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THE MECHANISM OF THE BARTON REACTION

A Thesis submitted for the
Degree of Doctor of Philosophy

by

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September 1977

ACKNOWLEDGEMENT

I would like to express my thanks to Professor Sir D. H. R. Barton and Dr. R. H. Hesse for supervision and guidance throughout this work. I would also like to thank Dr. M. M. Pechet for allowing me to study at the Research Institute for Medicine and Chemistry (RIMAC). All of my colleagues at RIMAC have contributed in some way to this work and I am particularly indebted to Dr. Dave Alker and Dr. Max Crossley of MIT who spent many tiring hours in assisting with the preparation of this Thesis. I am pleased to express my gratitude to the mass spectral and microanalytical staffs of Imperial College of Science and Technology, London, for their services and to Dr. J. S. Roberts of the University of Stirling for encouragement and advice from afar. Finally, but by no means least, I must thank my wife Jane for typing this Thesis and for her confidence that it could be done.

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ABSTRACT

A study of the by-products of the Barton reaction of steroidal nitrites has been made and the mechanisms of formation of these by-products have been elucidated. Epoxy by-products have been shown to result from the photochemical reaction of a nitroso monomer with nitric oxide. Alcoholic by-products have been shown to arise from intermolecular abstraction of hydrogen by the intermediate alkyl radicals. Ketonic by-products have been shown to be formed by a decomposition of the nitric oxide/alkoxy radical pair. The hyponitrous acid arising from this decomposition has been detected by UV spectroscopy and correlated with the amount of ketone formed. A brief study of solvent effects has demonstrated the unsuitability of aromatic solvents for the Barton reaction. Reaction parameters have been modified leading to the elimination of epoxy and alcoholic by-products and giving improved yields of oximino products. The ability of the Barton reaction to be triplet sensitised has been ascertained.

The Barton reaction in the presence of oxygen, affording nitrate esters, has been extended to 6β-nitrite esters and has been used to synthesise some novel 19-functionalised cholestane derivatives. The existence of a peroxynitrite as an intermediate in this reaction has been looked at and it has been found that the *in situ*

generation of a peroxynitrite by the reaction of a hydroperoxide with nitrosyl chloride and its subsequent rearrangement affords a new synthesis of nitrate esters. A steroidal phosphinate has been prepared in a similar manner by reaction of a hydroperoxide with a chlorophosphine. The reaction of 17α-hydroperoxyprogesterone with trifluoroacetic anhydride affords a further method of degrading the pregnane side-chain.

CONTENTS

CHAPTER 1

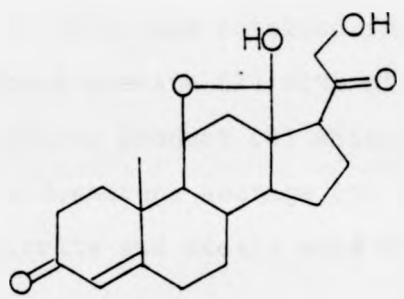
INTRODUCTION

Remote functionalisation in steroids and related molecules

The steroids comprise a large and important class of organic compounds of which many examples occur naturally in the plant and animal kingdoms and which serve a variety of functions in living systems. In addition to the naturally occurring steroids, the chemical modification of steroids has provided access to a wide variety of biologically useful compounds. The medicinal and biological roles of the steroids have been extensively described,[1] as has their chemistry[2,3] which is dictated to a large extent by both their three-dimensional structure and their conformational rigidity.

In organic chemistry, the removal of a specific hydrogen atom requires that the particular C-H bond to be broken can be differentiated chemically from the other C-H bonds in the molecule. Classically, the methods available for this selective hydrogen removal require that the hydrogen to be abstracted is adjacent to an electron-withdrawing group. The steroid nucleus contains a large number of C-H bonds of which at least several in each molecule are primary, secondary, and tertiary. Many of these centres are not adjacent to a labilising group and their functionalisation has been the subject of considerable investigation for many years. The functionalisation of the C18 and C19 methyl groups, in particular, posed an

unusually challenging problem since in many cases these groups were removed from electron-withdrawing functions by as many as four chemical bonds. Intense interest in the introduction of functionalisation at the angular methyl groups was stimulated by the discovery[4] that the powerful salt-retaining hormone aldosterone (1) contained such a group.

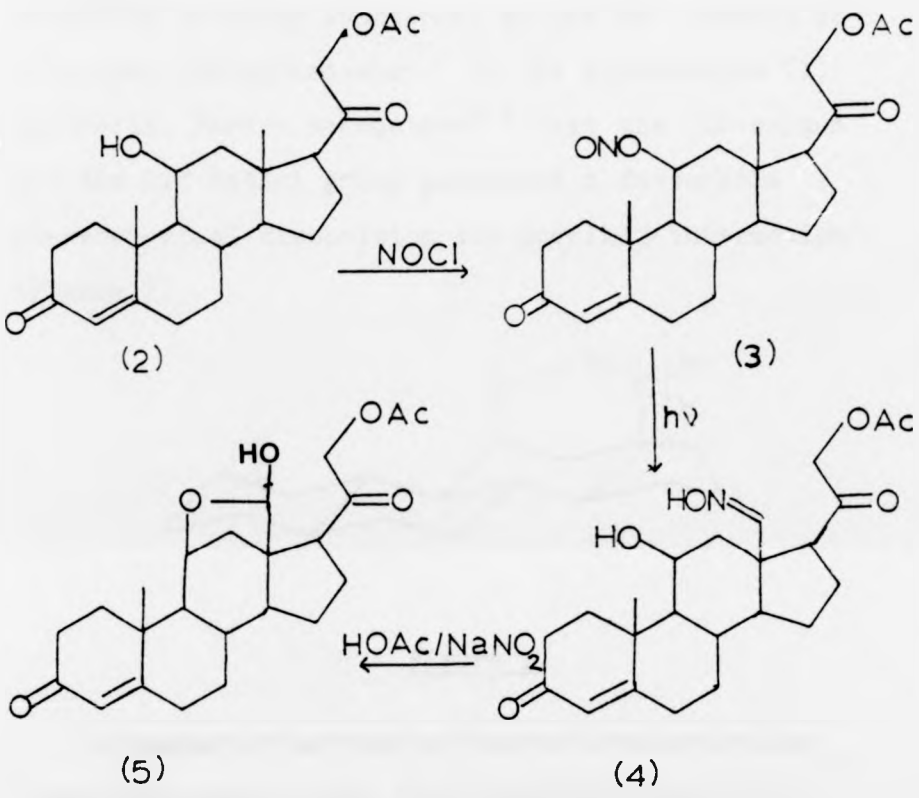


(1)

Although the total synthesis of aldosterone (1) from non-steroidal precursors was reported[5] shortly after the elucidation of its structure, the method used involved a lengthy series of transformations and the introduction of functionalisation at C18 from simple steroidal precursors continued to pose a difficult synthetic chemical problem. In contrast, Wettstein demonstrated[6] that an 18-hydroxy function

could be introduced efficiently into the steroid nucleus by incubation with beef adrenals and later proved[7] that the selective introduction of the oxygen function in aldosterone (1) occurs enzymatically in the adrenal cortex.

The problem of the synthesis of aldosterone (1) from available steroidal starting material was elegantly solved by Barton.[8,9] Thus the photolysis of the 11β-nitrite (3) which was obtained from the reaction of corticosterone acetate (2) with nitrosyl chloride gave the 18-oximino product (4) which was readily converted to aldosterone acetate (5) by treatment with sodium nitrite and acetic acid (Scheme 1).



Scheme 1.

This synthesis of aldosterone (1)[8,9] represented one of the earliest examples of the concept of remote functionalisation and in subsequent papers the theoretical and mechanistic aspects of the nitrite photolysis step were further adumbrated. The concept of remote functionalisation has since become widely accepted in organic chemistry and has become a powerful and versatile synthetic tool. Remote functionalisation of

carbon centres in this way relies primarily on their proximity to other functional groups as a result of molecular stereochemistry. In the aldosterone (1) synthesis, Barton recognised[8,9] that the 11β-oxygen and the C18 methyl group possessed a favourable stereochemical disposition for possible interaction (Figure 1).

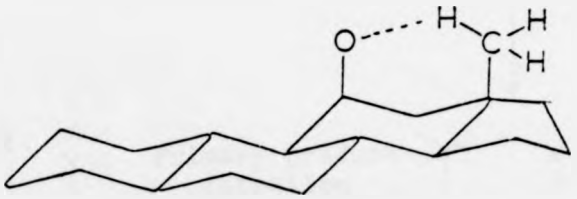
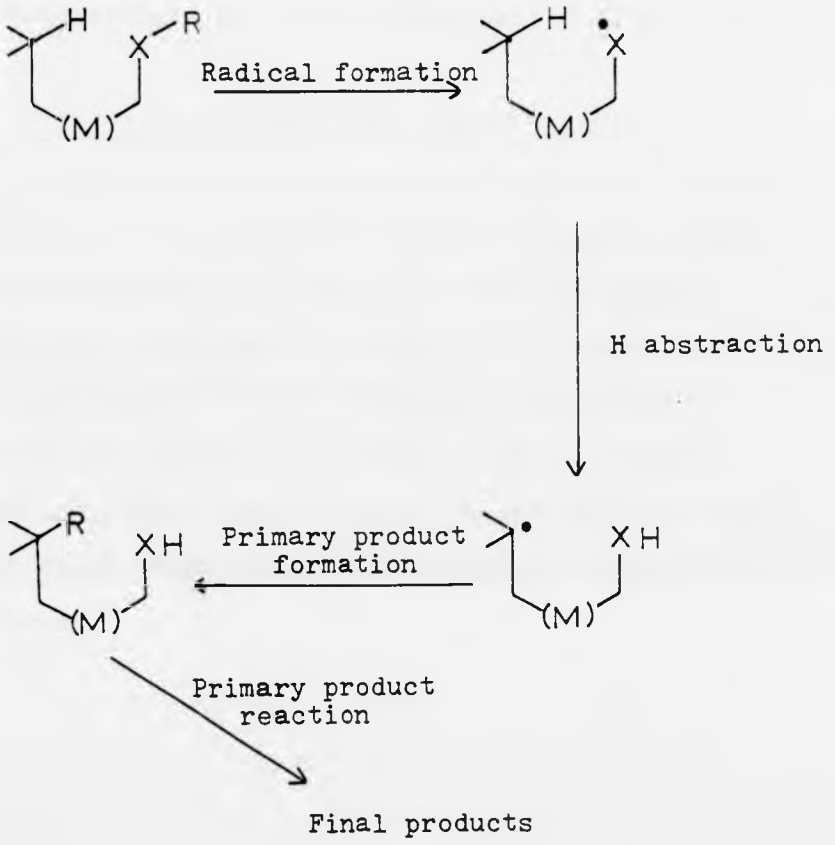


Figure 1.

A number of methods of remote intramolecular functionalisation have since been developed which without exception proceed through high energy intermediates which are either free radicals or photo-excited groups possessing radical character. Mechanistically, these reactions involve four discrete steps as follows (see Scheme 2):

1. Radical formation
2. Hydrogen abstraction
3. Reaction of the alkyl radical to give primary products
4. Reactions of the primary products



Scheme 2

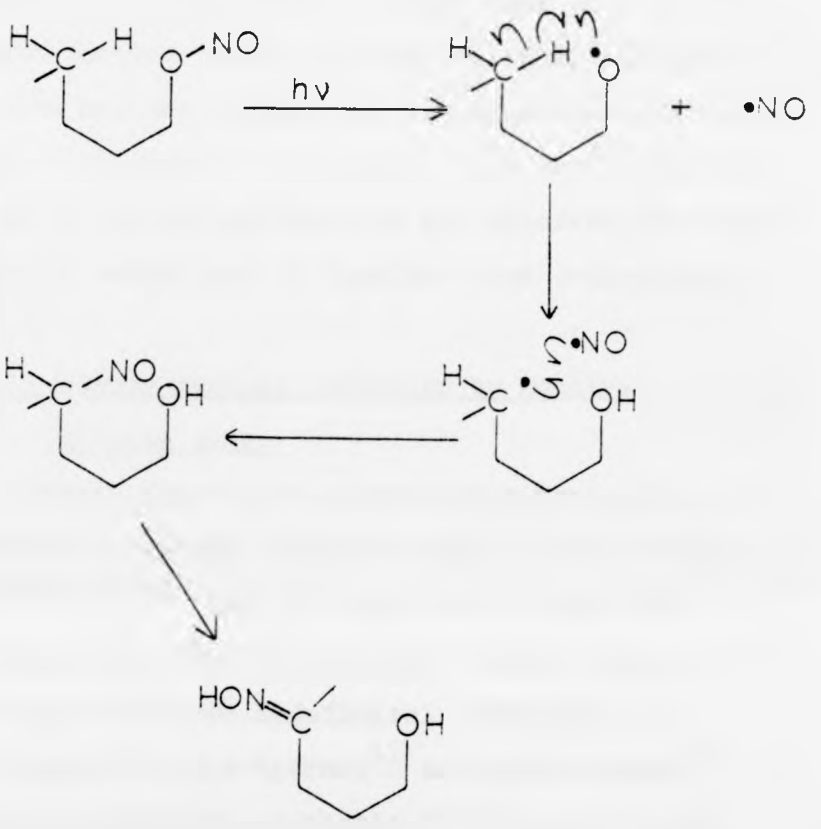
Though the general methods for remote functionalisation involve the generation of an alkoxy radical, other methods exist which utilise nitrogen-centred radicals or in certain cases carbon-centred radicals.

Many of the essential features of remote functionalisation are embodied in the nitrite photolysis reaction which will be discussed in the following section and should provide a basis for comparison with

the other methods which are subsequently discussed.

1.1 NITRITE PHOTOLYSIS: THE BARTON REACTION

Preparative nitrite ester photolysis as utilised by Barton and co-workers[8,9] in their elegant synthesis of aldosterone (1) has been named the Barton reaction and has been the subject of a number of review articles.[10,11,12] Formally the Barton reaction corresponds to a simple ligand exchange between an oxygen function and a δ-carbon atom with nitric oxide exchanging for hydrogen as represented in Scheme 3.



Scheme 3

The Barton reaction involves the sequential photochemical homolysis of the O-NO bond of a nitrite ester and hydrogen abstraction by the resulting alkoxy radical to form an alkyl radical. This alkyl radical recombines with the nitric oxide formed in the initial homolysis giving rise to a nitroso compound, which usually undergoes a thermal isomerisation to an oximino product. Scheme 3 represents

an ideal situation where no diversions of the intermediates occur. This is, however, never observed in practice and the diversion of intermediates is considered elsewhere in this work. The four steps involved in the Barton reaction are discrete processes and it is convenient to consider them individually.

1.1.1 Alkoxy radical formation by homolysis of the nitrite ester

Nitrite esters are conveniently prepared by the reaction of nitrosyl chloride with alcohols in pyridine[13,14,15,16] and, in the case of steroidal nitrites, are often crystalline, stable species which may be stored indefinitely when pure.

Studies of the thermal[17] and photochemical[18] reactions of simple aliphatic nitrites in the gas phase have indicated that in both cases alkoxy radicals are formed. However, in contrast to their photochemical behaviour, steroidal nitrites, on pyrolysis have not been observed to undergo the Barton reaction and it was originally considered[19,20] that thermally generated alkoxy radicals possessed insufficient energy to effect hydrogen abstraction. It has since been shown, however, that hydrogen abstraction will occur in thermally generated alkoxy radicals from simple molecules.[21]

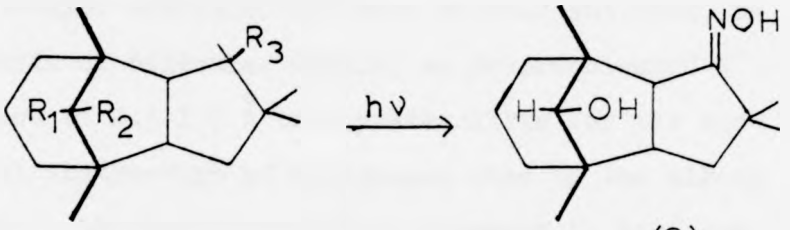
In their electronic spectra, nitrite esters exhibit two absorptions, one at 220-230 nm (ϵ = 1000-1500) and a series of fine structure bands at 300-400 nm (ϵ = 20-80), and it is considered that the Barton reaction arises as a result of absorption of radiation in the 300-400 nm region. Although Tarte[22] claims that nitroso compounds are formed only on irradiation at wavelengths below 330 nm, subsequent studies[23] using filtered radiation and monochromated light have since suggested this to be incorrect.

Calvert and Pitts[24] have reported that the quantum yield of the primary photodecomposition of nitrite esters is near unity, but studies in solution by Kabasakalian[25] suggest the value to be 0.76. Suginome,[23] using monochromated light, showed the quantum yields to be 0.7 at 365 nm, 0.6 at 338 nm and 0.5 at 311 nm. Quantum yield studies show therefore that in the Barton reaction no radical chain mechanism operates. Furthermore, isotopic labelling experiments by Akhtar[26] show that the primary decomposition step is a reversible process.

1.1.2 Hydrogen abstraction step

Although the nature of the alkoxy radical responsible for hydrogen abstraction in the Barton reaction has been the subject of discussion, it has recently

been proved[27,28] that ground state rather than excited alkoxy radicals perform the hydrogen abstraction. Thus, since photolysis of the epimeric caryophyllene nitrites (6) and (7) afforded the same oximino product (8), it was concluded[28] that in one case epimerisation of the alkoxy radical preceded hydrogen abstraction. Furthermore, photolyses of the 5β-deuterated epimers (9) and (10) showed[28] the same kinetic isotope effect. On the basis of these results it was argued that, since the alkoxy radicals derived from each of the epimers (6) and (7) behave the same in the transition state for the hydrogen abstraction step even though one of these radicals cannot be in an electronically or vibrationally excited state because it has to survive an epimerisation pathway before it can abstract a hydrogen, a ground state rather than an excited state alkoxy radical was responsible for the hydrogen abstraction process.



(8)

(6) R_1=H R_2=ONO R_3=H

(7) R_1=ONO R_2=H R_3=H

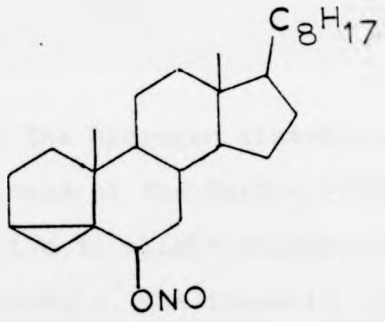
(9) R_1=H R_2=ONO R_3=D

(10) R_1=ONO R_2=H R_3=D

The Barton reaction relies totally for its success on the ability of the alkoxy radical to abstract a hydrogen atom from a saturated carbon centre in a specific manner. Almost without exception this abstraction proceeds through a six-centered transition state. Gray[29] has calculated that the abstraction of a C18 hydrogen by a 20-alkoxy radical via a six-membered transition state is exothermic (ΔH = 35.5 kJ mol^{-1}). The exact conformation of the six-membered transition state in the Barton reaction is uncertain although Akhtar[11] has argued on the basis of molecular model studies that a "quasi-chair" transition

state is the most likely.

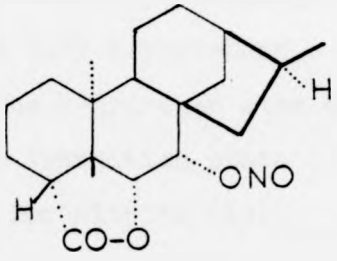
Heusler and Kalvoda[30] have pointed out that, on the basis of molecular models, an internuclear C-O distance of 2.5-2.7 Å is a prerequisite for the successful abstraction of a hydrogen atom by the alkoxy radical. The validity of this argument is born out by the observation[12] that the i-steroid nitrite (11), in which the internuclear C-O distance is 3 Å, does not undergo the Barton reaction.



(11)

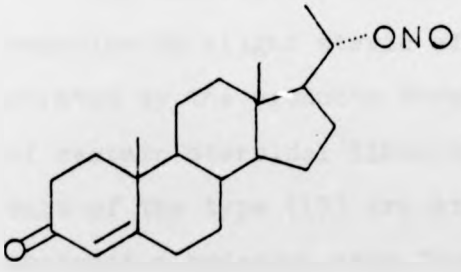
An exception to the requirement of a six-membered transition state has been described by Barton[31] who has shown that the diterpene (12) will undergo the Barton reaction. The transition state in this case for hydrogen abstraction is required to be seven-membered. Molecular models indicate that the distortion of the B ring in this molecule (12) forces the

alkoxy group into a favourable position for hydrogen abstraction. Similar results have been observed in the Barton reaction of certain lupan triterpenes.[32,33]

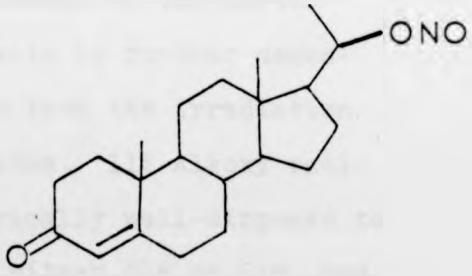


(12)

In practice, the hydrogen abstraction and therefore ultimate success of the Barton reaction is found to be very sensitive to slight changes in molecular structure. For example, the isomeric 20α- and 20β-nitrites (13) and (14) have been shown[34] to give 60% and 34% of oximino products, respectively.

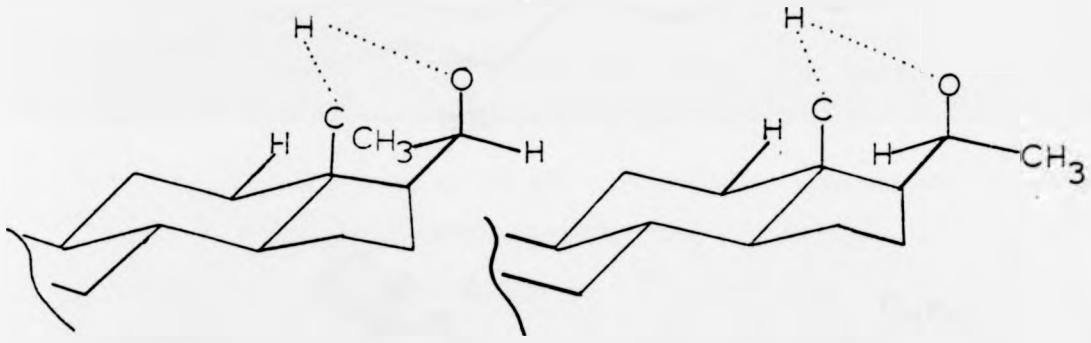


(13)



(14)

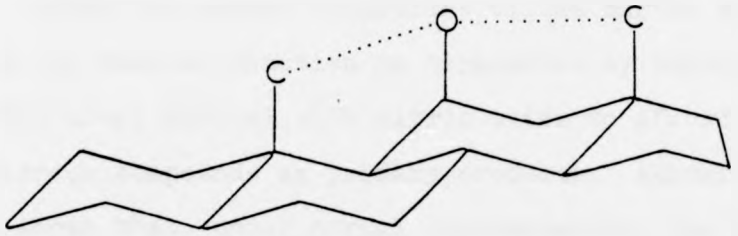
The preference of the 20α-nitrite (13) to undergo the Barton reaction has been discussed[35] in terms of the intermediate cyclic transition states. It has been pointed out that the 20-methyl substituent in the transition state (15) arising from photolysis of the 20β-nitrite (14) experiences a 1,3-diaxial interaction with the β-hydrogen atom on C12 which is not present in the transition state (16) arising from photolysis of the 20α-nitrite (13).



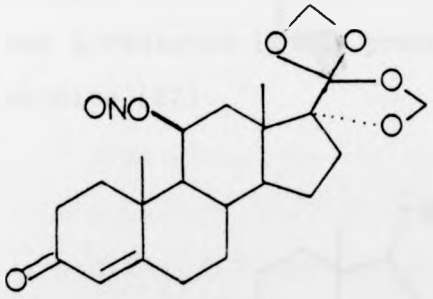
(15) (16)

The sensitivity of the outcome of the Barton reaction to slight steric effects is further demonstrated by the products formed from the irradiation of certain steroidal 11β-nitrites. 11β-Alkoxy radicals of the type (17) are sterically well-disposed to abstract a hydrogen atom from either C18 or C19, and it is found that the alteration of remote parts of the molecule has a considerable effect on the outcome

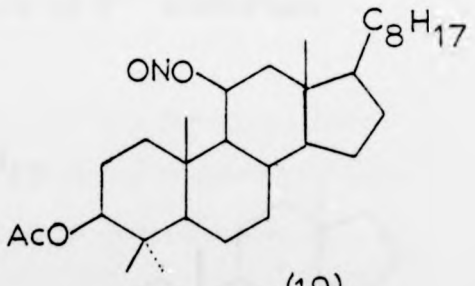
of the reaction. Thus, while irradiation of the nitrite (18) leads to the formation of both C18 and C19 functionalised products,[36] photolysis of the nitrite (19)[37] gives only 19-oximino products. In contrast, photolysis of the nitrite (20) leads to the sole formation of C18 activated products.[38]



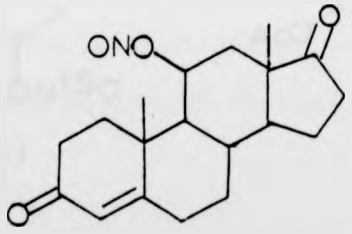
(17)



(18)



(19)

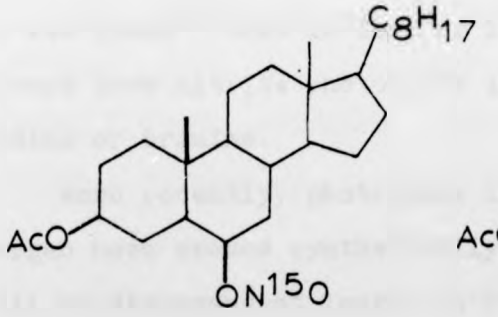


(20)

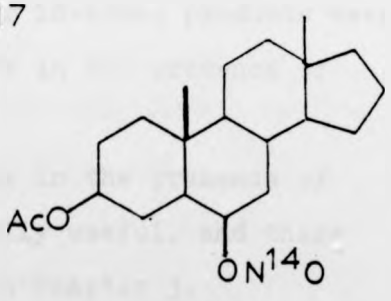
Functionalisation of 4,4-dimethylated steroids is found to be equally susceptible to minor steric changes and the substitution of C19 relative to C4 by photolysis of 6-nitrites has been investigated.[39,40,41]

1.1.3 Formation of primary products

Under the normal conditions of the Barton reaction the radical reaction is terminated by combination of the alkyl radical with nitric oxide to afford C-nitroso compounds as primary products. Akhtar[26] has shown that, under normal circumstances, the Barton reaction occurs without a solvent cage. This conclusion was reached as a result of a crossover experiment in which the N^{15}-labelled cholesteryl nitrite (21) was irradiated in the presence of N^{14} androstane nitrite (22).

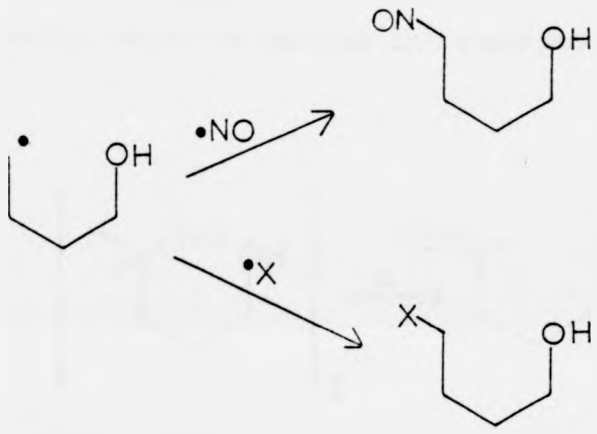


(21)



(22)

This proof of the absence of a solvent cage prompted speculation that exogenous radicals or radical-producing species might compete with nitric oxide in the termination step of the Barton reaction.

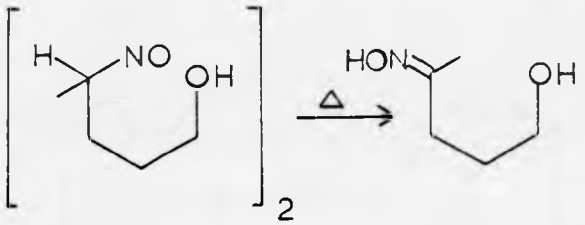


Substantiation for this idea was provided when it was found[38] that 18-iodo or 18-bromo products were formed from nitrite photolyses in the presence of iodine or bromine.

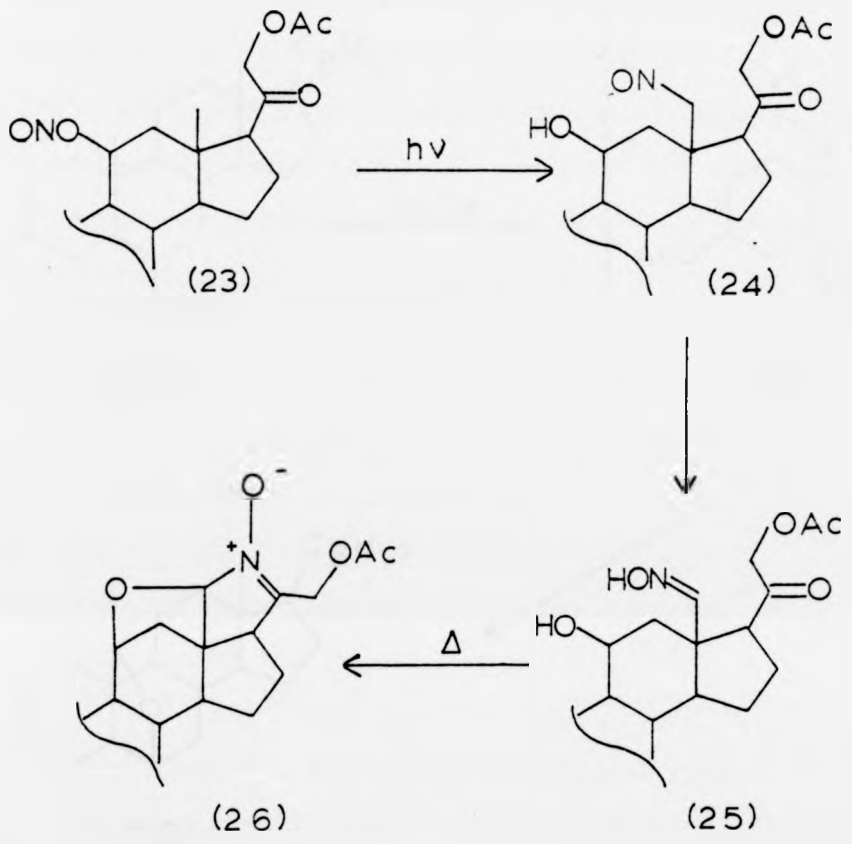
More recently, photolyses in the presence of oxygen have proved synthetically useful, and these will be discussed at length in Chapter 3.

1.1.4 Reaction of primary products

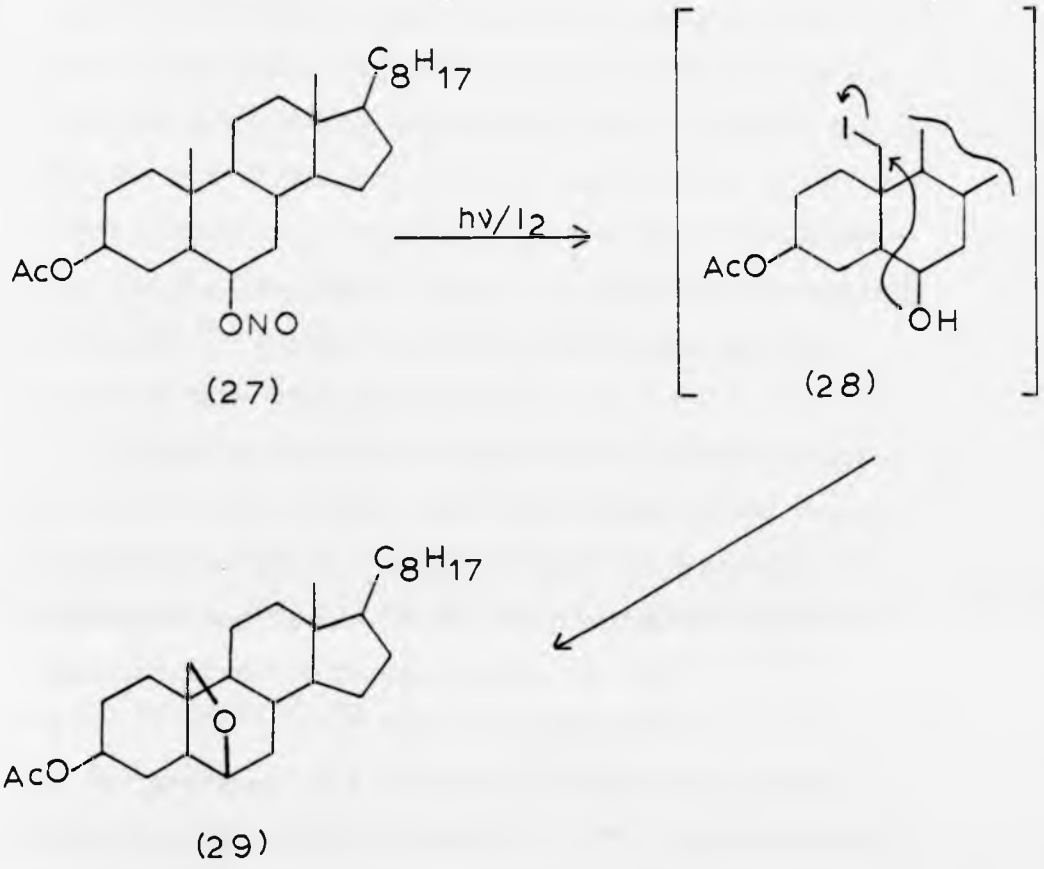
A tendency toward dimerisation is a distinctive property of the C-nitroso group[42] and the primary C-nitroso compound formed from the Barton reaction is often precipitated as the nitroso dimer which may be removed by filtration and isomerised to the corresponding oxime by heating in isopropanol.



In the photolysis of 11β-nitrites (23) having a 20-keto group, the oxime (25) formed from the initial C18 nitroso product (24) undergoes a further thermal isomerisation to the nitrone (26).[9,43].



When the 6β-nitrite (27) is irradiated in the presence of iodine, the isolated product is the 6β,19-epoxysteroid (29) which presumably arises by the intramolecular displacement of HI from the primary product, the iodohydrin (28).[38]



(27) (28) (29)

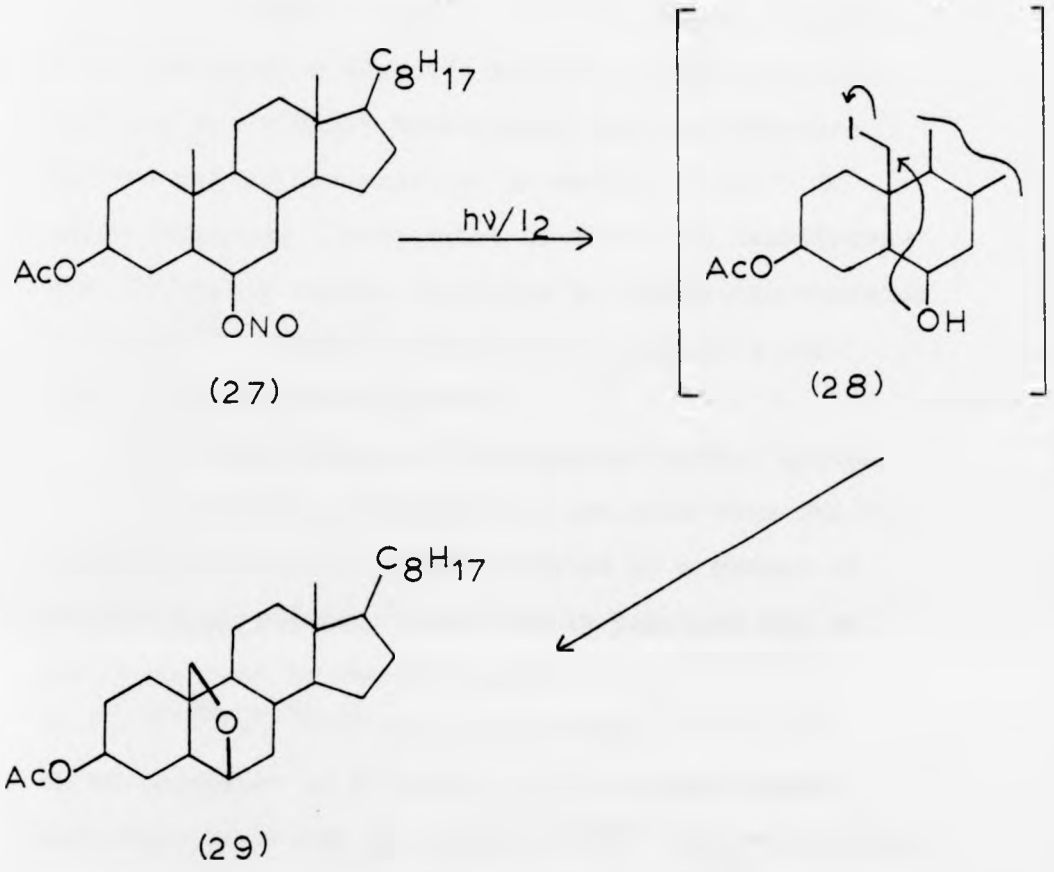
1.1.5 Applications of the Barton reaction

Since its introduction, the Barton reaction has found widespread usage in the synthesis of modified steroids. The nor-steroids are a series of compounds in which either of the angular methyl groups is replaced by hydrogen. These compounds are of considerable interest since the removal of the methyl groups often

results in marked changes in their biological profile. Since the oximino steroids resulting from the Barton reaction are readily transformed into nor-steroids, nitrite photolysis provides an excellent route to these compounds. Subsequent to the first transformation of the 19-oximino steroids to the 19-nor-steroids by Gardi,[44] further methods of synthesising nor-steroids have been reported.[3]

Functionalisation of the angular methyl groups in the steroid nucleus has been achieved from the irradiation of nitrite esters located at a number of different positions. Thus, the 19-position may be functionalised by the photolysis of 2β-,[45,46,47] 6β-[20,48,49,50,51,52] and 11β-nitrites[8,9,53,54,55] in the presence of a variety of functional groups and often in yields in excess of 60%. Optimal yields of 18-oximino products have been reported[36] from the photolyses of 11β-nitrites in the corticoid steroid series where the side chain is protected as the bismethylenedioxy derivative. 18-Oximino products have also been reported formed in 15-36% yield from 20β-nitrites[20] and in 60-65% yield from 20α-nitrites.[34,35]

Although 18-nitroso dimers are not often isolated from nitrite photolyses, Lenz[56] has recently reported the formation of such a compound in 60% yield on irradiation of a 20β-nitrite.



(27) (28) (29)

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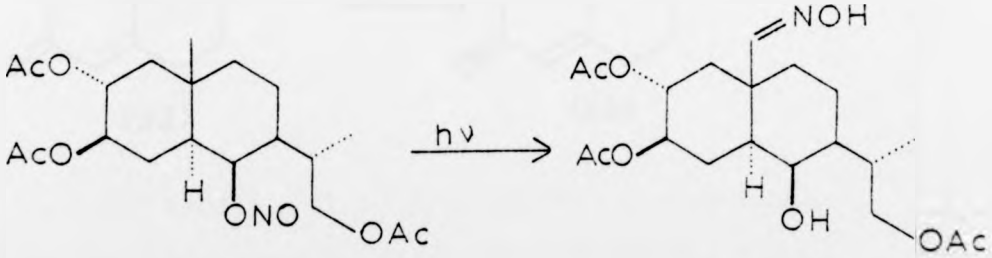
Further uses of the Barton reaction for the functionalisation of methyl groups in the steroid nucleus have been reported and include activation of C32 in the lanostanes from 7α-nitrites,[57,58] activation of 4α- and 4β-methyl substituents from 6-nitrites,[41] and activation of a 5β-methylated steroid from a 3β-nitrite.[59]

The Barton reaction has additionally found application in syntheses outside the field of steroid chemistry. Thus, Masamune[60] in the synthesis of the sesquiterpene phytoalexin rishitin has achieved a very good yield (78%) of the oximino product (31) from the photolysis of the nitrite (30).

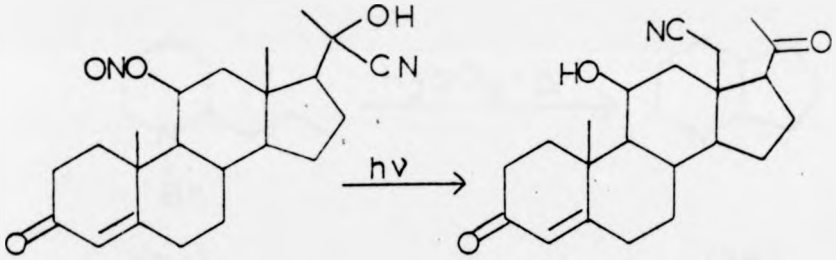


(30) (31)

Corey's synthesis[61] of the toad venom histrionicatoxin embodies a key step involving the Barton reaction, Magnus[62] availed himself of this reaction in a synthesis of certain insect juvenile hormones,

and Suginome[63] photolysed nitrites to arrive at modified veratrobasine alkaloids.

The Barton reaction in the presence of iodine has found application in the synthesis of the triterpenoid cycloartenol from lanosterol.[37] A further variation of the Barton reaction was reported by Kalvoda[64] who photolysed the 11β-nitrite (32) to give the 18-cyano steroid (33) as a result of migration of the 20-cyano group.



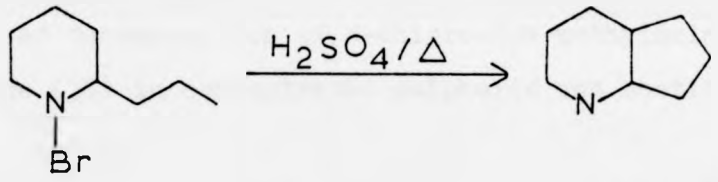
(32) (33)

1.2 N-CHLORAMINE REACTIONS: THE HOF MANN-LOFFLER-FREYTAG REACTION

Historically, at least, the Hof mann-Loffler-Freytag reaction which involves the decomposition of N-chloramines is of significance since it undoubtedly provides the first example of remote functionalisation in organic chemistry and probably

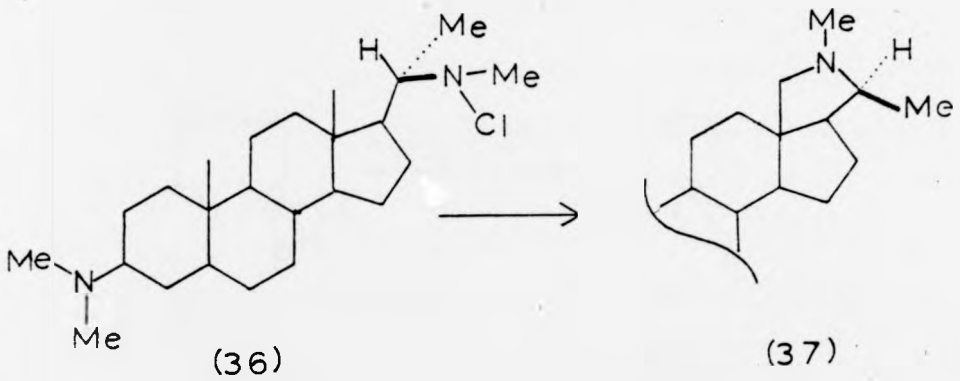
also provides the first example of the selective functionalisation of an angular methyl group in the steroid nucleus.

