyethyl)phthalimide (254).

Irradiation of *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255) in dichloromethane

N-(1-Benzyl-2-hydroxyethyl)phthalimide (255) (500 mg, 1.7 mmol) in dichloromethane (500 cm3) was irradiated through Pyrex for 18 hours. Reaction progress was monitored by TLC with no significant product formation observed. The solvent was removed under reduced pressure to yield a light brown crystaline solid (530 mgs) whose IR spectrum was identical in all respects to that of an authentic sample of *N*-(1-benzyl-2-hydroxyethyl)phthalimide (255).

Irradiation of *N*-(2-hydroxypropyl)phthalimide (256) in dichloromethane

N-(2-Hydroxypropyl)phthalimide (256) (1.0 g, 5.0 mmol) in dichloromethane (300 cm^3) was irradiated through Pyrex for 29 hours. TLC showed slow formation of one major and two minor products. The solvent was removed under reduced pressure to yield a light brown solid. This was purified by first filtering through a short silica column with an eluent of 100% dichloromethane to give in order of elution:

(i) The photoproducts (170 mgs) as a clear oil which solidified on standing.

(ii) *N*-(2-hydroxypropylethyl)phthalimide (256) (620 mgs) which was identical (^{1}H NMR and IR spectra) to an authentic sample.

The residual photoproducts were separated using flash chromatography with an eluent of light petroleum/ dichloromethane 50:50 to yield

(i) 8mg oily solid identity unknown.

(ii) *N*-methylphthalimide (NMP) (130 mgs) which was identical (^{1}H NMR and IR spectra) to an authentic sample.

Irradiation of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) in dichloromethane

N-(2-Hydroxy-2-methylpropyl)phthalimide (278) (600 mg, 2.7 mmol) in dichloromethane (500 cm^3) was irradiated through Pyrex for 10 hours. TLC indicated formation of one product. The solvent was removed under reduced pressure to yield 520 mgs of a brownish oil which was separated using flash chromatography with an eluent of 100% dichloromethane to yield in order of elution:

(i) *N*-methylphthalimide (NMP) (160 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *N*-(2-Hydroxy-2-methylpropyl)phthalimide (280 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

Irradiation of *N*-(2-hydroxy-2-*p*-methoxyphenylethyl)phthalimide (275) in dichloromethane

N-(2-Hydroxy-2-*p*-methoxyphenylethyl)phthalimide (600 mg, 2 mmol) in dichloromethane (500cm^3) was irradiated through Pyrex for 35 mins. TLC indicated formation of two major products. The solvent was removed under reduced pressure to yield a yield a brown oily solid (510 mg) . ^{1}H NMR analysis of the crude photolysis mixture suggested complete reaction of the starting material to form two major and one minor product the major products were identified as *N*-methylphthalimide (NMP) and *p*-anisaldehyde (297) on the basis of their charecteristic signals. The minor product which was present in approximately 10% yield was tentatatively identified as the oxidation product *p*-methoxyphenacyl phthalimide (298) based on its characteristic signal at 5.2 ppm in the ^{1}H NMR of the crude reaction mixture. Recrystallisation of the crude photolysis mixture in dichloromethane/light petroleum yielded *N*-methylphthalimide (NMP) (110 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample. The mother liquors were evapourated to dryness under reduced pressure and the residual products separated by flash column chromatography using dichloromethane/light petroleum 50:50 to give in order of elution

(i) *p*-anisaldehyde (297) (20 mgs) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *N*-methylphthalimide (NMP) (120 mgs) which was identical (IR and ^{1}H NMR spectra) to an authentic sample. The photooxidised product *p*-methoxyphenacyl phthalimide (298) was not isolated individually.

Irradiation of *N*-(2-hydroxy-2-*p*-bromophenylethyl)phthalimide (276) in dichloromethane

N-(2-Hydroxy-2-*p*-bromophenylethyl) phthalimide (276) (500mg ,1.4 mmol) in dichloromethane was irradiated through Pyrex for 35 mins. TLC indicated the formation of three products, however prolonged irradiation led to the formation of a large number of secondary photoproducts. The solvent was removed under reduced pressure to yield a brown oil. ^1H NMR analysis of the crude photolysis mixture indicated presence of three major products tentatatively identified by their charecteristic absorption frequencies these were (i) NMP (δ_H: 3.18 (s, 3H, CH_3)) (ii) *p*-bromophenacylphthalimide (300) (δ_H: 5.23 (s, 2H, CH_2)) (iii) *p*-bromobenzaldehyde (299) (δ_H: 10.01 (s, 1H, CH)) however the presence of a large number of secondary products made preparative isolation of these products impossible.

Irradiation of *N*-(2-hydroxy-2-styrylethyl)phthalimide (277) in dichloromethane

N-(2-Hydroxy-2-styrylethyl)phthalimide (500mg xxmmol) was irradiated through Pyrex for 18 hours . TLC indicated slow photodegradation, the solvent was removed under reduced pressure to yield a brown powder (480 mg). Analysis of the ^1H NMR of the crude reaction mixture indicated that expected fragmentation products *N*-methylphthalimide (NMP) and cinammaldehyde were not present and predominantly unreacted (277) was present.

Sensitised and unsensitised irradiation of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) in dichloromethane

Two solutions of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) (20 mg, 0.09 mmol)in dichloromethane (10 cm^3) were prepared benzophenone (48 mg, 0.27 mmol) was added to one tube. The tubes were irradiated through Pyrex using a merry go-round reactor for 45 mins. The solvent was removed under reduced pressure and ^1H NMR analysis of the crude photolysis mixture indicated in the case of the sensitised photoreaction absence of *N*-(2-hydroxy-2-

methylpropyl)phthalimide (278) and the sole product identifiable was *N*-methylphthalimide (NMP) (δ_H: 3.18 (s, 3H, CH_3), 7.71-7.94 (m, 4H, aromatic)). On examination of the ^1H NMR for the unsensitised case the mixture contained 85% unreacted *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) and 15% *N*-methylphthalimide(NMP) based on integration of the charecteristic signals. Formation of no other products was observed.

Sensitised and un-sensitised irradiation of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) in dichloromethane

Two solutions of *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) (20 mg, 0.075 mmol) in dichloromethane (10 cm^3) were prepared benzophenone (41 mg, 0.22 mmol) was added to one tube. The tubes were irradiated through Pyrex using a merry go-round reactor for 40 mins. The solvent was removed under reduced pressure and ^1H NMR analysis of the crude reaction mixture indicated in the case of the sensitised photoreaction the formation of *N*-methylphthalimide (NMP) (δ_H: 3.18 (s, 3H, CH_3) and benzaldehyde (279). The product mixture was calculated to contain 65% NMP and 35% *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) based on integration of their charecteristic signals. On examination of the ^1H NMR for the unsensitised case the mixture contained 99% unreacted *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) and 1% *N*-methylphthalimide(NMP) based on integration of the charecteristic signals. The other fragmentation product benzaldehyde (279) was also observed as a photoproduct in the sensitised case however loses during solvent removal made comparison of its integral with those of the substrate (232) unreliable.

Sensitised irradiation of *N*-(2-hydroxyethyl)phthalimide (254) in dichloromethane

A solution of *N*-(2-hydroxyethyl)phthalimide (50 mg, 10 mmol) and benzophenone (54 mg, 30 mmol) in dichloromethane (10 cm^3) was irradiated through Pyrex for six hours. The solvent was removed under reduced pressure to afford a brown oil. Analysis of the ^1H NMR spectrum of the crude reaction mixture suggested that no formation of *N*-methylphthalimide (NMP) had occured and the major signals were due to unreacted *N*-(2-hydroxyethyl) phthalimide (254) and the sensitiser benzophenone.

