Photochemical Reactions in Natural Product Synthesis

By P. G. Sammes
DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE, LONDON, S.W.7

1 Introduction

One of the most rewarding areas for synthetic innovations in recent years has been in the field of organic photochemistry. In general, absorption of light by a molecule can produce three types of activated molecule not accessible by normal thermal means. These are the electronically excited singlet and triplet states and, often, a vibrationally 'hot' ground state. Each of these excited states may undergo different chemical reactions in proceeding back to the ground state. The triplet excited state, which generally has a relatively long lifetime is frequently encountered in photochemical reactions.

The potential complexity of photochemical reactions has deterred many chemists from exploiting them in syntheses. However, with the increased understanding of the nature of photochemical processes, the chemist is now often able to quench undesirable reaction paths and to sensitise the required course of reaction. Furthermore, because excited states possess potential energy levels above that of the ground state, photochemical reactions often lead to products with strained structures. The controlled release of such strain energy can provide a suitable driving force for subsequent reactions, as illustrated below in the synthesis of caryophyllene alcohol (p. 48).

Although related reviews[1] have been written and several excellent textbooks[2] have appeared the present review is intended to illustrate recent examples of the scope and preparative significance of photochemical reactions as applied to the synthesis of natural products. As a consequence many important photochemical reactions, such as halogenation, nitrosation[2a] and alkylation,[3] have been omitted. However, because of the importance of protecting groups in any synthetic work, a final, brief section on photosensitive protecting groups has been included.

---

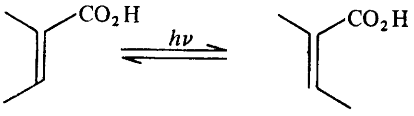
[1] (*a*) K. Schaffner, *Fortschr. Chem. org. Naturstoffe*, 1964, **22**, 1; (*b*) P. de Mayo and S. T. Reid, *Quart. Rev.*, 1961, **15**, 393; (*c*) P. de Mayo, *Adv. Org. Chem.*, 1960, **2**, 367.

[2] (*a*) A. Schönberg, 'Preparative Organic Photochemistry', Springer Verlag, Berlin, 1968; (*b*) J. G. Calvert and J. N. Pitts, 'Photochemistry', J. Wiley, New York, 1965; (*c*) R. O. Kan, 'Organic Photochemistry', McGraw-Hill Book Co., New York, 1966; (*d*) D. C. Neckers, 'Mechanistic Organic Photochemistry', Reinhold Publishing Corp., New York, 1967; (*e*) 'Organic Photochemistry', ed. O. L. Chapman, Marcel Dekker Inc., New York, 1967; (*f*) 'Advances in Organic Photochemistry', eds. W. A. Noyes, G. S. Hammond and J. N. Pitts, Interscience, New York, 1963; G. Sosnovsky, 'Free Radicals in Preparative Organic Chemistry', Macmillan Co., New York, 1964.

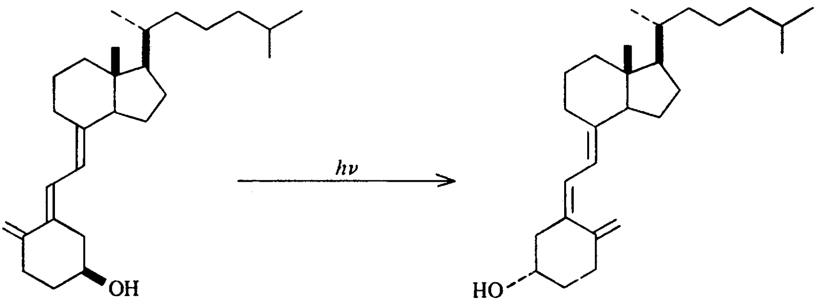
[3] D. Elad, *Fortschr. Chem. Forsch.*, 1967, **7**, 528.

2 *cis–trans* Isomerisation

The light induced isomerisation of *cis* and *trans* olefins is well documented.[4] For example, irradiation readily establishes an equilibrium between maleic (75%) and fumaric acid (25%).[5] Similarly, photolysis effects isomerisation between *cis*- and *trans*-cinnamic acids[6] and between tiglic (1) and angelic (2) acids.[7] *cis–trans* Isomerisation is of extreme importance in the visual processes associated with vitamin A[8] and in carotenoid chemistry.[3b] The conversion of *trans*-vitamin D_3 (3) into the active *cis*-isomer (4) proved crucial in the total synthesis of the vitamin.[9]



(1) (2)



(3) (4)

The mechanism of *cis–trans* isomerisation has been investigated in detail.[3,10] In the excited triplet state of simple olefins the lowest energy conformation is produced by rotation of 90° about the carbon–carbon bond.[11] It is believed that collapse to the ground state occurs from this orthogonally disposed excited

---

[4] (*a*) G. M. Wyman, *Chem. Rev.*, 1955, **55**, 625; (*b*) L. Zechmeister, '*Cis-trans* Isomeric Carotenoids, Vitamins A and Arylpolyenes', Academic Press, New York, 1962.

[5] A. R. Olsen and R. F. Hudson, *J. Amer. Chem. Soc.*, 1933, **55**, 1410.

[6] R. Stoermer, *Ber.*, 1909, **42**, 4865 and 1911, **44**, 637.

[7] S. W. Pelletier and W. L. McLeish, *J. Amer. Chem. Soc.*, 1952, **74**, 6292.

[8] M. Mousseron, *Adv. Photochem.*, 1966, **4**, 195.

[9] (*a*) H. H. Inhoffen, G. Quinkert, H. J. Hess, and H. Hirschfield, *Chem. Ber.*, 1957, **90**, 2544; (*b*) H. H. Inhoffen, H. Burchardt, and G. Quinkert, *Chem. Ber.*, 1959, **92**, 1564; (*c*) I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 1958, 837; (*d*) I. T. Harrison, R. A. A. Hurst, B. Lythgoe, and D. H. Williams, *J. Chem. Soc.*, 1960, 5176.

[10] (*a*) R. B. Cundall and P. A. Griffiths, *J. Amer. Chem. Soc.*, 1963, **85**, 1211; (*b*) G. S. Hammond, N. J. Turro, and P. S. Leermakers, *J. Phys. Chem.*, 1962, **66**, 1144.

[11] R. S. Mulliken and C. C. J. Roothan, *Chem. Rev.*, 1947, **41**, 219.

state, to form either the *cis*- or the *trans*-isomer. The isomerisation is often sensitised, since direct photolysis to the excited singlet state is often difficult to achieve, the energy required lying in the far ultraviolet region, and because intersystem crossing to give the required triplet level is inefficient. In sensitised reactions the triplet level can be reached directly by energy transfer from an excited triplet donor.[12] For stilbene Hammond's group found that high energy donors, those capable of transferring energy in excess of that required to promote either the *cis*- or *trans*-olefin to its triplet level, all afforded the same equilibrium ratio of *cis*- to *trans*-stilbene, as expected for diffusion controlled energy transfer.[12a] As lower energy sensitisers were used different ratios of the two isomers formed since the excitation energy required by either the *cis*- or the *trans*-stilbene differ, with the consequence that the sensitiser preferentially excites one of the two isomers, in this case the *trans*-isomer, so that the ratio of the *cis*-isomer in the equilibrium mixture increases. Isomerisation even occurred when the sensitiser energy was below that required to attain the usual triplet excited state of either of the starting olefins. This effect was explained by postulating that non-Franck–Condon processes occur in which excitation occurs *with*

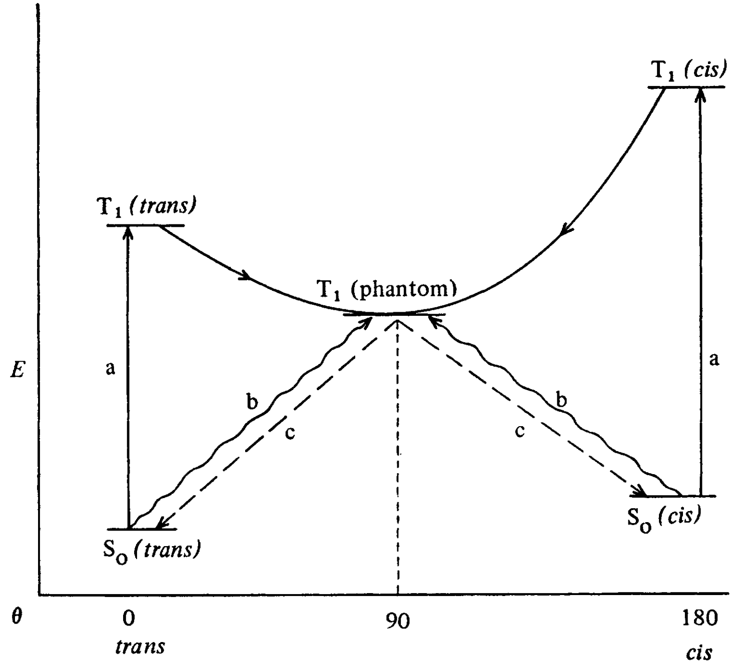


Figure 1 *Schematic representation of* cis–trans *isomerisation*
a. Sensitised excitation. b. 'Non-vertical' excitation. c. Internal conversion to the ground state. T. Triplet state. S. Singlet state. θ. Angle of twist

---

[12] (*a*) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, 1964, **86**, 3197; (*b*) P. J. Wagner and G. S. Hammond, *Adv. Photochem.*, 1968, **5**, 21.

rotation about the olefin carbon–carbon bond to give the so-called 'phantom' triplet state, *i.e.* the orthogonally oriented triplet (see Figure 1). For sensitisers of very low energy no isomerisation is possible.

3 Photolytic Electrocyclic Reactions

Conjugated olefinic systems can often undergo direct photocatalysed electrocyclic processes, recently reviewed.[13] Such reactions are extremely useful in natural product synthesis because they generally proceed along well defined stereochemical paths. An example is in the synthesis of vitamin D_2 from ergosterol (5).[14] The cyclic diene is isomerised, photolytically, into the acyclic triene, previtamin D_2 (6) by cleavage of the 9,10-carbon–carbon bond. The latter compound can undergo photocatalysed recyclisation to give back either starting material or lumisterol (7) in both of which the cyclisation has occurred in a conrotatory mode, as well as *cis–trans* isomerisation to (8). On heating, previtamin D_2 establishes an equilibrium with pyrocalciferol (9) and isopyrocalciferol (10), the thermal cyclisations occurring in a disrotatory manner. At the same time a thermal sigmatropic rearrangement occurs to give vitamin D_2 (11).

The photoisomerisation of a cyclic diene into a triene has also been used in an elegant synthesis of dihydrocostunolide (12).[15] Photolysis of the bicyclic lactone diene (14), derived from α-santonin (13), gives an equilibrium mixture with the medium ring triene (15), again by a conrotatory process. Because of strain in the medium ring triene conjugation is restricted and selective reduction of the central *cis*-disubstituted bond with Raney nickel is readily effected to yield dihydrocostunolide (12). A simple extension of this reaction has allowed the conversion of the *trans*-fused bicyclic precursor (16) into the *cis*-fused compound, occidentalol (17).[16] Cyclisation of the intermediate triene occurs thermally by a disrotatory process.

Since the hexatriene–cyclohexadiene isomerisation is reversible, suitable trienes are readily cyclised.[17] For example, *cis*-stilbene is cyclised on photolysis to 9,10-dihydrophenanthrene, the *trans*-isomer forming. Mild oxidation of the latter with air, iodine,[18] or cupric chloride,[19] produces phenanthrene. This very useful reaction has been applied to the synthesis of aporphine alkaloids.[20] For example, the substituted stilbene (18) on photolysis can lead to (±)-nuciferine (19).[21] The reaction is general and other triene systems will also cyclise. Thus the anil (20) cyclises upon irradiation, provided the nitrogen atom is

---

[13] G. B. Gill, *Quart. Rev.*, 1968, **22**, 338.