In the early 1880's, Hofmann[65,66,67] discovered, quite surprisingly, that the treatment of D-1-bromo-2-propylpiperidine (34) with hot sulphuric acid gave D-octahydroindolizine (35). This particular reaction was subsequently extended by Loffler and Freytag[68] to secondary amines who used it as a general synthesis of pyrolidines.



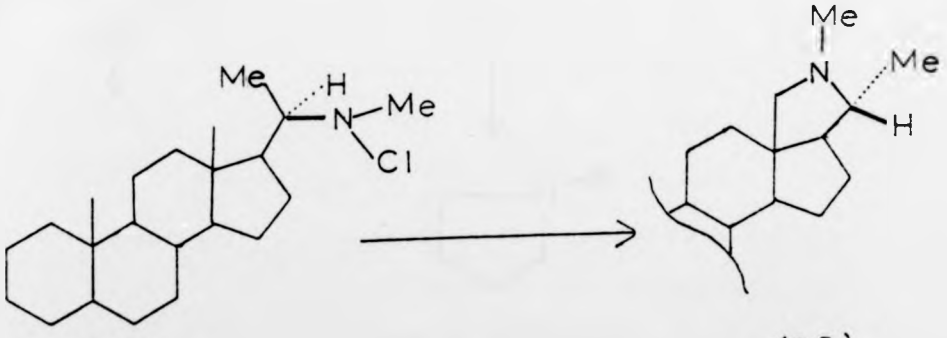
(34) (35)

The application of N-chloramine decomposition to the functionalisation of the C18 angular methyl group in steroids was announced simultaneously by Corey[69] and Buchschacher.[70] Corey's synthesis[69] of dihydroconessine (37) involved the key cyclisation of the chloramine (36) by means of the Hofmann-Loffler-Freytag reaction followed by base-induced elimination to afford dihydroconessine (37) in excellent yield.



(36) (37)

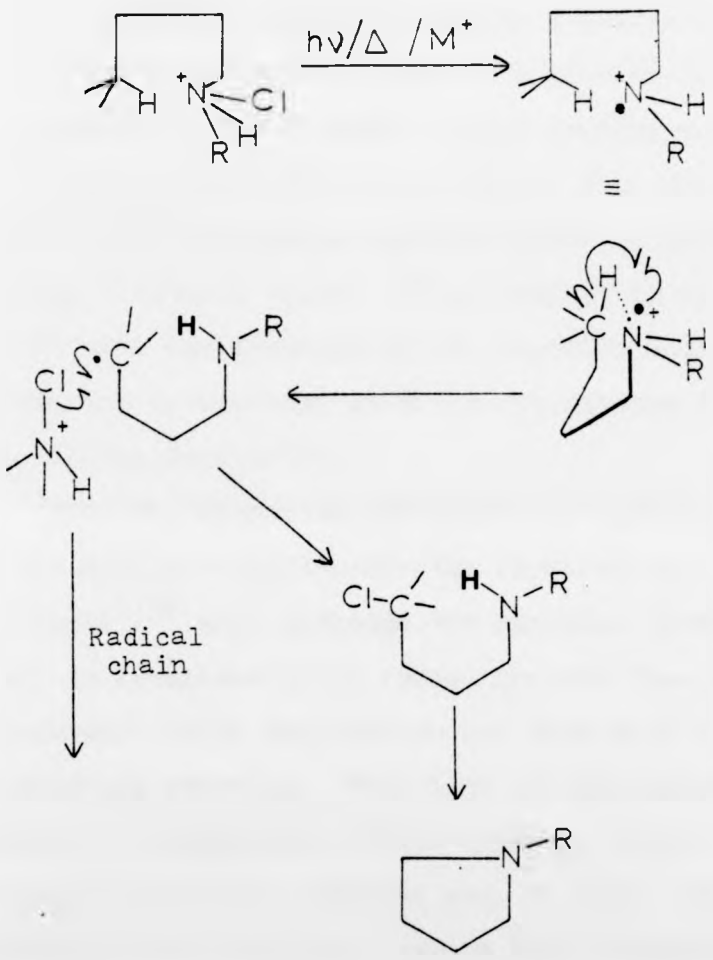
Similarly the Swiss group[70] synthesised the novel alkaloid conanine (39) by the ferrous ion catalysed decomposition of N-chloro-20α-methylamino-pregnane (38) in concentrated sulphuric and acetic acids.



(38) (39)

The mechanism of the Hof mann-Loffler-Freytag reaction has been elucidated by Wawzonek[71] and the radical intermediate required for hydrogen abstraction

shown to be an immonium radical (Scheme 4).



Scheme 4

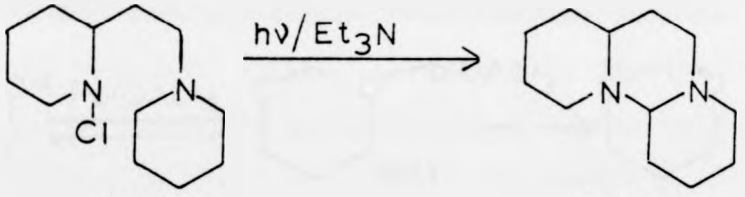
N-Chloramines are commonly generated by the reaction of an amine with chlorine and their subsequent decomposition is effected in acidic media generally

photochemically but alternatively by a metal ion (Fe^{2+} or Ag^{+}).[72] Hydrogen abstraction by the intermediate immonium radical occurs in a manner similar to the Barton reaction by way of a six-centred intermediate. The primary product forming process, the combination of the alkyl radical with chlorine, departs from the Barton reaction since it proceeds through a radical chain. Final product formation occurs when basification of the reaction medium causes the cyclisation of the δ-chloroamine to a pyrrolidine derivative.

Both the mechanism and synthetic application of the Hof mann-Loffler-Freytag reaction have been reviewed[73,74] and, although the reaction often proceeds in excellent yield (often greater than 75%), remarkably little application has been made of this interesting reaction. This lack of application is probably a consequence of the strongly acidic reaction conditions required and, to date, the only examples of its use have been in the 20-substituted steroids. Thus, a number of 18-functionalised steroids have been prepared by this method.[75,76,77] Additionally, Schrieber and Adam[78,79] have achieved synthetic access to the steroidal Solanum alkaloids by the functionalisation of the 16-position. The inability of the 6β-chloramines to undergo cyclisation

has been demonstrated by Ledger[80] who found that N-chloro-6β-methylaminocholestane decomposed spontaneously during its preparation.

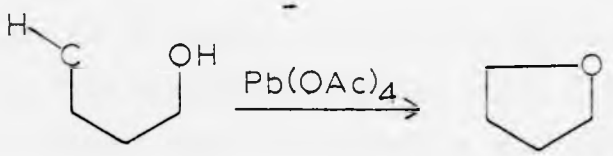
Japanese workers[81] have recently provided the first example of a Hof mann-Loffler-Freytag reaction proceeding under basic conditions when they claimed that, in ether solution in the presence of triethylamine, the photochemical cyclisation of the N-chloropiperidine (40) to the pyrimidine derivative (41) occurs essentially quantitatively.



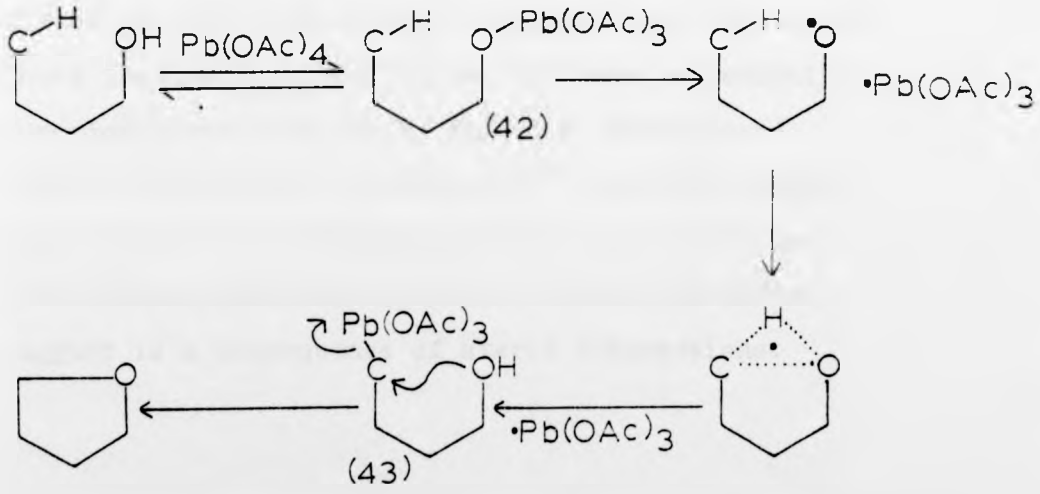
(40) (41)

1.3 LEAD TETRAACETATE OXIDATION

The oxidation of certain steroidal alcohols with lead tetraacetate was amongst the earliest reactions utilised[82] in the functionalisation of the angular methyl groups in steroids and provides a convenient and efficient method of forming tetrahydrofuran derivatives from alcohols as a result of hydrogen abstraction from a δ-carbon.[30,83,84]



Although the mechanism of this reaction is not definitively known, the products are thought to be formed as shown in Scheme 5. Thus, the primary step requires the formation of a readily cleavable intermediate (42) which has been formulated as an alkoxylead acetate.[86]

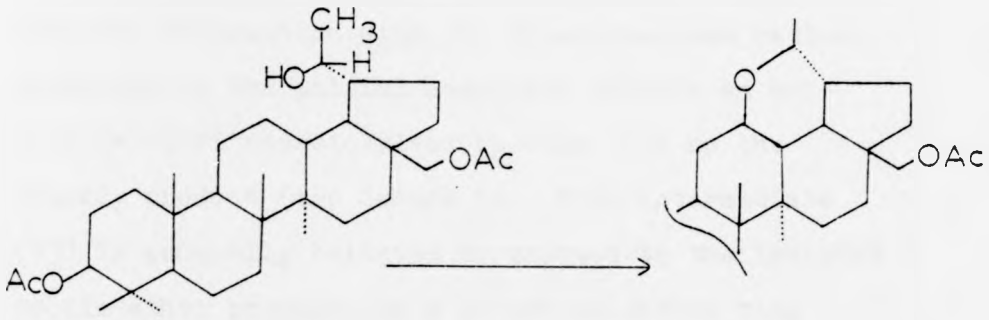


Scheme 5

Although the exact stoichiometry of the alkoxylead intermediate is not known , the representation (42)

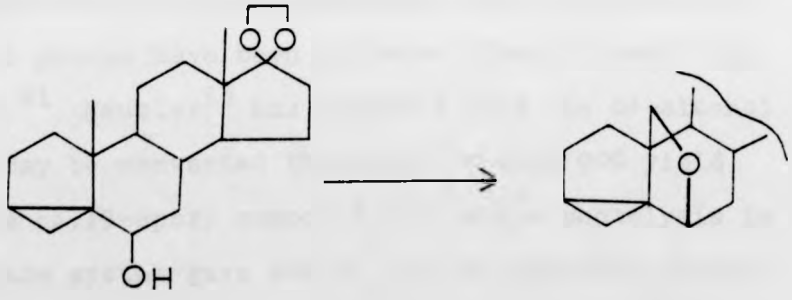
for this species in Scheme 5 is a convenient one. Homolysis of this alkoxylead acetate intermediate (42) may be brought about by thermal or photochemical means, although photolysis is generally the preferred method of cleavage since it gives rise to less of the by-products which are known[83] to arise from heterolytic cleavage of alkoxylead intermediates.

Although in simple aliphatic systems traces of products resulting from seven-membered transition states have been observed,[86,87] these same studies have shown that six-membered transition states are preferred for hydrogen abstraction. Analogously to the Barton reaction, several examples have been noted where lead tetraacetate oxidations lead to remotely functionalised products by way of seven-membered transition states. For example,[88] lead tetraacetate oxidation of the 12α-alcohol (44) results in formation of the pyran derivative (45) which the authors suggest is a consequence of steric compressions.



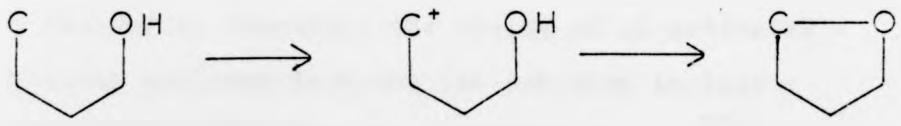
(44) (45)

In contrast to the Barton reaction, Tanabe[89] has shown that, on lead tetraacetate oxidation, the i-steroid (46) undergoes remote functionalisation to the 6β,19-epoxy compound (47). This observation suggests that in the lead tetraacetate reaction, the internuclear distances for hydrogen abstraction are less critical than those in the Barton reaction and Heusler[30] has proposed that the alkoxy radicals produced in lead tetraacetate oxidations are "stretched."



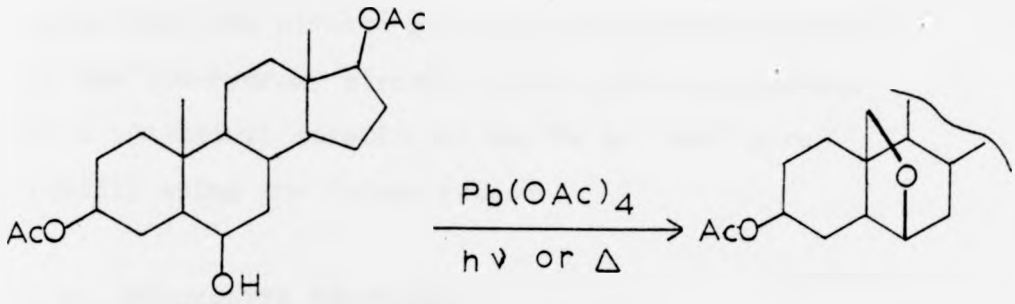
(46) (47)

Recombination of the alkyl radical formed from hydrogen abstraction with the triacetoxylead radical generated in the initial homolysis affords an unisolable alkyltriacetoxylead species (43) as the primary product (see Scheme 5). This intermediate (43) is generally believed to proceed to the isolated cyclic ether products by a direct oxidative ring closure.[30] However, it has been suggested[90] that in certain simple aliphatic systems an alternative mechanism involving a one electron transfer from carbon to lead to give the corresponding carbocation which then cyclises may operate (Scheme 6).



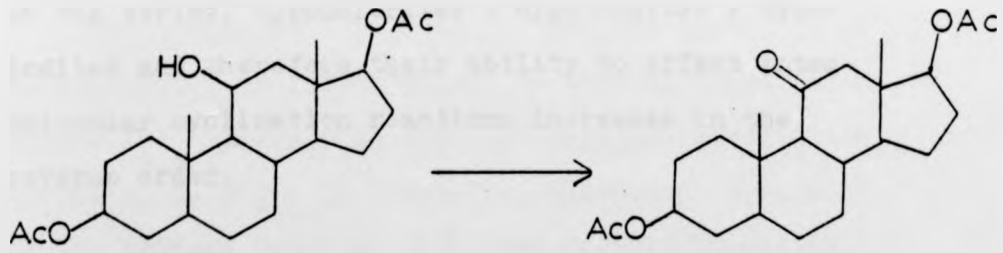
Scheme 6

Lead tetraacetate oxidations have been used extensively in steroid chemistry and oxidations of methyl groups have been achieved often in very high yield.[91] Heusler[93] has reported that the 6β-alcohol (48) may be converted thermally in some 90% yield to the 6β,19-epoxy compound (49) while photolysis in the same system gave 94% of the 19-activated product (49) as estimated by GLC.



(48) (49)

Similarly, 2β,19-epoxy products have been prepared thermally in 60-70% yield from 2β-alcohols and 18,20β-epoxy[93,94] products have been obtained in up to 50% yield from 20β-hydroxy steroids.[95] In contrast to the Barton reaction, the yields of 18-activated products achieved from the 11β-position in lead tetraacetate oxidations are generally poor.[93] In particular, attempts to effect a partial synthesis of aldosterone (1) from the 11β-hydroxy-3,17-diacetate (50) resulted in failure, the only isolable product being the 11-ketone (51).[96]



(50) (51)

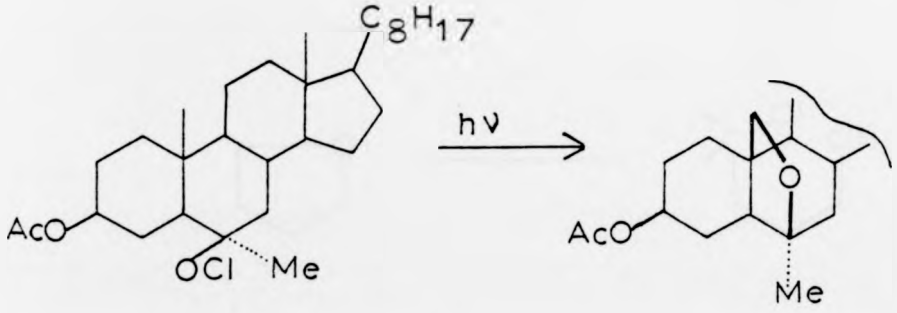
A favourable comparison of lead tetraacetate oxidation with nitrite photolysis has been reported[97] in the 12α-hydroxy steroids where functionalisation of a 17α-methyl substituent may be achieved more readily using the former method.

1.4 HYPOHALITE REACTIONS

In their preliminary work on the Barton reaction, Barton and co-workers[98,99] demonstrated that the photolysis of certain steroidal hypochlorites afforded functionalisation of the angular methyl groups. Subsequently, reactions of hypohalites have found general application in remote functionalisation.[11] Although the decomposition of hypochlorites and hypobromites have found some application in synthesis and are of mechanistic interest, by far the most important hypohalite decomposition reaction is that of the hypoiodites. In part this may be attributed to the fact that the tendency of secondary hypohalites to undergo α-cleavage to ketonic products decreases in the series, hypochlorites > hypobromites > hypoiodites and therefore their ability to effect intramolecular cyclisation reactions increases in the reverse order.

1.4.1 The hypochlorite reaction

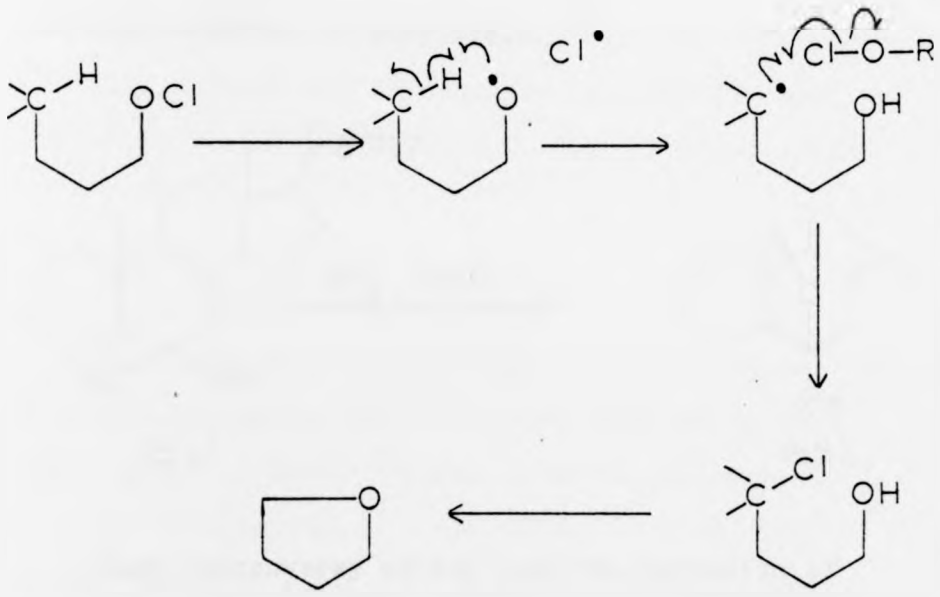
Hypochlorites are well known as photochemical sources of alkoxy radicals.[100,101] Thus it was found[98] that photolysis of the 6β-hypochlorite (52) followed by base treatment gave the 6β,19-epoxy-steroid (53) in good yield.



(52) (53)

Green[102] has shown, in contrast to the Barton reaction, that alkoxy radical formation in the hypochlorite reaction occurs by a radical chain mechanism, and Walling[103] has demonstrated that in a manner similar to the Barton reaction, the subsequent hydrogen abstraction is an intramolecular process.

The mechanistic pathway for the decomposition of hypochlorites by photochemical or thermal means to afford the primary products, the δ-chloro substituted alcohols, is shown in Scheme 7. Subsequent treatment of the primary products with base results in cyclisation to the ethers.



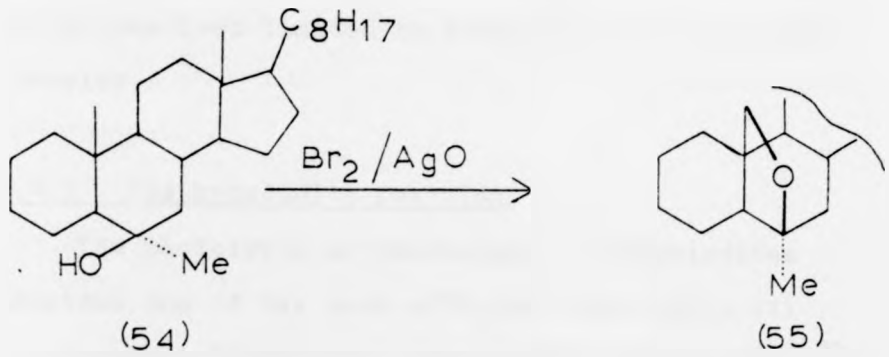
Scheme 7

Although this reaction constituted one of the earliest functionalisations of angular methyl groups, as a result of the susceptibility of hypochlorites to α-cleavage, its application has been restricted to only a few cases.

1.4.2 The hypobromite reaction

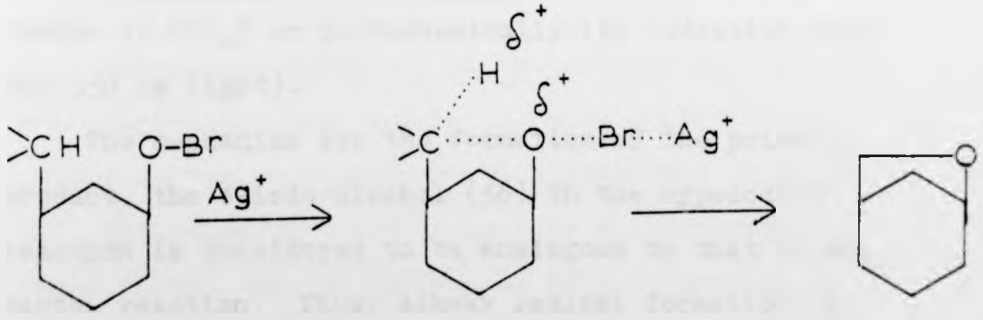
Hypobromites may be generated *in situ* by the reaction of bromine on alcohols and they have been shown[104] in the steroid field to afford remotely functionalised products when decomposed by silver ions. For example, the transformation (54) to (55)

has been effected in good yield.[104]



(54) (55)

Some controversy exists over the mechanism of the hypobromite reaction. Although Sneen[104] originally suggested that the cyclisation of hypobromites proceeded by the ionic mechanism shown in Scheme 8, Akhtar[105] later proposed a radical mechanism for this reaction. More recently, however, further evidence has been provided for the original ionic mechanism.[106]



Scheme 8

Once again little synthetic avail has been made of this reaction and in the steroid field its application has been limited to formation of 6β,19-epoxy-steroids.

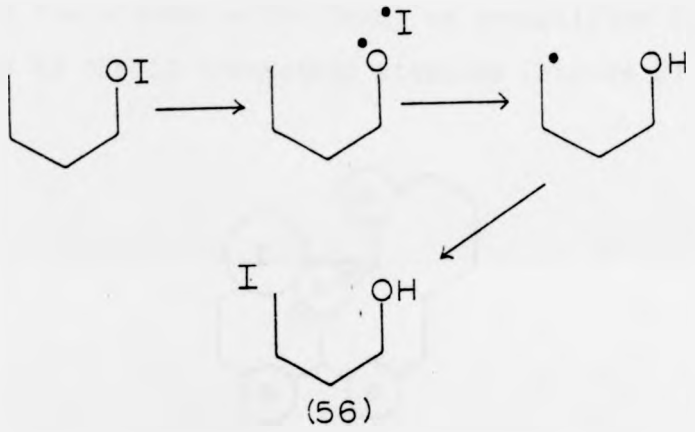
1.4.3 The hypoiodite reaction

The photolysis or thermolysis of hypoiodites provides one of the most efficient and widely utilised means of effecting remote functionalisation.[30] Although hypoiodites are themselves unknown, they may be prepared with ease *in situ* by the reaction of alcohols with a reagent containing "positive" iodine.[3] Most conveniently, hypoiodites may be generated by the reaction of an alcohol with a variety of metal acetates (Ag, Hg, and Pb) of which lead tetraacetate is particularly convenient.[107]

The homolytic decomposition of hypoiodites can be brought about either thermally (in refluxing cyclohexane or CCl_4) or photochemically (by radiation with 500-550 nm light).

The mechanism for the formation of the primary product, the δ-iodo-alcohol (56) in the hypoiodite reaction is considered to be analogous to that of the Barton reaction. Thus, alkoxy radical formation is followed by hydrogen abstraction through a six-membered transition state and recombination of the

resulting alkyl radical with an iodine atom (Scheme 9). In contrast to the hypochlorite reaction, no evidence has been found for the existence of a radical chain mechanism in the primary homolysis step of this reaction.



(56)

Scheme 9

Subsequent reactions of the primary product (56) are complex and the variety of paths available for ultimate product formation are illustrated in Scheme 10. The iodomethyl substituent is a large group which in the steroid nucleus is held quite rigidly and which adopts a specific conformation. The further reactions of the primary product (56) are governed

by the conformational rigidity of this iodomethyl group and its stereochemical disposition with respect to the alcohol group as well as the relative rates of formation and decomposition of additional hypoiodites.

The conformational rigidity of the iodomethyl group results in specific stereochemical relationships to the alcohol substituent as exemplified for the case of the 19-iodomethyl steroids (Figure 2).

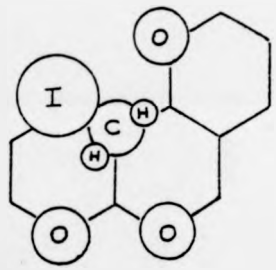
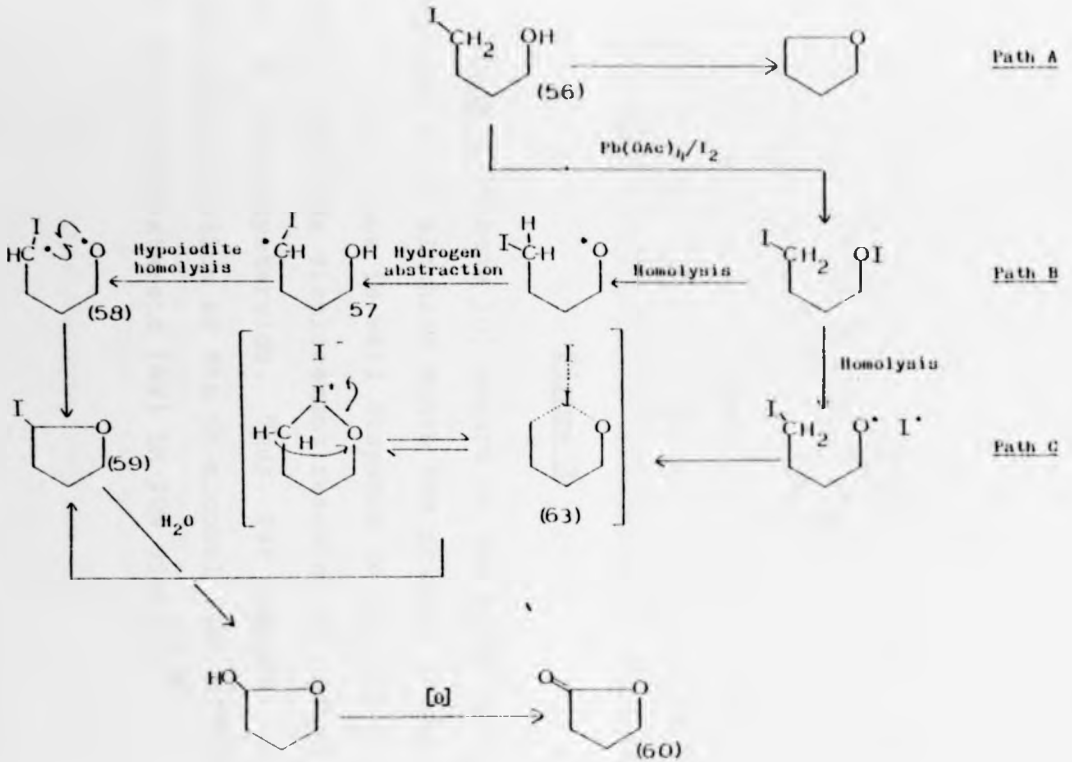


Figure 2

The relative positions of the alcohol group with respect to an iodomethyl group therefore give rise to the three relative stereochemistries A, B, and C depicted in Figure 3. These three relationships A, B, and C give rise to the distinct reaction pathways A, B, and C, respectively, shown in Scheme 10.


Path A
(56)
Pb(OAc)4/I2
Path B
Hypoiodite homolysis
Hydrogen abstraction
Homolysis
(58)
57
Homolysis
Path C
(59)
(63)
H2O
[O]
(60)

Scheme 10

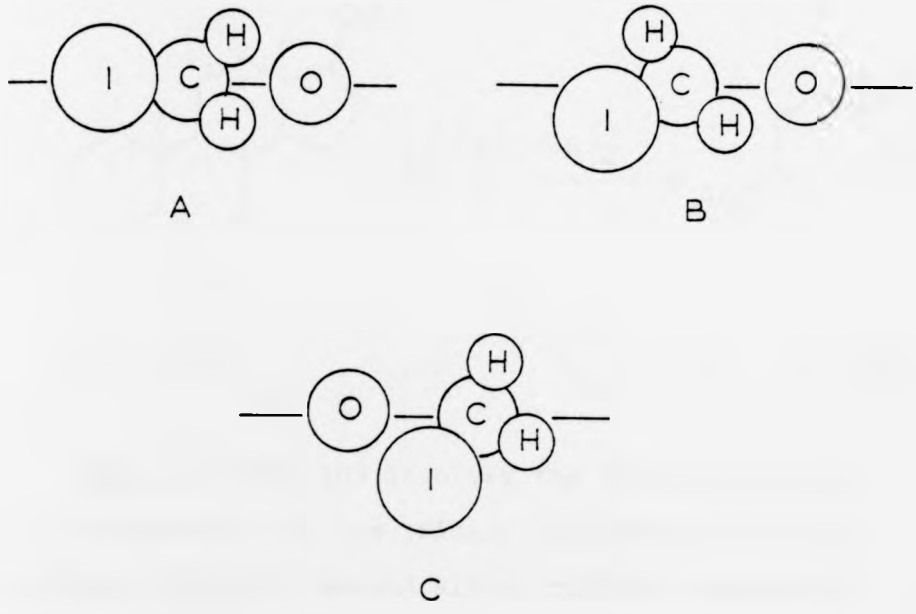
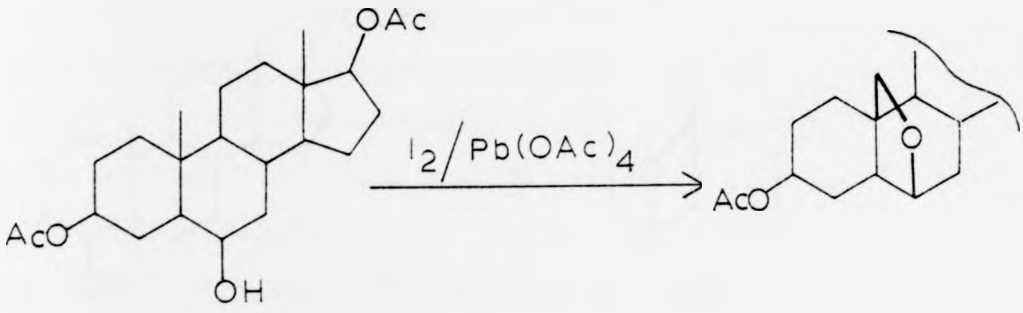


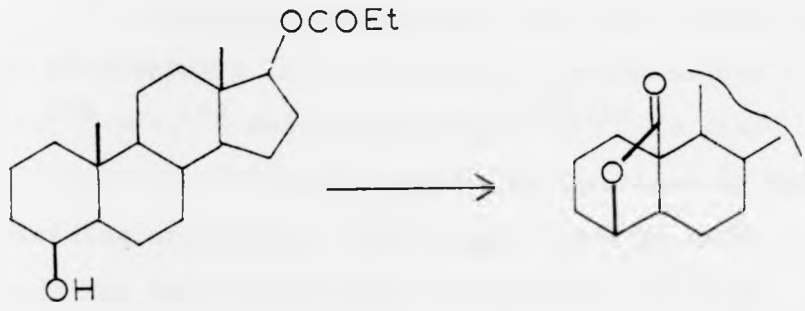
Figure 3

Path A (Scheme 10) occurs in the hypoiodite reaction of 6β-alcohols since the primary product (56) in this case is well disposed to undergo a facile, backside displacement reaction of iodine to give 6β,19-epoxysteroids. Thus, for example, the hypoiodite reaction of the 6β-alcohol (48) affords the 6β,19-epoxysteroid (49) in 90% yield.[108]



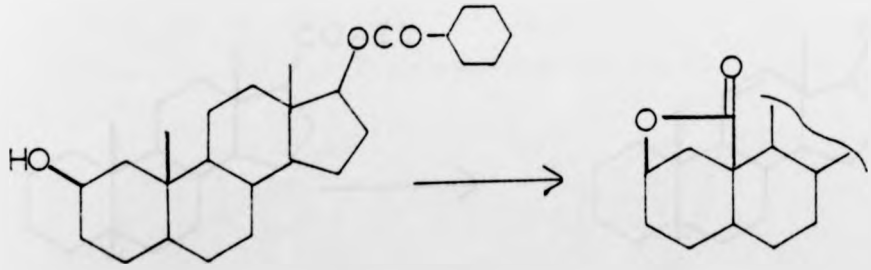
(48) (49)

Path B (Scheme 10) involves the further formation of a hypoiodite from the primary iodohydrin (56) and homolysis, giving a second alkoxy radical, results in the abstraction of a second hydrogen from the iodomethyl group. The resulting radical (57) to which added stability is imparted by the iodine, undergoes a further hypoiodite and homolysis reaction and the resulting diradical (58) cyclises to the iodofuran derivative (59). Hydrolytic and oxidative work-up affords the lactone product (60). This sequence of reactions may be exemplified by the hypoiodite reaction of the 4β-hydroxy steroids. Thus the hypoiodite reaction of the 4β-alcohol (61) affords,[109] on oxidative work-up, the lactone (62) in 85% yield.



(61) (62)

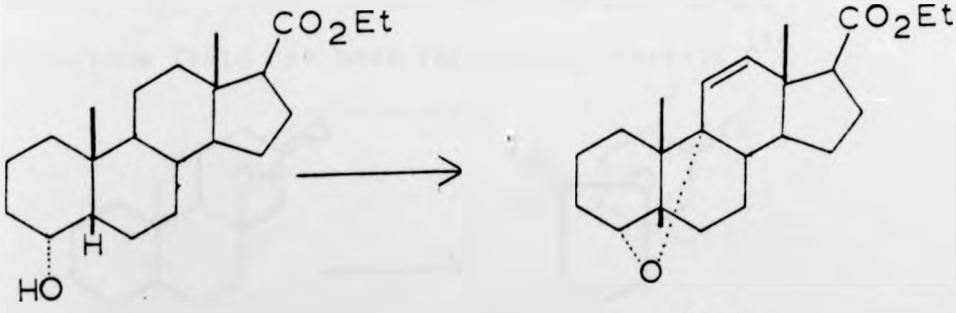
Path C (Scheme 10) involves the secondary hypoiodite reaction of the primary iodohydrin (56) to form an alkoxy radical which is unfavourably disposed for hydrogen abstraction and which thus forms an intermediate (63) whose subsequent decomposition affords the iodoether (59). Hydrolytic and oxidative work-up afford the lactone product (60). This series of reactions may be exemplified by the hypoiodite reaction of the 23-alcohol (64)[109] which on work-up furnishes the lactone (65) in 54% yield.



(64) (65)

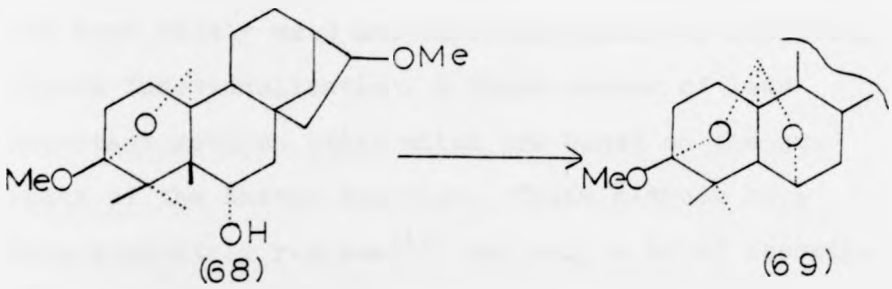
The hypoiodite reaction has been used extensively and successfully in the functionalisation of C19 from 2β-,[109] 4β-,[109] and 6β-alcohols[3,108,110] to give products whose formation may be rationalised by the preceding arguments. Additionally, the 18-methyl group has been functionalised from both the 20α- and 20β-alcohols in good yield to give lactone products which arise by path B.[95] In contrast to the Barton reaction and similar to lead tetraacetate oxidation, fairly poor yields of 18-functionalised products are obtained from the hypoiodite reaction of the 11β-alcohols.[111]

Functionalisation of the very hindered 8β-position in the steroid nucleus has been achieved by the hypoiodite reaction.[30] The isolation of the olefin (67) from the 4α-alcohol (66) demonstrates another example of a subsequent reaction of primary products of the hypoiodite reaction.[112]



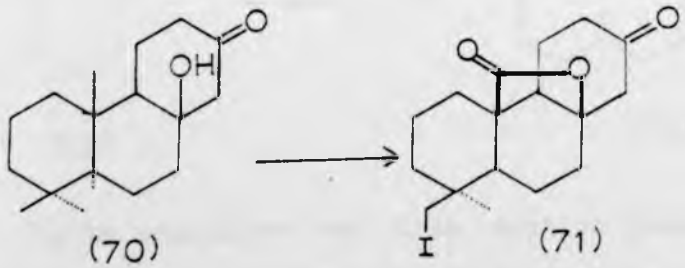
(66) (67)

The potential of the hypoiodite reaction as a method of remote functionalisation may be judged from the fact that application of this reaction to the terpene (68) gives essentially a quantitative yield of the product (69).[113]



(68) (69)

Of some interest is the observation by Wenkert[114] of a "billiard-ball" hypoiodite reaction in which the primary alkyl radical effects a further hydrogen abstraction. Thus the hypoiodite reaction of the manool derivative (70) gave the iodolactone (71). Further use of this interesting reaction in the diterpene field has been reported by Cortett.[115]



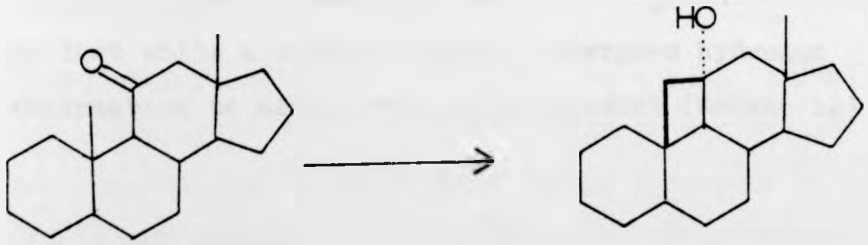
(70) (71)

The diversity of applications and consequences of the hypoiodite reaction are extensive and have been reviewed in depth by a number of authors.[11,30,116]

1.5 MISCELLANEOUS REMOTE FUNCTIONALISATION REACTIONS

Although the methods described above constitute the most widely used and important means of achieving remote functionalisation, a large number of less important methods exist which are based on the concepts of the Barton reaction. These methods have been adequately reviewed[117] and only a brief description of certain of them is presented here.

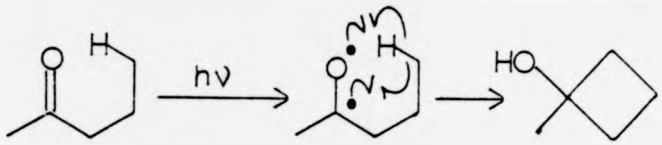
The UV irradiation of certain steroidal ketones is found to give rise to cyclobutane derivatives of the angular methyl groups often in good yield. Thus irradiation of the ketone (72) gave the cyclobutanol derivative (73).[118]



(72) (73)

It is considered that this reaction proceeds mechanistically as shown (Scheme 11) and the biradical

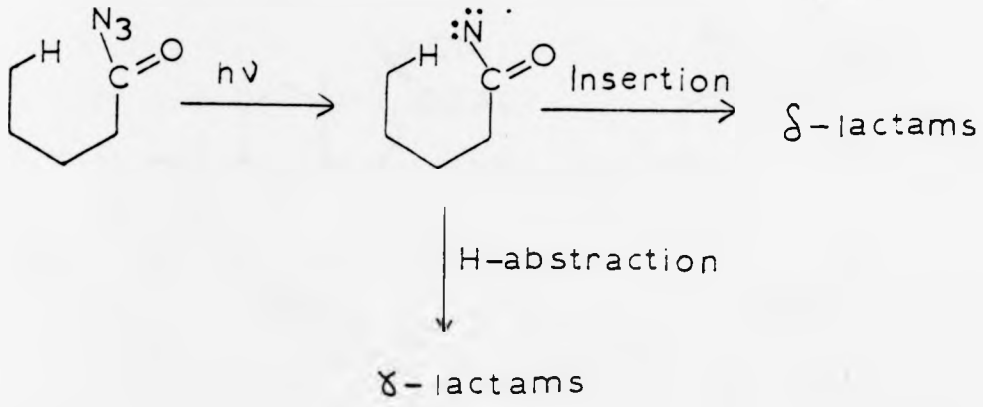
nature of the intermediate (74) has been investigated.[119]



(74)

Scheme 11

Alternative methods to the Hoffmann-Loffler-Freytag reaction for the generation of radical character on nitrogen have been described. Thus, the photolysis of acyl azides has found some application in the remote functionalisation of the methyl groups in certain natural products.[120,121,122,123] The mechanism of this reaction has been investigated in an attempt to account for the formation of both γ- and δ-lactams and it has been suggested[124] that a singlet radical undergoes insertion to give the former product while a triplet radical undergoes hydrogen abstraction to afford the latter product (Scheme 12).