Synthesis of *E*-*N*-styrylphthalimide (338)

N-(2-hydroxy-2-phenylethyl)phthalimide (232) (4.0 g, 15 mmol) and *p*-toluene sulphonic acid (0.4 g, 2.3 mmol) were placed in a 250 cm^3 round bottomed flask. Toluene (100 cm^3) was added and the flask was fitted with a Dean and Stark condenser. The reaction mixture was heated under reflux and monitored by TLC for consumption of starting material. After approximately 24 hours at which point the starting material had been completely consumed the rection mixture was allowed to cool and then washed twice with water to remove the catalyst. The organic layer was dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to afford a yellow solid. This yellow solid was recrystallised from chloroform/ethanol to give *E*-*N*-styryl phthalimide (338) (1.7 g, 48%) as yellow needles, m.p. 185-186^oC (lit[112] 185.5-186.5); λ_{max}: 225 (ε=23000), 280 (37000) and 310 nm(s) (19500); υ_{max}:1711 cm^{-1} (C=O); δ_H: 7.25-7.49 (m, 6H, aromatic and C=C$\underline{H}$(Ph)), 7.66 (d, 2H J=15.2 Hz, N-C$\underline{H}$=CH(Ph)), and 7.73-7.94 ppm (m, 4H, aromatic); δ_C: 117.5, 119.9 (vinylic), 123.5, 126.1, 127.5, 128.6, 131.5, 134.4, 135.8 (aromatic) and 166.3ppm (C=O).

Synthesis of *E-N*-styryltetrachlorophthalimide (339)

N-(2-Hydroxy-2-phenylethyl)tetrachlorophthalimide (234) (5.0 g, 12.3 mmol) and *p*-toluene sulphonic acid (0.03 g, 0.17 mmol) was placed in a 250 cm^3 round bottomed flask. Xylene (100 cm^3) was added, the flask was fitted with a Dean and Stark condenser and slowly brought to reflux. After 25 mins one drop of concentrated sulphuric acid was added and the reflux continued for two hours. The reaction mixture was allowed cool and washed three times with water. The organic layer was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to afford a dark yellow solid. The solid was dissolved in hot dichloromethane and filtered to remove insoluble impurities. The dichloromethane solution was concentrated under reduced pressure and passed through a plug of silica using dichloromethane as eluent to remove baseline impurities. The solvent was removed under reduced pressure to afford a yellow solid which was recrystallised twice from chloroform/ethanol to give yellow crystals of *E-N*-styryltetrachlorophthalimide (339) (0.9 g, 19%) m.p. 226-228^oC; λ_{max}: 230 (75000), 296 (37100) and 310 nm (s) (36800); υ_{max}: 1705 cm-1 (C=O); δ_H: 7.27-7.46 (m, 6H, aromatic and C=C$\underline{H}$(Ph)) and 7.67ppm (d, 1H J=14.6 Hz, N-C$\underline{H}$=CH(Ph)); δ_C: 116.7, 121.7 (vinylic), 126.3, 127.1, 128.1, 128.8, 130.0, 135.2, 140.6 (aromatic) and 161.5 (C=O); (Found: C, 49.41; H, 1.82; N, 3.51. $C_{16}H_7NO_2Cl_4$ requires C, 49.65; H, 1.82; N, 3.62%).

Irradiation of *E-N*-styrylphthalimide (338) in dichloromethane

E-N-Styrylphthalimide (338) (0.6 g, 2.4 mmol) in dichloromethane (300 cm^3) was irradiated through Pyrex for 38 hours. The slow formation of one product was observed by TLC. On ceasing irradiation the solvent was removed under reduced pressure to afford a yellow solid. The reaction mixture was separated on a 2mm Chromatotron plate using light petroleum/dichloromethane (60:40) as eluent which gave in order of recovery from the plate.

(i) *E*-*N*-styrylphthalimide (338) (330 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *Z*-*N*-styrylphthalimide (340) (90 mg, 21%) recrystallised from chloroform/ ethanol to afford light yellow needles, m.p. 114-116^{o}C; λ_{max}: 242 (26000), 242(s) (23,400) and 262 nm (ε=20,437); υ_{max}: 1711 cm^{-1}(C=O) ; δ_H: 6.26 (d, 2H J=8.8Hz, C=C$\underline{H}$(Ph)), 6.63 (d,2H J=8.8Hz, N-C$\underline{H}$=CH(Ph)), 7.11-7.23 (m, 5H, aromatic), and 7.64-7.82 ppm (m, 4H, aromatic); δ_C: 116.3, 123.8 (vinylic), 128.0, 128.2, 128.4, 130.0, 132.1, 134.4, 135.0 (aromatic) and 166.4ppm (C=O); (Found: C, 76.89; H, 4.36, N, 5.50; $C_{16}H_{11}NO_2$ requires: C, 77.10; H, 4.45; N, 5.62%).

Irradiation of *E*-*N*-styrylphthalimide (338) in toluene

E-*N*-Styrylphthalimide (0.6 g, 2.4 mmol) in toluene (300 cm^3) was irradiated through Pyrex for 18 hours, TLC showed formation of one product. This product was identified as *Z*-*N*-styrylphthalimide by comparitive TLC. The solvent was removed under reduced pressure to afford a yellow solid. The mixture was separated on a 2mm chromatotron plate using light petroleum/dichloromethane (60:40) as eluent. which gave in order of recovery from the plate

(i) *E*-*N*-styrylphthalimide (338) (290 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *Z*-*N*-styrylphthalimide (340) (130 mg, 31%) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

Irradiation of *E*-*N*-styrylphthalimide (338) in dichloromethane/isopropanol

E-*N*-Styrylphthalimide (338) (0.6 g, 2.4 mmol) in dichloromethane/isopropanol

(50:50) (300 cm^3) was irradiated through Pyrex for 22 hours. TLC showed formation of one product.This product was identified as *Z*-*N*-styrylphthalimide (340) by comparitive TLC. The solvent was removed under reduced pressure to afford a yellow solid. The mixture was separated on a 2mm Chromatotron plate using light petroleum/dichloromethane (60:40) as eluent which gave in order of elution from the plate.

(i) *E*-*N*-styrylphthalimide (338) (320 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *Z*-*N*-styrylphthalimide (340) (90 mg, 22%) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

Irradiation of *E*-*N*-styrylphthalimide (338) in dichloromethane/cyclohexene

E-*N*-Styrylphthalimide (338) (0.1 g, 0.4 mmol) in dichloromethane/cyclohexene (50:50) (20 cm^3) was irradiated in two separate sealed quartz tubes through Pyrex using a merry-go round apparatus. The formation of one product was observed by TLC whose identity was identified as *Z*-*N*-styryl phthalimide (340) by comparitive TLC. The solvent was removed under reduced pressure to afford a yellow solid which was separated on a 1mm Chromatotron plate using light petroleum/dichloromethane (50:50) as eluent which gave in order of recovery from the plate.

(i) *E*-*N*-styrylphthalimide (338) (45mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

.(ii) *Z*-*N*-styryl phthalimide (340) (18 mg, 29%) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

Irradiation of *E*-*N*-styryltetrachlorophthalimide (339) in dichloromethane

E-*N*-Styryltetrachlorophthalimide (339) (0.4 g, 1.0 mmol) in dichloromethane

(500 cm^3) was irradiated through Pyrex for 28 hours. The slow formation of a large number of photoproducts was observed by TLC. The solvent was removed under reduced pressure to afford a dark yellow solid. The solid was recrystallised from chloroform/ethanol to afford *E*-*N*-styryltetrachloro phthalimide (343) (150 mg) as a yellow powder which was identical (IR and ^{1}H NMR spectra) to an authentic sample. Repeated attempts to isolate the photoproducts which were present in very small amounts proved unsuccessful.