[14] (*a*) B. Lythgoe, *Proc. Chem. Soc.*, 1959, 141; (*b*) H. H. Inhoffen, *Angew. Chem.*, 1960, **72**, 875; (*c*) E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, 1961, **16**, 146.

[15] E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, 1963, **85**, 4033.

[16] A. G. Hortmann, *Tetrahedron Letters*, 1968, 5785.

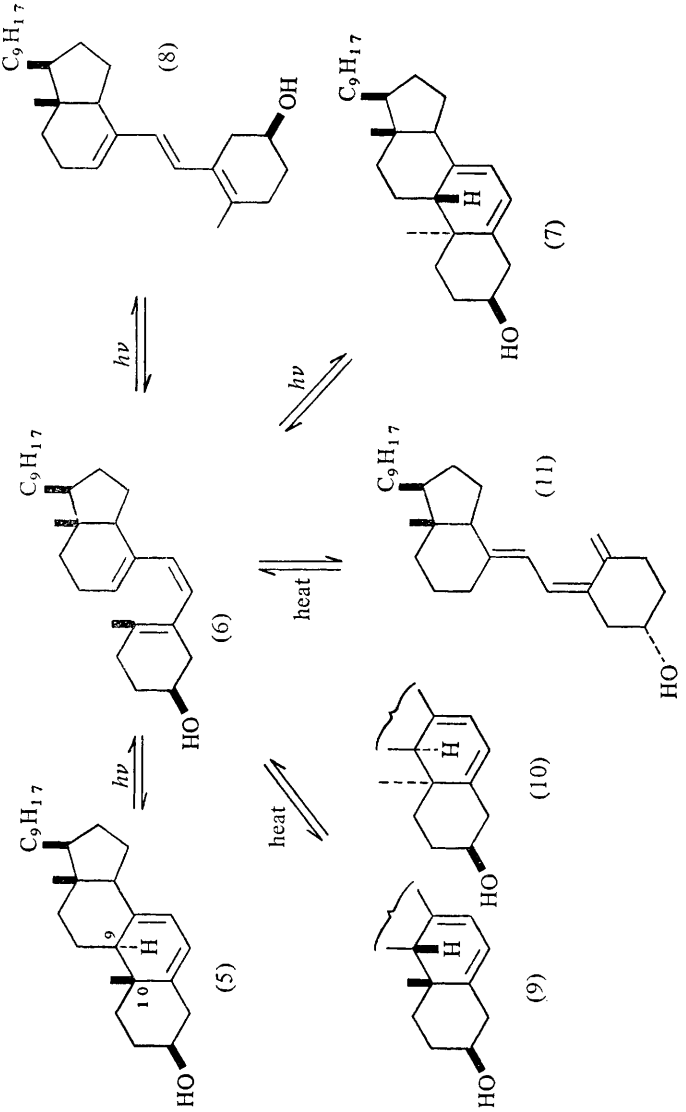
[17] F. R. Stermitz, 'Organic Photochemistry', ed. O. L. Chapman, Marcel Dekker Inc., New York, vol. 1, 1967, p. 247.

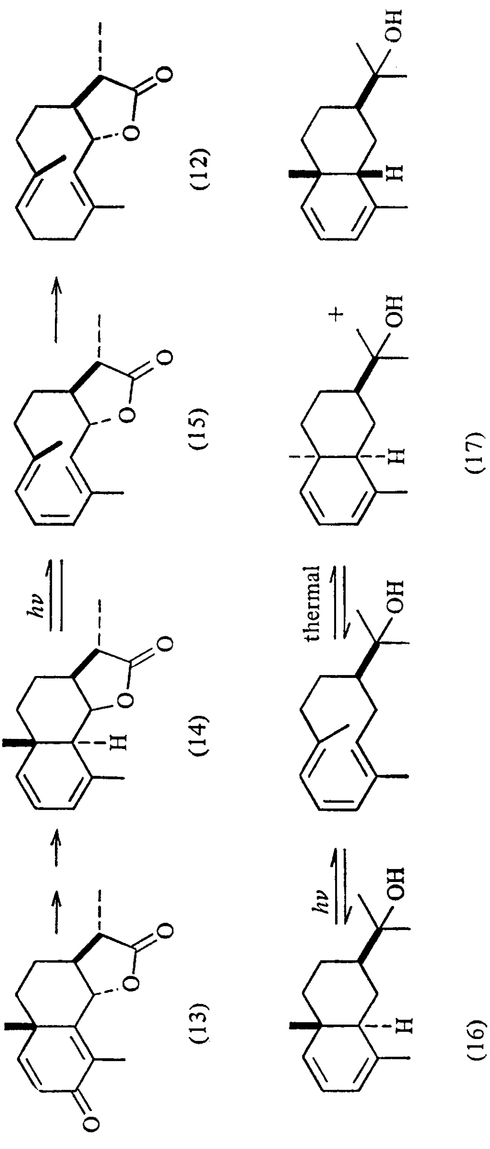
[18] C. S. Wood and F. B. Mallory, *J. Org. Chem.*, 1964, **29**, 3373.

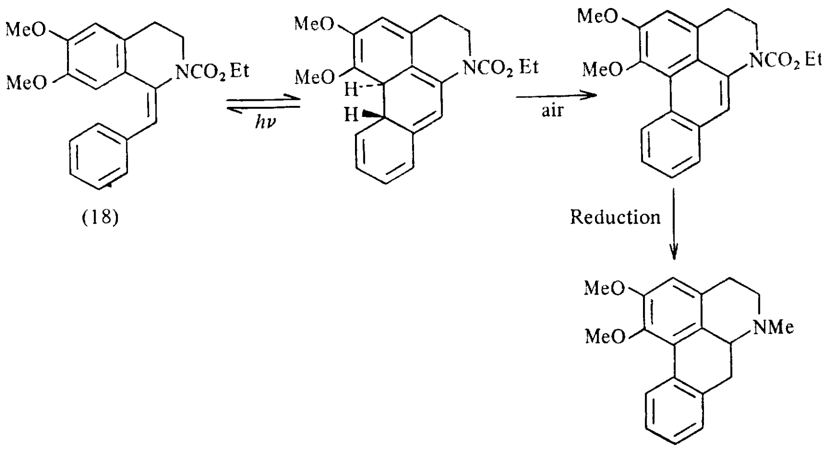
[19] D. J. Collins and J. J. Hobbs, *Chem. and Ind.*, 1965, 1725.

[20] N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Letters*, 1966, 2941.

[21] M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters*, 1966, 2937.

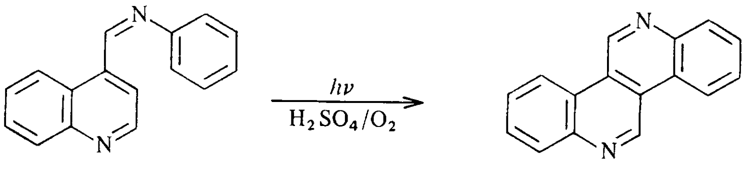

(8)
(7)
(6)
(11)
(5)
(10)
(9)
$h\nu$
$h\nu$
$h\nu$
heat
heat
C_9H_{17}
HO
OH
H
9
10


(13)
(14)
(15)
(12)
hν
(16)
(17)
(12)
hν
thermal
OH
H
O



(18)

(19)



(20)

(21)

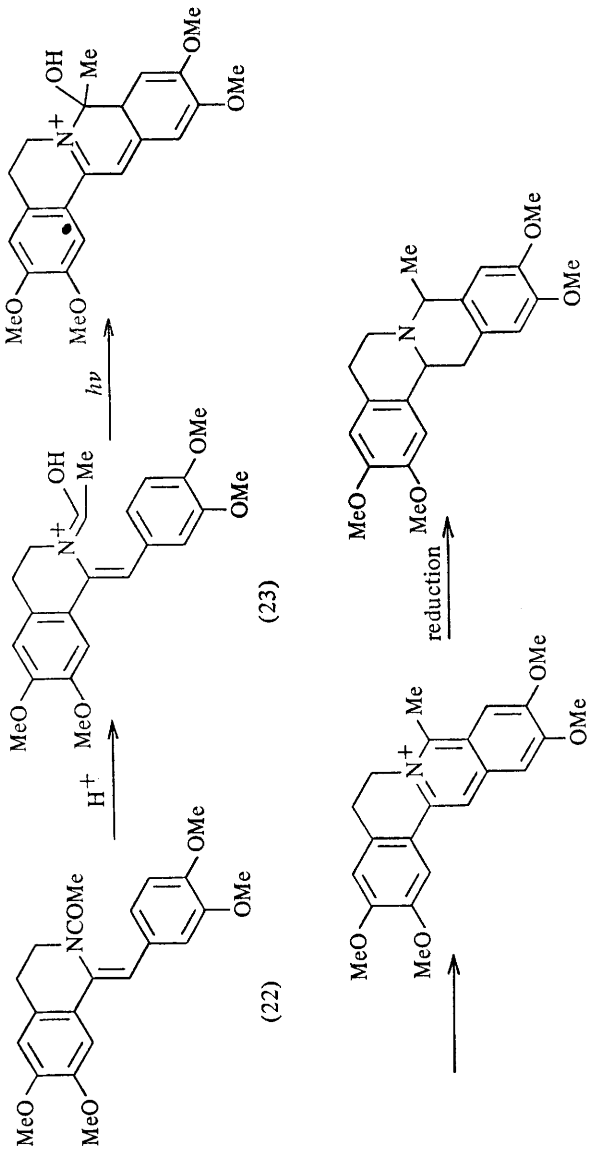
protonated, to give calycanine (21),[22] a degradation product of the alkaloid calycanthine.[23]

Under acidic conditions amides such as (22) can also be cyclised by irradiation. Presumably the acid protonates the amide group to give the immonium alcohol (23), which has increased carbon to nitrogen double bond character, so that it behaves as a hexatriene system. The cyclised isomer can re-aromatise by loss of water. Borohydride reduction of the salt (24) yields the protoberberine alkaloid, β-coryaldine (25).[24] The observed mode of cyclisation is of interest in that little of the competing reaction leading to the aporphine skeleton was obtained. It appeared, therefore, that cyclisations were preferred which aromatise without the need of oxidation. Using this argument Kupchan considered that a more efficient way of effecting similar conversions was to replace one of the hydrogen atoms, normally removed by oxidation, by a good leaving group. The iodo-

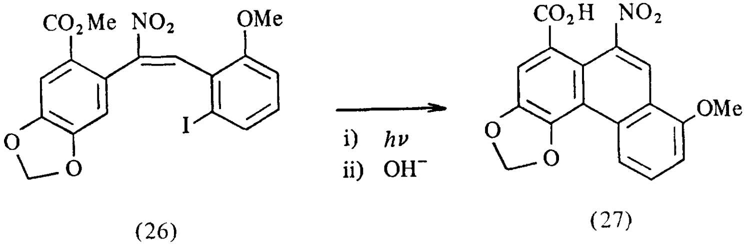
[22] V. M. Clark and A. Cox, *Tetrahedron*, 1966, **22**, 3421.

[23] R. B. Woodward, N. C. Yang, T. J. Katz, V. M. Clark, J. Harley-Mason, R. F. J. Ingleby, and N. Sheppard, *Proc. Chem. Soc.*, 1960, 76.

[24] G. R. Lenz and N. C. Yang, *Chem. Comm.*, 1967, 1136.