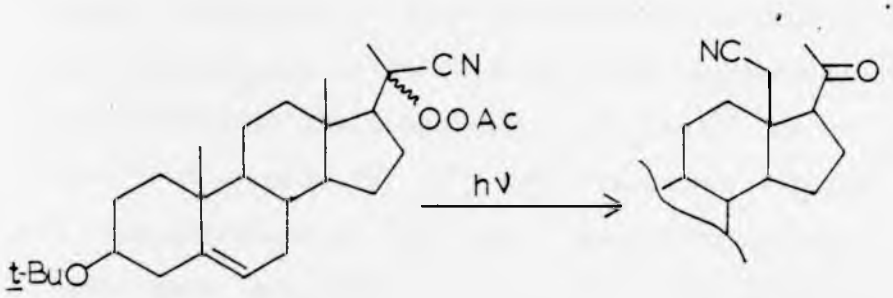


Scheme 12

Nitrenes may alternatively be generated by the photolysis of nitrile oxides[125,126] and this method, which is thought to proceed via oxazirine intermediates, has been applied to some complex molecules.

A further example of remote functionalisation via nitrogen centred radicals is provided by the photolysis of iodoamides.[127,128,129]

Several further examples also exist of remote functionalisation reactions involving alkoxy radicals. For example, in a manner very similar to the Barton reaction, Mills[130] has found that the pyrolysis of a 6β-nitrate gave a small yield (12%) of the corresponding 19-nitrosteroid while very recently photolysis of the 20-peroxyacetate (75) was shown to afford the 18-nitrile (76).[131]



(75) (76)

Finally, examples have been reported of the use of carbene insertion reactions for remote functionalisation where the carbene is generated either by the Wolff reaction[132] or the Arndt-Eistert reaction of diazoketones.[133,134]

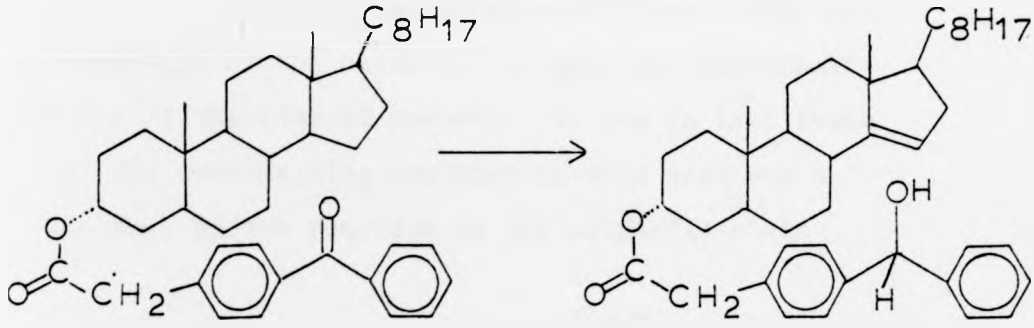
1.6 THE TEMPLATE REMOTE FUNCTIONALISATION REACTION

Though the principles and reactions discussed above are generally referred to as the remote functionalisation of unactivated carbon atoms, it is clear from stereochemical considerations that the very basis of such functionalisations are proximity effects of functional groups and the very proximity of such groups does in fact indirectly lead to activation of unactivated centres towards hydrogen abstraction. In recent years, Breslow has initiated the development of concepts which unarguably involve remote functionalisation in so far as they enable the

removal, for example, of the 17α-hydrogen in the cholestane nucleus by utilisation of the properties of a substituent at the 3-position. Breslow[135] has argued that despite the fact that six-membered rings are thermodynamically favourable transition states, thermodynamic considerations do not exclude the intermediacy of very large rings in intramolecular functionalisation reactions. Accordingly, he has redefined remote functionalisation as "a process in which we attach a rigid reagent to a substrate and then carry out a directed functionalisation of that substrate at a relatively large distance from the point of attachment."

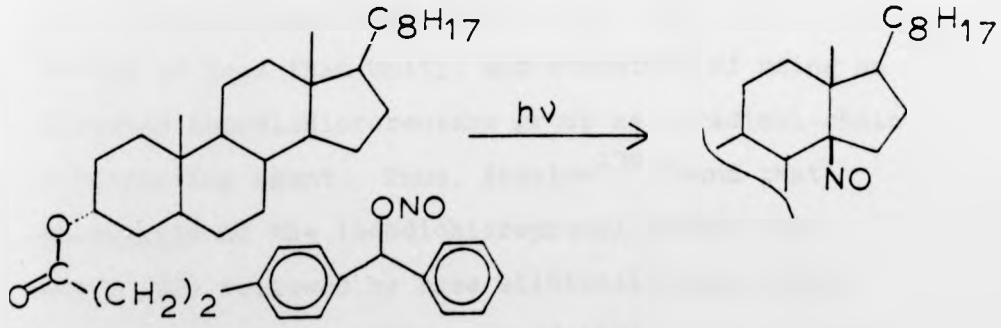
In some preliminary experiments, Breslow[136] found that the photolysis of long chain esters of benzophenone carboxylic acid afforded large ring lactones, in some cases with moderate selectivity. It was argued that the selectivity of functionalisation of these reactions might be enhanced in steroidal systems which would provide a more rigid structure. Breslow recognized from a consideration of molecular models that unfavourable steric interactions with the angular methyl groups made use of 3β-esters in these reactions unsuitable. Accordingly, Breslow[135] reported that, on photolysis, the 3α-benzophenone acetic acid ester (77) gave selective attack at C14

to afford the Δ^{14}-product (78) resulting from a preliminary hydrogen abstraction by the photochemically generated benzophenone triplet.



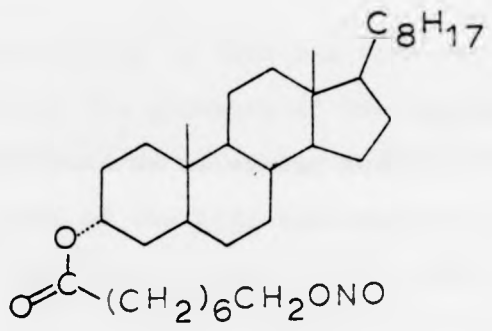
(77) (78)

With the success of this particular functionalisation, it was considered that the principles involved might be extended generally to functionalisation reactions. With this in mind, the nitrite (79) was photolysed whereupon the 14β-nitroso compound (80) was isolated in modest yields.[137]



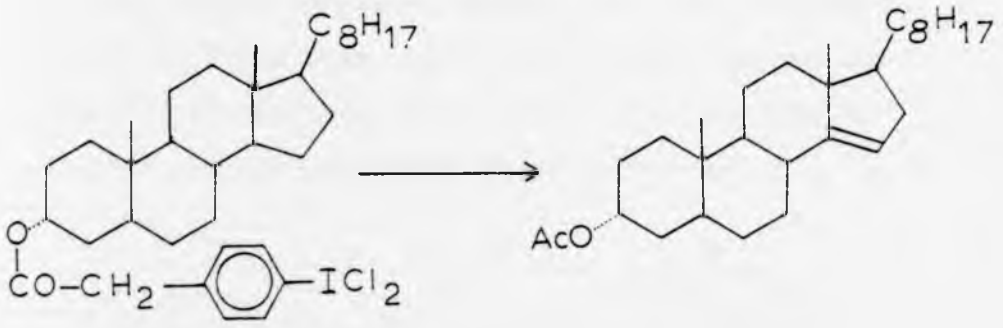
(79) (80)

The dependence of the above type of reaction on the use of a rigid chain, which cannot fold back and react with itself, as a carrier for the attacking centre was demonstrated by Baldwin[138] who found that irradiation of the nitrite (81) gave no functionalisation of the steroid nucleus. It was in fact found that the overwhelming reaction in this case was a classical Barton reaction on the aliphatic chain.



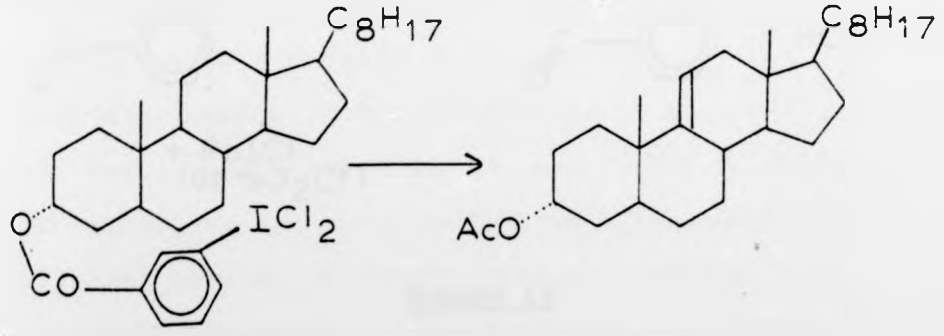
(81)

Breslow considered that the above reactions were of restricted practical value since they had quantum yields of less than unity, and conceived of using an attached iododichlorobenzene group as a radical-chain chlorinating agent. Thus, Breslow[139] found that photolysis of the iododichlorophenyl acetic acid ester (82) followed by base elimination and acetylation afforded the Δ 14-compound (83).



(82) (83)

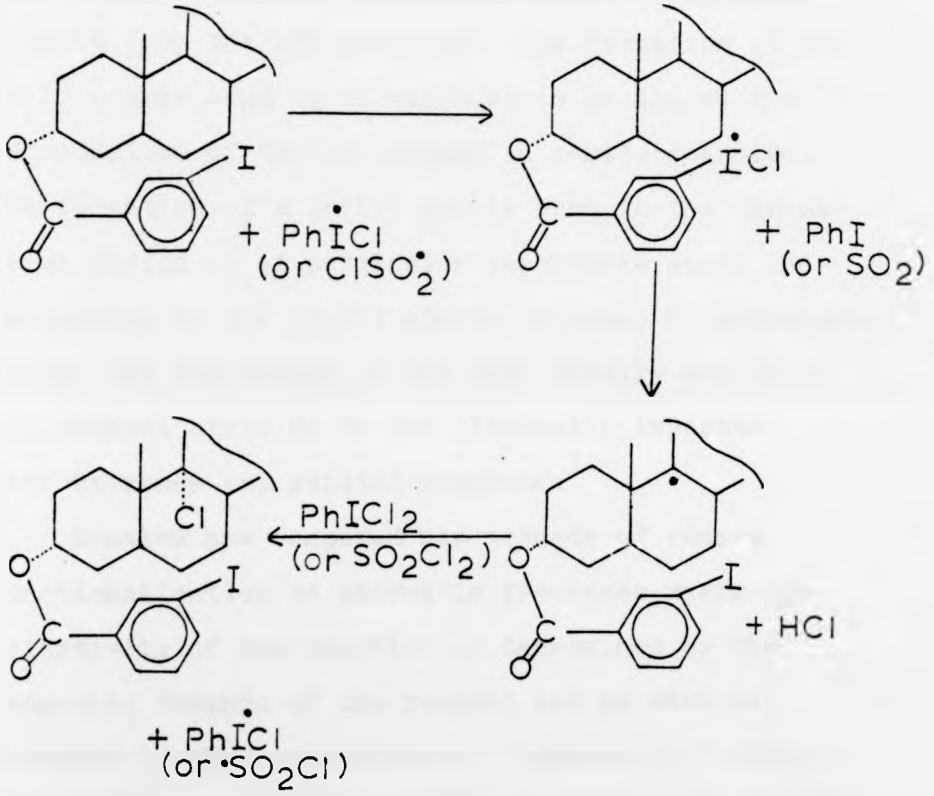
The selectivity of this reaction was found to be dependent on the geometry of the attached reagent. Thus, as predicted by molecular models, it was found that photolysis of the meta-iodobenzoate (84) gave, on work-up, the 9(11) olefin (85) as the major product.



(84) (85)

Improvement in the yield obtained by this method of remote functionalisation was attained[140] by using

a radical-relay mechanism whereby the actual attached iodochloro group responsible for hydrogen removal was generated by the transfer of a chlorine atom from an external radical species as shown in Scheme 13.



Scheme 13

Functionalisations by this method have been referred to as template remote functionalisations, and the concepts and applications of this type of reaction have been summarised in a recent paper.[141] By

varying the position of the substituent on the steroid nucleus, the number of atoms in the carbon chain and the position of the iodine group on the aromatic ring, the formation has been achieved of Δ9(11)-, Δ14-, and Δ16-steroids from the 3α-position and of a Δ9(11)-steroid from the 17α-position. The formation of the 9(11) double bond is of value since it allows the introduction of the C11 oxygen in corticosteroids. The formation of a 16(17) double bond in the cholesterol series is of particular importance since isomerisation to the 17(20) olefin followed by ozonolysis allows the conversion of the very readily available cholesterol steroids to the clinically important androsterones and related compounds.

Breslow has compared his methods of remote functionalisation to enzymatic processes where the selectivity of the reaction is determined by the geometric demands of the reagent and as such has referred to these reactions as "biomimetic." While the techniques described by Breslow offer novel and important methods of remote functionalisation, they in no way overshadow the great value and importance of the more "classical" methods of remote functionalisation. The biomimetic template methods in fact suffer from severe drawbacks in as much as only hydrogen abstractions from tertiary carbons have been

realised and the primary carbon atoms at C18 and C19 are considered inaccessible to the presently available methods.

In conclusion, therefore, it is considered that rather than detracting from the classical methods of remote functionalisation, these newer, biomimetic methods add to our understanding of the nature of those reactions which occur because of the spatial proximities of functional groups arising from molecular stereochemistry.

CHAPTER 2

The mechanisms of by-product formation during the Barton reaction

2.1 INTRODUCTION

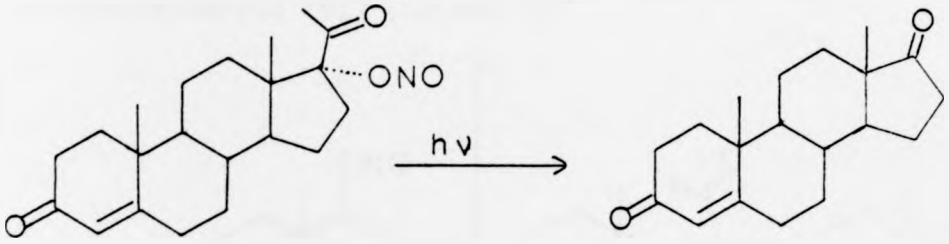
Though the mechanism and scope of the Barton reaction have been described in the preceding section, that material was concerned largely with the normal course of the Barton reaction, but in practice diversions invariably occur. Certain of these diversions arise from unusual structural properties of the reacting molecules and these are discussed as diversions of either the alkyl or alkoxy radical intermediates. The remaining diversions from the desired course of the Barton reaction give rise to by-products which always accompany this reaction. The mechanism of formation of these by-products forms a central part of this Thesis.

2.1.1 Diversions of the alkoxy radical

Although hydrogen abstraction by an alkoxy radical as found in the Barton reaction is a facile and thermodynamically favourable process, several examples are known in which the alkoxy radical undergoes alternative reactions.

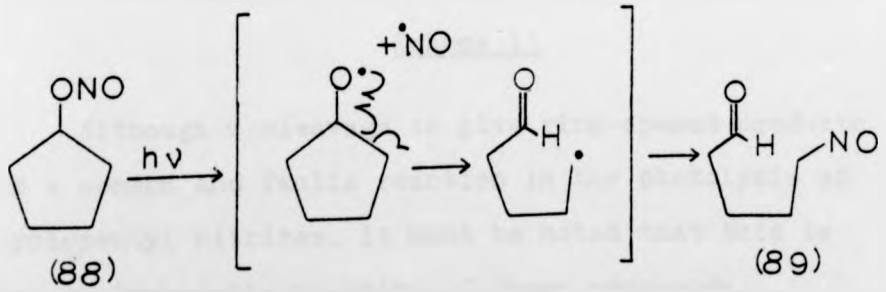
A common alternative mode of decomposition of the alkoxy radical intermediate in the Barton reaction is the α-cleavage reaction which is promoted by factors which either stabilise an extruded fragment or destabilise the alkoxy radical itself. Barton[142]

has made synthetic use of the former effect in the degradation of the pregnane side-chain when he showed, for example, that photolysis of the 17α-nitrite ester (86) afforded androst-5-ene-3,17-dione (87) in good yield.



(86) (87)

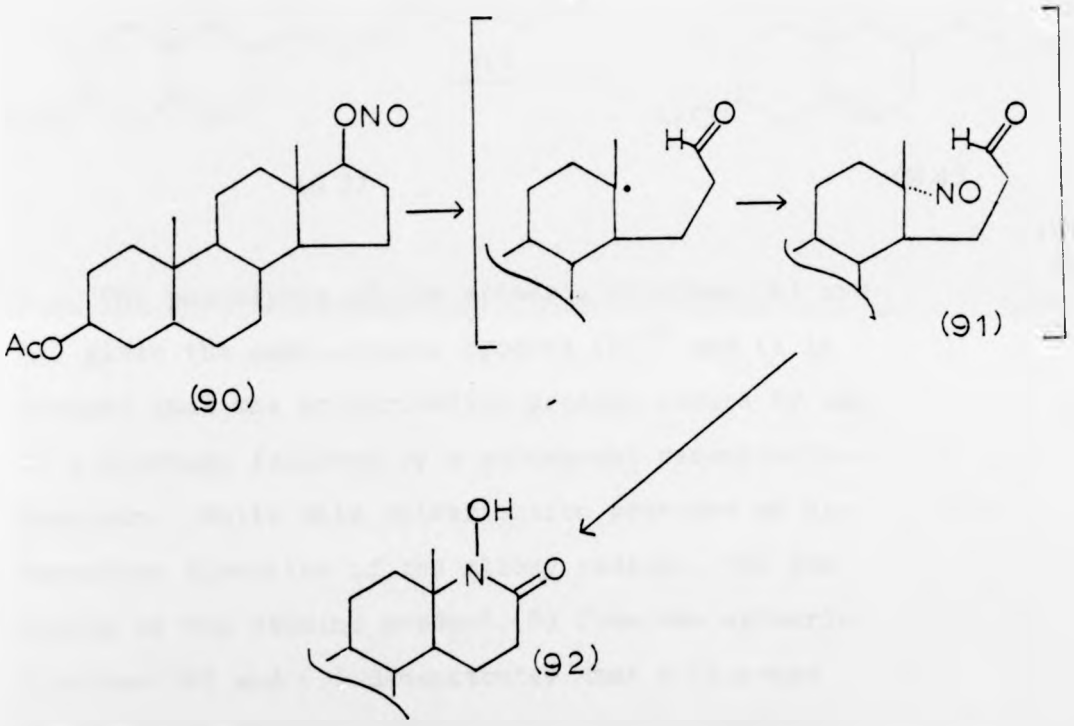
Kabasakalian[143] has found that small-ring alicyclic nitrites undergo α-cleavage to afford ring-opened nitroso-compounds. Thus, the photolysis of cyclopentyl nitrite (88) resulted in formation of the nitroso-aldehyde (89) by the pathway shown (Scheme 14).



(88) (89)

Scheme 14

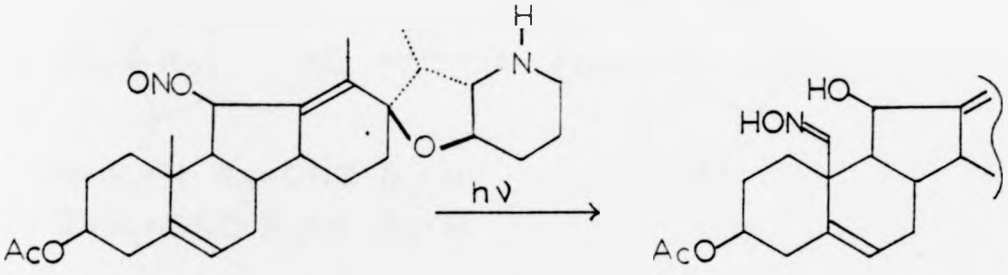
Robinson[144] has made synthetic use of this ring-opening reaction in the photolysis of certain steroidal nitrites. Thus, he found that photolysis of the 17-nitrite (90) affords the steroidal hydroxamic acid (92) via cyclisation of the primary product, the nitroso-aldehyde (91) (Scheme 15).



Scheme 15

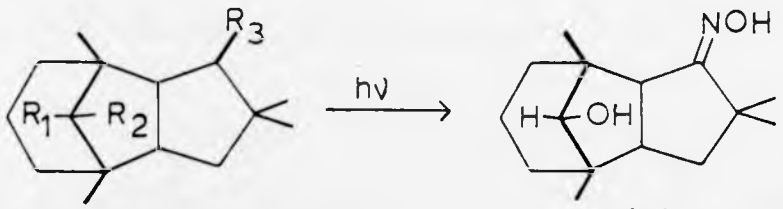
Although α-cleavage to give ring-opened products is a common and facile reaction in the photolysis of cyclopentyl nitrites, it must be noted that this is not an inevitable reaction of these compounds. Suginome[63] has provided one of the few exceptions

and has shown that the veratrobasine-derived 11β-nitrite (93) undergoes the Barton reaction in the normal way to give the 19-oxime (94).



(93) (94)

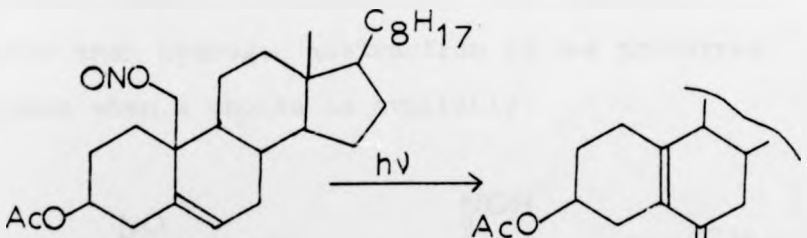
The photolysis of the epimeric nitrites (6) and (7) gives the same oximino product (8)[28] and it is thought that the epimerisation process occurs by way of α-cleavage followed by a subsequent recombination reaction. While this epimerisation provides an alternative diversion of the alkoxy radical, the formation of the oximino product (8) from the epimeric nitrites (6) and (7) demonstrates that α-cleavage need not necessarily preclude the Barton reaction.



(6) R_1 = H R_2 = ONO R_3 = H
(7) R_1 = ONO R_2 = H R_3 = H

(8)

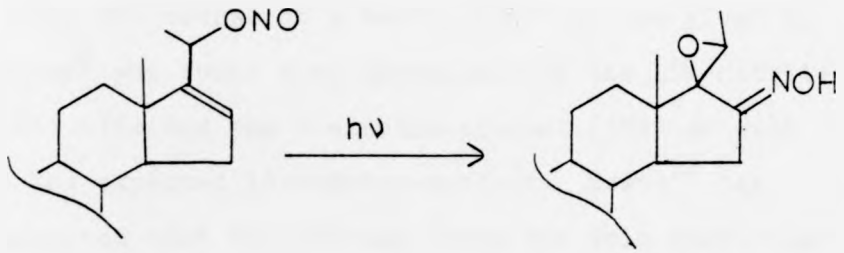
In certain systems where the Barton reaction cannot occur, α-cleavage may also be observed. Watanabe,[145] for example, found that photolysis of 19-nitroso-oxycholesteryl 3β-acetate (95) results in elimination of the angular hydroxymethyl group to give the 19-nor-6-oximino compound (96).



(95) (96)

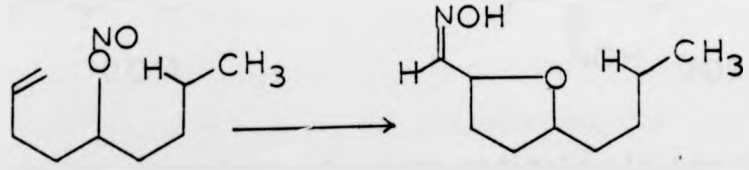
Besides the diversion of alkoxy radicals from the Barton reaction by α-cleavage, it has been found that they may undergo addition to a suitably located

olefin. For example,[146,147] photolysis of the 20-nitrite (97) gave the 17,20-epoxide (98) rather than the 18-functionalised products which would be expected from the normal Barton reaction.



(97) (98)

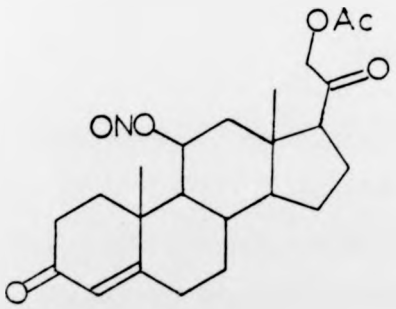
Additions of the alkoxy radicals to double bonds have been further investigated in some simple systems,[148,149] and the observation by Surzur[148] that photolysis of the nitrite (99) affords only the cycloaddition product (100) and no product resulting from a Barton reaction demonstrates that cycloaddition rather than hydrogen abstraction is the preferred process when a choice is available.



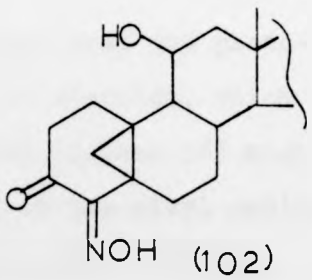
(99) (100)

2.1.2 Diversions of the alkyl radical

Diversions of the alkyl radicals, though less common than those of the alkoxy radicals, do occur and some of these reactions are now discussed. The first example of the diversion of an alkyl radical during the course of a Barton reaction was given by Barton[9] who found that photolysis of the 11β-nitrite (101) afforded the 4-oximino-product (102) as well as the expected 18-oximino-product. Hesse[12] has suggested that the driving-force for this particular reaction is not simply a consequence of the addition of the alkyl radical to the olefin but is a combination of the stability of the radical formed and the electrophilic nature of the β-position of the enone system.



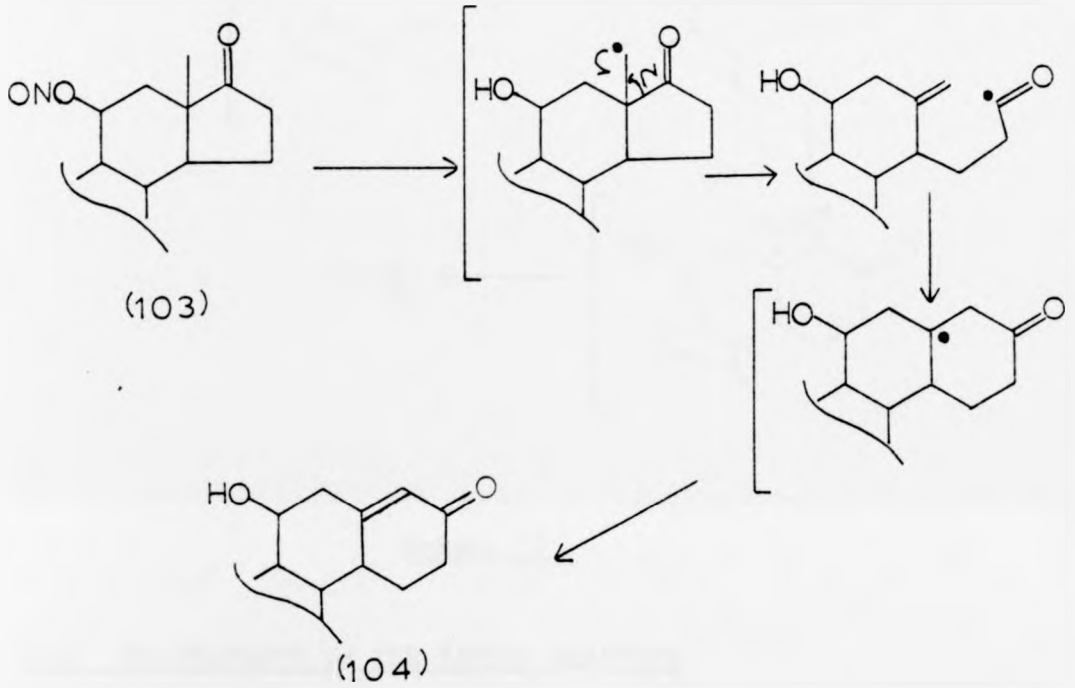
(101)



(102)

As in diversions of alkoxy radicals, it has been found that certain alkyl radical intermediates in the Barton reaction undergo α-cleavage. Thus, it was

suggested[150] that photolysis of the 11β-nitrite (103) gave the D-homo-enone (104) by the mechanism shown in Scheme 16.

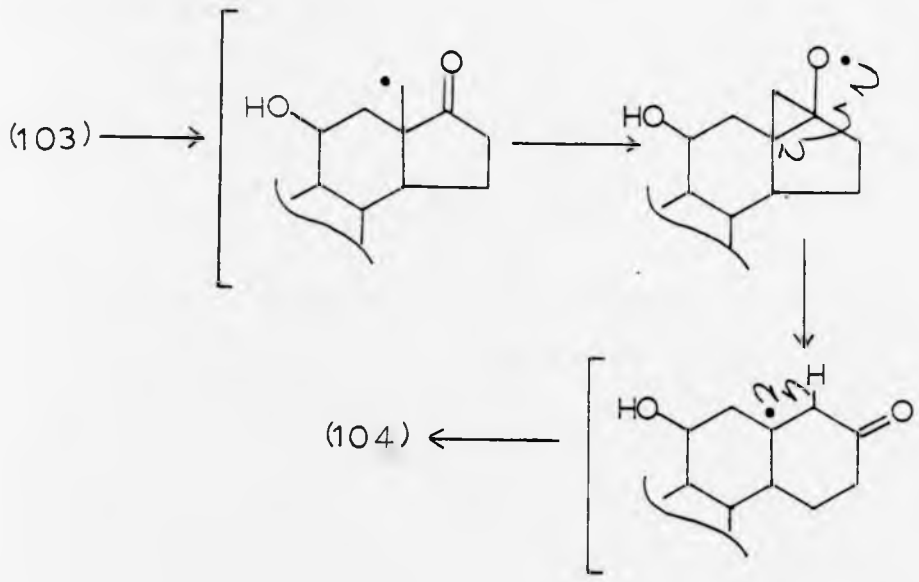


(103)

(104)

Scheme 16

Akhtar has observed,[11] however, that the photolysis of a number of 17-substituted steroids, which on the basis of the above mechanism (Scheme 16) might be expected to undergo α-cleavage of the alkyl radical, do in fact afford normal Barton products. He has therefore suggested that the rearrangement of the nitrite (103) to the enone (104) involves the direct reaction of the 18-alkyl radical with the 17-keto group by the alternative mechanism shown in Scheme 17.

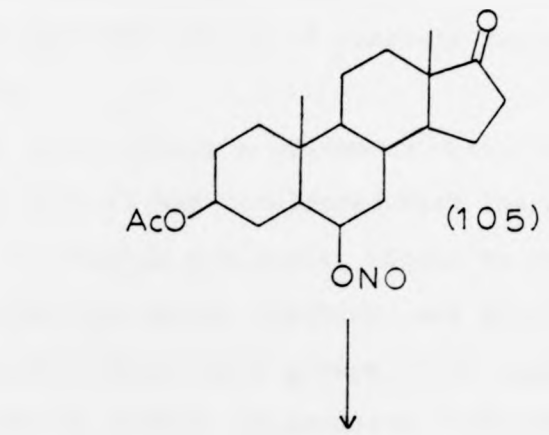


Scheme 17

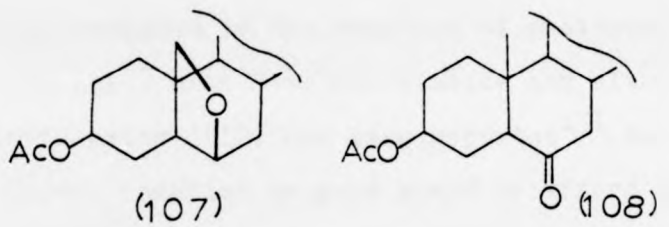
2.2 BY-PRODUCTS OF THE BARTON REACTION

The diversions described above of the alkoxy and alkyl radical intermediates of the Barton reaction arise as the result of certain unusual properties of the molecules being photolysed. It is found, however, in practice that even in those systems which undergo the Barton reaction efficiently, certain by-products almost always accompany this reaction. For example, Akhtar[38] has shown that photolysis of the 6β-nitrite (105) furnishes four products, the 6β,19-epoxysteroid (107), the 6-ketone (108), the 19-oxime (106), and

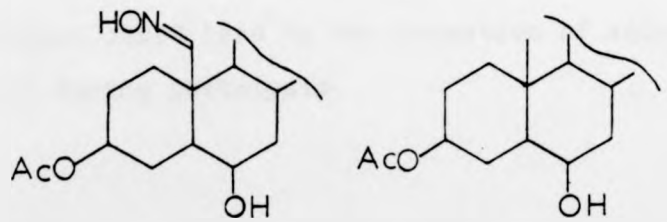
the 6β-alcohol (109).



(105)



(107) (108)

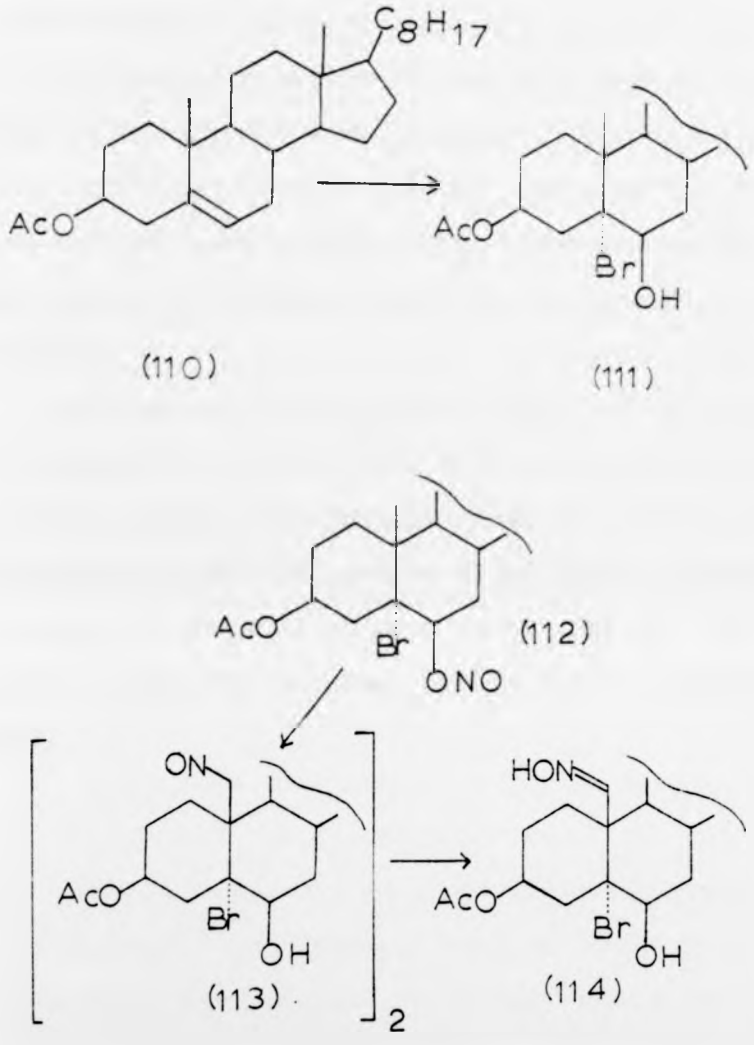


(106) (109)

In this work, the origins of the by-products of the Barton reaction were considered important. It was believed that an understanding of the modes of formation of these by-products might afford further

information on the various processes in operation during the Barton reaction and might be utilised to achieve improved yields of remotely functionalised products.

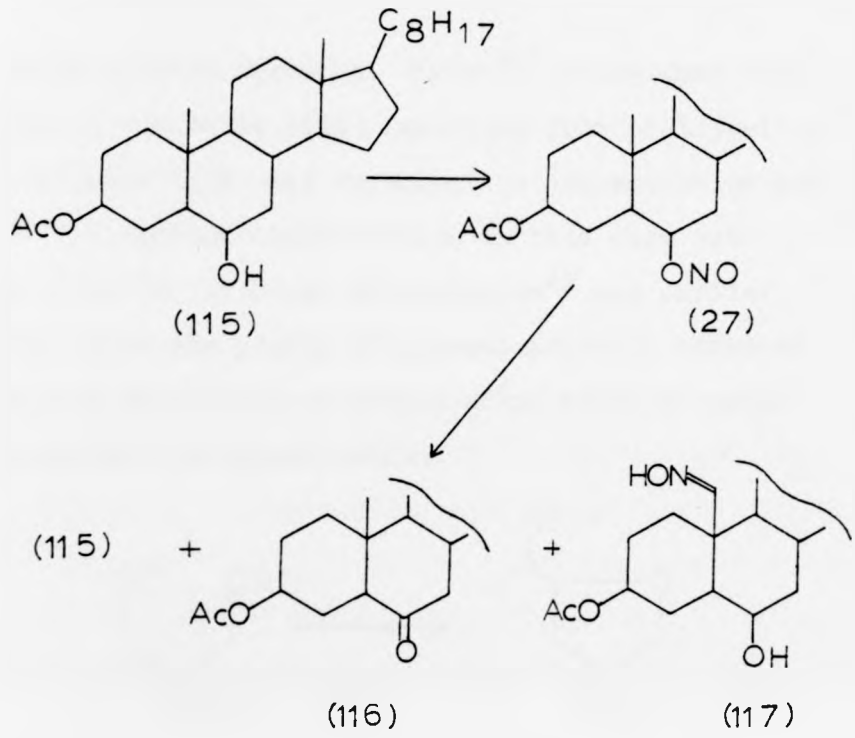
In establishing a system on which to base this present work it was considered that the system chosen should be readily available, should be well disposed to undergo the Barton reaction, and should possess a minimum of functional groups which might result in formation of further by-products under the conditions of the Barton reaction. The 5α-bromo-6β-alcohol (111) is readily prepared by the reaction of cholesteryl 3β-acetate (110) with N-bromoacetamide and although its nitrite ester (112) has been reported[151] to undergo the Barton reaction in good yield to afford the 19-oxime (114) by way of the 19-nitrosodimer (113) it was considered that the presence of the 5α-bromo substituent could lead to the formation of added by-products during photolysis.



In light of this possibility, it was considered that the 6β-nitrite (27) would provide a more suitable system upon which to base these studies. Therefore the 5α-bromo-6β-hydroxy steroid (111) was prepared

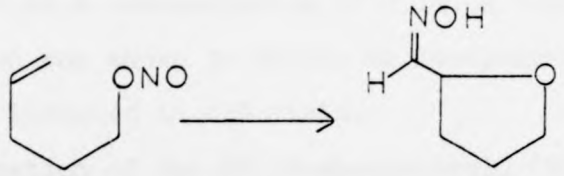
by the reaction of cholesteryl 3β-acetate (110) with N-bromoacetamide using literature methods[151] and chromous acetate reduction[152] of this compound was effected to afford the 6β-alcohol (115) in good yield. It was later noted that improved yields of the 6β-alcohol (115) were achieved when 2-mercaptoethanol was used as the hydrogen donor in the chromous ion reduction.

Reaction of the 6β-alcohol (115) with nitrosyl chloride gave the 6β-nitrite (27) as a stable, crystalline product. Photolysis of the 6β-nitrite (27) in toluene containing a trace of pyridine followed by refluxing in propan-2-ol gave three products, the 6β-alcohol (115), the 6-ketone (116), and the 19-oxime (117).



Although this reaction was repeated several times, it was found that the isolated yields of the oxime (117) (55%) were lower than those (65%) reported in the literature[20] and further, none of the 6β,19-epoxysteroid (29) obtained by Akhtar[38] could be isolated. The major difference between these experiments appeared to be the concentration at which the photolyses were performed. Thus, the literature photolysis[20] of the 6β-nitrite (27) was carried out at a concentration of 0.07M while the present photolysis was performed at a concentration of 0.01M. In

support of this argument, Rieke[149] found that the yield of the oxime (119) resulting from photolysis of the nitrite (118) was dependent on concentration and that the optimum concentration in this case was 7.52×10^{-2}M, although Kabasakalian[25] had earlier stated that the yields of nitroso products obtained from the photolysis of simple alkyl nitrites were independent of concentration.



(118) (119)

The 6β-nitrite (27) was photolysed in toluene at a number of different concentrations and, after isomerisation of any nitroso products by refluxing in propan-2-ol, the 19-oxime (117) was isolated in the yields shown in Table 1.

Nitrite (27) Concentration (M)	% Oxime (117)
0.1	41
0.05	58
0.04	65
0.01	52

Table 1

It is concluded from the results in Table 1 that the optimum concentration of 6β-nitrite (27) for 19-oxime formation occurs at about 0.04M and, in contrast to the findings of Kabasakalian,[25] the formation of oximino products from the Barton reaction of steroidal nitrites has been found to be concentration dependent.

When the photolysis of the 6β-nitrite (27) was performed at a concentration of 0.1M, a fourth product which was shown to be the 6β,19-epoxysteroid (29) was isolated in 22% yield.

Formation of the 6β,19-epoxysteroid (29) is readily avoided by carrying out the Barton reaction at suitable concentration of nitrite (27) and its mode of formation is now considered.

2.3 FORMATION OF EPOXIDES DURING THE BARTON REACTION

It was considered that increasing the concentration of the 6β-nitrite (27) solution would lead, during the course of the Barton reaction, to an increase in the concentration of the intermediate nitric oxide, and that this might have some bearing on the formation of the 6β,19-epoxysteroid (29). Barton has shown[20] that photolysis of a 20-nitrite in the presence of exogenous nitric oxide resulted in almost complete suppression of 18-oxime formation. However,

no further details of the products of this reaction were given and it was decided in this work to reinvestigate the effect of exogenous nitric oxide on the outcome of the Barton reaction.

A 0.03M solution of the 6β-nitrite (27) in chlorobenzene saturated with nitric oxide (shown to be 0.05M in nitric oxide by potassium permanganate titration),[53] was photolysed for 2 hours. Under these conditions, the 19-oxime (117) was obtained in only 11% yield while the 6β,19-epoxysteroid (29) was isolated in 25% yield. A number of photolyses of the 6β-nitrite (27) were then carried out with nitric oxide passing through the photolysing solution. In these reactions the rate of photolysis as monitored by TLC was reduced and after 3 hours some of the 6β-nitrite (27) remained. Work-up at this time, however, gave the 6β,19-epoxysteroid (29) as the major product (61% yield) while none of the 19-oxime (117) could be isolated from this reaction. In the absence of exogenous nitric oxide, photolysis at comparable concentrations of the 6β-nitrite (27) gave the 19-oxime (117) in greater than 50% yield with none of the 6β,19-epoxysteroid (29). It may therefore be concluded from these results that the formation of 6β,19-epoxysteroid (29) in concentrated solution at the expense of 19-oxime (117) formation

arises as a result of increased nitric oxide concentration.