Irradiation of *E*-*N*-styryltetrachlorophthalimide (339) in dichloromethane/cyclohexene

E-*N*-Styryltetrachlorophthalimide (339) (0.2 g, 0.52 mmol) in dichloromethane/ cyclohexene (50:50) (40 cm^3) in four sealed quartz tubes was irradiated through Pyrex for 28 hours using a merry go-round reactor. The formation of one product was observed by TLC. The solvent was removed under reduced pressure to afford a yellow solid. The mixture was separated by flash chromatography using light petroleum/dichloromethane as eluent which gave in order of recovery from the column

(i) *E*-*N*-styryltetrachlorophthalimide (339) (110mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *Z*-*N*-styryltetrachlorophthalimide (343) (45 mg, 29%) as a white powder recrystallisation from ethanol/chloroform gave white crystals m.p. (190-192^{o}C); λ_{max}: 240 (ε=64500), 270 (s) (19360), 318 nm (6450); υ_{max}: 1706 cm^{-1} (C=O);. δ_H: 6.27 (d, 1H J=9.24 Hz, C=C(Ph)$\underline{H}$), 6.76 (d, 1H J=9.24 Hz, N-C$\underline{H}$=C(Ph)H) and 7.19-7.28 ppm (m, 5H, aromatic); δ_C: 115.5, 127.5 (vinylic), 128.0, 128.4, 128.6, 130.0, 131.5, 134.4, 140.5 (aromatic) and 161.5 ppm (C=O). (Found: C, 49.73; H, 1.85; N, 3.60. $C_{16}H_7Cl_4NO_2$ requires C, 49.65; H, 1.82; N, 3.62%).

Irradiation of *E-N*-styryltetrachlorophthalimide (339) in light petroleum/ dichloromethane

E-N-styryltetrachlorophthalimide (0.3 g, 0.8 mmol) was irradiated in light petroleum/dichloromethane (3:1) (500 cm^3) for 38 hours. The slow formation of one product was observed by TLC. On ceasing irradiation the solvent was removed under reduced pressure to afford a yellow solid. The mixture was separated by flash chromatography using light petroleum/dichloromethane (40:60) as eluent giving in order of recovery from the column;

(i) *E-N*-styryltetrachlorophthalimide (338) (160 mg) which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

(ii) *Z-N*-styryltetrachlorophthalimide (343) (65 mg, 28%) as a white powder, which was identical (IR and ^{1}H NMR spectra) to an authentic sample.

Synthesis of phthaloyl glycine methyl ester (254)

Glycine methyl ester hydrochloride (248) (6.1 g, 48 mmol) was placed in a 250 cm^3 round bottomed flask. Sodium acetate (3.0 g), phthalic anhydride (6.4 g, 43 mmol) and glacial acetic acid (40 cm^3) were added and the flask was fitted with a magnetic follower and a reflux condenser. The flask was heated under reflux for 30 mins, on cooling water (100 cm^3) was added and a white crystalline precipitate formed. The solution was filtered and and the crystals were washed with light petroleum and allowed to dry at the pump to yield phthaloyl glycine methyl ester (4.6g, 48%) as white crystals. m.p. 91-93 ^oC; υ_{max}: 1773, 1751 and 1728 cm^{-1} (C=O); δ_H: 3.70 (s, 3H, OCH_3), 4.39 (s, 2H, NCH_2) and 7.68-7.82 ppm (4H, m, aromatic); δ_C: 38.2 (NCH_2), 52.2 (OCH_3), 123.2, 131.5, 133.3 (aromatic), 166.7 and 167.3 (C=O).

Synthesis of phthaloyl-*L*-leucine (361)

(i) using glacial acetic acid as solvent:

Phthalic anhydride (250) (2.0 g, 13.5 mmol) was placed in a 250 cm^3 round bottomed flask, to this was added *L*-leucine (360) (1.8 g, 13.5 mmol) and acetic acid (20 cm^3). The flask was heated under reflux for 30 mins, on cooling water (100 cm^3) was added and the resultant milky solution was extracted three times with ethyl acetate. The organic extracts were combined and washed three times with water and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to yield phthaloyl-*L*-leucine (361) (3.3 g, 93%) as a white cystalline solid, m.p. 114-115 ^oC (lit[162] 115-116 ^oC); υ_{max}: 1780, 1751 and 1708 cm^{-1}(C=O); δ_H: 0.93 (d, 3H, J=6.4 Hz, $CHC\underline{H}_3$), 0.95 (d, 3H, J=6.4 Hz, $CHC\underline{H}_3$), 1.51 (m, 1H, $C\underline{H}(CH_3)_2$), 1.95 (m, 1H, $C\underline{H}_ACH_BCH(CH_3)_2$), 2.35 (m, 1H,$CH_AC\underline{H}_BCH(CH_3)_2$), 4.96 (dd, 1H, J= 4.4 and 11.3 Hz, NCH), 7.50-7.70 (m, 4H, aromatic), and 10.0 ppm (br s, 1H, OH); δ_C: 20.9 (CH_3), 23.1 (CH_3) , 25.0($\underline{C}H(CH_3)_2$), 36.9 (CH_2), 50.4(NCH), 123.6, 131.6, 134.2, (aromatic C) , 167.7 and 175.9 ppm (C=O); $[\alpha_D]_{18}$= -22 (c= 0.01 g ml^{-1} (EtOH)), (lit[162] $[\alpha_D]_{20}$ = -22).

(ii) fusion without solvent

Phthalic anhydride (250) (2.0 g, 13.5 mmol) in a sealed 100 cm^3 round bottomed flask equipped with a magnetic follower was melted by heating with stirring on an oil bath at 145-150^oC. *L*-Leucine (360) (1.8 g, 13.5 mmol) was added and vigourous stirring was continued for 5 mins at this point the seal was removed and the reaction water was allowed to evaporate. Stirring was continued for a further 10 mins and the flask was allowed cool. On cooling a crystalline sold formed which was recrystallised from methanol/water to yield phthaloyl-*L*-leucine (361) (2.8 g, 80%) as white crystals, m.p. 116-117^oC (lit[162] 115-116^oC) which was identical in all respects to (361) prepared via the acetic acid method.

Synthesis of phthaloyl-*L*-leucine methyl ester (362)

Methanol (40 cm^3) was placed in a dry 2-necked 250 cm^3 round bottomed flask equipped with a magnetic follower and a calcium chloride drying tube. The flask was maintained with stirring at -5^{o}C (ice-salt bath) and thionyl chloride (2 cm^3) was added slowly via dry pipette. Phthaloyl-*L*-leucine (361) (2.0 g, 8 mmol) was added portion wise. The ice salt bath was removed and the solution was allowed to stir at room temperature overnight. After 20 hours the methanol was removed under reduced pressure to yield an oily residue which was dissolved in ethyl acetate (40 cm^3) and washed twice with cold saturated sodium bicarbonate solution and once with water. The ethyl acetate layer was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield phthaloyl-*L*-leucine methyl ester (362) as a clear oil (1.9 g 90%), υ_{max}: 1775, 1746 and 1715 cm^{-1} (C=O); δ_H: 0.64 (d, 3H J= 6.4 Hz, $CHC\underline{H}_3$), 0.68 (d, 3H J=6.4 Hz, $CHC\underline{H}_3$), 1.22 (m, 1H, $\underline{CH}(CH_3)_2$), 1.73 (m, 1H, $\underline{CH}_ACH_BCH(CH_3)_2$), 2.12 (m, 1H, $CH_AC\underline{H}_BCH(CH_3)_2$), 3.52 (s, 3H, OCH_3), 4.70 (dd, 1H, J=4.4 and 11.8 Hz, NCH) and 7.45-7.70ppm (m, 4H, aromatic); δ_C: 21.0 (CH_3), 23.3 (CH_3), 25.11 ($\underline{C}H(CH_3)_2$), 37.4 (CH_2), 50.4 (NCH), 52.7 (OCH_3) 123.4, 131.7, 134.1(aromatic C), 167.6 and 170.2ppm (C=O); $[\alpha_D]_{18}$= -66 (c= 0.01 g ml^{-1} ($CHCl_3$)).