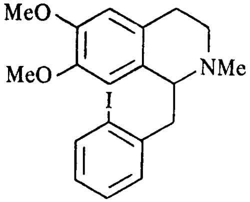

(22)
(23)
(24)
(25)
H+
hν
reduction
MeO
OMe
NCOMe
OH
Me
N+
N

group was found to be useful for this purpose.[25] Thus the iodostilbene (26) cyclised to give aristolochic acid (27), whereas classical methods for its synthesis had failed. In a detailed study of the mechanism of this reaction, however, it was concluded that the reaction does not proceed *via* a dihydrophenanthrene type of intermediate but instead by prior homolysis of the carbon to iodine bond.[26] Nevertheless, this alternative method of cyclisation is of general synthetic application. It has been used in an alternative synthesis of (±)-nuciferine (19), *via* photolysis of the precursor (28) as its hydrochloride salt.[27]



(26)

(27)



(28)

Further ramifications of the photocyclisation reactions have been exploited in syntheses. Brockmann has studied the cyclisation of bianthrone derivatives,[28] the work culminating in the synthesis of hypericine (30) from protohypericine (29).[29] This process is believed to be involved in the biosynthetic route to hypericine.

Diphenylamine and its derivatives form the corresponding carbazoles on irradiation.[30] The presence of a mild oxidising agent is beneficial but does not appear to be essential.[31] The alkaloid glycozoline (32) was readily prepared from the amine (31).[32]

[25] S. M. Kupchan and H. C. Wormser, *Tetrahedron Letters*, 1965, 359.

[26] S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, 1965, **30**, 3792.

[27] S. M. Kupchan and R. M. Kanojia, *Tetrahedron Letters*, 1966, 5353.

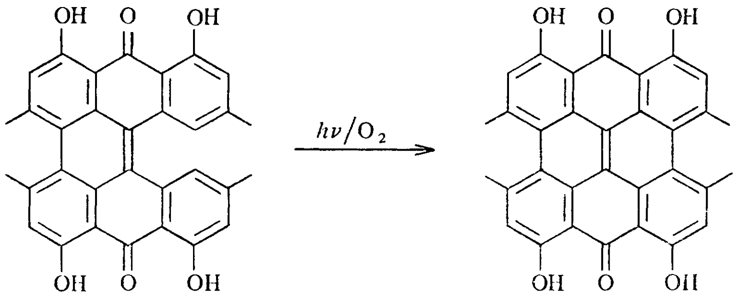
[28] H. Brockmann, R. Neef, and E. Mühlmann, *Chem. Ber.*, 1950, **83**, 467.

[29] H. Brockmann and H. Eggers, *Angew. Chem.*, 1965, **67**, 706.

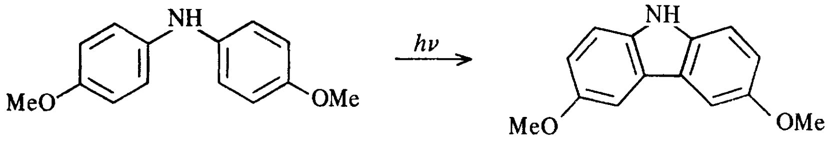
[30] C. A. Parker and W. J. Barnes, *Analyst*, 1957, **82**, 606.

[31] E. J. Bowen and J. H. D. Eland, *Proc. Chem. Soc.*, 1963, 202.

[32] W. Carruthers, *Chem. Comm.*, 1966, 272.

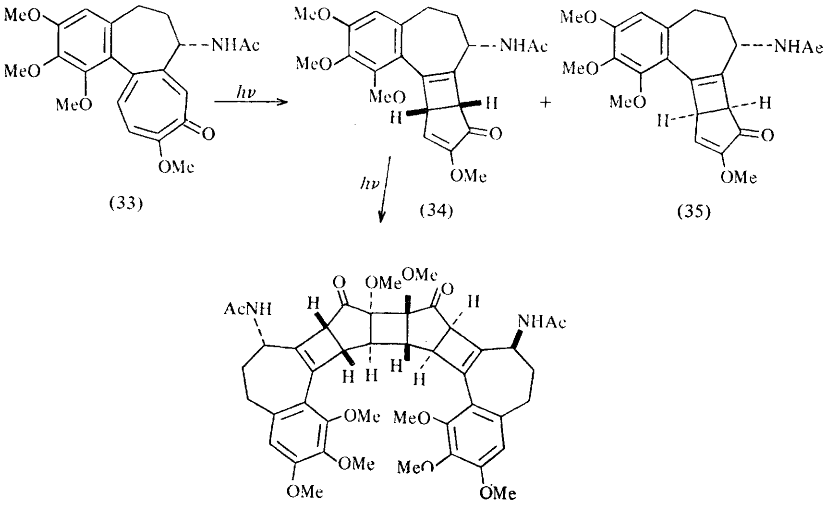


(29) (30)



(31) (32)

According to theory the electrocyclic process, hexatriene to cyclohexadiene, is one of a series of reactions.[13] Conjugated butadienes should also photoisomerise to the corresponding cyclobutenes by a concerted, disrotatory process.[33] Such



(33) (34) (35)

(36)

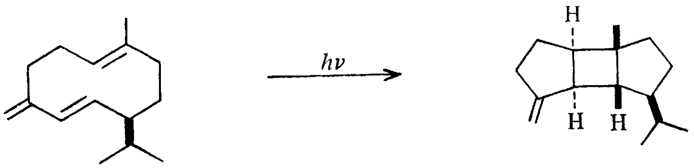
---

[33] R. Srinivasan, *Adv. Photochem.*, 1966, **4**, 113.

a reaction is realised in the conversion of colchicine (33) by sunlight to β-lumicolchicine (34) and its γ-isomer (35).[34] The β-isomer is further converted by light to give the dimer, α-lumicolchicine (36).[35] These processes have been achieved *in vitro*.[36]

4 Cycloaddition Reactions

The addition of an olefin to another double bond can be catalysed by light.[37] However, simple olefins absorb in the far ultraviolet region which is difficult to reach experimentally, particularly for preparative work. This problem can be overcome by either using sensitisers, in which case reactions can proceed *via* the triplet manifold,[12] or by using suitable derivatives of olefins which absorb at longer wavelengths, *i.e.* either by conjugation or suitable intramolecular interaction. Thus germacrene D (37), in which there is a strong transannular effect, has λ_{max} at 259nm (ϵ 4500). Direct photolysis gives mainly (−)-β-bourbonene (38).[38]



(37) (38)

A similar example is the photolysis of myrcene (39) which gave, besides the more favoured cyclobutene derivative (41), some β-pinene (40).[39] Better yields of the latter would be expected at higher temperatures where the cyclobutene could thermally reform starting diene. In contrast, the sensitised photolysis gives neither (40) nor (41) but instead the bicyclobutane (43).[40] The sensitised cyclisation proceeds *via* a triplet excited state. This state behaves as a diradical and the two bond forming steps occur consecutively.[41] Primary bond formation has a choice as to where it will occur. In such cases the preferred, initial, reaction will tend to form a five-membered ring, where possible, in preference to a smaller or bigger size.[42] This empirical guide is known as the 'rule of five'.[43]

---

[34] F. Santavy, *Coll. Czech. Chem. Comm.*, 1950, **15**, 552.

[35] O. L. Chapman, H. G. Smith, and R. W. King, *J. Amer. Chem. Soc.*, 1963, **85**, 806.

[36] (*a*) E. J. Forbes, *J. Chem. Soc.*, 1955, 3864; (*b*) P. D. Gardner, R. L. Brandon, and G. R. Haynes, *J. Amer. Chem. Soc.*, 1957, **79**, 6334.

[37] J. S. Swenton, *J. Chem. Educ.*, 1969, **46**, 7.

[38] K. Yoshihara, Y. Ohta, T. Sakai, and Y. Hirose, *Tetrahedron Letters*, 1969, 2263.

[39] K. J. Crowley, *Proc. Chem. Soc.*, 1962, 245.

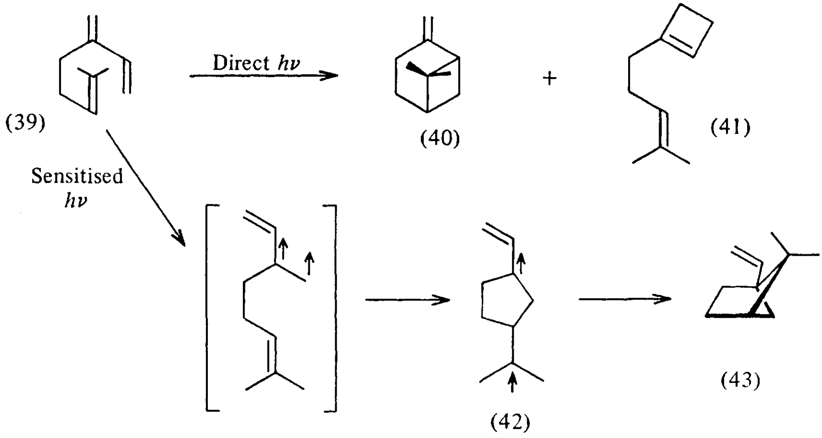
[40] R. S. H. Liu and G. S. Hammond, *J. Amer. Chem. Soc.*, 1967, **89**, 4936.

[41] *Cf.* P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.*, 1960, **82**, 3217.

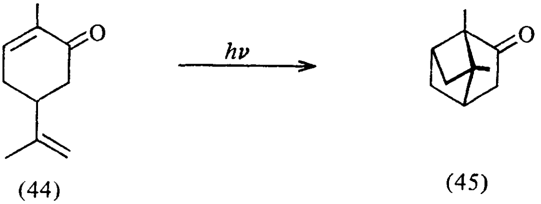
[42] (*a*) R. C. Lamb, P. W. Ayers, and K. M. Toney, *J. Amer. Chem. Soc.*, 1963, **85**, 3483; (*b*) N. O. Brace, *J. Amer. Chem. Soc.*, 1964, **86**, 523; (*c*) C. Walling and M. S. Pearson, *J. Amer. Chem. Soc.*, 1964, **86**, 2262.

[43] R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, 1967, **89**, 4932.

For myrcene the primary step probably yields the most stable diradical (42), followed by cyclisation to the bicyclobutane (43).



On irradiation conjugated ketones can add to olefins to give a cyclobutane derivative.[44] One of the first reported examples of this extremely important reaction was the intramolecular photocyclisation of carvone (44) to carvone-camphor (45).[45] Corey was the first to realise that intermolecular applications of this reaction could be useful for the synthesis of natural products.[46] In an elegant demonstration of its potential 4,4-dimethylcyclopentene (46) and 3-methylcyclohex-2-enone (47) were photolysed to give a mixture of *cis*- and *trans*-fused strained tricyclic ketones. The main isomer was the *cis-anti-cis* form (48). Addition of methyllithium gave the corresponding tertiary alcohol (49). Treatment of the alcohol with acid catalysed loss of water to give a carbonium ion followed by 1,2-bond rearrangement to relieve strain from the cyclobutane moiety. Quenching of the rearranged carbonium ion with water afforded, directly, α-caryophyllene alcohol (50).

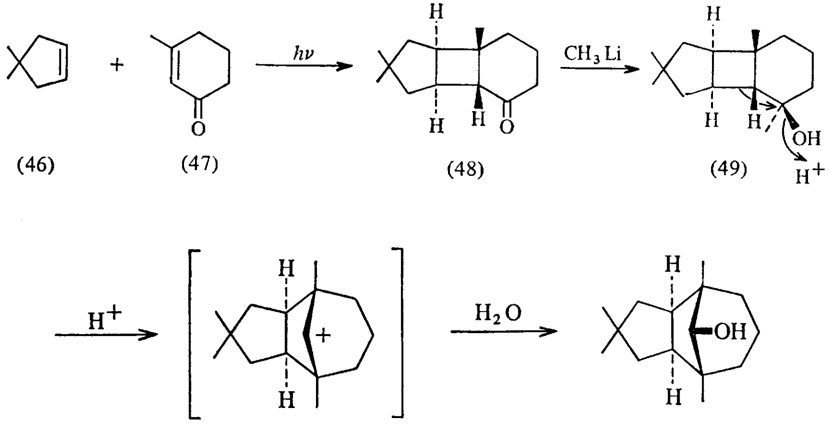


---

[44] (*a*) P. E. Eaton, *J. Amer. Chem. Soc.*, 1962, **84**, 2344 and 2454; (*b*) R. Criegee and H. Furrer, *Chem. Ber.*, 1964, **97**, 2949.