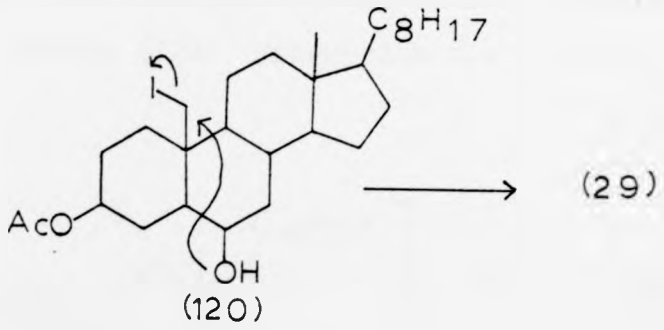
Akhtar[26] has suggested that the decrease in the rate of photolysis in the presence of excess nitric oxide is a result of an increase in the reverse of the primary dissociation step of the Barton reaction.

$$R\text{-}O\text{-}N{=}O \rightleftharpoons R\text{-}O\cdot + NO\cdot$$

Although this may in fact play a part in the decrease in the rate of photolysis, it was observed in this work that the UV spectrum of nitric oxide in chlorobenzene was almost superposable on that of the 6β-nitrite (27). It is therefore suggested that the decrease in the rate of photolysis in the presence of exogenous nitric oxide may be a consequence of the absorption of radiation by this species in competition with the 6β-nitrite (27).

It was thought that the mechanism of formation of the 6β,19-epoxysteroid (29) might involve the reaction of a substituent at the 19-position with nitric oxide to afford a good leaving group. The ability of certain 6β-hydroxy-19-substituted steroids to undergo a facile backside displacement of the 19-substituent was reported by Akhtar[38] who suggested that formation of the 6β,19-epoxysteroid (29) from photolysis of the 6β-nitrite (27) in the presence of

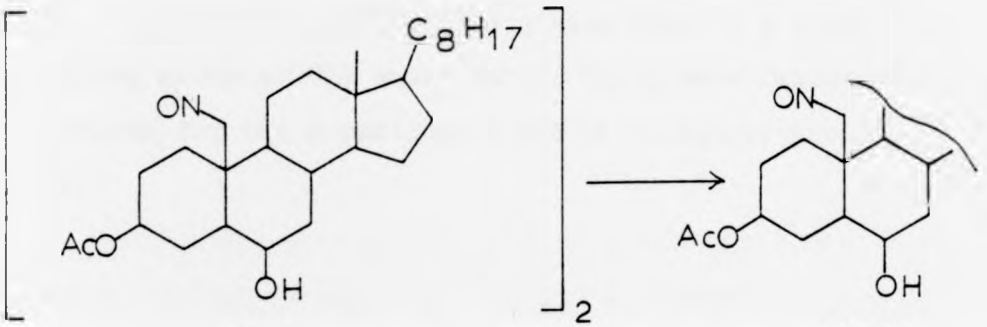
iodine arose by such a reaction of the intermediate 19-iodo compound (120).



(120) → (29)

The reactions of nitric oxide with both the 19-oxime (117) and the 19-nitroso dimer (121) were therefore investigated in order to determine the origin of the 6β,19-epoxysteroid (29). Thus, the 19-oxime (117) was treated with nitric oxide in chlorobenzene containing t-butylamine and TLC indicated that no reaction occurred either in the dark or with "black-light" irradiation. Treatment of the 19-nitroso dimer (121), which was obtained by photolysis of the 6β-nitrite (27) in hexane, with nitric oxide in the dark proceeded slowly to afford a complex product mixture which TLC indicated contained some of the 6β,19-epoxysteroid (29). "Black-light" irradiation of a suspension of the 19-nitroso dimer (121) in methylene chloride through which nitric oxide was passing gave fairly cleanly the 6β,19-epoxysteroid (29)

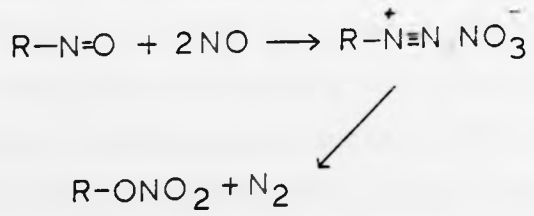
and the 19-oxime (117). Thus, the 6β,19-epoxysteroid (29) arises from the photo-reaction of nitric oxide with either the 19-nitroso dimer (121) or the 19-nitroso monomer (122), rather than the 19-oxime (117).



(121) (122)

Evidence for the involvement of the 19-nitroso monomer (122) rather than the 19-nitroso dimer (121) in the formation of the 6β,19-epoxysteroid (29) was provided by the observation that the reaction of nitric oxide with the 19-nitroso dimer (121) in the dark proceeded only slowly. It is known[156] that the photolysis of nitroso dimers to oximes proceeds via nitroso monomers and it was shown in this work that the 19-nitroso dimer (121) rapidly (several seconds) gave the 19-oxime (117) on UV irradiation. Thus it was deduced that the photo-reaction of the 19-nitroso monomer (122) with nitric oxide was responsible for formation of the 6β,19-epoxysteroid (29) in these

photolyses. Several workers[155,156,157] have investigated the reaction of nitroso compounds with nitric oxide and Tedder[155] has shown that nitroso compounds can react with nitric oxide by way of a diazonium nitrate (Scheme 18). It is therefore conceivable that a mechanism of this type operates during the photolysis of the 6β-nitrite (27) giving rise to a good leaving group at C19 whose facile backside elimination accounts for the formation of the 6β,19-epoxysteroid (29).



Scheme 18

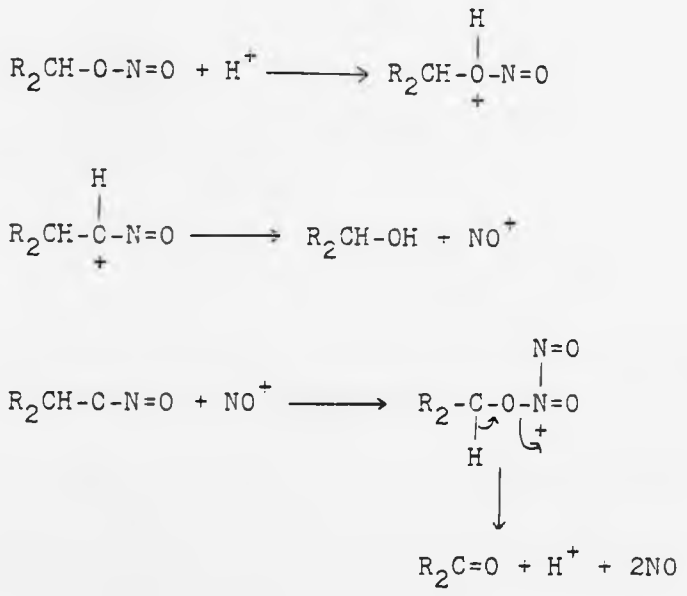
2.4 CONCOMITANT ALCOHOL AND KETONE FORMATION

Alcoholic and ketonic by-products almost invariably accompany the Barton reaction and it was of interest to investigate the mechanism of formation of these compounds.

The purpose of the preliminary investigation was to ascertain if the pathways leading to the formation of these products were independent since there are several conceivable mechanisms by which alcoholic and ketonic by-products might be formed concomitantly.

2.4.1 Hydrolysis of the nitrite ester

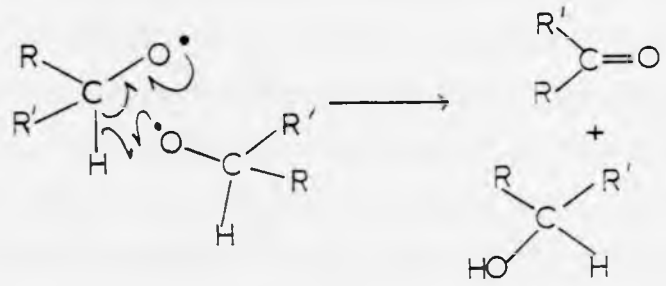
Acid hydrolysis plays an important part in the chemistry of alkyl nitrites and has long been known to be a rapid and facile process.[158,159] The mechanism of acid hydrolysis of alkyl nitrites has been investigated by Allen[160] who has provided a mechanism for alcohol formation in these reactions. Barton[21] later forwarded a mechanism explaining the formation of both alcoholic and ketonic products in the acid hydrolysis of alkyl nitrites (Scheme 19) in an attempt to rationalise the formation of alcoholic and ketonic products on the pyrolysis of steroidal nitrites, whose formation it was surmised was greatly influenced by traces of water.



Scheme 19

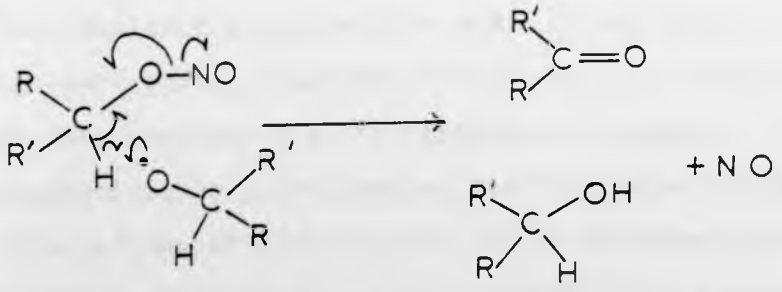
2.4.2 Alkoxy radical reactions

The initial step of the Barton reaction involves the formation of an alkoxy radical and there are two conceivable mechanisms by which this alkoxy radical might react to afford alcoholic and ketonic products concomitantly. The first of these mechanisms involves the simple bimolecular disproportionation of alkoxy radical intermediates, which is known[161] to be exothermic (ΔH = -290-380 kJ mol^{-1}) and is therefore thermodynamically plausible (Scheme 20).



Scheme 20

Although pyrolysis of alkyl nitrites has been the subject of extensive investigation in the gas phase,[17,161] the disproportionation of alkoxy radicals is often difficult to define. However, evidence for the existence of such a process has been claimed in the gas phase pyrolysis of ethyl nitrite.[162] Alternatively to this simple disproportionation reaction, it is also conceivable that decomposition of an undissociated nitrite molecule by an alkoxy radical might occur during nitrite photolysis (Scheme 21).



Scheme 21

Several authors have speculated on the mechanism of joint formation of ketonic and alcoholic by-products during the Barton reaction. Marples,[59] for example, proposed that the ketonic and alcoholic products arose as a result of the acid hydrolysis process suggested by Barton[21] while Suginome[163] attributed their formation to a disproportionation process.

In view of the lack of any substantiation for either of the above mechanisms, it was considered of interest to ascertain whether either of them in fact accounts for concomitant formation during the Barton reaction of alcoholic and ketonic by-products or whether they arise by independent processes.

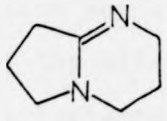
2.4.3 Nitrite ester hydrolysis during the Barton reaction

It has been shown[43] that the introduction of a nitrogenous base during the Barton reaction has a beneficial effect on the amounts of the remotely functionalised products obtained. It was found in this work that, in agreement with Barton's results,[43] the introduction of either pyridine, ethylamine, diisopropylamine, or t-butylamine into the photolysis solution of the 6β-nitrite (27) led to improved yields of the 19-oxime (117). It was thought that perhaps the increased yield of the 19-oxime (117) in the

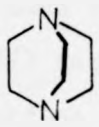
presence of base arose from the suppression of the acid decomposition of the 6β-nitrite (27). In support of this idea, it was shown that treatment of the 6β-nitrite (27) with excess HCl gave a complex mixture of products which was shown by TLC to contain considerable amounts of the 6β-alcohol (115) and the 6-ketone (116). That the introduction of base is sufficient to protect the 6β-nitrite (27) from acid hydrolysis was simply demonstrated by the fact that, in the presence of excess diisopropylamine, no decomposition of the 6β-nitrite (27) occurred on treatment with HCl. The continued formation of both the 6β-alcohol (115) and the 6-ketone (116) during photolysis of the 6β-nitrite (27) in the presence of base demonstrates that these products cannot arise by acid hydrolysis of the 6β-nitrite (27) under these conditions.

It was considered that, although the introduction of a base provided adequate protection against acid hydrolysis of the 6β-nitrite (27), a base hydrolysis process might now account for the continued presence of the 6β-alcohol (115) and the 6-ketone (116). If this were the case, the use of a sterically hindered non-nucleophilic base should suppress such a process. A series of photolyses of the 6β-nitrite (27) was therefore carried out in the presence of each of the

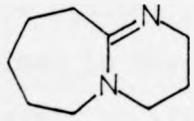
bases, DBN (1,5-diazabicyclo[4.3.0]non-5-ene) (123), DABCO (1,4-diazabicyclo[2.2.2]octane) (124), DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) (125), and 2,2,6,6-tetramethylpiperidine (126) since these compounds although basic show little nucleophilicity.[164,165]



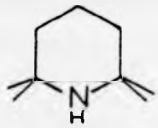
DBN
(123)



DABCO
(124)



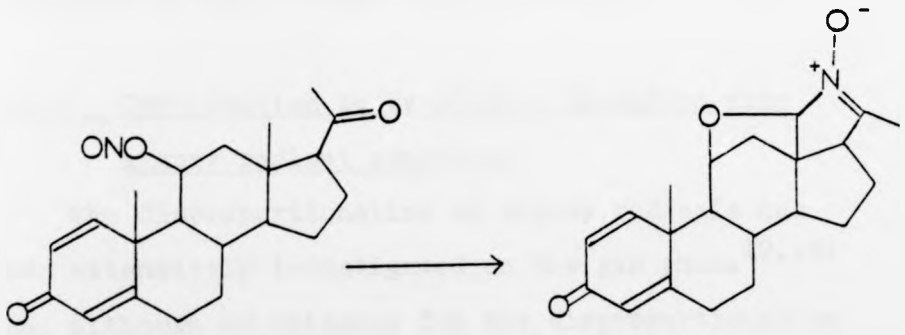
DBU
(125)



(126)

Resolution of these photolysis mixtures using HPLC showed that there was no significant difference between the amounts of the 6β-alcohol (115) and the 6-ketone (116) products formed in the presence of the bases (121) - (124) and the amounts formed in the presence of the simple amine bases. Thus in all cases, the amounts of the 6β-alcohol (115) and the 6-ketone (116) remained about 10-20% and 20%, respectively.

Further evidence for the lack of a base hydrolysis process in the photolysis of the 6β-nitrite (27) was acquired by studying the effect of the concentration of base. In a previous study,[166] the effect of the concentration of pyridine on the photolysis of the 11β-nitrite (125) to the nitrone (126) was studied and it was found that the optimal yield (47%) of the nitrone (126) was obtained in the presence of 20 equivalents of pyridine. However, no attempt was made to quantify the by-products formed in this reaction and it is unclear whether the improved yield of the nitrone (126) arose as a result of the suppression of either ketonic or alcoholic by-products.



(125) (126)

In order to determine the effect of base concentration on the reaction, the 6β-nitrite (27) was photolysed in the presence of 10, 50, 100, 200, and 400 equivalents of t-butylamine. It was shown by NMR and TLC that in the presence of more than 100 equivalents of t-butylamine, the amount of the 19-oxime

(117) formed decreased while the amount of the 6β-alcohol (115) increased. Over the concentration range studied, however, the amount of the 6-ketone (116) formed did not vary significantly. These results indicate that at high concentrations of base, hydrolysis of the 6β-nitrite (27) to the 6β-alcohol (115) does occur but that at lower base concentrations no variation in the amounts of the 6β-alcohol (115) and 6-ketone (116) formed is observed. It is concluded therefore, that in the presence of nitrogenous base, the concomitant formation of alcoholic and ketonic by-products in the Barton reaction by a hydrolytic mechanism is not a significant process.

2.4.4 Contribution to by-product formation from alkoxy radical reactions

The disproportionation of alkoxy radicals has been extensively investigated in the gas phase[17,161] and, although no evidence for the disproportionation of alkoxy radicals has been sought in solution, a process of this type has been proposed by a number of workers[25,163] to account for the formation of both alcoholic and ketonic by-products from the Barton reaction. However, Surzur[167] has recently remarked that at the concentrations at which the Barton reaction is usually carried out (0.1-2M), such a disproportion-

ation is an unlikely process. In addition, there exists some evidence in the literature that alcoholic and ketonic by-products in the Barton reaction do not arise by a disproportionation reaction. Disproportionation of the alkoxy radical is necessarily a bimolecular process and must give rise to equal amounts of alcohol and ketone. Thus, an inspection of certain of Kabasakalian's results[168] (Table 2) suggests that the disproportionation mechanism he proposed to account for the formation of alcoholic and ketonic by-products may be incorrect, since in these examples the amounts of alcohol and ketone formed are not equal.

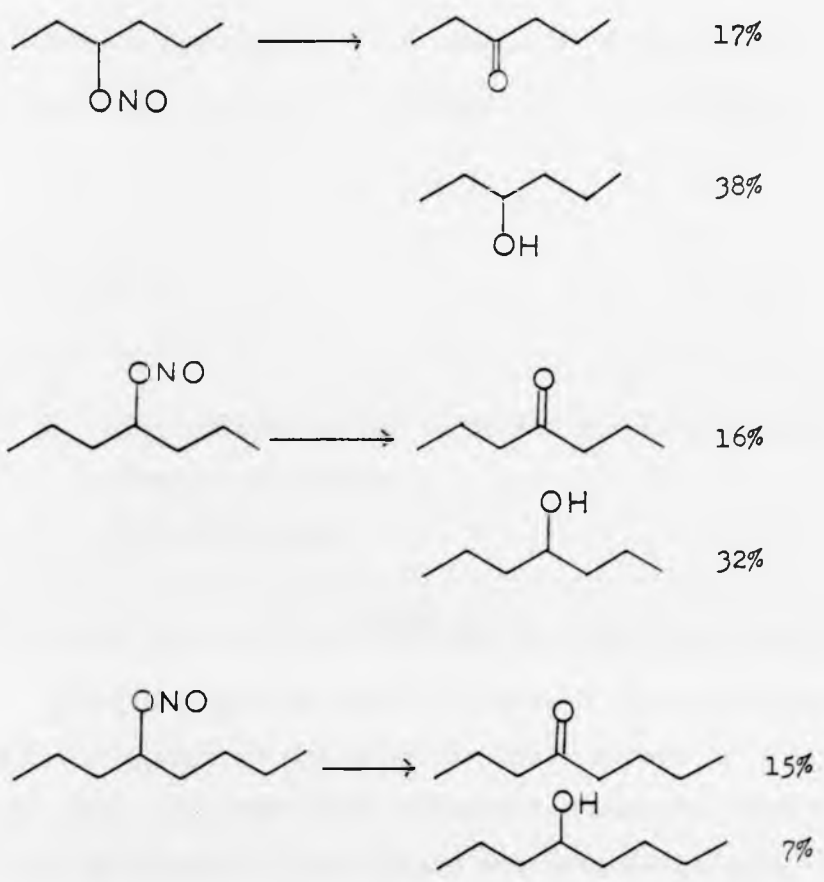


Table 2

In order to determine whether or not a disproportionation mechanism accounts for the formation of alcoholic and ketonic by-products in the Barton reaction, the 6β-nitrite (27) was photolysed over a large concentration range and the amounts of 6β-alcohol (115) and 6-ketone (116) formed determined, giving the results shown in Table 3.

Nitrite Concentration (M)		% Ketone (116)	% 6β-Alcohol (115)
3.4×10^{-6}	a	~ 15	~ 60
3.4×10^{-4}	b	14	40
2.1×10^{-2}	b	15	10
1.2×10^{-1}	b	17	11

a By-products estimated by TLC comparison with standard solutions

b Isolated yields

Table 3

From the results given in Table 3, it can be seen that the amount of the 6-ketone (116) formed in these photolyses is essentially invariant while the amount of the 6β-alcohol (115) formed not only differs in each case from the amount of the 6-ketone (116) but also varies in an inverse manner with concentration. Both these observations are wholly incompatible with a mechanism involving the disproportionation of alkoxy radicals since if such a mechanism was in operation, the amounts of the 6β-alcohol (115) and the 6-ketone (116) formed should be the same and those amounts should increase rather than decrease with increasing concentration. These results therefore irrevocably exclude the existence of any significant

contribution by an alkoxy radical disproportionation mechanism to the formation of alcoholic and ketonic by-products in the Barton reaction.

By a similar argument, the bimolecular mechanism involving the reaction of an alkoxy radical with an undissociated nitrite molecule to account for the concomitant formation of alcoholic and ketonic by-products in the Barton reaction may be definitively excluded.

It may be concluded from the preceding arguments that the alcoholic and ketonic by-products of the Barton reaction arise by independent mechanistic pathways and the remainder of this section is concerned with their elucidation.

2.5 MECHANISM OF ALCOHOL FORMATION DURING THE BARTON REACTION

The alcoholic by-products of the Barton reaction may be considered a little less undesirable than the ketonic by-products since, although they possess no remote functionalisation, they may at least be readily and quantitatively transformed to the nitrite. Two conceivable mechanisms exist which would lead only to alcoholic by-product formation. The first of these entails intermolecular hydrogen abstraction by the alkoxy radical. Although the tendency of alkoxy

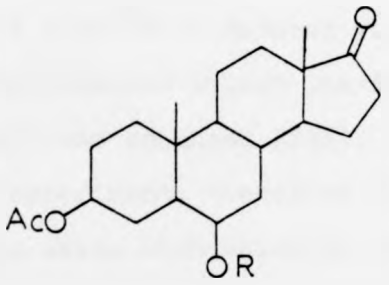
radicals to effect hydrogen abstraction is central to the success of the Barton reaction, it is possible that a less specific abstraction of hydrogen from either the solvent or another steroid molecule might account for alcohol formation. The second mechanism involves intermolecular hydrogen abstraction by the alkyl radical. Although the termination step of the Barton reaction involves the reaction of the alkyl radical with nitric oxide to form a nitroso compound, it is conceivable that, in the absence of nitric oxide with which to react, an alternative intermolecular hydrogen abstraction process could effect termination to afford alcoholic by-products.

The experimental evidence obtained for the mechanism of alcohol formation is now discussed.

2.5.1 Intermolecular hydrogen abstraction by the alkoxy radical

Although it is a formal possibility that alcoholic by-products in the Barton reaction arise by intermolecular hydrogen abstraction by the alkoxy radical, sufficient evidence exists in the literature to discount this process. Akhtar[38] has found that irradiation of the 6β-nitrite (105) in the presence of thiophenol gave predominantly the alcohol (109). In the presence of S-deuteriothiophenol, a good incorporation

of deuterium at C19 was observed, demonstrating that the formation of alcoholic by-products in the Barton reaction under normal conditions is a result of quenching of the alkyl radical rather than the alkoxy radical.



(105) R = NO
(109) R = H

2.5.2 Intermolecular hydrogen abstraction by the alkyl radical

The final step of the Barton reaction under normal conditions involves reaction of the alkyl radical with nitric oxide resulting in the formation of a nitroso compound. However, the propensity of alkyl radicals to abstract hydrogen is known.[169] It is therefore conceivable that, in the absence of nitric oxide with which to react, the reaction will terminate by abstraction of a hydrogen atom from the solvent or another steroidal molecule.

In order to test this hypothesis, the 6β-nitrite

(27) was photolysed in the presence of triphenylphosphine which is known[170] to be an efficient scavenger for nitric oxide. In the presence of a large excess (18 equivalents) of triphenylphosphine it was found that, on photolysis of the 6β-nitrite (27) at a concentration of 2×10^{-2}M, a reduced yield (21%) of the oxime (117) was obtained whilst the formation of the 6β-alcohol (115) was enhanced (70%). It was concluded from this experiment, therefore, that in the absence of nitric oxide with which to react, the alkyl radical attained stability by hydrogen abstraction.

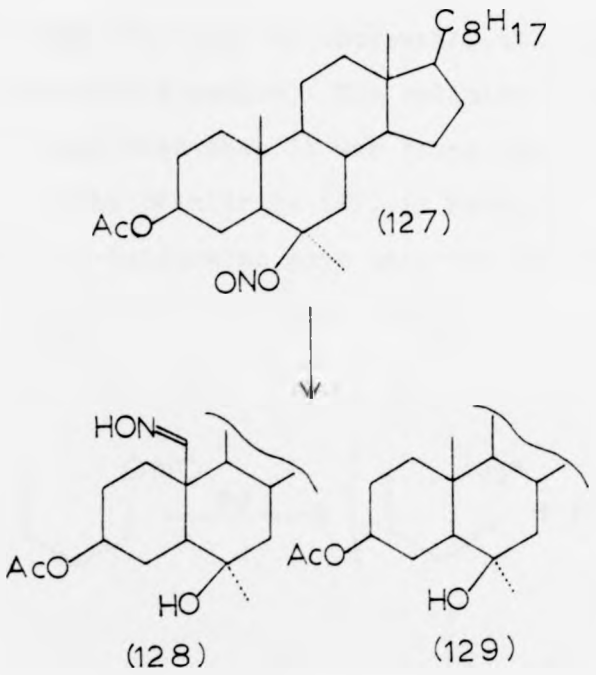
It was therefore of interest to determine whether during the normal Barton reaction hydrogen abstraction by the alkyl radical to give alcoholic by-products competes with recombination of the alkyl radical with nitric oxide or whether alcoholic by-products arise as a consequence of the diversion of nitric oxide. The 6β-nitrite (27) was photolysed in chlorobenzene at $0^{\circ}C$ with argon passing through the solution and after removal of the solvent the resulting yellow oil was shown by microanalysis to contain 93% of the nitrogen initially present in the reaction. This experiment demonstrates that relatively little nitric oxide is lost to the atmosphere during photolysis. Since these particular conditions normally afford approximately 60% of the 19-oxime (117), it was therefore

concluded that, although some nitric oxide may have escaped to the atmosphere, nitric oxide was also reacting with some species other than the alkyl radical. The isolation of a complex yellow fraction with a UV maximum at 275 nm (ϵ = 12,000) from this photolysis indicated that some of the nitric oxide was reacting with the solvent, chlorobenzene, to give nitroaromatics. The photolysis of alkyl nitrites has been used[154] to effect intermolecular nitrosations and it is considered therefore that this nitroaromatic fraction may arise by the oxidation of initially formed nitrosoaromatics.

In view of the demonstrated reactivity of aromatic solvents towards nitric oxide during photolysis it was decided to investigate the use of non-aromatic solvents in these reactions. It was considered that methylene chloride would be less reactive towards nitric oxide under the conditions of the Barton reaction. Thus, photolysis of the 6β-nitrite (27) in methylene chloride containing t-butylamine gave a colourless crystalline product mixture from which the 19-oxime (117), the 6β-alcohol (115), and the 6-ketone (116) were isolated in 73%, 9%, and 15% yield, respectively. Under these conditions, the amount of the 6β-alcohol (115) formed (9%) probably reflects that proportion of the nitric oxide lost to the atmosphere.

In agreement with these results, it was found that formation of the 6β-alcohol (115) is suppressed completely when the 6β-nitrite (27) is photolysed with nitric oxide passing through the solution.

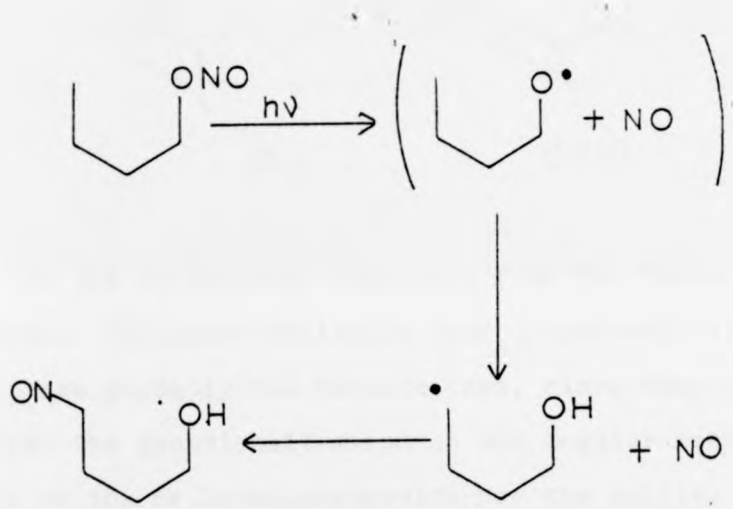
Thus it has been shown that in the absence of nitric oxide, the alkyl radical will abstract a hydrogen to give the alcoholic by-products. That the hydrogen abstracted did not come from the solvent was demonstrated in the following manner. Since toluene is a relatively good hydrogen donor while benzene is a poor hydrogen donor,[17] it would be expected that if the hydrogen was being abstracted by the alkyl radical from the solvent, photolyses in these solvents should lead to different quantities of the 6β-alcohol (115). On photolysis of the 6β-nitrite (27) in toluene and benzene containing nitrogenous base, no notable difference in the amount of the 6β-alcohol (115) formed was observed. These results support the idea that in general the solvent is not involved in the formation of alcoholic products in the Barton reaction. Further support for this idea was obtained by the observation that photolysis of the 6α-methyl-6β-nitrite (127) in deuteriochloroform solution gave in addition to the 19-oxime (128) (86%) the 6α-methyl-6β-alcohol (129) which was shown by MS and IR to contain no deuterium.



It is concluded therefore that alcoholic products arise in the Barton reaction as a consequence of hydrogen abstraction by the alkyl radical from other steroid molecules rather than from solvent molecules.

Having established the mode of formation of the alcoholic by-products from the Barton reaction, it was considered in what way its formation might be suppressed. Akhtar has demonstrated[26] that the Barton reaction proceeds by a "non-cage" mechanism (Scheme 22), and it was thought that photolysis at low temperature might reduce the escape of nitric oxide from the system either by restricting the nitric oxide to a

solvent cage or simply by increasing its solubility in the photolysis medium. The validity of this argument was confirmed when it was found that photolysis at -78° of the 6β-nitrite (27) in methylene chloride containing t-butylamine gave only the 19-oxime (117) (80%) and the 6-ketone (116) (15%).

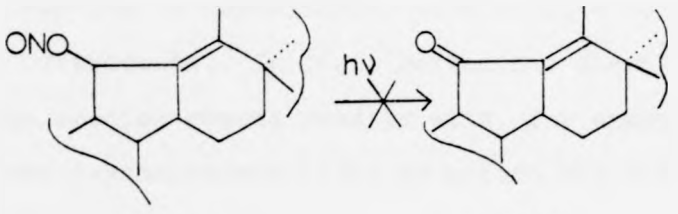


Scheme 22

2.6 MECHANISM OF KETONE FORMATION DURING THE BARTON REACTION

In those systems where molecular considerations do not preclude it and where by-products of the Barton reaction have been investigated, the formation of ketonic by-products invariably occurs. The only case where ketonic by-products were specifically sought

but not found was reported by Suginome[63] who noted that photolysis of the veratrobasine-derived 11β-nitrite (93), whilst affording functionalisation of the C19 angular methyl group, gave none of the ketone (130).



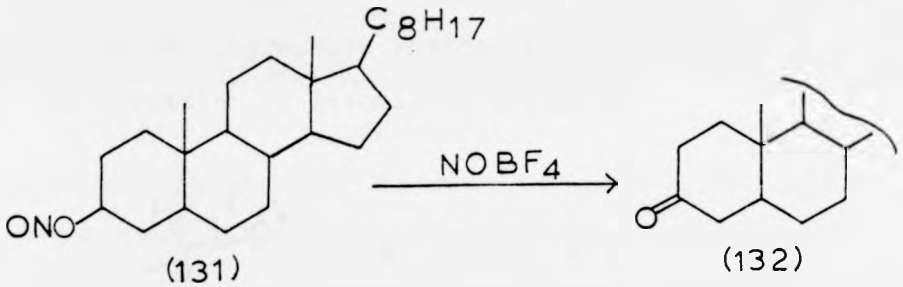
(93) (130)

Of the by-products resulting from the Barton reaction, the least desirable from a synthetic standpoint are probably the ketonic ones, since they possess neither the functionalisation at the angular methyl group of the 6β,19-epoxysteroids nor the ability of the alcoholic by-products to be converted quantitatively back to the starting nitrite.

It has been shown that the formation of the alcoholic and epoxysteroid by-products from the Barton reaction could be suppressed and it was therefore of considerable interest to elucidate the mechanism of formation of the ketonic by-products since this might suggest a means of suppressing their formation. It was shown that the ketonic by-products are not formed

concomitantly with the alcoholic by-products of the Barton reaction and mechanisms for their independent formation are now discussed.

The first mechanism involves the reaction of a nitrosonium ion NO^+, whose generation during the Barton reaction is conceivable, with nitrite to give ketonic by-products. In fact, Barton has shown[171] that this species reacts readily with, for example, 3β-nitroso-oxycholestane (131) to afford the 3-ketone (132) in good yield.



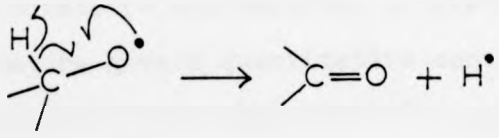
(131) (132)

An alternative mechanism for the formation of ketonic by-products involves simple oxidation of the alcoholic by-products normally formed in the course of the Barton reaction by an oxidising agent generated from nitric oxide. Although nitric oxide does not ordinarily combine with itself, except under conditions of high pressure[172] or high energy UV irradiation,[173,174] the instantaneous oxidation of nitric oxide to nitrogen dioxide by oxygen is well known.[153]

$$O_2 + 2NO \longrightarrow 2NO_2 \rightleftharpoons N_2O_4$$

The formation of nitrogen dioxide (or dinitrogen tetroxide), which is known[175] to be a fairly potent oxidising agent, could quite readily occur under the conditions of the Barton reaction by the reaction of nitric oxide with extraneous oxygen. Any nitrogen dioxide present could give rise to ketonic by-products by oxidation of either the alcoholic by-products or the alkoxy radical.

The direct extrusion of a hydrogen atom from the alkoxy radical represents another possible mechanism for the formation of ketonic by-products.



Finally, a further mechanism which must be considered for formation of ketonic by-products is the direct decomposition of the starting nitrite to give ketone and HNO, the monomer of hyponitrous acid.

The preceding mechanisms were investigated in this present work and the experimental evidence which finally ascertained the origin of the ketonic by-products is now presented.

2.6.1 Reaction of nitrite with nitrosonium ion, NO^+

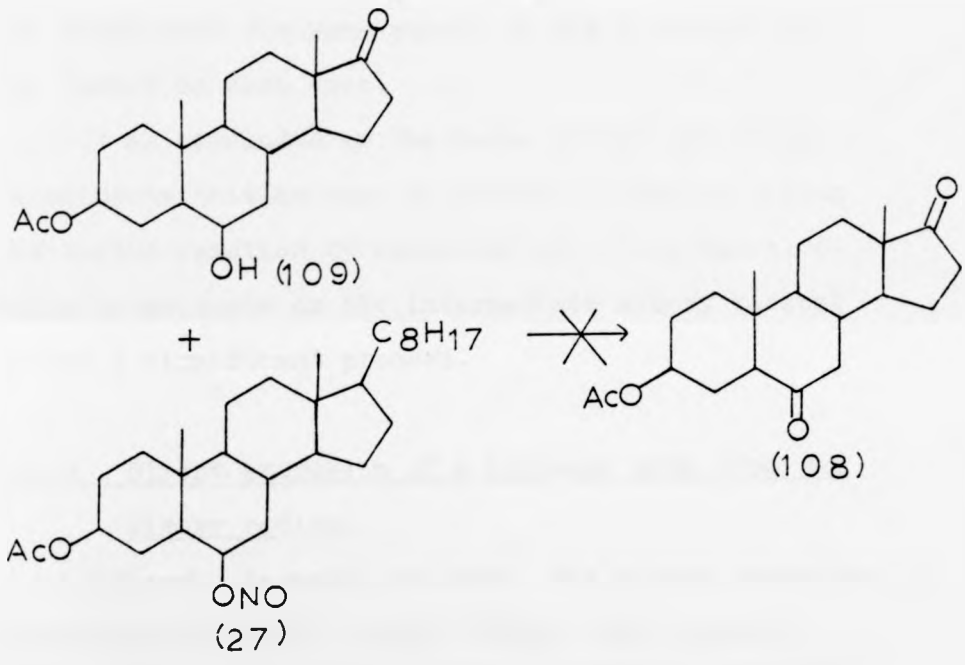
Under the relatively mild conditions of the Barton reaction, the generation of NO^+ is unlikely. However, in view of the demonstrated ability[171] of this species to react readily with nitrites to afford ketonic products, it was considered relevant to investigate its reaction with the 6β-nitrite (27). Thus it was shown that reaction of the 6β-nitrite (27) with nitrosonium tetrafluoroborate (4 equivalents) in acetonitrile at room temperature gave a quantitative conversion to the 6-ketone (116) (as indicated by TLC) in agreement with Barton's findings.[171] Under the same conditions in the presence of an excess of t-butylamine no decomposition of the 6β-nitrite (27) was observed even after several hours. Thus it is concluded that under the normal conditions of the Barton reaction in the presence of nitrogenous base the ketonic by-products cannot arise by reaction of the nitrite with NO^+ which may be present.

2.6.2 Photochemical generation of an oxidising species

Although it has been proved above that the alcoholic and ketonic by-products in the Barton reaction do not arise concomitantly, it may be conceived that the ketonic by-products arise as a consequence of the reaction of the alcoholic by-products with an oxidising species generated during the photolysis.

In a preliminary attempt to implicate a simple oxidation of alcoholic by-products, the 6β-nitrite (27) was photolysed in the presence of excess hydroquinone. Hydroquinone is known[176] to undergo a ready oxidation to quinone and it was argued that any oxidant formed during the Barton reaction would preferentially oxidise the hydroquinone rather than the 6β-alcohol (115) and thus lead to suppression of the 6-ketone (116). In this experiment, no notable decrease in the amount of the 6-ketone (116) formed was observed, suggesting that it does not arise by a simple oxidation process. Further substantiation for the absence of an oxidation process was obtained from the following crossover experiment. Photolysis of a mixture of the 6β-nitrite (27) and the 6β-alcohol (109) (ratio 1:1.2) gave a product mixture which contained none of the 6,17-dione (108) and showed no decrease in the amount of the 6-ketone (116) formed as monitored by TLC or separated by chromatography. This result confirms the absence

of a simple oxidation of the 6β-alcohol (115) to the 6-ketone (116) since, because the rates of oxidation of the 6β-alcohols (109) and (115) would be expected to be very similar, such a process should lead to the isolation of some of the 6,17-dione (108).



It might be argued that the preceding experiment does not specifically exclude the possibility that oxidation of an intermediate alkoxy radical rather than an alcohol might lead to formation of ketonic by-products. In order to discount this possibility, photolysis of the 6β-nitrite (27) was effected under

atmospheres of different oxygen/argon compositions since the presence of large amounts of oxygen should lead to increased formation of oxidising species and thence to increased amounts of the 6-ketone (116). When the 6β-nitrite (27) was photolysed under atmospheres of argon, argon/oxygen (1:1), and oxygen, it was found that the same amount of the 6-ketone (116) was formed in each case.

It is concluded on the basis of the preceding experiments that ketonic by-product formation during the Barton reaction by oxidation of either the alcoholic by-products or the intermediate alkoxy radical is not a significant process.

2.6.3 Direct extrusion of a hydrogen atom from the alkoxy radical

Although, formally at least, the direct extrusion of hydrogen from the alkoxy radical would lead to ketonic by-products in the Barton reaction, processes of this type have been found to be thermodynamically unfavourable and it has been reported[161] that they play no significant role in the chemistry of alkoxy radicals. On this basis the operation of such a mechanism during the Barton reaction leading to ketonic by-products was discounted.

2.6.4 Nitrite decomposition

The formation of ketonic by-products during the Barton reaction by direct decomposition of the starting nitrite would necessarily lead to the simultaneous formation of HNO, the monomer of hyponitrous acid. In view of this, it is of relevance to briefly describe the chemistry of this molecule and its dimer.[177]

The dimerisation[178] of HNO, the monomer of hyponitrous acid, which has been referred to alternatively as nitroxyl[179] and nitrosyl hydride,[180] and the decomposition of the resulting hyponitrous acid to nitrous oxide and water is known.[178]

$$HNO + HNO \longrightarrow (HNO)_2$$

$$(HNO)_2 \longrightarrow N_2O + H_2O$$

Thompson and Purkis[181] first suggested that HNO was formed on irradiation of simple alkyl nitrites in the gas phase to account for the detection of nitrogen and nitrous oxide during these photolyses, which have also been suggested as decomposition products of hyponitrous acid.[182,183] Levy detected[184] the formation of nitrous oxide during the pyrolysis of ethyl nitrite in the vapour phase and also forwarded a mechanism involving HNO formation. Conclusive evidence for the formation of HNO during nitrite photolysis was

provided by Brown and Pimentel[185] who, on photolysis of methyl nitrite in an argon matrix at 20°K, deduced the presence of this species by IR analysis.

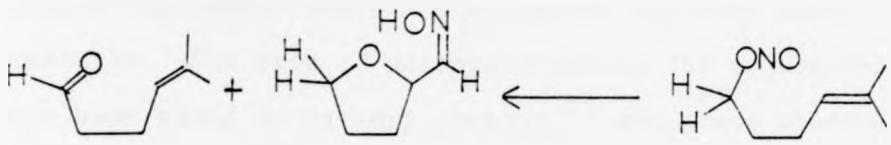
More recently, Ludwig and McMillan[186] have investigated the gas phase photolysis of isopropyl nitrite at varying wavelengths and, by considering the chemistry of excited and groundstate alkoxy radicals, have concluded that in the groundstate the only significant mechanism for the gas phase formation of ketonic products involves reaction of nitric oxide with the isopropoxy radical.

$$(CH_3)_2\overset{C}{\underset{\backslash}{H}}O^{\bullet} + NO \longrightarrow CH_3COCH_3 + HNO$$

Furthermore, these workers noted[186] that there is no available evidence to support the existence of a direct mechanism for the gas-phase decomposition of alkyl nitrites.

$$(CH_3)_2CHONO \longrightarrow CH_3COCH_3 + HNO$$

Bertram and Surzur[167] obtained both furan derivatives and aldehydic by-products (up to 15%) from the photolysis of nitroso-oxyolefins in solution (Scheme 23) and suggested that the aldehydic products arose as a result of the mechanism proposed by Ludwig and McMillan.[186]



Scheme 23

Recently de Boer[187] has provided evidence that the photodecomposition of 2-iodo-2-nitroadamantane in hydrogen-donating solvents proceeds via a mechanism involving the generation of hyponitrous acid.

The UV spectrum of hyponitrous acid in aqueous solution has been found to vary with pH.[180] In alkaline solutions (pH >12) the UV spectrum has a λ_{max} at 248 nm (ϵ_{max} = 3980) which is reportedly characteristic of the dianion $N_2O_2^{2-}$. At lower pH values (pH between 12 and 6) a hypsochromic shift in the spectrum occurs giving rise to a λ_{max} at 233 nm (ϵ_{max} = 3310) which is ascribed to the monoanion $HN_2O_2^-$, and under acid conditions (pH <6) a further hypsochromic shift occurs to give a λ_{max} at 208 nm (ϵ_{max} = 2740) arising from the free acid $H_2N_2O_2$. Hughes[180] has utilised the characteristic UV spectral properties of hyponitrous acid and its anions to determine the stabilities of these species in aqueous solution. As a result of these studies, it was found that the free acid and the dianion were

relatively stable while the monoanion was much more unstable. The rate of decomposition of the monoanion has been found to be very erratic[189] and these observations were ascribed to decomposition by a radical chain mechanism which was readily inhibited by the presence of acrylonitrile, allyl alcohol, or ethanol.