Attempted synthesis of *N*-(2-hydroxy-2-methylpropyl)phthalimide (278) via addition of methyl magnesium iodide to phthaloyl glycine methyl ester (354)

Phthaloylglycine methyl ester (354) (2.0 g, 9.1 mmol) was dissolved in anhydrous diethyl ether (50 cm^3) in a 250 cm^3 round bottomed flask. equipped with a magnetic follower. The flask was fitted with a rubber septum and was purged with nitrogen. Methyl magnesium iodide (2.4 equiv, 2 cm^3 of a 1.1M solution) was added slowly via syringe which led to formation of a milky precipitate. Stirring was maintained at room temperature for 45 mins. The reaction was quenched by addition of Ammonium chloride (30 cm^3 of 50% w/v solution). The solution which was dark in colour was transferred to a separatory funnel, the lower layer was discarded and the etheral solution was washed twice with water. The etheral layer was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield 1.8 g of a dark oily solid. TLC analysis indicated the complete disappearance of starting material and the formation of one major product with a number of minor impurities, including a dark baseline spot which was ascribed to some magnesium salts. The major product was isolated via flash chromatographic purification of a 0.4 g sample of the oil as a white solid which after recrystallisation from chloroform/light petroleum yielded white crystals of carbinol (355) (190 mg (45%) m.p. 125-126^{o}C; υ_{max}: 3318 (OH), 1746 (ester C=O), and 1677 cm^{-1} (amide C=O); δ_H: 1.61(s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.81 (d, 1H J=17.7 Hz, $NC\underline{H}_ACH_B$), 4.0 (s, 1H, OH), 4.20 (d, 1H, J=17.7 Hz, $NCH_AC\underline{H}_B$) and 7.53-7.70 ppm (m, 4H, aromatic); δ_C: 23.2 (CH_3), 38.9 (NCH_2), 52.1 (OCH_3), 91.8 (quaternary), 121.4, 123.0, 129.0, 131.2, 132.4, 147.4 (aromatic) 168.2 and 171.4 ppm (C=O); (Found: C, 61.12; H, 5.58; N, 5.88. $C_{12}N_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95%).

General procedure for addition of alkyl Grignard reagents to phthaloyl-α-amino acid esters

Synthesis of methyl (RS)-2-(2,3-dihydro-1-hydroxy-1-methyl-3-oxo-isoindol-2-yl)ethanoate (355)

Phthaloyl glycine methyl ester (354) (2.0 g, 9.1 mmol) was dissolved in anhydrous diethyl ether (50 cm^3) in a dry 250 cm^3 round bottomed flask equipped with a magnetic follower. The flask was fitted with a rubber septum and was purged with nitrogen. The flask was maintained with stirring at approximately -80^{o}C on a liquid nitrogen/toluene slush bath. Methyl magnesium iodide (1.4 equiv.,1.2 cm^3 of a 1.1M solution) was added slowly via syringe which led to immediate formation of a yellow milky precipitate. Stirring was maintained for 20 mins and the solution was allowed to approach room temperature. Ammonium chloride (30 cm^3 of a 50% w/v solution) was added to decompose magnesium salts and the etheral solution was seen to clarify. The solution was transferred to a separatory funnel. The aqueous layer was discarded and the etheral solution was washed twice with water and dried over anhydrous magnesium sulphate to yield a yellowish oil which solidified on standing. Recrystallisation from chloroform/light petroleum yielded carbinol (355) (1.3 g, 61%) as white crystals, m.p. 125-126^{o}C which was identical (^{1}H NMR and IR spectra) to an authentic sample.

Synthesis of methyl (RS)-2-(2,3-dihydro-1-hydroxy-1-ethyl-3-oxo-isoindol-2-yl)ethanoate (365)

Glycine methyl ester (354) (2.0 g, 9.1 mmol) was treated with ethyl magnesium bromide (1.3 equiv., 4 cm^3 of 3M solution in diethyl ether) in anhydrous diethyl ether according to the general procedure to yield after recrystallisation from chloroform/light petroleum ethyl (RS)-2-(2,3-dihydro-1-hydroxy-1-ethyl-3-oxo-isoindol-2-yl)ethanoate (365) (1.3 g, 50%) as white crystals; m.p. 124-126 ^{o}C;.υ_{max}: 3309 (OH), 1739 (ester C=O) and 1678 cm^{-1} (amide C=O); δ_H: 0.51 (t, 3H J=5.9 Hz $CH_2C\underline{H}_3$), 2.05 (m, 1H, $C\underline{H}_ACH_BCH_3$), 2.20 (m, 1H, $CH_AC\underline{H}_BCH_3$), 3.40 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 3.85 (d, 1H J= 17.6 Hz, NCH_2), 4.50 (d, 1H J= 17.6 Hz, NCH_2) and 7.41-7.78 ppm (m, 4H, aromatic); δ_C: 7.8 ($CH_2C\underline{H}_3$), 28.9 ($C\underline{H}_2CH_3$), 40.0 (NCH_2), 52.9 (OCH_3), 91.8 (quaternary), 122.2, 123.9, 129.9, 131.0, 132.9, 147.1 (aromatic C), 168.0 and 171.2 (C=O); (Found: C, 62.81; H, 6.11; N, 5.57. $C_{13}H_{13}NO_3$ requires C, 62.64; H, 6.11; N, 5.62%).

Synthesis of methyl (1'RS, 2S)-2-(2,3-dihydro-1-hydroxy-1-methyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (363) and (364)

Phthaloyl-*L*-leucine methyl ester (362) (2.0 g, 7.3 mmol) was treated with methyl magnesium iodide (1.3 equiv., 0.9 cm^3 of a 1.1M solution in diethyl ether) in diethyl ether according to the general procedure to yield (1.9 g, 89%) of a colourless oil. ^1H NMR analysis of the crude reaction mixture indicated the oil was a mixture of diastereoisomers major to minor ratio 65:35. TLC analysis (diethyl ether/light petroleum 9:1) indicated an R_f difference of 0.1 between the two diastereoisomers. Repeated flash chromatography using diethyl ether/light petroleum 9:1 as eluent led to isolation of the two diastereoisomers as crystalline solids.