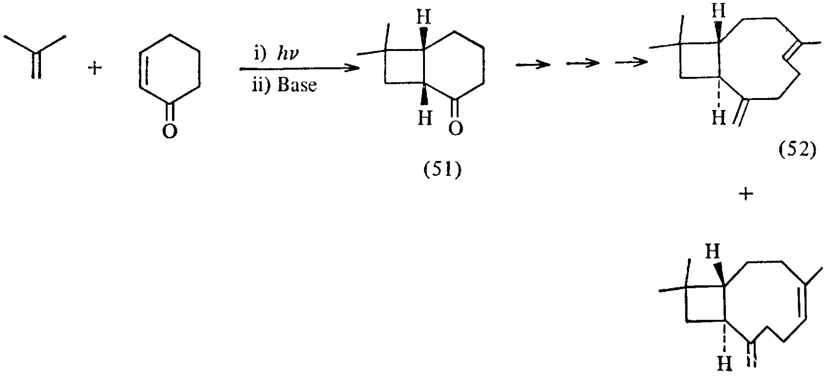
[45] (*a*) G. Ciamician and P. Silber, *Ber.*, 1908, **41**, 1928; (*b*) G. Büchi and I. M. Goldman, *J. Amer. Chem. Soc.*, 1957, **79**, 4741.

[46] E. J. Corey and S. Nozoe, *J. Amer. Chem. Soc.*, 1964, **86**, 1652.



(46) (47) (48) (49) (50)

In a related synthesis,[47] isobutene was added to cyclohexenone to give a mixture of (4,2,0)-bicycloketones. Mild base yielded mainly the *cis*-isomer (51) which was used as starting material in a synthesis of (±)-caryophyllene (52) and (±)-isocaryophyllene (53).



(51) (52) (53)

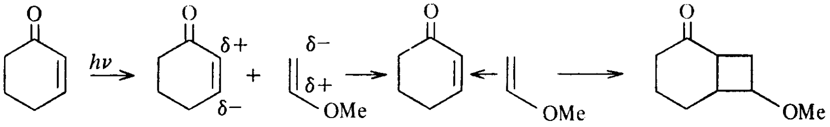
The addition of substituted olefins to cyclohexenones is often stereoselective. The direction of addition is that expected for a stepwise reaction with formation of an intermediate diradical. A probable explanation for the stereoselectivity involves initial excitation of the enone, by an $n \rightarrow \pi^*$ transition, to give a triplet state which is polarised (*e.g.* 54).[48] An approaching olefin (*e.g.* 55) would also be polarised to give an oriented complex, possibly even a charge transfer com-

---

[47] E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, 1964, **86**, 485.

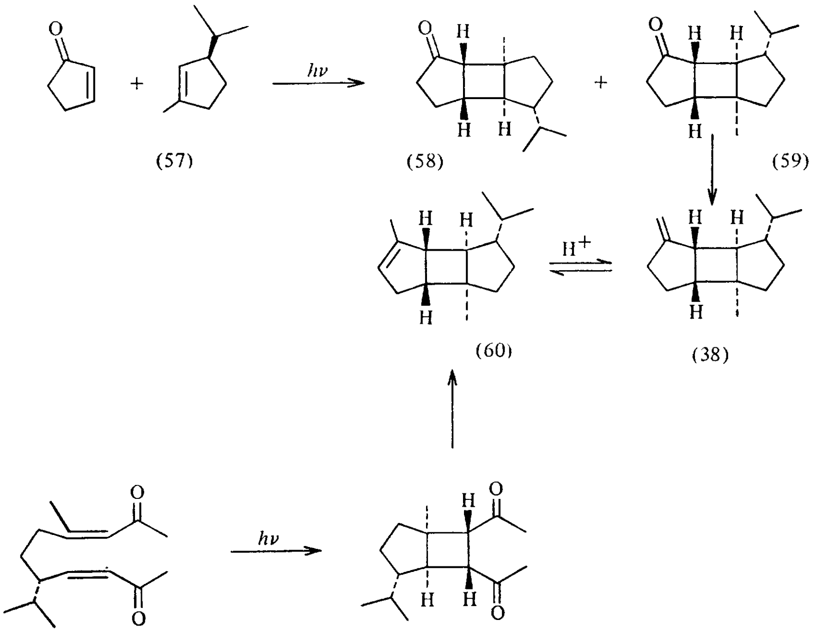
[48] E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, 1964, **86**, 5570.

plex, followed by bonding at the 2-position of the enone with the nucleophilic end of the olefin and final collapse to the observed product (56).



(54) (55) (56)

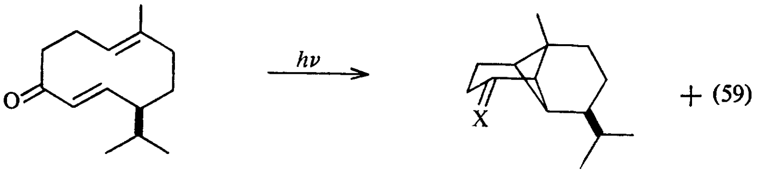
Several approaches to the synthesis of the bourbonenes have been reported. In one,[49] photolysis of a mixture of 2-cyclopentenone and the cyclopentene (57) gave a 1:1 mixture of *cis-anti-cis* head to tail (58) and head to head (59) adducts. Treatment of the latter ketone with methylenetriphenylphosphorane yielded β-bourbonene (38), which could be equilibrated with acid to give α-bourbonene (60). An alternative route started with the bis-enone (61) which was irradiated to give the diketone (62), that could be condensed and converted into α-bourbonene.[50]



(57) (58) (59) (60) (38) (61) (62)

[49] J. D. White and D. N. Gupta, *J. Amer. Chem. Soc.*, 1968, **90**, 6171.
[50] M. Brown, *J. Org. Chem.*, 1968, 33, 162.

In a related study[51] the cyclodecadienone (63) was photolysed to give substantial amounts of the ketone (64), an effective precursor of copaene (65)[52] and the ketone (59). In contrast germacrene D (37) gave only small amounts of

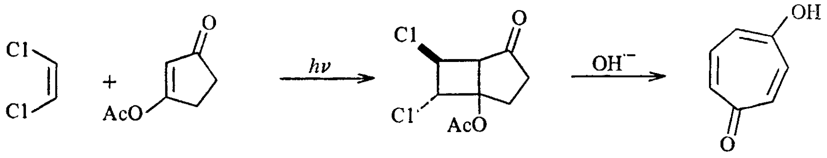


(63)

(64, X = O)
(65, X = CH_2)

copaene on photolysis (see above). It is probable that the cyclisation of germacrene D proceeds by a singlet excited state in a concerted manner. Sensitised photolysis of germacrene would be expected to give more copaene.

The synthetic utility of such photocycloaddition reactions has been considerably extended by de Mayo.[53] Irradiation of cyclic 1,3-diones, or their enol acetate esters, with olefins gives a strained cyclobutane of the β-hydroxyketone type. These may spontaneously deketolise to give the ring expanded cyclic system by the addition of two carbon atoms. The reaction is exemplified by the synthesis of γ-tropolone.[54] Dichloroethylene and the enol acetate of 1,3-cyclopentadione (66) were photolysed and the reaction product immediately hydrolysed with methanolic base to give, directly, γ-tropolone (67).



(66)

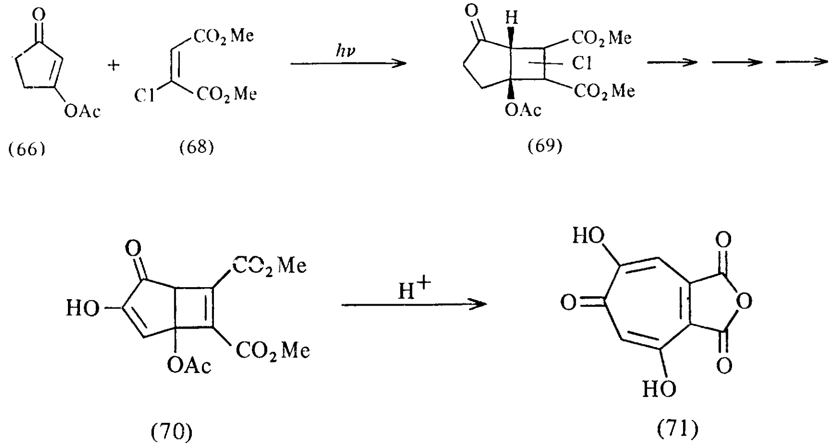
(67)

Cycloaddition of the enol acetate (66) to dimethyl chloromaleate (68) gave a mixture of isomeric adducts (69) which could be brominated with pyridinium perbromide, followed by treatment with silver oxide and oxidation with sodium bismuthate to give the bicyclic dione (70). Mild acid hydrolysis removed the acetate group and the resulting β-hydroxyketone spontaneously deketolised

---

[51] C. H. Heathcock and R. M. Badger, *Chem. Comm.*, 1968, 1510.
[52] (*a*) V. H. Kapadia, B. A. Nagsampagi, V. G. Naik, and S. Dev, *Tetrahedron*, 1965, **21**, 607; (*b*) P. de Mayo, R. E. Williams, G. Büchi, and S. H. Feairheller, *Tetrahedron*, 1965, **21**, 619.
[53] P. de Mayo, *Pure Appl. Chem.*, 1964, **9**, 597.
[54] H. Hikino and P. de Mayo, *J. Amer. Chem. Soc.*, 1964, **86**, 3582.