It was recognised that, if ketonic by-products arose during the Barton reaction by a process which also leads to the formation of HNO, proof for the existence of such a mechanism would be obtained by the detection of hyponitrous acid in the reaction mixture. It was thought that the relative stability and characteristic UV spectral properties of the dianion of hyponitrous acid would provide a convenient means for the detection of this species.

The 6β-nitrite (27) was photolysed using "black-light" at room temperature in methylene chloride containing no base and the solution was extracted after 30 min with 0.1M sodium hydroxide solution. The UV spectrum of this basic extract showed the presence of an absorption maximum at 248 nm characteristic of the $N_2O_2^{2-}$ dianion. Adjustment of the pH of this solution to pH 6 with HCl resulted in the characteristic hypsochromic shift of the UV absorption maximum to 233 nm accompanied by a decrease in intensity (Figure 4).

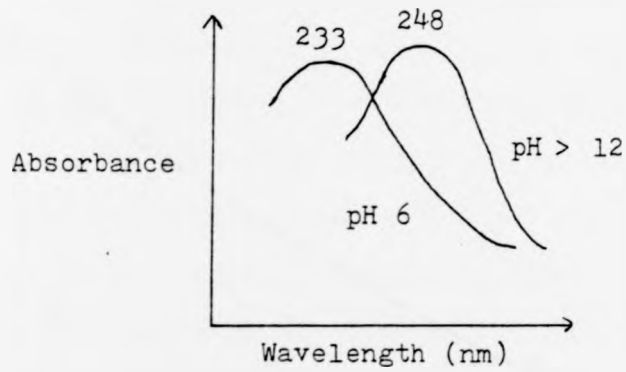


Figure 4

At this pH, the intensity of the UV absorption maximum at 233 nm was seen to decrease with time. The rate of decrease was measured and it was established that the half-life for the decomposition process was 80 min, in good agreement with the reported[177] half-life (97 min) for the decomposition of the monoanion under similar conditions (Figure 5). These results confirm the formation of hyponitrous acid during the Barton reaction.

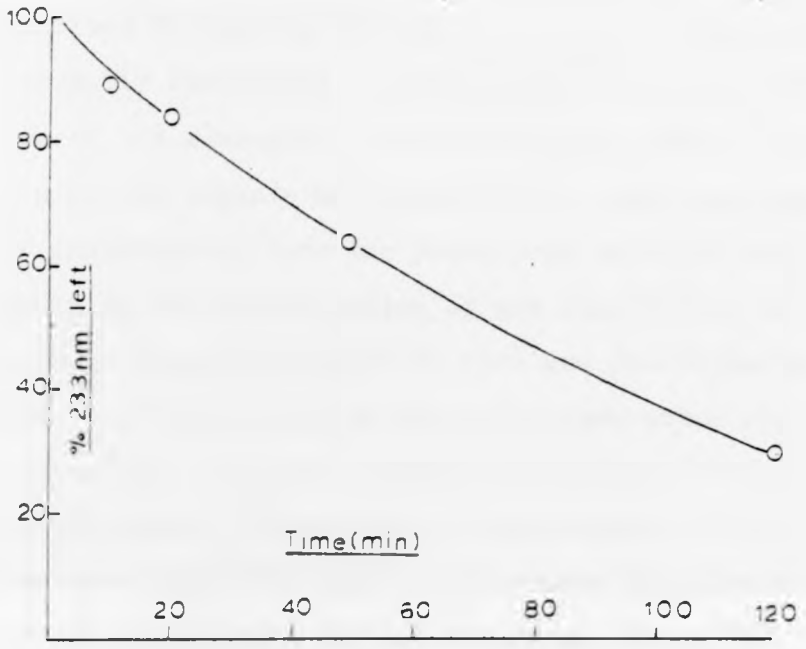
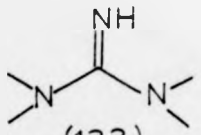


Figure 5

In an attempt to establish a direct correlation between the formation of hyponitrous acid and the amount of ketone formed during the Barton reaction, the 6β-nitrite (27) was photolysed as above in the presence of t-butylamine. However, the UV spectrum of the basic extract obtained in this case exhibited no UV absorption maximum at 248 nm. Since t-butylamine is not a strong base, this result was rationalised in terms of the presence, under these conditions, of a

radical decomposition of the monoanion of the type described by Bucholz[189] while in the absence of base presumably conditions are not suitable for the formation of the monoanion. Tetramethylguanadine (133) is a strong organic base and it was considered that its introduction into the photolysis solution would result in the stabilisation of any hyponitrous acid formed. Thus the 6β-nitrite (27) was photolysed as above in the presence of tetramethylguanadine (133). In this case, the basic extract exhibited a UV maximum at 248 nm. The amount of the 6-ketone (116) formed to which the absorbance of this solution at 248 nm corresponded was calculated as 16% on the basis of the reported extinction coefficient of 3980[188] for the dianion of hyponitrous acid. This value compares very well with the amount of the 6-ketone (116) isolated from photolysis.

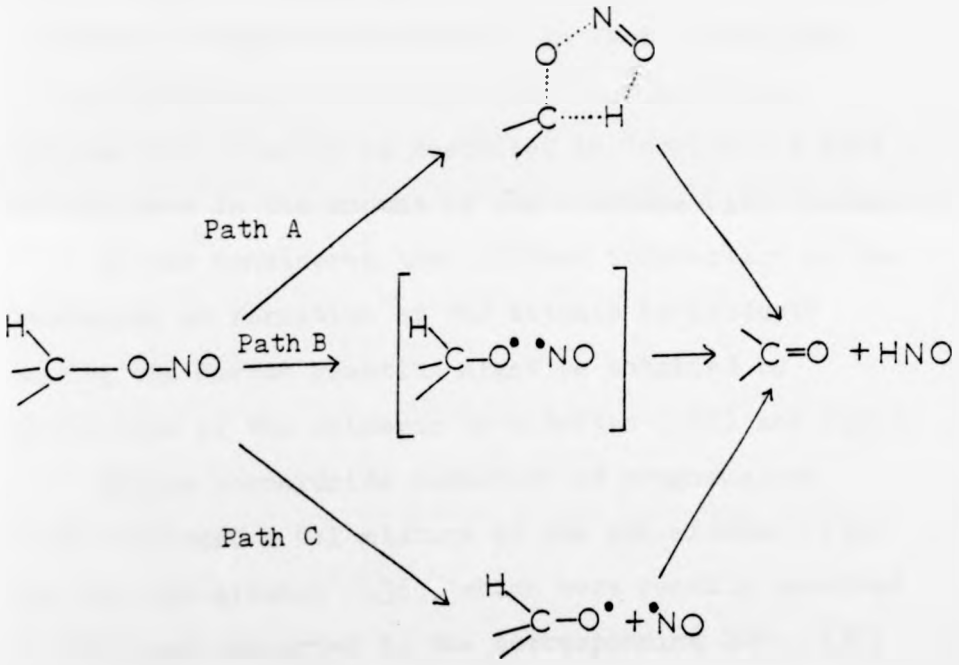


(133)

The above results prove that the process which gives rise to ketonic by-products during the Barton reaction also gives rise to the formation of hyponitrous acid and it is therefore concluded that these

ketonic by-products arise by direct decomposition of the starting nitrite ester.

Three mechanisms which would give rise to both ketonic by-products and hyponitrous acid during the Barton reaction should be considered. These are a concerted, cyclic mechanism, Path A, a radical-pair mechanism, Path B, and a free radical mechanism, Path C, as shown in Scheme 24.



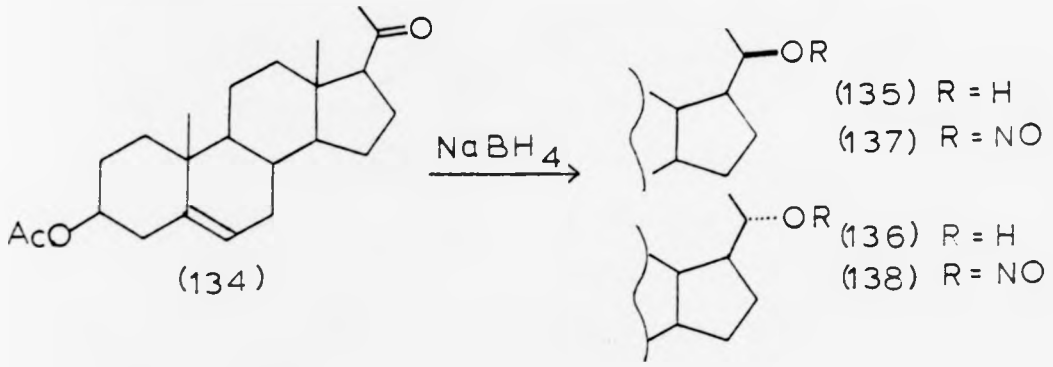
Scheme 24

Evidence has already been obtained in this work which indicates that the free radical process Path C is an unlikely mechanism for the formation of ketonic by-products. Thus, the concentration studies presented

in Table 3 (Section 2.4.4) show that the amount of the 6-ketone (116) formed in the photolysis of the 6β-nitrite (27) does not vary significantly with concentration as would be expected for an intermolecular process. Furthermore, should Path C be in operation during the Barton reaction, then it would be expected that the introduction of exogenous nitric oxide into the system would result in an increase in the amounts of ketonic by-products formed. In fact, photolysis of the 6β-nitrite (27) with nitric oxide passing through the solution as described in Section 2.3 gave no increase in the amount of the 6-ketone (116) formed.

It was considered that further information on the mechanism of formation of the ketonic by-products during the Barton reaction might be obtained by photolysis of the epimeric 20-nitrites (137) and (138).

Sodium borohydride reduction of pregnenelone (134) afforded a 4:1 mixture of the 20β-alcohol (135) and the 20α-alcohol (136), which were readily resolved by HPLC and converted to the corresponding 20β- (137) and 20α-nitrites (138) by treatment with nitrosyl chloride in pyridine.

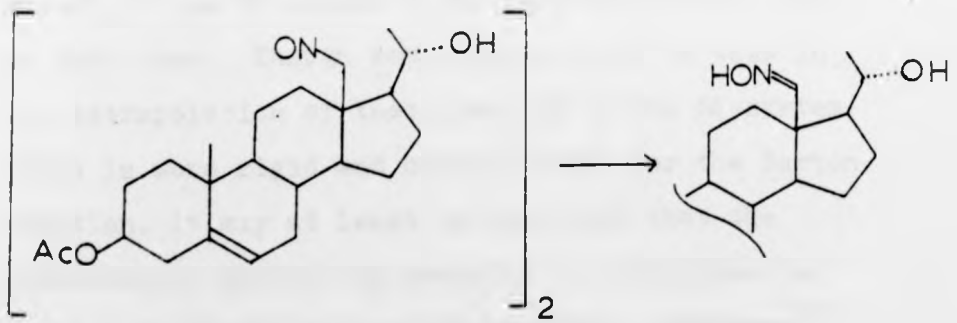


(134)

(135) R = H
(137) R = NO

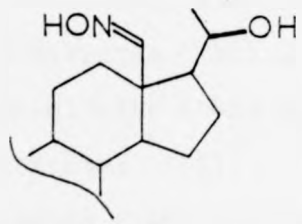
(136) R = H
(138) R = NO

Photolysis of the 20-nitrites (137) and (138) under identical conditions gave product mixtures from which the amounts of the compounds shown in Table 4 were isolated. During photolysis of the 20α-nitrite (136), white crystals precipitated, presumably the 18-nitroso dimer (139) and the reaction mixture was refluxed overnight in propan-2-ol to isomerise this putative dimer (139) to the 18-oxime (140). In both photolyses, a non-polar fraction was isolated which was not further investigated.



(139)

(140)



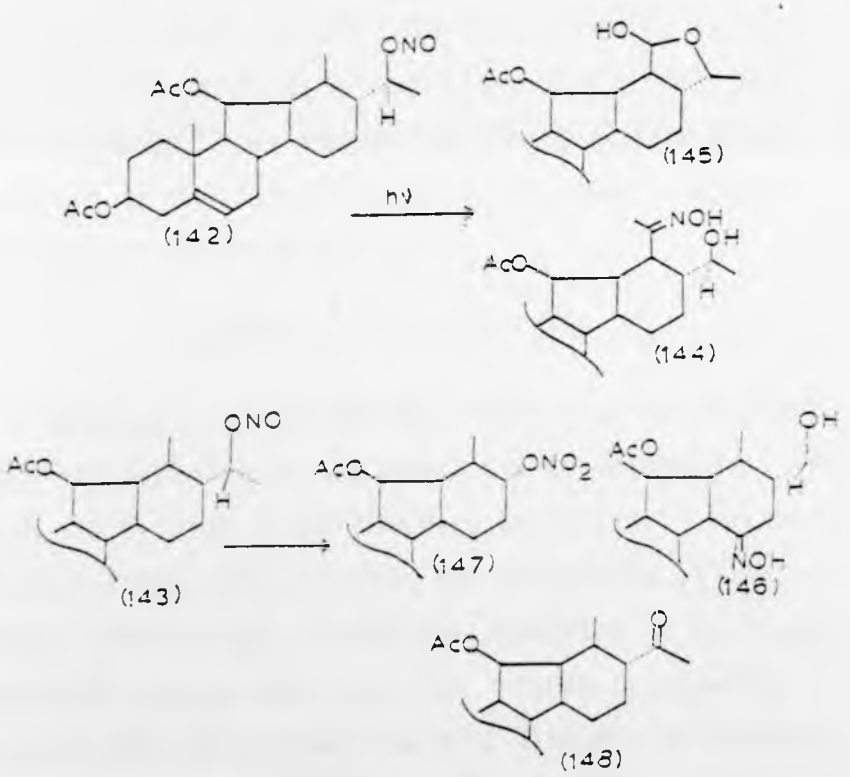
(141)

	20β-nitrite (137)	20α-nitrite (138)
Pregnenelone (134)	13%	13%
20-Alcohol	20%	14%
18-Oxime	44%	66%

Table 4

The results presented in Table 4 show that, while the 18-oximino products (140) and (141) from the Barton reaction are formed in differing amounts as are the alcoholic by-products (135) and (136), the amount of the 20-ketone (134) produced was the same in each case. Though some caution must be used in the extrapolation of these results to the 6β-system which is more rigid and better suited for the Barton reaction, it may at least be concluded that the formation of ketonic by-products is independent of the remote functionalisation reaction. Suginome[190]

has investigated the irradiation of the epimeric jervine related 20-nitrites (142) and (143) and found that, while the 20α-nitrite (142) gave the 18-oxime (144) and the hemi-acetal (145), the 20β-nitrite (143) gave the 15-oxime (146) and the 16-nitrate (147). However, both photolyses though giving rise to completely different products afforded essentially the same amount of the 20-ketone (148).



In view of the results obtained both here and by Suginome[190] it is concluded that formation of ketonic by-products during the Barton reaction does not occur by an intermolecular mechanism and probably arises from an inherent property of the nitrite esters photolysed.

The mechanism of formation of ketonic by-products is therefore Path A or Path B (Scheme 23). An examination of molecular models shows that the five-membered transition-state required for the concerted cyclic mechanism (Path A) is a distinct possibility. However, Ludwig[186] has stated that there are no known examples of the direct extrusion process in simple nitrites as required by Path A.

$$R_2CHONO \longrightarrow R_2C{=}O + HNO$$

Further evidence for the absence of any significant contribution to the formation of ketonic by-products by Path A was obtained as follows. Analysis by GLC of the products from the photolysis of cyclopentyl nitrite (88) showed the formation of no cyclopentanone during this reaction. Since cyclopentyl nitrite (88) is at least as well disposed to undergo a cyclic extrusion of HNO as the steroidal nitrites, the absence of cyclopentanone from this reaction demonstrates that Path A is not a significant process

in ketonic by-product formation. It is concluded therefore that ketonic by-products are formed by Path B and that the lack of products of this type from the photolysis of cyclopentyl nitrite (88) merely reflects the facility with which the cyclopentoxy radical undergoes α-cleavage.

In order to confirm that no HNO is formed during nitrite photolysis when no ketonic by-products are formed, cyclopentyl nitrite (88) was photolysed in the presence of tetramethylguanadine (133) and the reaction mixture extracted with 0.1M NaOH solution. The UV spectrum of this basic extract showed no absorption maximum at 248 nm characteristic of the hyponitrite dianion.

The single example of a nitrite photolysis which does not lead to ketonic by-products was reported by Suginome[63] in the photolysis of the veratrobasine-derived 11β-nitrite (93). This observation may readily be accounted for by examination of molecular models which reveals that the exocyclic enone (130) which would constitute the ketonic by-product is highly strained.

It has been concluded above that ketonic by-products arise during the Barton reaction by a mechanism which is inherent to the nitrite esters. Nitrite esters are known[191] to exist in two rotameric forms

(Figure 6) and Ludwig has suggested[186] that these rotamers may react in different ways photochemically.

Figure 6

Although a concerted elimination of HNO has been ruled out, the diversion of some nitrite to ketone during photolysis may be attributable to the different chemistries of the rotamers. In the liquid phase, isopropyl nitrite is known to contain 13% of the cis-rotamer[191] and it is considered possible that cis-nitrites give ketonic products while trans-nitrites result in the Barton reaction.

It is concluded then from the preceding results that ketonic products are formed during the Barton reaction by HNO elimination from the radical pair resulting from nitrite homolysis and it is thought that such a process is inherent to the nitrites themselves.

2.7 SOLVENT EFFECTS DURING THE BARTON REACTION

Having clarified the nature and origin of the products and by-products of the Barton reaction, it was considered of some interest to investigate the process leading to O-NO bond homolysis and the subsequent Barton reaction.

In this context it was of interest therefore to investigate the effects of several different types of radiation on steroidal nitrites. The 6β-nitrite has a UV spectrum which is typical of aliphatic nitrites, exhibiting absorption maxima in two regions. The fine structure absorption between 320 and 400 nm (Figure 7) has been attributed[24] to an $n \rightarrow \pi^*$ transition of non-bonding electrons on nitrogen to the anti-bonding π-system of the double bond and the absorption at 218 nm has been attributed to the $n \rightarrow \pi^*$ transition of a non-bonding electron on oxygen to the same anti-bonding π-orbital.

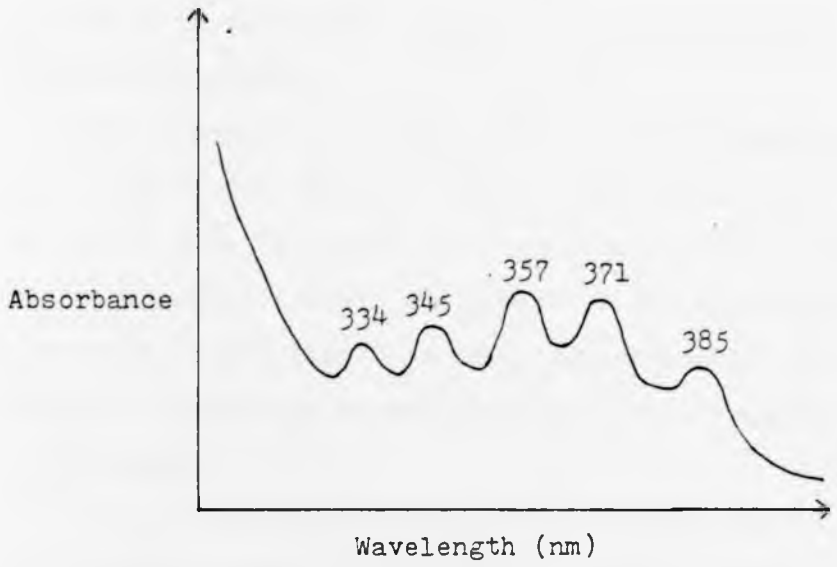


Figure 7

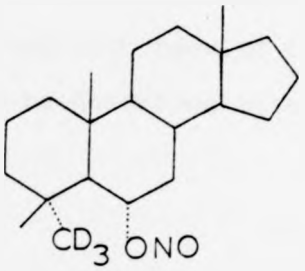
Tarte has claimed[22] that no nitroso products arise from the irradiation of nitrites at wavelengths greater than 330 nm. In practice, the Barton reaction is routinely effected using a medium-pressure Hanovia lamp with a Pyrex filter which cuts out all radiation below 290 nm and has the major output at 365 nm. In this present work, it was found that a tungsten lamp emitting visible light at wavelengths greater than 400 nm caused no decomposition of the starting 6β-nitrite (27) after irradiation for 8 hours. When the 6β-nitrite (27) was irradiated with light from a medium-pressure Hanovia lamp filtered through both Pyrex and a 10% methanolic solution of carbon disulphide which was found to cut out at 318 nm, the reaction

proceeded in the normal manner with no discernible difference in rate.

The radiation emitted by "black-light" lamps is a maximum at 366 nm and it was considered therefore that this type of radiation could be utilised in the Barton reaction. Thus, photolysis of the 6β-nitrite (27) with "black-light" at room temperature in methylene chloride containing t-butylamine gave the 19-oxime (117) in 70% yield.

It is concluded therefore that in contrast to Tarte's claim,[22] the Barton reaction may conveniently be carried out using either "black-light" or filtered medium-pressure mercury radiation, both of which have maximum output at 366 nm.

Although the photodecomposition of nitrite esters in solution has been shown to be a reasonably efficient process,[23,24,25] widely differing radiation times have been reported for the Barton reaction. Whalley, for example,[41] reported that photolysis of the 6α-nitrite (148) required irradiation for 98 hours for complete reaction. This inordinately high photolysis time was attributed to a combination of a kinetic isotope effect and the unfavourable nature of the transition-state for hydrogen abstraction in this particular molecule (148).



(148)

It has already been shown (Section 2.5.2) that photolysis of nitrites in aromatic solvents leads to the formation of nitroaromatics. Since nitroaromatics in general exhibit absorption maxima in the region 300 to 400 nm[42] with extinction coefficients between 1000 and 5000, it was considered that their generation during photolysis could have bearing on the variable reaction times reported in the literature. In order to investigate this possibility, the 6β-nitrite (27) was photolysed using "black-light" in the presence of diisopropylamine in both toluene and chloroform solutions and the rate of reaction determined in each case by monitoring the rate of disappearance of the UV absorption maximum at 371 nm. It is clear from the results given in Figure 8 that a filtering effect does become significant on irradiation in aromatic solvents after about 20 min leading to substantial inhibition of reaction. This effect is not observed

in chloroform. That the introduction of nitrobenzene into a photolysis solution results in the inhibition of photolysis will be described later.

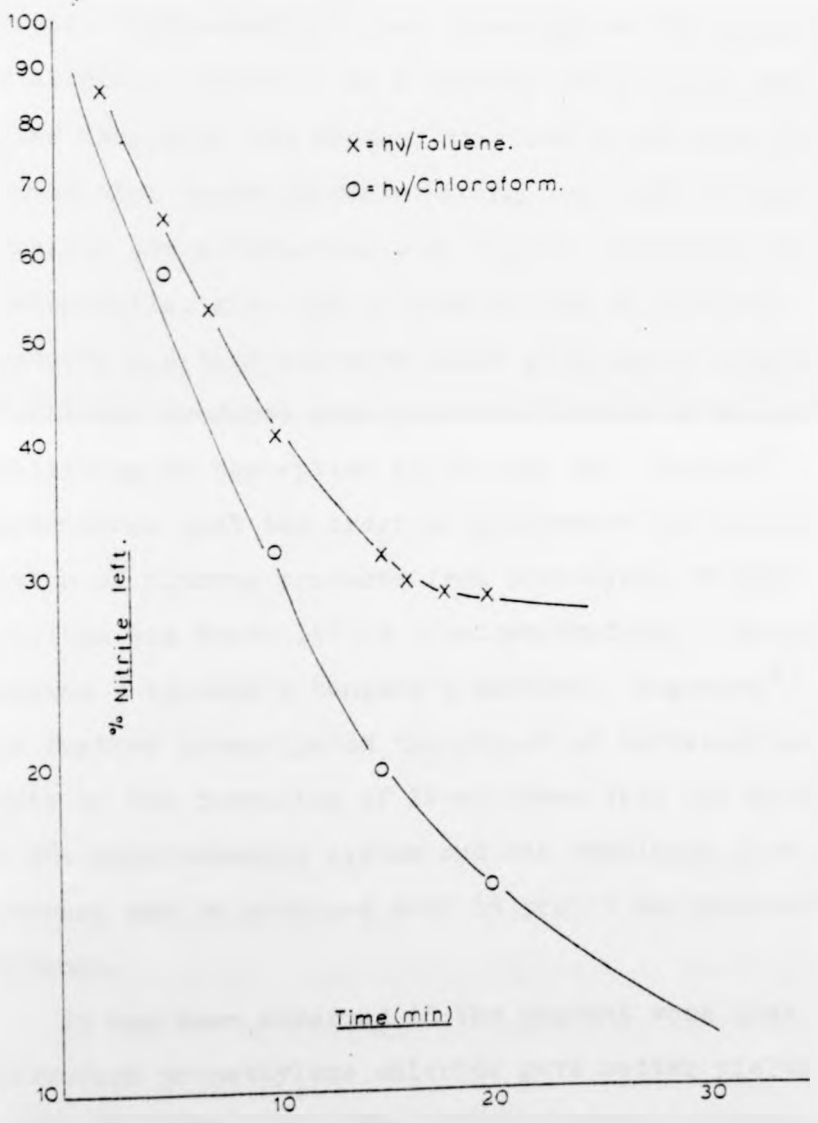


Figure 8

It has been shown that the solvent used for nitrite photolysis may have an effect on the outcome of the reaction. The use of different solvents in the Barton reaction has been investigated by several groups. Kabasakalian[25] has investigated the photolysis of aliphatic nitrites in a variety of solvents and, after analysing the product mixtures by UV, has concluded that those solvents having poor radical-chain transfer characteristics e.g. heptane, benzene, and acetonitrile, give the optimum yields of nitroso products and that solvents which gave poorer yields of nitroso products gave increased yields of by-products exhibiting UV absorption at 220-230 nm. Barton[43] ascertained that the order of preference for the formation of nitrone products from photolysis of 11β-nitrites was acetonitrile > tetrahydrofuran > chlorobenzene > toluene > benzene > acetone. Suginome[23] has further investigated the effect of different solvents on the formation of 18-nitrones from 11β-nitrites in the veratrobasine system and has concluded that nitrones may be produced both in protic and non-protic solvents.

It had been observed in the present work that chloroform or methylene chloride gave better yields of the 19-oxime (117) than either toluene or chlorobenzene (Section 2.2). Since these results were in

contrast to those of Kabasakalian,[25] a brief study was carried out on the effect of solvent on the amount of the 19-oxime (117) formed from photolysis of the 6β-nitrite (27) and the results of this study are presented in Table 5.

Solvent	% Oxime (117)[a]
Toluene	65
Chlorobenzene	62
Benzene	60
Dimethylformamide	52
Chloroform	68
Methylene chloride	70
Sym-tetrachloroethane	62
Tetrachloroethylene	66
Ethyl acetate	64

a - isolated yields by HPLC

Table 5

It may be concluded from the above results that a variety of solvents may be used successfully for the Barton reaction. However, in contrast to the report by Suginome[23] that nitrite photolysis could be successfully effected in protic solvents, it was found in this work that the introduction of ethanol into a photolysis solution resulted largely in the formation of the

6β-alcohol (115) whose formation is presumed to be a consequence of the very good hydrogen donating ability of ethanol. This observation explains the erratic yields of the 19-oxime (117) obtained from photolysis of the 6β-nitrite (27) in commercial chloroform which contains ethanol as a stabiliser.

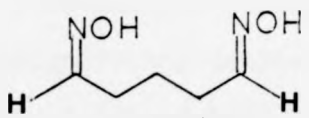
2.8 TRIPLET SENSITISATION OF THE BARTON REACTION

In determining the mechanism of a photochemical reaction, one of the important questions which arises is which electronic state of the molecule is involved in the primary photochemical event. As a result of the fast and usually totally efficient internal conversion of excited states, only two excited states of the molecule need normally be considered, the lowest excited singlet and the lowest excited triplet. Generally, most definitive information regarding the intermediacy of a triplet or singlet state in a photochemical reaction may be gathered by the execution of companion sensitising and quenching experiments. It was therefore decided to carry out a series of triplet-sensitisation and quenching studies in this present work. In addition to the potential mechanistic information which might be conveyed by such a study, it was considered that some synthetic benefit might also be achieved. For example, although the primary

photo-decomposition of nitrite esters has been shown[23,24,25] to be moderately efficient, it was considered that an improvement in the efficiency of this dissociation process using triplet sensitisation might result in increased efficiency of the Barton reaction. Furthermore, though the origins of the by-products of the Barton reaction have already been ascertained the suppression of ketone formation has not been achieved. Although the oximino and ketonic products of the Barton reaction probably arise from the different rotameric forms of the nitrite, it might alternatively be argued that they are formed from different photo-excited electronic states. This being the case, it may be possible to suppress ketone formation.

The system chosen as substrate for this study was cyclopentyl nitrite (88) since its rate of disappearance could be accurately monitored by GLC. The photolysis of cyclopentyl nitrite (88) is known[143] to result in ring-opening to afford the nitroso-aldehyde (89) as the primary product and it was found that the amount of ring-opening could be determined by integrating the aldehydic resonance at $\delta = 9.8$ against the methylene part of the NMR spectrum of the photolysis mixture. Confirmation of the formation of the nitroso-aldehyde (89) was obtained from the isolation of the

1,5-dioxime (149) by treatment of one of the photolysis mixtures with hydroxylamine hydrochloride as reported by Kabasakalian.[143]

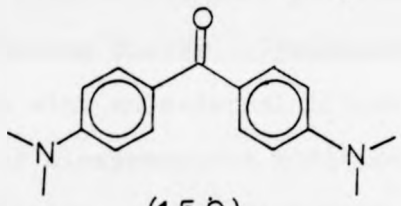


(149)

When choosing a sensitiser for a photochemical reaction, it is necessary to consider the energy of the triplet state, the efficiency of the intersystem-crossing process, and the absorption spectrum of the sensitiser. Michler's ketone, 4,4-bis(dimethylamino)-benzophenone (150) is a triplet sensitiser which has found use in organic chemistry.[192] Michler's ketone (150) has a triplet-excitation energy (E_T) of 260 kJ mol^{-1} which is in excess of the energy required for the cleavage of the O-NO bond (~ 170 kJ mol^{-1}),[193] a high efficiency in the energy transfer step (Φ_{isc} = 1.00) and a UV spectrum with a broad, intense absorption between 300 and 400 nm (ϵ_{max} at 366 = 2.8 x 10^4) and therefore appeared to be well suited for use in this case.

In a preliminary experiment, cyclopentyl nitrite (88) was photolysed in methylene chloride containing

t-butylamine using "black-light" and its rate of disappearance determined by GLC, to give the values shown in Figure 9. On repeating this photolysis under the above conditions in the presence of a ten-fold photochemical excess of Michler's ketone (150) it was found that no significant decrease in the rate of disappearance of the cyclopentyl nitrite (88) was observed (Figure 9). These experiments provide some support for the intermediacy of triplets during the Barton reaction.



(150)

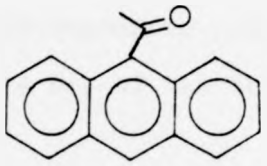
Further evidence for the intermediacy of triplets was provided as follows. Nitrobenzene has a broad UV absorption maximum at 330 nm (ϵ_{max} = 125) and it was considered that the introduction of this compound as a radiation filter into a photolysis mixture should inhibit the reaction. This idea was confirmed when it was shown that on photolysis of cyclopentyl nitrite (88) as above in the presence of a four-fold photochemical excess of nitrobenzene the rate of disappearance of cyclopentyl nitrite (88) was reduced considerably

(Figure 10). However, the rate of disappearance of cyclopentyl nitrite (88) on photolysis in the presence of nitrobenzene and excess Michler's ketone (150) (Figure 10) did not differ significantly from the rate observed on photolysis in the absence of nitrobenzene and this provides added evidence for the intermediacy of triplets in nitrite photolysis.

In order to eliminate the possibility that an interaction between nitrobenzene and Michler's ketone (150) might result in disappearance of cyclopentyl nitrite (88), experiments were performed using an external nitrobenzene filter. Cyclopentyl nitrite (88) was photolysed with an external nitrobenzene filter and the rate of disappearance monitored. After 30 minutes irradiation, excess Michler's ketone (150) was added and the reaction was monitored for a further 30 minutes at which time more Michler's ketone (150) was added and monitoring continued (Figure 11). The rate of disappearance of the cyclopentyl nitrite (88) in this experiment proves that nitrobenzene is not involved in the disappearance of cyclopentyl nitrite (88) and that the reaction is probably triplet sensitised.

When cyclopentyl nitrite (88) was photolysed in methylene chloride containing t-butylamine in the presence of 9-anthraldehyde (151) no significant

decomposition was observed after several hours. This result is to be expected since the low triplet energy of 9-anthraldehyde (151)[194] (E_T = 167 kJ mol^{-1}) should be insufficient to allow cleavage of the O-NO bond in nitrite esters.



(151)

In general, conclusive evidence for the intermediacy of triplets in a photochemical reaction requires not only the observation of a sensitising effect but also of a quenching effect. Benzophenone is a known[195] efficient triplet sensitiser (Φ_{isc} = 1.00, E_T = 288 kJ mol^{-1}) whose triplets may be quenched efficiently by trans-1,3-pentadiene (152).[196] The rate of photolysis of cyclopentyl nitrite (88) in the presence of excess benzophenone was shown to be essentially the same as the rate in the presence of Michler's ketone (150), showing that benzophenone is an efficient sensitiser for this reaction (Figure 12). That the cyclopentyl nitrite (88) was not reacting by direct absorption of light in this reaction was readily shown by the observation of a marked decrease

in the rate of reaction when the photolysis was performed in the presence of an external benzophenone filter (Figure 12). Photolysis of cyclopentyl nitrite (88) in the presence of both benzophenone and trans-1,3-pentadiene (152), a known triplet quencher,[196] gave no significant decomposition of the nitrite (88) after 1 hour. It is therefore concluded that nitrite photolysis occurs by way of the triplet state.

(152)

Having demonstrated that nitrite photolysis could be triplet sensitised, the effect of a triplet sensitiser on the photolysis of the 6β-nitrite (27) was investigated. The 6β-nitrite (27) was irradiated in the presence of excess Michler's ketone (150) and it was found that although the 19-oxime (117), the 6-ketone (116), and the 6β-alcohol (115) were present the amount of the 6β-alcohol (115) formed was greater than in the absence of this triplet sensitiser. This increased formation of the 6β-alcohol (115) is considered a consequence of the reaction of nitric oxide with Michler's ketone (150). The continued formation of the 6-ketone (116) in this case demonstrates that it does not arise from a different photo-excited electronic state which

is different from that which leads to the normal Barton reaction.

In conclusion, though the Barton reaction proceeds by a triplet intermediate, the use of triplet sensitisers does not offer any improvement over the previously established conditions since it results in the ccntinued formation of ketonic by-products.

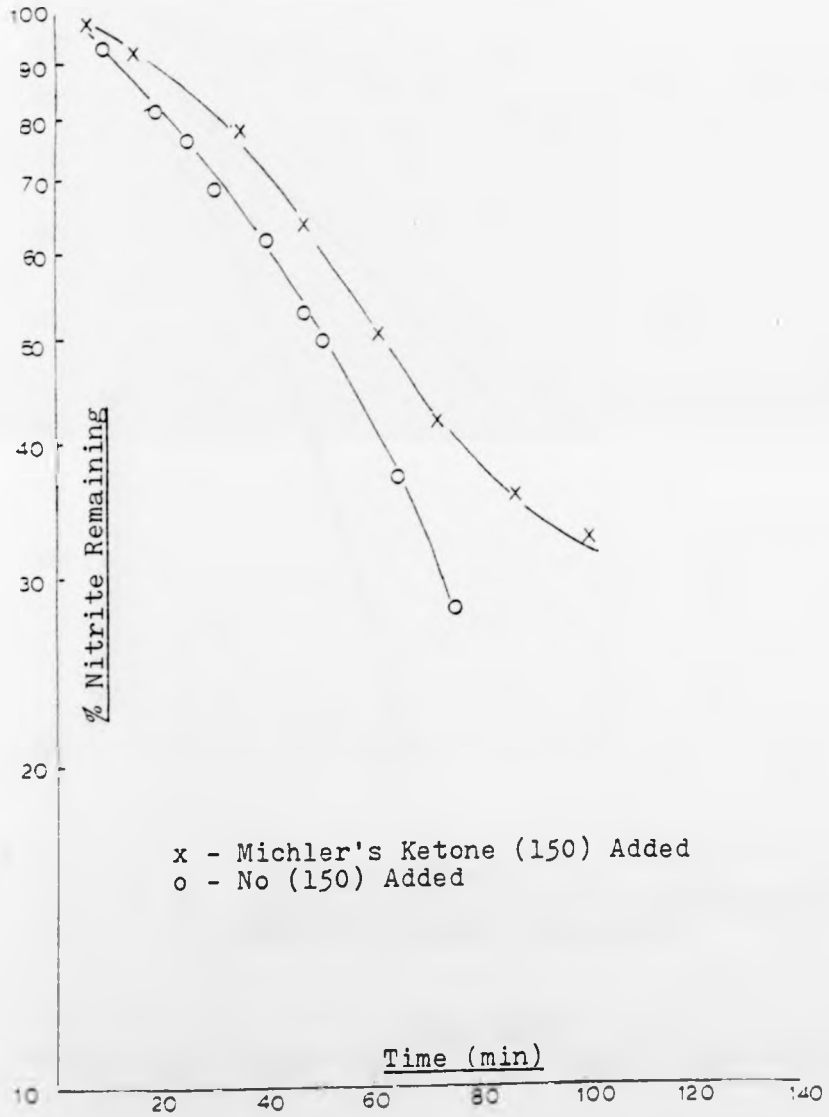

100
90
80
70
60
50
40
30
20
10
% Nitrite Remaining
x - Michler's Ketone (150) Added
o - No (150) Added
Time (min)
20
40
60
80
100
120
140

Figure 9

Photolysis of cyclopentyl nitrite (88) with an internal radiation filter

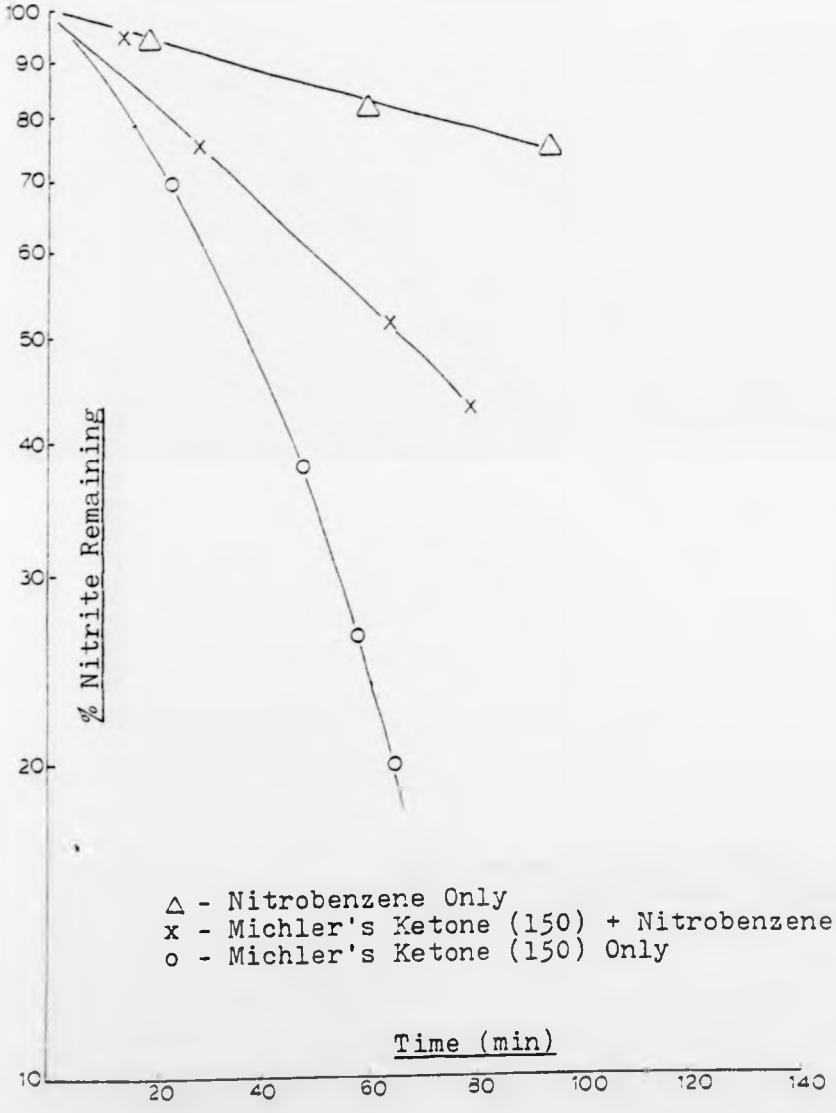


Figure 10

Photolysis of cyclopentyl nitrite (88)
with an external radiation filter

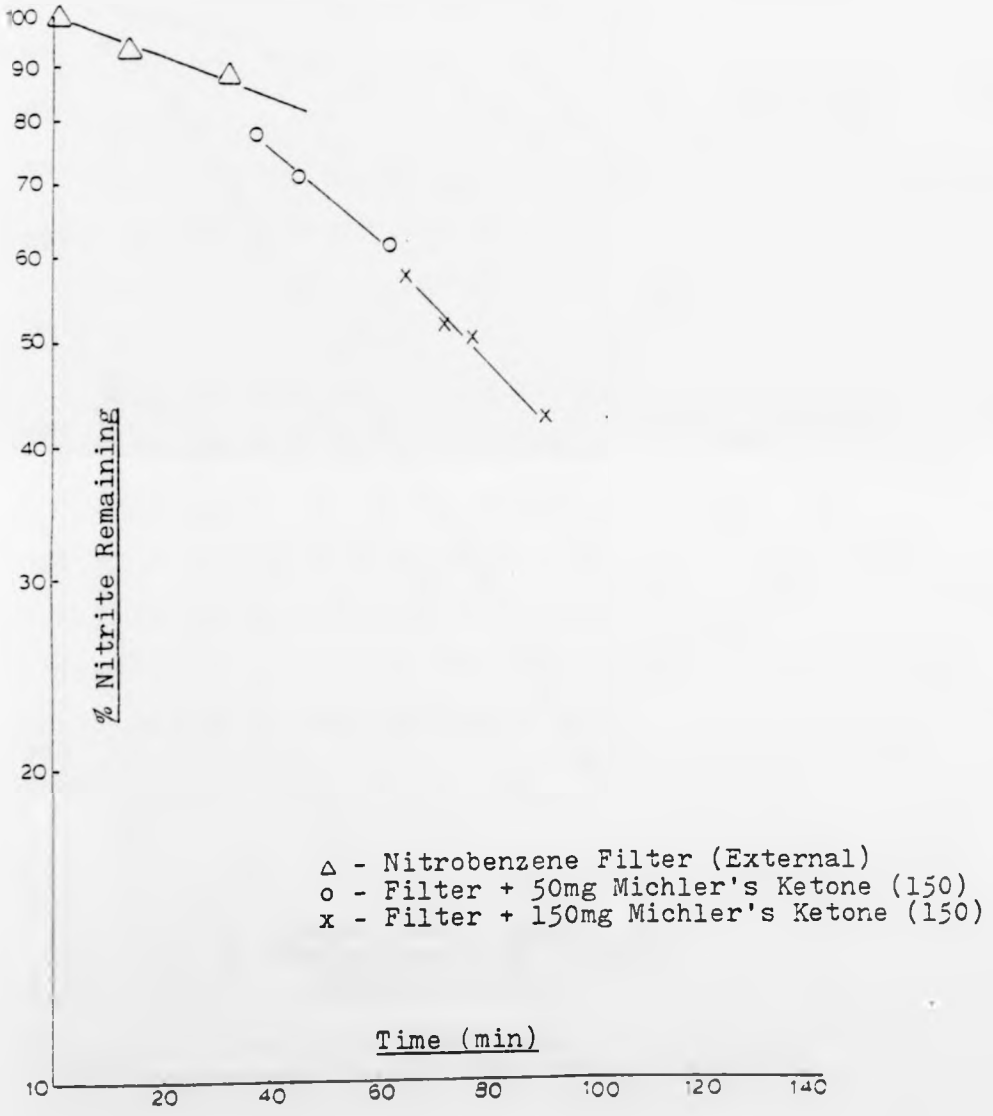


Figure 11

Photolysis of cyclopentyl nitrite (88) in the presence of benzophenone

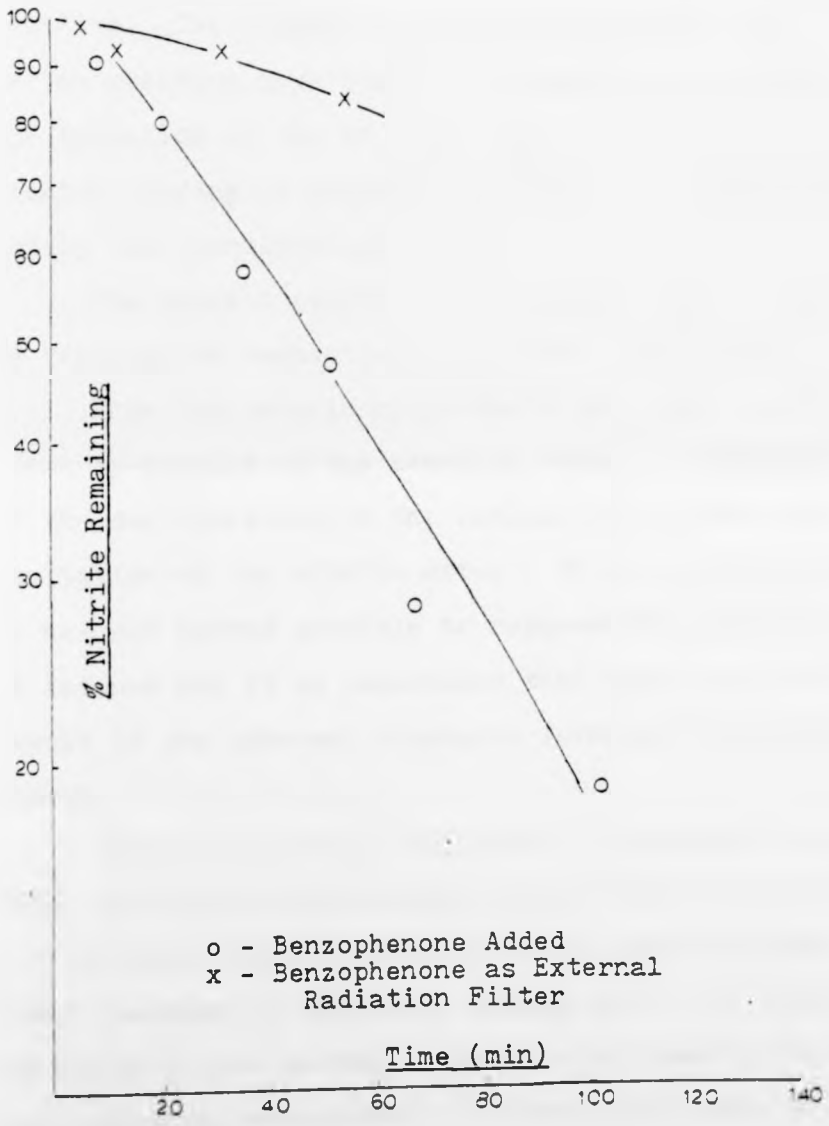


Figure 12

2.9 CONCLUSIONS

It has been shown that the Barton reaction is subject to diversions at various stages throughout the reaction. The origins of the by-products of the Barton reaction have been elucidated and as a result the formation of two of these by-products may be eliminated leading to improved yields of the desired remotely functionalised products.

The overall course of the Barton reaction may be represented sequentially as shown in Scheme 25.

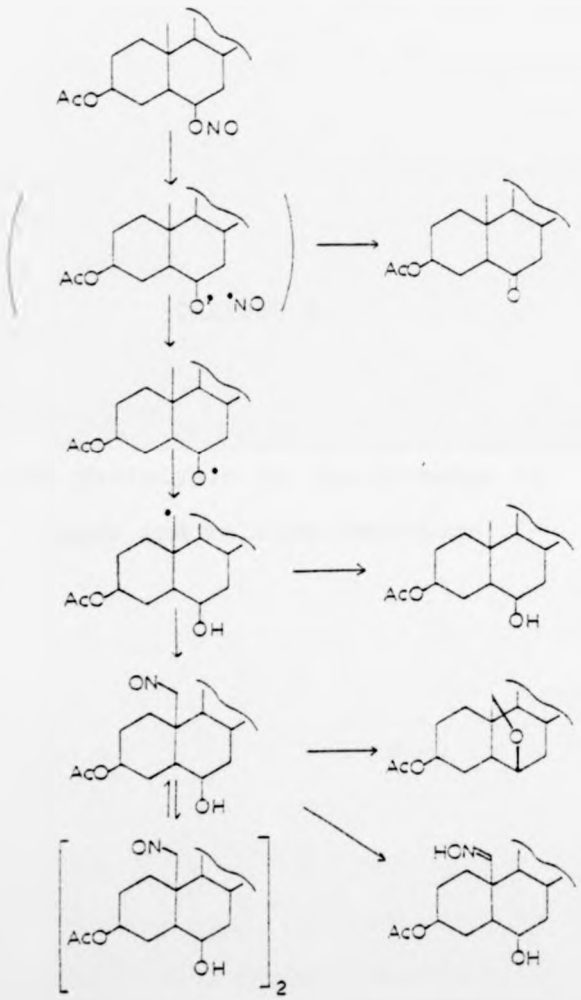
Thus the ketonic by-products are formed as the first by-product of the reaction being a consequence of the decomposition of the radical pair formed from excitation of the nitrite ester. Of all the products it has not proved possible to suppress the formation of ketones and it is considered that they arise as a result of the inherent rotameric forms of the nitrite esters.

Under the normal conditions of the Barton reaction, alcoholic by-products arise by the removal of nitric oxide from the reaction medium and the subsequent reaction of the alkyl radical with other steroidal molecules in the system. Formation of these by-products was completely suppressed by carrying the reaction out in methylene chloride at low temperatures.

Finally, the epoxy by-products of the Barton

reaction arise by way of the reaction of the primary product, the nitroso monomer with nitric oxide and the formation of this by-product was readily avoided by carrying the reaction out at a suitable concentration.

In conclusion, although the Barton reaction may be effected by triplet sensitisation, optimum yields of the oximino products are obtained by photolysis using either "black-light" or medium-pressure mercury arc radiation, at a concentration of about 1×10^{-2}M, in the presence of nitrogenous base, in methylene chloride, and at reduced temperatures.



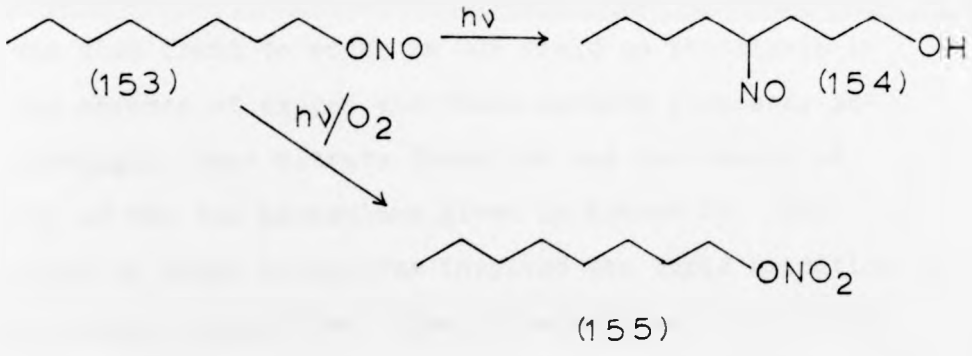
Scheme 25

CHAPTER 3

Nitrite photolysis in the presence of oxygen and related reactions

3.1 NITRITE PHOTOLYSIS IN THE PRESENCE OF OXYGEN

In his preliminary work on the photolysis of organic nitrites in solution, Kabasakalian found that the photolysis of n-octylnitrite (153) under normal conditions afforded the expected 4-nitrosooctan-1-ol (154) in moderate yield.[25] He found, however, that irradiation of n-octyl nitrite (153) in the presence of oxygen afforded none of the expected nitroso compound (154) and that the major identifiable product was n-octyl nitrate (155).



The formation of n-octyl nitrate (155) in this case was attributed[25] to a process described by Hanst[197] who had previously observed that the gas phase photolysis of methyl nitrite in the presence of oxygen gave rise to the formation of methyl nitrate.

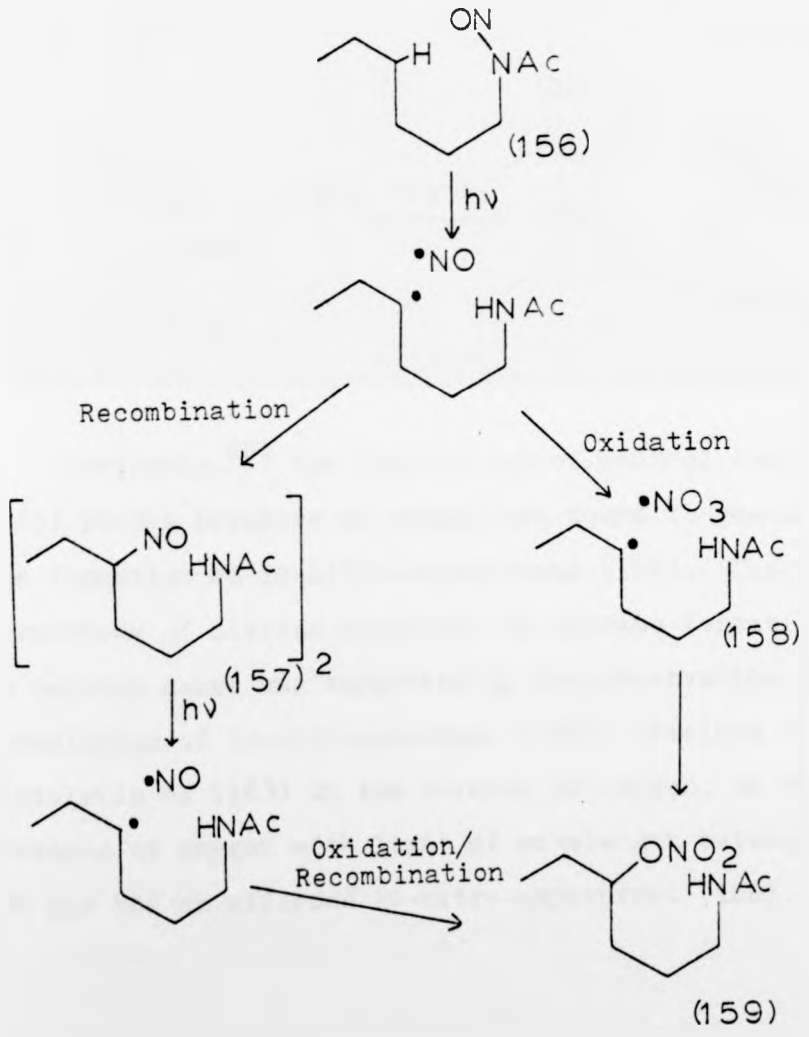
$$R\text{-}ONO \rightleftharpoons R\text{-}O\cdot + \cdot NO$$

$$2NO + O_2 \longrightarrow 2NO_2$$

$$R\text{-}O\cdot + NO_2 \longrightarrow R\text{-}ONO_2$$

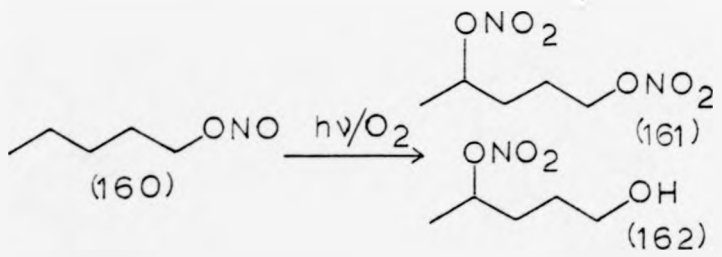
In subsequent studies on the photochemistry of N-nitrosoamides, it was observed by Chow and Tam[198] that the photolysis of N-hexyl-N-nitrosoacetamide (156) in the presence of oxygen furnished the remotely functionalised product (159) in 62% yield (Scheme 26). The formation of the nitrate ester (159) in this case was also found to occur in 20% yield on photolysis in the absence of oxygen and these workers proposed, accordingly, that nitrate formation was the result of one of the two mechanisms given in Scheme 26. The first of these mechanisms involved the rapid oxidation of nitric oxide formed from photodecomposition of the nitrosodimer (157) followed by recombination, while the second involved oxidation of the nitric oxide formed in the primary photodecomposition of nitrosoamide (156) and subsequent recombination of the resulting NO_3 radical with the alkyl radical (158). It had been previously demonstrated[199,200] that oxygen is formed as a result of the photodecomposition of excited nitric oxide molecules and Chow and Tam

proposed[198] that the formation of the nitrate ester (159) in the experiment where no oxygen was added could be ascribed to such a process.



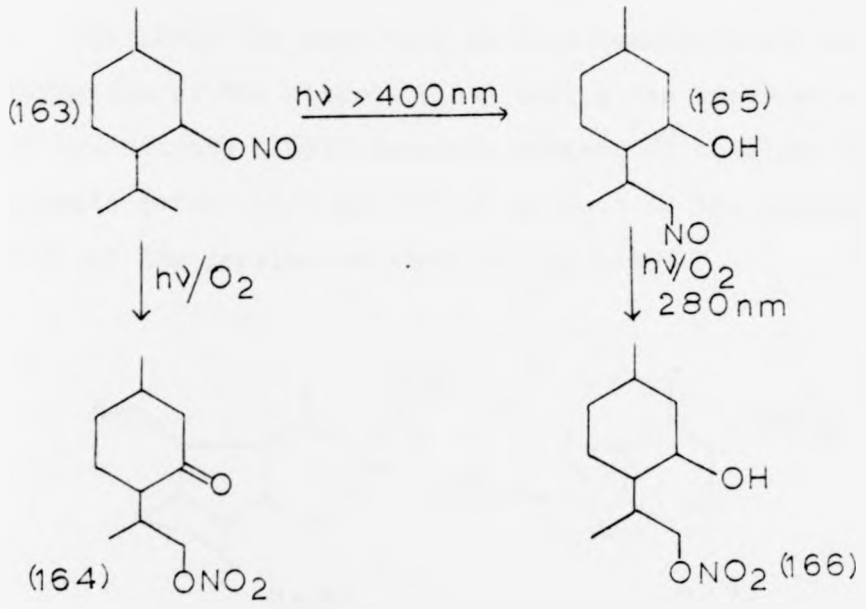
Scheme 26

In contrast to Kabasakalian's observations,[25] it was later shown[201] that the irradiation of n-pentyl nitrite (160) in the presence of oxygen gave rise to the remotely functionalised nitrate esters, (161) and (162).

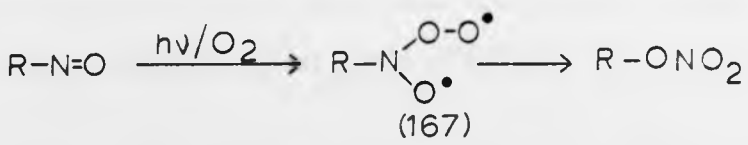


(160) (161) (162)

Similarly,[201] the irradiation of menthol 1-nitrite (163) in the presence of oxygen was found to result in the formation of 10-nitro-oxymenthone (164). The intermediacy of nitroso compounds in nitrate formation in certain cases was suggested by the observation that irradiation of 10-nitrosomenthol (165), obtained by photolysis of (163) in the absence of oxygen, in the presence of oxygen with light of wavelength between 280 and 400 nm afforded 10-nitro-oxymenthol (166).

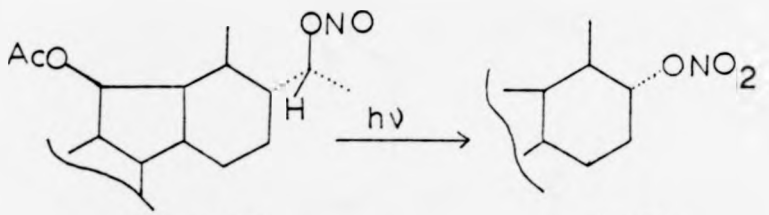


More recently, de Boer[202] forwarded a further mechanism to account for nitrate formation which involves the reaction of oxygen, itself a paramagnetic species, with a photo-excited nitroso compound to produce an intermediate of the type (167) which then rearranges to a nitrate ester.



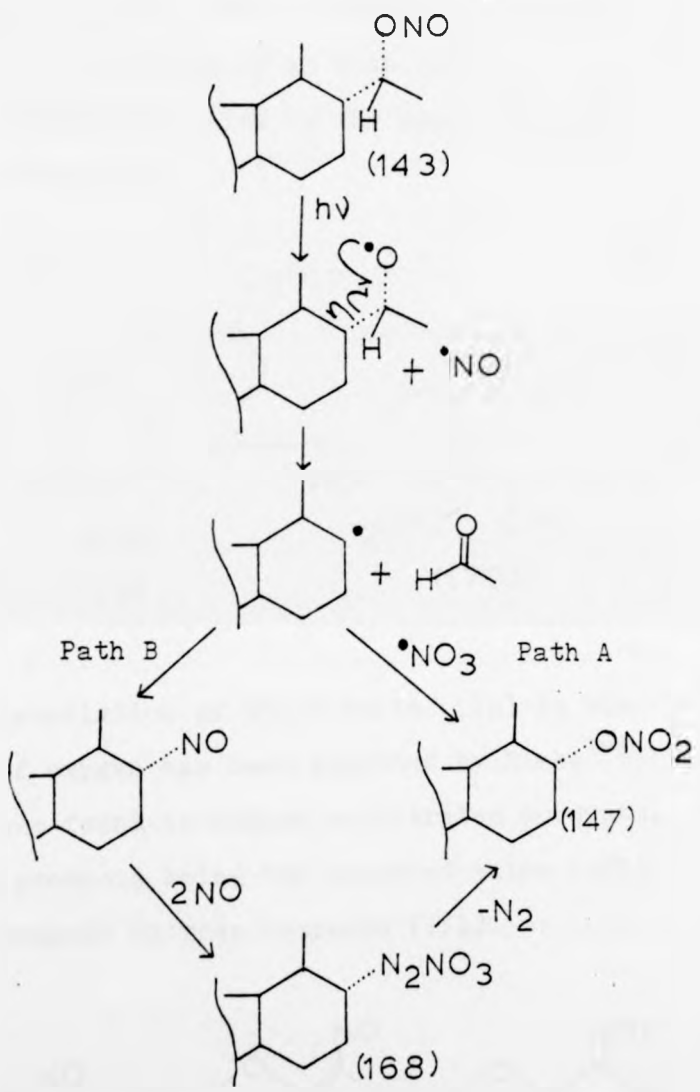
(167)

At about the same time as Chow demonstrated the formation of the nitrate (164) during the irradiation of the nitrite (163), Japanese workers[190] obtained the nitrate ester (147) as a minor product in the irradiation of the jervine-related nitrite (143).



(143) (147)

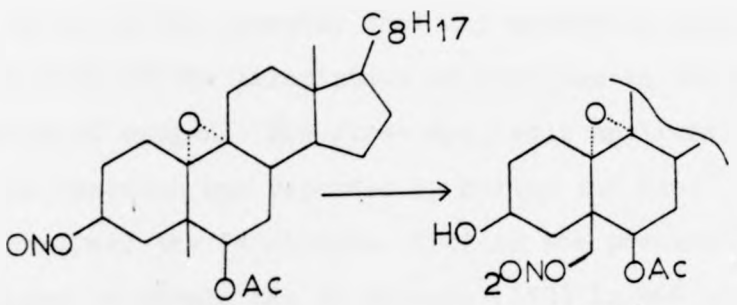
These workers proposed[190] that nitrates may arise from the irradiation of nitrites in the absence of oxygen by one of the two mechanisms given in Scheme 27. These mechanisms involve either the recombination of an alkyl radical with a higher oxide of nitrogen (Path A) or the formation of a nitroso compound in the normal manner and its subsequent reaction with nitric oxide via an intermediate diazonium nitrate (168) to a nitrate ester (147) (Path B).



Scheme 27

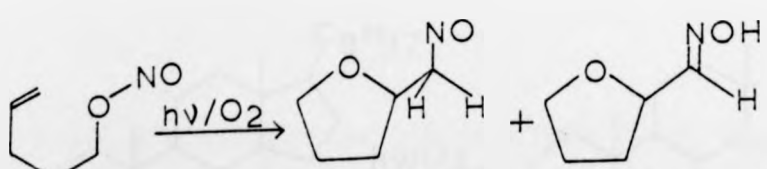
The formation of nitrate esters has been noted by Marples[59] who observed that the 5β-nitrate (170) was formed as a minor by-product during the photolysis of

the 3β-nitrite (169), and has speculated that it arose from the reaction of an intermediate nitroso compound with nitric oxide by the mechanism Path B shown in Scheme 27.



(169) (170)

The irradiation of the nitrite (120) in the presence of oxygen has been examined by Rieke[149] and has been found to afford no nitrated products, the major products being the expected oxime (121) and the isomeric nitroso compound (171).

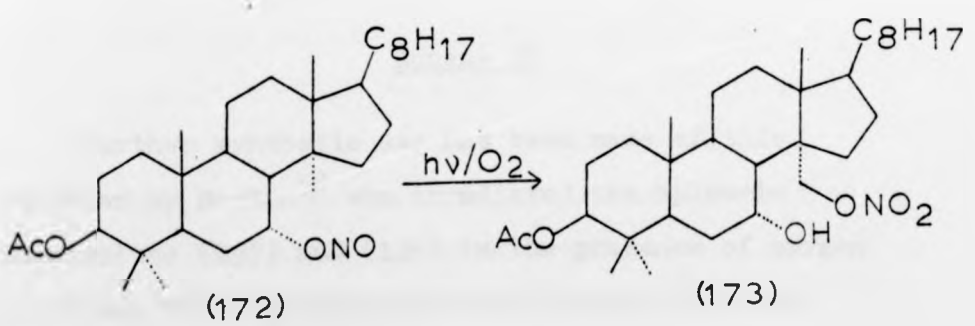


(120) (171) (121)

It was concluded as a result of the absence of nitrated products from this reaction that the cyclic addition of the alkoxy radical to the double bond is

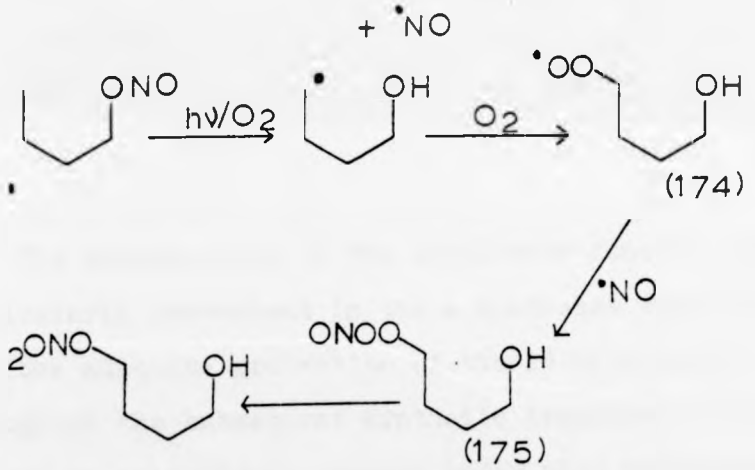
more rapid than the oxidative processes which result in nitrate formation.

It has been shown then, that the formation of nitrate esters as a result of the irradiation of nitrites is not an uncommon process. It was not, however, until recently that any synthetic application was made of the irradiation of nitrites in the presence of oxygen. The first synthetic application of this reaction was reported by Barton and Boar[203] who photolysed the 7α-nitrite (172) in the presence of oxygen to obtain the 32-nitrate (173) in 44% yield. The 32-nitrate function thus obtained provided convenient protection for the 32-alcohol group during the subsequent dehydration of the 7α-alcohol, and cleavage of the 32-nitrate (173) was then accomplished readily in 84% yield by treatment with zinc and acetic acid to provide synthetic access to the biosynthetically important[204,205] 32-oxygenated lanostanes.



(172) (173)

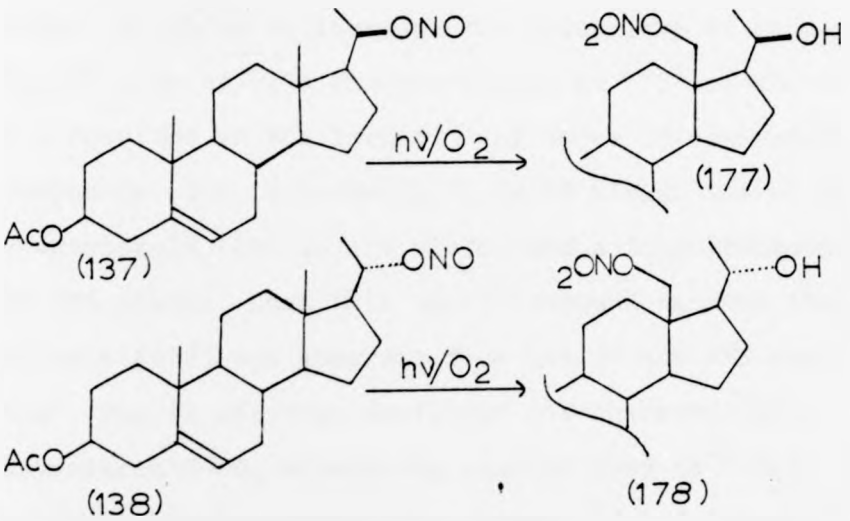
In the course of their work on the photolysis of the lanostane-related nitrite (172) in the presence of oxygen, Barton and Boar[203] proposed a further mechanism for nitrate formation, which involved the reaction of oxygen with the alkyl radical and the subsequent combination of the resulting peroxyalkyl radical (174) with NO followed by rearrangement of the peroxynitrite (175) to the nitrate ester (176) (Scheme 28).



Scheme 28

Further synthetic use has been made of this reaction by Barton[58] who irradiated the epimeric 20-nitrites (137) and (138) in the presence of oxygen to obtain the corresponding 18-nitrates (177) and (178) which were key intermediates in the synthesis of some biologically important 18-hydroxylated

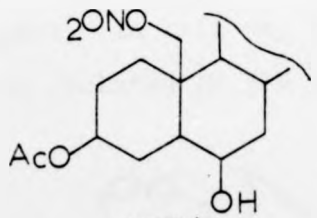
steroids.



The introduction of the 18-nitrate function is particularly convenient in these syntheses since it provides adequate protection of the 18-hydroxy group throughout the subsequent synthetic transformations and may be selectively removed under mild conditions.[206] Barton has also reported that 11β-nitrites could be photolysed in this way to afford useful 18-nitrates.[43]

In view of the reported synthetic utility of this modified Barton reaction, it was of interest to attempt to extend the synthetic applicability of this reaction to 6β-nitrites. Irradiation of the 6β-nitrite (27) at room temperature with a vigorous stream of

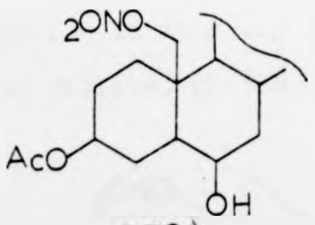
oxygen passing through the solution afforded the 19-oxime (117) as the only isolable 19-activated product. In order to increase the solubility of oxygen the 6β-nitrite (27) was photolysed at -78° as above and resulted in the formation of three 19-activated compounds, the 19-oxime (117) in 2% yield, the 6β,19-epoxysteroid (29) in 16% yield, and a third compound in 32% yield. That this third compound was the 19-nitrate (177) was apparent from its IR and NMR spectra. The IR spectrum exhibited the characteristic asymmetric O-NO_2 stretching band at 1645 cm^{-1} and the NMR spectrum showed the absence of a C19 methyl resonance and the presence of a signal at δ = 4.9 characteristic of a $\underline{CH_2}$-ONO_2 group.



(179)

Surprisingly, the microanalysis of the 19-nitrate (179) showed it to contain very little nitrogen while its mass spectrum had a molecular ion at m/e 444 and a fragmentation pattern identical to that of the

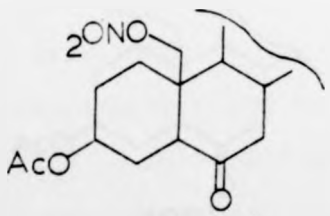
oxygen passing through the solution afforded the 19-oxime (117) as the only isolable 19-activated product. In order to increase the solubility of oxygen the 6β-nitrite (27) was photolysed at -78° as above and resulted in the formation of three 19-activated compounds, the 19-oxime (117) in 2% yield, the 6β,19-epoxysteroid (29) in 16% yield, and a third compound in 32% yield. That this third compound was the 19-nitrate (177) was apparent from its IR and NMR spectra. The IR spectrum exhibited the characteristic asymmetric $O-NO_2$ stretching band at 1645 cm^{-1} and the NMR spectrum showed the absence of a C19 methyl resonance and the presence of a signal at $\delta = 4.9$ characteristic of a $\underline{CH_2}-ONO_2$ group.



(179)

Surprisingly, the microanalysis of the 19-nitrate (179) showed it to contain very little nitrogen while its mass spectrum had a molecular ion at m/e 444 and a fragmentation pattern identical to that of the

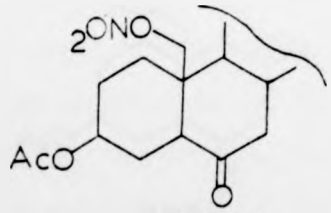
6β,19-epoxysteroid (29). These results implied that an intramolecular displacement of nitric acid was occurring since the propensity of 6β-hydroxy-19-iodosteroids to undergo backside HI elimination has been shown[38] and nitric acid may be expelled from the 19-nitrate (179) in an analogous manner to give the 6β,19-epoxysteroid.[29] Confirmation of the instability of the 19-nitrate (179) was obtained from the observation that the intensity of the characteristic band at 1645 cm^{-1} in its IR spectrum decreased by half on standing overnight. In fact, it was shown that the 19-nitrate (179) was converted to the 6β,19-epoxysteroid (29) on treatment with sodium hydrogen carbonate. This intramolecular elimination of nitric acid was readily avoided by oxidation of the photolysis mixture on completion of photolysis with Jones' reagent. In this way the 6-ketone-19 nitrate (180) was isolated in 52% yield.



(180)

Alternatively, zinc and ammonium acetate treatment of the photolysis mixture afforded the 6β,19-dihydroxy-

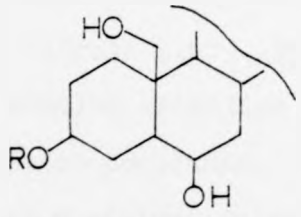
6β,19-epoxysteroid (29). These results implied that an intramolecular displacement of nitric acid was occurring since the propensity of 6β-hydroxy-19-iodo-steroids to undergo backside HI elimination has been shown[38] and nitric acid may be expelled from the 19-nitrate (179) in an analogous manner to give the 6β,19-epoxysteroid.[29] Confirmation of the instability of the 19-nitrate (179) was obtained from the observation that the intensity of the characteristic band at 1645 cm^{-1} in its IR spectrum decreased by half on standing overnight. In fact, it was shown that the 19-nitrate (179) was converted to the 6β,19-epoxysteroid (29) on treatment with sodium hydrogen carbonate. This intramolecular elimination of nitric acid was readily avoided by oxidation of the photolysis mixture on completion of photolysis with Jones' reagent. In this way the 6-ketone-19 nitrate (180) was isolated in 52% yield.



(180)

Alternatively, zinc and ammonium acetate treatment of the photolysis mixture afforded the 6β,19-dihydroxy-

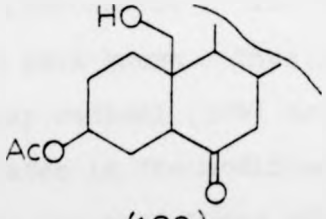
3β-acetate (181) in 38% yield. Mild hydrolysis of this compound gave a more direct synthesis of the known[20] 3β,6β,19-trihydroxysteroid (182).



(181) R = OAc

(182) R = H

Jones' oxidation followed by zinc and ammonium acetate treatment of the product mixture obtained from irradiation of the 6β-nitrite (27) in the presence of oxygen afforded 3β-acetoxy-19-hydroxycholestan-6-one (183) in 35% overall yield. This reaction sequence represents a method for the selective oxidation of a secondary alcohol in the presence of a primary alcohol.



(183)

In light of our interest in the mechanism of the Barton reaction, several experiments were carried out

in an attempt to elucidate the mechanism of nitrate formation in the modified Barton reaction. Since Chow[201] has claimed to have detected the photooxidation of the 10-nitroso menthol compound (166) to the corresponding nitrate (167), it was of interest to see whether a similar oxidation could be observed with steroidal nitroso compounds. The nitroso dimer (121) therefore was dissolved in methanol and irradiated using "black-light" at 18° in the presence of oxygen. No evidence was found for the formation of the 19-nitrate (179) and isomerisation to the corresponding 19-oxime (117) was observed to be rapid (< 10 secs) and clean.

Attempts to implicate the mechanism suggested by Barton and Boar[203] (Scheme 27) were also made. These workers had postulated the transient existence of both a peroxy radical (174) and a peroxynitrite (175) to account for the nitrate (176) formation. The use of triethylphosphite[207] for the cleavage of peroxy linkages is well known. Thus in an attempt to implicate the peroxy radical (174) or the peroxynitrite (175) as intermediates in the modified Barton reaction, the 6β-nitrite (27) was photolysed with oxygen passing through in the presence of triethylphosphite. The 19-nitrate (179) was formed as usual and none of the 19-hydroxylated product (181) which would arise from

cleavage of a peroxy linkage was observed. However, this observation may simply be a consequence of the cleavage reaction being slower than rearrangement of the peroxynitrite (175).

The 6β-nitrite (27) was irradiated at very low concentration (10^{-8}M) with oxygen passing through in the presence of tetrahydrofuran as a hydrogen donor, since it was thought that under these conditions the proposed peroxy radical (174) might abstract a hydrogen from the tetrahydrofuran to give an alkyl hydroperoxide. No evidence for hydroperoxide formation was observed on IR and NMR analysis of the product mixture from this reaction. Though this result suggests the absence of free peroxy radicals during the modified Barton reaction, it does not, however, preclude the existence of caged peroxy radicals under these conditions.

Although no evidence has been found to substantiate the mechanism suggested by Barton and Boar [203] for nitrate formation during the modified Barton reaction, the author considers that this is the most probable mechanism. The mechanism proposed for nitrate formation suggested by both Chow[201] and de Boer[202] may be discounted since it was shown that no nitrate was formed on photolysis of the nitrosodimer in the presence of oxygen. It has been shown, however, that

the modified Barton reaction, nitrite photolysis in the presence of oxygen, provides a useful synthesis of certain nitrate esters.

3.2 A NOVEL SYNTHESIS OF NITRATE ESTERS AND SOME RELATED REACTIONS

The general methods which are available for the synthesis of nitrate esters fall into two basic categories. The more commonly used of these involves the direct nitration of an alcohol with a variety of nitrating agents such as nitric acid alone;[208] a mixture of nitric and sulphuric acids;[209,210] nitric acid and acetic acid;[211] acetic acid, acetic anhydride, and nitric acid;[211] and dinitrogen pentoxide.[212] The direct nitration procedure generally affords good yields of nitrates but suffers from the drawbacks that the experimental conditions involved are often strongly oxidising or strongly acidic. The metathetical reaction of alkyl halides with silver nitrates presents an alternative synthesis of nitrates which does not require the extreme conditions often necessary for direct nitration. The metathetical reaction is found to be heterogeneous in solvents such as benzene,[213] ether,[214] nitromethane and nitrobenzene,[215] while the high solubility of silver nitrate in acetonitrile allows the reaction to be carried out in a

homogeneous medium.[216]

$$R\text{-}X + AgNO_3 \longrightarrow R\text{-}ONO_2 + AgX$$

Recently McKillop has reported[217] the application of the mercury assisted solvolysis of alkyl halides to the synthesis of a large number of nitrates. The experimental conditions used in these reactions are once again mild and with only a few exceptions yields are found to be in excess of 80%.

$$R\text{-}Br + Hg(NO_3)_n \longrightarrow R\text{-}ONO_2$$
$$n = 1 \text{ or } 2$$

Besides these general procedures, a number of less general methods exist for the synthesis of nitrate esters and these have been reviewed.[208] Since the appearance of the review further methods have been reported. For instance iodine nitrate may be generated *in situ* by the reaction of silver nitrate with iodine and this species has been reacted with steroidal olefins to afford α-iodo-nitrates.[218] Very recently, Barton[219] has utilised the reaction of N_2O_4 with amines to provide a further general route to nitrate esters.

The irradiation of nitrites in the presence of oxygen as described in Section 3.1 affords nitrate esters and Barton and Boar[203] proposed the intermediacy

of a peroxynitrite (175) in this reaction (Scheme 28). It was thought therefore that the generation of a peroxynitrite ester by a different route might afford a further synthesis of nitrate esters. Furthermore, the success of this reaction would provide good support for Barton and Boar's[203] mechanism.

Peroxynitrous acid, HOONO, is an unstable species which is known[220] to isomerise to nitric acid at room temperature with a half-life of several seconds. Although aqueous solutions of the sodium salt of peroxynitrous acid have been prepared, its organic esters are unknown. Their transient existence has, however, been forwarded by Barton and Boar[203] and by Shelton.[221] Shelton proposed the existence of t-butyl peroxynitrite to account for the complex reaction product mixture which resulted from the reaction of t-butyl hydroperoxide with nitric oxide (Scheme 29).

$$\text{t-BuOOH} + \cdot\text{NO} \longrightarrow \text{t-BuO}\cdot + \text{HONO}$$

$$\text{t-BuO}\cdot + \text{t-BuOOH} \longrightarrow \text{t-BuOH} + \text{t-BuOO}^{\bullet}$$

$$\text{t-BuOO}\cdot + \cdot\text{NO} \longrightarrow \text{t-BuOONO} + \text{t-BuONO}_2$$

Scheme 29

As long ago as 1901, Baeyer and Villiger[222] had reacted ethyl hydroperoxide with nitrous acid to afford some ethyl nitrate and it was thought that the generation of a peroxynitrite might be achieved by

the reaction of a hydroperoxide with a nitrosating agent such as nitrosyl chloride (Scheme 30). It was considered that a peroxynitrite generated in this way would undergo isomerisation to a nitrate ester as shown in Scheme 30.

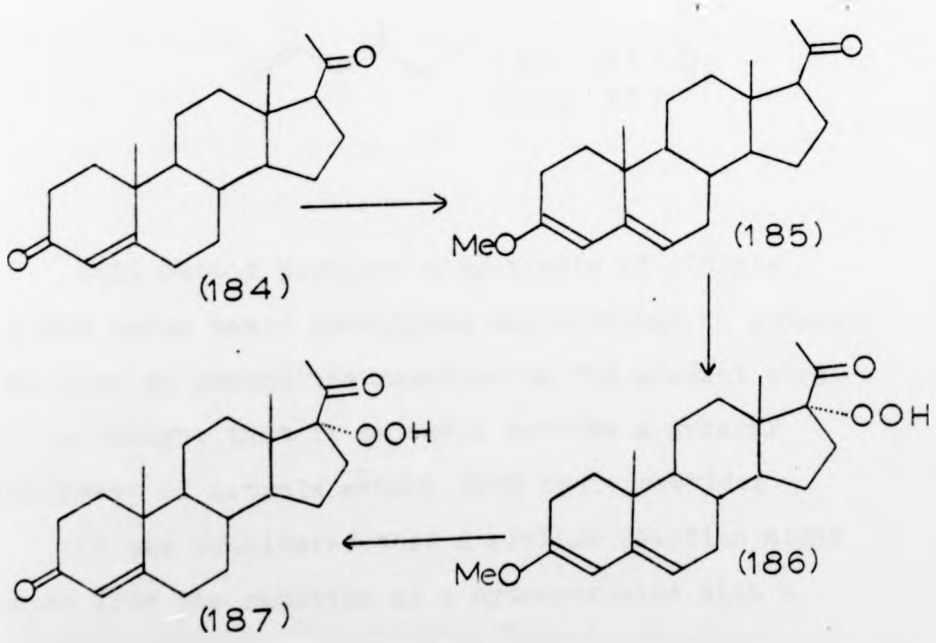
$$R\text{-}OOH + NOCl \longrightarrow R\text{-}OONO + HCl$$
$$\longrightarrow R\text{-}ONO_2$$

Scheme 30

Thus, reaction of t-butyl hydroperoxide with nitrosyl chloride in pyridine at -78° afforded t-butyl nitrate in 80% yield as a pale-yellow oil whose structure was confirmed by its spectral properties. The stability of this compound was demonstrated by the fact that its NMR spectrum showed no noticeable decomposition after several days at 33°. An attempt was made to observe the formation of an intermediate in the reaction of t-butyl hydroperoxide with nitrosyl chloride using NMR. At an NMR probe temperature of 33° the t-butyl signal at 5.13 was found to disappear instantly on the addition of a solution of NOCl in pyridine and the appearance of the signal attributable to t-butyl nitrate at δ=1.5 was immediately evident. A further experiment conducted at a probe temperature of -40° resulted, however, in the immediate precipitation of pyridinium hydrochloride and collapse of the

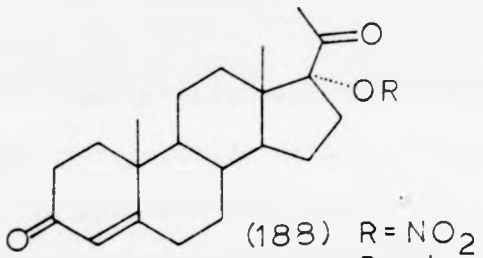
NMR signal. As a result of the synthesis of t-butyl nitrate by the reaction of t-butyl hydroperoxide with nitrosyl chloride it was considered that this reaction might provide a synthesis of certain steroidal nitrates.

Thus, 17α-hydroperoxyprogesterone (187) was prepared by Barton's method[223] which involves protection of the A ring enone of progesterone (184) as the enol ether (185), reaction of the enol ether (185) with oxygen and potassium t-butoxide to give the 17α-hydroperoxy enol ether (186), and regeneration of the A ring enone by hydrolysis of this 17α-hydroperoxy enol ether (186) with acid (Scheme 31).



Scheme 31

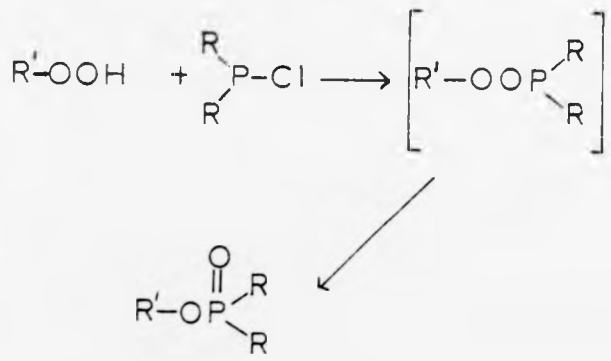
17α-Hydroperoxyprogesterone (187), prepared in this way, was reacted with excess nitrosyl chloride at -78° in pyridine and 17α-nitro-oxyprogesterone (188) was isolated in 71% yield. The direct nitration of 17α-hydroxyprogesterone (189) (itself prepared from 17α-hydroperoxyprogesterone (187)) has been reported[224] to proceed in only moderate yield and the hydroperoxide reaction therefore provides an improved synthesis of 17α-nitro-oxyprogesterone (188).



(188) R = NO_2
(189) R = H

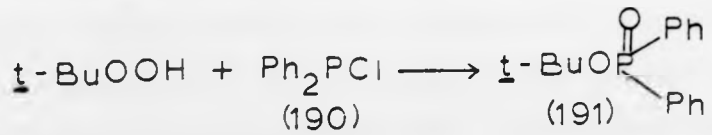
This method provides a synthesis of nitrate esters under basic conditions and although no attempt was made to extend the reaction in the present work, it is thought that it may well provide a general synthesis of nitrate esters from hydroperoxides.

It was considered that a similar reaction might arise from the reaction of a hydroperoxide with a disubstituted halophosphine (R_2PX) (Scheme 32) to afford a synthesis of phosphinate esters.



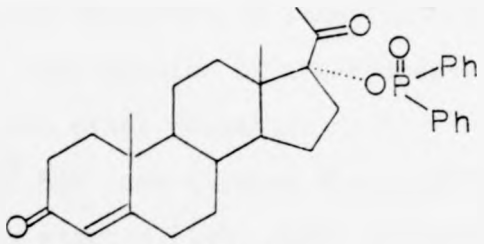
Scheme 32

Sosnovsky[225] has in fact reported that the reaction of t-butylhydroperoxide with chlorodiphenylphosphine (190) in pyridine afforded t-butyl-diphenylphosphinate (191), and it was thought that a similar reaction of 17α-hydroperoxyprogesterone (187) might afford a new type of steroidal ester.



Thus, 17α-hydroperoxyprogesterone (187) was reacted with chlorodiphenylphosphine (190) in the presence of pyridine and the novel ester, progesterone

17α-diphenylphosphinate (192) was isolated in 66% yield.



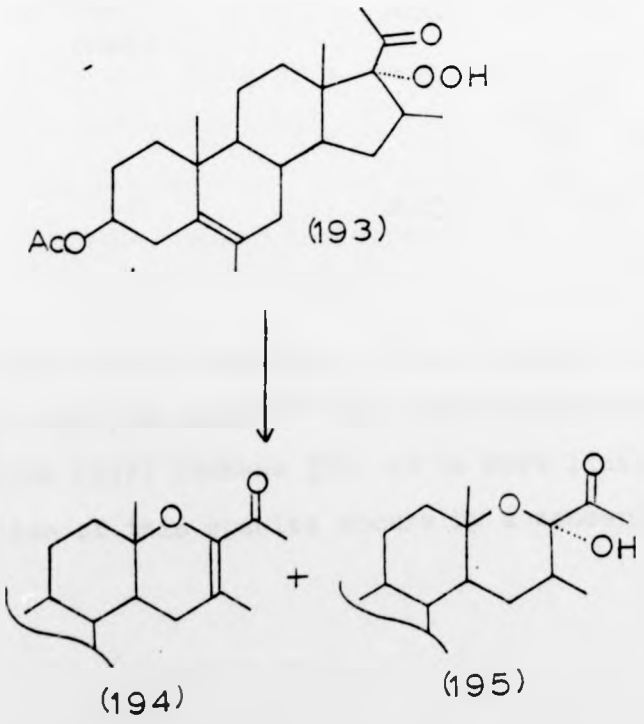
(192)

That the compound isolated in this case was in fact the phosphinate and not a "peroxyphosphine" was ascertained chemically as follows. The suspected phosphinate (192) was treated with triethylphosphite which, as has been described previously,[207] will cleave peroxy bonds to give the corresponding alcohol, and in this case no reaction was observed. Under the same conditions, however, 17α-hydroperoxyprogesterone (187) was rapidly and cleanly cleaved to 17α-hydroxyprogesterone (189). On this basis, combined with the spectral and microanalytical data, it was concluded that this compound was indeed the 17α-diphenylphosphinate (192).

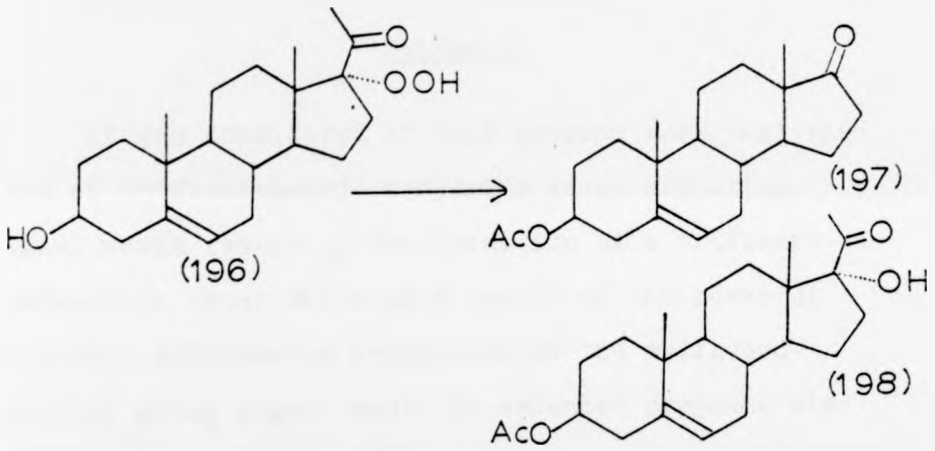
In the preceding reactions of 17α-hydroperoxyprogesterone (187) it had been found that the "peroxynitrite" had achieved stability by rearrangement to give the

corresponding nitrate (188), and the "peroxyphosphine" had achieved stability by rearrangement and valence expansion to give the corresponding phosphinate (192). It was considered therefore of some further interest to investigate the reaction of 17α-hydroperoxyprogesterone (187) with other reagents.

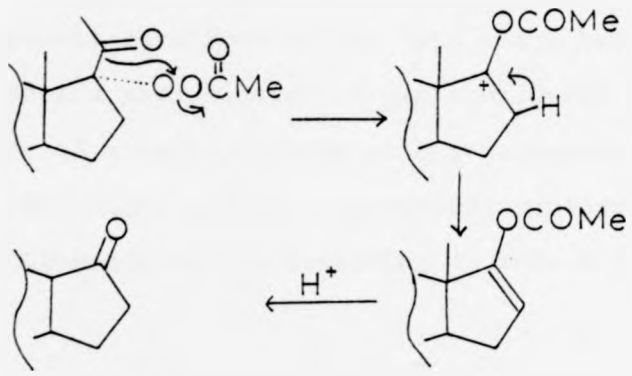
Gardner[226] has investigated the reaction of the 17α-hydroperoxy steroid (193) under acetylating conditions and has isolated the D-homo products (194) and (195), the formation of which was ascribed to a process similar to the Criegee[227] rearrangement.



It was found in this case that the distribution and nature of the products of this reaction were dependent on the substituent at the 16-position and that acetylation of the 17α-hydroperoxide (196) gave two products in poor yield, the 17α-hydroxide (198) and the 17-ketone (197) resulting from loss of the pregnane side-chain.

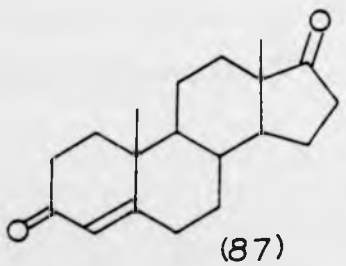


Although the existence of an oxonium ion intermediate was postulated[226] for the formation of the 17-ketone (197) (Scheme 33), it is more likely that formation of this species occurs by a concerted process.



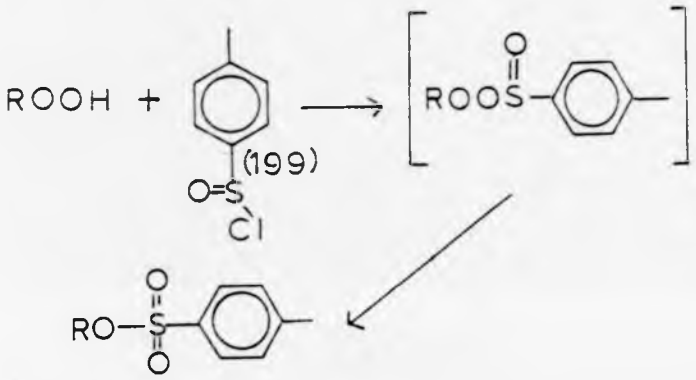
Scheme 33

It was considered in this present work that the use of trifluoroacetic anhydride as an acylating agent would result in the formation of a trifluoroperacetate ester which as a result of the powerful electron withdrawing properties of the trifluoroacetoxy group might result in enhanced pregnane side-chain cleavage. Thus 17α-hydroperoxyprogesterone (187) was treated with trifluoroacetic anhydride in pyridine and the 3,17-dione (87) isolated in 59% yield. This method therefore provides an additional method of achieving degradation of the pregnane side-chain.[3]



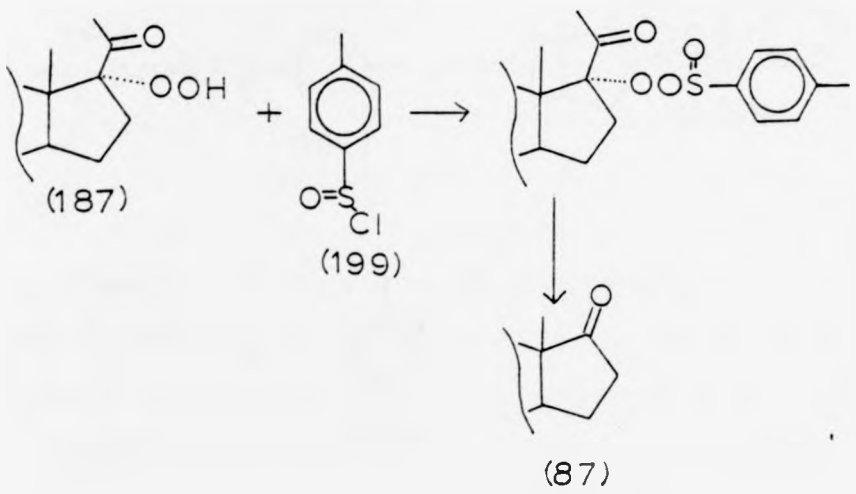
(87)

Finally, in an attempt to provide a further example of rearrangement reactions of the type which had afforded nitrates and phosphinates it was considered that the reaction of a hydroperoxide with p-toluenesulphinyl chloride (199) might afford a convenient synthesis of p-toluenesulphonate esters according to Scheme 34.



Scheme 34

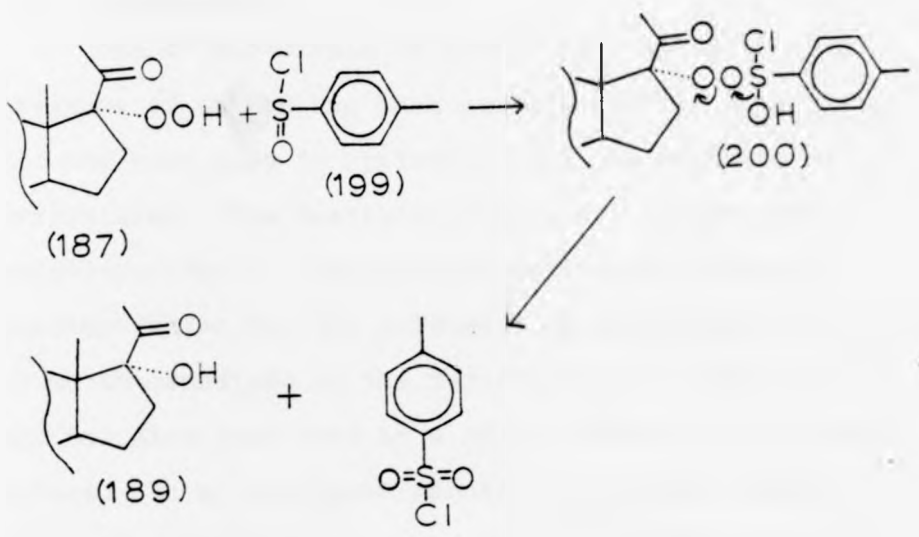
Thus, 17α-hydroperoxyprogesterone (187) was reacted with p-toluenesulphinyl chloride (199) in pyridine solution. The product mixture was complex but contained the 3,17-dione (87) and a compound believed to be 17α-hydroxyprogesterone (189). The former is considered to occur by way of a mechanism similar to that described for the reaction of the acetylating agents (Scheme 35).[226]



(187) (199) (87)

Scheme 35

17α-Hydroxyprogesterone (189) is considered to arise as a result of the attack of sulphur on the hydroperoxide (187) and decomposition of the intermediate (200) to give the 17α-alcohol (189) and p-toluenesulphonyl chloride (Scheme 36).



Scheme 36

3.3 CONCLUSIONS

Use of photolysis of steroidal nitrites in the presence of oxygen has been extended to the 6β-nitrites and has been used to synthesis some new cholesterol derivatives. The reaction of nitrosyl chloride with hydroperoxides to form nitrate esters has provided substantiation for the existence of a peroxynitrite as an intermediate in the modified Barton reaction and has also been used as a novel synthesis of nitrate esters. In an analogous manner, a steroidal phosphinate ester could be prepared by the reaction of a hydroperoxide with a chlorophosphine under basic conditions. The reaction of a sulphinyl chloride with a hydroperoxide failed to give an analogous synthesis of sulphonate esters but the reaction of a 17α-hydroperoxide with trifluoroacetic anhydride provided an efficient means of degrading the pregnane side-chain.

CHAPTER 4

Experimental

EXPERIMENTAL DIRECTIONS

Microanalyses were determined by the staff at Imperial College of Science and Technology, London. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured at room temperature using a Rudolph Photoelectric Polarimeter Model 70. Mass spectra (MS) were obtained with an Associated Electrical Industries (AEI) M59 high resolution mass spectrometer at Imperial College of Science and Technology, London. Infrared spectra (IR) were recorded on a Perkin-Elmer model 137 "Infracord" spectrophotometer. Peak intensities are denoted by s=strong, m=medium, and w=weak. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 instrument using deuterated solvents with 1% tetramethylsilane (TMS) added as an internal reference. Polysol-D refers to a d_6-dimethylsulphoxide based NMR solvent marketed by Stohler Isotopes and Chemicals, Waltham, Massachusetts, USA. Spectra are described as follows: ^{1}H-NMR (Solvent) δ-values in ppm multiplicity (coupling constants in Hz), number of protons (assignment). The multiplicity of the signals is expressed by the following symbols: s = singlet, d = doublet, and m = multiplet. All δ-values are related to tetramethylsilane (δ = 0) as an internal standard. Ultraviolet (UV) absorption spectra were

measured using a Carey model 11 ultraviolet spectrophotometer. The absorption maxima were recorded in nanometers (nm). High pressure liquid chromatography (HPLC) separations were performed using a Waters Associates ALC 201 unit equipped with a differential refractometer detector. Throughout this work, 2 linked 2 ft x 3/8" stainless steel columns packed with "Porasil A" were used with a solvent flow-rate of 4 ml min^{-1}. Gas liquid chromatography (GLC) was carried out with a Perkin-Elmer model 811 instrument equipped with a flame ionisation detector using nitrogen as a carrier gas. Thin layer chromatography (TLC) was carried out on silica gel GF 254 (E.M. Laboratories Inc., New York, USA) coated plates. The chromatograms were developed in solvent mixtures of appropriate polarity and were visualised by charring with concentrated sulphuric acid. Preparative TLC was performed on Analtech pre-coated preparative silica gel GF (1 mm thick) plates. Where necessary, commercial solvents were purified and/or dried using standard techniques. Purified chloroform refers to chloroform chromatographed rapidly through neutral-grade alumina and distilled from phosphorus pentoxide under an argon atmosphere. The medium-pressure Hanovia lamp is a mercury medium-pressure arc supplied by Hanovia Chemical and Manufacturing Co, USA, and photolyses

using this lamp were carried out in a medium scale photochemical reactor as illustrated by Murov.[194] "Black-light" irradiations were carried out using 2x4 watt General Electric "black-lights" in a small-scale photochemical apparatus supplied by Bradford Scientific Co., USA. Tungsten lamp refers to a 150 watt "Photoflood" lamp. Jones' reagent[164] is a solution of chromic acid and sulphuric acid in water. "Hi-flo" is a filtering aid marketed by Fisher Scientific Inc., USA.

3β-Acetoxy-5α-bromo-6β-hydroxycholestane (111)

To a solution of cholesteryl 3β-acetate (110) (20g, 0.04 mol) in dioxane (160ml) was added perchloric acid (10ml, 0.28M). The solution was stirred, in the dark, and N-bromoacetamide (17g, 0.12 mol) was added in four portions over a period of 30 min. Stirring was continued for a further 30 min, the solution was cooled to 0° and diluted with water. Extraction with methylene chloride (800ml) gave a solution which was washed successively with water, saturated $NaHCO_3$ solution, water, saturated NaCl solution, dried over Na_2SO_4, and concentrated. Crystallisation from methylene chloride gave 3β-acetoxy-5α-bromo-6β-hydroxycholestane (111) (14.7g, 65%) as colourless crystals.

m.p. = 175-177° (lit:[151] 177-179°)

^{1}H-NMR ($CDCl_3$) δ = 0.77s, (H_3-C18); 0.85d (J = 8Hz), (H_3-C26 and H_3-C27); 1.38s, (H_3-C19); 2.05s, (CH_3CO_2-C3); 4.16s, 1pr, (H-C6); 4.4-5.2m, 1pr, (H-C3).

OPTICAL ROTATION $[\alpha]_D$-33° (C 0.9 in $CHCl_3$)
(lit:[151] $[\alpha]_D$-34° C 1.0 in $CHCl_3$)

Chromous acetate

Chromium metal dust (9g, 0.17 mol) was dissolved in 6M HCl (50ml) through which carbon dioxide was passing. The solution was cooled to 0° and a solution

of sodium acetate (50g, 0.6 mol, in 100ml of deoxygenated water) was added, and stirring was continued for a further 10 min. Chromous acetate which appeared as a deep red precipitate was filtered under argon and washed successively with deoxygenated water, ethanol, and ether.

Yield = 12g (41%)

3β-Acetoxy-6β-hydroxycholestane (115)

To a solution of 3β-acetoxy-5α-bromo-6β-hydroxycholestane (111) (3.8g, 7 mmol) in tetrahydrofuran (20ml) through which carbon dioxide was passing was added 2-mercaptoethanol (2ml, 25 mmol). A solution of chromous acetate (5g, 40 mmol) in dimethylsulphoxide (50ml) was added and the mixture was stirred at room temperature for 3h. The solution was diluted with water, stirred for a further 15 min and the precipitate which formed was filtered and washed well with water. Crystallisation from methanol gave 3β-acetoxy-6β-hydroxycholestane (115) (2.6g, 80%) as colourless crystals.

m.p. = 148-150° (lit:[20] 141-142°)

^{1}H-NMR ($CDCl_3$) δ = 0.65s, (H_3-C18); 0.83d (J = 8Hz), (H_3-C26 and H_3-C27); 2.05s, (CH_3CO_2-C3); 3.8s, 1pr, (H-C6); 4.42-5.12m, 1pr, (H-C3).

OPTICAL ROTATION $[\alpha]_D$-6° (C 0.8 in $CHCl_3$)

(lit:[20] $[\alpha]_D$ = -6° C 0.8 in $CHCl_3$)

3β-Acetoxycholestan-6-one (116)

Jones' reagent (4ml) was added to a solution of 3β-acetoxy-6β-hydroxycholestane (115) (1g, 2 mmol) in acetone (20ml) and the solution was stirred for 10 min. Ethyl acetate (200ml) was added and stirring was continued for a further 10 min. The solution was diluted with water, filtered through "Hi-flo," and the ethyl acetate phase was washed successively with water, saturated $NaHCO_3$ solution, water, saturated NaCl solution and dried over Na_2SO_4 and concentrated. Crystallisation from methanol afforded 3β-acetoxy-cholestan-6-one (115) (730mg, 73%) as colourless plates.

	m.p. = 128-129° (lit:[228] 128-129°)
^{1}H-NMR ($CDCl_3$)	δ = 0.75s, (H_3-C18); 0.79s, (H_3-C19); 0.86d (J = 8Hz), (H_3-C26 and H_3-C27); 2.01s, (CH_3CO_2-C3); 4.20-5.00m, (H-C3).
IR (KBr)	ν_{max} = 3000s, 1720s, and 1710s, cm^{-1}
OPTICAL ROTATION	$[\alpha]_D$-15° (C 0.5 in $CHCl_3$)
	(lit:[228] $[\alpha]_D$-14 C 1.0 in $CHCl_3$)

3β-Acetoxy-6β-nitroso-oxycholestane (27)

Nitrosyl chloride was passed through a solution of 3β-acetoxy-6β-hydroxycholestane (115) (637mg, 1 mmol)

in dry pyridine (10ml) at 0° until a permanent brown colour appeared. The solution was stirred for 10 min, diluted with water, and the white precipitate which appeared was filtered and washed well with water. The precipitate was dissolved in methylene chloride and the solution dried over Na_2SO_4 and concentrated. Crystallisation from methanol/methylene chloride afforded 3β-acetoxy-6β-nitroso-oxycholestane (27) (640mg, 90%) as colourless crystals.

	m.p. = 151-153° (lit:[20] 152-153°)
^{1}H-NMR ($CDCl_3$)	δ = 0.68, (H_3-C18); 0.83d (J = 8Hz), (H_3-C26 and H_3-C27); 0.95s, (H_3-C19); 2.01m, 1pr, (CH_2CO_2-C3); 5.45s, 1pr, (H-C6).
IR (KBr)	ν_{max} = 3000s, 1720s, and 1640s (ONO) cm^{-1}.
UV (CH_2Cl_2)	λ_{max} = 334 nm (ϵ = 18), 345 nm (ϵ = 25), 357 nm (ϵ = 33), 371 nm (ϵ = 34), and 385 nm (ϵ = 19).
OPTICAL ROTATION	$[\alpha]_D$-31° (C 0.7 in $CHCl_3$) (lit:[20] $[\alpha]_D$-31° C 0.56)

Preliminary photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (900mg, 1.9 mmol) in toluene (200ml) to which

pyridine (1ml) had been added was photolysed for 3h with ice cooling and with argon passing through the solution using a medium-pressure Hanovia lamp. TLC at this time indicated the absence of starting material. The solution was concentrated, redissolved in propan-2-ol, refluxed overnight and concentrated to afford a yellow oil. This yellow oil was separated using HPLC (30% acetonitrile/benzene) into a polar and less polar fraction. The polar fraction crystallised on concentration and the less polar fraction was separated into two crystalline components using HPLC (10% ethyl acetate/benzene). The polar compound was recrystallised from methanol and water to give 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (477mg, 53%) as colourless crystals.

m.p. = 180-182° (lit:[20] 180-181°)

^{1}H-NMR (Acetone-d_6) δ = 0.62s, (H_3-C18); 0.70d (J = 8Hz), (H_3-C26 and H_3-C27); 1.88s, (CH_3CO_2-C3); 3.63-4.00m, 1pr, (H-C6); 4.08-5.00m, 1pr, (H-C3); 7.95s, 1pr, (HC=N-C19).

IR (KBr) ν_{max} = 3300s, 3000s, 1660m (C=NOH), and 1240s, cm^{-1}.

OPTICAL ROTATION $[\alpha]_D$ = -16° (C 0.5 in $CHCl_3$) (lit:[20] $[\alpha]_D$ -17° C 0.71 in $CHCl_3$).

The two crystalline components of the less polar fraction were crystallised from methanol to afford 3β-acetoxy-6β-hydroxycholestane (115) (150mg, 18%) which was characterised by TLC, IR, and NMR comparison with an authentic sample and 3β-acetoxy-cholestan-6-one (116) (175mg, 21%) which was also characterised by comparison with an authentic sample.

Photolyses at different concentrations

Solutions of 3β-acetoxy-6β-nitroso-oxycholestane (27) in toluene (20ml) containing pyridine (ca. 200µl) were photolysed in a small-scale photolysis apparatus using "black-light." After 2h photolysis, the solutions were concentrated and HPLC (20% acetonitrile/benzene) was used to separate 3β-acetoxy-6β-hydroxy-19-oximino-cholestane (117) which was characterised by NMR, IR, and TLC comparison with an authentic sample. After drying in vacuo, the following amounts of the oxime (117) were obtained.

6β-Nitrite (27) concentration	19-Oxime (117) recovered
950mg (0.1M)	387mg (41%)
470mg (0.05M)	270mg (58%)
380mg (0.04M)	247mg (65%)
95mg (0.01M)	49mg (52%)

TLC of the 0.1M photolysis mixture showed the

presence of a further less-polar product and HPLC (10% ethyl acetate/benzene) was used to isolate 3β-acetoxy-6β,19-epoxycholestane (29) (200mg, 22%) which crystallised from methanol as colourless plates.

	m.p. = 110-111° (lit:[38] 105-110°)
^{1}H-NMR ($CDCl_3$)	δ = 0.75s, (H_3-C18); 0.95d (J = 8Hz), (H_3-C26 and H_3-C27); 2.0s, (CH_3CO_2-C3); 3.75s, 2pr, (H_2-C19); 3.95d (J = 5Hz), 1pr, (H-C6); 4.2-5.2m, 1pr, (H-C3).
IR (KBr)	ν_{max} = 3000s, 1725s, 1460m, 1230s, and 1040s (C-O-C) cm^{-1}.
OPTICAL ROTATION	$[\alpha]_D$+21° (C 0.8 in $CHCl_3$)

Solubility of nitric oxide in chlorobenzene

Nitric oxide was passed through chlorobenzene for 5 min at room temperature and the resulting solution was titrated with an aqueous solution of potassium permanganate (1.2027g in 50ml, 0.152M) until a permanent pink colour was achieved (7ml).

The solubility of nitric oxide in chlorobenzene was calculated according to the equation,[153]

$$KMnO_4 + NO \longrightarrow KNO_3 + MnO_2,$$

and found to be 1.6g l^{-1} (0.05M).

Photolysis in the presence of nitric oxide

1. To a solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (250mg, 0.5 mmol) in chlorobenzene (110ml) was added a nitric oxide saturated solution of chlorobenzene (10ml) (0.5 mmol of nitric oxide). The solution was photolysed for 2h using a medium-pressure Hanovia lamp at which time TLC indicated the continued presence of starting material. Concentration of the photolysis solution gave a yellow oil from which 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (27mg, 11%) was separated using HPLC (20% acetonitrile/benzene) along with a less polar fraction. This fraction was concentrated and using HPLC (10% ethyl acetate/benzene) 3β-acetoxy-6β,19-epoxycholestane (29) (59mg, 25%) was isolated. Both these compounds were characterised by comparisons with authentic samples.

2. A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (65mg, 0.13 mmol) in purified chloroform (15ml) with diisopropylamine (ca. 200µl) added was photolysed using "black-light" for 110 min with nitric oxide passing through the solution. TLC at this time showed the continued presence of 3β-acetoxy-6β-nitroso-oxycholestane (27). No 3β-acetoxy-6β-hydroxycholestane (115) could be detected by TLC. Concentration and resolution of the product mixture using HPLC (15% ethyl acetate/benzene) gave 3β-acetoxycholestan-6-one

(116) (11mg, 18%) and 3β-acetoxy-6β,19-epoxycholestane (29) (37mg, 61%) both of which were characterised by comparison with authentic samples. No 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) could be isolated from this experiment.

Attempted reaction of 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) with nitric oxide

A solution of 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (50mg, 0.1 mmol) in chlorobenzene (10ml) with t-butylamine (ca. 100µl) added was treated with nitric oxide in the dark. TLC indicated no reaction after 10 min. This solution was irradiated using "black-light" with nitric oxide passing through it. TLC indicated no reaction after 10 min and 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) was recovered on concentration.

The dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (121)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (150mg, 0.3 mmol) in hexane (20ml) with t-butylamine (ca. 200µl) added was photolysed for 15 min using "black-light." The white precipitate which appeared was filtered off and washed with cold toluene to give the dimer of 3β-acetoxy-6β-hydroxy-19-nitroso-

cholestane (121) (54mg, 36%).

m.p. = 176-179° (lit:[20] 180-181°)

IR (KBr) ν_{max} = 3000s, 1740s, and 1180s, cm^{-1}.

UV (MeOH) λ_{max} = 296 nm (ϵ = 1000)

Since the nitrosodimer (119) was only sparingly soluble in common solvents, no ^{1}H-NMR spectrum could be obtained and the UV extinction coefficient may be only an approximate value.

Reactions of the dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (121) with nitric oxide

Nitric oxide gas was passed through a slurry of the dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (121) (10mg, 0.02 mmol) in methanol (5ml) with t-butylamine added (ca. 100µl). After 15 min, TLC comparison with an authentic sample indicated the presence of a little 3β-acetoxy-6β,19-epoxycholestane (29). The reaction was repeated with nitric oxide passing through a solution of the dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (121) (50mg, 0.1 mmol) in methanol (15ml) with t-butylamine added (ca. 100µl) and with "black-light" radiation. TLC indicated the rapid appearance (< 5 min) of 3β-acetoxy-6β,19-epoxycholestane (29). Preparative TLC (33% ethyl acetate/benzene) was used to isolate 3β-acetoxy-6β-hydroxy-19-oximino-

cholestane (117) (16mg, 23%) and 3β-acetoxy-6β,19-epoxycholestane (29) (19mg, 37%) both of which were characterised by comparison with authentic samples.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the absence of base

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) 220mg, 0.4 mmol) in chlorobenzene (200ml) was photolysed with argon passing through the solution using a medium-pressure Hanovia lamp. After 70 min irradiation, the solution was concentrated and HPLC (20% acetonitrile/benzene) was used to isolate 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (73mg, 33%), which was characterised by comparison with an authentic sample.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of pyridine

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (201mg, 0.4 mmol) in chlorobenzene (200ml) with pyridine added (1ml) was photolysed with argon passing through the solution using a medium-pressure Hanovia lamp. After 70 min irradiation, the solution was concentrated and HPLC (20% acetonitrile/benzene) was used to isolate 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (108mg, 54%) which was characterised by

comparison with an authentic sample.

Acid treatment of 3β-acetoxy-6β-nitroso-oxycholestane (27)

1. A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (50mg, 0.1 mmol) in tetrahydrofuran (10ml) was treated with aqueous HCl (4ml, 25%). After stirring for 10 min, the solution was diluted with water and the white precipitate which formed was filtered off and dissolved in methylene chloride. TLC of this solution showed it to be quite complex but comparison with authentic samples showed that it contained considerable quantities of 3β-acetoxy-6β-hydroxycholestane (115) and 3β-acetoxycholestan-6-one (116).

2. A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (50mg, 0.1 mmol) in tetrahydrofuran (10ml) with diisopropylamine added (3ml, 0.02 mol) was treated with aqueous HCl (4ml, 25%). The solution was stirred for 15 min and diluted with water. The white precipitate which appeared was filtered, washed with water and re-dissolved in methylene chloride. TLC of this solution showed no decomposition of the starting material which was recovered on drying over Na_2SO_4 and concentration.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of non-eliminating bases

Solutions of 3β-acetoxy-6β-nitroso-oxycholestane (27) (200mg, 0.4 mmol) in chlorobenzene (250ml) with 1 ml of different nitrogenous bases added were photolysed with argon passing through using a medium-pressure Hanovia lamp and after 80 min irradiation were washed successively with 10% aqueous HCl, water, NaCl, and dried over Na_2SO_4. The solutions were concentrated and resolved into a polar and a less-polar fraction using HPLC (20% acetonitrile/benzene). The less-polar fraction was further resolved using HPLC (10% ethyl acetate/benzene) to afford 3β-acetoxycholestan-6-one (116) and 3β-acetoxy-6β-hydroxycholestane (115). Yields are expressed as a percentage of the total material recovered after photolysis.

Base	% Ketone (116)	% Alcohol (115)
DBN (121)	22	17
DABCO (122)	16	14
DBU (123)	26	18
2,2,6,6-Tetramethyl-piperidine (124)	19	12

Photolyses in the presence of different amounts of base

A series of solutions of 3β-acetoxy-6β-nitroso-oxycholestane (27) (60mg, 0.13 mmol) in 10ml mixtures of

methylene chloride/t-butylamine was prepared (50% t-butylamine, 400 equivalents; 25%, 200 equivalents; 10%, 80 equivalents; 5%, 40 equivalents; and 1%, 8 equivalents). The solutions were photolysed with argon passing through for 60 min using "black-light" after which time they were concentrated then redissolved in acetone-d_6 (2ml). TLC and NMR comparison of these solutions showed that at concentrations of up to 80 equivalents of t-butylamine the amounts of 3β-acetoxy-6β-hydroxycholestane (115), 3β-acetoxycholestan-6-one (116), and 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) did not vary noticeably. In the presence of 200 and 400 equivalents of t-butylamine, although the 6-ketone (116) remained the same, the amount of the 6β-alcohol (115) increased considerably.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) at different concentrations

The following solutions of 3β-acetoxy-6β-nitroso-oxycholestane (27) were prepared: 1.2mg in 750ml methylene chloride (3.4×10^{-6}M) (1ml t-butylamine added); 120mg in 750ml methylene chloride (3.4×10^{-4}M) (1ml t-butylamine added); 200mg in 20ml methylene chloride (2.1×10^{-2}M) (ca. 200µl t-butylamine added); 950mg in 20ml methylene chloride (0.1M) (ca. 200µl t-butylamine added). The former two solutions (3.4×10^{-6}M and

$3.4x10^{-4}$M) were photolysed for 1h using a-medium-pressure Hanovia lamp with argon passing through and the latter two ($2.1x10^{-2}$M and 0.1M) were photolysed also for 1h with argon passing through using "black-light." The three more concentrated solutions ($3.4x10^{-4}$, $2.1x10^{-2}$, $1.2x10^{-1}$M) were concentrated and separated into a polar and a less-polar fraction using HPLC (20% acetonitrile/benzene). 3β-Acetoxy-6β-hydroxycholestane (115) and 3β-acetoxycholestan-6-one (116) were isolated from the less-polar fraction using HPLC (10% ethyl acetate/benzene) in the yields shown in Table 3 (Section 2.4.4). The amounts of 3β-acetoxy-6β-hydroxycholestane (115) and 3β-acetoxy-cholestan-6-one (116) in the very dilute solution ($3.4x10^{-6}$) were estimated after concentration and redissolving in methylene chloride (2ml) by TLC comparisons with standard solutions (equivalent to yields of 12.5, 15, 17.5, and 20%).

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of triphenylphosphine

Triphenylphosphine (1.1g, 4.2 mmol) was added to a solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (110mg, 0.23 mmol) in methylene chloride (20ml). The solution was photolysed for 1h using "black-light" with argon passing through and concentrated.

Chromatography on Florisil (40g) with toluene and increasing ethyl acetate/toluene mixtures gave in order of increasing polarity, triphenylphosphine (1g), 3β-acetoxycholestan-6-one (116) (13mg), 3β-acetoxy-6β-hydroxycholestane (115) (63mg), and 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (20mg). The steroidal components were characterised by comparison with authentic samples and their yields (9, 70, 21%, respectively) were calculated on the basis of recovered steroidal material (87%).

Nitrogen analysis of a photolysis mixture

3β-Acetoxy-6β-nitroso-oxycholestane (27) (700mg, 1.4 mmol) in chlorobenzene (150 ml) was photolysed for 2h using a medium-pressure Hanovia lamp with argon passing through the solution. The solution was concentrated to afford a yellow oil, dried under high vacuum, and submitted for microanalysis.

ANALYSIS 100% nitrogen retained,
requires: 3.03%
found: 2.82%

The reaction was repeated and the non-polar fraction which showed several spots on TLC was separated using preparative TLC.

UV (MeOH) λ_{max} = 275 nm (ϵ_{max} = 12000)

Photolysis of 3β-acetoxy-6α-methyl-6β-nitroso-oxy-cholestane (127)

1. A solution of 3β-acetoxy-6α-methyl-6β-nitroso-oxycholestane (127) (100mg, 0.2 mmol) in chloroform (20ml) with t-butylamine (ca. 200µl) added was photolysed for 1h using "black-light." Concentration and resolution using HPLC (25% ethyl acetate/benzene) gave 3β-acetoxy-6α-methyl-6β-hydroxycholestane (129) (10mg, 12%) characterised by comparison with an authentic sample and 3β-acetoxy-6β-hydroxy-6α-methyl-19-oximino-cholestane (128) (86mg, 86%) which crystallised from aqueous methanol as white plates.

	m.p. = 128-129°
MICROANALYSIS	(Found, %: C, 72.2; H, 10.8; N, 2.4. $C_{20}H_{51}NO_4 \cdot \frac{1}{2}H_2O$ (498.72) requires, %: C, 72.2: H, 10.5; N, 2.8).
^{1}H-NMR ($CDCl_3$)	δ = 0.62s, (H_3-C18); 0.88d (J = 8Hz) (H_3-C26 and H_3-C27); 1.83s, (H_3-C6 Me); 2.00s, (CH_3CO_2-C3); 4.5-5.2m, 1pr, (H-C3); 7.4s, 1pr, (HC=N-C19).
IR (KBr)	ν_{max} = 3300s, 3000s, 1720s and 1660s (C=NOH) cm^{-1}.
MS	m/e 489 (M^+), 412 (M-77), 368 (M-121, base).
OPTICAL ROTATION	$[\alpha]_D$-11° (C 0.4 in $CHCl_3$).

2. 3β-Acetoxy-6α-methyl-6β-nitroso-oxycholestane (127) (100mg, 0.2 mmol) was photolysed in deuteriochloroform (20ml) as above in the absence of base. 3β-Acetoxy-6β-hydroxy-6α-methylcholestane (129) was separated using preparative TLC and crystallised from methanol. MS and IR analyses indicated no incorporation of deuterium.

Irradiation of 3β-acetoxy-6β-nitroso-oxycholestane (27) at low temperature

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (350mg, 0.7 mmol) in methylene chloride (120ml) with t-butylamine added (1ml) was photolysed at -78° using a medium-pressure Hanovia lamp. After 80 min irradiation TLC indicated only two products and chromatography on Florisil (50g) with ethyl acetate/toluene mixtures as eluent gave 3β-acetoxycholestan-6-one (116) (48mg, 15%) and 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (280mg, 80%) both of which were characterised by comparison with authentic samples. No 3β-acetoxy-6β-hydroxycholestane (115) could be isolated in this experiment.

Reactions of 3β-acetoxy-6β-nitroso-oxycholestane (27) with nitrosonium tetrafluoroborate

1. Nitrosonium tetrafluoroborate (100mg, 0.8 mmol)

was added to a solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (100mg, 0.2 mmol) in a mixture of methylene chloride and acetonitrile (1:1, 10ml). The solution was stirred at room temperature for 5 min at which time TLC indicated by comparison with an authentic sample that the 3β-acetoxy-6β-nitroso-oxycholestane (27) had been converted cleanly to 3β-acetoxycholestan-6-one (116).

2. The above experiment was repeated in the presence of t-butylamine (1ml, 9 mmol) and after 2h no decomposition of the starting 3β-acetoxy-6β-nitroso-oxycholestane (27) was observed.

Photolysis in the presence of hydroquinone

Hydroquinone (50mg, 0.4 mmol) was added to a solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (160mg, 0.3 mmol) in methylene chloride (20ml) with t-butylamine added (ca. 200μl). The solution was photolysed using "black-light" with argon passing through the solution. After 80 min irradiation, TLC indicated the absence of starting material and comparison with standard solutions showed the presence of 15-20% 3β-acetoxycholestan-6-one (116).

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of 3β-acetoxy-6β-hydroxyandrostan-17-one (109)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (130mg, 0.3 mmol) and 3β-acetoxy-6β-hydroxyandrostan-17-one (109) (125mg, 0.4 mmol) in methylene chloride (20ml) with t-butylamine added (ca. 200ul) was photolysed for 1h with argon passing through using "black-light." After 1h the solution was concentrated and chromatography of the product mixture was effected on Florisil (20g) with ethyl acetate/toluene mixtures as eluent. Elution with 3% ethyl acetate/toluene afforded a crystalline compound (20mg) with an R_f on TLC the same as 3β-acetoxy-6β-hydroxycholestane (115) and 3β-acetoxyandrostan-3,17-dione (108). Crystallisation from methanol and NMR, IR, and m.p., comparison with an authentic sample showed this to be 3β-acetoxy-6β-hydroxycholestane (115).

Irradiations under different oxygen/argon atmospheres

A gas-burette system was used to prepare gas mixtures of different oxygen/argon composition (100% oxygen, 1:1 oxygen/argon, and 100% argon). Solutions of 3β-acetoxy-6β-nitroso-oxycholestane (27) (60mg, 0.13ml) in methylene chloride (10ml) with t-butylamine added (ca. 100 μl) were degassed by a freeze/thaw/evacuate

cycle and the gas mixtures were introduced into the solutions in a sealed system. The solutions were irradiated for 1h using "black-light" and the amount of 3β-acetoxycholestan-6-one (116) was estimated by TLC comparisons with a series of standard solutions (equivalent to 10, 12.5, 15, 17.5, and 20% yield of 3β-acetoxycholestan-6-one (115)). In the three photolysis mixtures, the amount of 3β-acetoxycholestan-6-one (116) formed was estimated by the above method to be between 15 and 20%.

Detection of hyponitrous acid

1. 3β-Acetoxy-6β-nitroso-oxycholestane (27) (70mg, 0.15 mmol) in methylene chloride (12ml) was photolysed for 30 min using "black-light" with argon passing through the solution. The photolysis mixture was extracted with 0.1M NaOH (10ml) and 2ml of the NaOH extract was diluted to 25ml with 0.1M NaOH. The UV spectrum of this solution was measured.

$$\lambda_{max} = 248 \text{ nm (Absorbance = 0.62)}$$

The pH of this solution was adjusted to 6 by careful addition of HCl and the UV spectrum was measured again.

$$\lambda_{max} = 233 \text{ nm (Absorbance = 0.56)}$$

The rate of decomposition of this solution was determined

by measuring the absorbance at different times (Table 6).

233 nm Absorbance	Time (min)
0.56	0
0.50	10
0.48	20
0.24	50
0.20	120

Table 6

These values give rise to Figure 5 (Section 2.6.4).

2. 3β-Acetoxy-6β-nitroso-oxycholestane (27) (69mg, 0.15 mmol) in methylene chloride (12ml) with t-butylamine added (ca. 100µl) was photolysed for 30 min with argon passing through using "black-light." The solution was extracted with 0.1M NaOH (10ml). 2 Ml of this NaOH extract was diluted to 25ml with 0.1M NaOH and the UV spectrum of this solution was measured and found to exhibit no UV maximum at 248 nm.

3. 3β-Acetoxy-6β-nitroso-oxycholestane (27) (135mg, 0.28 mmol) was dissolved in methylene chloride (20ml) with tetramethylguanadine (133) (300mg, 3 mmol) added and photolysed for 30 min with argon passing through the solution. The solution was extracted with 0.1M NaOH (10ml), 2ml of this extract was diluted to 25ml with 0.1M NaOH and the UV spectrum of the resulting solution

was determined.

$$\lambda_{max} = 248 \text{ nm (Absorbance = 0.78)}$$

Assuming $\epsilon_{248} = 3980$ for the hyponitrite dianion,[188] then it was calculated that an absorbance of 0.78 corresponded to 16.5% yield of 3β-acetoxycholestan-6-one (116).

Sodium borohydride reduction of pregnenelone 3β-acetate (134)

A solution of sodium borohydride (3.6g, 95 mmol) in water (0.96ml) was added to a solution of pregnenelone 3β-acetate (134) (7.2g, 20 mmol) in tetrahydrofuran and the mixture was stirred overnight at room temperature. Excess sodium borohydride was destroyed by the slow addition of acetic acid (5ml) and after dilution with water (500ml) the solution was extracted with ethyl acetate (500ml). The ethyl acetate extract was washed successively with water, saturated $NaHCO_3$ solution, water, saturated NaCl, dried over Na_2SO_4, and concentrated to give a white crystalline product. A portion of this product mixture was resolved using HPLC (15% ethyl acetate/benzene) to give in a 4:1 ratio 3β-acetoxy-20β-hydroxypregn-5-ene (135) and 3β-acetoxy-20α-hydroxypregn-5-ene (136). Crystallisation of the former from acetone gave 3β-acetoxy-20β-hydroxypregn-

5-ene (135) as white crystals.

m.p. = 163-165° (lit:[229] 165-166.5°)

^{1}H-NMR ($CDCl_3$) δ = 0.76s, (H_3-C18); 1.02s, (H_3-C19); 1.12d (J = 6Hz), (H_3-C21); 2.0s (CH_3CO_2-C3); 3.5-4.0m, 1pr, (H-C20); 4.3-4.9m, 1pr, (H-C3); 5.4m, 1pr, (H-C6).

3β-Acetoxy-20α-hydroxypregn-5-ene (136) crystallised from aqueous methanol as colourless crystals.

m.p. = 138-140° (lit:[229] 143-145°)

^{1}H-NMR ($CDCl_3$) δ = 0.65s, (H_3-C18); 1.0s, (H_3-C19); 1.16d (J = 6Hz), 2.0s, (CH_3CO_2-C3) 3.5-3.9m, 1pr, (H-C20); 4.40-4.95m, 1pr, (CH_3CO_2-C3); 5.4m, 1pr, (H-C6).

Photolysis of 3β-acetoxy-20β-nitroso-oxypregn-5-ene (137)

Nitrosyl chloride gas was passed through a solution of 3β-acetoxy-20β-hydroxypregn-5-ene (135) (250mg, 0.7 mmol) in pyridine (10ml) at 0° until a permanent brown colour appeared. Dilution with ice-water gave a white precipitate which was filtered, washed with water and crystallised from methanol/methylene chloride to give 3β-acetoxy-20β-nitroso-oxypregn-5-ene (137) (240mg, 90%) as colourless plates.

5-ene (135) as white crystals.

m.p. = 163-165° (lit:[229] 165-166.5°)

^{1}H-NMR ($CDCl_3$) δ = 0.76s, (H_3-C18); 1.02s, (H_3-C19); 1.12d (J = 6Hz), (H_3-C21); 2.0s (CH_3CO_2-C3); 3.5-4.0m, 1pr, (H-C20); 4.3-4.9m, 1pr, (H-C3); 5.4m, 1pr, (H-C6).

3β-Acetoxy-20α-hydroxypregn-5-ene (136) crystallised from aqueous methanol as colourless crystals.

m.p. = 138-140° (lit:[229] 143-145°)

^{1}H-NMR ($CDCl_3$) δ = 0.65s, (H_3-C18); 1.0s, (H_3-C19); 1.16d (J = 6Hz), 2.0s, (CH_3CO_2-C3) 3.5-3.9m, 1pr, (H-C20); 4.40-4.95m, 1pr, (CH_3CO_2-C3); 5.4m, 1pr, (H-C6).

Photolysis of 3β-acetoxy-20β-nitroso-oxypregn-5-ene (137)

Nitrosyl chloride gas was passed through a solution of 3β-acetoxy-20β-hydroxypregn-5-ene (135) (250mg, 0.7 mmol) in pyridine (10ml) at 0° until a permanent brown colour appeared. Dilution with ice-water gave a white precipitate which was filtered, washed with water and crystallised from methanol/methylene chloride to give 3β-acetoxy-20β-nitroso-oxypregn-5-ene (137) (240mg, 90%) as colourless plates.

m.p. = 145-149° (decomp.)
(lit.[206] 153-154.5°)

^{1}H-NMR: δ = 0.66s (H_3-C18); 1.0s, (H_3-C19); 1.3d (J = 6Hz), (H_3-C21); 2.0s, (CH_3CO_2-C3); 4.2-5.0m, 1pr, (H-C3); 5.15-5.65m, 2pr, (H-C6 and H-C20).

IR (KBr): ν_{max} = 3000s, 1725s, and 1640s (ONO), cm^{-1}.

A solution of this 20β-nitrite (137) (140mg, 0.36 mmol) in methylene chloride (20ml) with t-butylamine added (ca. 200µl) was photolysed for 90 min with argon passing through using "black-light." The solution was concentrated and resolution using HPLC (30% ethyl acetate/benzene) gave three products, pregnenelone 3β-acetate (134) (17mg, 13%), 3β-acetoxy-20β-hydroxypregn-5-ene (135) (34mg, 26%), both of which were characterised by comparison with authentic samples, and 3β-acetoxy-20β-hydroxy-18-oximinopregn-5-ene (141) (63mg, 44%) which was crystallised from methanol as colourless crystals.

m.p. = 156-159° (lit.[230] 159-160°)

^{1}H-NMR (C_6D_6): δ = 0.86s, (H_3-C19); 1.1d (J = 6Hz), (H_3-C21), 2.0s, (CH_3CO_2-C3); 3.3-3.9m, 1pr, (H-C20); 4.2-5.0m, 1pr, (H-C3); 5.3m, 1pr, (H-C6); 7.5s, 1pr, (H-C18).

IR ($CHCl_3$) ν_{max} = 3400m, 3000s, 1725s, and 1208s, cm^{-1}.

Photolysis of 3β-acetoxy-20α-nitroso-oxypregn-5-ene (138)

3β-Acetoxy-20α-nitroso-oxypregn-5-ene (138) was prepared by the action of nitrosyl chloride on the 20α-alcohol (136) as described above. Crystallisation from methanol/methylene chloride gave the 3β-acetoxy-20α-nitroso-oxypregn-5-ene (138) as colourless crystals.

m.p. = 104-106° (lit:[206] 110-111°)

^{1}H-NMR ($CDCl_3$) δ = 0.78s, (H_3-C18); 1.03s, (H_3-C19); 1.42d (J = 6Hz) (H_3-C21); 2.03s, (CH_3CO_2-C3); 4.18-5.00m, 1pr, (H-C3); 3.1-3.4m, 2pr, (H-C6 and (H-C20).

IR ($CHCl_3$) ν_{max} = 3000s, 1730s, 1640s (ONO), and 1250s, cm^{-1}.

A solution of this 20α-nitrite (136) (139mg, 0.36 mmol) in methylene chloride (20ml) with t-butylamine added (ca. 200μl) was photolysed for 90 min with argon passing through using "black-light." A white precipitate appeared and the photolysis mixture was concentrated and refluxed overnight in propan-2-ol (10ml). Resolution of the product mixture using HPLC (30% ethyl acetate/ benzene) gave pregnenelone 3β-acetate (134) (17mg, 13%),

3β-acetoxy-20α-hydroxypregn-5-ene (136) (18mg, 14%), both of which were characterised by comparison with authentic samples and 3β-acetoxy-20α-hydroxy-18-oximino-pregn-5-ene (140) (90mg, 66%) which was crystallised from methanol as colourless needles.

	m.p. = 206-208°
ANALYSIS	(Found, %: C, 70.8; H, 8.9; N, 3.6. $C_{23}H_{34}NO_4$ (388.51) requires, %: C, 71.1; H, 8.8; N, 3.6).
^{1}H-NMR ($CDCl_3$)	δ = 0.9s, (H_3-C19); 1.15d (J = 6Hz), (H_3-C21); 2.0s, (CH_3CO_2-C3); 3.6-4.2m, 1pr, (H-C20); 4.2-5.0m, 1pr, (H-C3); 5.4m, 1pr, (H-C6); 7.46s, 1pr, (H-C18).
IR ($CHCl_3$)	ν_{max} = 3500m, 3000s, 1720s, 1640m, (C=NOH), and 1250s, cm^{-1}.
MS	m/e = 389 (M^+) and 311 (M-78, base).
OPTICAL ROTATION	$[\alpha]_D$-20° (C 0.2 in $CHCl_3$)

Irradiation of 3β-acetoxy-6β-nitroso-oxycholestane (27) with a tungsten lamp

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (80mg, 0.17 mmol) in benzene (10ml) with diisopropylamine (ca. 100µl) added was irradiated with ice-cooling and argon passing through using a tungsten lamp. TLC of the solution after 5h irradiation indicated no

decomposition of the starting 6β-nitrite (27).

Photolysis using a carbon disulphide light filter

A 10% carbon disulphide in methanol solution was prepared and its UV spectrum was measured and found to exhibit a cut-out at wavelengths less than 330 nm. With this solution as a radiation filter, 3β-acetoxy-6β-nitroso-oxycholestane (27) (270mg, 0.6 mmol) in chlorobenzene (150ml) with pyridine (1ml) added was photolysed using a medium-pressure Hanovia lamp with argon passing through. After 80 min irradiation, TLC showed the absence of starting material and concentration gave a yellow oil. Resolution of this oil using HPLC (20% acetonitrile/benzene) afforded 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (161mg, 60%) which was characterised by comparison with an authentic sample.

Rates of photolysis in aromatic and non-aromatic solvents

The rate of photolysis was determined by measuring the rate of disappearance of the 383 nm absorption present in the UV spectrum of 3β-acetoxy-6β-nitroso-oxycholestane (27).

3β-Acetoxy-6β-nitroso-oxycholestane (27) (140mg, 0.3 mmol) in toluene (20ml) with diisopropylamine (ca. 200µl) added was photolysed with argon passing through

the solution using "black-light." The UV absorbance at 383 nm was measured at various times and the values are given in Figure 8 (Section 2.7).

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (140mg, 0.3 mmol) in purified chloroform (20ml) with diisopropylamine (ca. 200µl) added was photolysed using "black-light" and the rate of reaction was determined using UV as described above.

Photolysis in different solvents

3β-Acetoxy-6β-nitroso-oxycholestane (27) (160mg, 0.3 mmol) was photolysed in a variety of solvents (20ml) with diisopropylamine (ca. 200µl) or t-butylamine (ca. 200µl) added, argon passing through the solution, and using "black-light." After 60 min irradiation, the solutions were concentrated and 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117), characterised by comparison with an authentic sample, was separated using HPLC (20% acetonitrile/benzene) in the yields shown in Table 5 (Section 2.7).

Preparation of cyclopentyl nitrite (88)

Cyclopentanol (30ml, 0.3 mmol) was added to a solution of sodium nitrite (37.9g, 0.5 mol) in water (150ml) and the mixture stirred vigorously at 0^{o}. Sulphuric acid (66ml, 35%) was added over a period of

2h and the green oil which separated was decanted off, washed successively with water, saturated $NaHCO_3$ solution, water, saturated NaCl solution, and dried over Na_2SO_4. Distillation at atmospheric pressure gave cyclopentyl nitrite (88) as a pale yellow oil.

	b.p. = 113-115° (lit:[231] 102-105°)
^{1}H-NMR ($CDCl_3$)	δ = 0.8-2.6m, 8pr, and 5.8m, 1pr (H-Cl).
IR ($CDCl_3$)	ν_{max} = 3000s, 1630s (ONO), and 1365s, cm^{-1}.

Photolysis of cyclopentyl nitrite (88)

A solution of cyclopentyl nitrite (88) (150mg, 1.3 mmol) in purified chloroform (20ml) with diisopropylamine added (ca. 200µl) was photolysed with argon passing through the solution for 80 min using "black-light." Concentration afforded a yellow oil the NMR ($CDCl_3$) of which showed a resonance at δ = 9.8 (HCO-Cl) and the IR ($CHCl_3$) of which showed a strong absorbance at 1730 (HC=O) cm^{-1}. This yellow oil was dissolved in a mixture of water (1.2ml), 10% aqueous NaOH (1ml) and ethanol (1ml). Hydroxylamine hydrochloride (71mg, 1 mmol) was added and the solution was refluxed under argon for 30 min. Ethanol was removed in vacuo and 1,5-dialdoximinopentane (149) (60mg, 35%) crystallised as needles on cooling.

m.p. = 170-171° (lit:[143] 171°)

IR (KBr) ν_{max} = 3300m, 3000s, and 1610m (C=NOH), cm^{-1}.

No NMR of this compound was measured since it was virtually insoluble in most common solvents.

GLC studies of cyclopentyl nitrite (88) photolyses

The rates of photolysis in these experiments were determined by GLC monitoring of cyclopentyl nitrite (88) using a 6 ft, 11% QV-17 and 2F-1 column at an oven temperature of 40° and with a flow rate of 30 ml min^{-1}. Using this column cyclopentyl nitrite (88) had a retention time of 23 seconds and cyclopentanone 43 seconds. All photolyses were carried out using "black-light" in methylene chloride with argon passing through and samples were taken for GLC analysis as the reaction proceeded. The points shown in Figures 9 to 12 represent the cyclopentyl nitrite (88) peak-height at time (T) as a percentage of the initial (T=0) cyclopentyl nitrite (88) peak-height. No cyclopentanone was detected by GLC and in all cases NMR ($CDCl_3$) showed the presence of the resonance at δ = 9.8. External radiation filters were present as a 1mm solution in sym-tetrachloroethane (12ml).

1. Cyclopentyl nitrite (88) (200mg, 1.7 mmol) in methylene chloride (20ml) with t-butylamine added

(ca. 200µl) was photolysed as described above and monitored by GLC (Figure 9).

2. Cyclopentyl nitrite (88) (200mg, 1.7 mmol) in methylene chloride (20ml) with Michler's ketone (150) (100mg, 0.4 mmol) added was photolysed as described above and monitored by GLC (Figure 9).

3. Cyclopentyl nitrite (88) (120mg, 1 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200 l) and nitrobenzene (250mg, 1.9 mmol) added was photolysed as above and monitored by GLC (Figure 10).

4. Cyclopentyl nitrite (88) (120mg, 1 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200µl), nitrobenzene (250mg, 2.0 mmol), and Michler's ketone (150) (85mg, 0.3 mmol) added was photolysed as described above and monitored by GLC (Figure 10).

5. Cyclopentyl nitrite (88) (56mg, 0.5 mmol) in methylene chloride (8ml) with t-butylamine added (ca. 100µl) was photolysed with an external nitrobenzene filter (300mg, 2.4 mmol) as described above and monitored by GLC (Figure 11).

6. Cyclopentyl nitrite (88) (45mg, 0.5 mmol) in methylene chloride (8ml) with t-butylamine added (ca. 100µl) was photolysed with an external nitrobenzene filter (1.5mg, 2 mmol) and monitored by GLC. After 32 min irradiation, Michler's ketone (150) (50mg, 0.2 mmol) was added and the irradiation was continued with GLC

monitoring. After a further 30 min irradiation, more Michler's ketone (150) (100mg, 0.4 mmol) was added and photolysis and GLC monitoring continued (Figure 11).

7. Cyclopentyl nitrite (88) (212mg, 0.25 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200µl) and 9-anthraldehyde (151) (50mg, 0.25 mmol) was photolysed as described above. GLC indicated no reaction after 30 min irradiation.

8. Cyclopentyl nitrite (88) (200mg, 1.7 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200µl) and benzophenone (350mg, 2 mmol) added was photolysed as described above and monitored by GLC (Figure 12).

9. Cyclopentyl nitrite (88) (200mg, 1.7 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200µl) added was photolysed with an external benzophenone filter (700mg, 3.8 mmol) as described above and monitored by GLC (Figure 12).

10. Cyclopentyl nitrite (88) (200mg, 1.7 mmol) in methylene chloride (20ml) with t-butylamine (ca. 200µl), benzophenone (350mg, 1.9 mmol), and trans-1,3-pentadiene (152) (200mg, 3 mmol) added was photolysed as described above. GLC monitoring showed no reaction after 1h irradiation.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of Michler's ketone (150)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (100mg, 0.2 mmol) in methylene chloride (15 ml) with Michler's ketone (150) (60mg, 0.2 mmol) added was photolysed with argon passing through the solution using "black-light." TLC after 80 min indicated the absence of starting material and comparison with standard solutions showed the presence of 3β-acetoxycholestan-6-one (116) (15%), 3β-acetoxy-6β-hydroxy-cholestane (115) (50%), and 3β-acetoxy-6β-hydroxy-19-oximino-cholestane (117).

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of oxygen

An ice-cooled solution of 3β-acetoxy-6-nitroso-oxycholestane (27) (700mg, 1.5 mmol) in toluene (450ml) containing triethylamine (1ml) through which oxygen was passing was photolysed using a medium-pressure Hanovia lamp. After irradiation for 75 min, TLC indicated the absence of starting material. The solution was concentrated and the resulting yellow oil was chromatographed on a short Florisil column (10g) using 10% ethyl acetate/benzene as eluent. Concentration, purification by preparative TLC, and crystallisation from methanol afforded 3β-acetoxy-6β,19-epoxycholestane (29) (250mg,

36%) as colourless crystals.

	m.p. = 110-111° (lit:[38] 105-110°)
ANALYSIS	(Found, %: C, 77.7; H, 11.2. $C_{29}H_{48}O_3$ (444.67) requires, %: C, 77.5; H, 11.1)
^{1}H-NMR ($CDCl_3$)	δ = 0.75s, (H_3-C18); 0.95d (J = 8Hz), (H_3-C26 and H_3-C27); 2.0s, (CH_3CO_2-C3); 3.75s, 2pr, (H_2-C19); 3.95d (J = 5Hz), 1pr, (H-C6); 4.2-5.2m, 1pr, (H-C3).
IR (KBr)	ν_{max} = 3000s, 1725s, 1460m, 1230s, and 1040s (C-O-C) cm^{-1}.
MS	m/e = 444 (M^+), 385 (M-59, base), 373 (M-71).
OPTICAL ROTATION	$[\alpha]_D$+20° (C 0.82 in $CHCl_3$)

3β-Acetoxy-6β-hydroxy-19-nitro-oxycholestane (179)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (225mg, 0.47 mmol) in purified chloroform (200ml) containing triethylamine (1ml) through which oxygen was passing was photolysed with dry-ice cooling using a medium-pressure Hanovia lamp. After irradiating for 40 min, TLC showed the absence of starting material

and the solution was concentrated at 30°. HPLC (30% acetonitrile/benzene) was used to separate 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) (12mg, 5%) (characterised by comparison with an authentic sample) from a non-polar fraction. The less-polar fraction was concentrated and on resolution by HPLC (8% ethyl acetate/benzene) gave 3β-acetoxy-6β,19-epoxycholestane (29) (34mg, 16%), characterised by comparison with an authentic sample, and a further compound believed to be 3β-acetoxy-6β-hydroxy-19-nitro-oxycholestane (179) (72mg, 32%) which was crystallised from methanol/water as colourless crystals which decomposed slowly on standing.

m.p. = 79-83°

^{1}H-NMR ($CDCl_3$) δ = 0.67s, (H_3-C18); 0.85d (J = 8Hz), (H_3-C26 and H_3-C27); 2.0s, (CH_3CO_2-C_3); 3.58-3.90m, 1pr, (H-6C); 4.88s, 2pr, (H_2-C19); 4.36-5.17m, 1pr, (H-C3).

IR (KBr) ν_{max} = 3550w, 1720s, 1645s (ONO_2), 1280s (ONO_2), 1240s, and 865m (ONO_2), cm^{-1}.

OPTICAL ROTATION $[\alpha]_D$+28° (C 0.3 in $CHCl_3$)

The IR spectrum of the 19-nitrate (179) was also measured in chloroform and on standing overnight in solution it was found that the absorption at 1645 cm^{-1} decreased by

half.

3β-Acetoxy-19-nitro-oxycholestan-6-one (180)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (175mg, 0.37 mmol) in toluene (150ml) containing triethylamine (1ml) through which oxygen was passing was photolysed for 75 min with dry-ice cooling using a medium-pressure Hanovia lamp. The solution was concentrated at 40° and the resulting yellow oil was redissolved in acetone (50ml). The acetone solution was treated with Jones' reagent (2ml) and stirred at room temperature for 10 min. Ethyl acetate (150ml) was added and stirring was continued for a further 30 min after which time water (200ml) was added. Filtration through "Hi-flo" gave a pale yellow ethyl acetate fraction which was washed successively with water, saturated $NaHCO_3$ solution, water, saturated NaCl solution, and dried over Na_2SO_4. Concentration afforded a pale yellow oil which was subjected to a preliminary purification using preparative TLC (10% ethyl acetate/benzene) and the fraction at R_f = 0.7 was resolved by HPLC (15% ethyl acetate/benzene) to afford 3β-acetoxycholestan-6-one (116) (100mg, 58%) (characterised by comparison with an authentic sample) and 3β-acetoxy-19-nitro-oxycholestan-6-one (180) (53mg, 30%) which crystallised from methanol as colourless plates.

	m.p. = 103-107°
ANALYSIS	(Found, %: C, 69.2; H, 9.4; N, 2.6. $C_{29}H_{47}NO_6$ (505.67) requires, %: C, 68.9; H, 9.4; N, 2.8).
^{1}H-NMR ($CDCl_3$)	δ = 0.66s, (H_3-C18); 0.85d (J = 8Hz), (H_3-C26 and H_3-C27); 2.0s, (CH_3CO_2-C3); 4.13-5.00m, (H-C3); 4.45s, (H_2-C19).
IR ($CHCl_3$)	ν_{max} = 1725s, 1645s (ONO_2), 1255s (ONO_2), and 850m (ONO_2) cm^{-1}.
MS	m/e = 505 (M^+), 459 (M-46), 399 (M-106, base), 370 (M-135), 368 (M-137).
OPTICAL ROTATION	$[\alpha]_D$+32° (C 0.5 in $CHCl_3$)

3β-Acetoxy-6β,19-dihydroxycholestane (181)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (250mg, 0.5 mmol) in purified chloroform (200ml) containing diisopropylamine (1ml) was photolysed with dry-ice cooling and oxygen passing through the solution for 75 min using a medium-pressure Hanovia lamp. Concentration gave a white solid which was dissolved in methanol (15ml) and the solution treated with ammonium acetate (1g, 15 mmol) in methanol (15ml). The solution was cooled with ice, stirred for 40 min, ethyl acetate (150ml) was added, and filtered through "Hi-flo." The

ethyl acetate solution obtained was washed successively with water, and saturated NaCl solution and dried over Na_2SO_4. Concentration gave a white solid which was purified by HPLC (24% acetonitrile/benzene) and crystallised from methanol to give 3β-acetoxy-6β,19-dihydroxycholestane (181) (116mg, 52%) as colourless crystals.

m.p. = 179-179.5°

ANALYSIS (Found, %: C, 75.3; H, 10.9. $C_{29}H_{50}O_4$ (462.72) requires, %: C, 75.4; H, 10.9).

^{1}H-NMR ($CDCl_3$) δ = 0.72s, (H_3-C18); 0.85d (J = 8Hz), (H_3-C26 and H_3-C27); 2.02s, (CH_3CO_2-C3); 3.25-4.10m, 3pr, (H-C6 and H_2-C19); 4.11-5.10m, 1pr, (H-C3).

IR (KBr) ν_{max} = 3450s (OH), 3000s, and 1720s, cm^{-1}.

MS m/e = 462 (M^+), 382 (M-80), 371 (M-91), 353 (M-109, base).

OPTICAL ROTATION $[\alpha]_D$ +75° (C 0.3 in $CHCl_3$)

3β-Acetoxy-19-hydroxycholestan-6-one (183)

A solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (220mg, 0.48 mmol) in chloroform (200ml) with diisopropylamine (1ml) added was photolysed for 75 min with dry-ice cooling and with oxygen passing through using a medium-pressure Hanovia lamp. Concentration

and oxidation with Jones' reagent (2ml) as described above gave a colourless oil which was purified by HPLC (8% ethyl acetate/benzene). Purification in this way gave a non-polar fraction which was concentrated, treated with zinc and ammonium acetate as described above and purified using HPLC (8% ethyl acetate/benzene). Concentration and crystallisation from methanol/water gave 3β-acetoxy-19-hydroxycholestan-6-one (183) (50mg, 25%) as colourless crystals.

	m.p. = 111-116°
ANALYSIS	(Found, %: C, 75.3; H, 10.5. $C_{29}H_{48}O_4$ (460.70) requires, %: C, 75.6; H, 10.5).
^{1}H-NMR (Polysol D)	δ = 0.70s, (H_3-C18); 0.85d (J = 8Hz), (H_3-C26 and H_3-C27); 2.01s, (CH_3CO_2--C3); 3.46-4.08m, 2pr, (H_2-C19); 4.25-5.03m, 1pr, (H-C3).
IR (KBr)	ν_{max} = 3550m, 3000s, 1720s, and 1710s, cm^{-1}.
MS	m/e = 460 (M^+), 370 (M-90), 197 (M-263, base).
OPTICAL ROTATION	$[\alpha]_D$ +28° (C 0.3 in $CHCl_3$)

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of oxygen and treatment with base

A solution of 3β-acetoxy-6β-nitroso-oxycholestane

(27) (230mg, 0.5 mmol) in chloroform (200ml) with di-isopropylamine (1ml) added was photolysed for 75 min in the presence of oxygen as described above. Concentration gave a white solid which was dissolved in methanol (10ml), treated with sodium bicarbonate (1g), and stirred overnight at room temperature. Dilution with water (100ml) and extraction with ethyl acetate (100ml) gave an ethyl acetate solution which was washed successively with water, saturated NaCl solution, dried over Na_2SO_4, and concentrated. The resulting colourless oil was purified by HPLC (8% ethyl acetate/benzene) to give, on crystallisation from methanol, 3β-acetoxy-6β,19-epoxycholestane (29) (78mg, 35%) whose structure was confirmed by comparison with an authentic sample.

3β,6β,19-Trihydroxycholestane (182)

Potassium carbonate (100mg, 0.7 mmol) was added to a solution of 3β-acetoxy-6β,19-dihydroxycholestane (182) (50mg, 0.11 mmol) in methanol (5ml) and the solution was heated under reflux overnight. Dilution with water (50ml) and extraction with ethyl acetate (50ml) gave an ethyl acetate solution which was washed successively with water, saturated NaCl solution, and dried over Na_2SO_4. Concentration and crystallisation from methanol gave 3β,6β,19-trihydroxycholestane (182) (25mg, 55%) as colourless crystals.

m.p. = 228-232° (lit:[20] 235-237°)

^{1}H-NMR (CD_3OD) δ = 0.75s, (H_3-C18); 0.86d (J = 8Hz), (H_3-C26 and H_3-C27), 3.5-4.3m, (H-C3, H-C6, and H_2-C19).

IR (KBr) ν_{max} = 3500s and 3000s, cm^{-1}

Photolysis of the dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (119) in the presence of oxygen

A solution of the dimer of 3β-acetoxy-6β-hydroxy-19-nitrosocholestane (119) (50mg, 0.1 mmol) in methanol (15ml) was photolysed using "black-light" with oxygen passing through the solution. After 5 min irradiation, TLC indicated only a polar product and concentration afforded only 3β-acetoxy-6β-hydroxy-19-oximinocholestane (117) which was characterised by comparison with an authentic sample.

Photolysis of 3β-acetoxy-6β-nitroso-oxycholestane (27) in the presence of triethylphosphite

Triethylphosphite (300μl, 3 mmol) was added to a solution of 3β-acetoxy-6β-nitroso-oxycholestane (27) (230mg, 0.5 mmol) in purified chloroform (250ml) with diisopropylamine (1ml) added. The solution was photolysed with dry-ice/acetone cooling and with oxygen passing through the solution. The solution was chromatographed rapidly through Florisil (50g) and concentrated.

NMR ($CDCl_3$), IR and TLC analysis of the product mixture showed the major product to be 3β-acetoxy-6β-hydroxy-19-nitro-oxycholestane (180).

t-Butyl nitrate

Nitrosyl chloride was passed through a dry-ice cooled solution of t-butyl hydroperoxide (500mg, 5.5 mmol) in dry methylene chloride (20ml) with pyridine (1ml) added until a permanent brown colour was achieved. Stirring was continued for a further 10 min and ice-water (100ml) was added. The methylene chloride solution was washed successively with water, dilute HCl, water, saturated $NaHCO_3$ solution, saturated NaCl solution, and dried over Na_2SO_4. Concentration at 35° gave t-butyl nitrate (480mg, 73%) as a pale yellow, sweet-smelling oil which was pure by NMR.

	b.p. = 26° at 10mm (lit:[232] 23° at 5mm)
^{1}H-NMR ($CDCl_3$)	δ = 1.53s, $((CH_3)_3C)$.
IR (liquid film)	ν_{max} = 1645s (ONO_2), 1375m, 1300s (ONO_2), and 1160s, cm^{-1}.
UV (Heptane)	λ_{max} = 272 nm (shoulder), (ε = 21) (lit:[233] λ_{max} = 270 nm, shoulder)
MS	m/e = 119 (M^+), 104 (M-15), 84 (M-35), 57 (M-62, base).

3-Methoxypregna-3,5-dien-20-one (185)

A solution of progesterone (184) (6g, 19 mmol) in a mixture of 2,2-dimethoxypropane and dimethylformamide (100ml, 1:1) was treated with para-toluenesulphonic acid monohydrate (0.16g, 0.84 mmol) and methanol (2ml). The solution was heated under reflux for 3.5h after which time TLC indicated the absence of starting material. On cooling to room temperature, the solution was neutralised with aqueous sodium bicarbonate solution (0.9g in 1500ml water) and the white precipitate which formed was filtered off, washed well with water and crystallised from methanol/acetone in the presence of a trace of pyridine, to give 3-methoxypregna-3,5-dien-20-one (185) (5.5g, 90%) as colourless plates.

m.p. = 130-135° (lit:[233] 135-160°)

^{1}H-NMR ($CDCl_3$) δ = 0.66s, (H_3-C19); 0.97s, (H_3-C18); 2.10s, (H_3-C21); 3.57s, 3pr, (CH_3O-C3); 5.0-5.37m, 2pr, (H-C4 and H-C6).

OPTICAL ROTATION $[\alpha]_D$-59° (C 0.82 in $CHCl_3$) (lit:[234] $[\alpha]_D$-61°, C 1.0 in $CHCl_3$).

17α-Hydroperoxyprogesterone (187)[223]

3-Methoxypregna-3,5-dien-20-one (185) (1.8g, 5.5 mmol) in dry benzene (50ml) was added to a solution of potassium (2g) in t-butanol (50ml). The resulting yellow solution was stirred vigorously with a rapid

stream of oxygen passing through it, poured into water and extracted with ethyl acetate (300ml). The ethyl acetate solution was washed successively with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated to give a pale yellow oil. This oil was dissolved in THF (50ml), dilute HCl (50ml, 20%) was added, and the solution was stirred for 30 min, and extracted with ethyl acetate (400ml). The resulting ethyl acetate solution was washed successively with water, saturated $NaHCO_3$ solution, saturated NaCl solution, dried over Na_2SO_4, and concentrated. Crystallisation from methanol afforded 17α-hydroperoxyprogesterone (187) (1.3g, 71%) as colourless plates.

m.p. = 190-192° (lit:[223] 185-189°)

^{1}H-NMR (Polysol-D) δ = 0.67s, (H_3-C19); 1.17s, (H_3-C18); 2.25s, (H_3-C21); 6.47m, (H-C5); 10.85s, (OO<u>H</u>-C17).

OPTICAL ROTATION $[\alpha]_D$+130° (C 0.6 in methanol) (lit:[223] $[\alpha]_D$+116°, C 0.5 in methanol)

17α-Nitro-oxyprogesterone (188)

A solution of 17α-hydroperoxyprogesterone (187) (190mg, 0.54 mmol) in dry pyridine (25ml) was cooled to -30° with a methylene chloride/dry-ice bath and nitrosyl chloride was passed through until a permanent brown

colour appeared. The solution was warmed to room temperature, diluted with ice-water (500ml) and the resulting white precipitate was collected and washed with water. Crystallisation from methanol/water gave 17α-nitro-oxyprogesterone (188) (145mg, 71%) as colourless needles.

	m.p. = 173-174° (lit:[224] 174-174.5°)
ANALYSIS	(Found, %: C, 65.6; H, 7.9; N, 3.6. $C_{21}H_{29}NO_5.\frac{1}{2}H_2O$ (384.46) requires, %: C, 65.6; H, 7.9; N, 3.6).
^{1}H-NMR ($CDCl_3$)	δ = 0.78s, (H_3-C19); 1.25s, (H_3-C18); 2.18s, (H_3-C21); 5.72s, (H-C4).
IR (KBr)	ν_{max} = 1750s, 1720s, 1650s (ONO_2), 1302s (ONO_2) cm^{-1}.
OPTICAL ROTATION	$[\alpha]_D$+59° (C 1.0 in $CHCl_3$) (lit:[224] $[\alpha]_D$+54°, C 1.0 in $CHCl_3$).

17α-Hydroxyprogesterone (189)

Ammonium acetate (100mg, 1 mmol) and zinc dust (100mg, 1 mmol) were added to an ice-cooled solution of 17α-nitro-oxyprogesterone (188) (30mg, 0.08 mmol) in methanol (15ml). After stirring for 30 min, ethyl acetate (100ml) was added and the solution was filtered through "Hi-flo." The ethyl acetate fraction was washed with water, filtered again through "Hi-flo,"

colour appeared. The solution was warmed to room temperature, diluted with ice-water (500ml) and the resulting white precipitate was collected and washed with water. Crystallisation from methanol/water gave 17α-nitro-oxyprogesterone (188) (145mg, 71%) as colourless needles.

m.p. = 173-174° (lit:[224] 174-174.5°)

ANALYSIS (Found, %: C, 65.6; H, 7.9; N, 3.6. $C_{21}H_{29}NO_5.\frac{1}{2}H_2O$ (384.46) requires, %: C, 65.6; H, 7.9; N, 3.6).

^{1}H-NMR ($CDCl_3$) δ = 0.78s, (H_3-C19); 1.25s, (H_3-C18); 2.18s, (H_3-C21); 5.72s, (H-C4).

IR (KBr) ν_{max} = 1750s, 1720s, 1650s (ONO_2), 1302s (ONO_2) cm^{-1}.

OPTICAL ROTATION $[\alpha]_D$+59° (C 1.0 in $CHCl_3$) (lit:[224] $[\alpha]_D$+54°, C 1.0 in $CHCl_3$).

17α-Hydroxyprogesterone (189)

Ammonium acetate (100mg, 1 mmol) and zinc dust (100mg, 1 mmol) were added to an ice-cooled solution of 17α-nitro-oxyprogesterone (188) (30mg, 0.08 mmol) in methanol (15ml). After stirring for 30 min, ethyl acetate (100ml) was added and the solution was filtered through "Hi-flo." The ethyl acetate fraction was washed with water, filtered again through "Hi-flo,"

dried over Na_2SO_4, and concentrated. Crystallisation from methanol/water gave 17α-hydroxyprogesterone (189) as colourless crystals.

m.p. = 197-208° decomp.
(lit:[235] 200-208° decomp.)

ANALYSIS (Found, %: C, 76.1; H, 9.3. $C_{21}H_{30}O_3$ (330.47) requires, %: C, 76.3; H, 9.2).

^{1}H-NMR ($CDCl_3$) δ = 0.72s, (H_3-C19); 1.0s, (H_3-C18); 2.25s, (H_3-C21); 5.64s, (H-C4).

NMR study of the reaction of t-butyl hydroperoxide with nitrosyl chloride

1. A solution of t-butyl hydroperoxide (50mg, 0.5 mmol) in pyridine-d_5 (1ml) was treated in an NMR tube at a probe temperature of 32°, with a saturated solution of nitrosyl chloride in pyridine-d_5 (1ml). The NMR spectrum measured immediately after addition showed the disappearance of the resonances at δ = 1.3 ($(CH_3)_3C$) and δ = 8.8 (OOH) with the appearance of a sharp singlet at δ = 1.5 ($(CH_3)_3C$-ONO_2).

2. A solution of t-butyl hydroperoxide (100mg, 1.0 mmol) in pyridine-d_5 (1ml) was treated with a saturated solution of nitrosyl chloride in pyridine-d_5 (1ml) at a probe temperature of -40°C. A white precipitate appeared causing the collapse of the NMR signal at

δ = 1.3, which adjustment of resolution failed to restore.

Progesterone 17α-diphenylphosphinate (192)

To a solution of 17α-hydroperoxyprogesterone (187) (100mg, 0.3 mmol) in dry pyridine (10ml) was added chlorodiphenylphosphine (190) (200µl, 1.4 mmol) and the mixture was heated at 50° under argon for 1h. The solution was allowed to cool to room temperature, poured into ice-water and extracted with ether (100ml). The ethereal extract was washed successively with water, dilute HCl, saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The resulting yellow oil was purified by HPLC (30% acetonitrile/benzene) and crystallised from methanol/water to give progesterone 17α-diphenylphosphinate (192) (100mg, 66%) as colourless crystals.

m.p. = 190-191°

ANALYSIS (Found, %: C, 74.8; H, 7.4; P, 5.9. $C_{33}H_{39}O_4P$ (530.61) requires, %: C, 74.7; H, 7.4; P, 5.8).

^{1}H-NMR ($CDCl_3$) δ = 0.70s, (H_3-C19); 1.20s, (H_3-C18); 2.36s, (H_3-C21); 5.75s, 1pr, (H-C4); 7.2-8.2m, 10pr, ($2x C_6H_5$).

IR (KBr) ν_{max} = 1720s, 1680s, 1601m, 1240s (R_2PO_2), 1130, and 945s (R_2PO_2) cm^{-1}.

UV (CH_3CH)	λ_{max} = 241 nm (ϵ = 12,900)
MS	m/e = 530 (M^+), 487 (M-43), 269 (M-261, base).
OPTICAL ROTATION	$[\alpha]_D$ +90° (C 0.9 in $CHCl_3$)

Treatment of progesterone 17α-diphenylphosphinate (192) with triethylphosphite

Triethylphosphite (100µl, 0.7 mmol) was added to a solution of progesterone 17α-diphenylphosphinate (192) (30mg, 0.05 mmol) in benzene (5ml) and the solution stirred at room temperature for 1h. TLC indicated no reaction and the starting material was recovered using preparative TLC.

Reaction of 17α-hydroperoxyprogesterone (187) with triethylphosphite

Triethylphosphite (100µl, 0.7 mmol) was added to a solution of 17α-hydroperoxyprogesterone (187) (30mg, 0.06 mmol) in benzene (5ml) and the solution was stirred at room temperature for 1 h. TLC indicated the presence of a less-polar product which was isolated by preparative TLC and crystallised from methanol to afford 17α-hydroxyprogesterone (189) (20mg, 60%) which was identified by comparison with an authentic sample.

Reaction of 17α-hydroperoxyprogesterone (187) with trifluoroacetic anhydride

Trifluoroacetic anhydride (210µl, 1.5 mmol) was added to a solution of 17α-hydroperoxyprogesterone (187) (200mg, 0.6 mmol) in pyridine (15ml) and the solution stirred at -5° for 15 min. During this time, a deep brown colour appeared which disappeared on dilution with ice-water (100ml). Extraction with ether (100ml) gave a solution which was washed successively with water, dilute HCl, saturated $NaHCO_3$ solution, water, saturated NaCl solution, dried over Na_2SO_4, and concentrated to give a yellow oil. Purification by HPLC (15% ethyl acetate/benzene) and crystallisation from methanol gave androst-5-ene-3,17-dione (87) (142mg, 59%) which was characterised by comparison with an authentic sample.

4-Methyl-benzenesulphinyl chloride (199)[236]

Sodium 4-methyl-benzenesulphinate (9g, 0.05 mmol) was added over 15 min to thionyl chloride (21ml, 1.5 mmol) in a round-bottomed flask. Effervescence occurred and the mixture was stirred at room temperature for 1h and filtered under argon. The excess thionyl chloride was removed *in vacuo*. Distillation *in vacuo* gave pure 4-methyl-benzenesulphinyl chloride (199) as a pale green oil.

b.p. = 81° at 0.3 mm

(lit:[236] 99-105° at 0.5 mm)

^{1}H-NMR ($CDCl_3$) δ = 2.42s, 3pr, (CH_3); 7.85-8.35m, 4pr, (C_6H_4)

Reaction of 17α-hydroperoxyprogesterone (187) with 4-methyl-benzenesulphinyl chloride (199)

A solution of 4-methyl-benzenesulphinyl chloride (199) (200µl, 1.8 mmol) in methylene chloride (10ml) was added slowly to an ice-cooled solution of 17α-hydroperoxyprogesterone (187) (110mg, 0.3 mmol) in methylene chloride (10ml) to which pyridine (1ml) had been added. The mixture was stirred for 1h, excess water was added and the methylene chloride phase was washed successively with water, dilute HCl, water, saturated NaCl solution, dried over Na_2SO_4, and concentrated to afford a yellow oil. Androst-5-ene-3,17-dione (87) (23mg, 25%) was separated using HPLC (17% acetonitrile/benzene) and a more polar fraction which could not be obtained pure even on repeated recycling was thought, from its spectral data, to contain 17α-hydroxyprogesterone (188). In particular the MS of this compound showed a strong m/e at 329.

CHAPTER 5

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