(i) Major diastereoisomer methyl (1'S, 2S)-2-(2,3-dihydro-1-hydroxy-1-methyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (363)

m.p. 122-123 ^oC;.υ_{max}: 3331 (OH), 1745 (ester C=O) and 1679 cm^{-1} (amide C=O); δH: 1.01 (pd, 6H , J=6.4 Hz, $CH(C\underline{H}_3)_2$, 1.65-1.80 (m&s, 4H, $C\underline{H}(CH_3)_2$) & CH_3), 2.12 (m, 1H, $C\underline{H}_ACH_BCH(CH_3)_2$), 2.35 (m, 1H, $CH_AC\underline{H}_BCH(CH_3)_2$), 3.15 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 4.20 (dd, 1H J=5.1 and 9.4 Hz, NCH), 7.48-7.78 ppm (m, 4H, aromatic); δ_C: 21.9 ($CH(C\underline{H}_3)_2$), 23.1 ($CH(C\underline{H}_3)_2$), 24.0 ($C\underline{H}(CH_3)_2$), 25.1 (CH_3), 38.1 (CH_2), 52.6 (NCH), 52.9 (OCH_3), 88.9 (quaternary), 121.7, 123.5, 129.7, 130.2, 132.7, 148.4, (aromatic C), 168.1 and 173.3 ppm (C=O); Found: C, 65.56; H, 7.21; N, 4.66. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%); $[\alpha_D]_{18}$= -61 (c= 0.01 g ml^{-1} ($CHCl_3$)).

(ii) Minor diastereoisomer methyl (1'R, 2S)-2-(2,3-dihydro-1-hydroxy-1-methyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (364)

m.p. 119-120 ^oC;υ_{max}: 3329 (OH), 1748 (ester C=O) and 1681cm^{-1} (amide C=O); δH: 1.01 (pd, 6H J=7.4 Hz, $CH(C\underline{H}_3)_2$), 1.65 (m, 1H, $C\underline{H}(CH_3)_2$), 1.75(s, 3H, CH_3), 2.00 (m, 1H, $C\underline{H}_ACH_BCH(CH_3)_2$), 2.35 (m, 1H, $CH_AC\underline{H}_BCH(CH_3)_2$), 2.90 (s, 1H, OH), 3.70 (s, 3H, OCH_3), 4.51 (dd, 1H J=5.0 and 9.8 Hz, NCH), and 7.48-7.78 ppm (m, 4H, aromatic); δ_C:21.4 ($CH(\underline{C}H_3)_2$), 23.1 ($CH(\underline{C}H_3)_2$), 24.7 ($\underline{C}H(CH_3)_2$), 25.1 (CH_3), 38.2 (CH_2), 52.4 (NCH), 52.6 (OCH_3), 89.3 (quaternary), 121.5, 123.6, 129.7, 130.2, 132.6, 148.2 (aromatic), 167.7 and 172.6 ppm (C=O); (Found: C, 66.07; H, 7.31; N, 4.85. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%).

Synthesis of methyl (1'RS, 2S)-2-(2,3-dihydro-1-hydroxy-1-ethyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (366) and (667)

Phthaloyl-*L*-leucine methyl ester (354) (1.0 g, 3.7 mmol) was treated with ethyl magnesium bromide (1.4 equiv, 1.7 cm^3 of 3M solution in diethyl ether) in anhydrous diethyl ether (30 cm^3) according to the general procedure to afford after work-up 0.9 g of a light brown oil. ^1H NMR analysis of the crude reaction mixture indicated that it was a pair of diastereomers major to minor ratio 70:30. TLC analysis diethyl ether/light petroleum (9:1) indicated an R_f difference of 0.1 between the two diastereomers. Repeated flash chromatography using diethyl ether light petroleum 9:1 as eluent led to isolation of the two diastereomers as colourless oils.

Major diastereomer methyl (1'S, 2S)-2-(2,3-dihydro-1-hydroxy-1-ethyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (366)

υ_{max}: 3329 (OH), 1741 (ester C=O), and 1679 cm^{-1} (amide C=O); δ_H:0.65 (t, 3H J= 7.4 Hz, $CH_2C\underline{H}_3$), 1.01 (d, 6H J=6.4 Hz, $CH(C\underline{H}_3)_2$), 1.83 (m, 1H, $\underline{CH}(CH_3)_2$), 2.01-2.35 (m, 4H, $C\underline{H}_2CH_3$ & $C\underline{H}_2CH(CH_3)_2$), 3.31 (s, 1H, OH), 3.74 (s, 3H, OCH_3), 4.10 (t, 1H J= 6.9 Hz, NCH) and 7.38-7.59 ppm (m, 4H, aromatic); δ_C: 8.1 ($CH_2\underline{C}H_3$), 22.1 ($CH(\underline{C}H_3)$), 22.5 ($CH(\underline{C}H_3)$), 25.5 ($\underline{C}H(CH_3)_2$), 28.7 ($\underline{C}H_2CH_3$), 39.1 ($\underline{C}H_2CH(CH_3)_2$), 52.3 (NCH), 52.8 ($OCH_3$), 92.1 (quaternary), 121.9, 123.5, 129.5, 131.1, 132.6, 146.7 (aromatic), 168.9

and 173.5 ppm (C=O); (Found: exact mass 305.16251. $C_{17}H_{23}NO_4$ requires 305.16271).

Minor diastereomer methyl-(1'R, 2S)-2-(2,3-dihydro-1-hydroxy-1-ethyl-3-oxo-isoindol-2-yl)-4-methyl-pentanoate (367)

υ_{max}(film): 3331 (OH), 1743 (ester C=O) and 1678 (amide C=O); δ_H: 0.7 (t, 3H, J= 7.4 Hz, $CH_2C\underline{H}_3$), 0.98 (pd, 6H J= 6.4 Hz, $CH(CH_3)_2$), 1.66 (m, 1H, $C\underline{H}(CH_3)_2$), 2.01-2.22 (m, 4H, $C\underline{H}_2CH_3$ & $C\underline{H}_2CH(CH_3)_2$), 3.24 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 4.48 (t, 1H J= 6.9 Hz, NCH) and 7.48-7.57 ppm (m, 4H, aromatic); δ_C: 8.4 ($\underline{C}H_2CH_3$), 21.9 ($CH(\underline{C}H_3)$), 22.6 ($CH\underline{C}H_3$)), 25.2 ($\underline{C}H(CH_3)_2$)), 30.2 ($\underline{C}H_2CH_3$), 38.5 ($\underline{C}H_2CH(CH_3)_2$), 52.4 (NCH), 52.5 ($OCH_3$), 92.5 (quaternary), 121.8, 123.5, 129.5, 131.1, 132.3, 146.6 (aromatic), 167.3 and 172.6 ppm (C=O);(Found: exact mass 305.16278. $C_{17}H_{23}NO_4$ requires 305.16271).

Synthesis of 2-[[(2-hydroxy-2-phenylethyl)amino] carbonyl] benzoic acid (372)

Sodium hydride (0.35 g, 11 mmol) (80% dispersion in oil) was placed in a two necked 100 cm^3 round bottomed flask. The oil was removed by swirling and decanting with light petroleum. The final traces of light petrol were removed by slow flushing with dry nitrogen. Dried THF (20 cm^3) was added via a quick fit dropping funnel, the flask was fitted with a calcium chloride guard tube and stirring was begun. *N*-(2-hydroxy-2-phenylethyl)phthalimide (232) (2.0 g, 7.5 mmol) was added slowly leading to evolution of hydrogen. When hydrogen evolution had ceased after approximately 45 mins water (5 cm^3) was added slowly to remove excess sodium hydride. The solution was left to stir for a further 10 mins and water (30 cm^3) and dil HCl (10 cm^3) were added leading to a white precipitate. This milky solution was extracted three times with diethyl ether. The etheral layer was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield a white powdery solid which on recrystallisation from ethyl acetate afforded (372) as white crystals, (1.3 g, 61%), m.p. 146-148 ^{o}C (dec); υ_{max}: 3516 (OH), 3302 (NH), 1715 (C=O) and 1697 cm-1 (C=O); δ_H (DMSO): 3.35 (dd, 1H, J= 13.8 and 3.2 Hz, $C\underline{H}_ACH_B$), 3.50 (dd, J= 13.8 and 8.2 Hz, $CH_AC\underline{H}_B$) 4.65 (m, 1H, CH), 7.31-7.82 (m, 9H, aromatic), 8.21 (t, 1H J= 6.3 Hz, NH) and 13.32 ppm (br s, 1H, OH (acid)); δ_C (DMSO): 47.8 (CH_2), 71.4 (CH), 126.3, 127.2, 127.8, 128.2, 129.2, 129.3, 131.2, 131.3, 138.4, 143.8 (aromatic) 168.4 and 168.9 ppm (C=O); (Found: C, 66.97; H, 5.30; N, 4.80. $C_{16}H_{15}NO_4$ requires C, 67.36; H, 5.30; N, 4.91%).