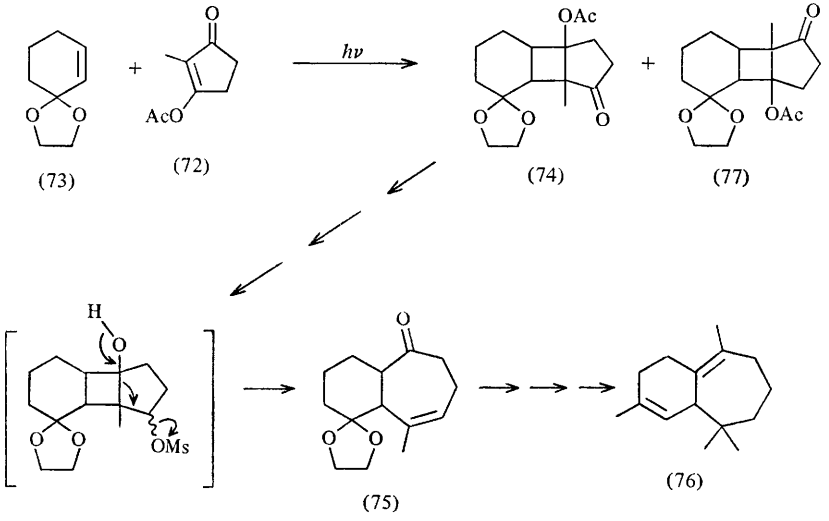
to give the naturally occurring tropolone, stipitatonic acid (71), a synthesis that would be difficult to achieve by classical means.[55]



(66) (68) (69)

(70) (71)

By the use of the appropriate precursors fused bicyclic systems containing a seven membered ring can also be synthesised. Thus β-himachalene (76) has been prepared from the enol acetate (72) and the acetal (73). Photolysis gave a good yield of the required adduct (74) but, as an alternative to dealdolisation, the ketone moiety was reduced to the alcohol followed by formation of the mesylate



(73) (72) (74) (77)

(75) (76)

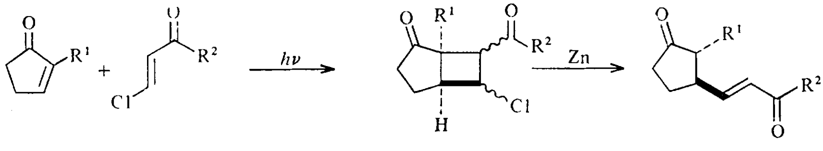
---

[55] G. L. Lange and P. de Mayo, *Chem. Comm.*, 1967, 704.

ester and then hydrolysis. Fragmentation to the keto-olefin (75) occurred, which was eventually converted into the desired hydrocarbon.[56]

A study of the factors affecting the initial photocyclisation in the latter case showed that, for non-polar solvents, addition was highly stereoselective giving mainly (74), but as solvent polarity increased this preference decreased and more of the isomer (77) formed. This result again points to the importance of dipolar interactions between reactants.[57] That these reactions may also be sensitised indicates operation of a triplet mechanism.[58]

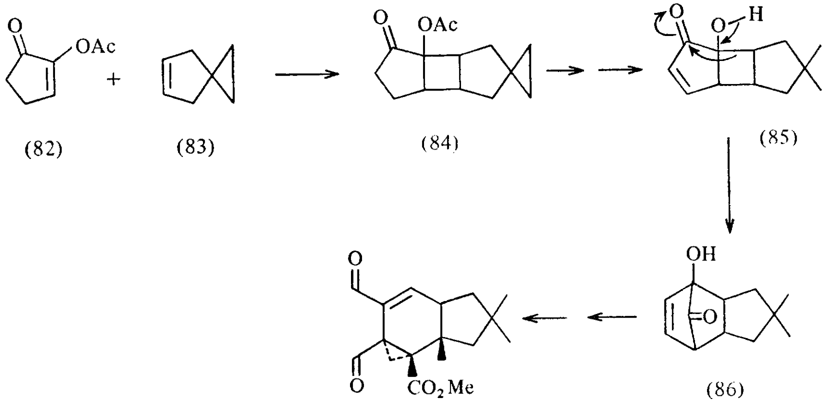
Various ramifications of these additions to enones have recently been applied to synthetic work. A route to the prostanoic acids, *e.g.* (81), started from the cyclopentenone (78) and the chloro-olefin (79).[59] This approach takes advantage of the fact that strained 1,4-diketones, such as the adduct (80), are readily reduced by zinc dust with opening of the cyclobutane ring to give the diketone (81). de Mayo has recently discovered that enol esters of cyclopenta-1,2-diones also add to olefins. Thus the acetate (82) adds to the cyclopentene (83) to give an adduct (84). This particular cyclopentene was chosen because of its ready



(78) (79) (80) (81)

$R^1 = (CH_2)_6CO_2CH_3$

$R^2 = (CH_2)_4CH_3$



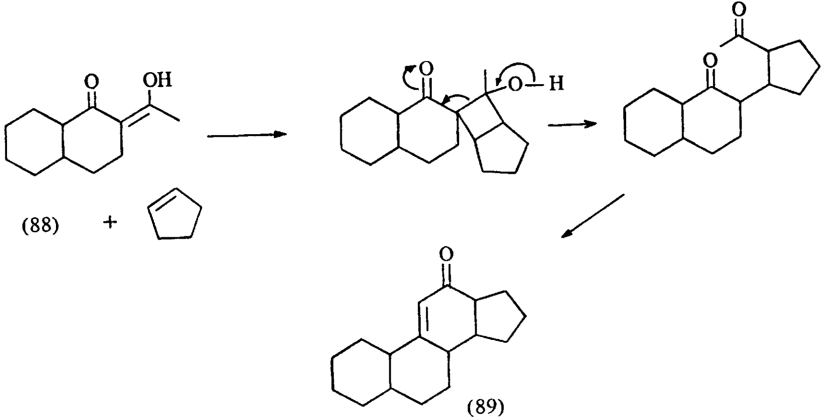
(82) (83) (84) (85) (86) (87)

---

[56] B. D. Challand, G. Kornis, G. L. Lange, and P. de Mayo, *Chem. Comm.*, 1967, 704.
[57] B. D. Challand and P. de Mayo, *Chem. Comm.*, 1968, 982.
[58] H. Nozaki, M. Kurita, T. Mori, and R. Noyori, *Tetrahedron*, 1968, **24**, 1821.
[59] J. F. Bagli and T. Bogri, *Tetrahedron Letters*, 1969, 1639.

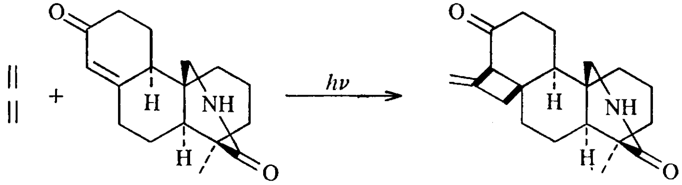
availability and because the cyclopropane ring in the adduct is readily hydrogenated to the required dimethyl derivative. Subsequent oxidation gave the cyclopentenone (85), which rearranged on hydrolysis, with mild base, to relieve strain in the fused cyclobutane ring. The ring expanded product (85) was used in an approach to the synthesis of methyl isomarasmate (87).[60]

The usefulness of these cycloaddition reactions is further clearly demonstrated by the synthesis of the steroid skeleton (89) in good yield from the β-diketone (88) and cyclopentene.[58]

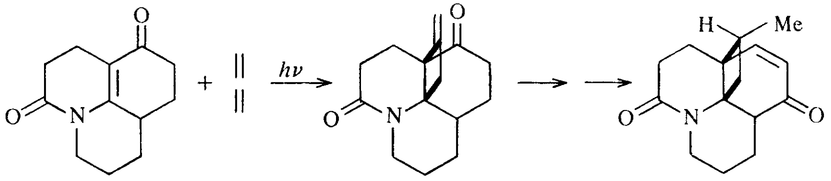


(88) +

(89)



(90) (91)



(92) (93) (94)

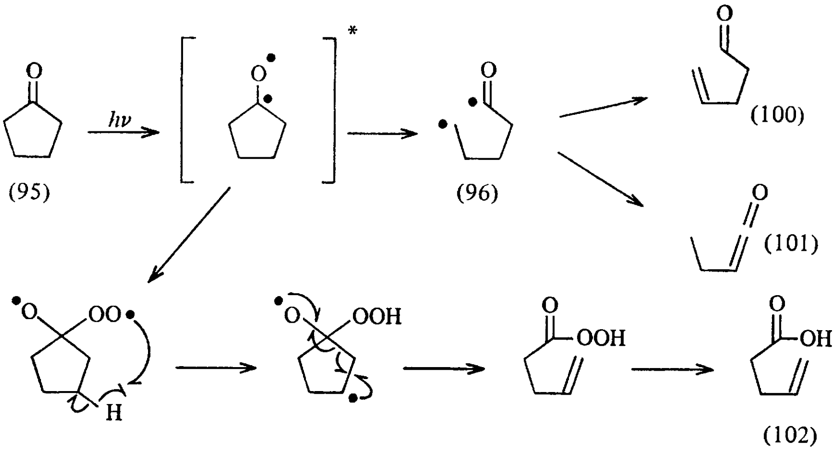
---

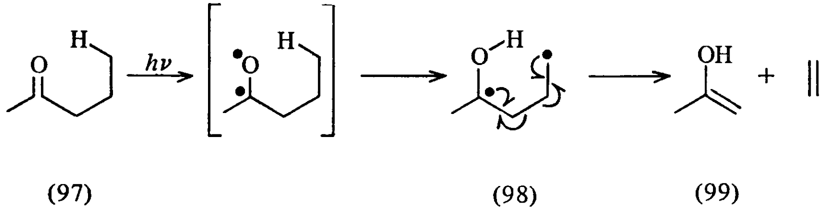
[60] P. de Mayo, D. Helmlinger, R. B. Yates, and L. Westfelt, Abstracts International Symposium on 'Synthetic Methods and Rearrangements in Alicyclic Chemistry', Oxford, July, 1969, The Chemical Society, London, p. 32.

The addition of allene to the $\alpha\beta$-unsaturated ketone (90) has been used in the synthesis of the diterpenic alkaloids atisine[61] and veatchine,[62] *via* the intermediate (91). Similarly, vinylogous amides also add to allene and this has been made the basis of an approach to the lycopodium alkaloids.[63] For example, reaction of the amide (92) with allene gives the cyclobutene (93), further converted into the known degradation product, annatonine (94).[64]

5 Photolysis of Carbonyl Groups

General trends in the reactivity of carbonyl groups have been well established.[65] Saturated ketones react, principally, either by α-cleavage (*e.g.* 95 to 96), the Norrish Type I process, or by γ-hydrogen abstraction (*e.g.* 97 to 98), often followed by further fragmentation, as in the Norrish Type II process (98 to 99). Both reactions are believed to take place *via* an excited $n \rightarrow \pi^*$ triplet state.[66]





---

[61] R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1966, 4645.

[62] K. Wiesner, S. Uyeo, A. Philipp, and Z. Valenta, *Tetrahedron Letters*, 1968, 6279.

[63] K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Letters*, 1968, 5643.

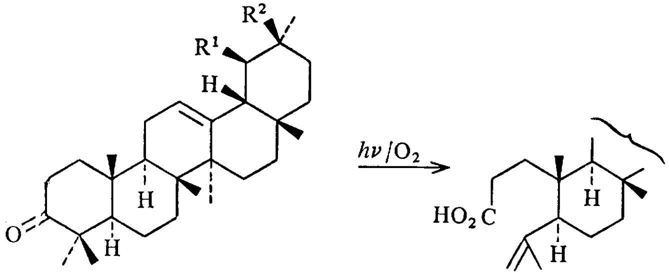
[64] K. Wiesner, I. Jirkovsky, M. Fishman, and C. A. J. Williams, *Tetrahedron Letters*, 1967, 1523.

[65] J. S. Swenton, *J. Chem. Educ.*, 1969, **46**, 217.

[66] R. Srinivasan, *Adv. Photochem.*, 1963, **1**, 83.

A. Cyclic Ketones.—These very often do not possess an available hydrogen atom and, therefore, α-cleavage is often favoured. The diradical (*e.g.* 96) can collapse to either an aldehydo-olefin (100) or a keten (101).[67] In the presence of oxygen an olefin-carboxylic acid can result, formed by addition of oxygen to the excited carbonyl group (*e.g.* 95 to 102).

In this way Quinkert has been able to synthesise nyctanthic acid (105) from β-amyrone (103), and roburic acid (106) from α-amyrone (104).[68]

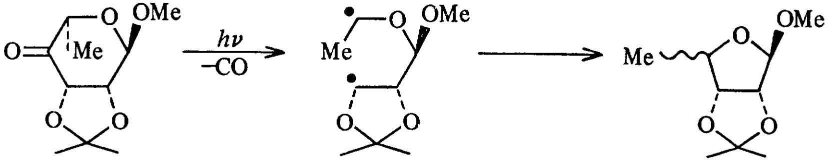


(103, R^1 = H, R^2 = Me)
(104, R^2 = Me, R^2 = H)

(105, R^1 = H, R^2 =Me)
(106, R^1 = Me, R$_2$ = H)

Loss of carbon monoxide from the diradical formed during α-cleavage (*e.g.* 96) only occurs, in solution, if the resulting diradical is stabilised.[69] Thus the sugar pyranosidulose (107) collapses to the diradical (108) by extrusion of carbon monoxide since both the radicals are stabilised by α-oxygen substituents; recombination leads to the furanoid pentoses (109).[70]

Suitably α-substituted cyclic ketones which possess an available γ-hydrogen atom also collapse by the Norrish Type II process.[71] Thus colupulone (110),



(107) (108) (109)

---

[67] G. Quinkert, *Angew. Chem. Internat. Edn.*, 1962, **1**, 166.

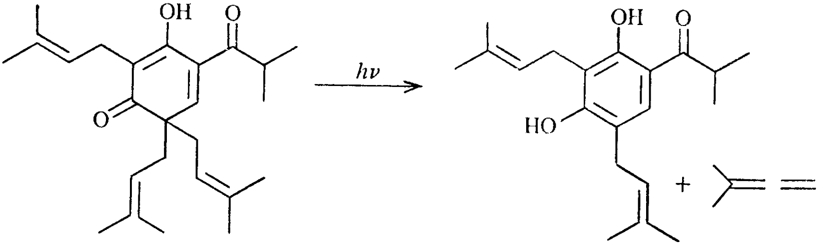
[68] G. Quinkert and H.-G. Heine, *Tetrahedron Letters*, 1963, 1659.

[69] (*a*) G. Quinkert, *Pure Appl. Chem.*, 1964, **9**, 607; (*b*) M. P. Cava, and D. Mangold, *Tetrahedron Letters*, 1964, 1751; (*c*) K. Mislow and A. J. Gordon, *J. Amer. Chem. Soc.*, 1963, **85**, 3521.

[70] (*a*) P. M. Collins, *Chem. Comm.*, 1968, 403; (*b*) For a review on the photochemistry of carbohydrates see G. O. Phillips, *Adv. Carbohydrate Chem.*, 1963, **18**, 9.

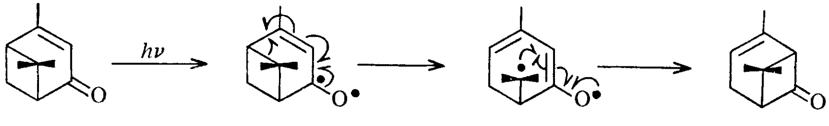
[71] J. E. Gano, *Tetrahedron Letters*, 1969, 2549.

which is very sterically crowded about the ring carbonyl function, gives a good yield of 4-deoxycohumulone (111).[72] Similar reactions of quinones are well documented.[73]

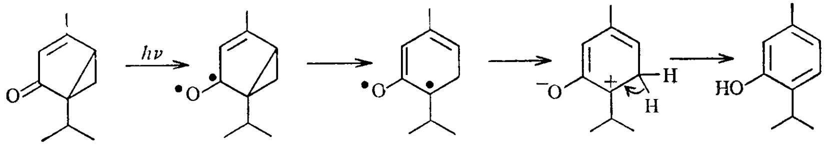


(110) (111)

B. Conjugated Cyclic Ketones.—In the absence of a suitable addend, so that cycloaddition reactions (see above) are not observed, conjugated cyclic ketones tend to react so that the absorbing chromophore is lost.[74] A simple case is the rearrangement of verbenone (112) to the unconjugated chrysanthenone (113).[75] Similarly, umbellulone (114) rearranges to the phenol, thymol (115).[76]



(112) (113)

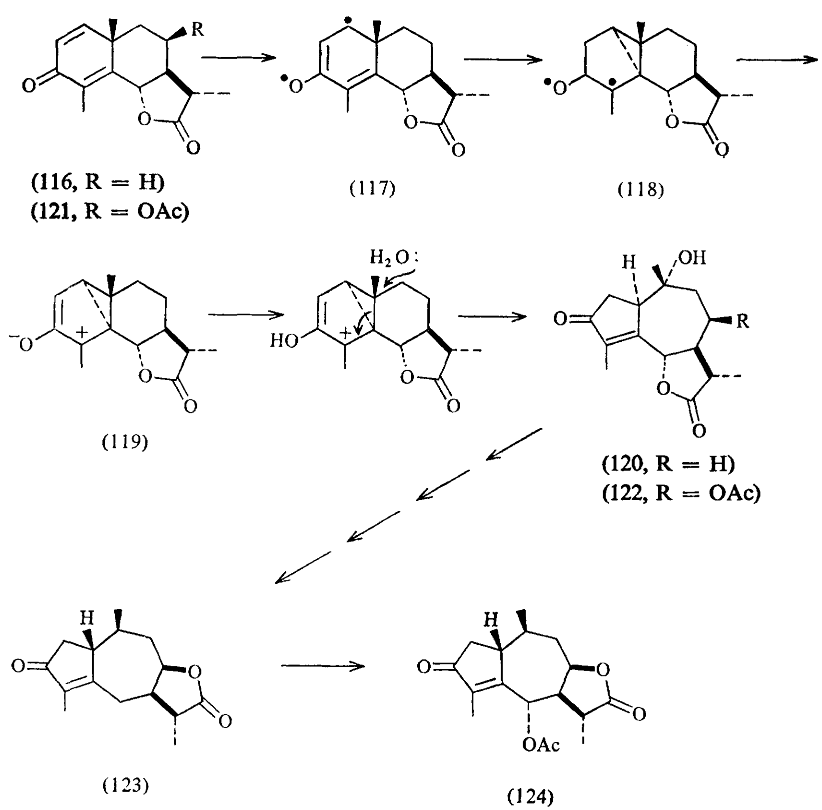


(114) (115)

More complex are the transformations of the cross-conjugated ketones, such as α-santonin (116), which has long been known to be sensitive towards light.[77] The mechanisms of the photochemical transformations of santonin have been

---

[72] C. M. Fernandez, *Chem. Comm.*, 1967, 1212.
[73] *Cf.* J. E. Baldwin and J. E. Brown, *Chem. Comm.*, 1969, 167.
[74] K. Schaffner, *Adv. Photochem.*, 1966, **4**, 81.
[75] J. J. Hurst and G. H. Whitham, *Proc. Chem. Soc.*, 1959, 160.
[76] J. W. Wheeler and R. H. Eastman, *J. Amer. Chem. Soc.*, 1959, **81**, 236.
[77] Kahler, *Arch. Pharm.*, 1830, **34**, 318.



(116, R = H)
(121, R = OAc)

(117)

(118)

(119)

(120, R = H)
(122, R = OAc)

(123)

(124)

the subject of much study.[78] They are best rationalised in terms of Zimmerman's explanation.[79] An initial $n \rightarrow \pi^*$ transition produces a diradical (117) which isomerises to (118), followed by collapse to a dipolar species (119). In aqueous acetic acid the anion is protonated and the resulting carbonium ion rearranges to isophotosantonic acid lactone (120), which has a guaianolide skeleton. This rearrangement has been shown to be general[80] and consequently it has been used in the synthesis of several perhydroazulenes of the guaianolide series. For example, 8-*epi*-artemisin acetate (121) on photolysis afforded 8-*epi*-isophotoartemisic acid lactone acetate (122). Dehydration and reduction, followed by

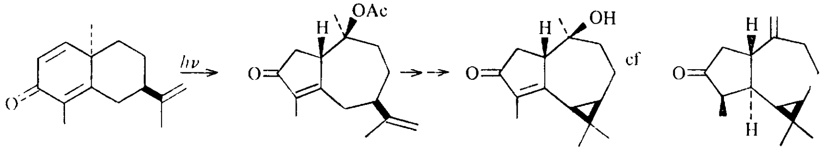
---

[78] (*a*) P. J. Kropp, 'Organic Photochemistry', ed. O. L. Chapman, Marcel Dekker Inc., New York, 1967, vol. 1, p. 1; (*b*) D. H. R. Barton, P. de Mayo and M. Shafiq, *Proc. Chem. Soc.*, 1957, 205; (*c*) D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 1958, 140; (*d*) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger, and L. J. Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732; (*e*) O. L. Chapman and L. F. Englert, *J. Amer. Chem. Soc.*, 1963, **85**, 3028; (*f*) M. H. Fisch and J. H. Richards, *J. Amer. Chem. Soc.*, 1963, **85**, 3029.

[79] (*a*) H. E. Zimmerman, *Pure Appl. Chem.*, 1964, **9**, 493; (*b*) H. E. Zimmerman and D. I. Schuster, *J. Amer. Chem. Soc.*, 1962, **84**, 4527.

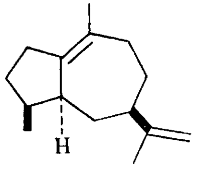
[80] D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 1962, 3472.

chromous chloride reduction of the lactone gave an isomeric lactone, 11-*epi*-deoxygeigerin, which with mild base was isomerised to deoxygeigerin (123). Oxidation with lead tetra-acetate eventually produced geigerin acetate (124).[81] Related syntheses include an approach to aromadendrene (127),[82] *via* the dienone

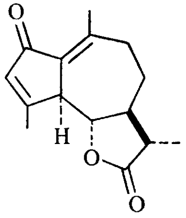


(125) (126) (127)

(125) and its isophoto-derivative (126). Also synthesised in this manner have been α-bulnesene (128)[83] and desacetoxymatricarine (129).[84]

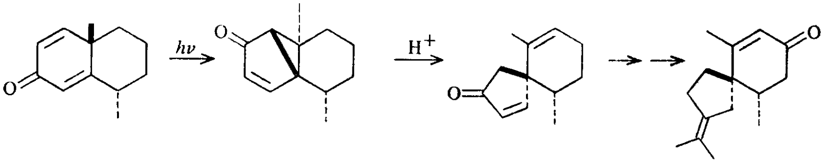


(128)



(129)

In an approach to the spirovetivane sesquiterpenoids, Marshall has also used the rearrangement of the dienone (130).[85] In aprotic solvents the dipolar intermediate (*e.g.* 119) immediately collapses to the lumi-isomer (131), since no protons are available to quench the anion. Compound (131) was readily transformed into the spiro-compound (132), itself eventually converted into vetivone (133).



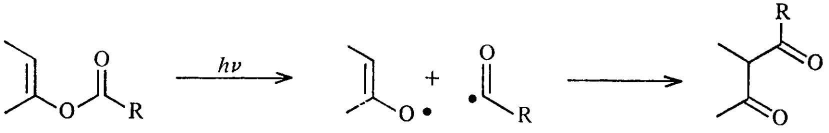
(130) (131) (132) (133)

C. Vinyl Esters.—Upon photolysis vinyl esters (*e.g.* 134) are often cleaved to give two radical species which can recombine, *via* resonance forms to give a

---

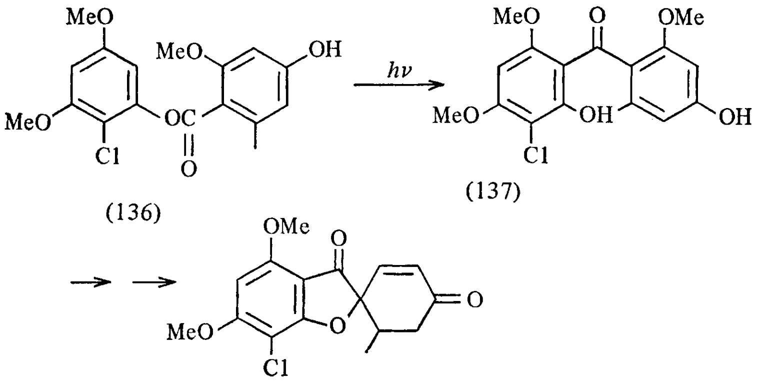
[81] D. H. R. Barton, J. T. Pinhey, and R. J. Wells, *J. Chem. Soc.*, 1964, 2518.
[82] J. Streith and A. Blind, *Bull. Soc. chim. France*, 1968, 2133.
[83] E. Piers and K. F. Cheng, *Chem. Comm.*, 1969, 562.
[84] E. H. White, S. Eguchi, and J. N. Marx, *Tetrahedron*, 1969, **25**, 2099.
[85] J. A. Marshall and P. C. Johnson, *Chem. Comm.*, 1968, 391.

β-diketone (135).[86] Phenolic esters are similarly cleaved by irradiation to give, eventually, *ortho*- or *para*-acylated phenols, a photochemical type of Fries rearrangement.[87] This reaction can therefore be used when the ester bears



(134) (135)

functional groups that are sensitive to Lewis acid catalysts. Use of this reaction has been made in a synthesis of racemic griseofulvin (138).[88] The substituted aromatic ester (136) was rearranged by photolysis to the ketone (137), a precursor of griseofulvin.[88]



(136)

(137)

(138)

6 Photosensitised Addition of Oxygen

An important method of oxidation involves the photosensitised addition of oxygen to olefins.[89] Although alternative mechanisms are available, the sensitising dye generally acts as a catalyst in the conversion of oxygen from its ground triplet state to either of its metastable singlet states (Figure 2). In most cases it is the lower excited state, $^1\Delta_g$, that appears to be responsible for the autoxidations.[90] The chemistry of the upper excited state, $^1\Sigma_g^+$, has not been well studied, although it does appear to have a different reactivity from that of the $^1\Delta_g$ state.[91]

---

[86] *Cf.* A. Yogev, M. Gorodetsky, and Y. Mazur, *J. Amer. Chem. Soc.*, 1964, **86**, 5208

[87] D. Bellus and P. Hrdlovic, *Chem. Rev.*, 1967, **67**, 599.

[88] D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1.

[89] C. S. Foote, *Science*, 1968, **162**, 963.

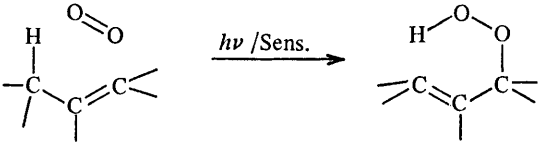
[90] C. S. Foote, S. Wexler, R. Higgins, and W. Ando, *J. Amer. Chem. Soc.*, 1968, **90**, 975.

[91] (*a*) D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Amer. Chem. Soc.*, 1967, **89**, 5455; (*b*) D. R. Kearns, R. A. Hollins, A. U. Khan, and P. Radlick, *J. Amer. Chem. Soc.*, 1967, **89**, 5456.

State	*Highest occupied orbitals*		*Energy*
$^1\Sigma_g^+$	↑	↓	37 kcal.
$^1\Delta_g$	↑↓	—	22 kcal.
$^3\Sigma_g^-$	↑	↑	0 (Ground state)

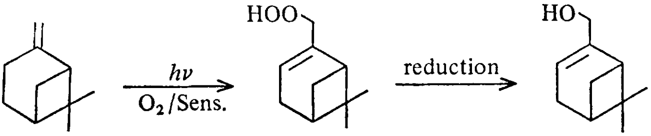
Figure 2 *Energy levels of molecular oxygen*

Two modes of addition to olefinic systems may be recognised. Isolated double bonds react by addition with allylic migration of the double bond in a highly specific manner, (139) to (140).[92] Thus β-pinene (141) can be readily, and



(139) (140)

specifically, converted into myrtenol (142).[93] Conjugated dienes prefer to react by normal Diels–Alder type of cycloaddition, as in the conversion of α-terpenene (143) into the anthelmintic, ascaridole (144).[94] An interesting variant of the latter reaction lead to the synthesis of the powerful vesicant cantharidin (146) from the anhydride (145).[95]



(141) (142)

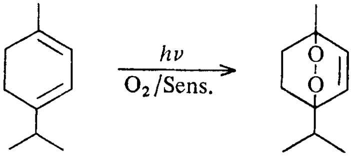
---

[92] (*a*) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, 1961, **83**, 1498; (*b*) A. Nickon and W. L. Mendelson, *J. Amer. Chem. Soc.*, 1963, **85**, 1894; (*c*) *cf.* K. Alder and H. von Brachel, *Annalen*, 1962, **651**, 141.

[93] G. O. Schenck, H. Eggert, and W. Denk, *Annalen*, 1953, **584**, 176.

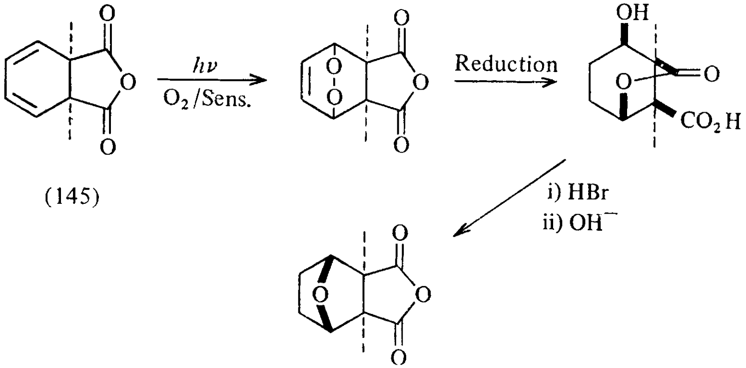
[94] K. Ziegler and G. O. Schenck, *Naturwiss.*, 1944, **32**, 157.

[95] G. O. Schenck and R. Wurtz, *Naturwiss.*, 1953, **40**, 581.



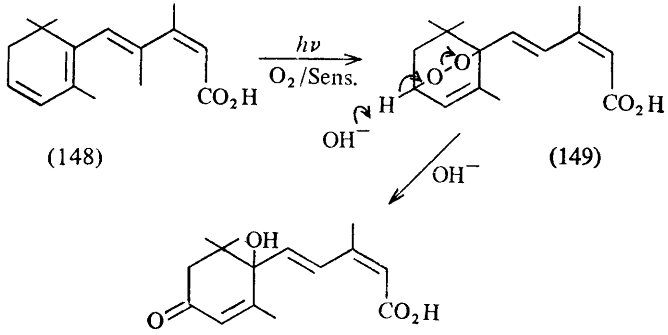
(143) (144)

Similarities between photosensitised oxygenations and certain biological oxidations have often been noted,[96] for example in the biosynthesis of abscisin-II (147).[97] The diene precursor (148) was oxidised *in vitro* with oxygen to give the cyclic peroxide (149), which gave abscisin after treatment with dilute base.[97,98]



(145)

(146)



(148) (149)

(147)

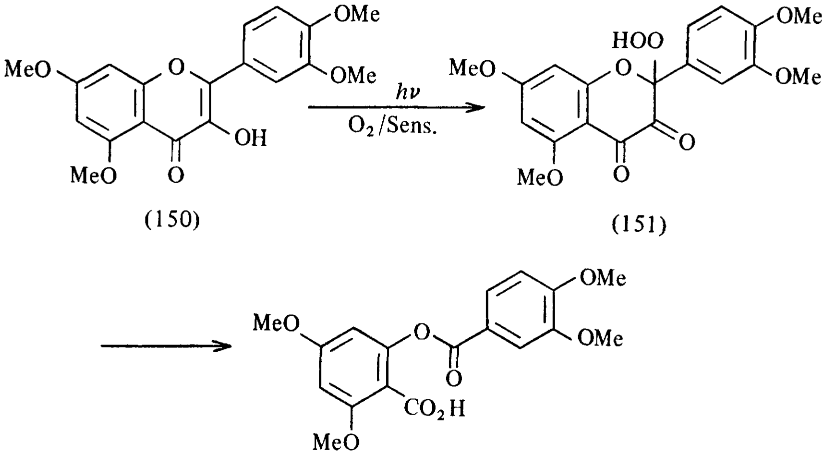
---

[96] (*a*) See refs. 90 and 92a; (*b*) W. Waters and E. McKeown, *J. Chem. Soc.* (*B*), 1966, 1040; (*c*) J. E. Baldwin, H. H. Basson, and H. Krauss, *Chem. Comm.*, 1968, 984.

[97] J. W. Cornforth, B. V. Milborrow, and G. Ryback, *Nature*, 1965, **206**, 715.

[98] (*a*) M. Mousseron-Canet, J. C. Mani, J. L. Olive, and J. P. Dalle, *Compt. rend.* 1966, **262**, *C*, 1397; (*b*) *cf.* R. LeMahieu, M. Carson, and R. W. Kierstead, *J. Org. Chem.*, 1968, **33**, 3660.

Oxidation of quercetin tetramethyl ether (150) gave the depside (152) *via* the peroxide (151), by a process analogous with that occurring naturally.[99] Singlet oxygen is also often involved in the oxidation of fatty acids,[100] carotenoids,[101] and naturally occurring heterocyclic systems.[89]



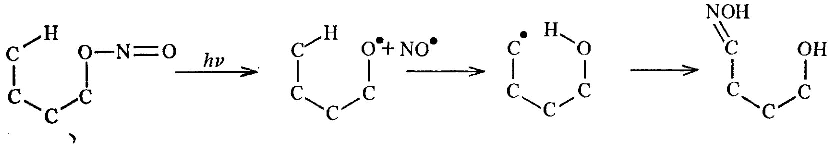
(150)

(151)

(152)

7 Intramolecular Hydrogen Abstraction

Several, very specific, photoreactions are known which involve intramolecular chemical attack at a carbon atom some distance removed from a functional group. A short list with leading references is given in the Table. These reactions proceed by intramolecular formation of a carbon radical which can then be quenched by such reagents as nitric oxide, iodine, *etc.* For example, nitrite esters (*e.g.* 153) react with preferential abstraction of a γ-hydrogen atom, *via* a six-membered transition state, to give an oximino-alcohol (154).[102] Many applica-



(153)

(154)

---

[99] T. Matsuura, H. Matsushima, and H. Sakamoto, *J. Amer. Chem. Soc.*, 1967, **89**, 6370.

[100] (*a*) H. R. Rawls and P. J. von Santen, *Tetrahedron Letters*, 1968, 1675; (*b*) *cf.* S. Bergström, *Science*, 1967, **157**, 382.

[101] (*a*) M. Mousseron-Canet, J. P. Dalle, and J. C. Mani, *Photochem. and Photobiol.*, 1969, **9**, 91; (*b*) S. Isoe, S. B. Hyeon, H. Ichikawa, S. Katsumura, and T. Sakan, *Tetrahedron Letters*, 1968, 5561.

[102] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1961, **83**, 4076.

Table *Photolytic, intramolecular hydrogen abstraction reactions*

Functional group	*Derivative*	*Principal products*	*Comments*	*Reference*
Alcohol	Nitrite	γ-Oximino-alcohol		a
	Hypochlorite	γ-Chloro-alcohol	Alkoxy radical formed, RO·	b
	Hypoiodite	γ-Iodo-alcohol or tetrahydrofuran		c, d
Amine	*N*-Chloro-amine	γ-Chloro-amine or pyrrolidine	Hofmann–Loeffler–Freytag reaction. Photolysed with acid present	e
Amide	*N*-Iodoamide	γ-Lactone	*Via C*-iodide	f
	N-Bromo-*t*-butylamide	γ-Lactone or imino-ether		g
	N-Nitroso-acetamide	γ-Oximino-acetamide		h
	N-Chloro-amide	γ-Chloro-amide		i
Nitrile	Nitrile oxide	γ- and δ-lactams	Note formation of mixtures, if possible	j
Carboxylic acid	Acyl azide			k
Sulphonamide	*N*-Chloro-sulphonamide	γ- and δ-chloro-sulphonamides		l

a A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 1961, **17**, 35.
b M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1961, **83**, 2213.
c M. Akhtar, *Adv. Photochem.*, 1964, **2**, 263.
d K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Ed.*, 1964, **3**, 525.
e M. Wolff, *Chem. Rev.*, 1963, **63**, 55.
f D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 1965, 181.
g R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Amer. Chem. Soc.*, 1966, **88**, 3051.
h Y. L. Chow and A. C. H. Lee, *Chem. and Ind.*, 1967, 827.
i R. C. Petterson and A. Wambsgans, *J. Amer. Chem. Soc.*, 1964, **86**, 1648.
j G. Just and W. Zehetner, *Tetrahedron Letters*, 1967, 3389.
k J. W. ApSimon and O. E. Edwards, *Canad. J. Chem.*, 1962, **40**, 896.
l M. Okahara, T. Ohashi, and S. Kanai, *Tetrahedron Letters*, 1967, 1629.

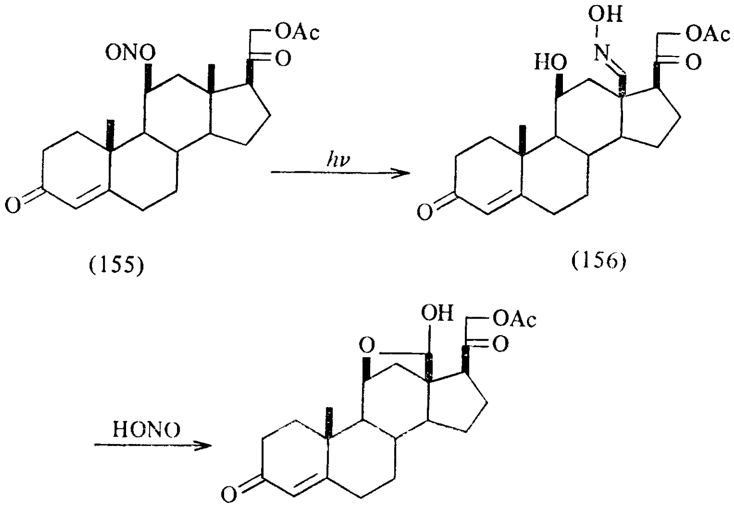
tions of these reactions to the synthesis of natural products have been reported and only a few are presented here to illustrate their usefulness.

The readily available corticosterone acetate was converted into its nitrite ester (155) before photolysis in benzene solution. Nitrous acid treatment of the derived oxime (156) gave the important hormone aldosterone acetate (157) in overall 15% yield.[103]

N-Chloroamines are very sensitive to light[104] and under acidic conditions the

---

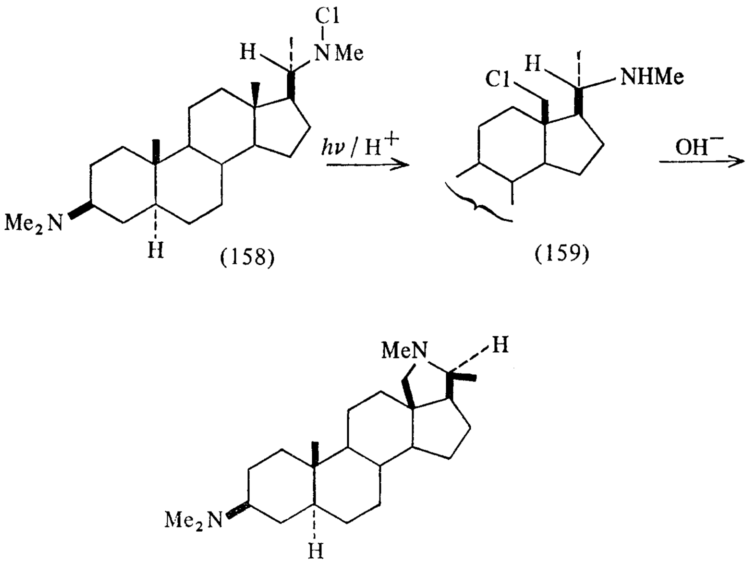
[103] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1961, **83**, 4083.
[104] M. Wolff, *Chem. Rev.*, 1963, **63**, 55.



(155) (156)

(157)

chloro-amine (158) gives the γ-chloroammonium salt (159). Mild base treatment affords the pyrrolidine (160), the steroidal alkaloid dihydroconnessine.[105]



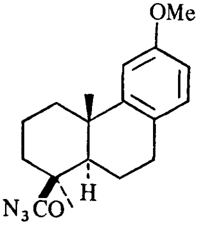
(158) (159)

(160)

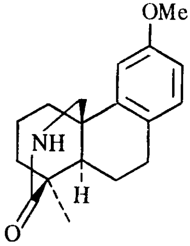
---

[105] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, 1960, **82**, 1657.

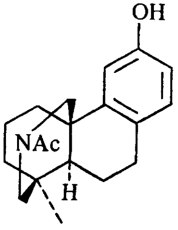
Most intramolecular hydrogen abstraction reactions proceed *via* the favoured 6-membered transition state leading to γ-substituted products. A notable exception is for the acyl nitrenes, generated from either the acyl azide or nitrile oxide, which prefer to abstract hydrogen from the δ-position.[106] For example the acyl azide (161) affords mainly the δ-lactam (162) as well as a minor amount of γ-lactams. The major product was converted into the phenol (163), a degradation product of the alkaloid atisine.[107] An explanation for the required larger transition state is that singlet nitrene is responsible which inserts, in a concerted manner, into the δ-carbon-hydrogen bond (*e.g.* 161A) with carbon to nitrogen bond formation in the transition state, that is, again *via* a formally 6-membered intermediate.[108] Isocyanates are also formed during this photolysis and again involve singlet excited species, probably of the excited azide.[109] Sensitised photolysis inhibits the rearrangement to isocyanate but also retards lactam formation.[108]



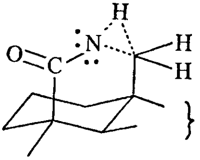
(161)



(162)



(163)



(161A)

8 Photosensitive Protecting Groups

Protecting groups, employed in synthetic work, are usually removed chemically, for example by acid or base, or by hydrogenolysis.[110] Problems often arise when the substrate itself is also sensitive under the conditions required to regenerate the protected group. The use of protecting groups which may be

---

[106] (*a*) W. L. Meyer and A. S. Levington, *J. Org. Chem.*, 1963, **28**, 2859; (*b*) R. F. C. Brown, *Austral. J. Chem.*, 1964, **17**, 47.

[107] J. W. ApSimon and O. E. Edwards, *Canad. J. Chem.*, 1962, **40**, 896.

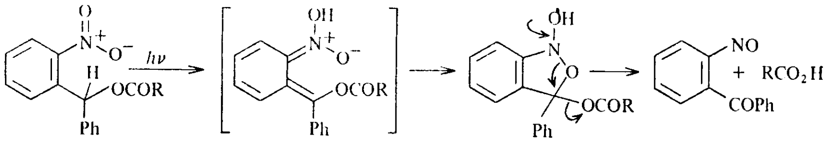
[108] I. Brown and O. E. Edwards, *Canad. J. Chem.*, 1967, **45**, 2599.

[109] (*a*) W. Lwowski, *Angew. Chem. Internat. Edn.*, 1967, **6**, 897; (*b*) G. T. Tissue, S. Linke, and W. Lwowski, *J. Amer. Chem. Soc.*, 1967, **89**, 6303, 6308.

[110] J. F. W. McOmie, *Adv. Org. Chem.*, 1963, **3**, 191.

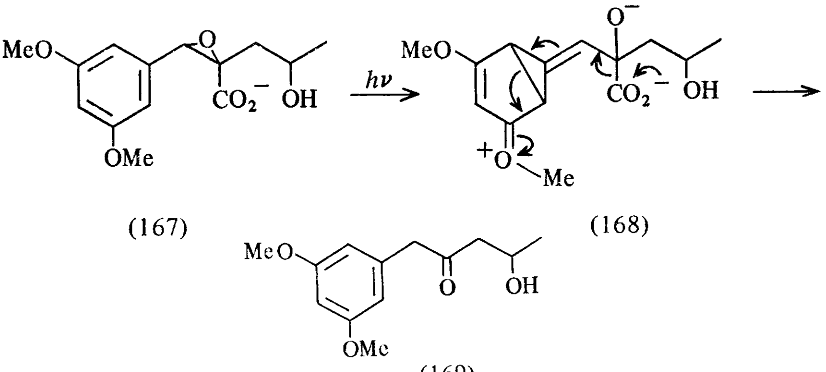
removed by irradiation, avoiding the need for chemical treatment of the substrate, is an attractive alternative.

Two approaches to the design of such photosensitive protecting groups have been developed. In the first, the internal redox reaction of substituted *o*-nitrotoluenes has been used.[111] Brief irradiation of *o*-nitrodiphenylmethyl esters (*e.g.* 164) gives the corresponding *o*-nitrosohemiacetal (165) which collapses spontaneously into *o*-nitrosobenzophenone (166) and the free acid. Amines can also be protected with this group.



(164) (165) (166)

In an alternative approach use is made of the greater reactivity of excited aromatic compounds compared to that of their ground states.[112] Thus *m*-nitrophenyl esters are photosensitive and, in protic solvents, the acid is displaced.[113] Similarly, 3,5-dimethoxybenzyl esters react with liberation of the protected group.[114] Related to the latter reaction is the observed photolytic decarboxylation of the 3,5-dimethoxybenzene derivative (167).[115] This probably reacts *via* the



(167) (168) (169)

---

[111] J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Comm.*, 1966, 822.

[112] For a recent summary see (*a*) E. Havinga and M. E. Kronenberg, *Pure Appl. Chem.*, 1968, **16**, 137; (*b*) E. Havinga, R. O. de Jongh, and M. E. Kronenberg, *Helv. Chim. Acta*, 1967, **50**, 2550.

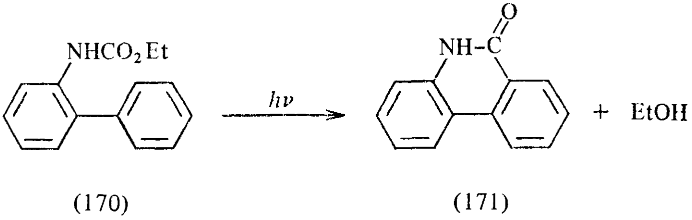
[113] T. Wieland and C. Lamperstorfer, *Makromol. Chem.*, 1966, **31**, 1658.

[114] J. W. Chamberlain, *J. Org. Chem.*, 1966, **31**, 1658.

[115] J. D. White and J. B. Bremner, Abstracts, 155th meeting of the American Chemical Society, San Francisco, 1968, 170th abstract.

excited species (168), which eventually collapses to the ketone (169), used in a synthetic approach to mitorubrin.[116]

Other photosensitive protecting groups have been described, including the benzyloxycarbonyl moiety,[117] desyl derivatives,[118] and 2,4-dinitrobenzenesulphenyl esters.[119] It should be emphasised that many organic photochemical reactions have been reported which could be adapted for use in removing photosensitive protecting groups. An example is with the biphenylurethane (170), which is smoothly transformed by photolysis to phenanthridone (171) with liberation of the alcohol.[120]



---

[116] G. Büchi, J. D. White, and G. N. Wogan, *J. Amer. Chem. Soc.*, 1965, **87**, 3484.
[117] J. A. Barltrop and P. Schofield, *J. Chem. Soc.*, 1965, 4758.
[118] J. C. Sheehan and R. M. Wilson, *J. Amer. Chem. Soc.*, 1964, **86**, 5277.
[119] D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 1965, 3571.
[120] N. C. Yang, A. Shani, and G. R. Lenz, *J. Amer. Chem. Soc.*, 1966, **88**, 5369.