Synthesis of 2-[[(1-benzyl-2-hydroxyethyl)amino] carbonyl] benzoic acid (373)

Sodium hydride (0.51 g, 17 mmol) (80% dispersion in oil) was placed in a two necked 100 cm^3 round bottomed flask. The oil was removed by swirling and decanting with light petroleum. The final traces of light petrol were removed by slow flushing with dry nitrogen. Dried THF (20 cm^3) was added via a quick fit dropping funnel , the flask was fitted with a calcium chloride guard tube and stirring was begun. *N*-(1-Benzyl2-hydroxyethyl)phthalimide (255) (3.0 g 10 mmol) was added slowly leading to evolution of hydrogen. When hydrogen evolution had ceased after approximately 45 mins water (5 cm^3) was added slowly to remove excess sodium hydride. The solution was left to stir for a further 10 mins and water (30 cm^3) and dil HCl (10 cm^3) were added leading to a white precipitate. This milky solution was extracted three times with diethyl ether. The etheral layer was dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield a white powdery solid which on recrystallisation from acetone afforded (373) as white crystals, (1.6 g, 54%), m.p. 128-130 ^{o}C (dec.); υ_{max}: 3488 (OH), 3302 (NH), 1701 and 1663 cm^{-1} (C=O); δ_H (DMSO): 2.73 (dd, 1H, J= 11.2 and 6.8 Hz, $PhC\underline{H}_ACH_B$), 2.97

(dd, 1H, J= 11.2 and 3.2 Hz, $PhCH_AC\underline{H}_B$), 3.38 (dd, 1H, J= 11.4 and 3.6 Hz, $C\underline{H}_ACH_BOH$), 3.59 (dd, 1H, J= 11.4 and 7.2 Hz, $CH_AC\underline{H}_BOH$), 4.05 (m, 1H, CH), 4.61 (br. s, 1H, OH), 7.14-7.78 (m, 9H, aromatic), 8.23 (d, 1H, J= 8.4 Hz, NH) and 13.48 ppm (br. s, 1H, OH (acid)); δ_C (DMSO): 35.7 ($PhCH_2$), 52.4 (CH_2OH), 62.0 (CH), 125.4, 126.9, 127.6, 128.5, 128.6, 128.7, 130.0, 138.3, 138.9 (aromatic), 167.5 and 167.8 ppm (C=O); (Found: C, 68.10; H, 5.77; N, 4.63. $C_{17}H_{17}NO_4$ requires C, 68.21; H, 5.72; N, 4.63%).

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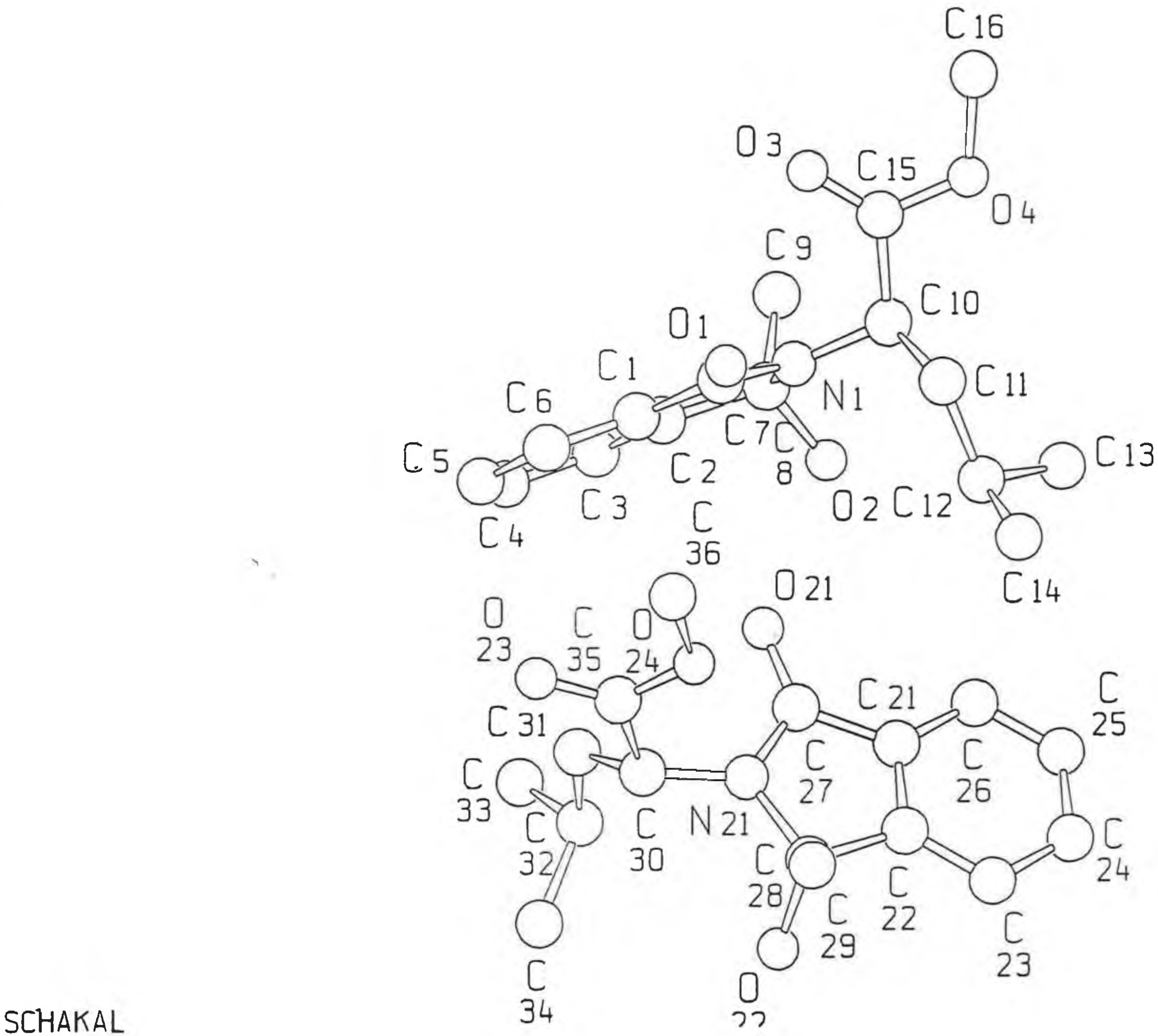
APPENDIX 1:

Bond lengths and angles for methyl (1'-R, 2S)-2-(2,3-dihydro-1-hydroxy-1-methyl-3-oxo-isoindol-2-yl) ethanoate (364)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C15
O4
C9
C10
O1
C1
N1
C11
C6
C7
C8
C5
C2
O2
C12
C13
C3
C4
C36
C14
O21
O23
C35
O24
C21
C25
C31
C27
C26
C33
C32
C30
N21
C24
C28
C29
C22
C23
C34
O22
SCHAKAL

Table 4. Bond lengths [A] and angles [deg] for 1.

O(1)-C(7)	1.226(6)
O(2)-C(8)	1.405(6)
O(3)-C(15)	1.177(7)
O(4)-C(15)	1.320(7)
O(4)-C(16)	1.433(7)
N(1)-C(7)	1.359(7)
N(1)-C(10)	1.455(6)
N(1)-C(8)	1.484(6)
C(1)-C(6)	1.373(8)
C(1)-C(2)	1.372(8)
C(1)-C(7)	1.477(8)
C(2)-C(3)	1.397(8)
C(2)-C(8)	1.507(7)
C(3)-C(4)	1.368(10)
C(4)-C(5)	1.384(11)
C(5)-C(6)	1.386(10)
C(8)-C(9)	1.524(8)
C(10)-C(11)	1.522(7)
C(10)-C(15)	1.520(7)
C(11)-C(12)	1.524(8)
C(12)-C(13)	1.514(10)
C(12)-C(14)	1.516(10)
O(21)-C(27)	1.227(6)
O(22)-C(28)	1.392(6)
O(23)-C(35)	1.195(8)
O(24)-C(35)	1.302(8)
O(24)-C(36)	1.466(9)
N(21)-C(27)	1.350(6)
N(21)-C(30)	1.463(6)
N(21)-C(28)	1.493(6)
C(21)-C(22)	1.361(7)
C(21)-C(26)	1.397(8)
C(21)-C(27)	1.478(7)
C(22)-C(23)	1.395(8)
C(22)-C(28)	1.506(7)
C(23)-C(24)	1.387(10)
C(24)-C(25)	1.381(10)
C(25)-C(26)	1.369(8)
C(28)-C(29)	1.529(7)
C(30)-C(35)	1.514(9)
C(30)-C(31)	1.530(8)
C(31)-C(32)	1.484(9)
C(32)-C(34)	1.537(10)
C(32)-C(33)	1.531(9)

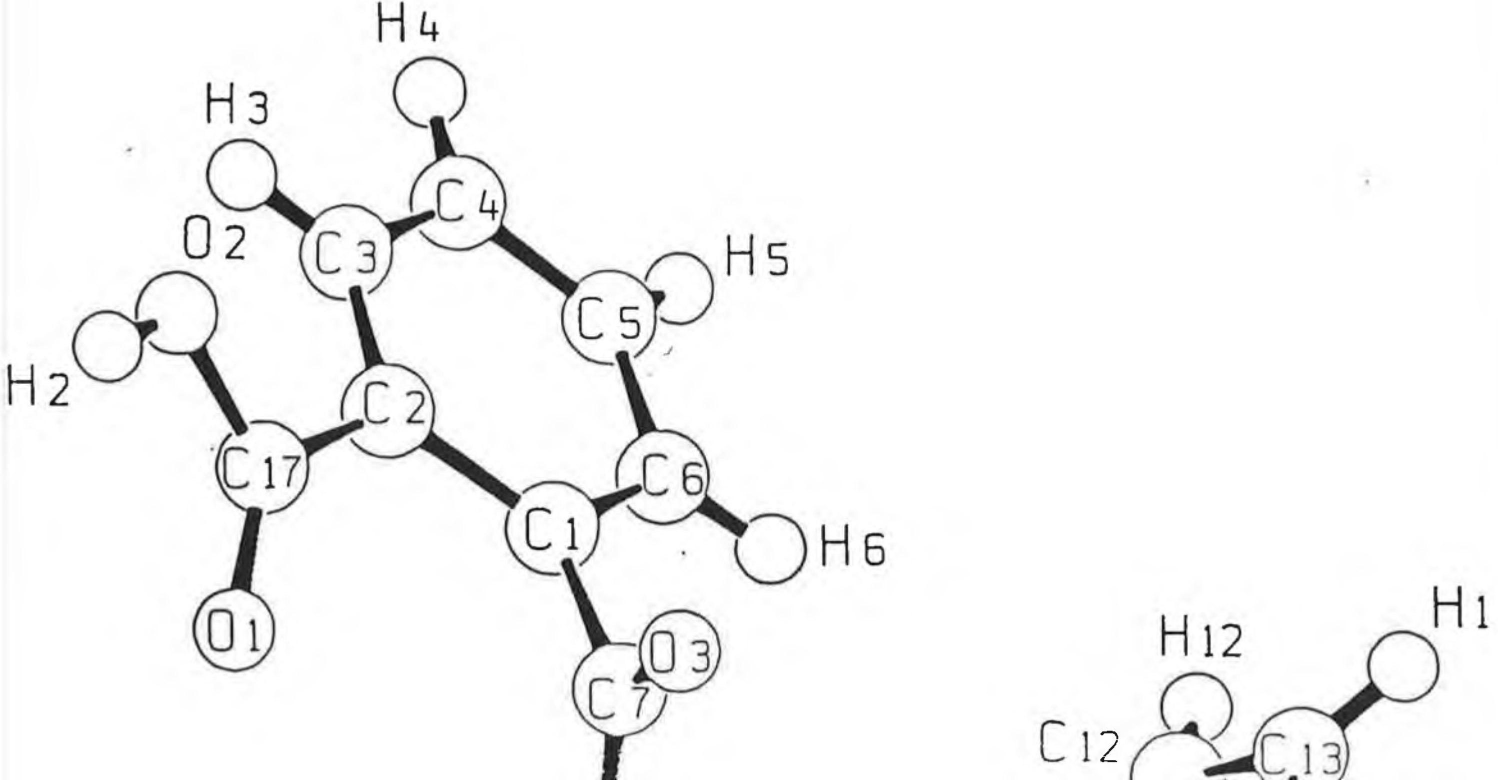
C(15)-O(4)-C(16)	116.9(5)
C(7)-N(1)-C(10)	124.0(4)
C(7)-N(1)-C(8)	113.6(4)
C(10)-N(1)-C(8)	122.2(4)
C(6)-C(1)-C(2)	122.0(5)
C(6)-C(1)-C(7)	129.6(5)
C(2)-C(1)-C(7)	108.4(5)
C(1)-C(2)-C(3)	120.2(6)
C(1)-C(2)-C(8)	111.1(5)
C(3)-C(2)-C(8)	128.7(5)
C(4)-C(3)-C(2)	117.8(6)
C(3)-C(4)-C(5)	121.8(6)
C(4)-C(5)-C(6)	120.2(6)
C(1)-C(6)-C(5)	118.0(6)
O(1)-C(7)-N(1)	125.6(5)

O(1)-C(7)-C(1)	127.8(5)
N(1)-C(7)-C(1)	106.6(4)
O(2)-C(8)-N(1)	110.3(4)
O(2)-C(8)-C(2)	112.7(4)
N(1)-C(8)-C(2)	100.3(4)
O(2)-C(8)-C(9)	107.6(4)
N(1)-C(8)-C(9)	111.6(4)
C(2)-C(8)-C(9)	114.3(5)
N(1)-C(10)-C(11)	113.7(4)
N(1)-C(10)-C(15)	111.0(4)
C(11)-C(10)-C(15)	112.2(4)
C(10)-C(11)-C(12)	114.5(5)
C(11)-C(12)-C(13)	111.2(5)
C(11)-C(12)-C(14)	109.4(6)
C(13)-C(12)-C(14)	109.5(6)
O(3)-C(15)-O(4)	124.3(5)
O(3)-C(15)-C(10)	126.3(5)
O(4)-C(15)-C(10)	109.4(5)
C(35)-O(24)-C(36)	114.8(6)
C(27)-N(21)-C(30)	124.9(4)
C(27)-N(21)-C(28)	113.2(4)
C(30)-N(21)-C(28)	121.8(4)
C(22)-C(21)-C(26)	121.7(5)
C(22)-C(21)-C(27)	109.0(4)
C(26)-C(21)-C(27)	129.2(5)
C(21)-C(22)-C(23)	121.3(5)
C(21)-C(22)-C(28)	110.6(4)
C(23)-C(22)-C(28)	128.1(5)
C(24)-C(23)-C(22)	116.5(6)
C(25)-C(24)-C(23)	122.0(6)
C(26)-C(25)-C(24)	120.9(6)
C(25)-C(26)-C(21)	117.4(6)
O(21)-C(27)-N(21)	125.8(5)
O(21)-C(27)-C(21)	127.8(5)
N(21)-C(27)-C(21)	106.4(4)
O(22)-C(28)-C(22)	108.9(4)
O(22)-C(28)-N(21)	111.1(4)
C(22)-C(28)-N(21)	100.5(4)
O(22)-C(28)-C(29)	111.9(4)
C(22)-C(28)-C(29)	113.1(4)
N(21)-C(28)-C(29)	110.8(4)
N(21)-C(30)-C(35)	114.8(5)
N(21)-C(30)-C(31)	113.5(4)
C(35)-C(30)-C(31)	108.5(5)
C(32)-C(31)-C(30)	117.8(5)
C(31)-C(32)-C(34)	112.0(6)
C(31)-C(32)-C(33)	109.5(6)
C(34)-C(32)-C(33)	109.4(6)
O(23)-C(35)-O(24)	123.4(6)
O(23)-C(35)-C(30)	123.4(6)
O(24)-C(35)-C(30)	113.3(6)

Symmetry transformations used to generate equivalent atoms:

APPENDIX 2:

Bond lengths and angles for 2-[[1-benzyl2-hydroxyethyl)amino] carbonyl] benzoic acid (373)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C3
C4
H5
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C2
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C6
C1
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O1
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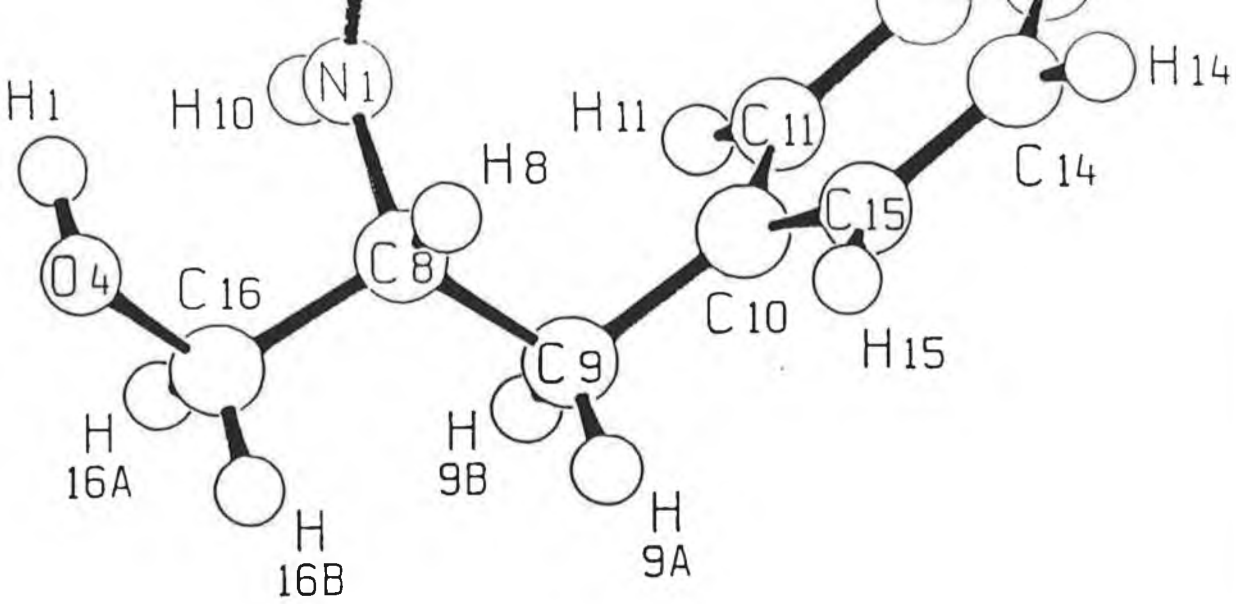
H12
H1
C12
C13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H10
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H11
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H14
H8
C14
C15
O4
C16
C8
C10
C9
H15
H
16A
H
9B
H
16B
H
9A

Table 4. Bond lengths [A] and angles [deg] for 1.

N(1)-C(7)	1.319(9)
N(1)-C(8)	1.462(10)
O(1)-C(17)	1.200(9)
O(2)-C(17)	1.317(10)
O(3)-C(7)	1.203(9)
O(4)-C(16)	1.421(10)
C(1)-C(2)	1.424(11)
C(1)-C(6)	1.416(11)
C(1)-C(7)	1.509(12)
C(2)-C(3)	1.374(11)
C(2)-C(17)	1.481(11)
C(3)-C(4)	1.379(12)
C(4)-C(5)	1.349(11)
C(5)-C(6)	1.388(11)
C(8)-C(16)	1.507(12)
C(8)-C(9)	1.535(11)
C(9)-C(10)	1.497(13)
C(10)-C(15)	1.366(14)
C(10)-C(11)	1.374(13)
C(11)-C(12)	1.347(13)
C(12)-C(13)	1.33(2)
C(13)-C(14)	1.37(2)
C(14)-C(15)	1.37(2)

C(7)-N(1)-C(8)	121.5(7)
C(2)-C(1)-C(6)	118.1(8)
C(2)-C(1)-C(7)	121.4(8)
C(6)-C(1)-C(7)	120.2(7)
C(3)-C(2)-C(1)	118.9(8)
C(3)-C(2)-C(17)	121.2(8)
C(1)-C(2)-C(17)	119.8(8)
C(4)-C(3)-C(2)	122.1(9)
C(5)-C(4)-C(3)	119.7(9)
C(4)-C(5)-C(6)	121.3(9)
C(1)-C(6)-C(5)	119.8(8)
O(3)-C(7)-N(1)	127.7(9)
O(3)-C(7)-C(1)	119.3(8)
N(1)-C(7)-C(1)	113.0(7)
N(1)-C(8)-C(16)	107.4(7)
N(1)-C(8)-C(9)	111.8(7)
C(16)-C(8)-C(9)	115.3(8)
C(10)-C(9)-C(8)	110.4(7)
C(15)-C(10)-C(11)	117.6(11)
C(15)-C(10)-C(9)	117.9(11)
C(11)-C(10)-C(9)	124.3(10)
C(10)-C(11)-C(12)	121.7(11)
C(13)-C(12)-C(11)	121.7(14)
C(12)-C(13)-C(14)	117.5(14)
C(15)-C(14)-C(13)	122.4(13)
C(10)-C(15)-C(14)	119.2(13)
O(4)-C(16)-C(8)	112.2(8)
O(1)-C(17)-O(2)	123.7(8)
O(1)-C(17)-C(2)	124.9(9)
O(2)-C(17)-C(2)	111.3(8)

Symmetry transformations used to generate equivalent atoms: