Studies into the photochemistry of steroidal nitronate anions and n-alkyloxaziridines

STUDIES INTO THE PHOTOCHEMISTRY OF STEROIDAL NITRONATE ANIONS AND N-ALKYLOXAZIRIDINES.

BY

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A thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of the Loughborough University of Technology

September 1985

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Acknowledgements

I am very grateful to my supervisor, Dr. Brian A. Marples, for his help and guidance throughout the execution of this work described in this thesis.

I would like to thank the technical staff and members of the Department of Chemistry, who have been of assistance during the work.

Finally, I would like to thank Mrs. C. Dadswell for typing this thesis.

TO MY WIFE, ANNE

Contents

Summary

The photochemistry of nitro-compounds is well documented in the literature, however, the photochemical behaviour of nitronate anions has not been widely reported. We have studied the photochemical behaviour of a number of steroidal nitronate anions and found that the major products are hydroxamic acid, ketone and alkene.

It was found that the yield of products is influenced by the position of the nitro-group. The hydroxamic acids were found to be the major products in the photolysis of 17-nitronate anions. However, it was observed that in these systems the yield of hydroxamic acid was influenced by the C/D ring geometry. In the photolysis of nitronate anions derived from 3,6 and 20-nitro steriods only tentative evidence for hydroxamic acid formation was found in the photolysis of the 6-nitronate anion.

The formation of hydroxamic acids from the 17-nitronate anions was observed to be both regio- and stereo-specific and it was postulated that these reactions proceeded via a N-hydroxy-oxaziridine anion intermediate.

In order to further investigate the possible intermediary of an oxaziridine the synthesis of steroidal N-alkyl oxaziridines was carried out, and their photochemical behaviour examined. It was found that the N-alkyl-17-spiro-oxaziridine rearranged efficiently to a lactam whereas the N-alkyl-20-oxaziridine only gave a poor yield of amide. These results were consistent with those obtained for the nitronate anions. However the lactam formed was of different regio-chemistry to that observed in the photochemical formation of hydroxamic acid. However the observed photochemical rearrangement of the steriodal oxaziridines was fully in accord with theoretical predictions.

INTRODUCTION

Although it has been known since the nineteenth century that nitro-compounds undergo photochemical reactions,[1] it is only in recent years with the development of techniques such as e.s.r. spectroscopy,[2] and laser flash photolysis,[3] that these reactions have been fully investigated and characterised.

Although there has been considerable interest in recent years in the photochemistry of nitro-compounds relatively little attention has been paid to the photochemistry of related species, namely, the nitronate-anion and the aci-nitro system.

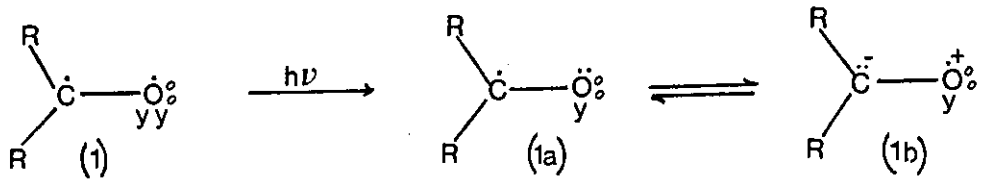
It will be shown that any investigation into the photochemistry of nitro-compunds must also consider the role of the nitrones and oxaziridines in these reactions from a mechanistic view-point.

The U.V. spectra of nitroalkanes show an intensive $\pi \rightarrow \pi^*$ transition at ca 210 nm ($\varepsilon \sim 15000$) and a much weaker $n \rightarrow \pi^*$ transition at ca 280 nm ($\varepsilon \sim 50$) due to the excitation of a non-bonding electron on oxygen and it is this latter transition with which photochemists are primarily concerned. In examining the O.R.D. and C.D. curves of nitro-steroids Djerrasi,[4] found evidence of a third absorption at ~350 nm which he was unable to explain. That there was an equivalent absorption in the U.V. spectra of simple nitroalkanes was finally shown by Paszyc,[5] who made careful measurements on nitromethane which as well as the expected absorptions also showed an absorption at 330 nm, but again no explanation was advanced to account for this.

In considering the excited states involved in the photochemistry of the nitro group only the lowest lying singlet and triplet excited states need be considered. This is because as a general rule molecules fluoresce and phosphoresce from their lowest singlet and triplet states respectively, since radiationless decay from higher excited states is too rapid to allow competition from these states. It has been postulated,[6] that there should be similarities between the photochemistry of the

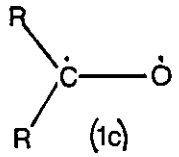
nitro group and that of the carbonyl group. The n → π* transition of the carbonyl group may be represented as shown in Scheme 1. The structure (1a) suggests that the excited state should show diradical character.

Scheme 1

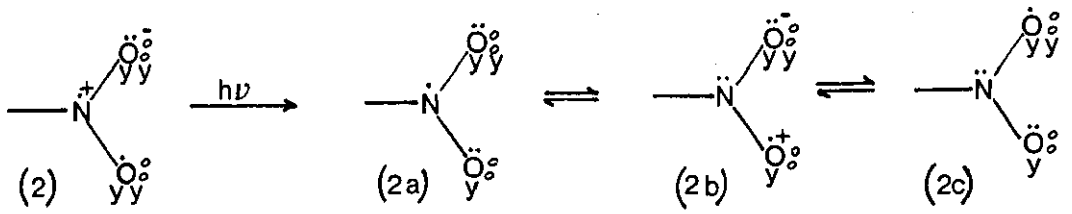


•=π electrons ∘=s electrons y=py electrons

The structures (1a) and (1b) can be combined and represented as shown in structure (1c).



Using similar representation the n → π* transition of the nitro group is as shown below.



From these it can be seen that both structure (1a) and (2a) are diradicals. Also the structure (2c) implies that the nitro excited state may also exhibit 1,3-diradical properties.

1) Photochemistry of Nitroalkanes

A) Vapour Phase Photolysis of Nitroalkanes

Initial investigations into the photochemistry of nitroalkanes were concerned with reactions in the vapour phase and the primary photochemical processes are now well documented.[7]

It was originally postulated,[8] that the initial photochemical process was an intramolecular rearrangement to alkyl nitrife (Reaction 1) which subsequently underwent photochemical decomposition.

However it is now accepted that the initial process is a photochemical homolytic cleavage of the C-N bond to give an alkyl radical and a

nitryl radical (Reaction 2). The photoproducts isolated from these reactions then arise by secondary reactions of the above radicals or by photolysis of the corresponding alkyl nitrite, formed by recombination of the above radicals (Reaction 3).

$$CH_3\text{-}NO_2 \xrightarrow{h\nu} CH_3\text{-}ONO \qquad \text{Reaction 1}$$

$$CH_3\text{-}NO_2 \xrightarrow{h\nu} \dot{C}H_3 + \dot{N}O_2 \qquad \text{Reaction 2}$$

$$\dot{C}H_3 + \dot{N}O_2 \longrightarrow CH_3\text{-}ONO \qquad \text{Reaction 3}$$

That homolytic C-N bond cleavage was the primary process was postulated by Gray, Yoffe and Roselar,[9] while the alternative rearrangement to an alkyl nitrite was put forward by Brown and Pimentel,[8] who extrapolated their results on the photolysis of nitromethane in a solid argon matrix at 20K, which gave isomerisation to methyl nitrite, to account for vapour phase reactions.

Support for C-N homolytic cleavage came from the work of Nicholson,[10] who examined the vapour phase photolysis of nitromethane and concluded that the primary process was $CH_3NO_2 + h\nu \rightarrow \dot{C}H_3 + \dot{N}O_2$. One of the main products from this reaction was methane which was postulated as arising via a hydrogen abstraction process by the methyl radical on nitromethane.

$$\dot{C}H_3 + CH_3NO_2 \longrightarrow CH_4 + \dot{C}H_2NO_2$$

The above results were put forward as being consistent with those of Brown and Pimentel as it was suggested that at 20K the methyl radical and nitryl radical would be held in a cage of the solid matrix and recombine to give methyl nitrite.

Further support for this view came from Bielski and Timmons,[11] who examined the photolysis of nitromethane at 77K in a water and

carbon tetrachloride matrix by means of e.s.r. spectroscopy and were able to assign signals corresponding to the methyl radical and nitryl radical thus confirming the postulated primary process.

Further support for this primary process came from opto-acoustic spectroscopy measurements peformed during the photolysis of nitromethane and from which the full reaction sequence was put forward as being:[12]

$$CH_3NO_2 \xrightarrow{h\nu} \dot{C}H_3 + \dot{N}O_2$$

$$\dot{C}H_3 + \dot{N}O_2 \longrightarrow CH_3O + NO$$

$$\dot{N}O_2 \xrightarrow{h\nu} NO + O$$

$$\dot{C}H_3 + \dot{N}O_2 \longrightarrow CH_3NO_2$$

$$CH_3O + \dot{N}O_2 \longrightarrow CH_3ONO_2.$$

If the nitroalkane posseses a hydrogen on the β-carbon then one of the products obtained is an alkene. This reaction was demonstrated by the work of Polovitzyn,[13] who examined the photolysis of nitroethane again using matrix isolation techniques. This work again showed the primary process to be homolytic C-N bond cleavage. This reaction is followed by two parallel, secondary processes one being the previously discussed formation of an alkylnitrite, the second being hydrogen abstraction by the nitryl radical to give ethylene and nitrous acid as shown below.

$$CH_3\text{-}CH_2\text{-}NO_2 \xrightarrow{h\nu} CH_3\text{-}\dot{C}H_2 + \dot{N}O_2$$

$$H\text{-}CH_2\text{-}CH_2\cdot \longrightarrow CH_2{=}CH_2 + HNO_2$$
$$\quad \cdot NO_2$$

B Liquid Phase Photolysis of Nitroalkanes

Carbon-nitrogen homolysis has been observed in the liquid phase photolysis of nitroalkanes although the quantum yields of such processes are considerably lower than in the vapour phase, due to

vibrational deactivation of the excited state or of a reversal of the primary process by radical recombination.

However, in the liquid phase a second primary process becomes important, namely hydrogen abstraction from suitable solvents by the excited nitro group and in recent years a considerable amount of evidence has been gathered concerning this process. Evidence for this reaction was first obtained by Chachaty and Forechioni,[14] who examined the photolysis of nitromethane and nitroethane in alcoholic solutions using e.s.r. spectroscopy and were able to assign signals due to the radicals $Me\dot{N}O_2H$ and $Et\ \dot{N}O_2H$,

The full reaction sequence was as follows:

$$RNO_2 \xrightarrow{h\nu} \dot{R} + \dot{N}O_2$$

$$RNO_2 \xrightarrow{h\nu} (RNO_2)^*$$

$$(RNO_2)^* + R'H \longrightarrow R\dot{N}O_2H + \dot{R}'.$$

$$2\ R\dot{N}O_2H \longrightarrow RNO_2 + RNO + H_2O$$

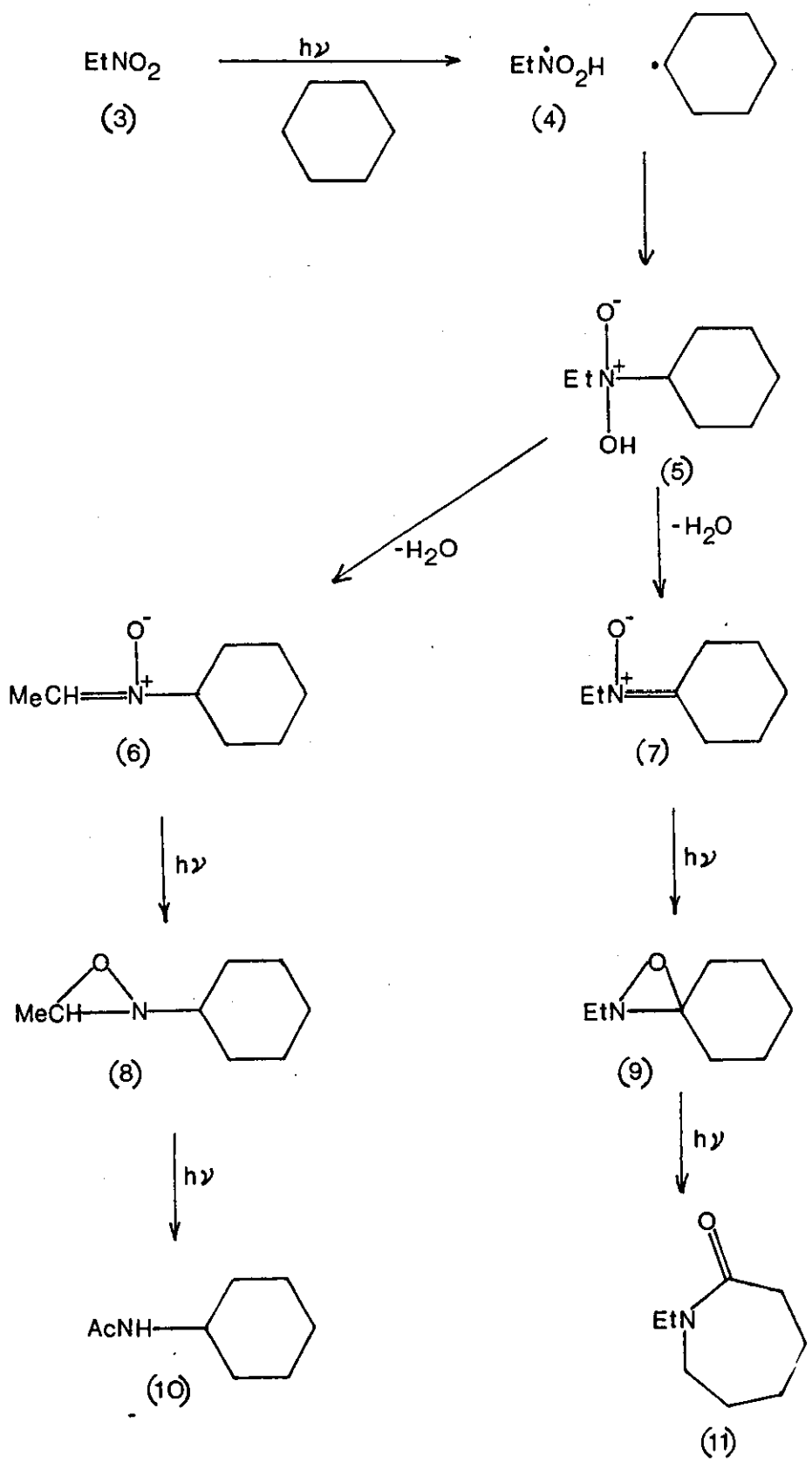
$$RNO + \dot{R} \text{ or } \dot{R}' \longrightarrow R\text{-}\underset{\underset{O.}{|}}{N}\text{-}R \text{ or } R\text{-}\underset{\underset{O.}{|}}{N}\text{-}R'$$

$R = CH_3$ or CH_3CH_2

Chemical evidence for this hydrogen abstraction pathway was provided by Reid *et al*,[15] who found that on photolysis with a medium pressure mercury arc lamp of nitroethane (3) in cyclohexane the major products were N-cyclohexyl-acetamide (10) (7%) and N-ethylcaprolactam (11) (6%) for which the proposed mechanism is given in Scheme 3.

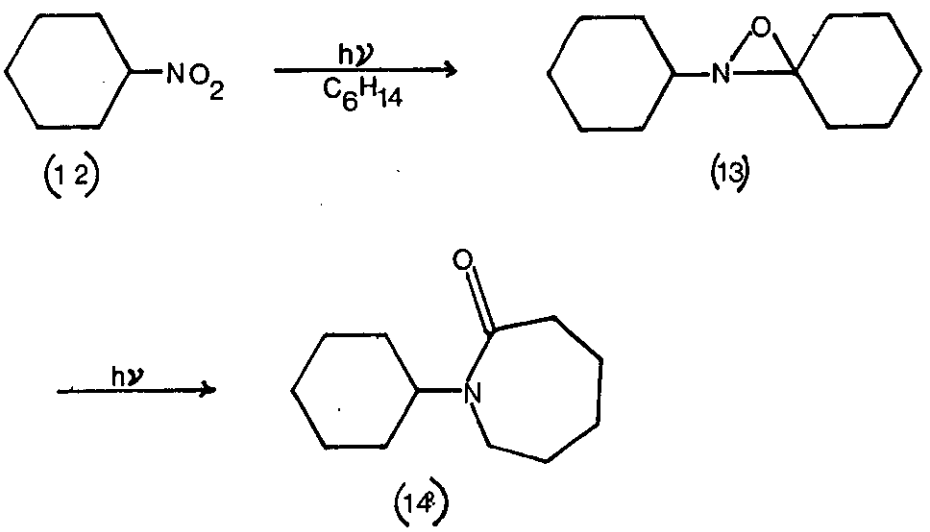
The initial hydrogen abstraction by the excited nitro group to give (4) corresponds with that put forward above. The radical recombination to give (5) and elimination of water affords the two nitrones (6) and (7). Photochemical isomerisation of these species to give oxaziridines (8) and (9) is a well documented process,[16] as is

Scheme 3


EtNO2
hν
(3)
EtṄO2H
(4)
O-
EtN+
OH
(5)
-H2O
-H2O
MeCH=N+
O-
(6)
EtN+
O-
(7)
hν
hν
MeCH
O
N
(8)
EtN
O
(9)
hν
hν
AcNH
(10)
EtN
O
(11)

the resultant cleavage of the oxaziridines to give amides,[17].

Although no direct evidence for the postulated intermediates was found, both oxaziridines were unambiguously synthesised and shown to readily undergo photochemical rearrangement to the desired products. In the case of secondary nitroalkanes cleavage of the oxaziridine must be accompanied by alkyl migration and this was clearly observed in the photolysis of nitrocyclohexane (12) where only one intermediate nitrone and oxaziridine are possible. In this case a higher yield (16%) of N-cyclohexylcaprolactam (14) was obtained.



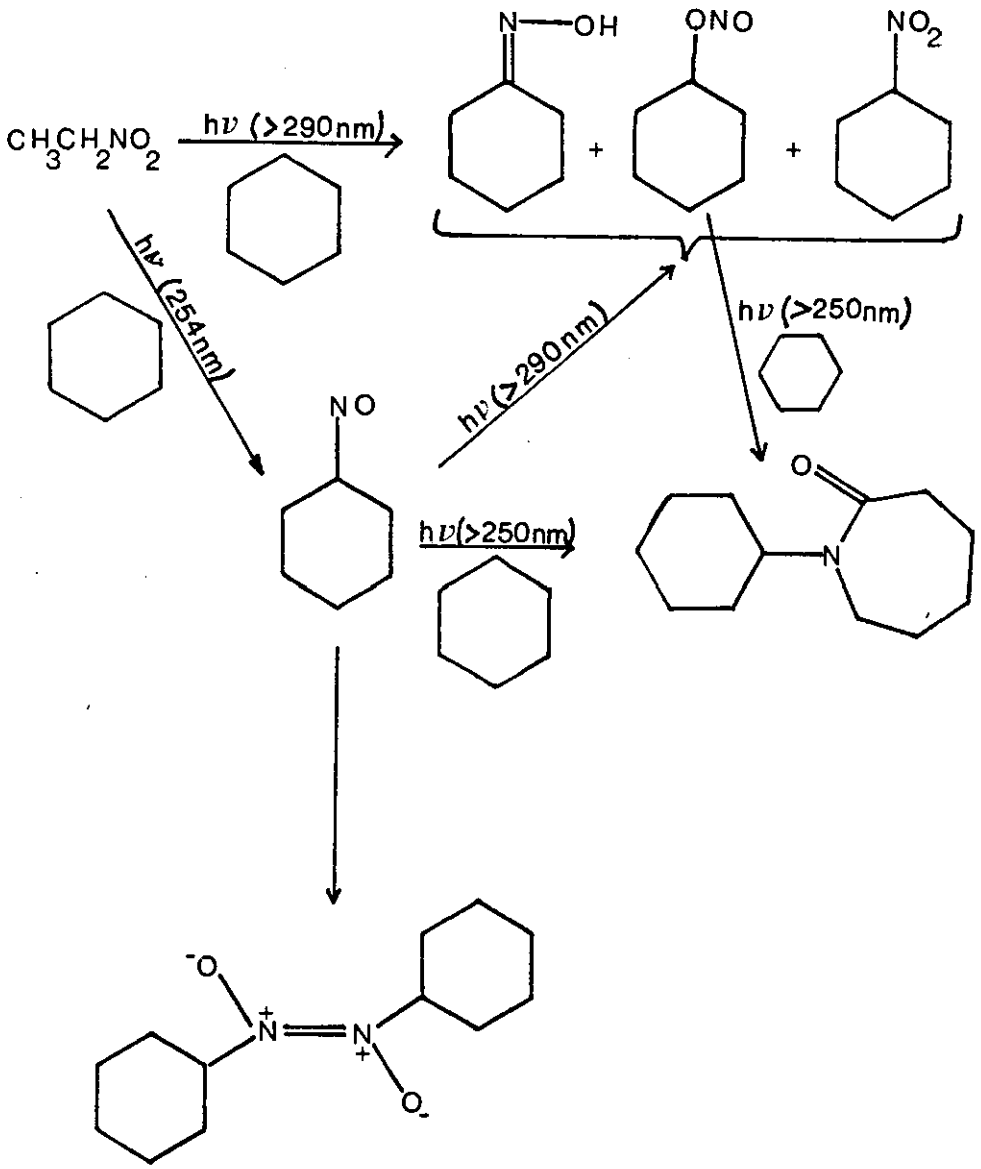
(12) (13) (14)

In the above reactions, alcohols were also formed as co-products and were thought to arise via the previously described homolytic fission and photochemical reaction of the intermediate nitrite.

These results thus provide the chemical evidence for two competing primary processes in the solution photochemistry of nitroalkanes.

The work of Reid and Wilcox,[15] showed that the photochemical reactions of a nitroalkane are influenced by the wavelength of radiation used as outlined in Scheme 4 .

Scheme 4

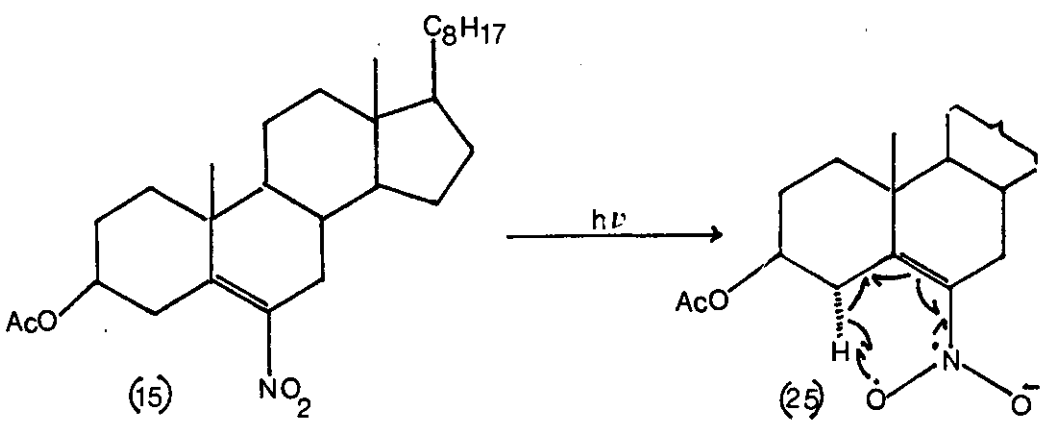


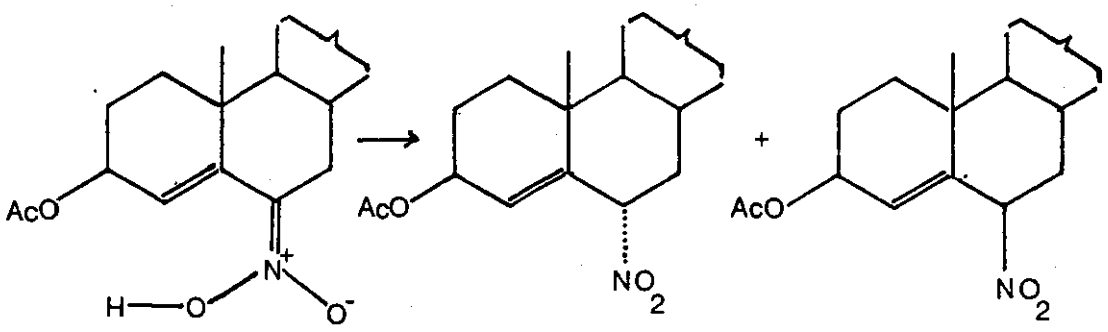
2. Photochemistry of α, β-Unsaturated Nitro-compounds

In contrast to nitroalkanes, α, β-unsaturated nitro-compounds are markedly more photo-labile and depending on the structure of the nitroalkene and the photochemical conditions used, these compounds may undergo cis-trans isomerisation,[18] dimerisation,[19] and [2+2] cyclo-addition reactions,[20] with alkenes.

One of the most important differences with respect to nitroalkanes is the ability of α, β-unsaturated nitroalkenes to undergo photochemically initiated intramolecular hydrogen abstraction reactions. This type of photochemical reaction is exemplified by the work of Pinhey and co-workers,[21] on the reactions of 3β-acetoxy-6-nitrocholest-5-ene (15) and 6-nitrocholest-5-ene (16). The photolyses on these compounds were carried out using a medium pressure mercury arc lamp, pyrex glassware and a variety of solvents. The results from these reactions are summarised in schemes (5) and (6) together with those of Chapman,[22] and Coombes,[23] who examined the photochemical behaviour of the nitroalkene (16).

The intramolecular hydrogen abstraction process to give β,γ-unsaturated nitro-compounds was considered to arise by the mechanism shown below for the nitro-compound (15) and an exactly analogous mechanism operates for the nitro-compound (16).

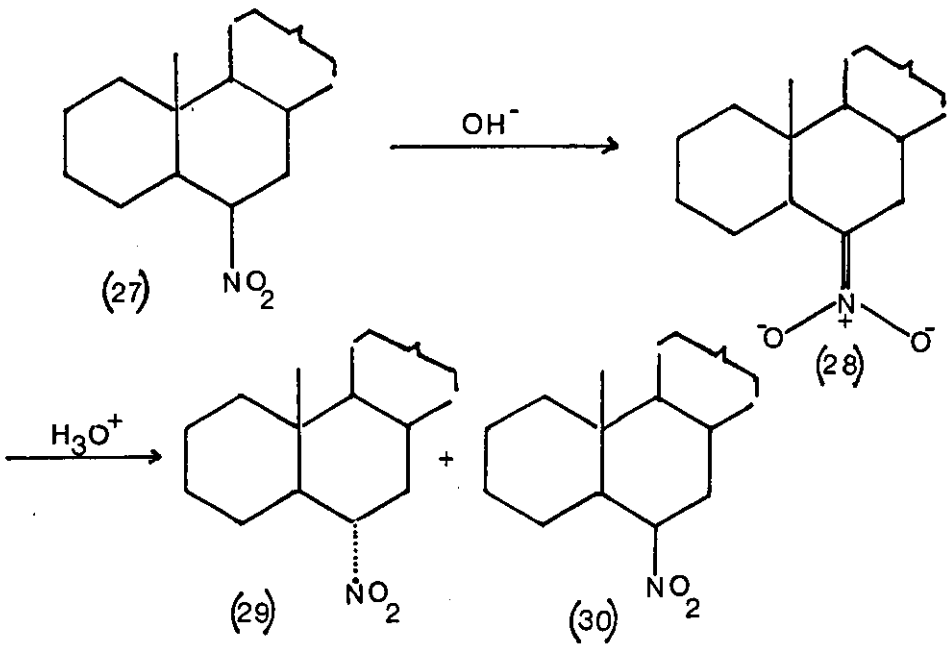




(26) (17) (18)

This mechanism involves an initial n→π* transition, to give (25), analogous to that observed in α, β-unsaturated ketones, a 1,5-hydrogen shift gives the aci-nitro compound (26) which undergoes tautomerisation to give the nitroalkenes (17) and (18) as an inseparable mixture in 20% yield in a ratio of 1:2.

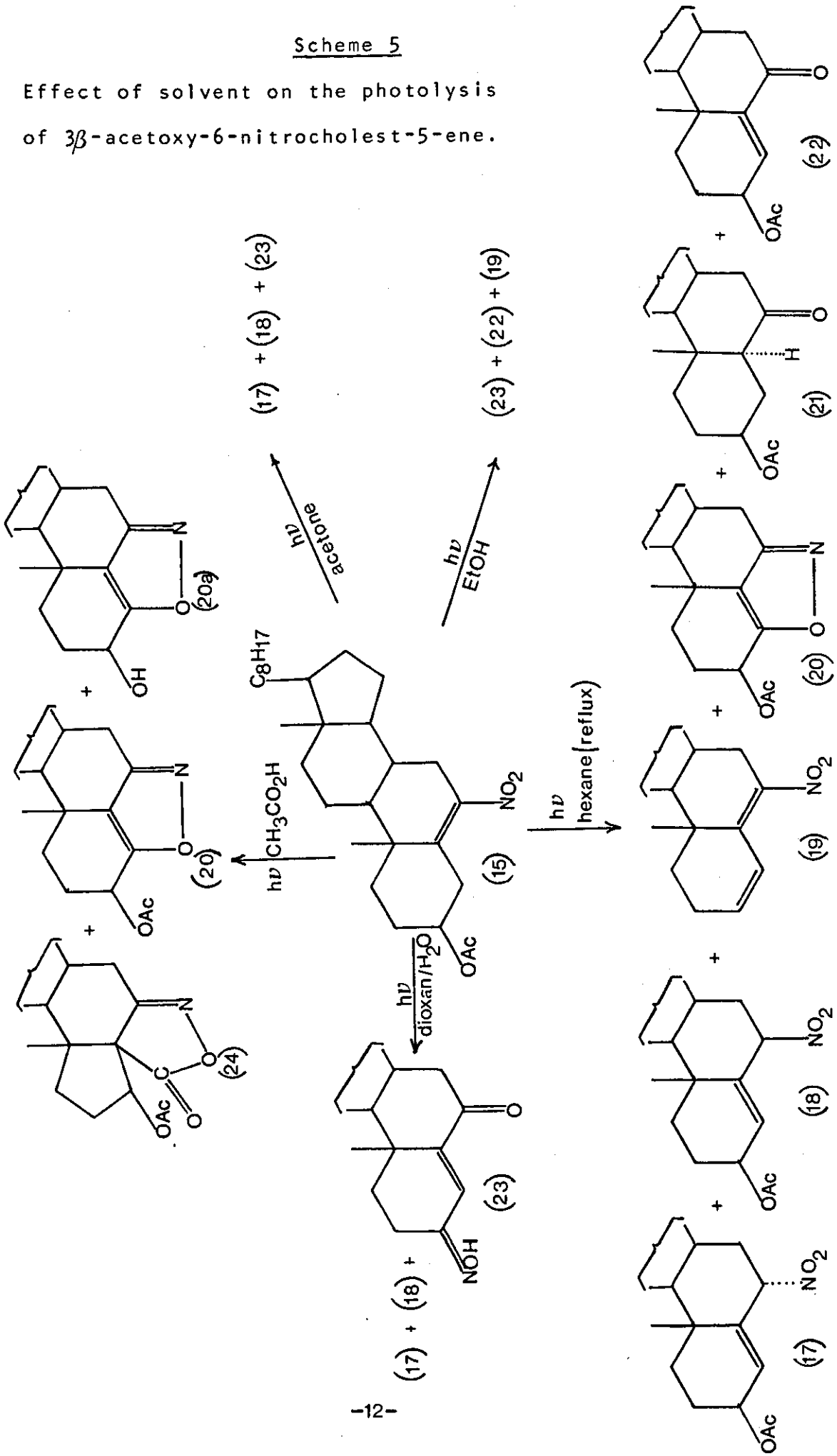
An interesting feature of this reaction is the ratio of the two nitroalkenes produced. The ratio observed is not that expected for kinetically controlled protonation of the aci-nitro intermediate (26) which would theoretically give the 6β-nitro alkene as the major product. In separate experiments it has been shown,[24] that acidification of a chemically generated aci-nitro anion (28) with acetic acid gave the 6α (29) and 6β (30) nitro compounds in a ratio of 1:9.



(27) (28) (29) (30)

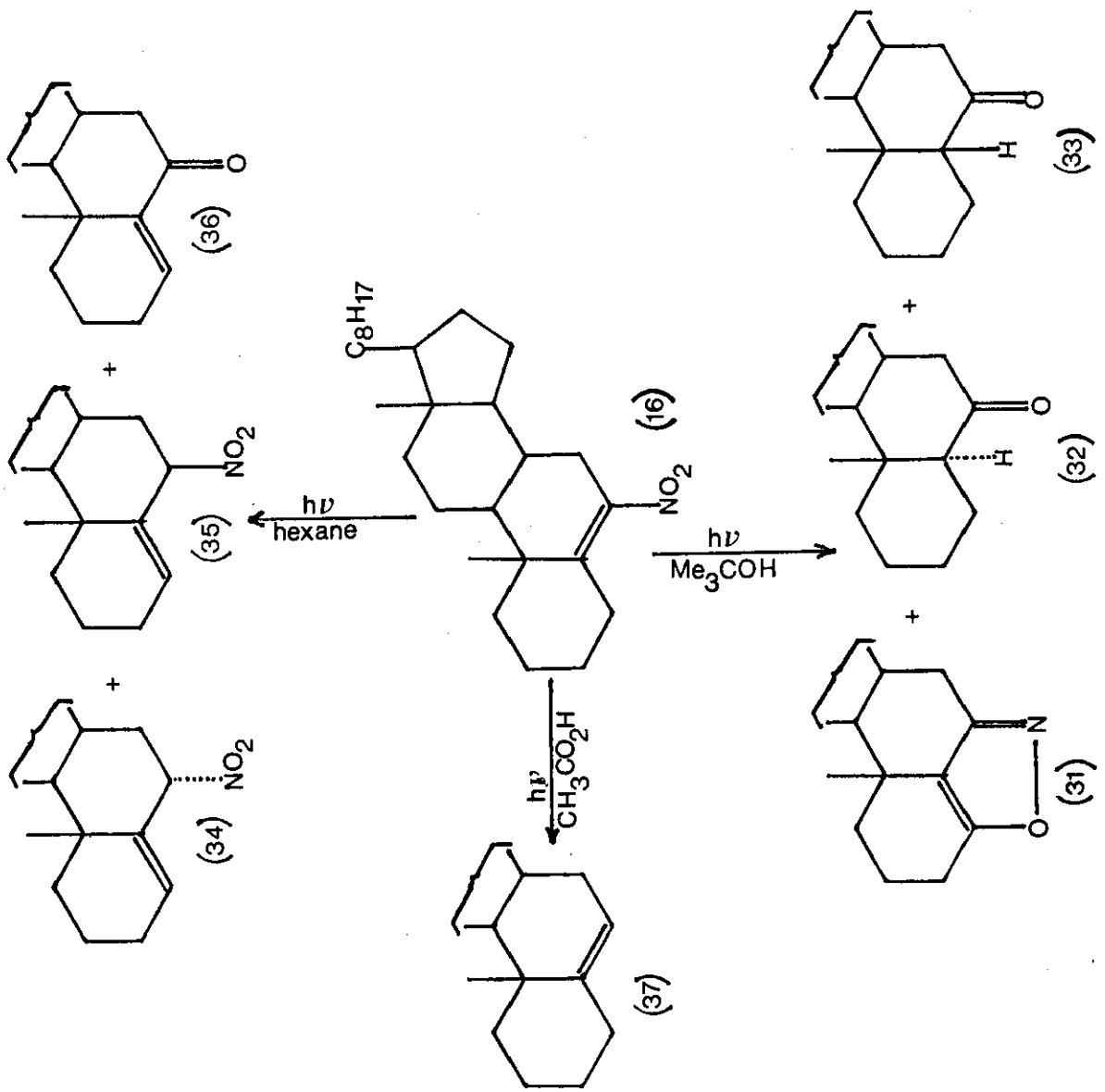
Scheme 5

Effect of solvent on the photolysis of 3β-acetoxy-6-nitrocholest-5-ene.



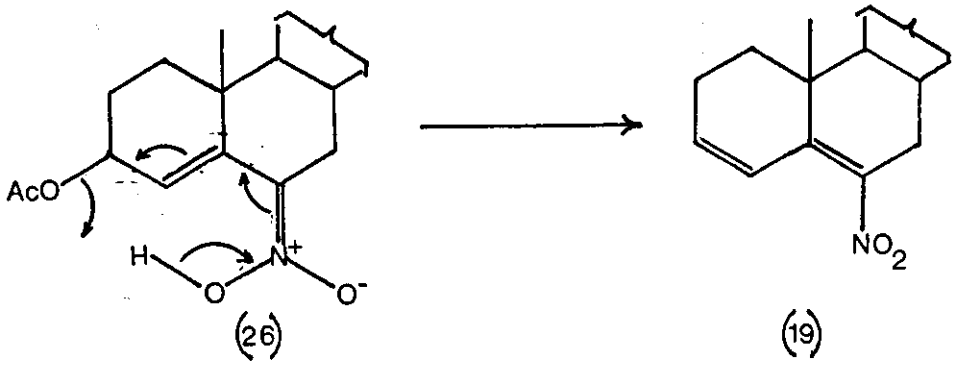
Scheme 6

Effect of solvent on the photolysis of 6-nitro-cholest-5-ene



The aci-nitro system (26) was also invoked as the key intermediate involved in the formation of several other products isolated from these photochemical studies.

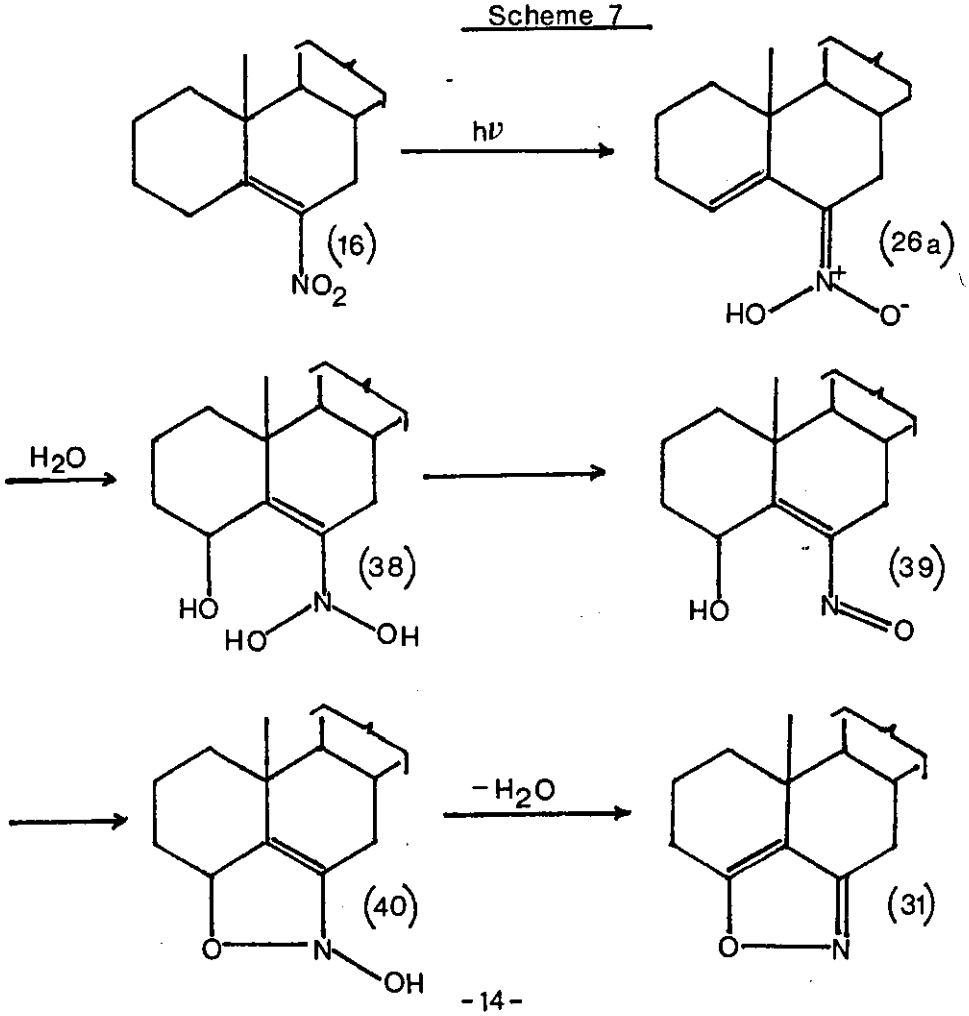
For example the 6-nitro-cholest-3,5-diene (19) was formed by elimination of acetic acid from (26) as inciated below:



(26) (19)

The isoxazoles (20) and (31) were also considered to arise via an aci-nitro intermediate (26a) as shown in Scheme (7) below for the formation of (31) from the nitroalkene (16).

Scheme 7



It was observed that the yield of isoxazole (31) was markedly solvent dependent. In hexane no isoxazole was obtained, in t-butyl alcohol a 20% yield, and in refluxing acetic acid a 40% yield of isoxazole was obtained. These observations led Pinhey and co-workers to the conclusion that the isoxazole arose via an intermediate photo-product which required a proton source. This condition is fulfilled by the aci-nitro intermediate which undergoes protonation to give the intermediate (37).

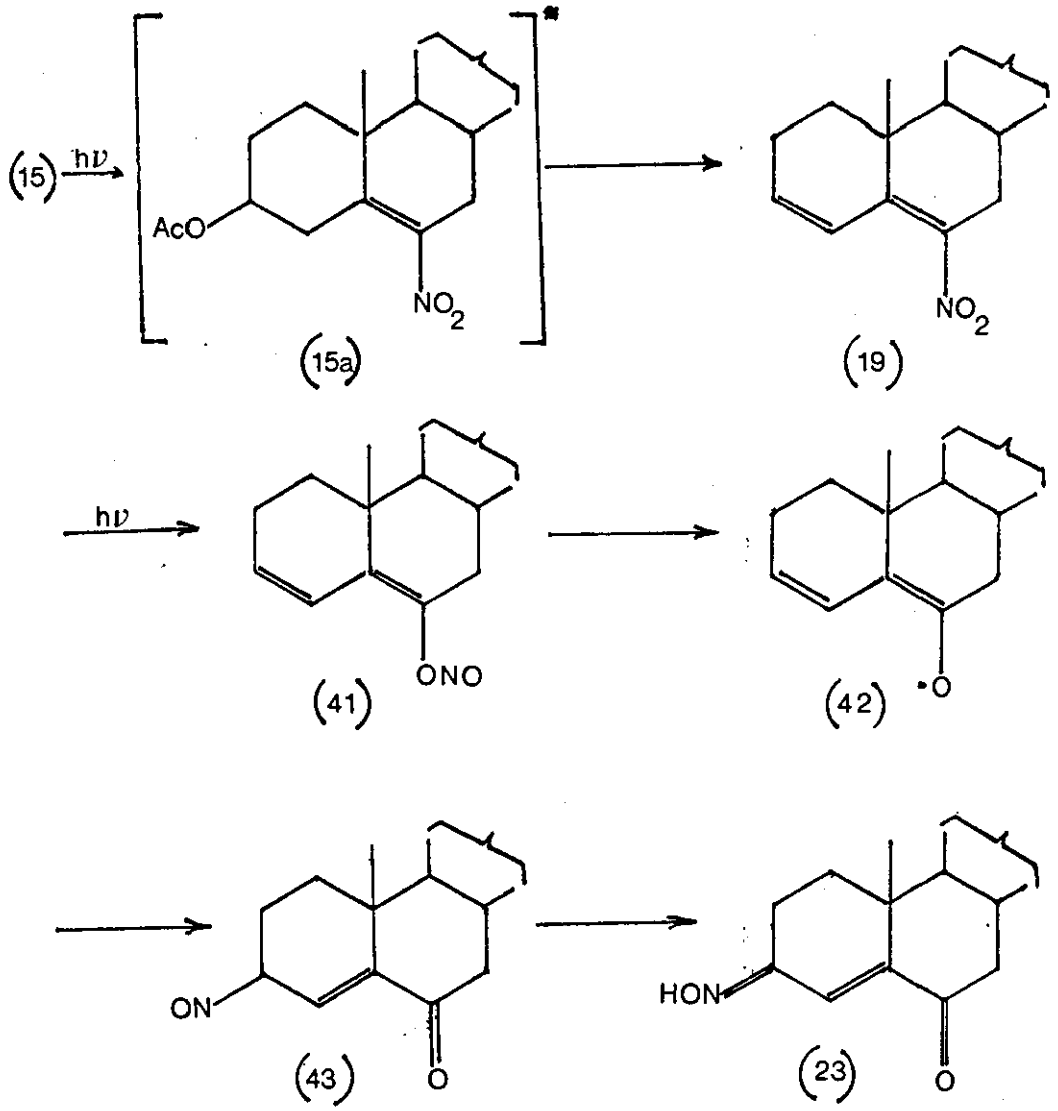
It is apparent from the work of Pinhey that the efficiency of the hydrogen abstraction process to give β,γ-unsaturated nitroalkenes is markedly solvent dependent. This point can be seen more clearly from a consideration of the results of other workers who have examined the photochemical behaviour of 3β-acetoxy-6-nitrocholest-5-ene (15).

It was shown by Chapman that if acetone was used as the solvent the products arising via the hydrogen abstraction pathway were obtained in higher yield. The isomeric mixture of the β,γ-unsaturated nitro-compounds (17) and (18) were obtained in 50% yield and a 1:1 ratio. However, Chapman did not advance a mechanism to account for the formation of (17) and (18).

The other main product obtained by Chapman was the 3-oximinocholest-4-en-6-one (23) (20% yield), and it was postulated that the acetone acted not only as a solvent but also as a sensitizer. The reaction sequence was visualised as involving an initial $n\rightarrow\pi^*$ excitation to the excited singlet which then underwent conversion to an excited triplet. This excited species (15a) then underwent the reaction sequence shown in Scheme (8).

The key step in this mechanism is the conversion of $R\text{-}NO_2$ to R-O-NO, that is the conversion of (19) to (41). This process can be rationalised as occuring via a dissociation-recombination process as in nitroalkanes or by an intramolecular rearrangement.

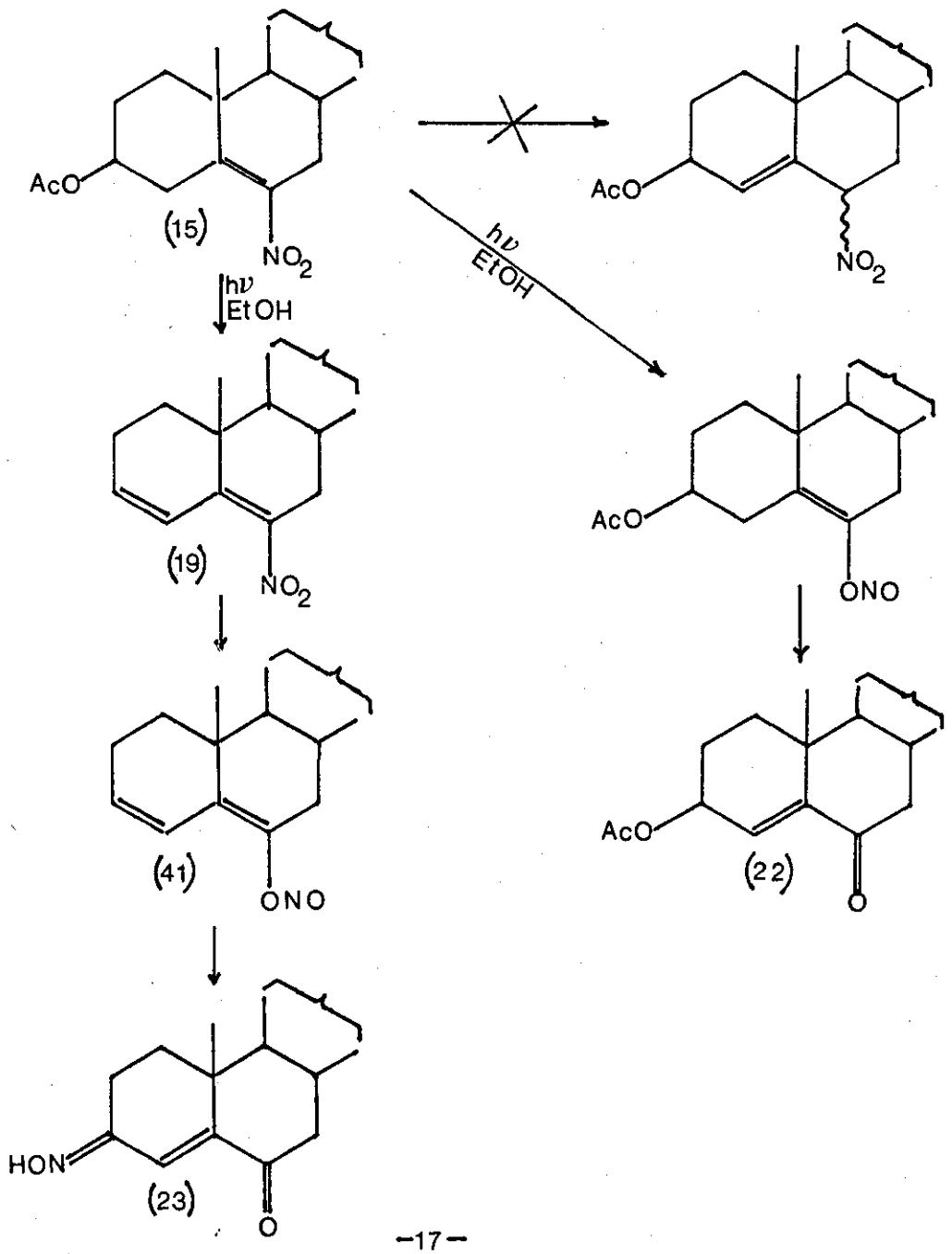
Scheme 8



The role of acetone as a sensitizer for this reaction was brought into question by the work of Coombes who examined the photochemical behaviour of 3β-acetoxy-6-nitrocholest-5-ene with and without a pyrex filter and ethanol as solvent. The major product obtained both with and without a pyrex filter was the 3-oximinocholest-4-en-6-one (23) in 38% yield, thus showing that the wavelength used was not critical. Since the product (23) was obtained in higher yield using ethanol as solvent then when acetone was used this result casts doubt upon the assertion that acetone was acting as a sensitizer in the formation of (23). The other products obtained from the photolysis of the

nitro-compound (15) in ethanol were 6-nitrocholest-3,5-diene (19) (2.5%) which was shown, in a separate photolysis experiment, to be converted to the 3-oximino -compound (23) and 3β-acetoxy-4-ene-6-one (22) (7%). The latter compound was postulated as arising from the nitrite intermediate. However, there was no evidence for the formation of products arising from the intramolecular hydrogen abstraction process. To account for the products the following reaction scheme was put forward (Scheme 9).

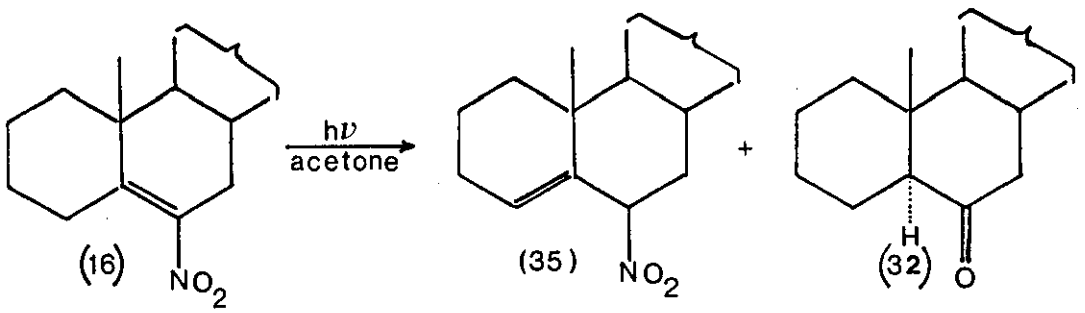
Scheme 9



It is clear from the work discussed above that the choice of solvent is of paramount importance in the photolysis of α, β-unsaturated nitro compounds.

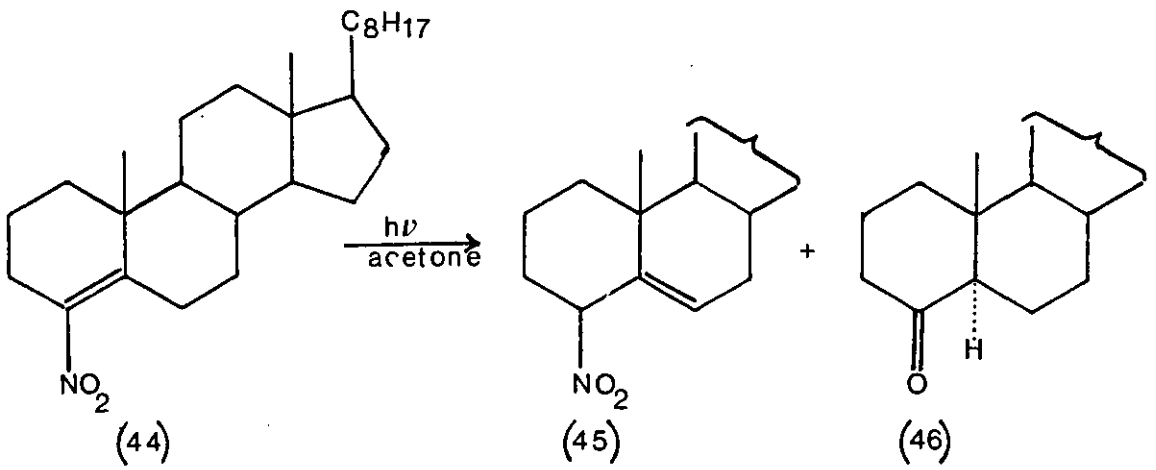
For the hydrogen abstraction process to operate another factor is also important, namely the geometry of the molecule. In order for the hydrogen abstraction process to occur the α, β-unsaturated nitroalkene must posess a hydrogen favourably orientated for abstraction via a six-membered transition state.

This point was demonstrated by Cridland and co-workers,[25] who examined the photochemistry of cyclic and acyclic α, β-unsaturated nitroalkenes. Photolysis of 6-nitrocholest-5-ene (16) in acetone gave 6-nitrocholest-4-ene (35) (45%), in agreement with results obtained by other workers, and the 6-keto compound (32) (20%).



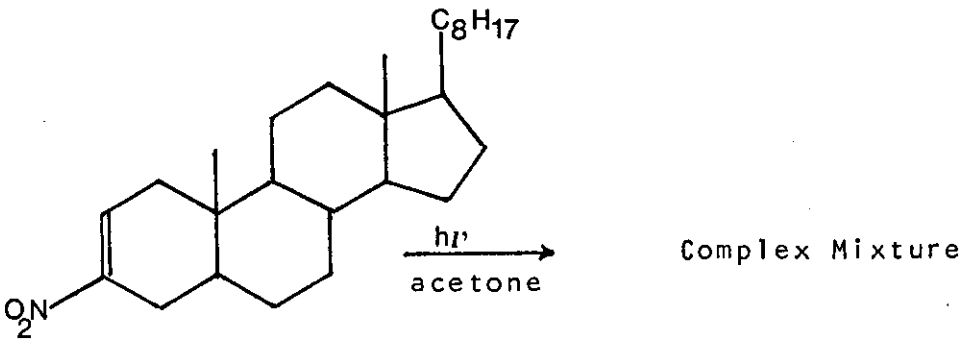
(16) (35) (32)

An analogous reaction was observed in the photolysis of 4-nitrocholest-4-ene (44).

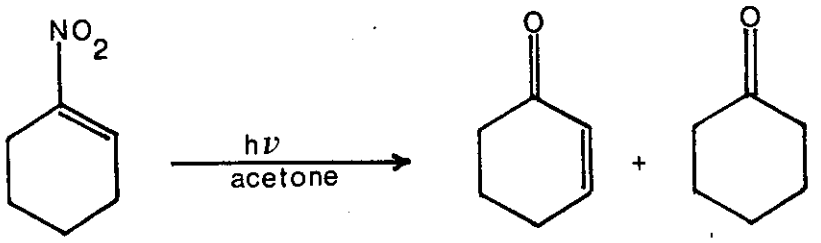


(44) (45) (46)

In contrast 3-nitrocholest-2-ene (47) and 1-nitrocyclohexene (48) which do not posess a suitable γ-hydrogen do not give the products of intramolecular hydrogen abstraction under the same experimental conditions.



(47)

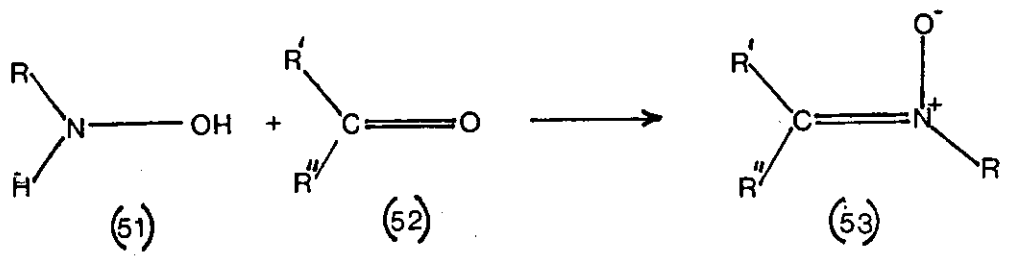


(48) (49) (50)

3) The Preparation of Nitrones and Oxaziridines

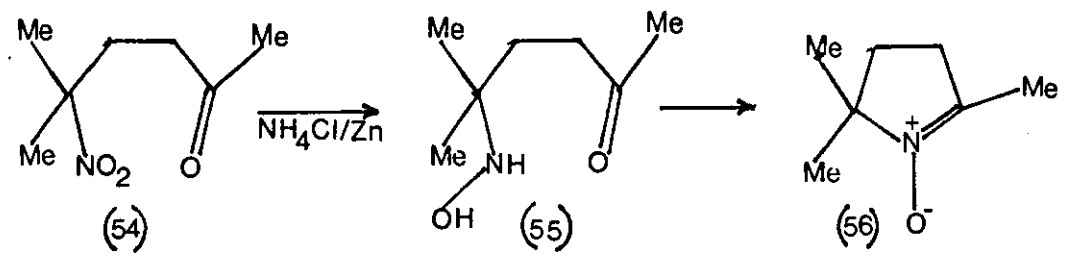
A) The Preparation of Nitrones

The most common method of nitrone preparation is the condensation of an N-alkyl or N-aryl-hydroxylamine (51) with an aliphatic or aromatic aldehyde or ketone (52).[26] This method often gives the desired nitrone (53) in yields of 80-90%.



(51) (52) (53)

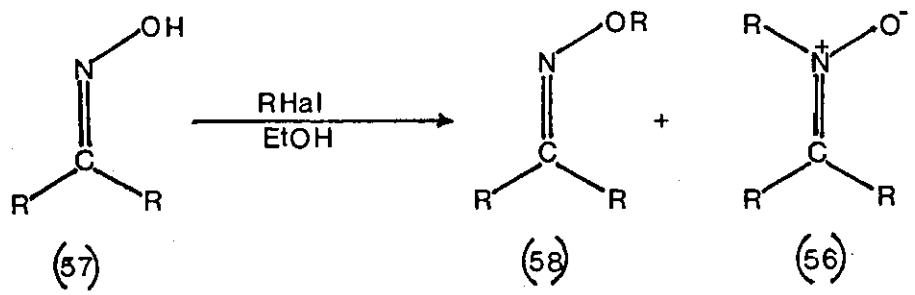
The usefulness of this procedure is limited by two factors. The first is its susceptibility to steric hinderance whereby bulky substituents on either the carbonyl compound or the N-substituted hydroxylamine can severely affect the efficiency of the reaction. The second limitation is the relative inaccessibility of the required N-substituted hydroxylamine starting materials. This second limitation has been overcome in many cases by generating in situ the N-substituted hydroxylamine required from more readily available precursors. An example of this approach is the synthesis of Δ'-pyrroline-1-N-oxides (56) which have been prepared according to the route below.[27]



(54) (55) (56)

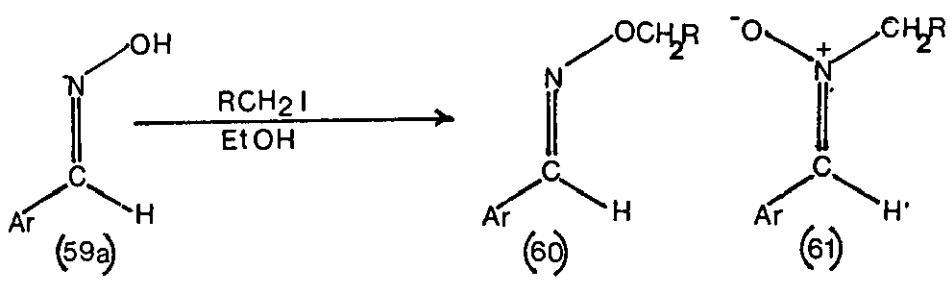
This reaction is an illustration of the commonly used procedure of converting a nitro group into a N-substituted hydroxylamine. In this particular case the intermediate N-substituted hydroxylamine-carbonyl compound (55) undergoes spontaneous ring closure to give the nitrone (56).

An alternative procedure for the preparation of nitrones is the alkylation of an oxime (57). However, oximes are ambident nucleophiles and the use of common alkylating agents such as alkyl halides results in both alkylation of oxygen to give the oxime ether (58) and at nitrogen to give the nitrone (56) thus limiting the applicability of this procedure.



(57) (58) (56)

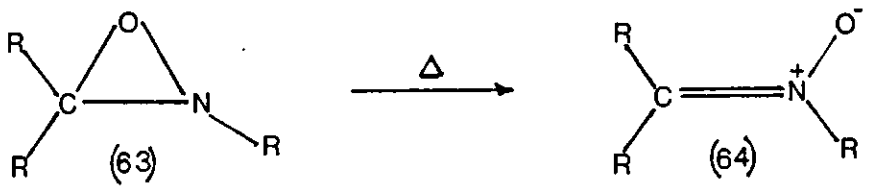
The preferred site of alkylation is dependent on a number of factors including oxime structure, the nature of the alkylating agent and the reaction conditions. For example Buehler,[28] has shown that alkylation of the syn-benzaldoxime (59a) with an alkyl halide gives predominately the oxime ether (60) and some of the nitrone (61), whereas alkylation of the anti-benzaldoxime (59b) under the same conditions gave exclusively the nitrone (61).



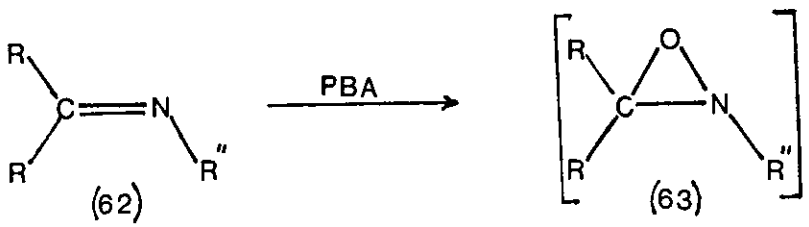
(59a) (60) (61)

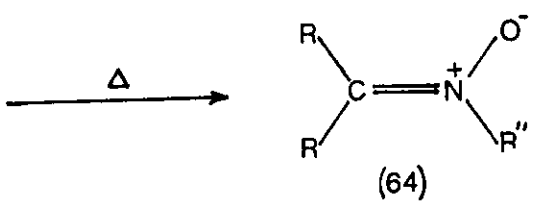
(59b) (61)

A third procedure for nitrone preparation, which has been reported,[29] is the thermal rearrangement of oxaziridine (63) under carefully controlled conditions, in order to avoid the alternative rearrangement to amide, which is discussed later.



In the procedure the oxaziridine is formed by peracid oxidation of an imine (62) and is often rearranged to the nitrone (64) without isolation. This method has been shown to be applicable to nitrone formation from imines containing alkyl, cycloalkyl and aryl substituents (R").



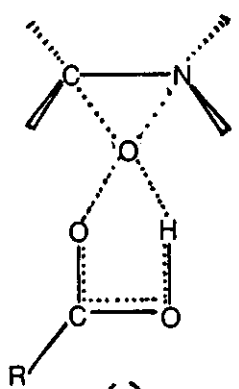


(64)

B) Preparation Of Oxaziridines

Since their discovery, firstly by Krimm,[30] then later but independently by Emmons,[31] a great deal of interest has been shown both theoretically and practically in the chemistry of oxaziridines. In recent years several procedures have been developed for oxaziridine synthesis, for example the use of alkyl hydroperoxides with catalytic amounts of molybdenum compounds,[32] or mixtures of hydrogen peroxides and nitriles,[33].

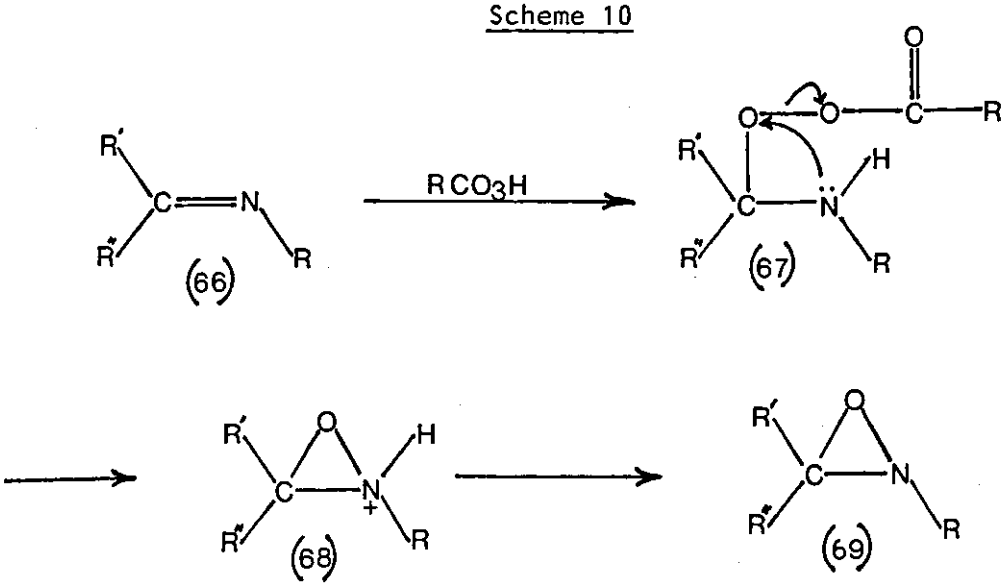
However, despite these advances the most widely used procedure for their preparation is the original reaction of peracids with an imine (Schiffs base) which is analogous to the peracid epoxidation of alkenes. Although the peracid oxidation of an imine to give an oxaziridine has been known for almost thirty years the mechanism is still in doubt. Emmons postulated two possible mechanisms,[34] . The first is a concerted mechanism involving electrophilic attack by the peracid on the imine to form a "butterfly-type" intermediate (65) analogous to that accepted as occurring in the peracid epoxidation of alkenes.



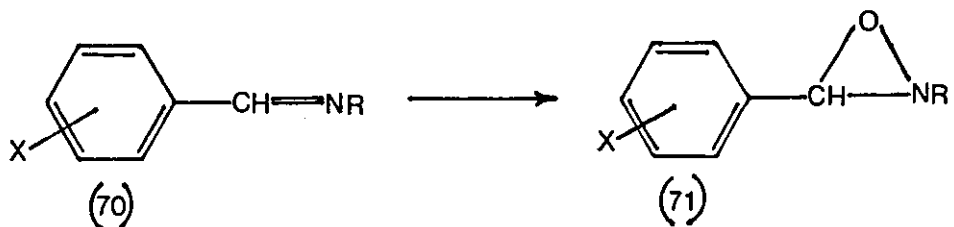
(65)

The second mechanism proceeds through addition of the peracid to the imine followed by internal nucleophilic displacement of the basic nitrogen atom on the peroxide bond, this reaction sequence is shown in Scheme 10.

Scheme 10

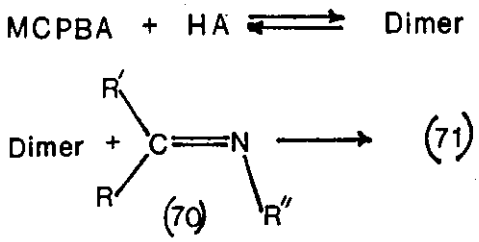


In an attempt to determine which mechanism operates many workers have carried out extensive kinetic studies. Madan and Clapp,[35] examined the kinetics of the reaction between benzylimines (70) and meta-chloroperbenzoic acid (MCPBA) to give oxaziridines of the general formula (71)

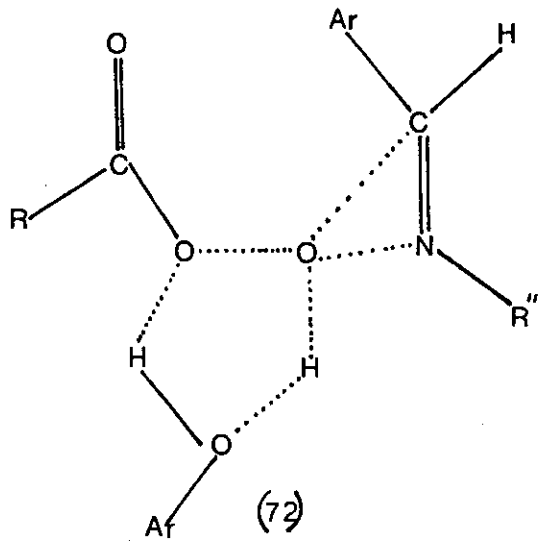


X = p-CH_3, p-NO_2 ; R=alkyl

It was found that the formation of the oxaziridines (71) was catalysed by the presence of carboxylic acids and this effect was explained as being due to the formation of a dimer between the peracid and the carboxylic acid. The oxaziridine is formed by a concerted reaction between the dimer and the imine.

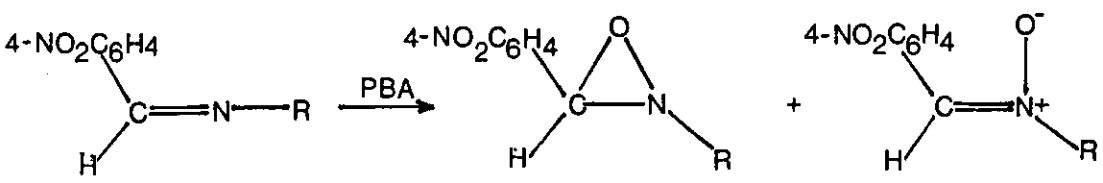


The actual intermediate (72) of the oxidation is formed by nucleophilic attack of the π-electrons of the C=N on the sterically less hindered peracid hydroxylic oxygen in a manner analogous to that suggested for alkene epoxidation.



(72)

However, this interpretation of the kinetic data in terms of a modified one-step mechanism was questioned by Ogata and Sawaki[36]. Ogata and Sawaki examined the reaction between benzylimines (73) and perbenzoic acid (PBA) and found that depending on the solvent conditions employed the reaction could lead to both oxaziridine (74) and nitrone (75) formation.

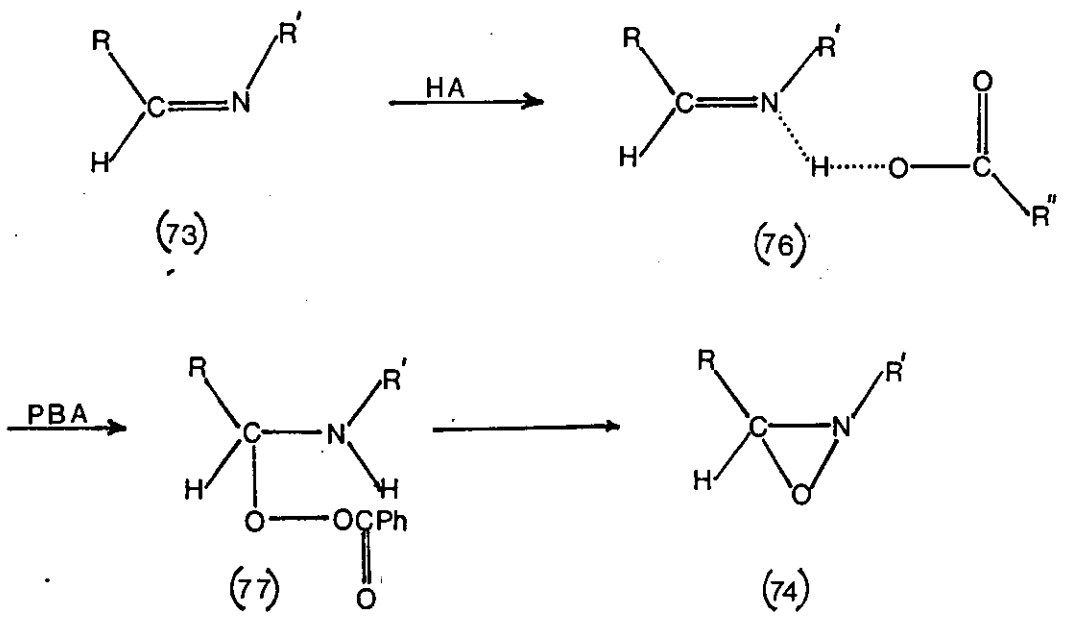


(73) (74) (75)

R = alkyl

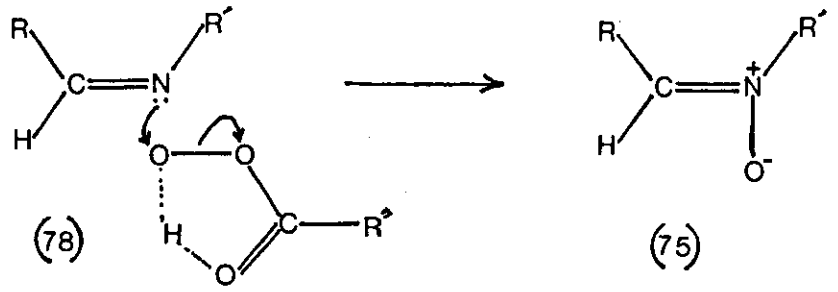
From a study of the kinetic data obtained on the reaction between the Schiffs base (73) and PBA under a variety of solvent conditions, Ogata and Sawaki concluded that the modified one-step oxidation mechanism did not adequately explain their observations. Most importantly, they concluded that there was no evidence to support the formation of the dimer . Instead the acid catalysis observed was postulated as arising from hydrogen bonding between the added carboxylic acid (HA) and the Schiffs base nitrogen to give the intermediate (76). The formation of the intermediate (76) would result in increased nucleophilicity of the C=N of the Schiffs base. The oxidation to give the oxaziridine (74) then proceeds by interaction between the C=N π-bonding electrons and the peracid to give the intermediate (77), which undergoes internal nucleophilic substitution to give the oxaziridine (74). This two-step oxidation mechanism is shown in Scheme 11.

Scheme 11



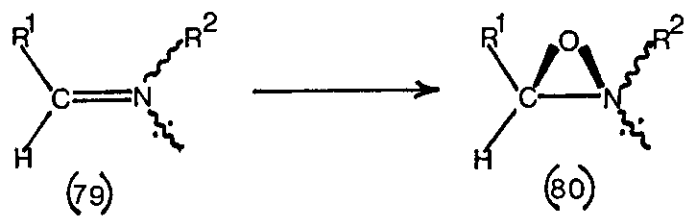
R = $NO_2C_6H_4$ R = alkyl

The formation of the nitrone (75) which was observed as the co-product in several of the Schiffs base oxidations was postulated as arising via nucleophilic attack by the nitrogen lone-pair on the peroxide oxygen (78)



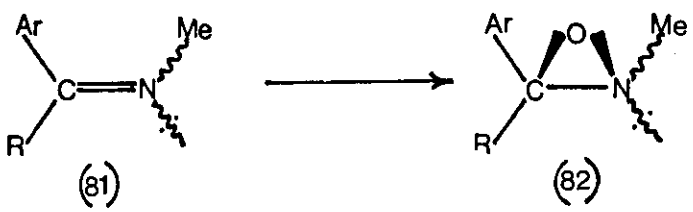
(78) (75)

To try and resolve the problem as to which mechanism operated, Boyd *et al*,[37] investigated the stereochemistry of the peracid oxidation of imines to oxaziridines in order to examine the possible relevance of reactant and product molecular geometry in distinguishing between concerted and step-wise mechanisms. Measurements of the *cis*-*trans* ratio of a number of C-arylaldimines (79) and their oxaziridines (80) and of C-arylketimines (81) and their oxaziridines (82) were made by n.m.r. spectroscopy.



(79) (80)

R^1 = 4-$NO_2C_6H_4$; Ph , Et R^2 alkyl



(81) (82)

R = Me; Et; Bu^t

It was found in the conversion of (79) to (80) the proportion of cis-oxaziridine was always greater than the proportion of cis-imine initially present. For example when R'=4-$NO_2C_6H_4$ R^2= Et the oxaziridine contained 54% cis-isomer whereas the amount of cis-isomer present in the imine was less than 1%.

In the conversion of (81) to (82) it was found that the proportion of cis-imine varied with the size of the group R. When R=Me the imine contained 7% cis-isomer, the product oxaziridine 68%, and when R=Bu^t both imine and oxaziridine were 100% cis.

The authors concluded that the preferential formation of cis-oxaziridine from trans-imine was difficult to rationalise in terms of a concerted mechanism and although this could not be entirely eliminated it was felt that the two-step mechanism put forward by Ogata and Sawaki was more probable.

Further support for the two-step mechanism came from the theoretical work of Azman and co-workers,[38] who examined the oxidation of an imine with peroxyformic acid by ab initio molecular orbital calculations. These calculations showed the calculated energetics of the two-step mechanism were in closer agreement with experimental observations than were the energy requirements of the concerted mechanism.

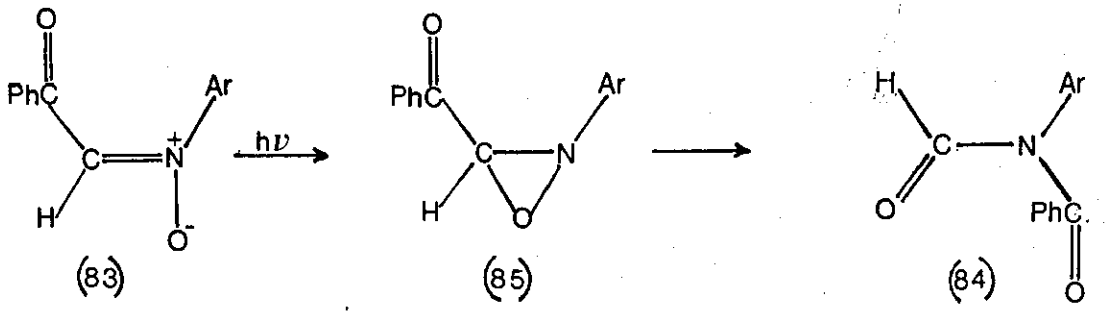
4) The Photochemistry of Nitrones and Oxaziridines

A) Nitrone Photochemistry

It has been known since the beginning of this century that nitrones are unstable to light and by the early 1950's it was clearly established that amides were the major products arising from the photochemical reactions of nitrones.

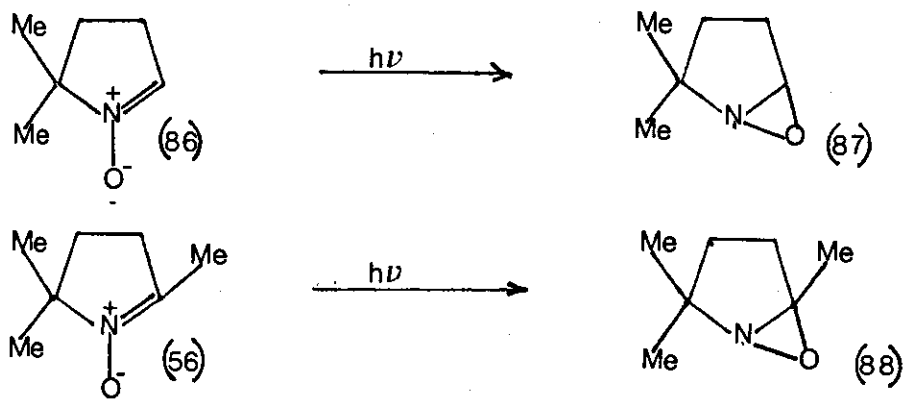
That oxaziridines were involved as intermediates in these reactions was first postulated by Krohnke,[39] who examined the irradiation of

N-aryl-α-benzoylnitrones (83) to give N-aryl-N-formyl benzamides (84), via the oxaziridine (85), as shown below:



(83) (85) (84)

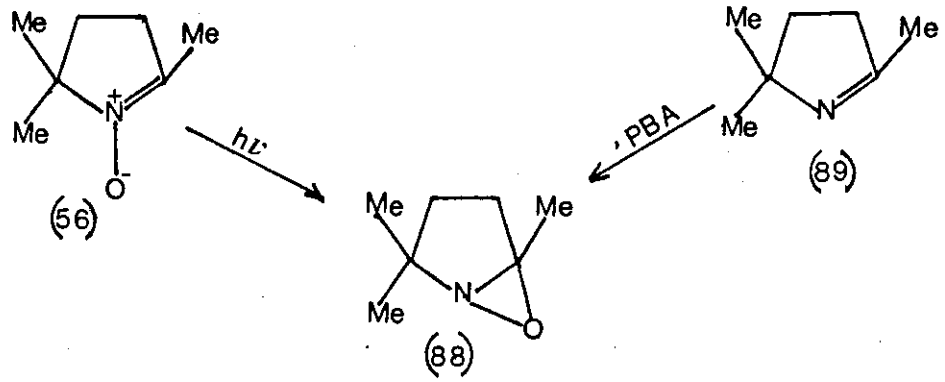
That nitrones could be photochemically isomerised to oxaziridines was firmly established by Kamlet and Kaplan;[40] and subsequently many workers demonstrated that this was a general reaction of nitrones. In the early work, all of the nitrones converted to oxaziridines posessed a proton on the nitrone carbon atom and this was thought to be a necessary structural requirement for oxaziridine formation. For example, Todd and co-workers;[41] in examining the reactions of pyrroline oxides found that 5,5-dimethyl-1-pyrroline-1-oxides (86) produced an oxaziridine on irradiation, whereas 2-substituted-1-pyrroline-1-oxides (56) failed to do so despite having very similar ultraviolet absorption spectra .



(86) (87)

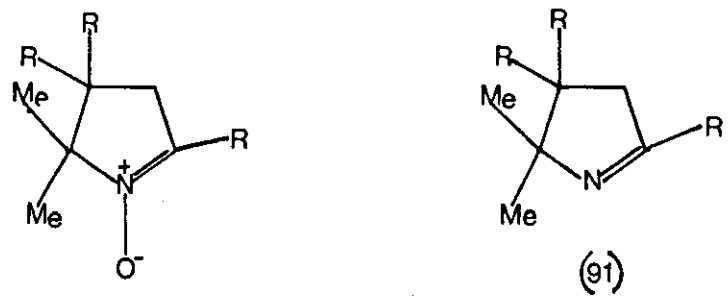
(56) (88)

That this theory was incorrect was demonstrated by Kaminsky and Lamchen;[42] who successfully converted the 2-substituted-1-pyrroline-1-oxide (56) to its oxaziridine (88) by photolysis, the product obtained being identical with that obtained by peracid oxidation of the imine (89).



(56) (88) (89)

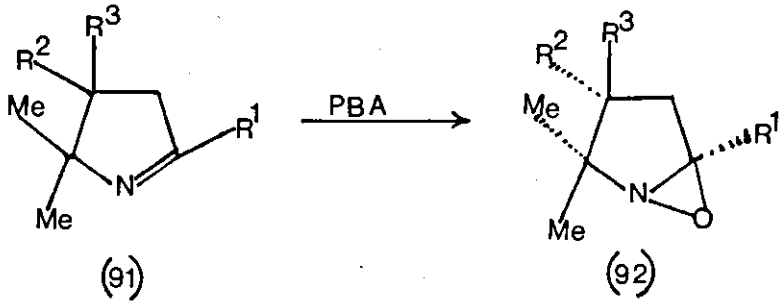
This work was extended by Bapat and Black[43] who prepared a number of oxaziridines by both photoisomerisation of 1-pyrroline-1-oxides (90) and by the peracid oxidation of 1-pyrrolines (91).



(90) (91)

The aim of this work was to determine whether or not the peracid oxidation was a stereospecific process and to compare the stereochemistry of the oxaziridines prepared by the two procedures. To do this Bapat and Black used nitrones and imines unsymmetrically substituted at C-4. They determined the geometrical relationship of the substituent at C-2 with respect to those at C-4 in the product oxaziridine ie was the substitutent at C-2 cis or trans to the substituent at C-4?

From this work the authors determined that in the peracid oxidation only the cis-oxaziridine (92) was produced irrespective of the nature of the substituent at C-2.

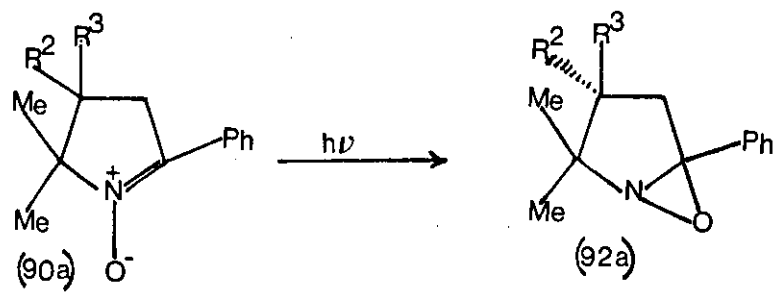


(91) (92)

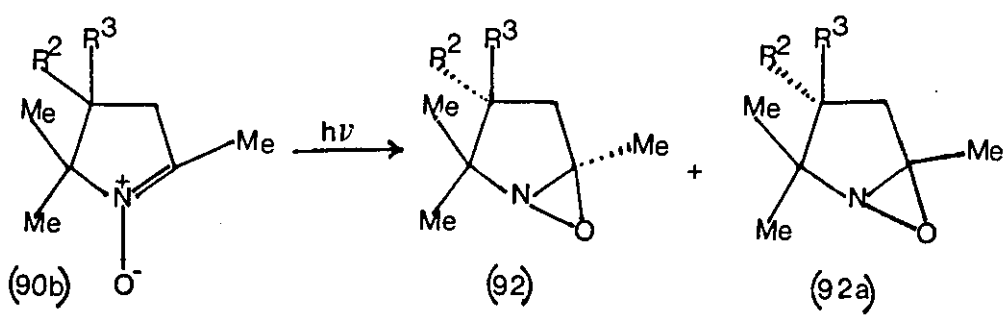
R^1 = Ph or Me R^2 = Ph or Me R^3 = H

The observed stereoselectivity is due to attack by the peracid from the less hindered face of the pyrroline ring ie on the side opposite to the group R^2. This forces the substituent R^1 into a cis-relationship with R^2 as shown above. This behaviour is analogous to that observed in the peracid epoxidation of alkenes.

However, in the photochemical studies on nitrones the situation was more complicated. It was found that if the substituent R^1 was phenyl then only the trans-oxaziridine (92a) was obtained. But if R^1 was methyl then a mixture of cis and trans-oxaziridines (92) and (92a) was obtained.



(90a) (92a)

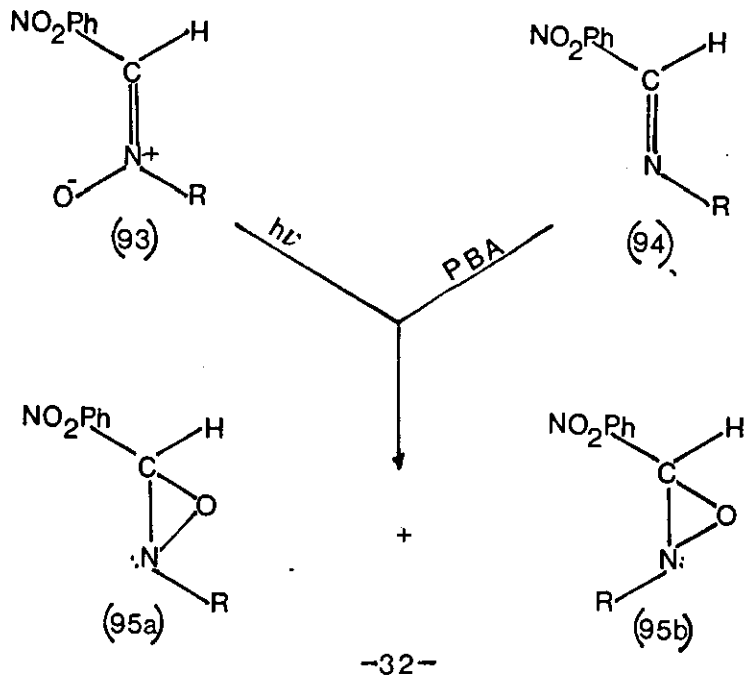


(90b) (92) (92a)

The authors had expected that photolysis of a nitrone would always lead to a mixture of isomers since it was expected the excited state of the nitrone would be planar, allowing for equal formation of both isomers. The formation of only one isomer in the case of the 2-phenyl compounds, was thought to be due to the excited state not being planer but adopting the trans-geometry leading to the more thermodynamically stable trans-oxaziridine.

The work discussed above was concerned with the determination of the cis-trans relationships of ring-substitutents in fused bicyclic oxaziridines.

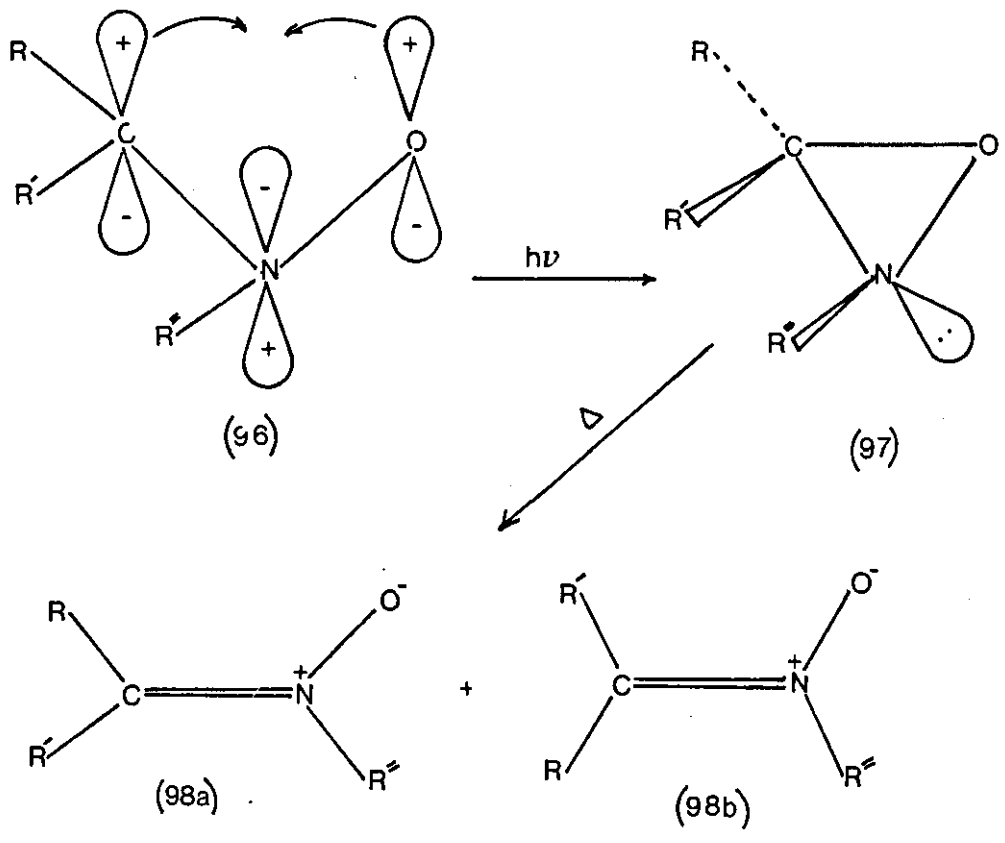
However, there have been many investigations in recent years into the stereochemical features of the nitrone to oxaziridines reaction which have been concerned with stereochemistry with respect to the C=N bond. That is whether or not an E or Z nitrone will react with retention or loss of stereochemistry and conflicting results have been reported. For example Boyd,[44] examined the formation of a series of oxaziridines by both nitrone photolysis and peracid oxidation of imines and analysed the cis-trans ratio of the products. The reaction scheme examined is shown below.



It was found that by changing the substituent R the product ratio was also altered. For example when R=methyl, photolysis of the trans-nitrone (93) gave a product ratio of 60% trans (95a) 40% cis (95b) but when R=Bu^t trans-nitrone gave only trans-oxaziridine. Measurements on the peracid oxidation of the imine (94), specifically where R = Me, showed that the product ratios were markedly solvent dependent.

However, it has been proposed that, contrary to the above, the photochemical conversion of nitrones to oxaziridines is stereospecific.

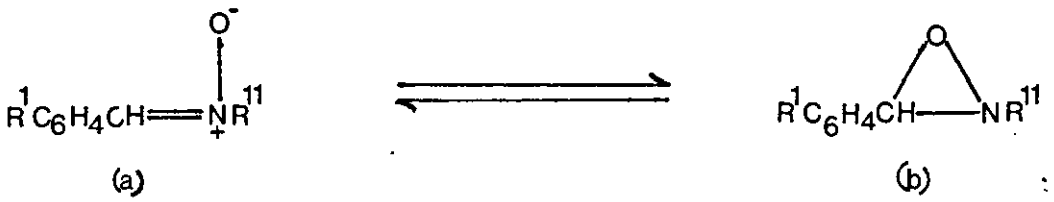
These contradictory results were finally rationalised by the work of Splitter and Calvin[45]. According to orbital symmetry rules the formation of an oxaziridines from a nitrone by photochemical means should be a stereospecific process, whereas the thermal ring opening back to nitrone has two possible conrotatory motions of the C-O bond cleavage which should result in a mixture of cis and trans isomers, (98a) and 98b respectively, as illustrated below.



(96) (97) (98a) (98b)

Splitter and Calvin examined the irradiation of several nitrones at -60°C so as to avoid thermal isomerisation of both oxaziridines and nitrone (Table 1).

Table 1



I $R^1 = (CH_3)_2N$; $R^{11} = CH_3$

II $R^1 = H$; $R^{11} = CH_3$

III $R^1 = NO_2$; $R^{11} = CH_3$

IV $R^1 = NO_2$; $R^{11} = CH_2CH_3$

It was shown by n.m.r. spectroscopy that at -60°C all of the nitrones Ia to IVa consisted of only the trans-isomer.

Irradiation of nitrones Ia and IIa were shown by n.m.r. spectroscopy to give only trans-oxaziridines. However, the nitrones IIIa and IVa on photolysis gave a mixture oxaziridines consisting of 69% cis-isomer and 31% of the trans isomer. To try and explain the formation of the cis-oxaziridine the authors made measurements of the quantum yield for photochemical reactions occurring, (table 2).

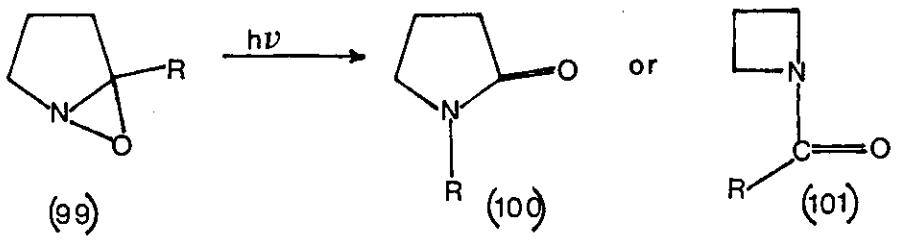
Table 2

Reaction	ø
trans-IVa → IVb	0.016
trans-IVa → cis-IVa	0.18
cis -IVa → trans-IVa	0.46
cis -IVa → cis IVb	0.087

From these results it is possible to calculate the expected composition of oxaziridine IVa to be 68% cis:32% trans if a stereospecific process is involved. As stated above the observed ratio is 69% cis:31% trans confirming the reaction to be stereospecific.

B) Oxaziridine Photochemistry

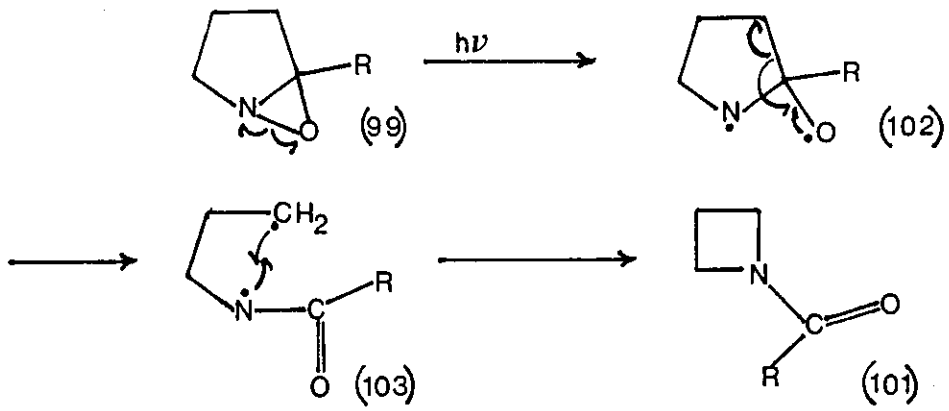
In the work reported by Bapat and Black,[43] on nitrones the predominant reaction observed on photolysis of the product oxaziridines was cis-trans isomerisation and little evidence was found of further reactions. However, further reports on such systems show that they undergo rearrangement reactions to give amides as shown below:



(99) (100) (101)

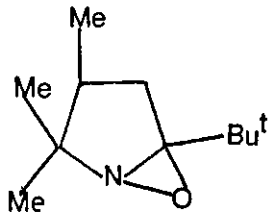
In the oxaziridine (99) where R= H the predominant product of rearrangement is the pyrrolidone (100) whereas when R= alkyl the azetidine (101) is formed.

Kaminsky and Lamchen,[42] explained the formation of the azetidine (101) by the mechanism below:-

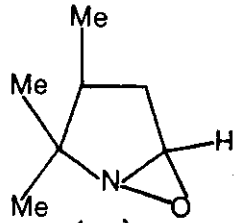


The general mechanistic aspects of the photolysis of these bicyclic oxaziridines were examined in detail by Black and Watson,[42] who

investigated the photolysis of the two oxaziridines (104) and (105).

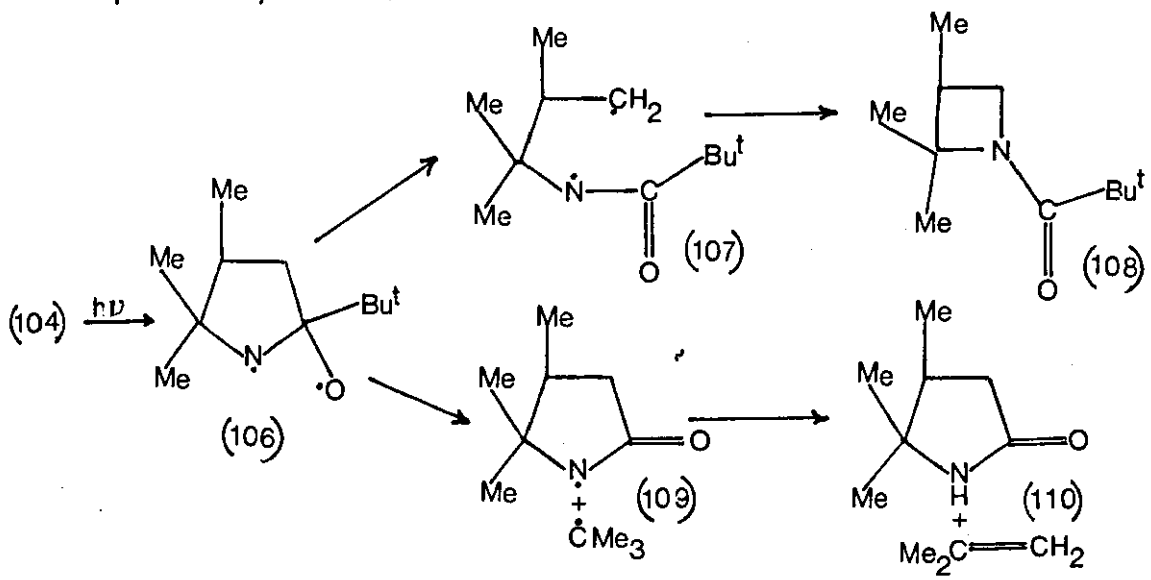


(104)



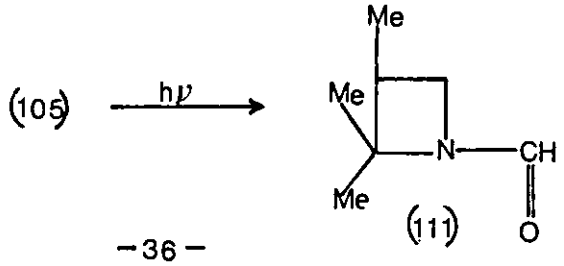
(105)

On irradiation of oxaziridine (104) or extensive irradiation of its nitrone precursor two products were observed, (108) and (110), which were explained by the mechanism below:



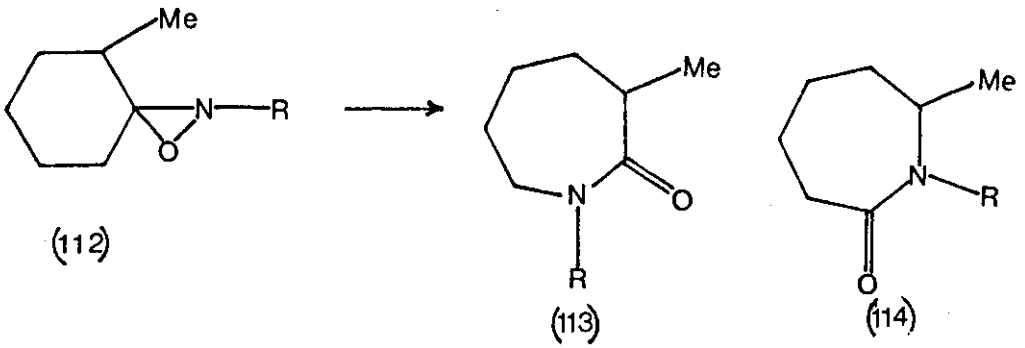
The first step in the mechanism is homolytic N—O bond cleavage as put forward by Kaminsky and Lamchen,[42]. The resulting biradical (106) can then rearrange via two alternative pathways, one leading to the azetidine (108) via the intermediate (107) as observed by Kaminsky and Lamchen,[42]. The lactam (110) arises because the t-butyl radical formed is sufficiently stable to allow this pathway to become competitive and also provides the hydrogen atom necessary for lactam formation.

The photolysis of oxaziridine (105) gives rise to only one product, the azetidine (111) as expected



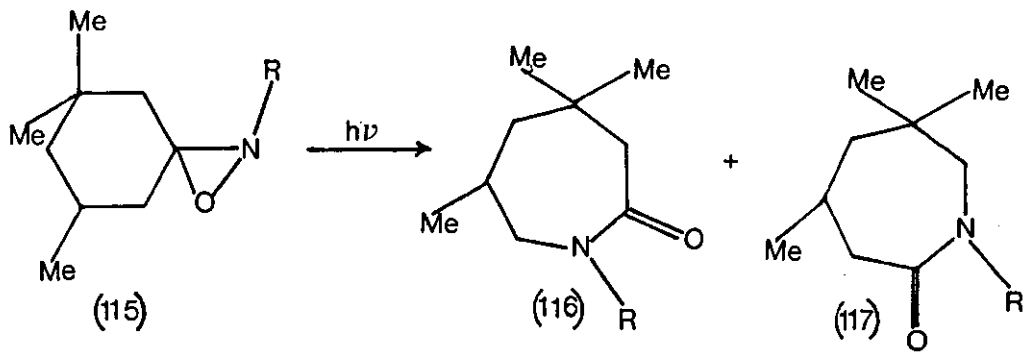
These results are consistent with the general free-radical mechanism put forward by Kaminsky and Lamchen.

The theory that a free-radical mechanism satisfactorily explained the photochemical reactions of oxaziridines was brought into question by the studies into the photochemical and thermal behaviour of spiro-oxaziridines reported by Decherches and Oliveros,[47] the result of which are summarised below:



(112) (113) (114)

	Ratio of (113) to (114)
a) Photolysis	95 : 5
b) Thermolysis	65 : 35



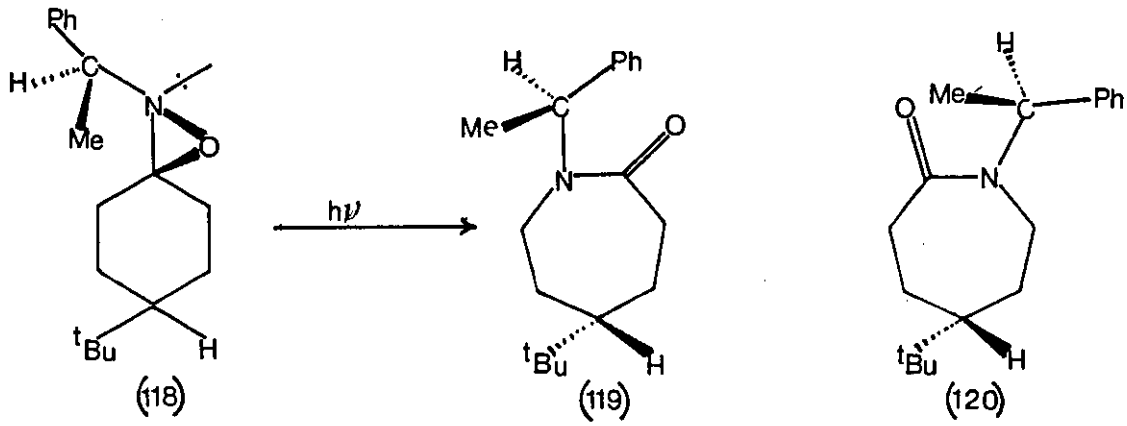
(115) (116) (117)

50 : 50

From these results it can be seen that the oxaziridine (112) which has an α-substituent exhibits almost complete regioselectivity on photolysis and a marked regioselectivity on thermolysis. Whereas the oxaziridine (115) which has β-substituents does not show any

regioselectivity. More importantly in the α-substituted spiro-oxaziridine (112) photolysis results in migration of the less-substituted carbon which is contrary to what would be expected if a normal radical mechanism were operating, since cleavage of C-C bond to the more highly substituted α-carbon to give the more stable radical would be expected.

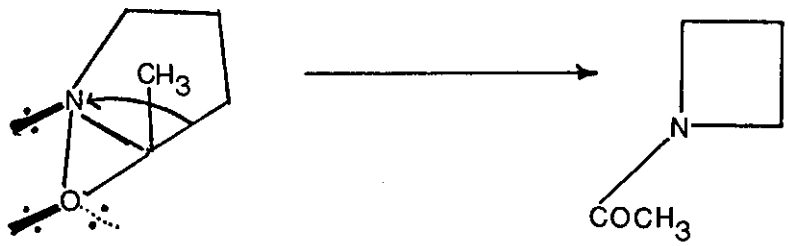
Oliveros,[48] suggested that the high regioselectivity observed with spiro-oxaziridines was due to the reaction being stereoelectronically controlled and the carbon which underwent migration lay antiperiplanar to the nitrogen lone pair in the oxaziridine. To demonstrate this, Oliveros and co-workers,[49] photolysed the spiro-oxaziridine (118) which was obtained as single pure enantiomeer of known absolute configuration. This compound does not posess α-substituents and therefore the bonds C-3—C-4 and C-3—C-8 are chemically equivalent thus eliminating the possibility of substituent effects being responsible for the observed selectivity. Photolysis of the spiro-oxaziridine (118) could theoretically lead to the two lactams (119) and (120), which are diastereoisomeric.



(118) (119) (120)

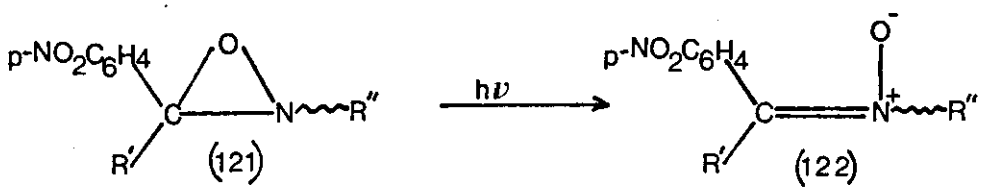
It was found that on photolysis only the lactam (119) was obtained which could only be interpreted as involving cleavage of the C-C bond anti to the nitrogen lone pair. This demonstrated clearly that stereoelectronic control operated in photochemical breakdown of spiro-oxaziridines.

The observed formation of the azetidines (92) from the fused bycyclic oxaziridines (90) discussed earlier can also be accounted for in terms of stereoelectronic control. In this, migration of a group anti to the nitrogen lone pair results in the observed ring-contraction to an azetidine as shown below:



(90) (92)

It is commonly accepted that the main photochemical reaction of an oxaziridine is intramolecular rearrangement to give an amide. However, in recent years evidence has been obtained to show that oxaziridines can be converted photochemically as well as thermally to nitrones. Bjorgo and co-workers,[50] prepared the series of optically active oxaziridines (121) shown below:



(121) (122)

trans-121 R' = H ; R'' = Me; Pr^{i}; Bu^{t}. cis-121 R' = Me ; R'' = Bu^{t}

It was found that on irradiation the trans-oxaziridines gave only trans-nitrones and partially racemised trans-oxaziridines. Whereas, the cis-oxaziridines gave trans-nitrones, cis-oxaziridine and racemic trans-oxaziridine.

C) Theoretical Investigations In Oxaziridine Photochemistry

To elucidate the actual sequence of events occuring in the photochemical breakdown of oxaziridines several groups have employed quantum mechanical techniques to examine both the oxaziridine to amide rearrangement and the nitrone-oxaziridine reversibility.

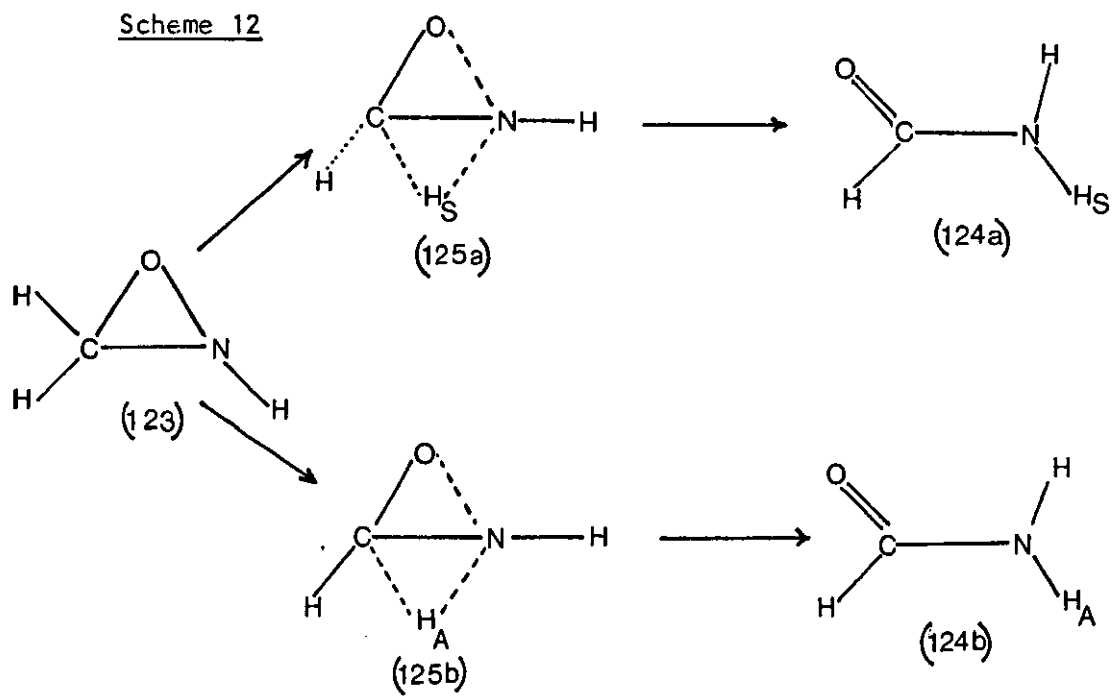
The theoretical aspects of the photochemical rearrangement have been examined by Oliveros and co-workers,[48] who took the following as the model system.

(123) (124)

This system differs from the chemical systems discussed above in that it involves C-H bond breaking and H migration as opposed to C-C bond cleavage and alkyl migration. This change is forced on the investigators because of the limitations of the quantum mechanical techniques employed.

Two possible reaction pathways were considered. The first which is shown below (Scheme12) is direct rearrangement corresponding to synchronous N-O bond bond opening and H-migration.

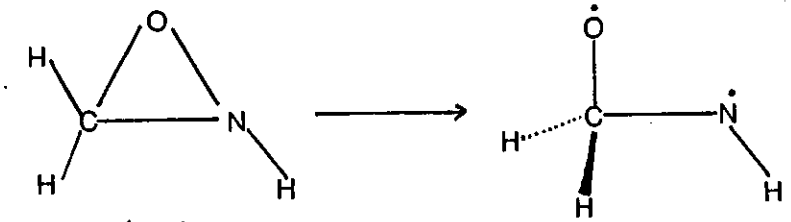
Scheme 12



(125a) (124a) (123) (125b) (124b)

In this reaction sequence the two hydrogen atoms H_S and H_A (syn and anti with respect to the nitrogen lone pair) are not equivalent in the oxaziridine (123). For this reason the two possible reaction intermediates (125a) and (125b) must be considered. However, this concerted mechanism was rejected after calculation of the energies of the intermediates (125a) and (125b) showed that the concerted process was of too high energy.

The second reaction sequence examined was a step-wise process involving initial cleavage of the N-O bond to give the intermediate (126) followed by migration of either H_S or H_A to the final products (124a) and (124b) respectively.



(123) (126)

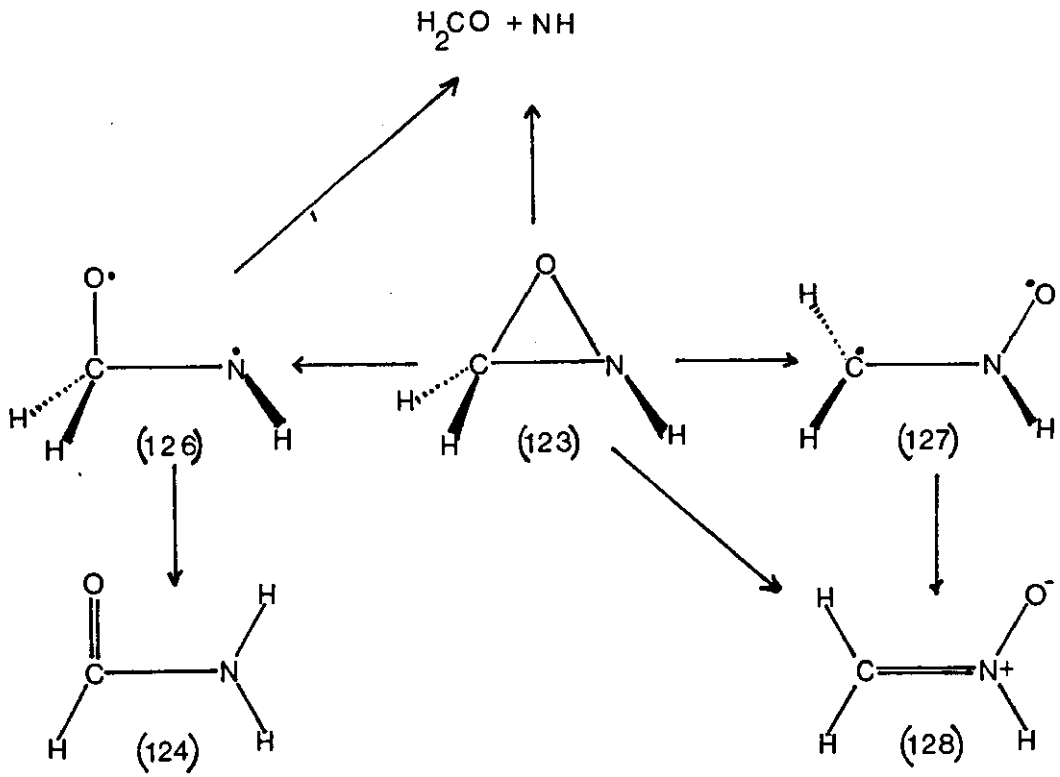
By making calculations of the potential energy curve (P.E.C.) between the intermediate (126) and the final products (124a) and (124b) it was shown that a lower energy barrier existed for migration of H_A compared to the energy required for migration of H_S.

From these calculations the following reaction sequence was put forward to account for the photochemical rearrangement of an

oxaziridine to give an amide. The ground state oxaziridine on irradiation gives an excited singlet which undergoes N-O bond cleavage. This intermediate undergoes a de-excitation process to the ground state from which migration of a hydrogen atom takes place to give the product, the hydrogen atom anti to the nitrogen lone-pair migrating preferentially.

This theoretical reaction sequence agrees well with the observed experimental data discussed earlier, although no comment is made on whether the rearrangement proceeds via homolytic or heterolytic bond cleavage.

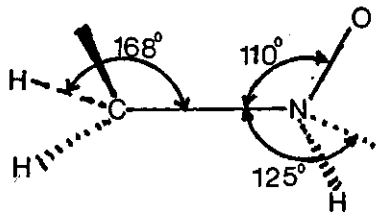
A further theoretical treatment of oxaziridine behaviour was carried out by Bigot,[51] who used an ab initio S.C.F. treatment to examine the reactions illustrated below.



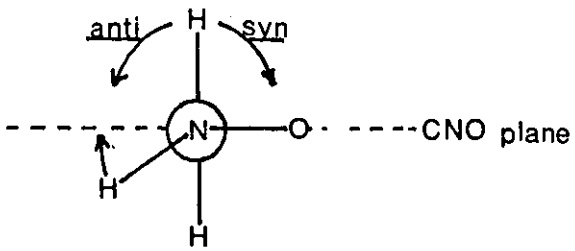
The conversion of the oxaziridine (123) to the nitrone (128) can be considered to arise by two different reaction pathways. The first is a single-step process involving synchronous C-O bond cleavage and

methylene group rotation to give the nitrone (128). However, this was shown to be a high energy process and to be less favourable than the alternative pathway.

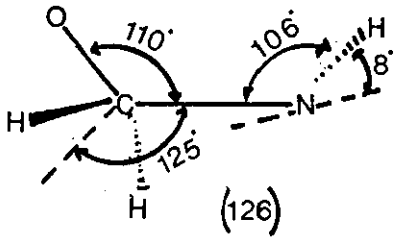
The alternative is a two step process. The first step is C-O bond cleavage to give the diradical species (127) the optimised structure of which is shown below:



This intermediate can then undergo molecular rotation to give the nitrone (128). To form the nitrone from the intermediate (127) it is necessary for the N-linked hydrogen to move into the C-N-O plane while the methylene group rotates around the C-N bond. The methylene group rotation can be in the same direction as that of the N-linked hydrogen (<u>syn</u> process) or in the opposite direction (<u>anti</u>-process) as shown below.

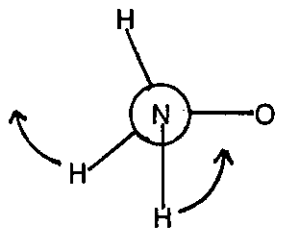


In considering the oxaziridine (123) to amide (124) rearrangement Bigot, as does Oliveros, considers the first step to be N-O bond cleavage, to give the intermediate (126), the optimised structure of which is:-

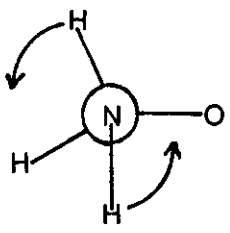


(126)

During this ring-opening there is a retention of configuration of the N-linked hydrogen. This means there are two distinct migration pathways. In one the migrating hydrogen is <u>cis</u> to the N-linked hydrogen (the <u>syn</u> process) and in the other pathway it is <u>trans</u> (the <u>anti</u> process) these two pathways are shown below.



<u>syn</u>



<u>anti</u>

Calculations of the potential energy curves corresponding to these two processes show the <u>syn</u> process to be the favoured route, although the energy differences between the two processes are not significant.

Bigot concluded that the migrating hydrogen atom (or carbon in the physical process) was not determined by orbital factors but by general migratory aptitude, strain energy, and geometrical requirements of the transition state.

This is in contrast to Oliveros who believes that there is a

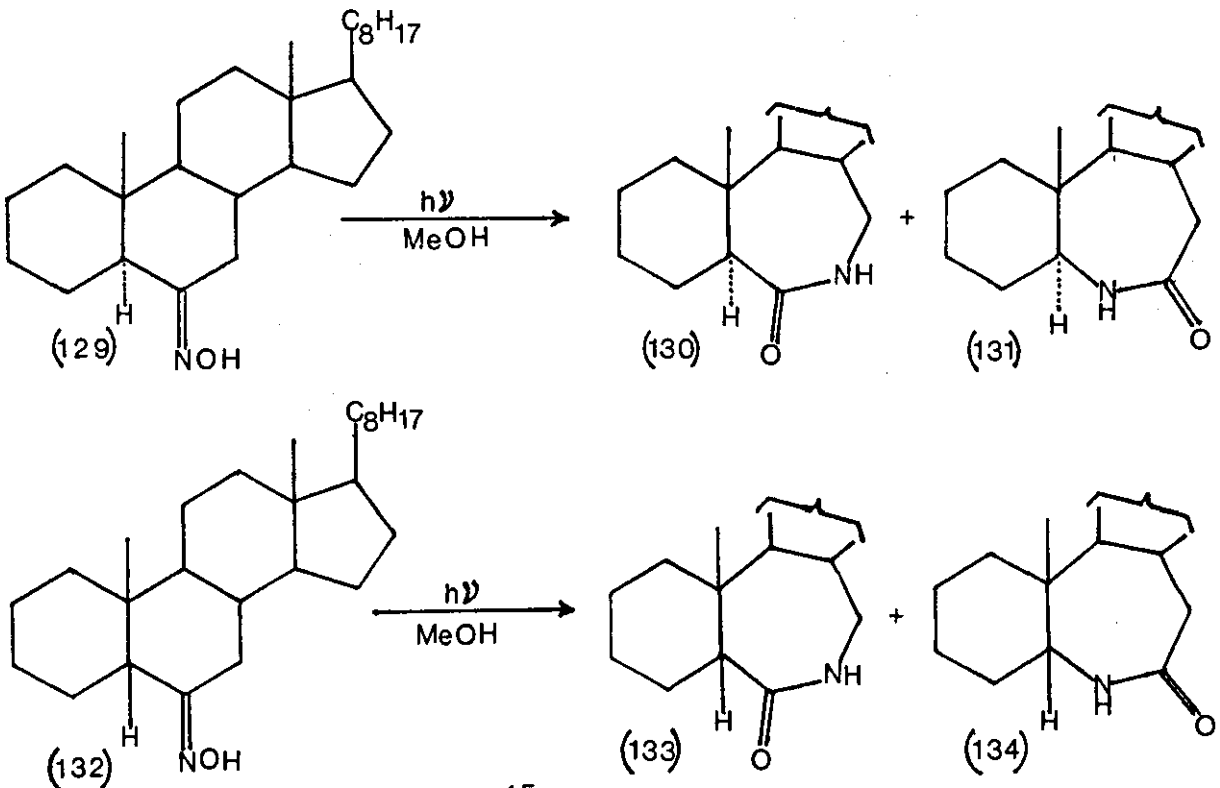
significant difference in the two possible pathways and the group anti to the nitrogen lone pair will migrate preferentially.

In conclusion it can be seen that both theoretical and experimental evidence shows that there is a difference in the migrating aptitude of groups α- to the oxaziridine carbon and that the orientation of the groups with respect to the nitrogen-lone pair is of paramount importance in determining the migration pathway.

5) The Photochemistry Of Oximes

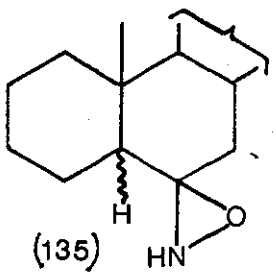
As has been shown earlier the intramolecular rearrangement of a spiro-oxaziridine (112) leads to the formation of a lactam (113). It is therefore of interest to examine the work of Suginome who has investigated the photo-Beckmann rearrangement of steroidal oximes to give lactams.

In the initial work on cholestan-6-one oximes Suginome,[52] found that photolysis of 5α-cholestan-6-one oxime (129) gave the two lactams (130) and (131) in yields of 11% and 15% respectively and that 5β-cholestan-6-one oxime (132) yielded the two lactams (133) and (134) in yields of 28% and 11% respectively.



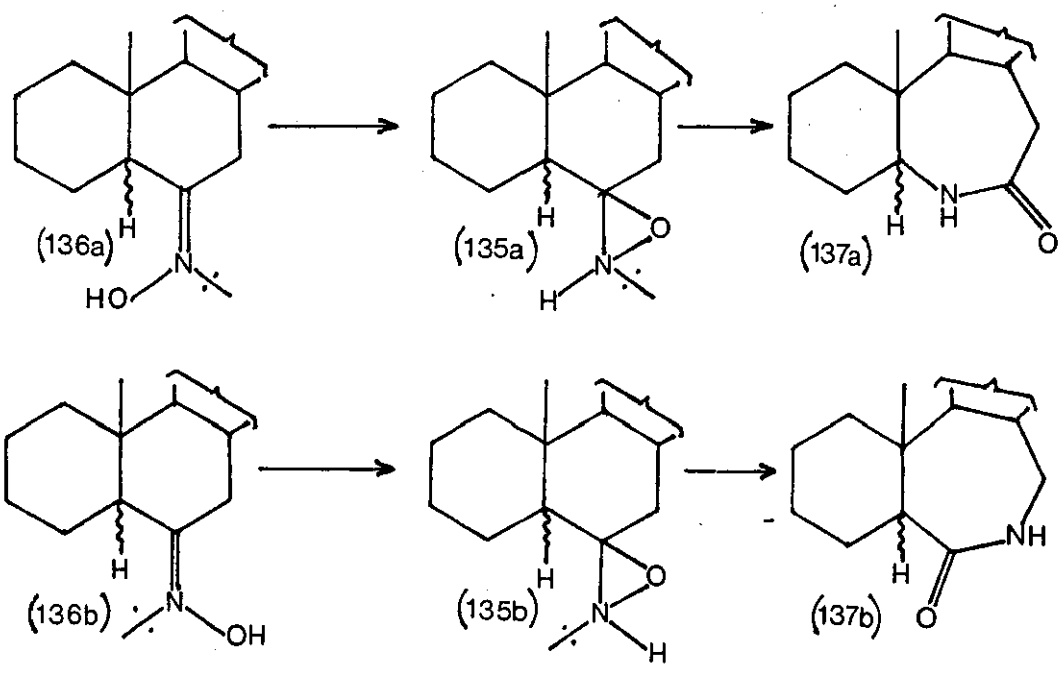
These results indicated that the reactions were not regiospecific, although a preference for migration of the more substituted carbon was observed. It was also observed that the stereochemical integrity of the migrating group was retained.

Suginome proposed that the reactions proceeded via an intermediate oxaziridine (135) which rearranged in a concerted manner to give the observed products.

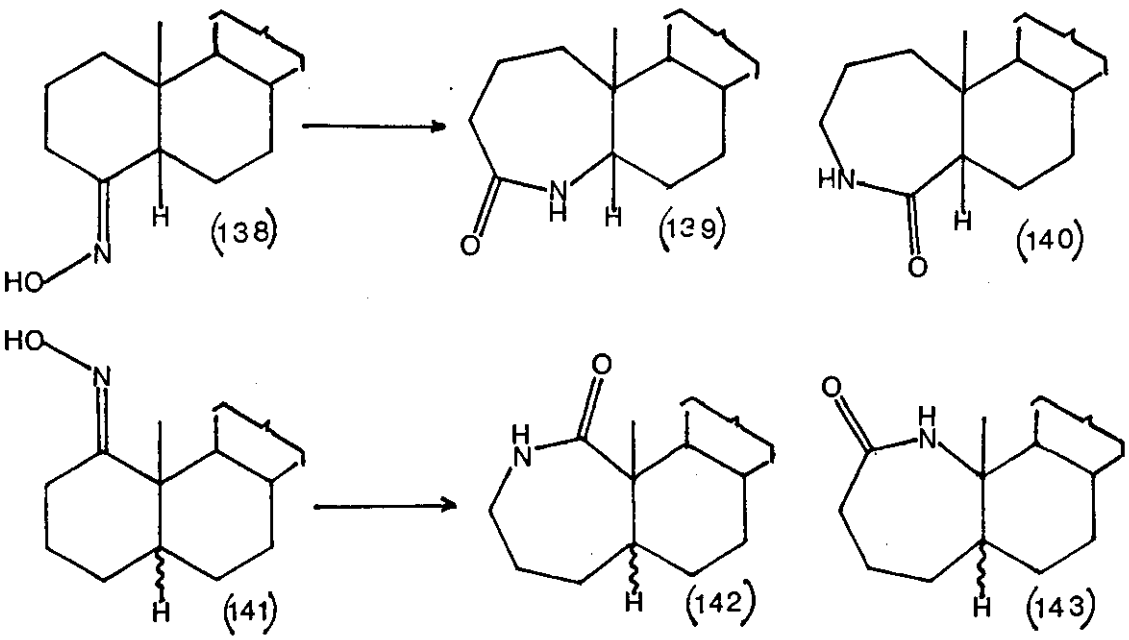


(135)

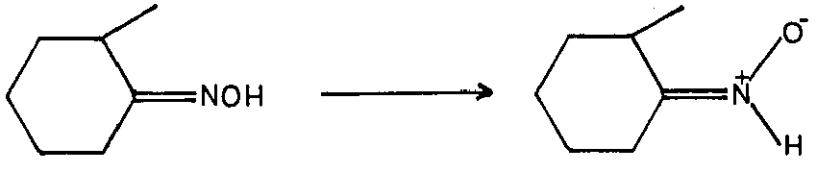
The lack of regiospecificity in the breakdown of the oxaziridine (135) is in contrast to the results obtained by Oliveros discussed earlier. This could be accounted for by the existence of the oximes (129) and (130) as mixtures of E and Z isomers (136a) and (136b) which could give the oxaziridines (135a) and (135b) respectively. Normal stereoelectronic control would result in the formation of the 6 -aza lactam (137a) from (135a).



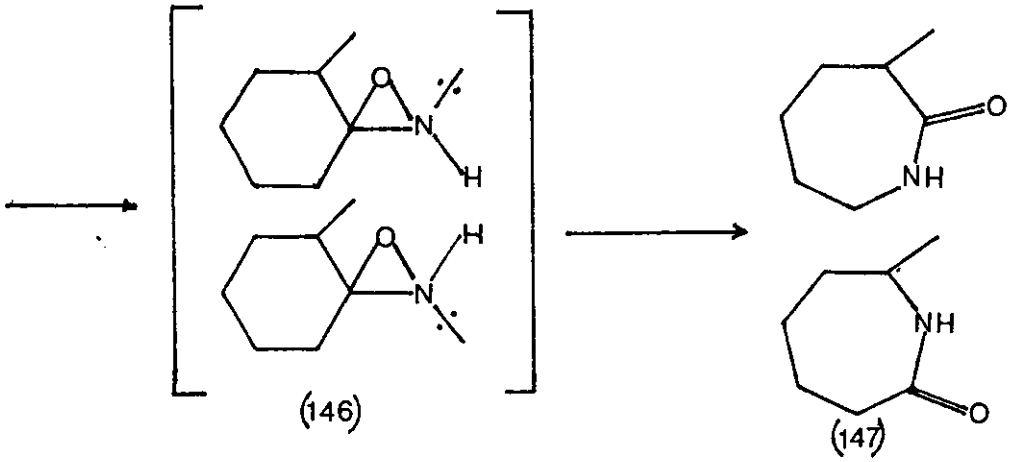
To examine this, Suginome[53] investigated the photo-Beckmann reaction on 5β-cholestan-4-one oxime (138) which gave the lactams (139) and (140) and on 5α-and 5β-cholestan-1-one oxime (141) which gave the lactams (142) and (143). These oximes were obtained as the E-isomersbut still gave a mixture of regioisomeric lactams. To account for this it was proposed that the photochemical E/Z isomerisation of the oximes was a more efficient process than their conversion to oxaziridines.



The view that these photo-Beckmann rearrangements proceed via two isomeric oxaziridines which then undergo normal stereoelectronically controlled rearrangement has been supported by Oliveros. However, Oliveros postulated that the lack of regioselectivity was due to inversion of the intermediate nitrone (145) the full mechanism being as shown below for the oxime (144).

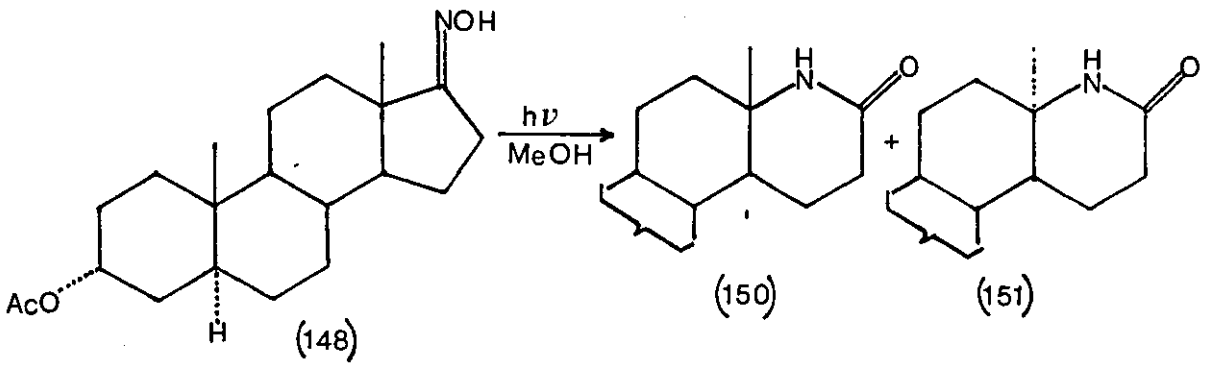


(144) (145)

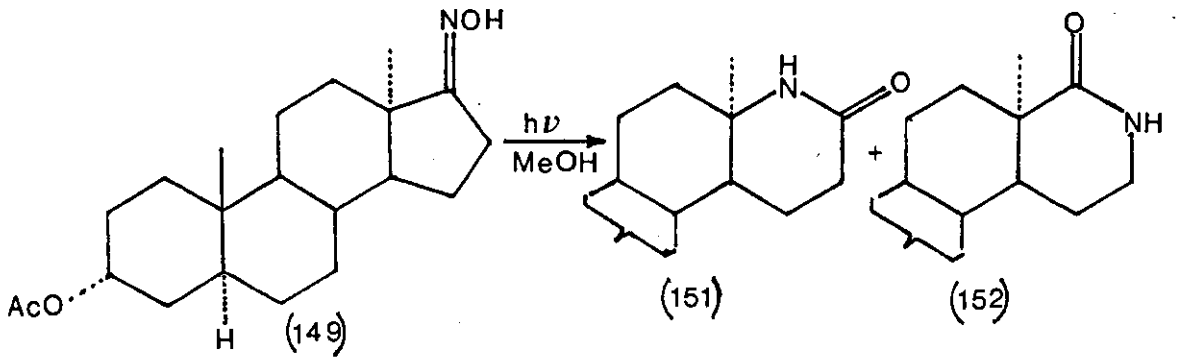


(146) (147)

In the photo-Beckmann reactions discussed above the stereochemistry of the migrating group was retained. However, this was shown not to be the case in the photo-Beckmann reaction of the 17-keto-oximes (148) and (149),[54] which gave the lactams shown below.



(148) (150) (151)

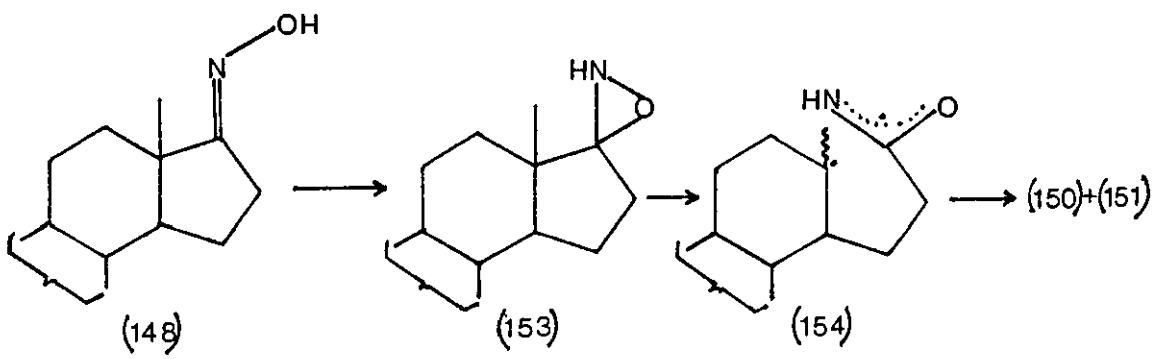


(149) (151) (152)

The 17-keto-oxime (148) gave two lactams (150) and (151) but no evidence was found for any regioisomeric lactam. Whereas the 17-keto-oxime (149) gave two regioisomeric lactams (151) and (152) but no evidence of products arising from epimerisation at C-13 was obtained. However, full analysis of the products of those photolyses was

complicated by the low yields obtained. For example the lactams (151) and (152) were obtained in approximately 1% yield thus making detection of any epimeric product difficult.

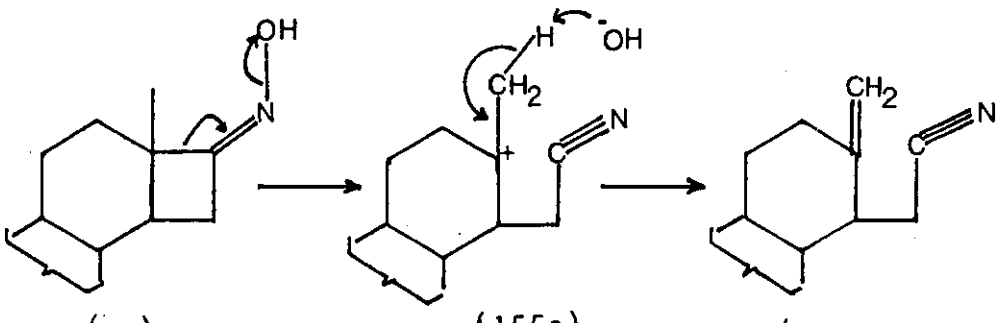
To account for the observed epimerisation Suginome,[55] again postulated an oxaziridine intermediate. However, instead of a concerted breakdown as postulated for photo-Beckmann reactions discussed earlier, a step-wise mechanism is involved in which the oxaziridine (153) breakdowns to the species (154). The species (154) is postulated as being a stable ionic or radical species in which the migrating centre is released and able to undergo epimerisation prior to bonding with the nitrogen.



(148) (153) (154)

To obtain further information on the photochemical behaviour of steroidal D-ring oximes Suginome,[56] prepared and photolysed the cyclobutanone oxime, (155). This compound was obtained as a mixture of E/Z - isomers and the photolysis results are shown in Scheme (13).

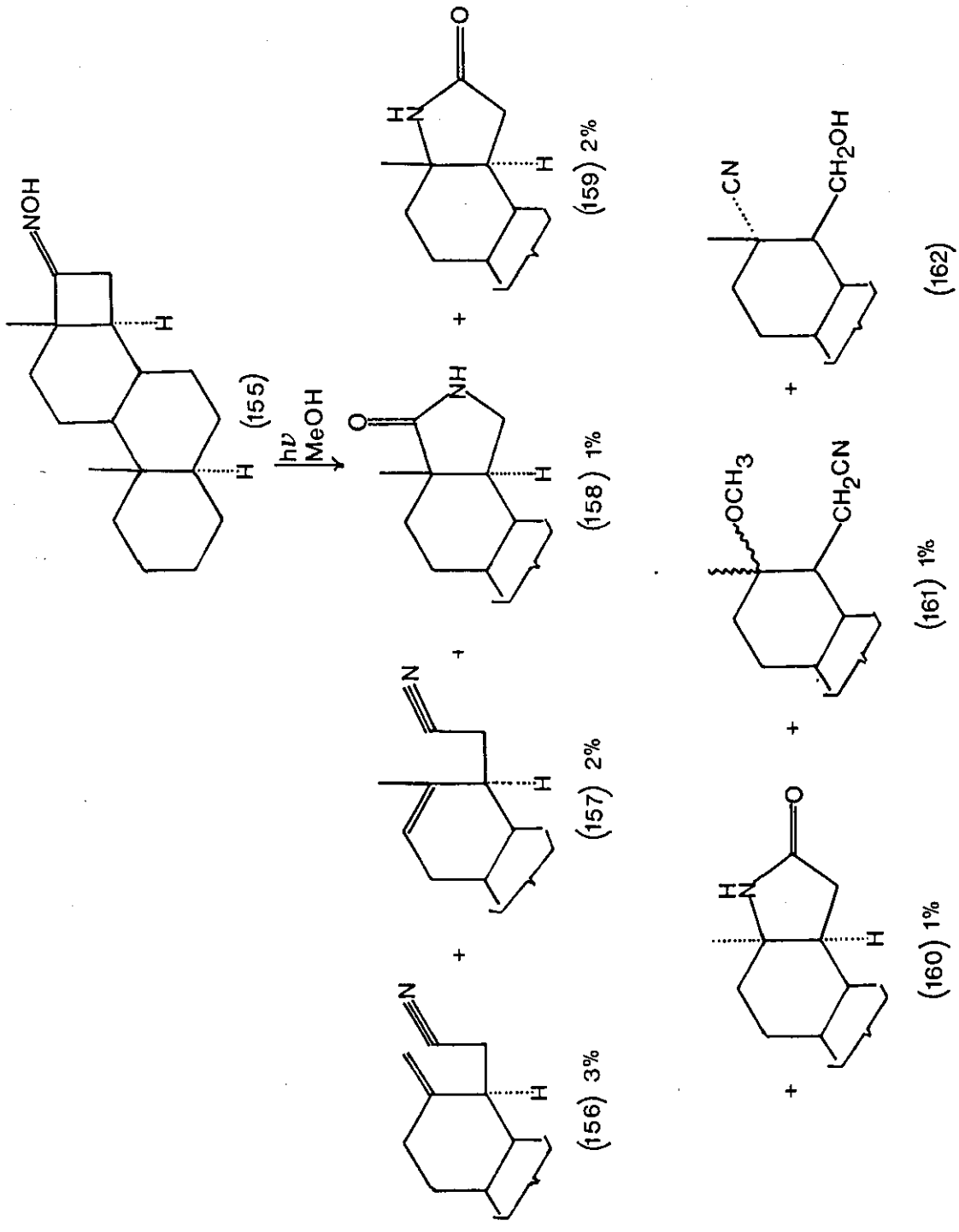
It was proposed that the predominant reactions occurring were those due to an ionic α-fission. An example of which is the formation of the seco-nitrile (156).



(155) (155a) (156)

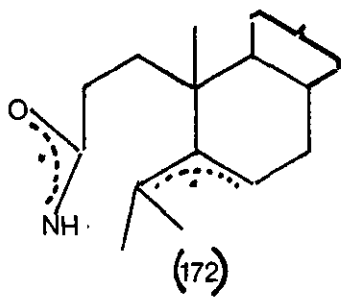
Scheme 13

Photolysis of D-ring oximes (155)



Although the lactams (158), (159) and (160) were obtained in low yield it was established that as in the case of the 17-keto oxime (148) the stereochemistry at C-13 was not retained.

To investigate further the mechanistic pathway involved in the photo-Beckmann rearrangement of oximes, Sugimome,[56] examined the photochemical behaviour of two steroidal β,Y-unsaturated-keto-oximes (163) and (164). These compounds were chosen since they were considered to be susceptible to fission into the biradical or ionic species (172) by virtue of the generation of the stabilised allyl radical or ion which is analogous to the postulated intermediate (154) discussed earlier.



(172)

The results obtained on photolysis of the compounds (163) and (164) are shown below (Scheme 14). The main products obtained were the lactams (166) and (167) from (163) and (168) and (169) from (164). If these reactions had proceeded via an intermediate such as (172) the expected products would not have been the lactams, but seco-nitriles such as (170) which was only obtained as a minor product.

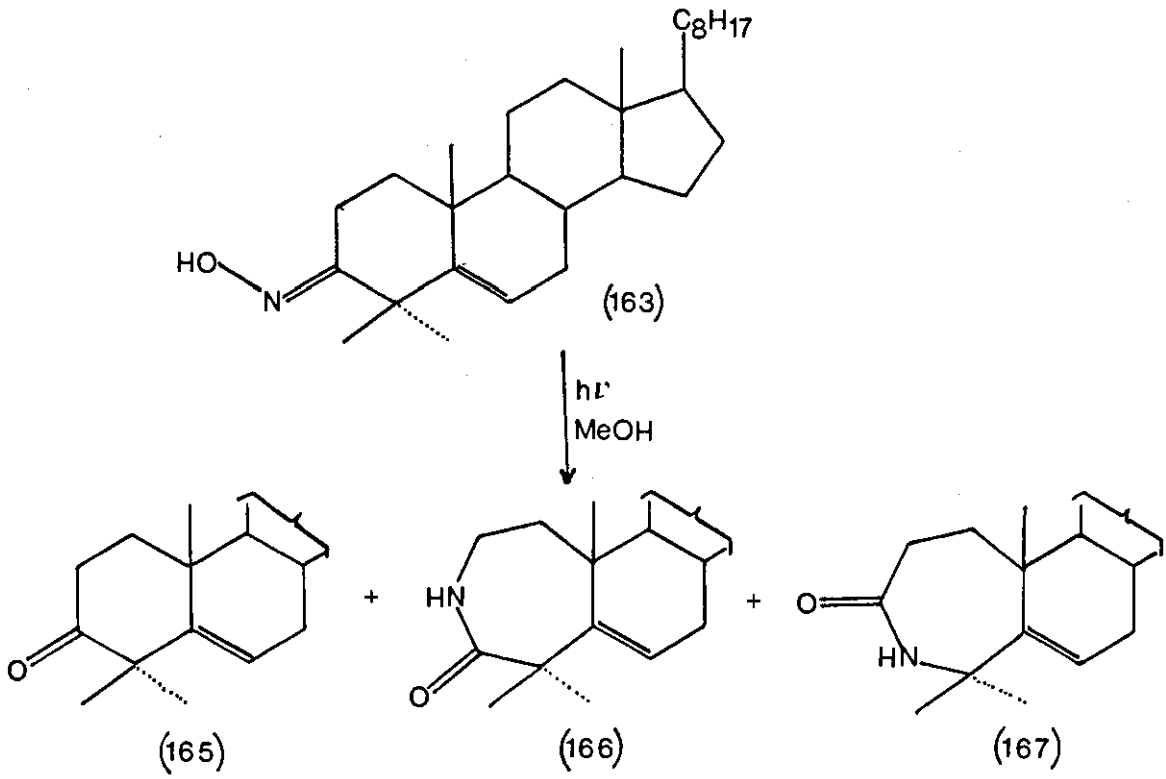
6) Aci-Nitro and Nitronate Anion Photochemistry

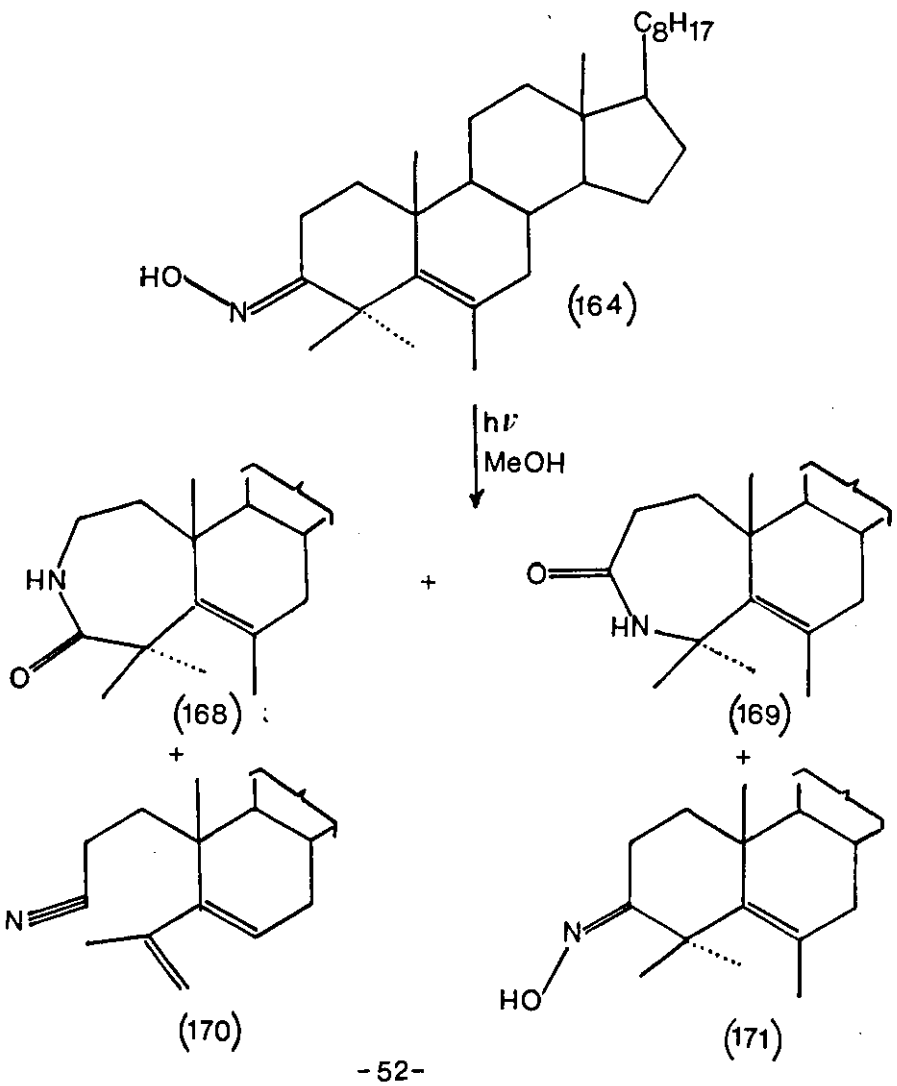
As previously stated relatively little work has been carried out on the photochemistry of the aci-nitro group and the nitronate anion.

The main reason for the lack of information on the aci-nitro system is their instability making isolation of pure materials almost impossible. However, Pinhey,[57] found that 4-t-butyl-aci-nitrocyclohexane (173) can be obtained as a relatively stable solid which on irradiation

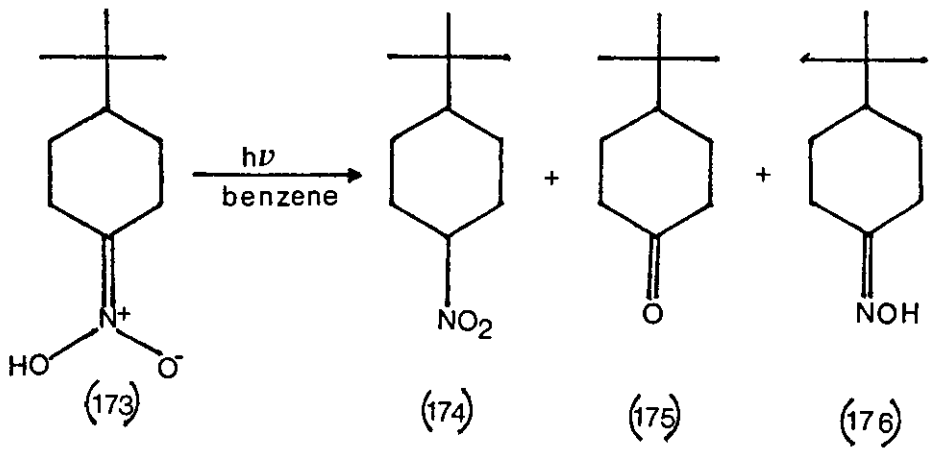
Scheme 14

Photolysis of compounds (163) and (164)





using a medium pressure lamp and benzene as solvent gives cis-4-t-butylnitrocyclohexane (174, 14%), trans-4-t-butylnitrocyclohexane (174, 35%), 4-t-butylcyclohexanone (175, 14%) and 4-t-butylcyclohexanone oxime (176, 33%).



(173) (174) (175) (176)

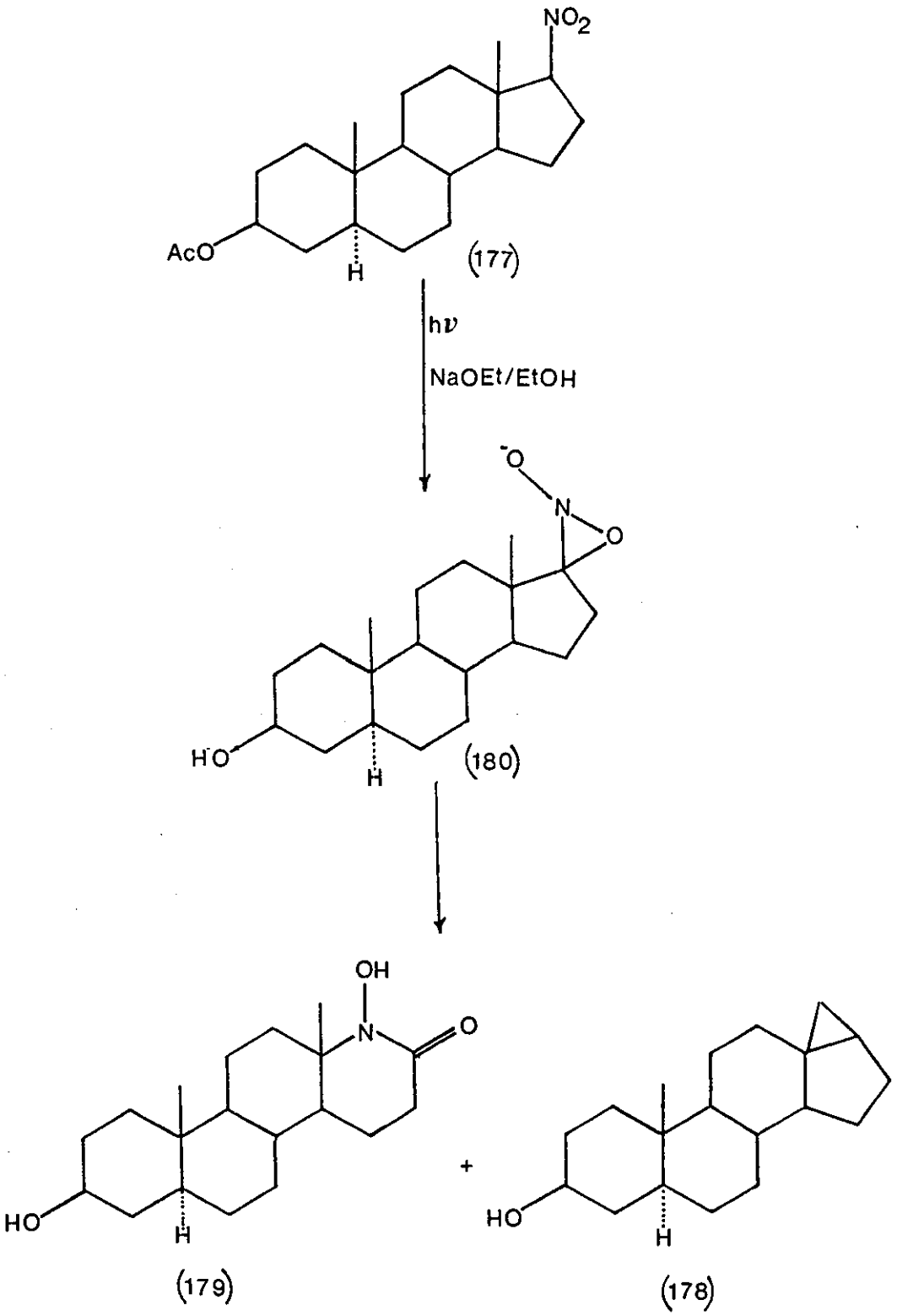
It was shown that the ketone did not arise from the oxime or the nitro-compound and it was postulated that it arose from photochemical breakdown of an intermediate N-hydroxyoxaziridine formed from a $\pi \rightarrow \pi^*$ singlet state of the aci-nitro compound while formation of the oxime was due to loss of oxygen from the aci-nitro group via a triplet excited state.

The photochemistry of the nitronate anion has been examined by Imam and Marples,[58] who examined the photochemical behaviour of a steroidal nitronate anion prepared in situ from 3β-acetoxy-17β-nitro-5α-androstane (177) dissolved in NaOEt/EtOH.

Two products were isolated namely the 17,18-cyclosteroid (178) which was a minor product and the hydroxamic acid (179, 30%). It was proposed that the N-hydroxy-oxaziridine anion (180) was the intermediate in this reaction and at the time of commencing this study into nitronate anion photochemistry this was the only published work in the field.

Scheme 15

Photolysis of 17-nitronate anion

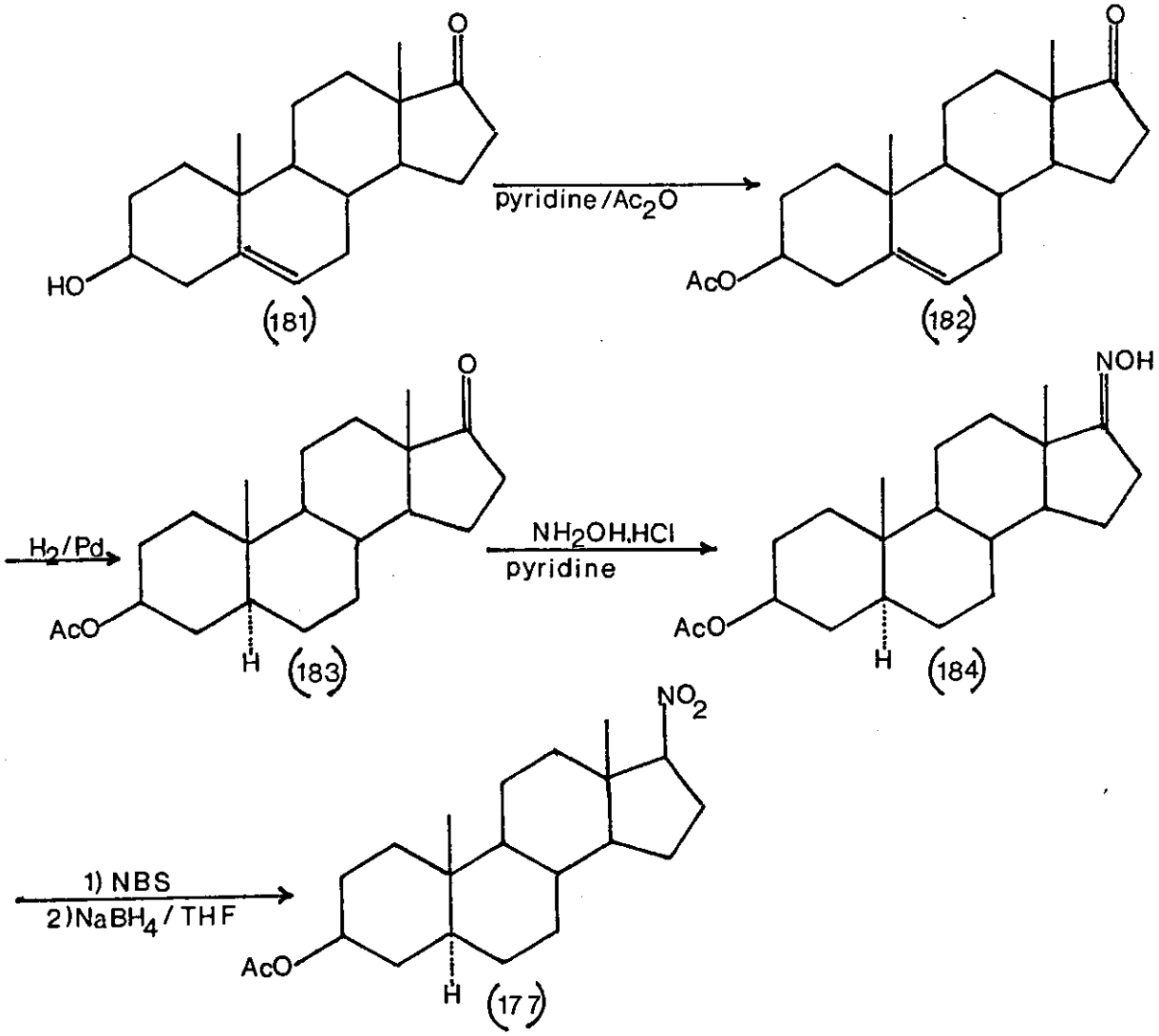


RESULTS AND DISCUSSION

1) Preparation of the 17-nitro-compounds

A) Preparation of 3β-acetoxy-17β-nitro-5α-androstane (174)

The 17β-nitro-compound (177) was prepared from androstenolone (181) by the route shown below :-

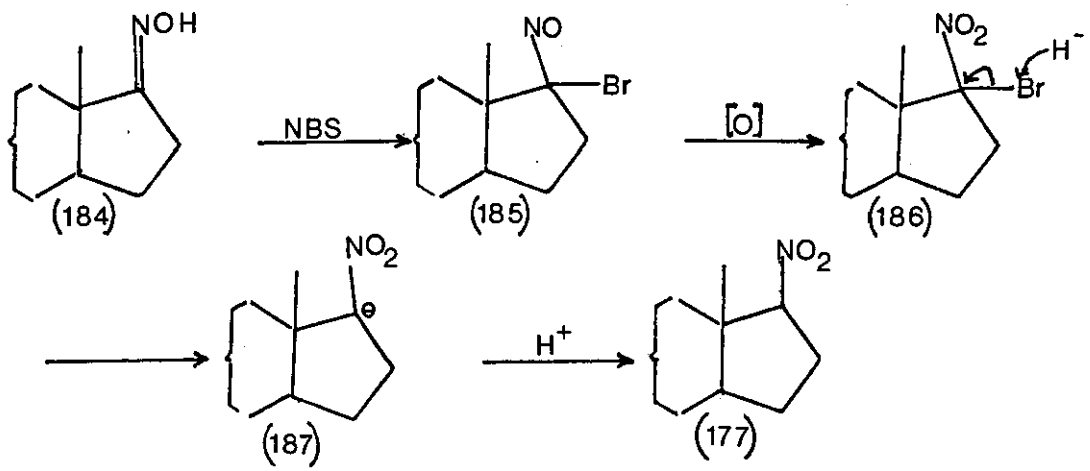


Acetylation was performed using the normal procedure of treating the 3β-hydroxy compound (181) with pyridine and acetic anhydride to give the desired 3β-acetoxy compound,[59] (182) in quantitative yield.

The hydrogenation reaction to convert the Δ^5-compound (182) to the 5α-compound (183) was performed in high yield without difficulty using

standard conditions.[60] The known oxime (184),[61] was prepared by heating the ketone under reflux in ethanol containing hydroxylamine hydrochloride and pyridine.

The preparation of nitro-compounds from oximes by means of N-bromosuccinimde (NBS) was first developed for simple nitroalkanes by Iffland,[62] and was later developed by Patchett and co-workers,[63] for the preparation of steroidal 17β-nitro-compounds. The first step in the reaction is the formation of the bromonitroso intermediate (185) which readily undergoes air-oxidation to give the bromo-nitro-compound (186). This in turn is treated, without isolation, with sodium borohydride ($NaBH_4$) and tetrahydrofuran (THF) to give the species (187) which upon quenching with acid gives the desired nitro-compound (177).



The nitro-group was assigned the β-configuration in compound (177) on the basis that on protonation of the anion (187) the nitro-group would adopt the thermodynamically more stable (β) configuration. Additionally kinetic protonation would also be expected to give the 17β-nitro-configuration.

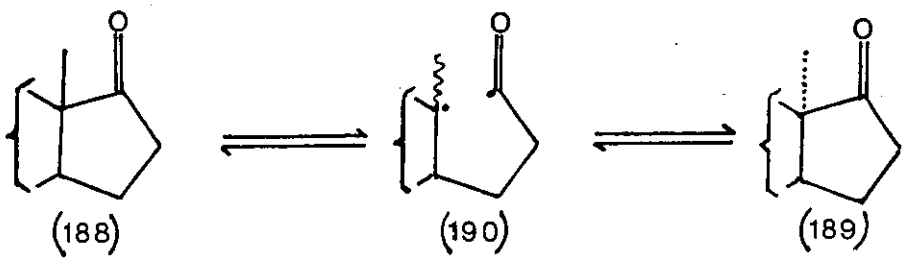
This assignment of configuration was confirmed by examination of the ^1H n.m.r. spectrum of the 17β-nitro-compound (177) which showed a

triplet centred at δ4.35 (J 6Hz) which was assigned to the 17α-proton. This is the normal finding[64] for a 17α-proton resonance; whereas a 17β-proton is normally observed as a doublet. The 17β-nitro compound (177) gave spectroscopic and analytical data fully in accordance with literature values[64].

B) Preparation of 3β-acetoxy-17 -nitro-5α,13α-androstane (203)

The crucial step in the preparation of the 13α-17-nitro compound (203) is the efficient conversion of a suitable precursor from the 13β to the 13α configuration.

The original method for performing this epimerisation was developed by Butenandt[65] and was the photochemical conversion of a 13β-17 keto compound (188) to the 13α epimer (189) via the diradical intermediate (190). The driving force for this reaction is the conversion of the trans C/D ring junction to the thermodynamically stable cis C/D ring junction.



(188) (190) (189)

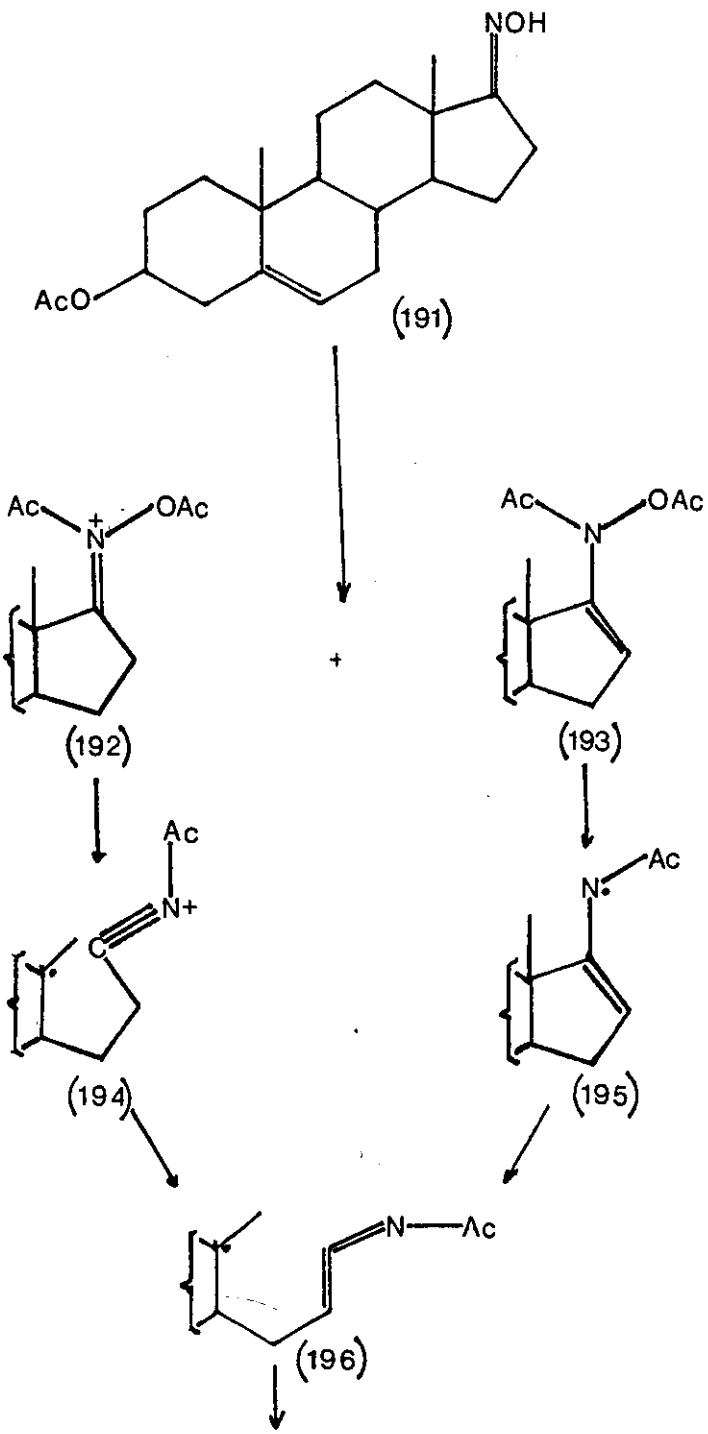
The reversibility of this reaction was demonstrated by Werhli[66] who showed that at the photostationary state the 13α-isomer (189) was the major product.

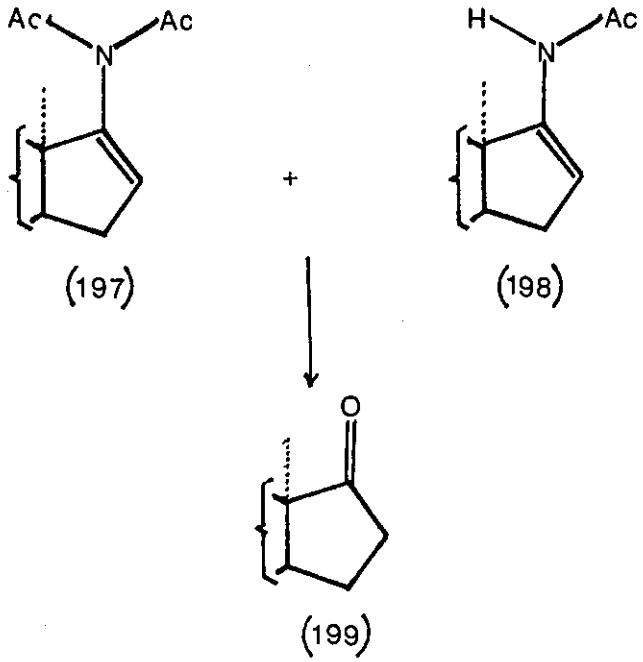
The disadvantage of this procedure is that after separation of the isomeric product mixture, based on the differential reactivity of the isomeric ketones toward's Girards Reagent T, the required 13α-isomer is only obtained in 30% yield.

However, in 1974 Boar and co-workers[67] developed a thermal procedure

for the preparation of the 13α-17-keto-compound (199). This method involved heating 3β-acetoxy-androst-5-ene-17-one oxime (191) under reflux in pyridine and acetic anhydride to give after isolation a mixture of the enimide (197) and the enamide (198). Treatment of these compounds with dilute HCl in methanol gave the desired 13α-compound (199) in 60% yield. A possible mechanism for this reaction is shown in Scheme 17.

Scheme 17

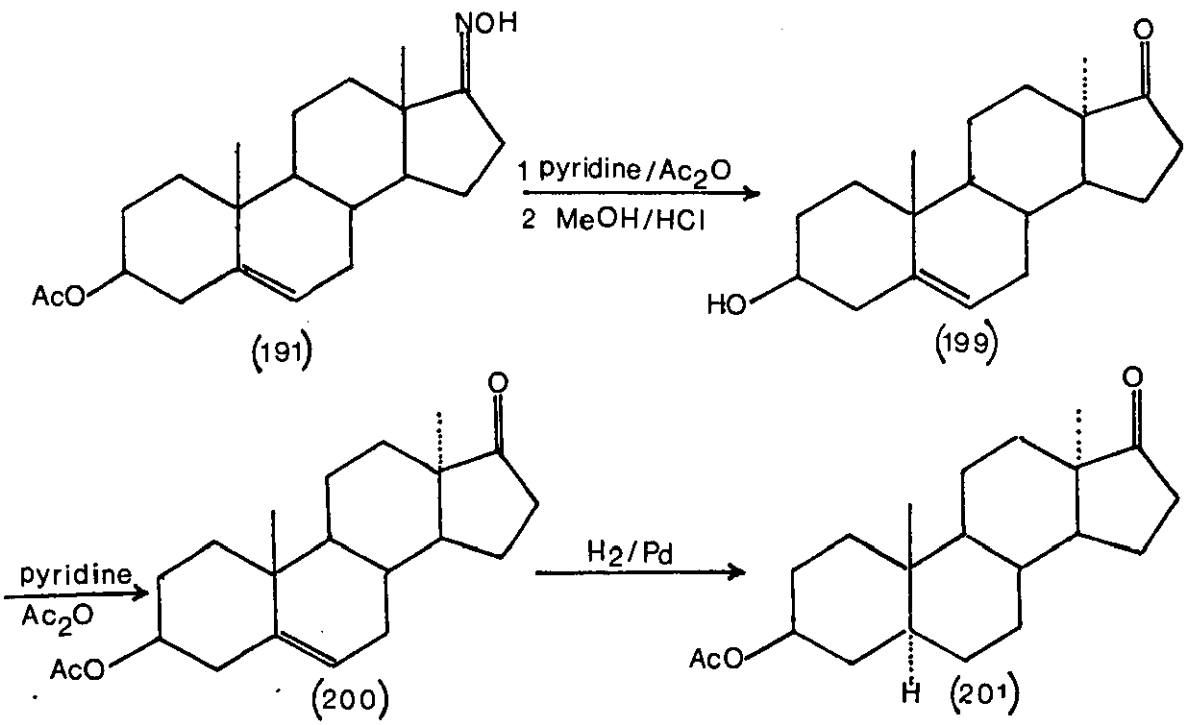




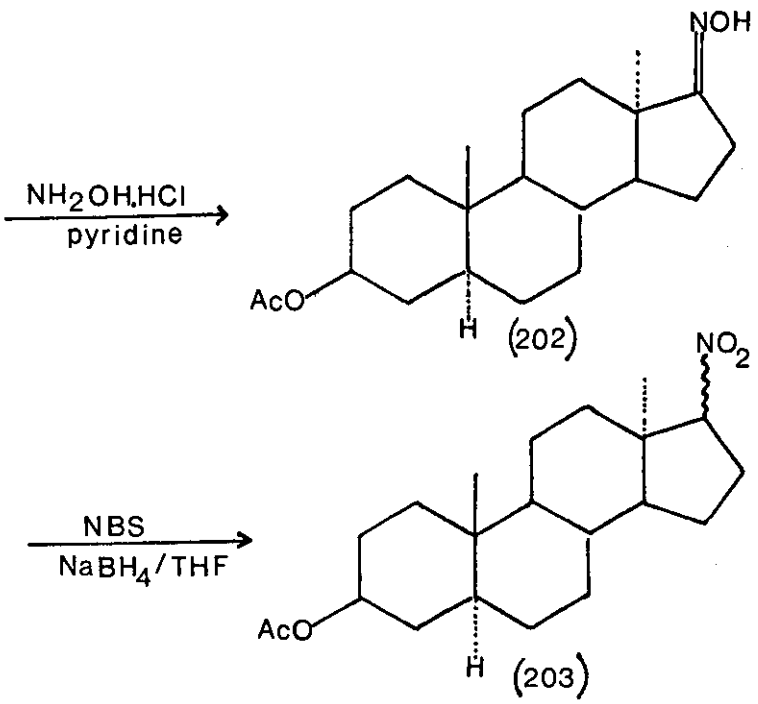
(197) (198) (199)

The full reaction sequence used to prepare the 13α-17-nitro-compound (203) is shown in Scheme 18 below

Scheme 18



(191) (199) (200) (201)



This reaction sequence is analogous to that used for the preparation of the 13β-17β-nitro compound (177) described earlier. However, differences were observed in the efficiency of certain of the reactions.

Following preparation of the 13α-17-keto-compound (200) the next stage was to hydrogenate the Δ^5-double bond to give the 5α -compound (201). This reaction was also performed in the preparation of the 13β-17β-nitro-compound (177) where no difficulties were encountered.

However, it was found that hydrogenation of the 13α-ketone (200) did not proceed as readily and that much longer reaction times were required in order to achieve the complete reaction. This was probably due to steric effects.

The mechanism of hydrogenation generally accepted was that proposed by Horiutu and Polanyi[68]. This mechanism involves bonding by the alkene to the catalyst surface with subsequent hydrogenation on the sterically less hindered face of the alkene. In the hydrogenation of Δ^5-steroids this results in attack on the α-face. However, in the

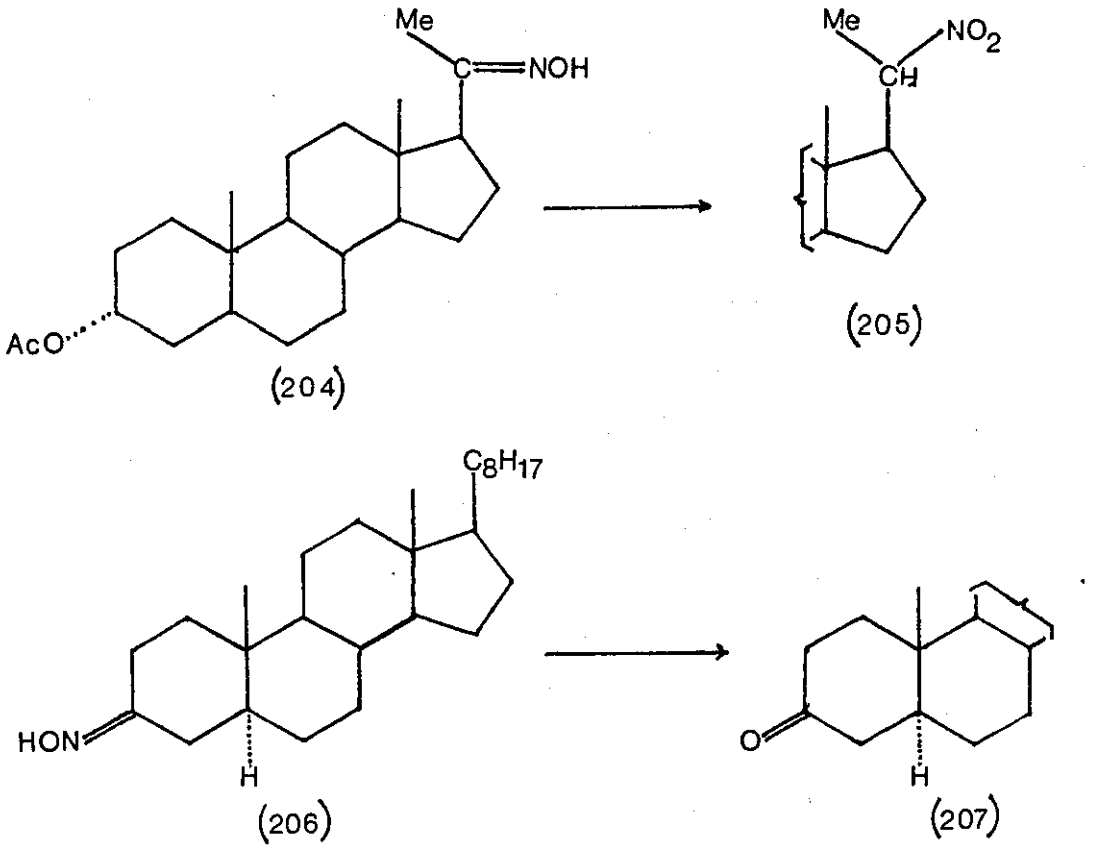
compound being considered the C-18 angular methyl is also on the α-face and may well result in difficulty in forming the alkene-catalyst bond.

The ketone (201) was then converted to the oxime (202) using the conditions adopted previously for the preparation of (184). However, again longer reaction times were required reflecting the lower reactivity of the 17-keto group in the 13α-steroids which has previously been observed by Bots. This again is a consequence of the C-18 angular methyl group being on the α-face of the steroid since this reduces the availability of the 17-position to attack because of steric crowding.

The oxime (202) was converted to the 17-nitro-compound (203) using the $NBS/NaBH_4$ procedure adopted previously. The nitro-compound was obtained in 25% yield by this method. This is a significantly lower yield than that observed in the preparation of (177). The other product obtained from this reaction was the 13α-17-keto compound (201) also in 25% yield. The formation of this compound was unexpected as there had been no evidence of ketone formation in the preparation of the other 17-nitro-compound (177). However, it is known that the NBS procedure cannot be used as a general procedure for the preparation of nitro-steroids. For example, Robinson,[69] has reported that the attempted preparation of 20-nitro-pregnanes (205) from the oxime (204) results in complex mixtures and more importantly Bull,[70] found that the reaction between 3-oximino-5α-cholestane and NBS gave the parent ketone (207) as the major product, as shown overleaf, Scheme 19.

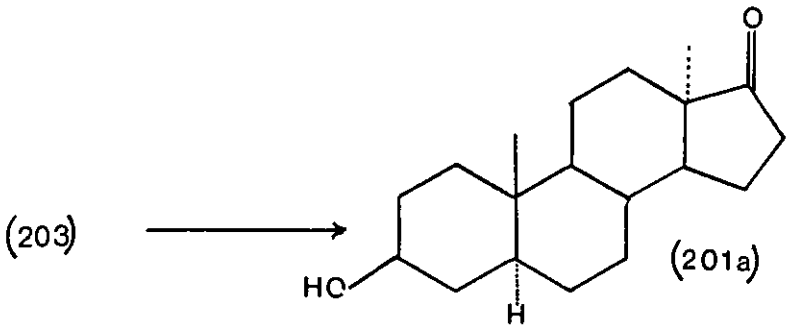
The infra-red (i.r.) spectrum of the 13α-17-nitro compound (203) gave characteristic nitro group absorptions at $1530cm^{-1}$ due to asymmetric NO stretching and at $1360cm^{-1}$ due to symmetric NO stretching. The ^1H n.m.r. spectrum gave signals at δ0.80 (s,10βMe) and δ0.90 (s,13α-Me) δ2.00 (s,COMe) and a 2-proton multiplet centred at δ4.5 and assigned to the 3α-and 17β-methines. Due to the superimposition of the two methine signals it was not possible to use this ^1H n.m.r. spectrum

Scheme 19

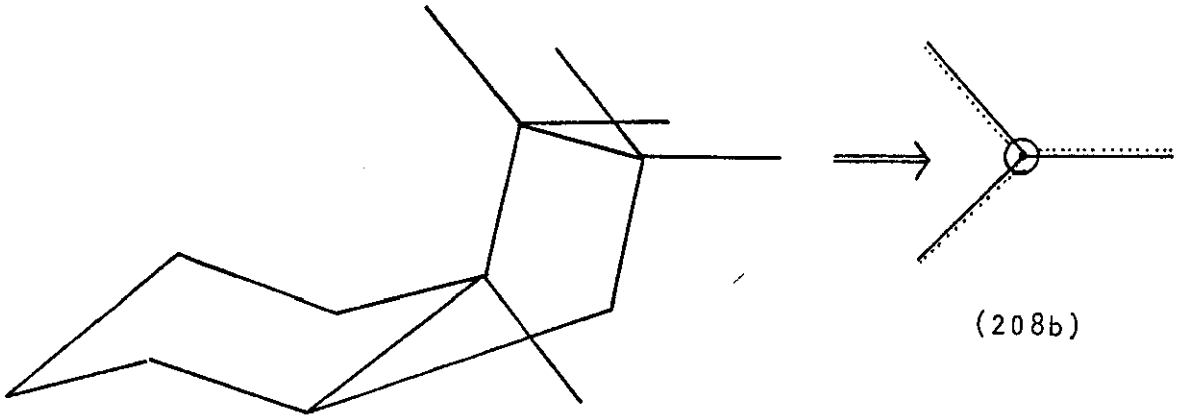


to determine the nitro groups configuration.

To try and determine the splitting pattern of the signal for the 17-methine proton alone, the 3β-acetoxy-17ε-nitro-compound (203) was treated with base and reacidified. It was expected that the signal for the 3α-methine proton in the ^{1}H n.m.r. would be shifted upfield by 1 p.p.m. and thus separated from the 17-methine proton signal. However, on carrying out this procedure only the 17-keto-compound (201a) was obtained, showing that the nitro-compound (203) readily underwent the Nef reaction. This observation may well explain the formation of ketone observed during the preparation of the nitro-compound (203) since the last step involved quenching with acid.



It is not certain that had the base treatment been successful the ^{1}H n.m.r. spectrum splitting pattern of the signal for 17-methine proton would have unambiguously allowed assignment of configuration about the 17-position.

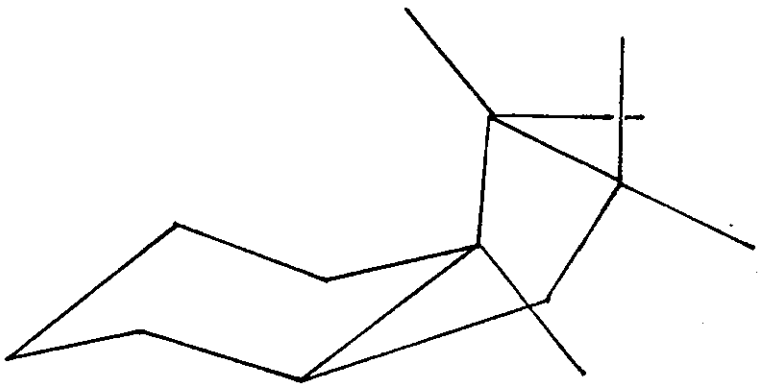


(208a)

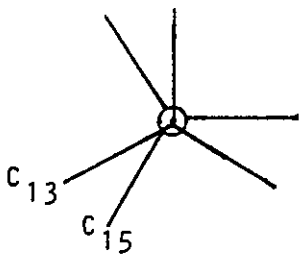
Construction of a molecular model shows that a normal conformation of ring D would result in the fully eclipsed structure (208a) and (208b) in which the dihedral angles between the C-17-methine and the C-16-methylene protons would be the same whether the C-17-methine was in the α or β configuration.

However, owing to the flexible nature of the C/D ring it is conceivable that the conformation (203) discussed above may not be preferred in which case the ^{1}H n.m.r. spectral data may have revealed the

configuration at C-17. An example of an alternative conformation is shown below (209) and (209a).



(209)



(209a)

The dihedral angles between the 17-methine and 16-methylene protons and the expected coupling constants (J) are shown in table 3 below,

Table 3

	Dihedral angle	J_{Hz}
17α - 16α	30°	7
17α - 16β	90°	1
17β - 16α	30°	7
17β - 16β	150°	8

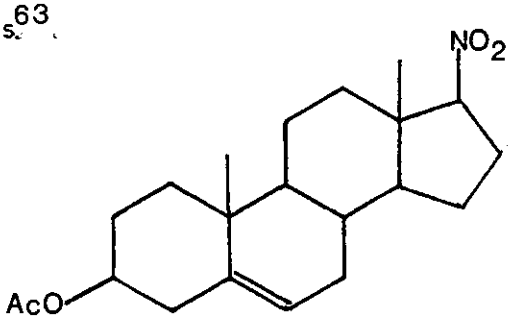
From the above values it can be seen that in this conformation a 17α-methine would be expected to be observed as a doublet ($J_H \sim 7H_z$) whereas a 17β-methine would be observed as a triplet ($J \sim 7H_z$) in the ^1H n.m.r. spectrum.

Thus this possible variation in the conformation of the D-ring makes determination of the configuration about C-17 by means of ^1H n.m.r. spectroscopy difficult.

An alternative approach is to consider which of the alternative configurations would give themore thermodynamically stable product. Examination of molecular models leads to the conclusion that the nitro group would prefer to be in the 17α-configuration since this is less sterically crowded than the alternative 17β-configuration.

C) Preparation of 3β-acetoxy-17β-nitro-androst-5-ene (210)

This compound was prepared from the 17-keto-oxime (191) by the method of Patchett and co-workers,[63] to give the desired compound in high yield with spectroscopic and analytical data in accord with literature values.[63]



(210)

2) Photolysis of the 17-Nitronate Anions

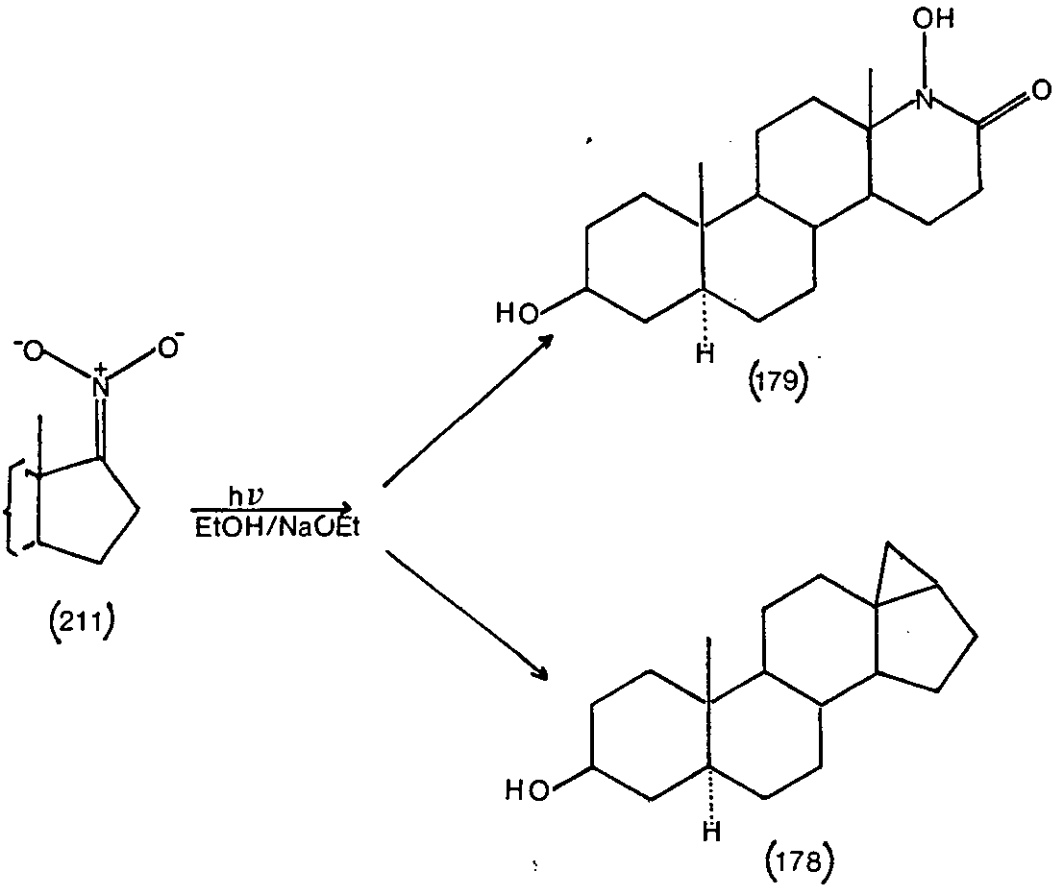
A) Photolysis with a Medium Pressure Mercury Arc Lamp

i) Photolysis of the 17-Nitronate Anion (211) Derived From 3β-Acetoxy-17β-Nitro-5α-Androstane (177)

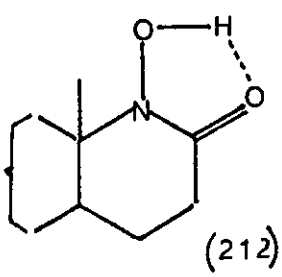
The 17-nitronate anion(211) was prepared from the 17β-nitro-compound (177) prior to photolysis by dissolving the 17β-nitro-compound in absolute ethanol containing 10 molar equivalents of sodium ethoxide. The sodium ethoxide was added from a bulk solution prepared by dissolving sodium metal in anhydrous ethanol under nitrogen in the usual way.

Photolysis was performed with a medium pressure mercury arc lamp until no starting material could be detected by t.l.c. At the completion of the photolysis the reaction mixture was subjected to a neutral/acid separation from which two products were obtained. The major product from the acid fraction was the hydroxamic acid (179)

(10% yield) which gave a typical violet colour with $FeCl_3$ solution. The major product from the neutral fraction was the known 17, 18-cyclosteroid (178),[71] (7% yield).



The i.r. spectrum of the hydroxamic acid (179) showed absorptions at 3350cm^{-1} due to the 3β-OH group and at 1620cm^{-1} due to the carbonyl groups of the hydroxamic acid function. This value for the carbonyl group is typical of a six-membered cyclic hydroxamic acid and is lower than the carbonyl absorption in analogous lactams or other cyclic hydroxamic acids due to the geometry of six-membered system which allows effective intramolecular hydrogen bonding to occur.(212)



(212)

The ^1H n.m.r. spectrum gave singlets at $\delta 0.80$ and $\delta 1.27$ assigned to the 10β-methyl and 13β-methyl respectively and a multiplet centred at $\delta 3.6$ assigned to the 3α-H.

The mass spectrum of the hydroxamic acid gave a molecular ion at $\frac{m}{z}$ 321 corresponding to the molecular formula $C_{19}H_{31}NO_3$

The known 17, 18-cyclosteroid (178) gave analytical and spectroscopic data in accord with literature values. However, it was observed that the extraction and separation procedure was not reproducible and that hydroxamic acid (179) was being extracted into the neutral fraction. This was thought to be caused by the use of chloroform as solvent, which was probably contaminated with traces of HCl which were prematurely releasing a proportion of the hydroxamic acid.To try and overcome this, the separation was carried out using ether as solvent, but no improvement in the efficiency of separation was obtained.

More importantly it was observed that the yield of hydroxamic acid was significantly lower than previously reported and appeared to vary with the age of the lamp used.

To try and find an explanation for this a series of photolysis were performed comparing an "old lamp" i.e. one that had been used for > 50 hours against a "new lamp". It is known that the emission characteristics of medium pressure mercury arc lamps are age dependent and that the most significant changes occur within the first few hours of use.

The yields of products from four experiments are shown in table (4) overleaf. As can be seen the yield of hydroxamic acid (179) was increased significantly by the use of a new lamp, although the yield of cyclosteroid (178) was not so sensitive.

The main change in the emission characteristics of a medium pressure

Table 4

Dependence of Yield of Photoproducts on Age of Lamp

		OLD	NEW	OLD	NEW
Hydroxamic acid	%	11	20	9	11
Cyclosteroid	%	5	7	7	7

mercury arc lamp with age is that the proportion of 254 nm light is reduced.

As was stated in the introduction the free nitro group in nitro alkanes exhibits absorbtions at caλ278 nm ($\varepsilon \sim 100$) due to an $n \rightarrow \pi^*$ transition and at $\sim\lambda$ 218 nm ($\varepsilon \sim 5000$) due to a $\pi \rightarrow \pi^*$ transition. In contrast the U.V. spectra of nitronate anions in general exhibit an absorption of $\lambda\sim$ 240 nm ($\varepsilon \sim 10^4$) arising from a $\pi \rightarrow \pi^*$ transition. The 17-nitronate anion derived from the nitro-compound (177) was shown to absorb at λ max 238 nm (ε9500). Similarly the nitronate anions derived from the 6β-nitro and 20β-nitro compounds (240b) and (245) (see pp 85 and 86) were shown to have λ max ca 240 nm ($\varepsilon \sim 10000$).

Accordingly it seemed reasonable that the variability in yield using a medium pressure mercury arc lamp correlated with the variation of the intensity of the 254 nm emission in which region the nitronate anions have their principle absorption band. It was therefore decided to investigate the use of a low pressure mercury arc lamp which has its principle emission at 254 nm.

B) Photolysis of 17-Nitronate Anions with a Low Pressure Mercury Arc Lamp

i) Photolysis of the 17-Nitronate Anion (211)

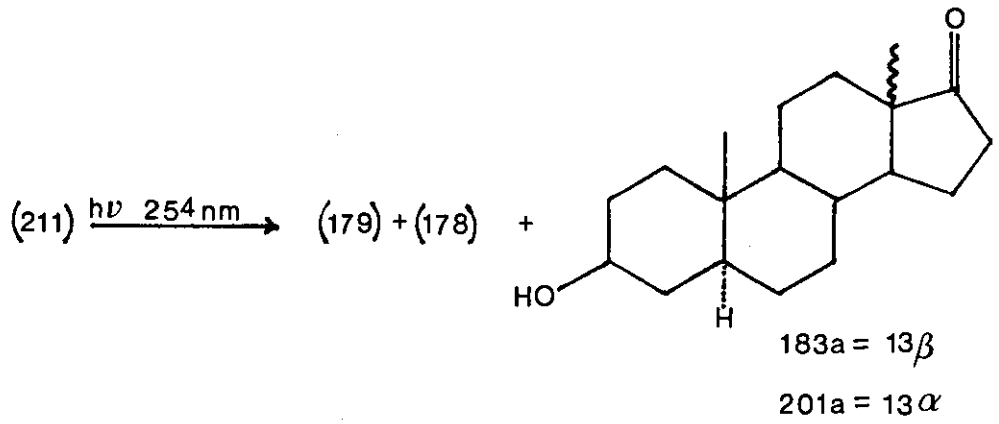
The photolysis conditions were the same as described previously. At the completion of the photolysis it was decided not to perform the neutral/acid separation but to acidify the whole reaction mixture and

extract with chloroform.

On carrying out this procedure followed by crystallisation from methanol the hydroxamic acid (179) was obtained in 55% yield, thus demonstrating the effect of the wavelength used on the course of the reaction. The mother liquors from the crystallisation were combined and subjected to preparative t.l.c. from which two fractions were obtained.

The least polar fraction on crystallisation from acetone/pet ether afforded the 17,18-cyclosteroid (178) in 7% yield. The more polar fraction gave a carbonyl absorption of 1735 cm^{-1} in the i.r. spectrum, consistent with the value expected for five-membered ring ketone. Examination of the material by t.l.c. gave Rf. data consistent with the product being 3β-hydroxy-5α-androstan-17-one (183a). The ^1H n.m.r. spectrum gave a broad singlet at δ0.80 assigned to the 10β and 13β methyls indicating the product to be the 13β-17-keto compound (183a). However, additional singlets were observed at δ0.64 and δ0.97 consistent with values for the 10β and 13α-methyls of the 13α-17-keto-compound (201a), indicating the product to be a mixture of isomeric ketones.

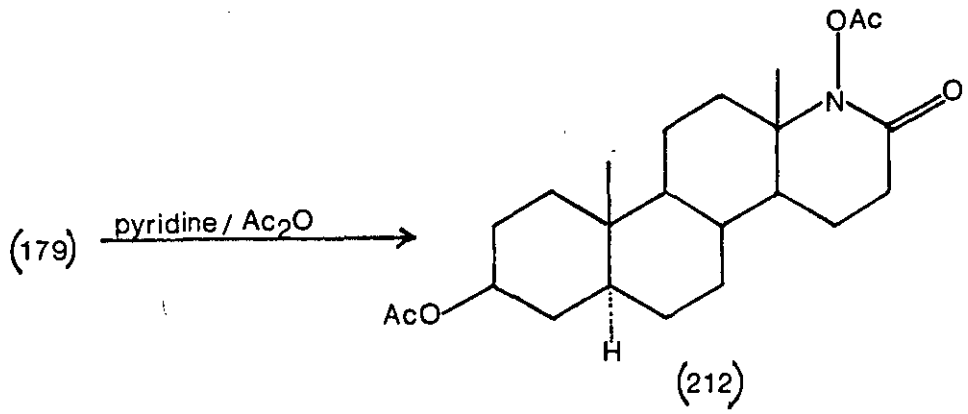
Attempts to separate the isomers by either t.l.c. or crystallisation were unsuccessful.



It was observed during the isolation of the products from the above photolysis that the hydroxamic acid (179) was a highly polar

compound and that the efficient isolation of small quantities of this material were difficult to achieve. Thus in order to facilitate handling, optimise the yield and fully characterise the hydroxamic acid it was decided to prepare a series of derivatives.

The first derivative to be prepared was the diacetate (212) by treatment of the hydroxamic acid (179) with pyridine and acetic anhydride.

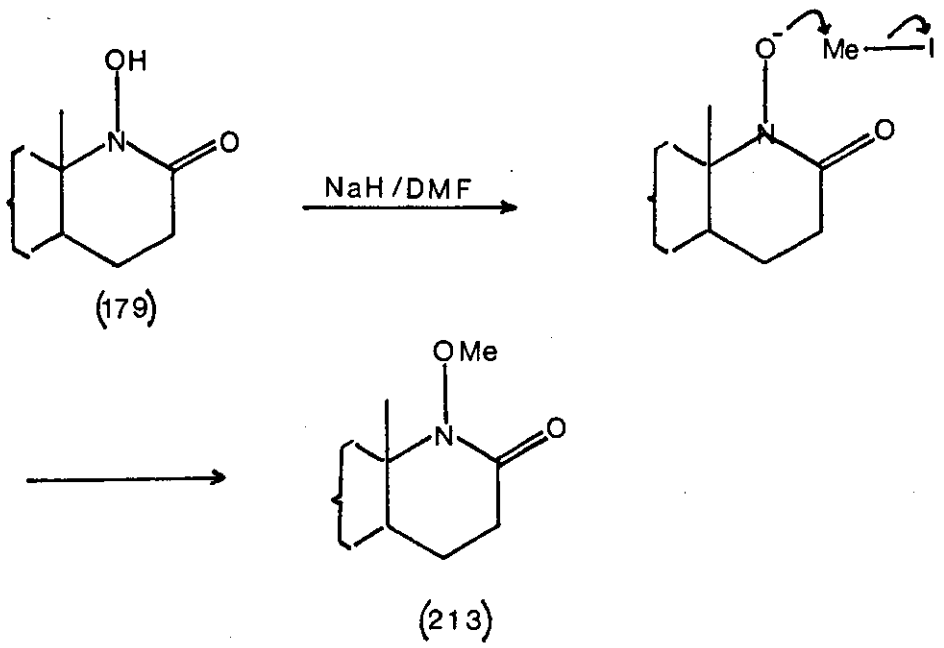


The diacetate (212), obtained in 80% yield, gave spectroscopic data in accord with the proposed structure, namely, the i.r. spectrum exhibited carbonyl absorptions at 1800 cm^{-1} (NOAc) at 1735 cm^{-1} (3β-OAc) and at 1675 cm^{-1} (δ-lactam). The ^1H n.m.r. spectrum gave signals at δ0.80 and δ1.22, both singlets, which were assigned to the 10β and 13β methyl groups respectively. Two further methyl signals were observed at δ2.00 singlet (3β-COCOMe) and at δ2.16 singlet (N-OCOMe). Further evidence in support of the proposed structure came from satisfactory micro-analysis and high resolution mass-spectrometry.

The second derivative prepared was the O-methyl compound (213), by treatment of the hydroxamic acid with sodium hydride and methyl iodide in dimethylformamide (D.M.F.) according to scheme (7) overleaf.

The O-methyl compound (213) gave spectral data in accord with the proposed structure. The i.r. spectrum gave absorptions at 3420 cm^{-1} (3β-OH) and at 1665 cm^{-1} (C17-carbonyl). The ^1H n.m.r. spectrum gave

Scheme (20)



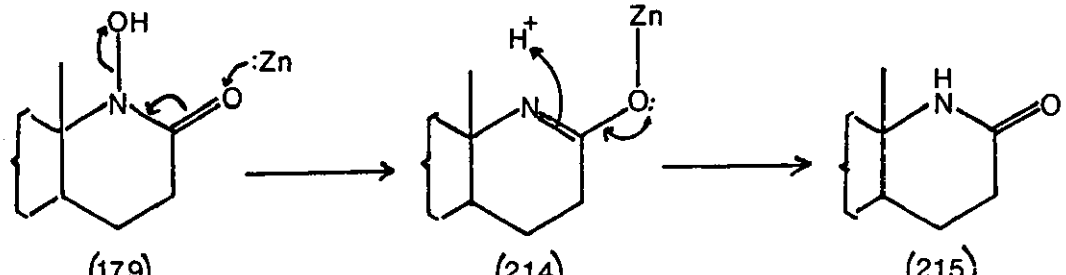
(179)

(213)

signals at, δ0.80 and δ1.20, both singlets, for the 10β- and 13β-methyl groups respectively and at δ3.5 a broad one proton signal due to the 3α-proton. A singlet obtained at δ3.72 is assigned to the methyl of the O-Me group. Accurate mass measurement gave a molecular ion consistent with the expected formula. The final yield of this compound was disappointingly only 60%.

The third derivative of the hydroxamic acid to be prepared was the known lactam,[72] (215). This was prepared by heating the hydroxamic acid in acetic acid containing zinc dust under reflux.

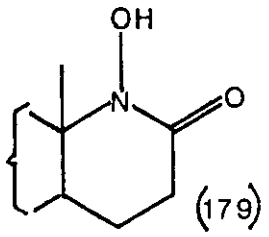
The reaction can be rationalised as proceeding by the following mechanism.



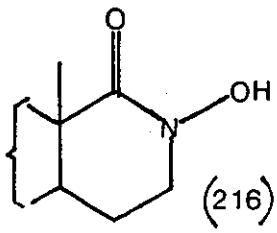
(179) (214) (215)

The lactam (215) was identified from examination of its spectroscopic data. The i.r. spectrumgave carbonyl absorptions at 1735 cm^{-1} (3β-OAc) and 1650 cm^{-1} (δ-lactam). The ^1H n.m.r. spectrum gave singlets at δ0.8 and δ1.1 for 10β and 13β methyl groups respectively and δ2.00 (3β-OAc). Multiplets observed at δ4.5 and δ5.6 wereassigned to the 3α-H methine proton and the N-H proton respectively. This assignment was confirmed by the observation that the latter signal was exchangeable with D_2O.

The main reason for preparing the known lactam (215) was in order to determine the exact regiochemistry of the hydroxamic acid (179). The hydroxamic acid (179) must arise via a molecular rearrangement which can be postulated as arising by either cleavage of the C-13-C-17 bond to give the hydroxamic acid (179) or of the C-16-C-17 bond to give the hydroxamic acid (216).

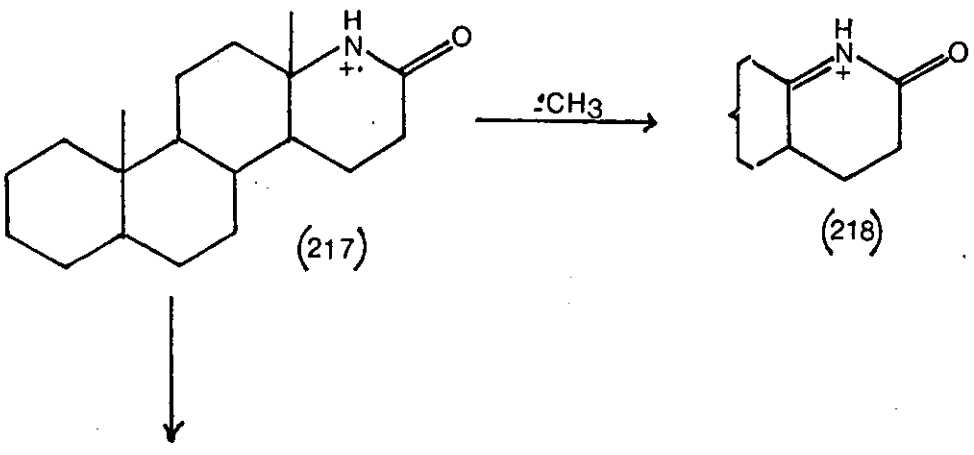


(179)



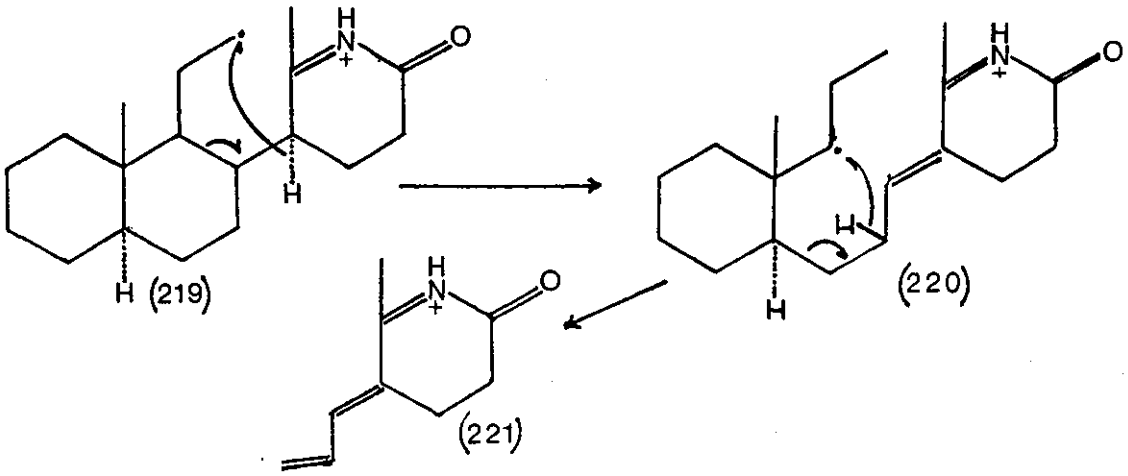
(216)

It has been shown,[73] that the general fragmentation pattern in the mass spectrum of D-ring lactams of the general type (217) proceed as indicated below.



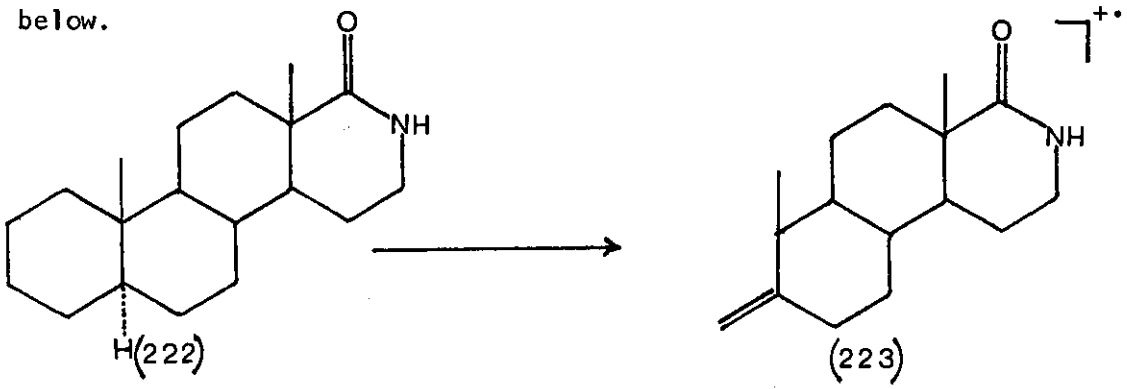
(217)

(218)



As can be seen the fragmentation pattern of 17a-aza-D-homolactams which would be theproduct from the 17a-aza-D-homo-hydroxamic acid (179) gives two main fragment ions at (M^+-15)due to loss of C-18 (218) angular methyl and at $\frac{m}{z}$ 150 (221).

The alternative 17-aza-D-homo-lactam (222) have been shown to undergo the general fragmentation pattern in the mass spectrum shown below.



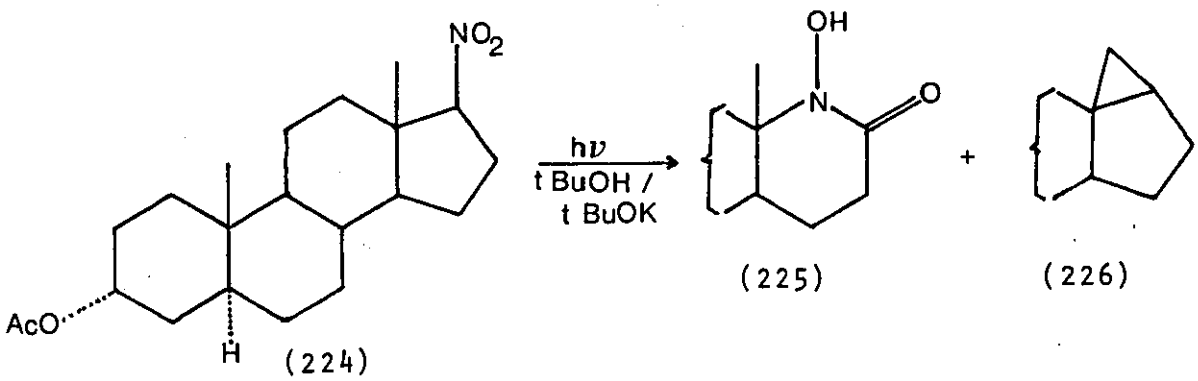
As can be seen the most significant difference in the inability of 17-aza-D-homo-lactams to undergo loss of the angular methyl group.

As can be seen from the mass spectrum of lactam (215) (fig 1) the principle fragmentation gives rise to an ion at M^+-15 ($\frac{m}{z}$ 332) due to loss of C-18 thus confirming the structure of the lactam (215) and the parent hydroxamic acid (179).

In order to be certain that the regioisomeric 17-aza-hydroxamic acid (216) was not formed during the photolysis of the nitronate anion (211) the photolysis was repeated and the total crude photolysate was

reduced with Zn/acetic acid and subjected to careful chromatographic and spectroscopic examination. Only the 13β-17a-aza-D-homolactam (215) was detected there being no evidence for the formation of the 13β-17-aza-D-homolactam (210). Neither was there any evidence for the formation of isomeric 13α-lactams. That such epimerisation may have occurred during the photolysis of the nitronate anion (211) is based on the observations of Suginome concerning the photo-Beckmann rearrangement discussed in the introduction.

Since the commencement of this work and after the preliminary communication by Imam and Marples, Yamada[74] has reported the photochemical behaviour of the nitronate anion of the 13β,17β-nitro compound (224) with the result shown below.



(224) (225) (226)

The formation of the 17a-aza-D-homo-compound (225) and the 17,18-cyclosteroid (226) in yields of (78%) and (17%) respectively are consistent with our results.

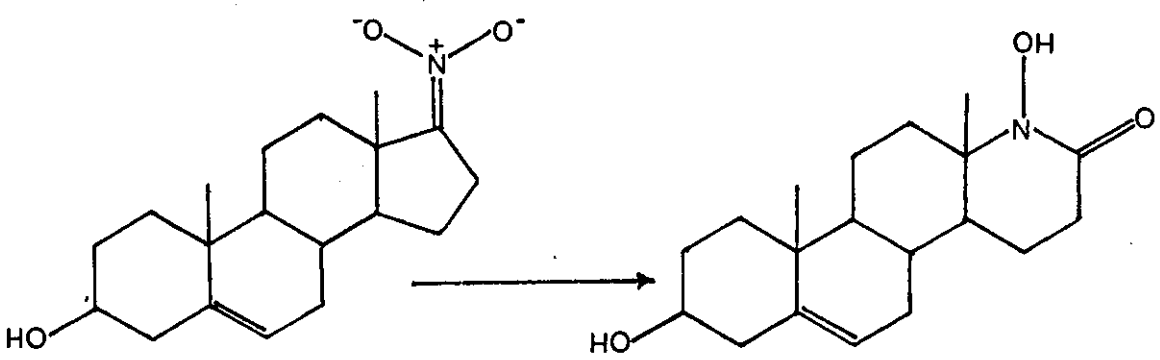
It is suggested that the cyclo-steroid (226) formed in these reactions is not derived from the nitronate anion but from a small amount of free-nitro compound, which is in equilibrium with the anion. If this is true the conversion of the free nitro-compound (177) to the cyclo-steroid (178) should be a highly efficient photochemical process. Therefore it was decided to photolyse the free-nitro compound (177) in ethanol using a medium pressure mercury arc lamp since under these

conditions a 17,18-cyclo-steroid should be obtained as the major product.

On performing this reaction it was found that a complex reaction mixture was obtained with no evidence for one major product. This may have been due to the secondary photolysis of the first formed products. Thus the reaction was repeated but stopped after 50% conversion of the nitro-compound (177). However, a complex reaction mixture was again obtained. Extensive preparative t.l.c. and spectroscopic analysis did not indicate the presence of a 17,18-cyclo-steroid, thus indicating that this is not formed from the free nitro compound.

ii) Photolysis of the 17-Nitronate Anion (227) Derived from 3β-Acetoxy-17β-Nitro-androst-5-ene (210)

The nitronate anion (227) was formed as before and photolysed and worked up as for the photolysis of the nitro-compound (177). Crystallisation of the crude product yielded the hydroxamic acid (228) in 65% yield.

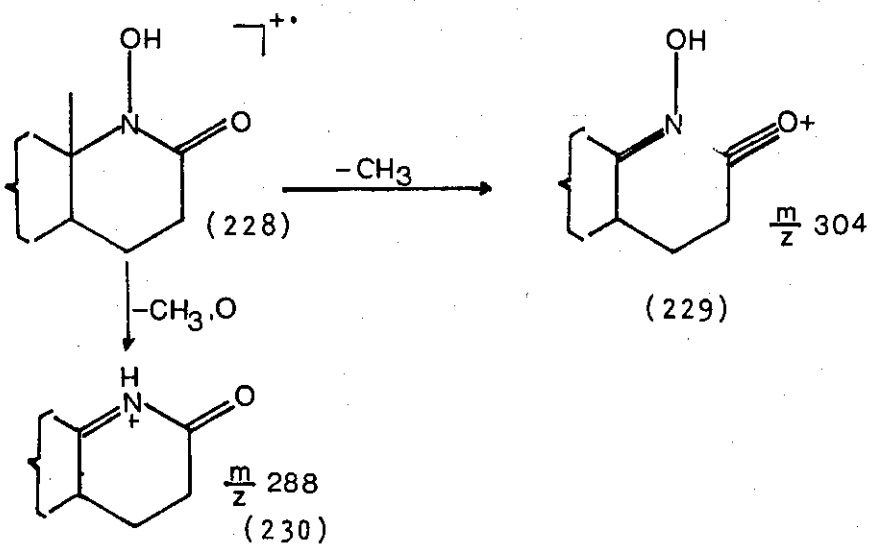


(227) (228)

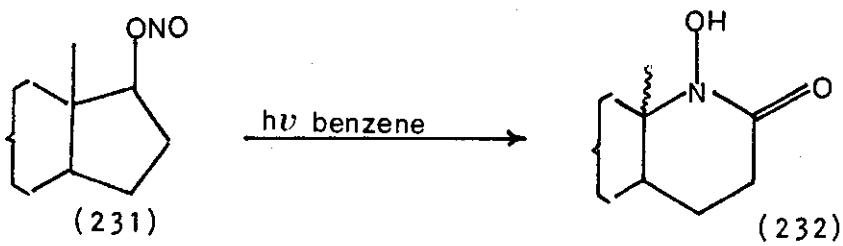
The i.r. spectrum of the hydroxamic acid (228) gave an absorption at 1610 cm^{-1} consistent with that expected for the carbonyl group of a six-membered ring hydroxamic acid.

The ^{1}H n.m.r. spectrum showed singlets at δ1.00 (10β-Me) and at δ1.25 (13β-Me) consistent with the data obtained for the hydroxamic acid (179).

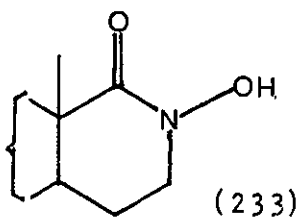
The hydroxamic acid (228) gave a molecular ion at $\frac{m}{z}$ 319 consistent with the above structure and fragment ions at $\frac{m}{z}$ 304 and 288. These last two ions can be plausibly rationalised as arising by the pathways below.



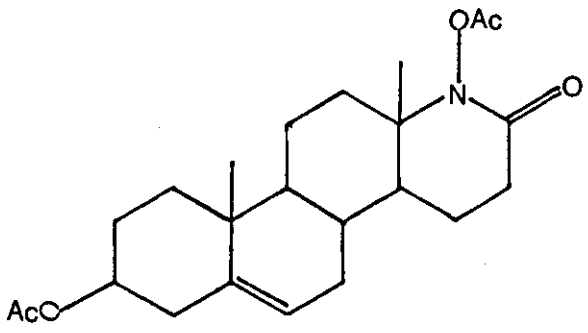
Such fragmentation patterns were observed by Suginome and co-workers[75] in the mass-spectrum of 17a-aza-hydroxamic acid (232) formed in the photolysis of steroidal-17-nitrite (231).



From consideration of the mass-spectrum of D-ring lactams discussed earlier it seems unlikely that the regioisomeric 17-aza-hydroxamic acid (233) would undergo the observed fragmentation.



In order to further characterise the novel hydroxamic acid (228) it was treated with pyridine and acetic anhydride to give the diacetate (234), (90% yield).

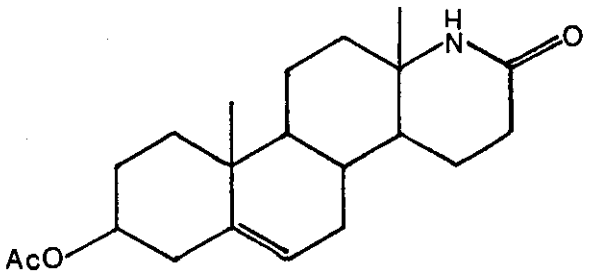
(228) $\xrightarrow{\text{pyridine/Ac}_2\text{O}}$ 

(234)

The i.r. spectrum of the diacetate (234) gave carbonyl absorptions at 1790 cm^{-1} (NOAc); 1735 cm^{-1} (3β-OAc) and 1670 cm^{-1} (C_{17} carbonyl).

The ^1H n.m.r. spectrum showed singlets at δ1.0 and δ2.25 assigned to the 10β and 13β-methyls respectively and further singlets at δ2.02 and δ2.15 assigned to the methyl groups of the 3β-OAc and NROAc respectively. Two multiplets observed at δ4.5 and δ5.3 were assigned to the 3αH and 6-H respectively. Further support for the proposed structure came from[a] satisfactory elemental analysis.

To fully investigate the photochemical behaviour of the nitronate anion (227) the photolysis was repeated and the photolysate treated with zinc and acetic acid under reflux to give the known lactam (235) (70%) which gave analytical data consistent with literature values,[76].

(228) $\xrightarrow{\text{Zn/CH}_3\text{COOH}}$ 

(235)

Extensive examination of the mother liquors of this reaction did not provide any evidence for the formation other isomeric lactams showing the reaction again to be both regio-and stereo-specific.

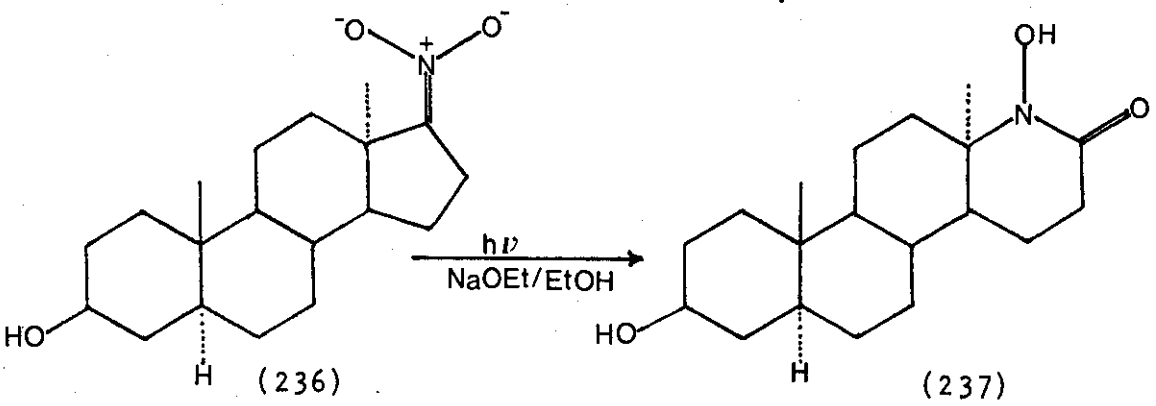
There were significant differences in the photochemical behaviour of the nitronate anions (211) and (227). Namely, no ketone or cyclo steroid was obtained from the photolysis of the nitronate anion (227)

and the yield of hydroxamic acid was significantly increased. This could indicate that the photochemical behaviour of the 17-nitronate anion is susceptible to long range changes in structure.

In order to investigate the influence of the stereochemistry of the C/D ring junction the photochemical behaviour of the nitronate anion (23€) derived from the 13α-17-nitro compound (203) was investigated.

iii) Photolysis of the 17-Nitronate Anion (236) Derived From 3β-Acetoxy-17ξ-nitro-5α-13α-androstane (203)

The conditions used were the same as for the low pressure mercury arc lamp photolysis of the nitronate anions (211) and (227). At the completion of the reaction the crude photolysate after isolation was subjected to preparative t.l.c. from which two fractions were obtained. The most polar fraction was identified as the novel hydroxamic acid (237) isolated in 25% yield, which was significantly lower than previously observed.



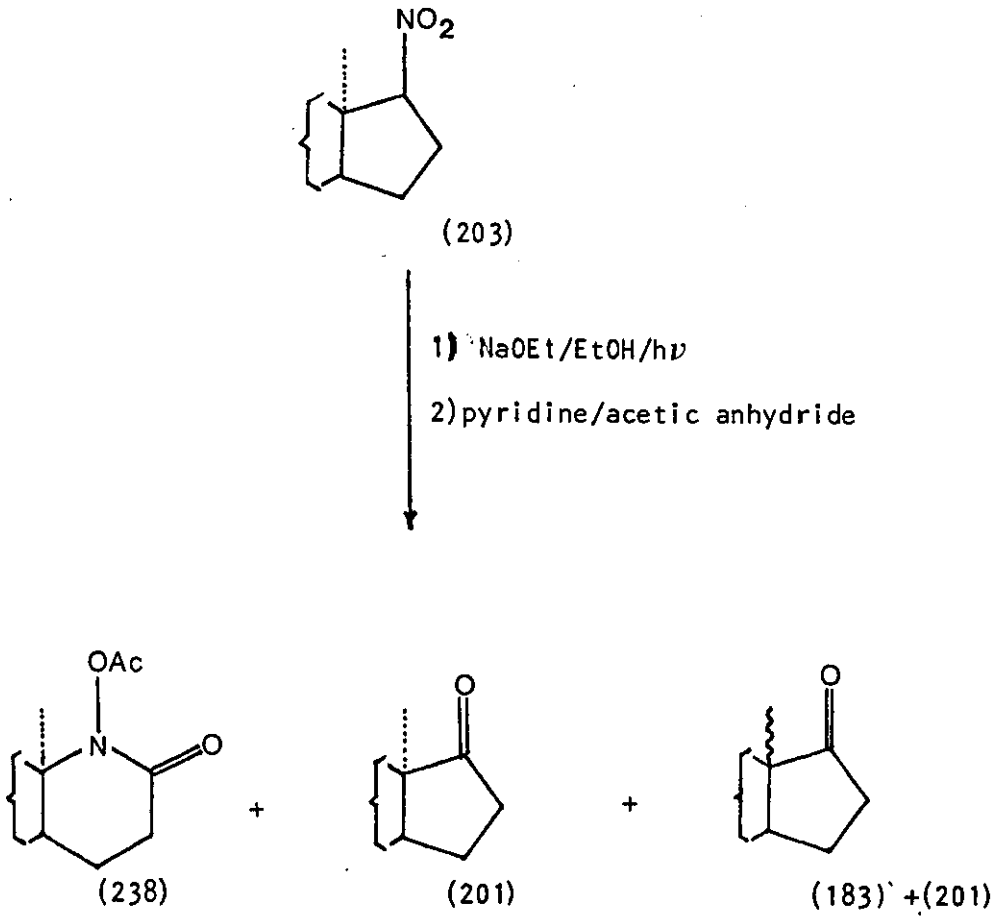
This compound was identified on the basis of the following spectroscopic data. The i.r. spectrum showed the OH group absorption at 3550 cm^{-1} and the typical C=O absorption at 1610 cm^{-1} consistent with previously obtained values. The ^1H n.m.r. spectrum gave a singlet at δ0.72 which was assigned to the 10β methyl. As expected this was little changed from its value of δ0.80 in the original nitro-compound (203). However, the signal for the 13α-methyl which occurs as a singlet at δ0.90 in the parent nitro-compound (203) was assigned

at δ1.35 in the hydroxamic acid (237). This is a significant deshielding of 0.45 p.p.m. and is similar to the deshielding effects observed in the hydroxamic acids (179) and (228) where values of 0.55 p.p.m. and 0.45 p.p.m. respectively were observed.

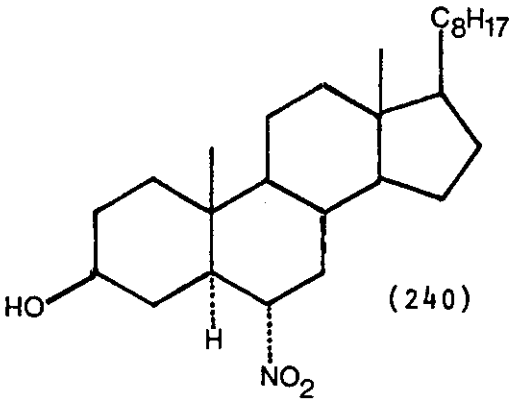
The mass spectrum of the hydroxamic acid (237) gave a molecular ion at $\frac{m}{z}$321 corresponding to the molecular formula $C_{19}H_{31}NO_3$. The main fragmentation ions were at $\frac{m}{z}$306 and $\frac{m}{z}$290 corresponding to loss of CH_3 and CH_3O respectively and are consistent with the fragmentation pathway observed for the hydroxamic acid (228).

The second fraction obtained from the preparative t.l.c. was identified as a mixture of isomeric 13α-and 13β-17-keto-compounds (201a) and (183a). The i.r. spectrum showed a carbonyl absorptions at 735cm^{-1} typical of a five membered ring ketone. The ^{1}H n.m.r spectrum exhibited singlets at δ0.63 and δ0.93 identical with literature values[93] for the C-19 and C-18 methyl groups of the 13α-17-keto-compound (183a). Analysis by t.l.c. gave Rf. values identical with those obtained from authentic samples of the 17-keto-compounds (183a) and (201a). However the two isomers could not be seperated by t.l.c. or crystallisation. To fully characterise the products, the photolysis was repeated and the crude reaction mixture acetylated using pyridine and acetic anhydride. Following preparative t.l.c. and recrystallisation from methanol, the diacetate (238) was obtained in 30% yield. The i.r. spectrum showed absorptions at 1790cm^{-1} (CONROCOMe) 1735cm^{-1} (3β MeCOO) and 1670cm^{-1} (CONROCOMe). The H^1 n.m.r spectrum showed singlets at δ0.80 and δ1.30 which were assigned to the 10β-Me and 13α-Me respectively and further singlets at δ2.00 (3β-COMe) and δ2.15 (NOCOMe) and a multiple at δ4.35 assigned to the 3α-H.

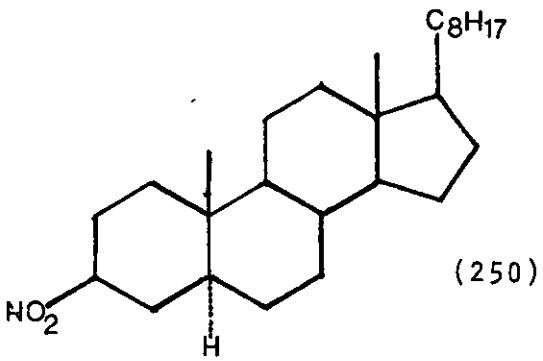
Two further fractions were obtained from the preparative t.l.c. The first,which was crystallised from methanol,was the 3β-acetoxy-5α-13α-androstan-17-one (201) which gave spectroscopic and melting point data in accord with literature values and was identical to an authentic sample. The final fraction was again shown to be an inseparable mixture of the isomeric 17-keto-compounds (183) and (201).



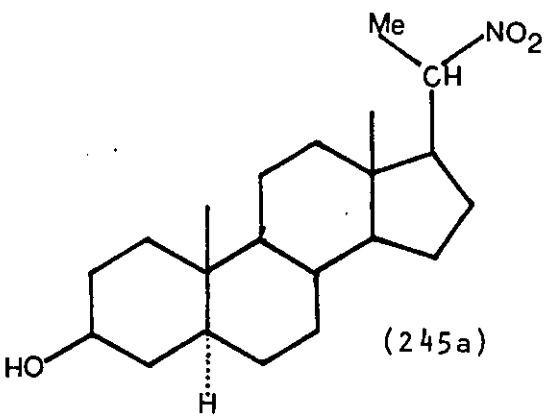
Having examined the photochemical behaviour of the nitronate anions prepared from 17-nitro-compounds a second series of nitro-steroids, shown below, was prepared and the photochemical behaviour of their nitronate anions investigated.



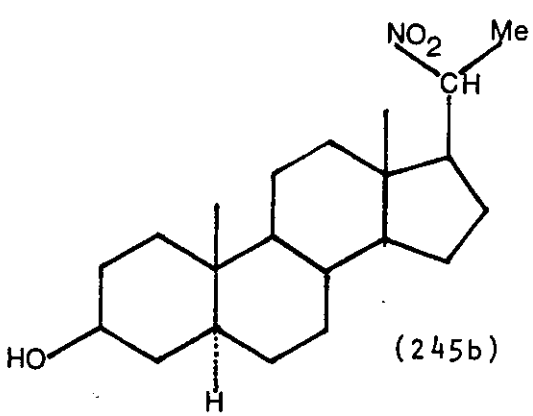
(240)



(250)



(245a)



(245b)

From this series the effects of the 6-membered ring in compounds (240) and (250) can be compared with those observed for the 5-membered ring compounds discussed above.

3) Preparation of the 3,6, and 20-Nitro-steroids

A) Preparation of 6α-Nitro-5α-cholestan-3β-ol (240)

Attempts were made to prepare 6-nitrocholesteryl acetate (15) using the standard and widely reported[77] procedure of treating a solution of cholesteryl acetate (239) in dry ether with fuming nitric acid. However, this reaction proved to be unreliable in our hands, t.l.c. examination revealing the product to be a complext mixture.

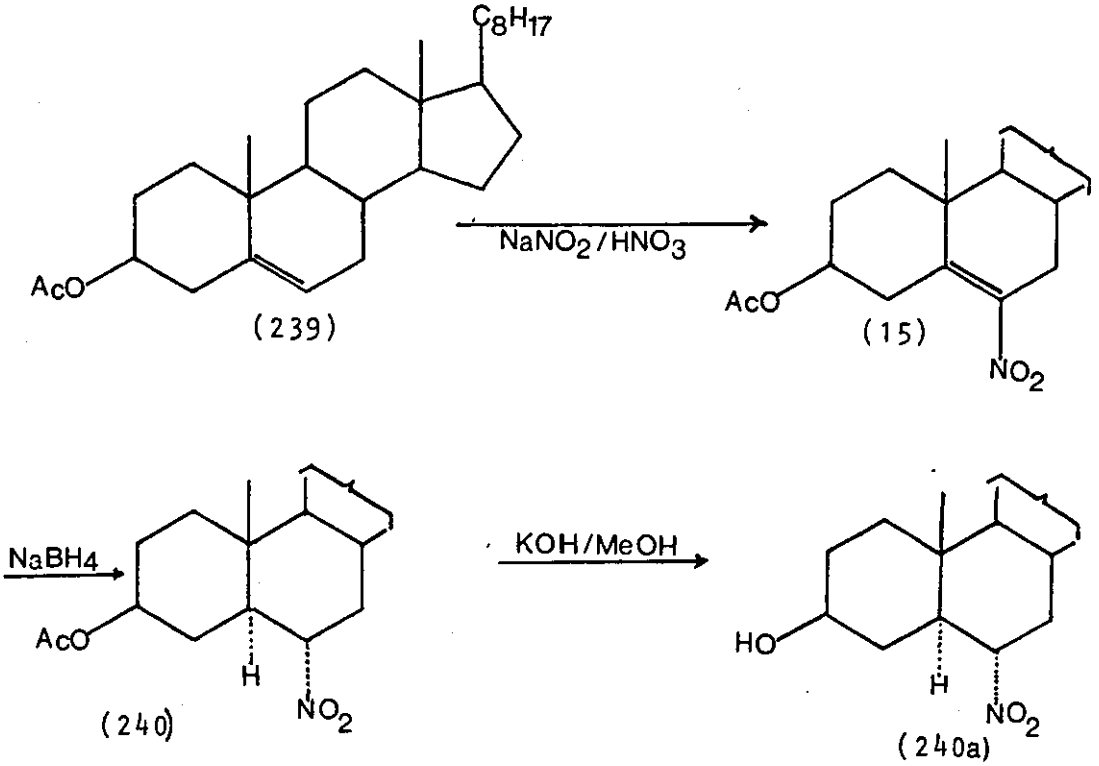
The required product was, however, reliably obtained in 60% yield by following the original procedure of Mauthner[78], namely suspending cholesteryl acetate (239) in concentrated nitric acid to which was added solid sodium nitrite. After stirring at room-temperature for several hours the reaction mixture was diluted with water and the desired product filtered off.

The 6-nitrocholesteryl acetate (15) was converted to 6α-nitro-5α-cholestan -3β-ol (240) by reduction with sodium borohydride in ethanol. During this reaction partial hydrolysis of the 3β-acetoxy group occurred. Therefore after reduction, the hydrolysis of the 3β-acetoxy group was completed by heating the crude product under reflux in 0.5% potassium hydroxide in methanol from which the 6α-nitro-compound (240a)(65% yield) was isolated by dilution with water. (Scheme 21)

The structure of the 6α-nitro-compound (240a)was confirmed by spectroscopic data. The i.r. spectrum showed the characteristic twin absorptions at 1550 and 1375 cm^{-1} of the nitro-group. The ^1H n.m.r. spectrum confirmed the 6α-configuration of the nitro-group since the signal for the 6β-proton appeared at δ4.4 as a broad mutltiplet ($W_{\frac{1}{2}}$ 34Hz) due to spin-spin coupling between the axial 6β-proton and

the axial 5α-and 7α-protons and the equatorial 7β-proton.

Scheme 21



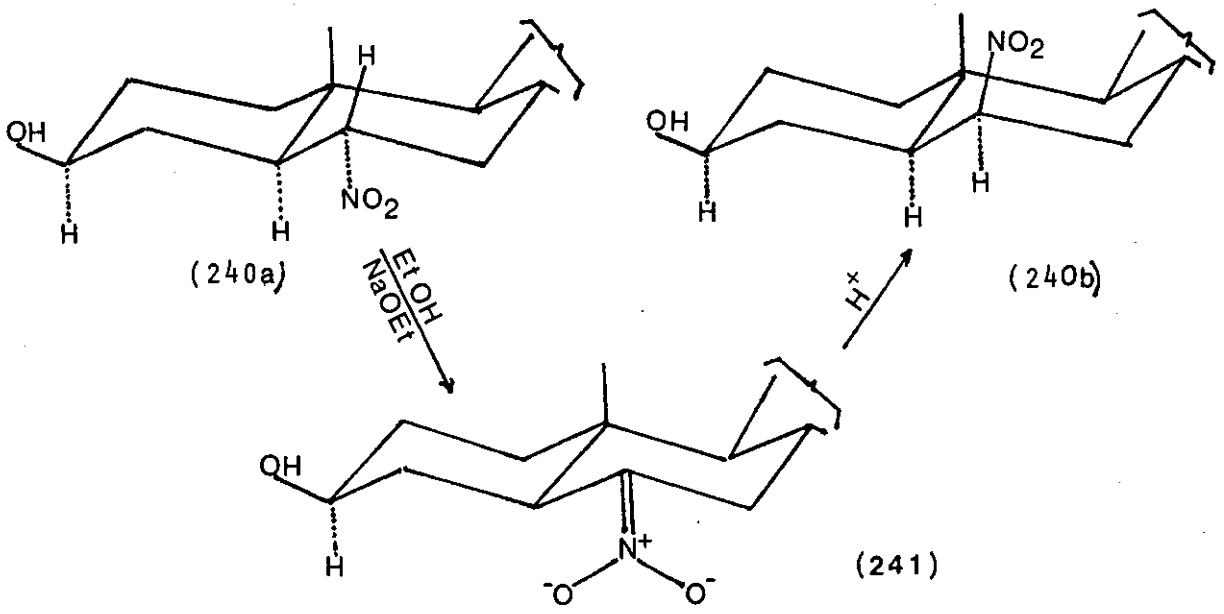
B) Preparation of 6β-nitro-5α-cholestan-3β-ol (241)

This was prepared by treatment of the 6α-nitro compound (240a) with excess sodium ethoxide/ethanol at room temperature overnight. Acidification and filtration yielded the 6β-nitro-compound (240b) in quantitative yield. The ^1H n.m.r. spectrum showed a narrow multiplet at δ4.4($W_{\frac{1}{2}}$ 10Hz) due to the equatorial 6α proton coupling with the axial 5α and 7α protons and the equatorial 7β-proton. The value of $W_{\frac{1}{2}}$ is lower for the 6β-nitro compound because there is no axial-axial coupling as in the 6α-nitro compound.

In converting the 6α-nitro-compound (240a) to the 6β-isomer (240b) one is preparing the kinetic product from the thermodynamic one. The 6α-nitro-compound (240a) would be expected to be the more stable since in this conformation the nitro-group is in the equatorial conformation. In strong alkaline solution the 6α-nitro-compound (240a) would be present as its nitronate anion (241) and on acidification this would

be expected to yield the 6β-nitro-compound (240b) as shown below.

This is because from studies,[79] carried out on the analogous aci-nitro tautomerisation, there is a kinetic preference for protonation from the least hindered side. In this case this is the α-face giving rise to the product of steric approach control namely the 6β-nitro-compound (241).

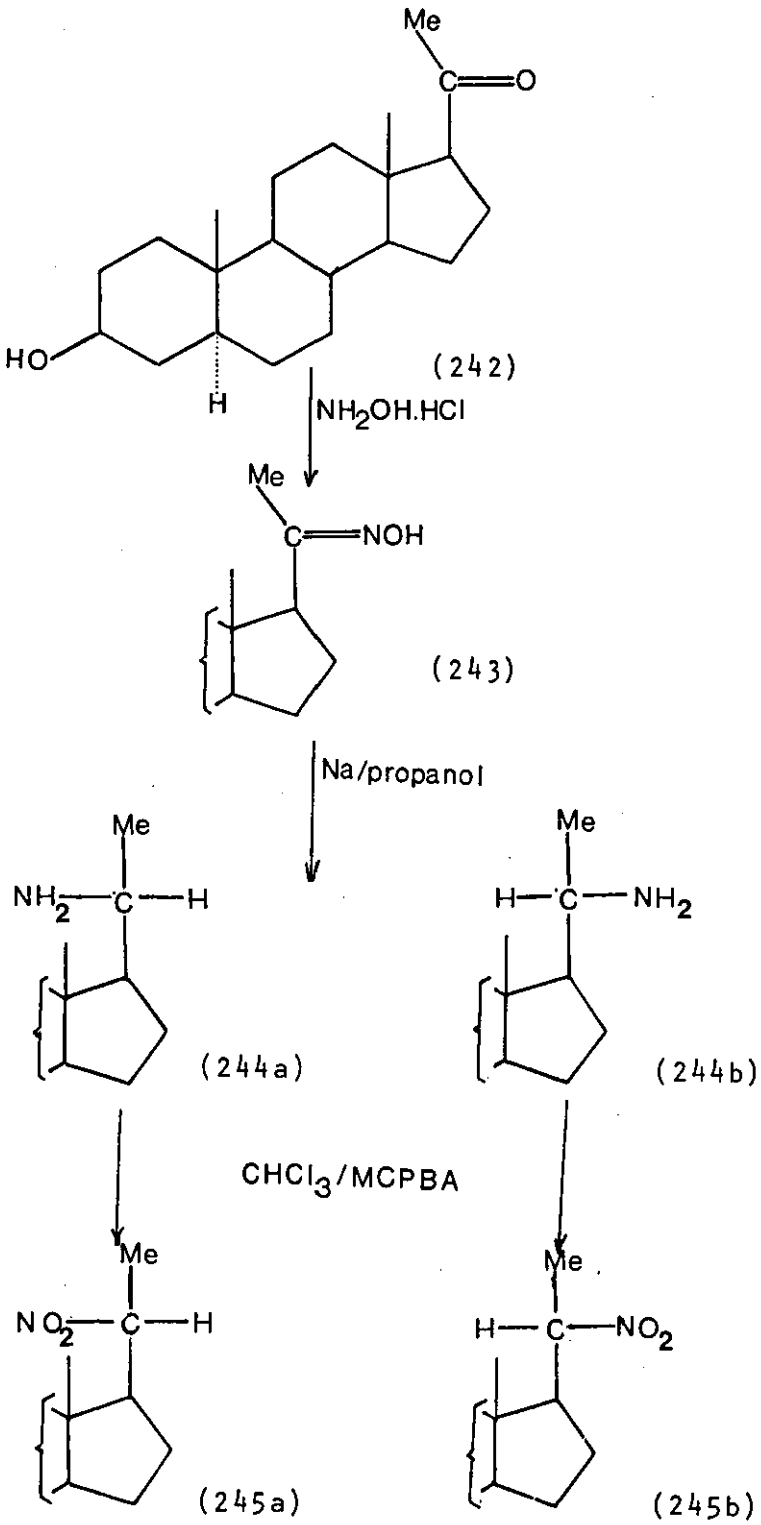


C) Preparation of the 20α and 20β-Nitro-5α-pregnan-3β-ol (245)

As stated earlier the Patchett procedure for the preparation of 3-nitro or 20-nitro steroids. However, a procedure for the preparation of these compounds has been developed by P Robinson,[69].

The 20α and 20β-nitro-compounds (245a) and (245b) were prepared according to the procedure of Robinson which is shown in Scheme 22 below.

Scheme 22


Me
C=O
HO
H
(242)
NH2OH.HCl
Me
C=NOH
(243)
Na/propanol
Me
NH2—C—H
(244a)
Me
H—C—NH2
(244b)
CHCl3/MCPBA
Me
NO2—C—H
(245a)
Me
H—C—NO2
(245b)

The reduction of the 20-oxime compound (243) with sodium/isopropanol gave an isomeric mixture of the know 20-amines (244a) and (244b) in a ratio of 20β:20α of approximately 3:2. This ratio was also observed by Robinson who concluded that it was a reflection of the thermodynamic control of this reaction.

Following chromatographic separation, the two amines (244a) and (244b) were subjected to oxidation with m-chloroperbenzoic acid to give the 20-nitro compound (245a) and (245b). The 20β-nitro compound (245a) showed the expected absorption at 3450cm^{-1} due to the 3β-hydroxy group and absorptions at 1550cm^{-1} and 1380cm^{-1} due to the nitro group. The ^{1}H n.m.r. spectrum gave singlets at δ 0.75 and 0.80 assigned to the 13β-Me and 10β-Me respectively and multiplets at δ 3.5 and δ 4.5 assigned to the 3α-H and 20α-H respectively. The mass spectrum gave a molecular ion at $\frac{m}{z}$ 349 corresponding to the molecular formula $C_{21}H_{35}NO_3$. The 20α-nitro compound (245b) gave absorptions in the i.r. spectrum at 3340cm^{-1} due to the 3β-OH and at 1550cm^{-1} and 1380cm^{-1} due to the NO_2 group. The ^{1}H n.m.r. spectrum gave singlets at δ 0.78 and δ 0.80, 13$\beta$and 10β-Me respectively. Multiplets at δ 3.5 and δ 4.4 were assigned to 3α-H and 20β-H respectively.

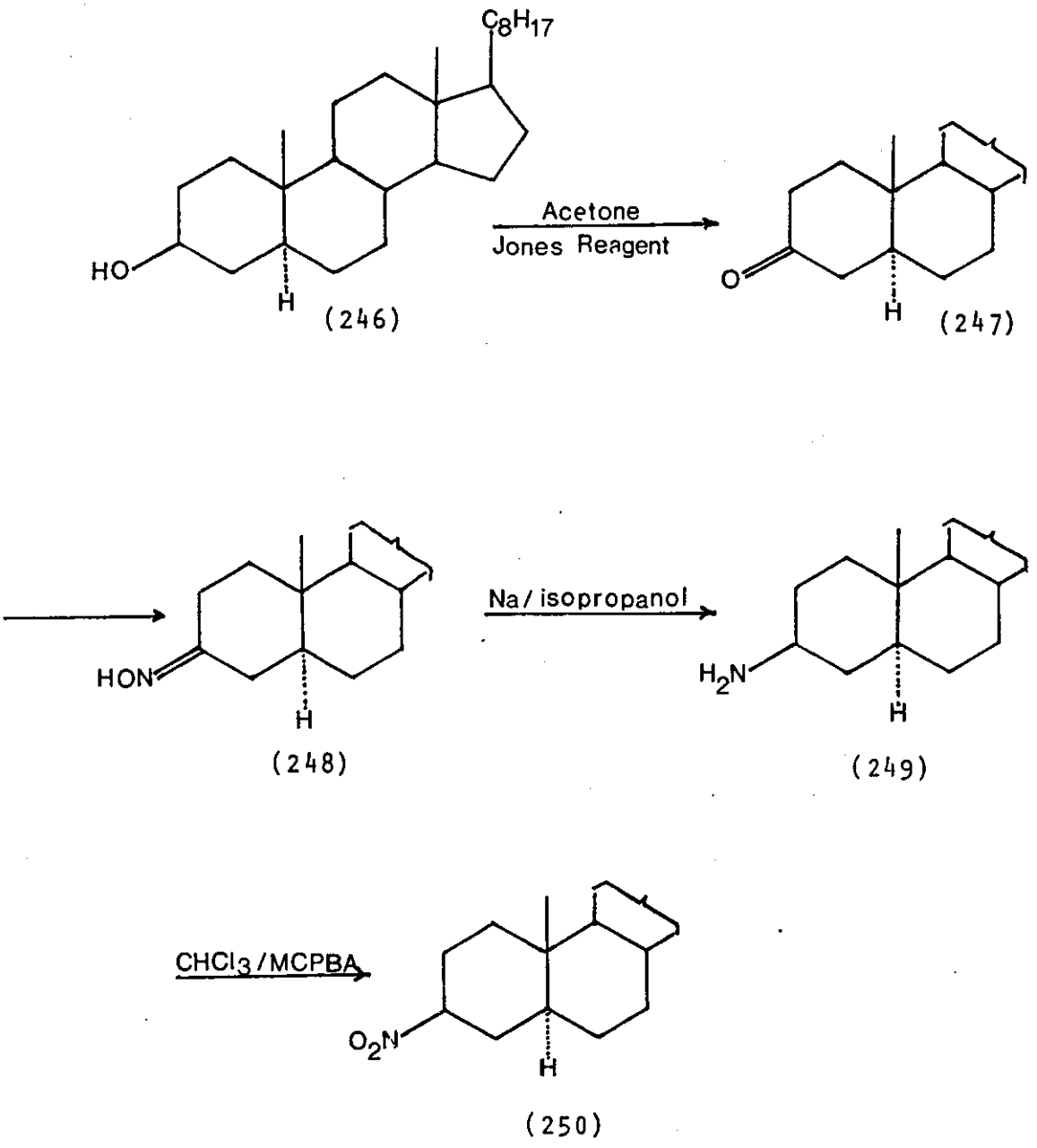
D) Preparation of 3β-Nitro-5α-Cholestane (250)

The known, 3β-nitro compound (250) was prepared by route analogous to that used for the 20-nitro compounds (245a) and (245b) and is shown in Scheme 23.

The reduction of the oxime (248) to the 3β-amine (249) with sodium in isopropanol was first developed by Bull,[70]. It is of interest to observe that the 3β-amine is formed exclusively unlike in the reduction of the 20-oxime (243) discussed above.

The conversion of the 3β-amine to the 3β-nitro compound (250) has been fully reported by Robinson,[69].

Scheme 23



4) Low Pressure Mercury Arc Lamp Photolysis of the 3-, 6-, and 20-Nitronate Anions

A) Photolysis of the 6-Nitronate anion (241) Derived from 6α- or 6β-Nitro-5α-cholestan-3β-ol (240a) and (240b)

The anion was preformed prior to the photolysis as before by

dissolving the 6α-nitro-compound (240a) or the 6β-nitro isomer (240b) in ethanol containing 10 molar equivalents for sodium ethoxide.

As discussed earlier the U.V. spectrum of this anion showed λmax 240 nm (ε 9,000) arising from a $\pi \rightarrow \pi^*$ transition. Accordingly it was decided to again perform the photolysis using a low pressure mercury arc lamp.

The photolysis was continued until no starting material could be detected by t.l.c.,(approximately 24 hours). The length of photolysis is quite different from that observed for the 17-nitronate anion and is in marked contrast to that reported by Yamada who photolysed the same nitronate anion using t-BuOH/BuOK for thirty minutes only. However, our photolysis was repeated several times and it was firmly established that at least 24 hours reaction time was required.

A similar work up and isolation procedure was used to that developed for the 17-nitronate anions. Qualitative t.l.c. showed the crude product consisted of four products, in approximately equal amounts and preparative t.l.c. was used for purification since crystallisation failed to produce any pure compounds.

The least polar component (ca 25%) did not show any characteristic absorptions in the i.r. spectrum except for a hydroxy group at 3340 cm^{-1}.

The ^1H n.m.r. spectrum showed singlets at δ0.65 assigned to 13β-methyl and at δ0.78 assigned to the 10β-methyl. Further signals were observed as multiplets at δ3.5 assigned to the 3α-methine and at δ5.3 indicating the product to be an alkene. Further t.l.c. purification on $AgNO_3$/silica plates allowed the fraction to be separated into two components. The major component, crystallised from methanol, was identified as cholesterol (25))(17%) by comparison with authentic material.

The second fraction from the initial preparative t.l.c. exhibited absorptions in the i.r. at 3340 cm^{-1} due to the hydroxyl group and a carbonyl absorption at 1705 cm^{-1}. Crystallisation from acetone/pet ether

gave 3β-hydroxy-5α-cholestan-6-one (20%)(252) which gave spectroscopic and analytical data in accord with literature values. To confirm this identification the product (252) was treated with pyridine/acetic anhydride to give the 3β-acetoxy compound (252a) which gave spectroscopic and physical data in accord with literature values.

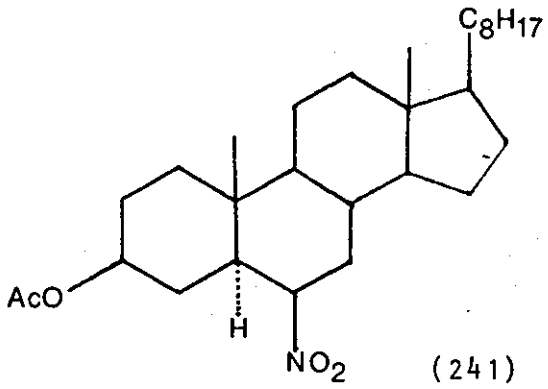
The third fraction from the preparative t.l.c. was identified as 3β-hydroxy-5α-cholestane (253) (20%) which was shown to be identical in all respects with authentic material.

The above results are similar to those obtained by Yamada,[74] who investigated the photochemistry of the 6-nitronate anion (242), formed by treatment of the 6β-nitro compound with $KOBu^t$, from which was isolated cholesteryl acetate (239) and 3β-acetoxy-5α-cholestan-6-one (252a)(37%). Yamada also isolated the hydroxamic acid (254a)(12%). Yamada's results are shown in Scheme (24).

However, in our photolysis we found tentative evidence for the existence of the hydroxamic acid (254). From the initial preparative t.l.c. a very polar fraction (20%) was obtained which gave a violet colour with ferric chloride, indicating the material to be a hydroxamic acid. The i.r. spectrum showed a carbonyl absorption at 1660 cm^{-1}, which is comparable with the value of 1640 cm^{-1} reported by Yamada. The mass spectrum did not show a molecular ion but gave a peak at $387 = \overset{+}{M}-16$ which is typical of some 7-membered ring hydroxamic acids. However, attempts to obtaina pure sample of the compound in order to carry out a full characterisation were unsuccessful due to the compound undergoing decomposition during recrystallisation.

To try and obtain a more stable compound in order to fully characterise the product, the photolysis was repeated and the crude photolysate was treated with zinc and acetic acid to convert the proposed hydroxamic acid (254) to the lactam (130). The lactam (130) and its regioisomer (131)

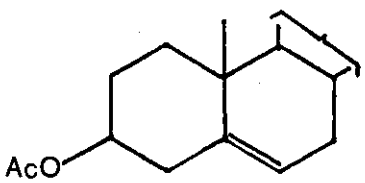
Scheme 24



(241)

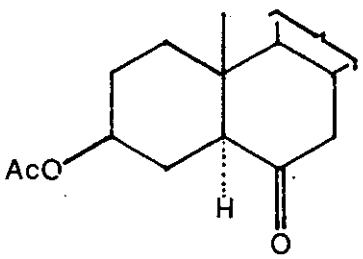
$h\nu$

t BuOH / t BuOK



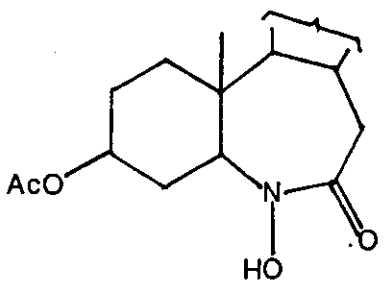
(239)

+



(252)

+

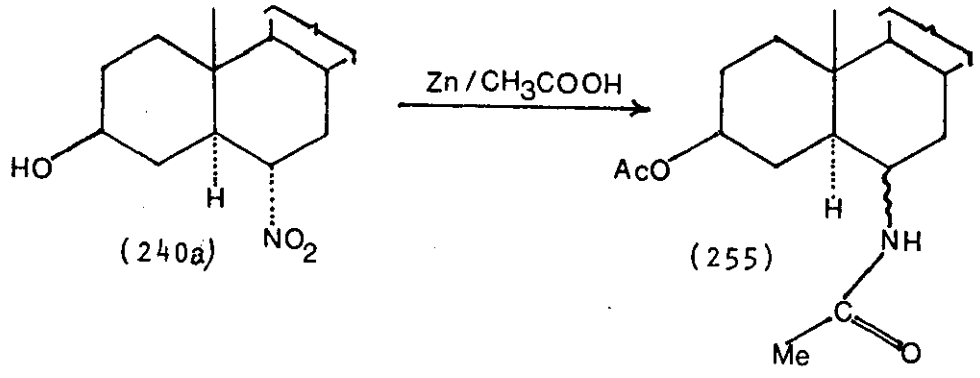


(254a)

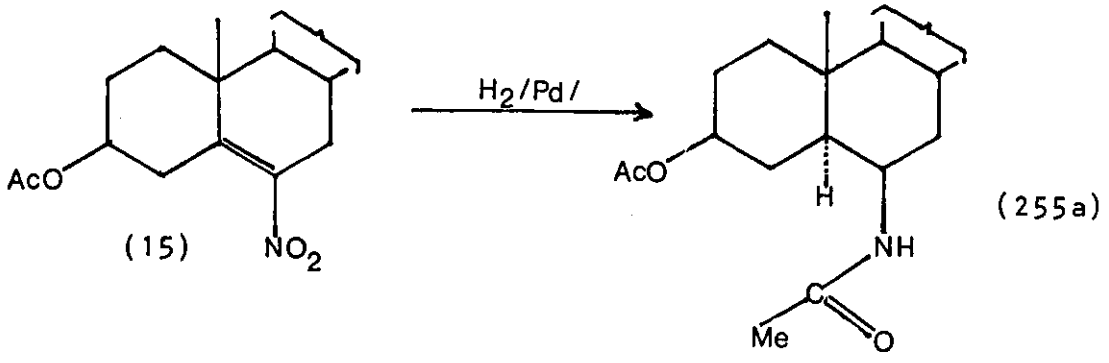
had been previously obtained by Suginome in his studies on the photo-Beckmann rearrangement of the 6-ketone oxime .

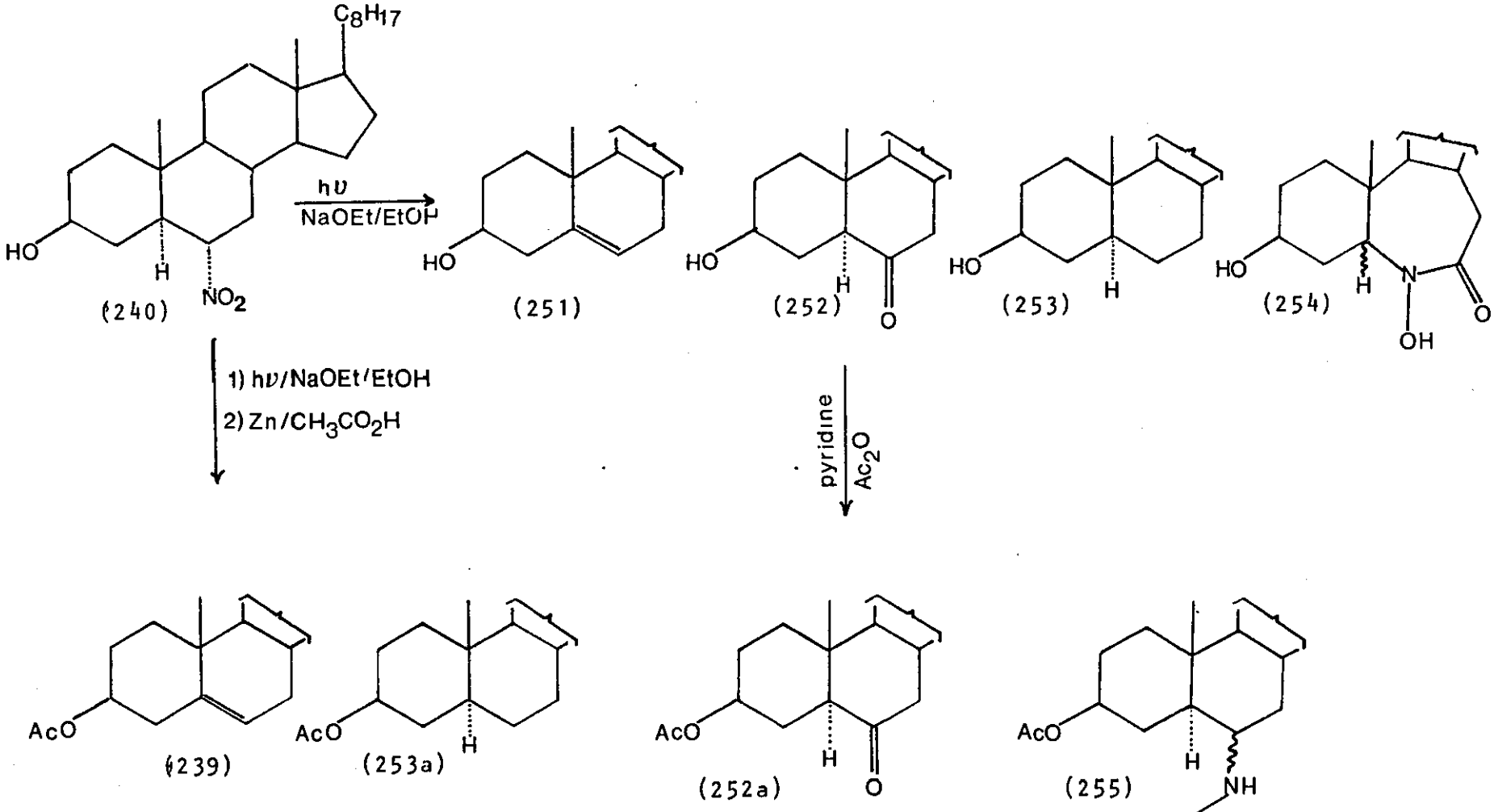
On performing the reduction and separating using preparative t.l.c. two fractions were obtained which gave typical lactam carbonyl absorptions at 1660 cm^{-1} for the major component and 1650 cm^{-1} for the minor product. Following recrystallisation, both of these compounds were found from their mass spectrum to have molecular weights of 487. The expected compounds would be expected to have a molecular ion at $\frac{m}{z}$ 459.

This molecular weight was consistent with the products being two isomers of the 3β-acetoxy-6-acetamido compound (255) formed from a reduction and acetylation of the unphotolysed nitro-compound (18) on treatment with zinc and acetic acid.



This was confirmed by preparing the 6β-acetamide compound (255a) by the literature procedure[80], and showing it to be identical with the major amide component of the mixture isolated from the zinc/acetic acid treatment of the photolysate.



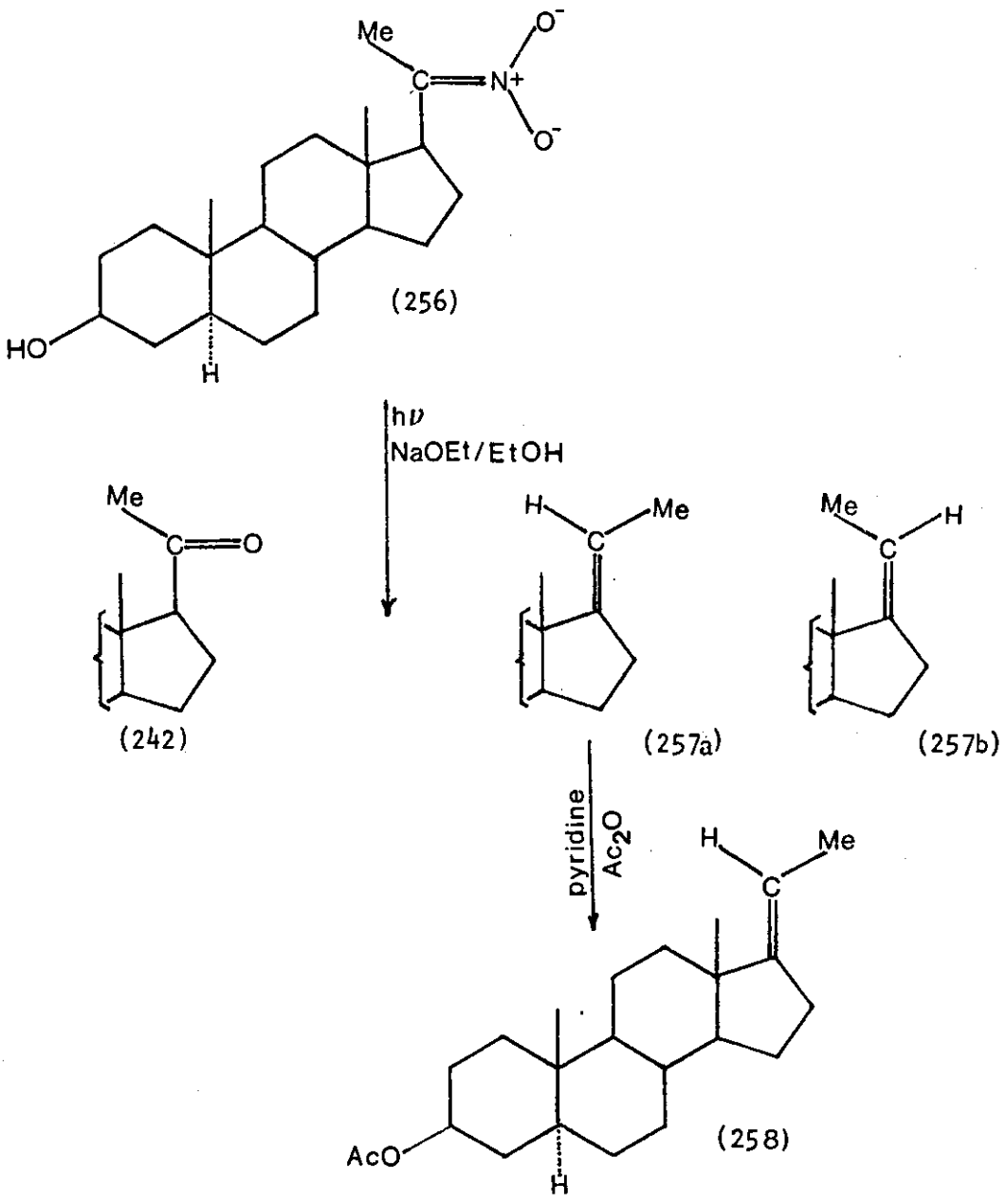

C8H17
HO
H
NO2
(240)
hυ
NaOEt/EtOH
(251)
(252)
(253)
(254)
OH
1) hν/NaOEt/EtOH
2) Zn/CH3CO2H
pyridine
Ac2O
AcO
(239)
(253a)
(252a)
(255)
NH
C
O
Me

Scheme 25

The results from the 6-nitronate anion photolysis are illustrated in Scheme 25.

B) Photolysis of the 20-Nitronate Anion (256) derived from the 20-Nitro Compounds (245a) and (245b)

Although both 20α and 20β-nitro-compounds (245a) and (245b) were prepared either could be used to generate to 20-nitronate anion (256). The 20-nitronate anion (256) was subjected to the normal photolysis and work up, after which the crude photolysate was subjected to preparative t.l.c. and recrystallisation to give the 20-keto compound (242) (20%) and the $\Delta^{17,20}$compound (257) (17%).



The 20-keto compound (256) was identified by comparison with authentic material and from its spectroscopic data.

The alkene was identified as the $\Delta^{17(20)}$ compound (257) and not the alternative isomeric Δ^{20} compound by consideration of its ^{1}H n.m.r. spectrum which showed only one alkene proton signal as a multiplet at δ5.0. The signal for the C-20 methine in these systems is a complex multiplet due to coupling with the C-21 methyl protons and the C-16 methylene protons. Signals for the angular methyl groups were observed as singlets at δ0.75 and δ0.83. These data are similar but not identical to those reported[91] for the Z-isomer of the $\Delta^{17(20)}$ compound (257b) namely δ0.80 (s C-19); δ0.85 (s C-18) and δ5.0 m (C-20-H).

The ^{1}H n.m.r. spectrum of the E-$\Delta^{17(20)}$ compound (257a) has not been reported in the literature. However, the assignment of the E-structure for compound (257) was confirmed by its melting point and by the preparation of it 3β-acetoxy derivative (258), by treatment with pyridine and acetic anhydride, which gave a melting point and ^{1}H n.m.r. spectroscopic data in accord with that reported[92].

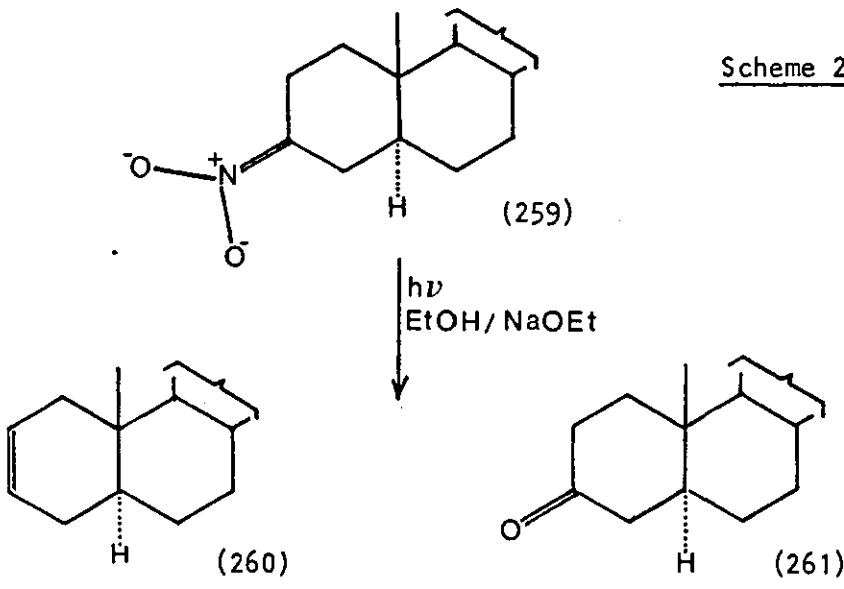
C) Photolysis of the nitronate anion of 3β-nitro-5α-cholestane

Photolysis with a low pressure mercury lamp, of the 3-nitronate anion (259) derived from the 3β-nitro cholestane (246) was performed using the same procedure as before.

Following the normal work up the crude reaction mixture was subjected to preparative t.l.c. from which two fractions were obtained.

The less polar fraction was crystallised from methanol to afford cholest-2-ene (260) (25%) which was identified from its spectroscopic and physical data by comparison with authentic material. Further t.l.c. examination of this fraction on $AgNO_3$ impregnated silica did not reveal the presence of further components.

The more polar fraction failed to crystallise satisfactorily but its i.r. spectrum 1735cm^{-1} (C=O) and ^{1}H n.m.r. spectrum δ 0.70 (s 13β-Me); δ0.83 (s 10β-Me) were identical with those obtained for cholestan-3-one (261).



(259) (260) (261)

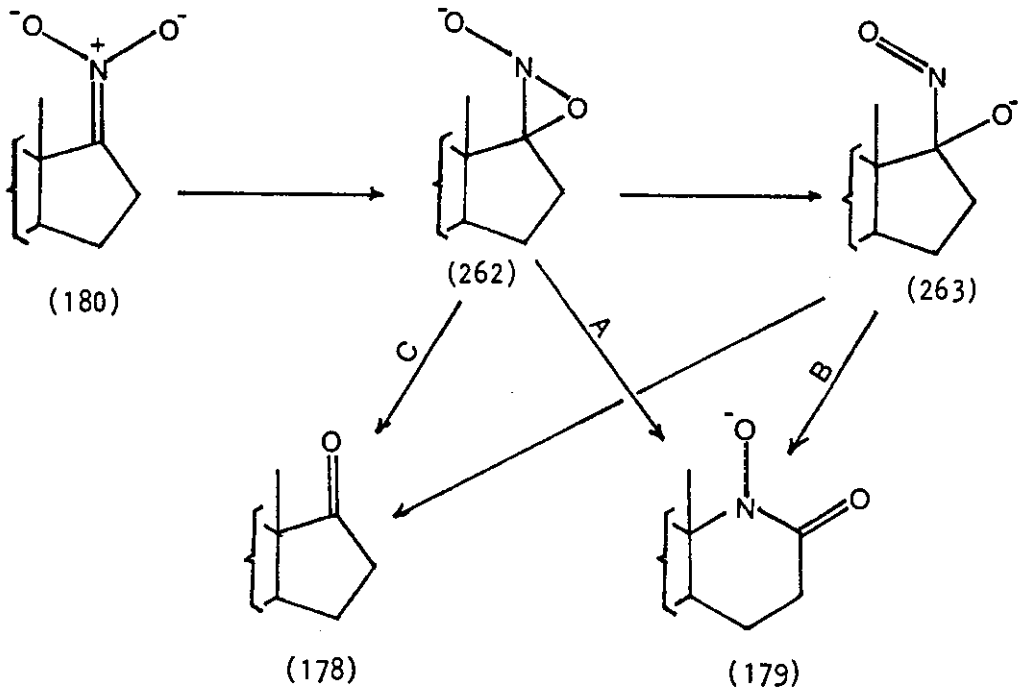
Scheme 26

5) Possible Reaction Pathways Involved in the Photolyses of Nitronate Anions.

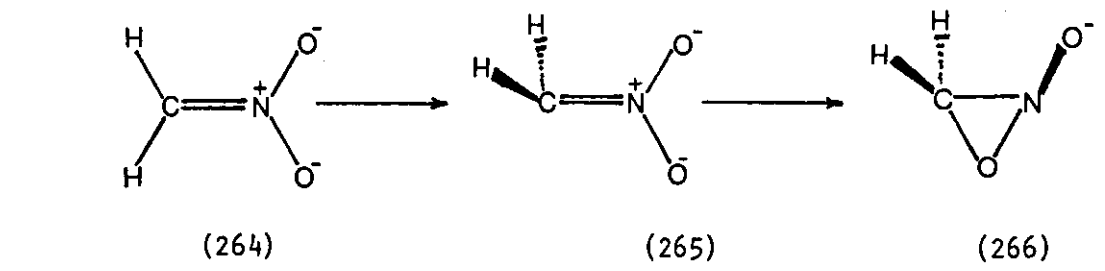
A) Mechanisms of 17-nitronate anion photolyses

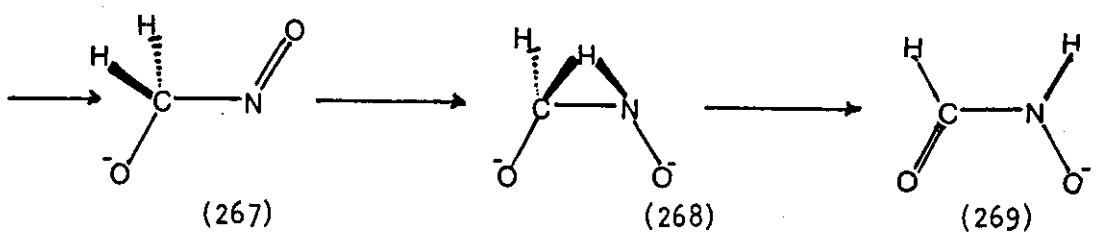
The general feature of these photolyses are seen to be the formation of a hydroxamic acid and a ketone, and these products may be plausibly rationalised as involving a photochemically generated common intermediate, namely a N-hydroxy-oxaziridine anion (262). The hydroxamic acids (179), (228), and (237) may be considered to arise via a concerted breakdown of this intermediate (Path A) or may by analogy with the N-alkyl oxaziridines discussed in the introduction, first undergo N-O bond cleavage to give the species (262) which subsequently undergoes C-C bond cleavage and alkyl migration (Path B). The formation of the 17-keto compound may be considered to arise either from the species (262) or (263) by loss of hyponitrite ion (Path C), Scheme 27.

Scheme 27

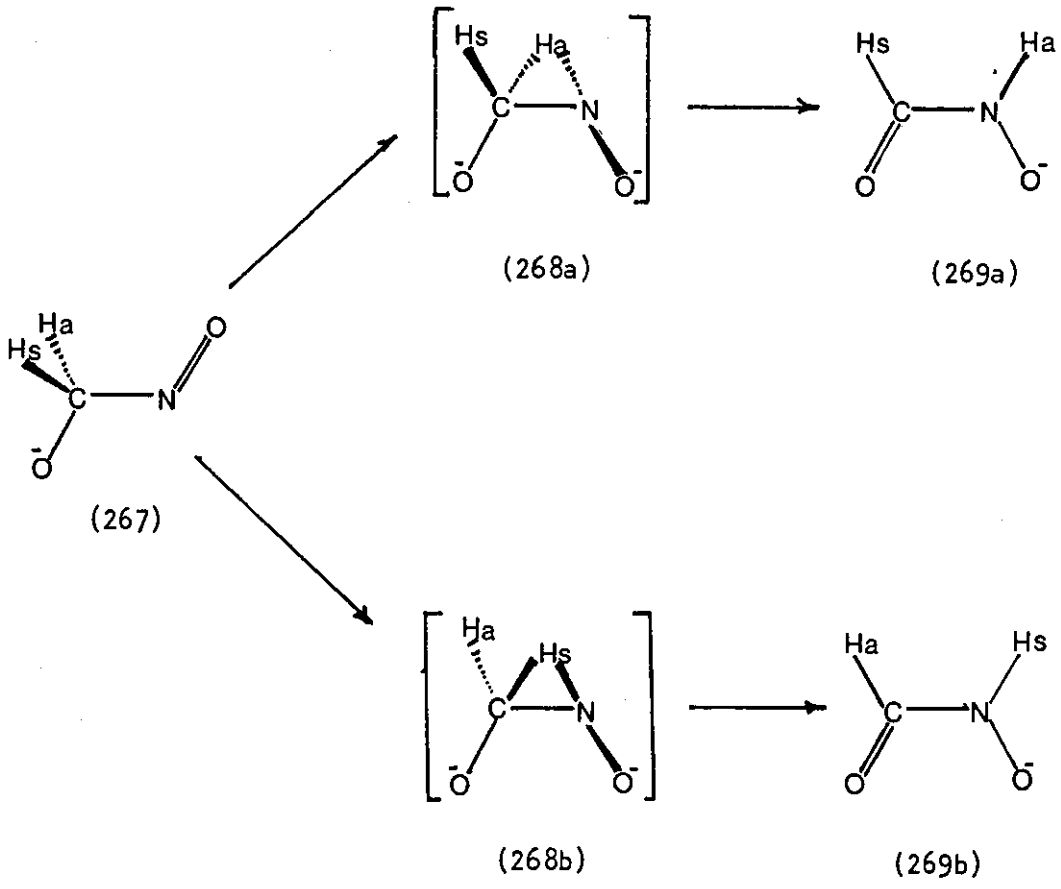


The photochemical behaviour of alkane-nitronate anions to give hydroxamic acid has been examined theoretically by Yamada,[84] and co-workers using molecular orbital (MO) theory. In this study Yamada examined the nitronate anion (264) which was postulated as undergoing the following reaction sequence.





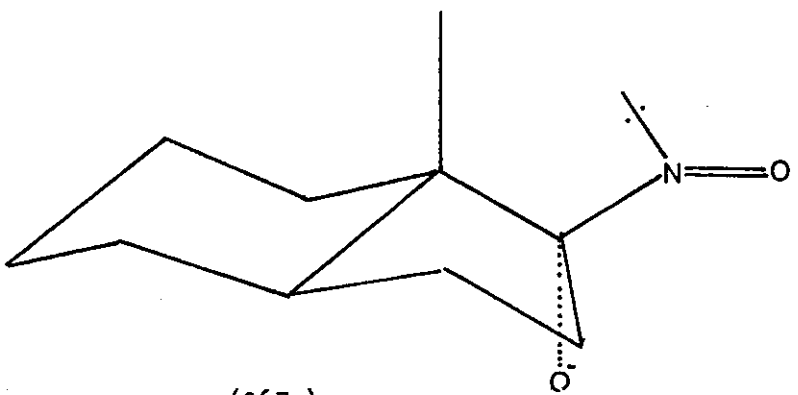
From the calculations made the main conclusion was that the N-hydroxy-oxaziridine anion (266) wasahighly reactive transient species which rapidly underwent conversion to the nitroso species (267). It is the nitroso species (267) which is the true intermediate of the reaction and the one from which hydrogen migration occurs. Due to the geometry of the nitroso species (267) the two hydrogen atoms are non-equivalent, one being <u>syn</u> (Hs) to the N=O bond, the other <u>anti</u> (Ha), thus giving rise to the two possible reaction pathways shown below:-



Calculations of the energy requirements for these two processes showed that migration of Ha to be preferred. It was postulated that during the conversion of the nitroso species (267) to the hydroxamic acid anion (269) there is a significant interaction between the C-H bond involved in migration and the N=O antibonding orbital. As a result of this stereoelectronic effect migration of Ha is preferred.

As discussed earlier, the photolysis of the 17-nitronate anions were regiospecific with migration of the most substituted carbon. Yamada has postulated that in substituted systems the nitroso intermediate will be in conformation in which the steric interaction between the ring substituent and the N=O oxygen will be minimised.

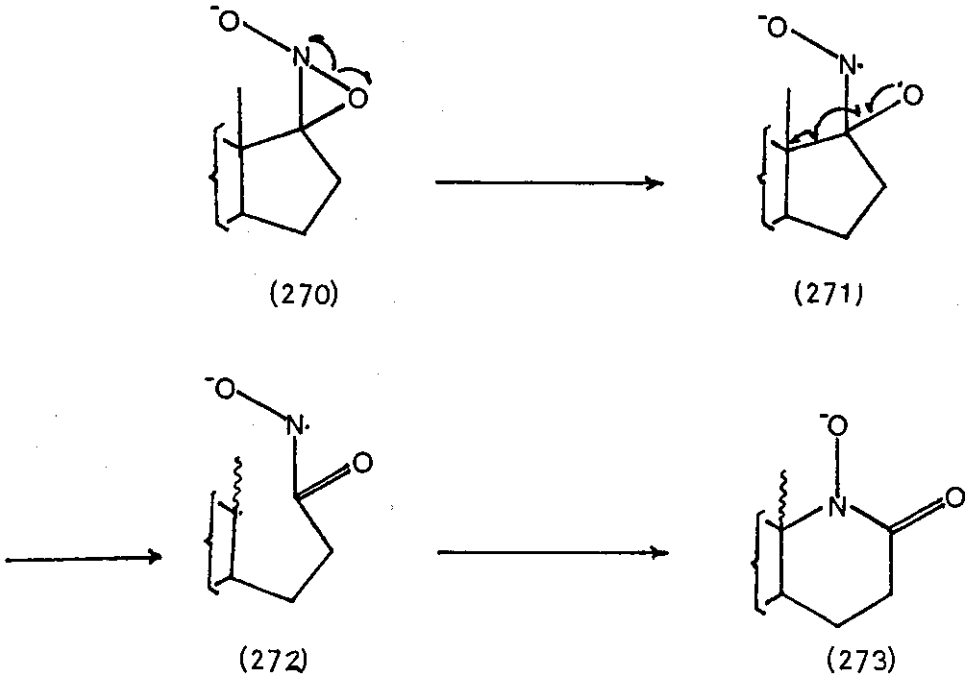
In the 17-nitronate anions this would result in the postulated nitroso intermediate (267a) having the conformation shown, in which the more substituted C_{13} is <u>anti</u> to the N=O and therfore migrates preferentially.



(267a)

However, such regiospecificity may also be plausibly rationalised in terms ofafree-radical mechanism from the ring opened species (263), Scheme 28.

Scheme 28



(270) (271)

(272) (273)

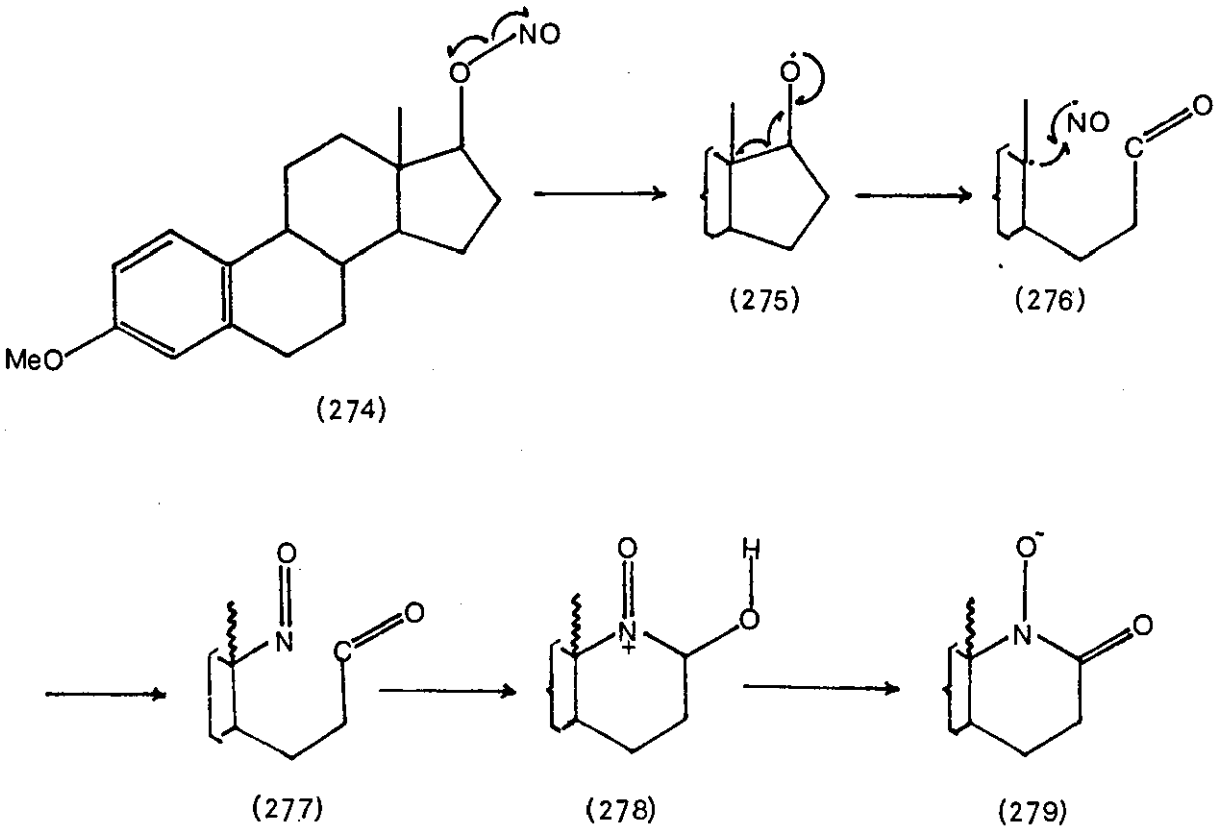
In this mechanism cleavage of the C_{13}-C_{17} bond would be preferential to cleavage of C_{16}-C_{17} since it would give the more stable tertiary radical at C_{13}.

However, if a radical was formed at C_{13} it may be expected to be sufficiently long-lived for epimerisation to occur.

As indicated earlier a mixture of stereoisomers at C_{13} was observed in the photo-Beckmann rearrangement of the 17-keto-oximes which are believed to arise from similar radical intermediates.

Similarly, formation of a stereoisomeric mixture was observed in the work of Robinson,[85] on the photolysis of steroidal nitrites to give hydroxamic acids. For example, photolysis of estradiol-3-methyl ether-17-nitrite (274) gave two hydroxamic acids (279) isomeric at C_{13} which are postulated as arising by the free-radical mechanism shown below (Scheme 29). As can be seen this reaction proceeds via preferential cleavage of the C_{13} -C_{17} bond and is regiospecific.

Scheme 29

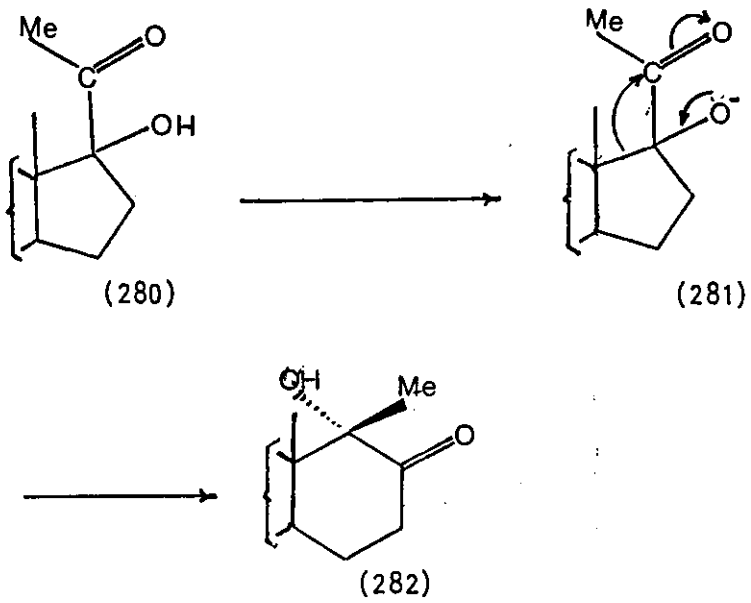


Thus the stereoselectivity observed in the formation of the hydroxamic acids from the 17-nitronate anions would not appear to support a free-radical mechanism.

That the alternative mechanism involving the nitroso intermediate (267a) would give regio- and stereospecificity is supported by considering the base-catalysed D-homoannulation of the 17α and 17β-hydroxy-20-keto steriods,[86] (280). This reaction has been shown to be regio- and stereospecific with preferential cleavage of the C-13-C-17 bond.

The postulated mechanism of the 17-hydroxy compound (276) is shown below, Scheme 30.

Scheme 30



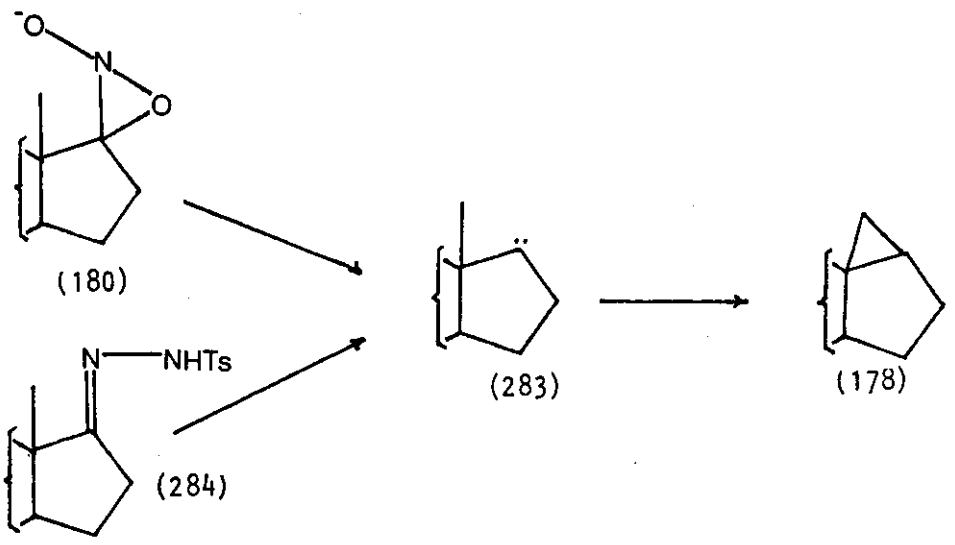
(280) (281) (282)

As can be seen the intermediate (281) has similar structural characteristics to the nitroso intermediate (267a) and therefore analogous behaviour of the two species is not unreasonable.

In such D-homoannulations release of intracyclic strain at the C/D ring junction is recognised as an important driving force for C/D trans-compounds. The absence of this driving force in the 13α 17-nitronate anion may well be a contributing factor towards the low yield of the 13α-hydroxamic acid (237).

The formation of the 17-keto compound may also be explained by extrusion of the hyponitrite ion from the nitroso intermediate (269a).

Formation of the 17,18-cyclosteriod (178) may be considered to arise from the N-hydroxy-oxaziridine anion by loss of the nitryl radical to give a C_{17} carbene (283) which inserts into the C_{18}-H bond. The 17,18-cyclosteriod (178) has previously been reported as a product of the base treatment in an aprotic solvent of the tosyl-hydrazone (284). This reaction was also proposed as proceeding via the C_{17}-carbene (283).

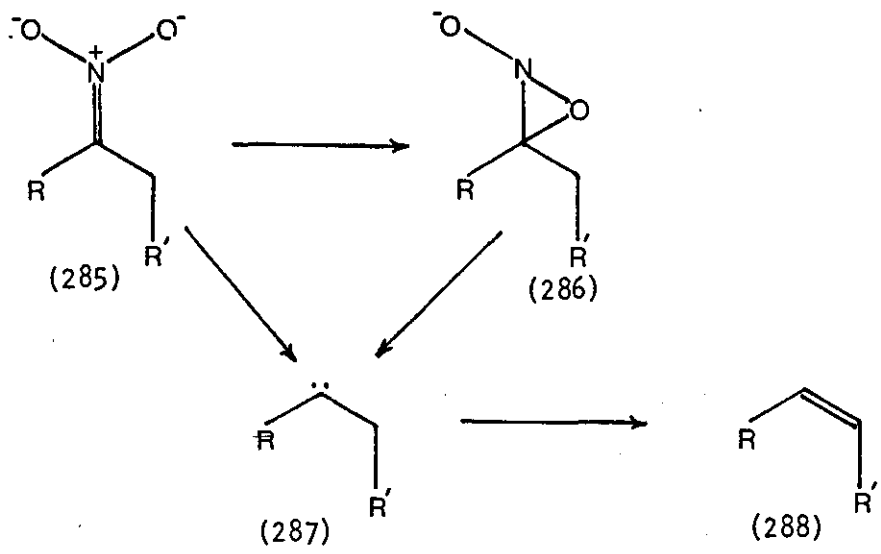


B) Mechanisms in other Steriodal Nitronate anions.

As can be seen from the results there are considerable differences in the photochemical behaviour of the 17-nitronate anions and that of the 3,6 and 20-nitronate anions. The former react faster and undergo rearrangements of the D-ring, expanding it to a 6-membered hydroxamic acid. The latter do not rearrange to hydroxamic acids except possibly for the 6-nitronate anion (242). Instead the major reaction in these cases appears to be the formation of an alkene and a ketone. The formation of the ketone is also observed with the 17-nitronate anions and a mechanism for its formation has been put forward previously.

The previous mechanistic discussion above invoked the formation of an N-hydroxy-oxazaridine anion and this same type of species could explain the alkene formation, assuming that it may break down by loss of nitrite ion to a carbene (283). Alternatively, the formation of the carbene ring may be postulated as arising directly from the nitronate anion, Scheme 31.

Scheme 31



The formation of 5α-cholestan-3β-ol is difficult to rationalise in terms of the photochemical behaviour of a nitronate anion, and may well arise directly from the free-6α-nitro compound (240). Unfortunately attempts to confirm this by photolysis of the free-nitro compound (240) were unsuccessful due to the photolysis product being an extremely complex mixture. That free 6α-nitro compound (240) would be present during the photolysis of the 6-nitronate anion (242) is not surprising in view of the expected low kinetic acidity of the 6α-nitro compound (240) due to the 6β-proton being relatively sterically hindered.

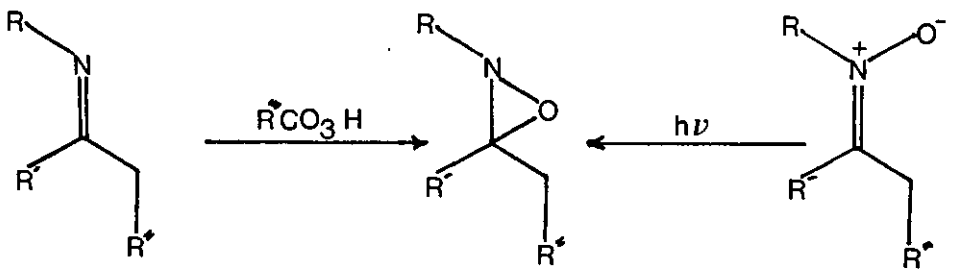
6) Preparation and Photolysis of Steriodal N-alkyl oxaziridines.

The N-hydroxy-spiro-oxaziridines (180) are postulated as either intermediates or short-lived species in the photolysis of the nitronate anions previously discussed. It is noteworthy that in the photolysis of the 17-nitronate anions the rearrangement to the hydroxamic acid involves the exclusive migration of the more substituted C-13 rather than the less substituted C-16. As indicated in the introduction, this behaviour contrasts markedly with the results obtained by other workers on the photorearrangement of N-alkyl-spiro-oxaziridines which rearrange by stereoelectronically controlled migration of the less substituted carbon.

It was therefore of interest to examine the photochemical behaviour of the steriodal N-alkyl oxaziridines analogous to the N-hydroxy oxaziridines proposed as intermediates in the photolysis of nitronate anions.

Two approaches to the synthesis of the N-alkyl oxaziridines were followed. These were the chemical generation of an oxaziridine by peracid oxidation of an imine and the photochemical conversion of a nitrone as shown below:-

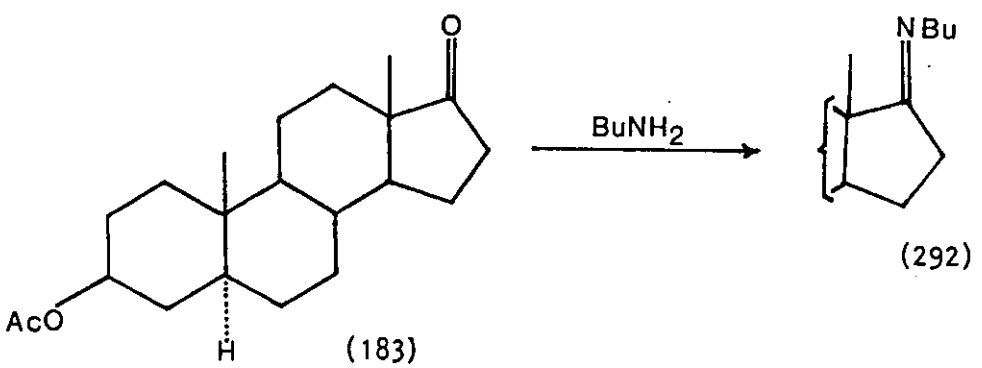
Scheme 32



(289) (290) (291)

A) Preparation of N-butyl-17-spiro-oxaziridine

i) Preparation of the N-butyl-17-imine (292)



(183) (292)

Several methods have been developed for the preparations of imines from ketones. The method of choice is dependent upon the nature of the groups on the ketone. The larger the groups the more drastic the conditions which need to be employed to overcome the problems of steric crowding. The nature of the substituents on the amine used do not normally influence the conditions needed.

The first preparative method used was to allow the 17-keto-steroid (183) and n-butylamine to react together in benzene in the presence of $TiCl_4$ as a catalyst. N-Butylamine was chosen as the amine because its relatively low volatility made it suitable for the reaction conditions used. Although the desired N-butyl-17-imine (292) was prepared by this route it was found that the product could not be isolated free of inorganic matter.

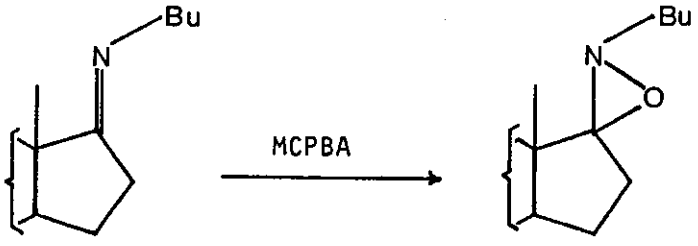
The second preparative method used involved heating the 17-keto compound (183) and N-butylamine together under reflux in benzene with PTSA as the catalyst, in conjunction with a Dean-Stark trap. The reaction was followed by t.l.c. and judged complete after 12 hours. Removal of the solvent gave the crude imine (292) which was identified from its spectroscopic characteristics. The i.r. spectrum showed an absorption at $1675cm^{-1}$ due to the C=N group. The ^1H n.m.r spectrum showed a two proton triplet at δ 3.1 (J 7Hz) due to the N-αCH_2 group. This value was consistent with those reported in the literature.

It is likely that the imine (292) had the thermodynamically stable E-configuration, although this was never rigorously established. Attempts to obtain a ^{13}C n.m.r. spectrum failed owing to decomposition of the imine (292).

The crude imine (292) was used for the preparation of the N-butyl-17-spiro-oxaziridine because attempts at purification by

chromatography resulted in the decomposition of the imine (292).

ii) Preparation of the N-butyl-17-spiro-oxaziridine (293)



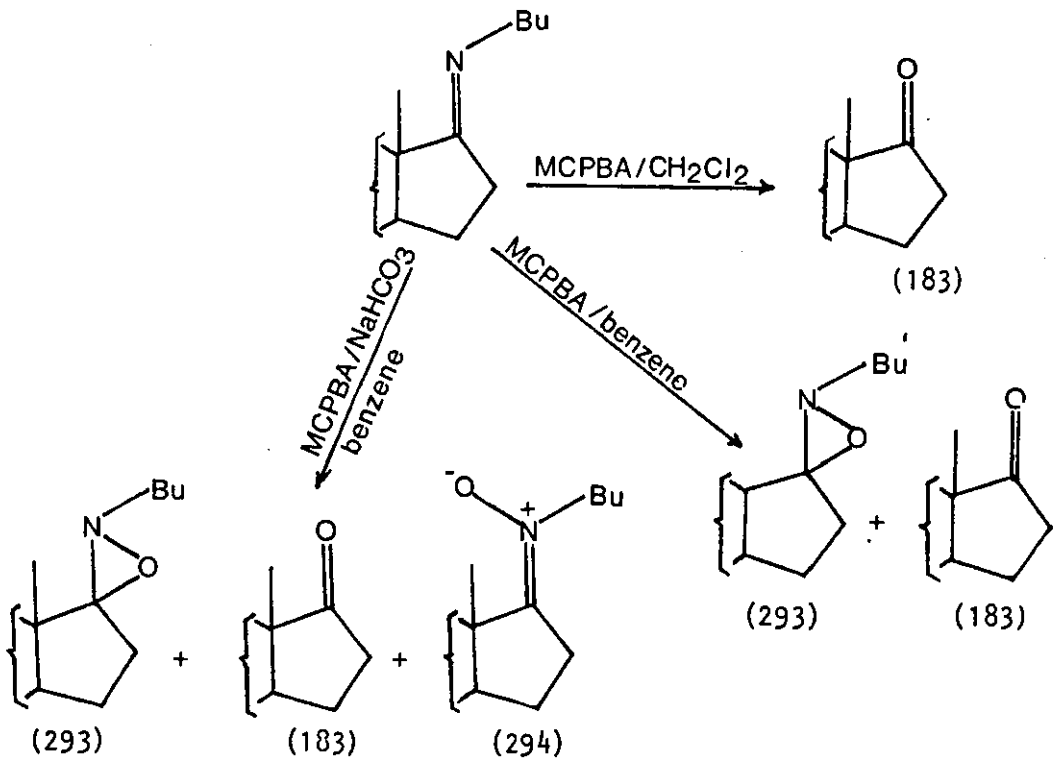
(292) (293)

As has been stated in the introduction, the reaction between an imine and a peroxyacid is the method of choice for the preparation of a wide range of oxaziridines. However, over the years a variety of solvents have been used for this reaction in an attempt to optimise the yield of oxaziridines.

One of the most widely used procedures is to take up the imine in dichloromethane and allow it to react with 1.2 equivalents of m-chloroperbenzoic acid (MCPBA). When this procedure was applied to the preparation of the N-butyl-17-spiro-oxaziridine (293) it was found that the major product was the 17-keto-steroid (183). This was felt to be caused by hydrolysis of the imine and it was decided to use anhydrous benzene as the solvent and to have anhydrous sodium bicarbonate present to neutralize the carboxylic acid as it was formed. On using this procedure the yield of the 17-keto-steriod (183) was reduced and the yield of the N-butyl-17-spiro-oxaziridine (293) was increased as indicated by the increase in the intensity of the signal at (δ 2.8) in the ^{1}H n.m.r. spectrum assigned to the N-CH_2 group. However, the ^{1}H n.m.r. spectrum also showed the presence of an impurity (δ 4.1t) which was not identified although attempts were made to isolate it.

Ogata and Sawaki have shown that the conditions used for the peracid oxidation are critical and that in aprotic solvents as well as the desired oxaziridine, a nitrone can be formed. It is therefore possible that under aprotic conditions used above the by-product observed was the nitrone (294) which was not sufficiently stable to survive preparative t.l.c.

The results of these attempted preparations are summarised below:-



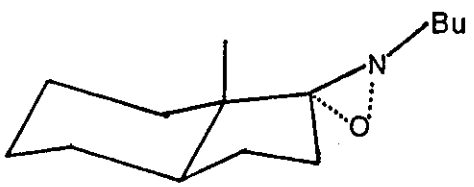
To try and optimise the yield of oxaziridine it was decided to use the conditions developed by Ogata and Sawaki, namely to use benzene containing a small amount of ethanol as the solvent system and 1.2 equivalents of MCPBA

Under these conditions it was shown by t.l.c. analysis that the major product was the desired oxaziridine (293). The by-products were minimised and here identified as the 17-keto-steriod (183) and the postulated nitrone (294). The crude reaction mixture was subjected to

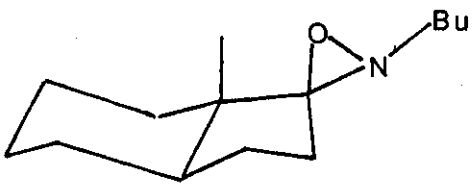
preparative t.l.c. to give the N-butyl-17-spiro-oxaziridine in 60% yield.

The ^1H n.m.r. spectrum of the N-butyl-17-spiro-oxaziridine showed a two-proton triplet centred at δ2.8 (J 7Hz) assigned to the $N\text{-}CH_2$ protons, which was consistent with literature values obtained for other N-alkyl-spiro-oxaziridines. Also an accurate mass measurement confirmed the molecular formula.

As stated in the introduction the stereochemical nature of the imine to oxaziridine pathway has been widely investigated. In considering the formation of the N-butyl-17-spiro-oxaziridine (293) four possible configurations can be considered. The first consideration is whether the oxygen will add via an α or β -face attack to give either structure (295) or (296) respectively.



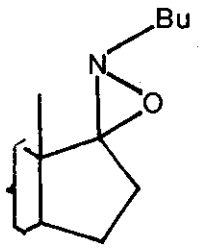
(295)



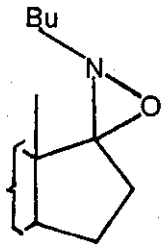
(296)

From the construction of molecular models it can be seen that greater steric crowding will occur if the peracid attacks on the β-face (296). The preferred α-face attack at C_{17} is a general phenomena in steriod chemistry, and therefore it was predicted that the oxygen atom would have the configuration as in (295).

The second configurational varient is the geometry of the N-butyl group with respect to the steroid nucleus, i.e. whether it is anti or syn as in (297) and (298) respectively.



(297)



(298)

To determine this, a ^{13}C n.m.r. spectrum was obtained on the pure N-butyl-17-spiro-oxaziridine and its 17-keto-steroid precursor, the assignments of which are shown in table (5).

It has been shown,[88] that the geometry of an oxaziridine can be obtained by examination of the changes in the chemical shift of the α-carbons in the ^{13}C n.m.r. spectra in the conversion of a ketone to an oxaziridine. For the αcarbon syn to the N-alkyl chain an upfield shift of between 12 - 15 p.p.m. is observed, whereas for the carbon anti to the N-alkyl chain it is only ca. 5.0 p.p.m.

In the N-butyl-17-spiro-oxaziridine to be assigned one of the α carbons is the C-13 which being fully substituted can be unambiguously assigned without difficulty. In the 17-keto compound (183) the signal due to this carbon occurs at 47.4 p.p.m. and in the N-butyl-17-spiro-oxaziridine it was assigned at 42.3 p.p.m., thus showing an upfield shift of 5.1 p.p.m.

The other α - carbon is the C-16 methylene carbon which is assigned at 35.0 p.p.m. in the 17-ketone (183). In examining the

TABLE 5

^{13}C.n.m.r. spectroscopy data for the N-butyl spiro-oxaziridine (294).

in $CDCl_3$

NUCLEUS	KETONE (183)	OXAZIRIDINE (294)
1	36.75	36.85
2	27.73	27.5
3	73.28	73.7
4	34.35	34.06
5	44.62	44.72
6	28.44	28.48
7	32.05	31.44
8	35.00	35.48
9	54.36	54.23
10	35.55	35.65
11	20.57	20.28
12	30.79	30.51
13	47.41	42.32
14	51.59	51.22
15	21.72	23.18
16	35.00	25.53
17	212.30	96.0
18	13.68	13.94
19	11.99	12.19
N-butyl Groups		
α-CH_2	-	56.75
β-CH_2	-	30.4
γ-CH_2	-	21.38
Me	-	14.78
OAc		
CO	169.66	170.69
Me	20.95	20.61

^{13}C. n.m.r. spectrum of the N-butyl-17-spiro-oxaziridine assignment of the C-16 carbon was complicated by the presence of butyl side chain methylene carbons. It is not possible to distinguish unequivocally between the C-16 signal and that for the α - CH_2 of the N-butyl group. However, it is still possible to put limits on the minimum and maximum upfield shifts of the C-16 group and these were determined as 9.5 p.p.m and 13.5 p.p.m.

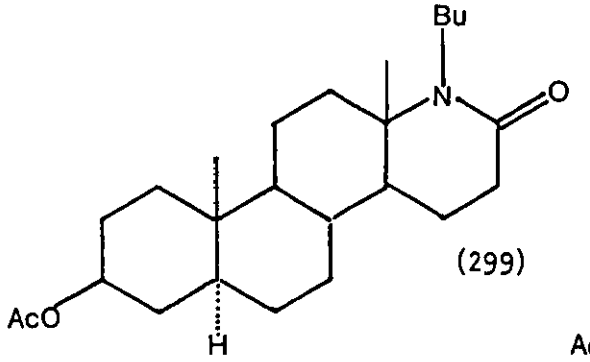
From these assignments it was determined that the N-butyl-17-spiro-oxaziridine (293) existed as the anti-isomer (297).

iii) Photolysis of the N-butyl-17-spiro-oxaziridine

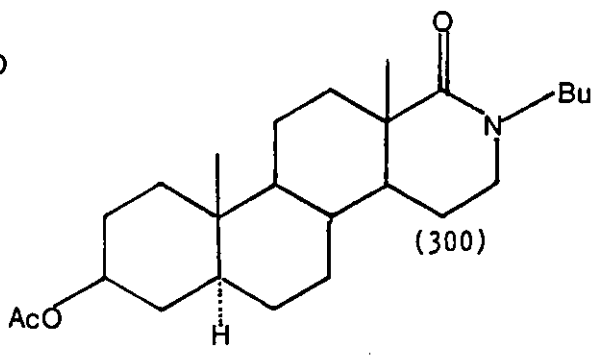
The pure oxaziridine (293) was subjected to photolysis with a low pressure mercury arc lamp using ethanol as solvent until no starting material could be detected by t.l.c. Removal of the solvent and preparative t.l.c. yields two fractions.

The less polar fraction was identified as the 17-keto-steriod (183). The second more polar fraction was identified as the N-butyl-lactam (300) from the following data. The i.r. spectrum showed two carbonyl absorptions at 1735cm^{-1} assigned to the 3β -acetoxy group and at 1650cm^{-1} assigned to the lactam. The mass spectrum gave M^+ at $^m/_z$ 403 corresponding to the expected molecular formula $C_{25}H_{41}NO_3$. The ^1H n.m.r. spectrum gave important signals at δ0.80 (s 13β -Me); δ1.07 (s, 10β -Me); δ 2.00 (s, 3β -OCOMe); and δ 3.3 (m,4-H, N-αCH_2 and 16 - CH_2).

The photolysis of the oxaziridine (293) can, as explained above, give rise to two possible regio-isomeric lactams, namely (299) and (300).



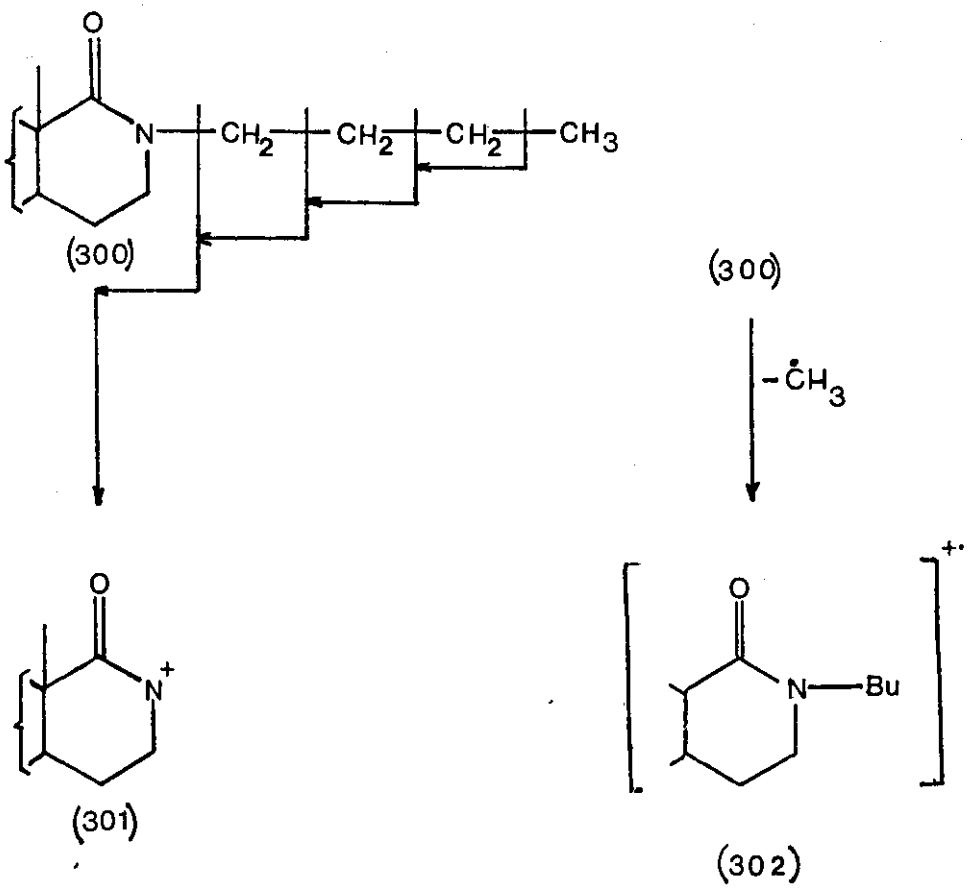
(299)



(300)

As to which isomer is formed can be readily determined by examination of the ^1H n.m.r. spectrum. Isomer (300) has two chemically similar methylene groups attached to the nitrogen which would be expected to be observed as one signal in the ^1H n.m.r. spectrum, and this is what was observed. Isomer (299) would be expected to give one signal due to the C-16 methylene group attached to the carbonyl group and a separate signal due to the methylene group attached to nitrogen.

Although the mass spectrum of the N-alkyl lactam (300) was examined it was not possible to use this as an unequivocal means of identification as the predominant fragmentation arises from sequential cleavage of the side chain shown below, thus masking any loss of the C_{13} angular methyl group. This contrasts with the earlier observations made on the mass spectra of the N-H regio-isomeric lactams.

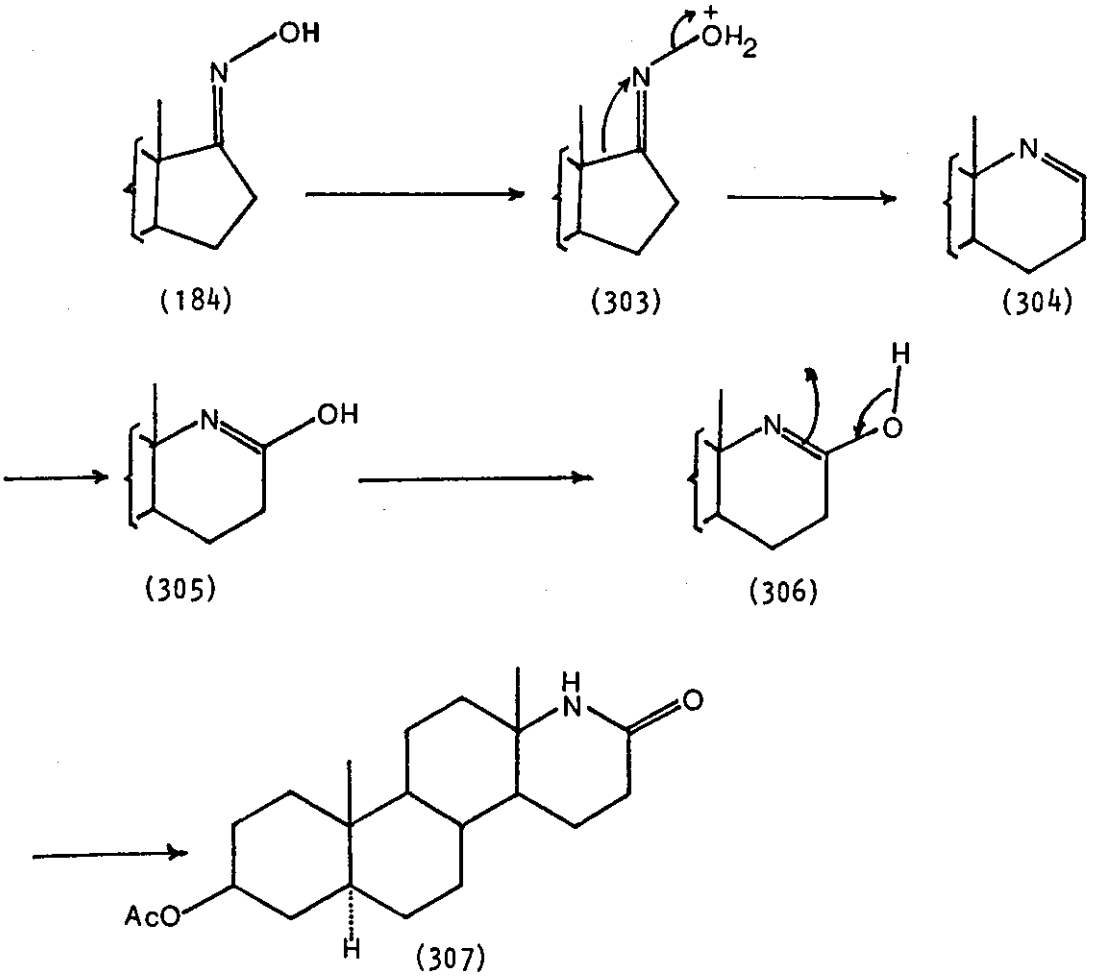


B) Preparation of the 17a - aza N-butyl-lactam (299)

To completely assign the structure of the lactam obtained from the photolysis of the N-butyl-spiro-oxaziridine (293) the alternative regio-isomer (299) was prepared.

The first stage was the preparation of the lactam (307) in an unambiguous manner. This was obtained by performing a Beckmann rearrangement on the oxime (184) as shown below:-

Scheme 33

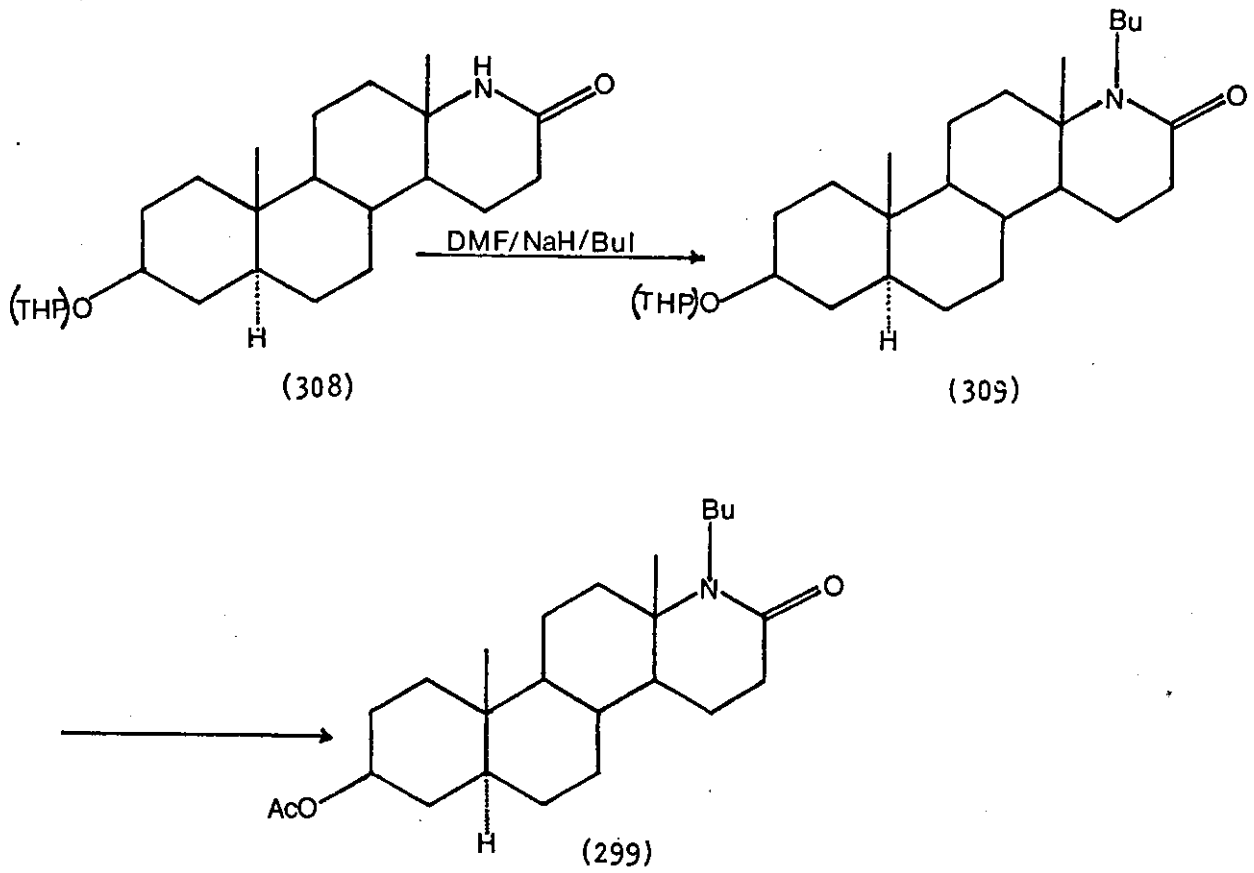


The lactam (307) gave spectroscopic data in accord with literature values and was identical to the lactam prepared from the hydroxamic acid (179), providing further evidence in support of the structure for the hydroxamic acid (179) obtained from the photolysis of the 17-nitronate anion (201).

To prevent side reactions occuring during the alkylation of the lactam (299), the acetoxy lactam (299) was converted to the tetrahydropyranyl-ether (THP) derivative (308).

The alkylation was performed using sodium hydride and butyl iodide in DMF. Removal of the protecting THP group and acetylation gave the final product (299) according to the scheme below (34):-

Scheme 34



(308) (309) (299)

The i.r. spectrum of the N-alkyl lactam (299) showed carbonyl absorptions at 1735cm^{-1} (3β - OAc) and at 1650cm^{-1} (CONBu)

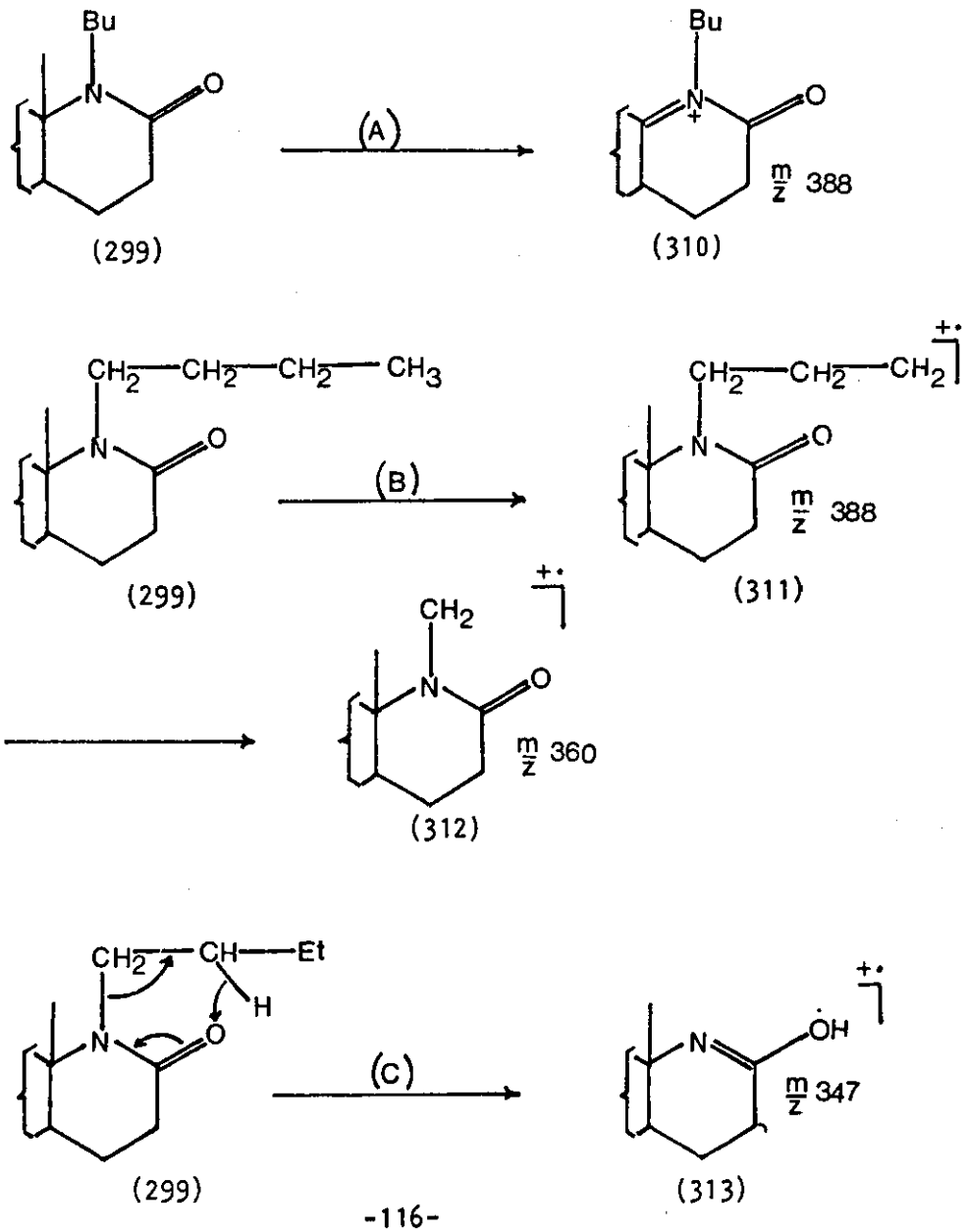
The ^{1}H n.m.r. spectrum showed signals at δ 0.80 (s, 10β -Me); δ 1.27 (s, 13β -Me); δ 2.00 (s, 3β -OAc); δ 2.6 (m, C-16CH_2) and δ 2.9 and δ 3.5 two one-proton signals.

These last two signals were assigned to the N-methylene protons

The observations of two signals may be due to hindered rotation of the alkyl side-chain because of interaction between the α-methylene group of the side-chain with C-12 β-methine.

The mass spectrum of the N-butyl lactam (299), showed a base peak at $^{m}/_{z}$ 388 (M^{+}-15) (310) which can arise by two fragmentation pathways. Path (A) conforms with that expected for 17a-aza-lactams and Path (B) is similar to that observed for the N-butyl lactam (300), further cleavage of the side-chain accounts for the fragment at $^{m}/_{z}$ 360 (312).

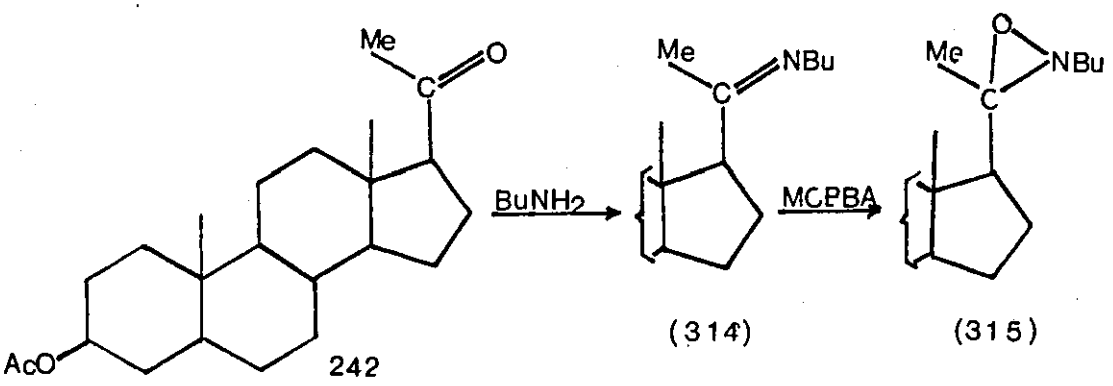
The fragment at $^{m}/_{z}$ 347 can be rationalised as arising by a McLafferty rearrangement to give the species (313) (Path C).



c) Preparation of the N-Butyl-20-Oxaziridine (315)

The 20-keto-pregnane (242) was heated under reflux with n-butylamine, benzene and PTSA to give the 20-imine compound (314). The reaction was judged by t.l.c. to be complete after 48 hours. Removal of the solvent gave the crude imine (314) which exhibited the expected C=N absorption in the i.r. spectrum at 1650 cm^{-1}. The ^{1}H.n.m.r. spectrum gave a two proton triplet centred at δ2.8 (J7Hz) assigned to the N-CH_2 of the imine.

The crude imine (314) was subjected to oxidation with MCPBA using the conditions of Ogata and Sawaki to give the N-butyl-20-oxaziridine (315) which was obtained pure in 40% yield following preparative t.l.c.



The ^{1}H.n.m.r. spectrum of the N-butyl-oxaziridine (315) gave signals at δ0.7 (s, 13β-Me) and δ0.82 (s, 10β-Me). A two proton triplet at δ2.75 (J7Hz) was assigned to the N-$\underline{CH_2}$ protons.

To determine the configuration of the butyl side chain with respect to C-17 and C-21a ^{13}C.n.m.r. spectrum was obtained for the N-butyl-20-oxaziridine and compared to the data for the 20-keto-pregnane (242). The chemical shift data are shown in Table 6.

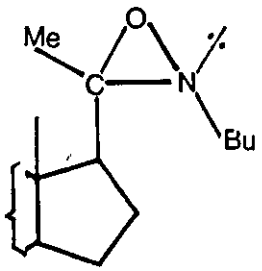
TABLE 6

^{13}C.n.m.r. spectroscopy data for the N-butyl oxaziridine (315)

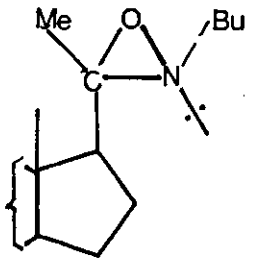
in $CDCl_3$

NUCLEUS	KETONE (242)	OXAZIRIDINE (315)
1	37.0	36.9
2	32.0	27.5
3	71.0	73.7
4	38.1	34.1
5	44.8	44.7
6	28.6	28.6
7	31.4	31.9
8	35.4	35.5
9	54.2	54.3
10	35.4	35.9
11	21.2	21.1
12	39.0	39.7
13	44.2	42.5
14	56.6	53.3
15	24.3	23.9
16	22.8	21.4
17	63.7	57.3
18	13.4	13.3
19	12.3	12.3
20	209.3	79.7
21	31.4	21.1
N-butyl Groups		
α-CH_2	-	56.7
β-CH_2	-	30.4
γ-CH_2	-	21.2
Me	-	13.9
OAc		
CO	170.6	170.6
Me	20.85	20.70

The N-butyl-oxaziridine can theoretically have the butyl group anti to C-21 as in structure (315a) or anti to C_{17} structure (315b).



(315a)



(315b)

From the ^{13}C.n.m.r. spectra the upfield shifts in going from the 20-keto compound (242) to the N-alkyl oxaziridine (315) were 6.5 p.p.m. for C-17 and 10.5 p.p.m. for C-21.

Using the same arguments as for the N-butyl-17-spiro-oxaziridine (297) these values indicate that the compound (315) had the anti structure (315a).

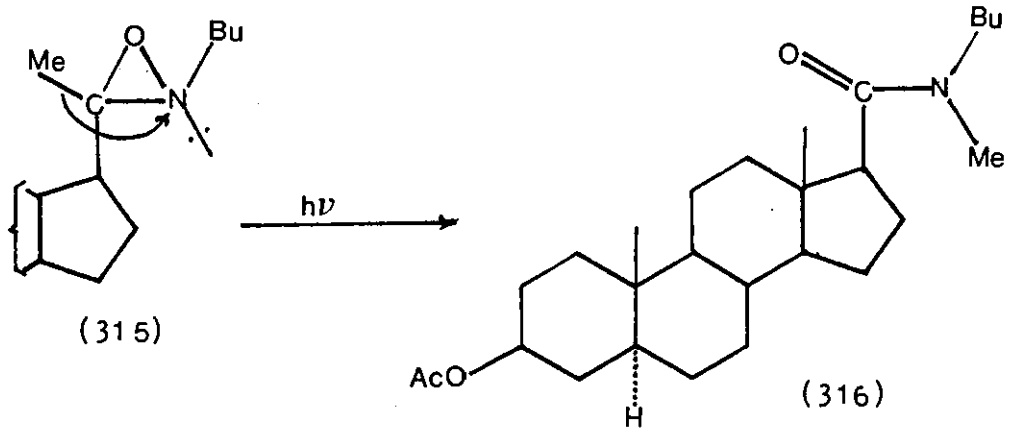
D) Photolysis of the N-butyl-20-oxaziridine (315)

The pure N-butyl-20-oxaziridine (315, was taken up in absolute ethanol and photolysed with a low pressure mercury arc lamp until no starting material remained (20 hours). This reaction time was in marked contrast to the N-butyl-17-spiro-oxaziridine which was completely decomposed in 3 hours under the same photolysis conditions.

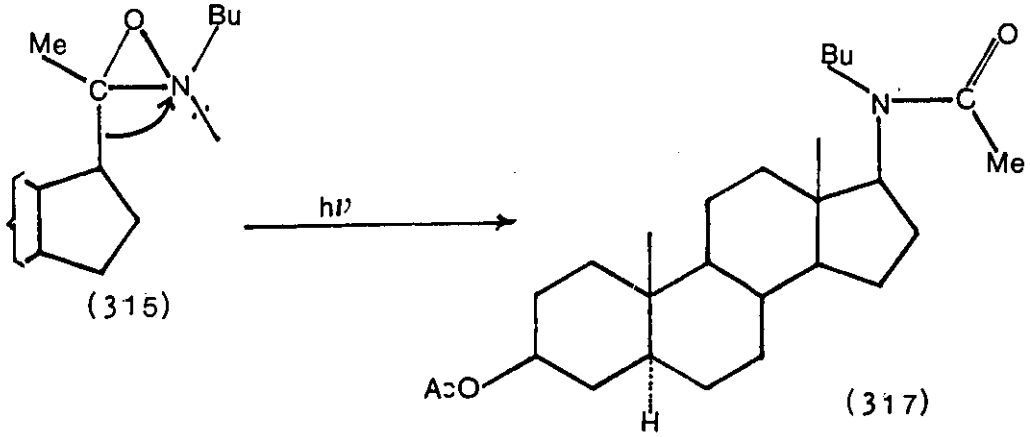
Removal of solvent and preparative t.l.c. gave two fractions. The major fraction (50%) was identified by spectroscopic analysis and comparison with authentic material as the 20-keto-pregnane (242).

The minor fraction on recrystallisation from methanol was shown to be amide (316) (15%) from the following spectroscopic data. The i.r. spectrum contained the normal amide carbonyl absorption at 1650 cm^{-1}. The ^{1}H.n.m.r. spectra gave singlets at δ0.75 (13β-Me); δ0.85 (10β-Me); δ2.00 (3β-OAc) and δ2.9 (C-21-Me) The occurrence of the C-21 signal at δ2.9 confirmsthe structure of the amide tobethat shown in structure (316). This indicated the N-butyl-20-oxaziridine (315) to have undergone the normal stereoelectronically controlled migration of the alkyl group anti-to the nitrogen lone pair.

No evidence was found for the alternative regio-isomer (317) in which the C-21 methyl group would be expected to give a singlet at ~δ2.0 in the ^{1}H.n.m.r. spectrum.



(315) (316)



(315) (317)

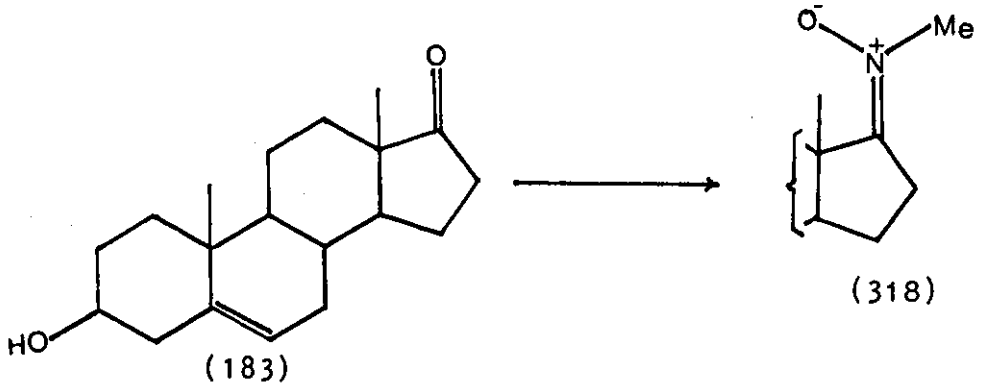
E)Thermal Behaviour of the Steroidal N-butyl-Oxaziridines

Having shown that the N-butyl-oxaziridines (297) and (315) rearrange to the amides (291) and (316) respectively it was important to determine whether these products were the result of photochemical or thermal rearrangement. Ethanol solutions, of the N-butyl-oxaziridines (297) and (315) were prepared at the same concentrations used in the photolyses and kept in the dark at room temperature. The rate of decomposition of the oxaziridines was then monitored by t.l.c. and ^{1}H.n.m.r. spectroscopy. It was shown that there was no observable decomposition of the N-butyl-17-spiro-oxaziridine after 6 hours which is twice the length of time required for complete reaction under photolytic conditions. Similarly the N-butyl-20-oxaziridine (315) was shown to be unchanged after being kept in the dark for several days. These results show that the products observed arise via a photochemically induced rearrangement.

7)Preparation and Photolysis of Steroidal-N-Methyl Nitrones

A) Preparation of N-Methyl-17-Nitrones (318)

The preparation of N-methyl-17-nitrones was developed by Barton and co-workers[89] for the 17-keto-compound (183) with N-methyl-hydroxylamine oxalate in pyridine at room temperature.

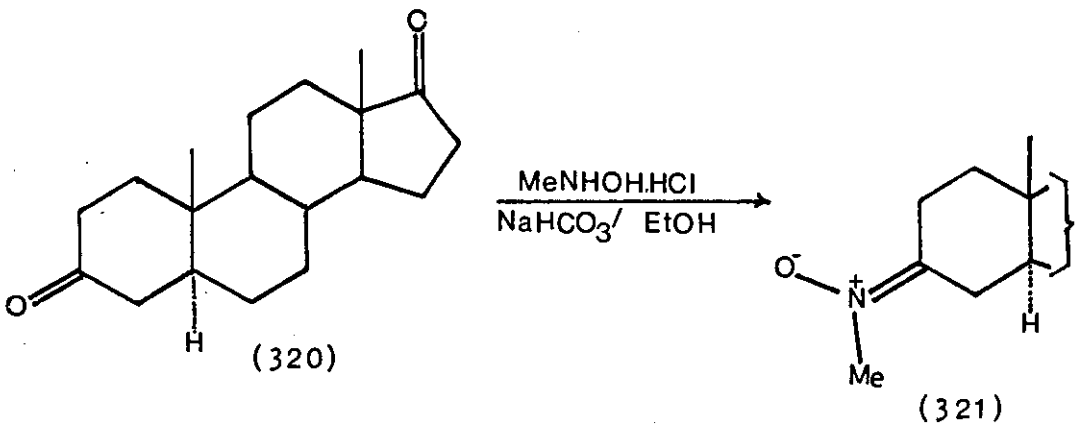


(183) (318)

Attempts to repeat this reaction according to literature procedure were unsuccessful in our hands. Further attempts were made to perform this reaction using different conditions. Firstly the reaction was attempted at 50°C but without success. Secondly ethanol was added to the reaction mixed and the solution heated under reflux for 24 hours but no reaction was observed.

B) Preparation of the N-Methyl-3-Nitrone (321)

The preparation of N-methyl-3-nitrones has been developed by Weintraub and co-workers.[90] The reaction was performed according to literature procedure by heating under reflux a mixture of the 3,17-diketone (320) N-methyl-hydroxylamine hydrochloride, sodium bicarbonate and absolute alcohol, to give the desired nitrone (321) in 60% yield.



(320) (321)

It is of interest to note that no evidence of any reaction of the 17-keto group in compound (320) was observed during the course of the reaction exhibiting the marked contrast in the reactivity of the 3 and 17-positions.

C) Photolysis of the N-Methyl-3-Nitrone (321)

Nitrones are known to absorb at ~300 nm (ϵ max. 5000) due to $n \rightarrow \pi^*$ transition and for this reason the photolysis was carried out using a medium pressure mercury arc lamp and ethanol as solvent. The photolysis was continued until no starting material could be detected by t.l.c. approximately 18 hours photolysis. Removal of the solvent and recrystallisation from acetone/pet ether yield the 3,17 diketone (320) (100%). This result was shown to be a genuine photochemical reaction as the nitrone was shown to be thermally stable under the conditions used.

Conclusions.

The results from the photolyses of the nitronate anions investigated show the major products to be hydroxamic acids, ketones and alkenes[102].

It is postulated that these products can be accounted as arising from a common N-hydroxy-oxaziridine anion intermediate which undergoes three distinct modes of breakdown.

The hydroxamic acids can arise via a two step process involving initial N-O bond cleavage followed by C-C bond cleavage and rearrangement. It was observed from investigation of the 13α-and 13β-17-nitronate anions that the efficiency of the hydroxamic acid formation was influenced by C/D ring geometry although in both cases the formation of hydroxamic acid was both regio- and stereo-specific.

The formation of the alkenes and the cyclo-steroid can be accounted for by the formation of a carbene from the N-hydroxy-oxaziridine anion with extrusion of hyponitrous acid. However the formation of carbenes can also be envisaged as arising directly from the nitronate anion.

The ketones can be considered as arising via an initial N-O bond cleavage of the N-hydroxy-oxaziridine anion and extrusion of nitrous acid.

It has been proposed that the true intermediate in the photolysis of nitronate anions is not a N-hydroxy-oxaziridine anion but a nitroso species formed from it. This intermediate can be shown to give hydroxamic acid and the ketones. The cyclo-steroid being postulated as arising from free nitro compounds present in equilibrium with the nitronate anion. However in our hands no evidence was found to support this

mechanism of cyclo-steroid formation.

Photolysis of N-butyl-oxaziridines produced amides with regio- and stereo chemistry in accord with the theorectical predictions of oxaziridine behaviour. It was observed that the efficiency of both imine and oxaziridine was influenced by the carbon position at which the reaction was attempted. It is of interest to compare this variation with that observed in the preparation of the steroidal nitrones. It was found that it was not possible to prepare the 17-nitrone compound whereas the preparation of the 17-oxaziridine proceeded smoothly and in high yield. In contrast the 3-nitrone was prepared without difficulty whereas the 3-oxaziridine was found to be highly unstable with complete reversion of the imine to ketone during the oxaziridine preparation.

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulphate and solvents were removed in vacuo on a rotary evaporator. Plates (1 m x 0.5 mm thick) of Kieselgel PF 254 (Merck) were used for preparative t.l.c. Degassed absolute ethanol was used for photolyses. I.r spectra were determined with a Perkin Elmer 177 spectrophotometer ^{1}H n.m.r. spectra were determined in deuteriochloroform solution at 60 and 90 MHz with a Varian EM360A and a Perkin Elmer R32 spectrometer, and mass spectra were recorded with AE1 MS12 and Kratos MS50 and MS80 spectrometers. Melting points were recorded on a Kofler hot stage apparatus. Rotations were determined for chloroform solutions using an Optical Activity digital polarimeter.

3β-Acetoxy-androst-5-ene-17-one (182). A solution of 3β-hydroxy-androst-5-ene-17-one (181) (10 g), pyridine (100 ml) and acetic anhydride (10 ml) was allowed to stand overnight at room temperature. The solution was poured onto ice and filtered. The solid material collected and recrystallised from aqueous methanol to give 3β-acetoxy-androst-5-ene-17-one (182) (10.5 g, 97%) m.pt. 172-174°C(lit.[66] 173-174°C)

3β-Acetoxy-5α-androstan-17-one (183). The 3β-acetoxy compound (171) (10 g) was taken up in glacial acetic acid (250 ml) and hydrogenated for 8 hours using 10% Pd/C as catalyst. The solution was filtered its volume reduced by half and poured onto ice. The solid product was filtered off, washed with water and recrystallised from methanol to give 3β-acetoxy-5α-androstan-17-one (183) (9.5 g 95%) m.pt. 94-96°C (lit.[72] 95-97°C)

3β-Acetoxy-androst-5-ene-17-one-oxime (191). The 17-keto-compound (182) (5 g), hydroxylamine hydrochloride (1.6 g), pyridine (5 ml) were heated together under reflux in absolute ethanol (50 ml) for one hour.

The reaction mixture was poured onto ice and filtered. The solid product was recrystallised from aqueous methanol to give 3β-acetoxy--5-ene-17-one oxime (191) (4.7 g, 95%) m.pt. 181-182° (lit. value[72] 182-186°C)

3β-Acetoxy-5α-androstan-17-one-oxime (184). The 5α-17 keto compound (183) (5 g) was treated in the same way as for the 17-keto compound (182) to give 3β-acetoxy-5α-androstan-17-one-oxime (184) (4.5 g, 90%) m.pt. 185-186° (lit.[76] 185-186°)

3β-Acetoxy-13α-androstan-5-ene-17-one (200). The 17-oxime (191) (1.0 g), pyridine (50 ml) and acetic anhydride (30 ml) were heated together under reflux and under a nitrogen atmosphere for 18 hours. The reaction mixture was cooled and evaporated to dryness and ether/1N Na_2CO_3 solution (1:1) added. The organic material was extracted with ether (3x). The ether extracts were combined, washed with water, dried and the solvent removed to give the crude product (1.3 g). The crude products were separated by preparative tlc using benzene/ethyl acetate 3:1 as eluent to give the enimide (197) (0.3 39%), δ 0.95 (s 10β-Me), 0.1 (s 13α-Me); 2.00 (s OCOC$\underline{H}_2$), 2.40 (s N-(COC$\underline{H}_3$)$_2$), 4.6 (m 3α-H), 5.3 (d 6-H), 6.6 (16H), and the enamide (198) (0.35 g 39%), δ 0.9 (s 10β-Me), 1.0 (s 13α-Me), 2.00 (s OCO$\underline{Me}$), 2.1 (s N-CO$\underline{Me}$), 4.6 (m 3α-H) 5.3 (d 6-H), 6.0 (16-H), 6.9 NH. The enamide (198) and enimide (197) were combined dissolved in methanol (50 ml) containing 2M Hcl (10 ml) and heated under reflux for 1 hour. The mixture was poured onto ice/water and filtered. The crude solid product was recrystallised from methanol to give 3β-hydroxy-13α-androsten-5-ene--17-one (199) (0.5 g 50%) m.pt. 184-186°C (lit.[91] 187-198°C) δ 0.85 (s 10β-Me), 1.0 (s 13α-Me), 3.55 (m 3α-M), 5.3 6H. Treatment with pyridine (10 ml) and acetic anhydride (2 ml) and recrystallisation

from methanol gave 3β-acetoxy-13α-androst-5-ene-17-one (200) (0·5g 95%) m.pt.143-145°(lit.[94] 143-144°C)

3β-Acetoxy-5α,13α-androstan-17-one (201). The 13α-compound (200) (1 g) was dissolved in acetic acid (25 ml) and hydrogenated for 24 hours in the presence of 10% Pd/C catalyst. Work up as for the 5α-compound (183) gave 3β-acetoxy-5α,13α-androstan-17-one (190) (0.95g, 95%) m.pt. 131-133°C (lit.[65] 133°C)

3β-Acetoxy-5α,13α-androstan-17-one-oxime (202). The 17-keto-compound (1.0 g) (0.9 g) hydroxylamine hydrochloride (0.4 g), pyridine (2 ml) and absolute ethanol (20 ml) were heated together under reflux for 6 hours. The solution was then treated as for the preparation of the 17-oxime (184) to give 3β-acetoxy-5α,13α-androstan-17-one-oxime (202) (0.95 g, 95%) m.pt. 164-166°C, δ_{CDCl_3} 0.70 (s,10β-Me); 1.03 (s,13α-Me); 2.00 (s,3β OCO$\underline{CH_3}$); 4.65 (m,3α-$\underline{H}$); 9.1 (br C=NO$\underline{H}$) exchanged with D_2O.

3β-Acetoxy-17ξ-nitro-5α,13α-androstane (203) A solution of potassium bicarbonate (0.65 g) in water (5 ml) was added to a vigorously stirred mixture of N-bromosuccinimide (1.2 g), dioxan (3 ml) and water (3 ml) followed by a solution of the oxime (0.75 g, m.p. 164-166°) in dioxan (20 ml). The mixture was stirred at room temperature for two days during which the initially formed blue colour changed to pale yellow. Water was added and the mixture was extracted with ether (x2). The combined ether extracts were washed successively with ferrous sulphate solution (10%) and water and dried. Removal of the solvent gave a residue which was taken up in tetrahydrofuran (15 ml) and water (5 ml). Sodium borohydride (0.25 g) was added over 15 min. after which the solution was stirred for 1 hour at room temperature. A further portion of sodium borohydride (0.1 g) was added and after a further

period of 1 hour the solution was acidified with hydroxylamine hydrochloride and extracted with ether (x2). The combined ether extracts were washed with water and dried and removal of the solvent gave a pale yellow gum (0.7 g) which after preparative t.l.c, eluting with benzene:ethyl acetate (3:1), afforded the 17-nitro-compound (203) (150 mg) (20%) m.p. 145-146°, $[\alpha]_D$ - 33°, (c, 5.0), ν_{max} ($CHCl_3$) 1735 (MeCOO), 1540 and 1370 (NO_2) cm^{-1}, δ 0.80 (s, 13β-Me), 0.90 (s, 10-βMe), 2.0 (s, OAc), and 4.55 (m, 3-H and 17-H) (Found C, 69.1; H, 9.3; N, 3.7 $C_{21}H_{33}NO_4$ requires C, 69.4; H, 9.15; N, 3.85%).

3β-Acetoxy-17β-nitro-5α-androstane (177). The 17β-nitro compound (177) was prepared by the same procedure used for the 17ξ-nitro compound (203), using the 17-oxime (184) (5 g), N-bromosuccinimide (7 g), potassium bicarbonate (5 g), water (10 ml) and dioxan (25 ml) to give the bromo nitro compound (186). The bromonitro compound was treated without purification with sodium borohydride (2 g) in T.H.F. (30 ml) water (10 ml). After normal work-up the 17β-nitro compound (177) was obtained (3 g 60%) m.p. 189-190°, (lit.[64] 188-190°), ν_{CHCl_3} 1735 (C=O), 1540 and 1370 (AcO_2) cm^{-1} δ 0.8 (hrs 10β and 13β-Me) 2.02 (s OCOMe) 4.3 (t 17α-H) 4.5 (m 3α-H).

3β-Acetoxy-17β-nitro-androst-5-ene (210). The 17β-nitro compound (210) was prepared from the 17-oxime (191) (5 g) by the same procedure to give the 17β-nitro compound (3.2 g 65%) m.pt. 210-212° (lit.[63] 210-212°)

6-Nitrocholestryl acetate (15). Cholesteryl acetate (239) (3 g) was suspended in concentrated nitric acid (100 ml) at 5° and solid sodium nitrite (3 g) added. The mixture was stirred at 5° for 1 hour, poured onto ice and extracted with ether. The ether extracts were washed with water until judged acid free by pH paper, dried and the solvent removed. The residual gum (3 g) was subjected to column

chromatography using silica and eluted with benzene/ethyl acetate 2:1 to give the crude product (2.3 g). Recrystallisation from methanol afforded 6-nitrocholesteryl acetate (15) (2.0 g, 60%) m.pt. 102-104°C (lit. value[77] 103-104°C) ν_{CHCl_3} 1540 cm^{-1}, 1370 cm^{-1} NO_2.

6α-Nitro-5α-cholestan-3β-ol (240a). 6-Nitrocholesteryl acetate (1 g) in absolute ethanol (50 ml) and sodium borohydride ($NaBH_4$) (200 mg) were stirred together overnight at room temperature. The mixture was poured onto ice, extracted with ether. The ether extracts were dried and the solvent removed to give a yellow gum (1.5 g). The gum was taken up in 25 ml of 0.5% NaOH/MeOH and heated under reflux for 30 minutes. The solution was poured onto ice and extracted with ether. The ether extracts were washed with water, dried and the solvent removed to give a residual gum (1.1 g). The gum was subjected to preparative tlc using benzene/ethyl acetate 2:1 which gave 6α-nitro--5α-cholestan-3β-ol (240a) (0.6 g, 66%) m.pt. 78-80°C (lit.[95] 78-82°C)

6β-Nitro-5α-cholestan-3β-ol (240b).[70] The 6α-nitro compound (240a) (500 mg) was taken up in ethanol (100 ml) containing five equivalents of sodium ethoxide and stirred at room temperature overnight. The solution was poured onto ice/water and acidified with 2N HCl and extracted with ether. The ether extracts were washed with water, until acid free, dried and the solvent removed to give the crude product. Recrystallisation from methanol gave the 6β-nitro compound (240b) (450 g 90%), m.pt. 148-150°C. ν_{CHCl_3} 3340 (OH) 1540, 1360 (NO_2) cm^{-1} δ_{CDCl_3} 0.70 (s, 10β-Me) 0.89 (s, 13β-Me) 0.82 (s C_{21}Me) 3.65 (m 3α-H) 4.4 (m 6α-H) (Narrow $W_{\frac{1}{2}}$ 10Hz).

3β-Acetoxy-5α-cholestane (246a) Cholesteryl acetate (5 g) in glacial acetic acid (250 ml) was hydrogenated over 10% Pd/C for 12 hours. The solution was filtered, the volume of the filtrate reduced to one-third and the solution poured onto ice. The solid product was filtered off washed with water and recrystallised from methanol to give 3β-acetoxy-5α-cholestane (24 a) (5 g, 100%) m.pt. 109-110°C (lit.[96] 110-111°C)

3β-Hydroxy-5α-cholestane (246). The 3β-acetoxy compound (246a) (5 g) was dissolved in 150 ml of 0.5% NaOH/MeOH and heated under reflux for 30 minutes. The solution was poured onto ice filtered and the solid material recrystallised from methanol to give 3β-hydroxy-5α-cholestane (242) (4.4 g, 97%) m.pt. 141-142°C (lit. value[96] 142°C)

5α-Cholestan-3-one (247). Cholestanol (246) (5 g) was dissolved in acetone and 1.3 M Jones reagent added until no further reaction, as detected by colour change was observed. The reaction mixture was poured onto ice, filtered and washed with water to remove inorganic material. Recrystallisation from aqueous methanol afforded cholestan--3-one (247) (3.2 g, 65%) m.pt. 127-129°C (lit.[97] 129°C)

5α-Cholestan-3-one-oxime (248). Cholestan-3-one (247) (3 g), hydroxylamine hydrochloride (1 g), pyridine (3 ml) and absolute ethanol (30 ml) were heated together under reflux for 1 hour. The solution was poured onto ice, filtered and the crude solid product recrystallised from methanol to afford cholestan-3-one-oxime (3.0 g, 96%), m.pt. 195-197°C (lit.[98] 196°C)

3β-Amino-5α-cholestane (249). Cholestan-3-one-oxime (248) (1 g) was heated under reflux in propan-2-ol (50 ml) and sodium metal (2 g) added over a 2 hour period. Water was added and the product extracted

with chloroform to give a yellow gum (900 mg). Recrystallisation from methanol afforded 3β-amino-5α-cholestane (249) (600 mg, 60%) m.pt. 116-118°C (lit.[98] 118-119°C)

3β-Nitro-5α-cholestane (250). The 3β-amino compound (249) (0.5 g) was dissolved in chloroform (20 ml) and added dropwise, over 15 minutes, to a refluxing solution of MCPBA (2.5 g) in chloroform (20 ml). The solution was allowed to reflux for a further 15 minutes and then cooled to room temperature. The solution was washed with saturated sodium sulphite (2x), saturated sodium bicarbonate solution (2x) and then water (2x). The organic extracts were dried and the solvent removed to give a pale-yellow gum (300 mg). The residual gum was taken up in boiling acetonitrile and filtered. The solvent was removed and the crude product was recrystallised from methanol to give the 3β-nitro-compound (250) (150 mg, 30%) double m.pt. 97-99° and 108-110°C (lit.[69] 98-99° and 109-110°C)

3β-Acetoxy-5α-pregnane-20-one-oxime (243). 3β-Acetoxy-5α-pregnane-20-one (5g) hydroxylamine hydrochloride (1.6 g), pyridine (6 ml) and absolute ethanol were heated together under reflux for 2 hours. The reaction mixture was treated as for the preparation of the 17-oxime (191) to give the 20-oxime (243) (4.7 g, 90%) m.pt. 191-193°C (lit.[103] 191-193°C)

20α and 20β-Amino-5α-pregnane (244a) and (244b). The 20-oxime (243) (1 g) was heated under reflux in propan-1-ol (40 ml) and sodium metal (2 g) was added over two hours. The reaction mixture was cooled diluted with water and extracted with ether (3x). The ether extracts were dried and the solvent removed to give a yellow gum (0.9 g). Preparative tlc using ether saturated with ammonia/methanol 85:15 gave the 20α-amine (0.3 g) m.pt. 174-175°C (lit.[103] 173-175°C) and the 20β-amine (0.5 g) m.pt. 176-177°C (lit. value 176-177°C)

20β-Nitro-5α-pregnan-3β-ol (245a). The 20β-amine (244a)[103] (0.5 g) in chloroform (15 ml) was added dropwise to a boiling solution of MCPBA (2 g) in chloroform (15 ml). The reaction mixture was heated under reflux for ½ hour after which it was allowed to cool and washed with saturated sodium sulphite solution, saturated sodium bicarbonate solution and water and dried. Removal of the solvent followed by recrystallisation from methanol afforded the 20β-nitro-pregnane (244a) (350 mg) (65%) m.p. 225-227°, $[\alpha]_D$ + 11° (C, 10.0), ν_{max} ($CHCl_3$) (OH), 1150 and 1380 (NO_2) cm^{-1}, δ 0.75 (s, 13β-Me) 0.80 (s, 10β-Me), 3.5 (m, 3α-H), and 4.5 (m, 20α-H) (Found: $M^{+\cdot}$ 349.2599 $C_{21}H_{35}NO_3$ requires 349.2617).

20α-Nitro-5α-pregnan-3β-ol (245b). This was prepared from the 20α-amine (0.5 g) by the same procedure as the 20β-nitro compound (245a) to give the 20α-nitro compound (245b) (300 mg, 60%) m.pt. ν_{max} ($CHCl_3$) 3440 (OH), 1550 and 1380 (NO_2) cm^{-1}, δ 0.73 (s, 13β-Me) 0.78 (s, 10β-Me) 3.5 (m, 3α-H) 4.4 (m 20α-H) (Found: M^+ 349.2708 $C_{21}H_{35}NO_3$ requires 349.2617.

Photolysis of nitro-compounds. The nitro-compound (100 mg), in a solution of absolute ethanol (100 ml) containing 10 equivalents of sodium ethoxide, was photolysed using a low pressure mercury lamp (3 W) in a water-cooled quartz apparatus. After complete reaction (assessed by t.l.c) the solvent was removed and the residue was dissolved in a minimum volume of water. Acetic acid (1%) was added to bring the pH of the solution to ca. 6 after which the mixture was extracted with chloroform (x2) and the combined chloroform extracts were washed with water and dried. Removal of the solvent gave the crude product which was purified as indicated below.

17β-Nitro-compound (177). The crude product, a yellow gum (100 mg) was crystallised from methanol to give the 3β,17a-dihydroxy-17a-aza-D-homo-5α-androstan-17-one (179) (60 mg) which was recrystallised to afford a pure sample (50 mg) m.p. 247-250°, $[\alpha]_D$ 0° (c, 5.0), ν_{max} (KBr) 3350 (OH) and 1620 (-CONROH) cm^{-1}, δ 0.80 (s, 10β-Me), 1.27 (s, 13β-Me), and 3.61 (m, 3α-H) (Found: C, 70.8; H, 10.1; N, 4.35, $C_{19}H_{31}NO_3$ requires C, 71.0; H, 9.7; N, 4.35%). Preparative t.l.c. of the mother liquors yielded the 17,18-cyclosteroid (178) (5 mg) m.p. 149-150° (lit., m.p. 149-151°) and a mixture (10 mg) (ν_{max} 1735 cm^{-1}) of the 13β-ketone (183a)[δ 0.80 (br s, 10β- and 13β-Me)] and the 13α-ketone(201a)[δ 0.63 (s, 10β-Me) 0.93 (s, 13α-Me)]. T.l.c. of authentic samples confirmed the ketones(183a)and(201a)have very similar Rf values.

17β-Nitro-Δ^5-compound (210). The crude product, a yellow gum (96 mg) was crystallised from methanol to give the 3β,17a-dihydroxy-17a-aza-D-homoandrost-5-en-17-one (228) (70 mg) which was recrystallised to afford a pure sample (60 mg) m.p. 227-229°, $[\alpha]_D$ -82° (c, 10.0), ν_{max} ($CHCl_3$) 3400 (OH) and 1610 (-CONROH-) cm^{-1}, δ 1.0 (s, 10β-Me), 1.25 (s, 13β-Me), 3.55 (m, 3α-H), and 5.3 (m, 6-H) (Found: $M^{+\cdot}$ 319.2146, $C_{19}H_{20}NO_3$ requires 319.2147).

17ξ-Nitro-13α-compound (203). The crude product, a yellow gum (100 mg) was separated into two fractions by preparative l. eluting with benzene:ethyl acetate (3:1). The more polar fraction (30 mg) was crystallised from methanol to afford the 3β,17a-dihydroxy-17a-aza-D-homo-5α,13α-androstan-17-one (237) m.p. 130-131°, ν_{max} ($CHCl_3$) 3350 (OH) and 1610 (-CONROH-) cm^{-1}, δ 0.72 (s, 10β-Me), 1.37 (s, 13α-Me) and 3.53 (m, 3α-H) (Found: $M^{+\cdot}$ 321.2302, $C_{19}H_{31}NO_3$ requires 321.2304). The less polar fraction (50 mg) was identified as a mixture of the

13β-ketone (8) [δ 0.80 (brs, 10β- and 13β-Me)] and the 13α-ketone (7) [major component δ 0.63 (s, 10β-Me and 0.93 (s, 13α-Me)].

6α-Nitro-compound (240). The crude product, a yellow gum (100 mg) was separated into four fractions by preparative tlc eluting with benzene: ethyl acetate (2:1). The alkene-containing fraction (30 mg) was further subjected to preparative tlc (benzene:ethyl acetate 2:1) on silver nitrate (10%) impregnated silica to afford cholesterol (251) (15 mg), m.p. and mixed m.p. 146-148°, and a minor component (3 mg) which was not identified. The second fraction (25 mg) was crystallised from methanol to afford 3β-hydroxy-5α-cholestan-6-one (252) (20 mg) m.p. 142-144°C (lit.,[99] m.p. 143°C) ν_{max} ($CHCl_3$) 1705 (C=O) cm^{-1}, 3-O-acetyl (252a) derivative m.p. 126-128°C (lit.,[99] m.p. 128°C). The third fraction (20 mg) was crystallised from methanol to afford 3β-hydroxy-5α-cholestane (253) m.p. and mixed m.p. 138-140° (lit.,[96] m.p. 142°C). The fourth fraction (15 mg) was crystallised from methanol to give a solid (5 mg) tentatively identified as the hydroxamic acid (254) m.p. 220° (decomposition), ν_{max} ($CHCl_3$) 3300-3400 (OH) and 1660 (CONHOH-) cm^{-1}, (Found: $[M-16]^{+\cdot}$ 417, $C_{27}H_{47}NO_3$ requires 433).

3β-Nitro-compound (259). The crude product, a yellow gum (100 mg) separated into three fractions by preparative tlc eluting with toluene:etheyl acetate (2:1). The least polar fraction (130 mg) was crystallised from methanol to afford 5α-cholest-2-ene (260) (20 mg) m.p. 68-70°C (lit.,[100] m.p. 75°C, no depression of mixed m.p.). A second fraction (15 mg) was identified as 5α-cholestan-3-one (261) ν_{max} ($CHCl_3$) 1710 (C=O) cm^{-1}, δ 0.70 (s, 13β-Me) 0.83 (s, 10β-Me) by comparison with authentic material although it was not crystallised. The remainder was largely polymeric material.

20β-Nitro-compound (245). The crude product, a yellow gum (95 mg) was separated into two fractions by preparative tlc eluting with toluene:ethyl acetate 2:1. The less polar alkene fraction (30 mg) was further purified by preparative t.l.c. on silver nitrate (10%) impregnated silica (toluene:ethyl acetate 2:1) to afford the major component (18 mg) which crystallised from aqueous methanol to afford E-3β-hydroxy-5α-pregn-17(20)-ene (15 mg) (257) m.p. 132-134°C (lit.,[92] 136-137°C,) 3-O-acetyl derivative m.p. 117-119°C (lit.,[92] m.p. 120-121°C). The more polar fraction (20 mg) was identified as 3β-hydroxy-5α-pregnan-20-one (242), ν_{max} ($CHCl_3$) 3400 (OH) and 1720 (C=O) cm^{-1}, δ 0.55 (s, 13β-Me), 0.8 (s, 10β-Me) and 2.1 (s, 20-Me), by comparison with authentic material although it was not crystallised.

Conversion of hydroxamic acid (179) to the lactam (215). A solution of the hydroxamic acid (179, (50 mg) in acetic acid (20 ml) was heated under reflux with zinc powder (250 mg) for 6 hours after which the reaction mixture was filtered and the solids were washed with a small volume (3x) of acetic acid. The combined filtrate and washings were poured onto ice and the resultant mixture was extracted with methylene chloride (x3). The combined organic extracts were washed with saturated sodium bicarbonate solution until neutral and then with water and dried. The solvent was removed to afford an oily residue which was taken up in pyridine (1.5 ml) and acetic anhydride (0.2 ml). The solution was allowed to stand at room temperature overnight and poured onto ice, after which the resultant solid was removed by filtration and washed thoroughly with water. The dry solid was crystallised from acetone-petroleum-ether (b.p. 40:60) to afford 3β-acetoxy-17a-aza-D-homo-5α-androstan-17-one (215) (40 mg) (74%) m.p. 277-280°C (lit.,[72] m.p. 275-277°C).

In a further experiment, the crude photolysate from the 17β-nitro-compound (174) (100 mg) was reduced and acetylated as above to afford a crude product (100 mg) which was crystallised from methanol to afford the lactam (215) (60 mg) m.p. 277-280°C. Examination of the mother liquor by t.l.c and ^{1}H nmr spectroscopy did not provide evidence of any other lactam.

3β-Hydroxy-17a-methoxy-17a-aza-D-homo-5α-androstan-17-one (213). A mixture of the hydroxamic acid (179) (25 mg), NaH (5 mg) and DMF (20 ml) was stirred under an atmosphere of nitrogen at room temperature for 1 hour. Methyl iodide (0.1 g) was added and the mixture was stirred under nitrogen at room temperature overnight after which water was added and the product was extracted into ether (x2). The combined ether extracts were washed with water and dried and removal of the solvent and crystallisation of the residue (20 mg) from acetone-petroleum-ether (b.p. 40-60°) gave the O-methyl derivative (213) (15 mg) (58%) m.p. 235-236°C, ν_{max} ($CDCl_3$) 3420 (OH) and 1665 (-COROMe-) cm^{-1}, δ 0.80 (s, 10β-Me), 1.20 (s, 13β-Me), 3.5 (m, 3α-H), and 3.72 (s, N-OMe) (Found: $M^{+\cdot}$ 335.2451, $C_{20}H_{33}NO_3$ requires 33.2460).

3β,17a-diacetoxy-17a-aza-D-homo-5α-androstan-17-one (212). Acetylation of the hydroxamic acid (179) (25 mg) with acetic anhydride (1 ml) and pyridine (10 ml) at room temperature overnight followed by the normal work-up provided a crude product which crystallised from methanol to give the di-O-acetyl derivative (212) (25 mg) (80%) m.p. 215-217°C, $[\alpha]_D$ + 23° (c, 1.0), ν_{max} ($CHCl_3$) 1800 (-CONROCOMe), 1735 (MeCOO), and 1670 (-CONROCOMe) cm^{-1}, δ 0.80 (s, 10β-Me), 1.22 (s, 13β-Me), 2.00 (s, 3OAc), 2.16 (s-NROAc), and 4.7 (m, 3α-H) (Found: C, 68.0; H, 9.0; N, 3.5, and $M^{+\cdot}$ 405.2504 $C_{23}H_{35}NO_5$ requires C, 68.1; H, 8.6; N, 3.5% and 405.2515).

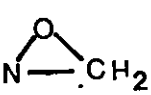
3β,17a-diacetoxy-17a-aza-D-homoandrost-5-en-17-one (234). Acetylation of the hydroxamic acid (228) (50 mg) as above afforded the di-O-acetyl derivative (234) (55 mg) (87%) m.p. 196-197° (from methanol), ν_{max} ($CHCl_3$) 1790 (-CONROCOMe), 1735 (MeCOO), and 1670 (-CONROCOMe) cm^{-1}, δ 1.0 (s, 10β-Me), 1.25 (s, 13β-Me), 2.02 (s, 3-OAc), 2.15 (s, -NROAc), 4.5 (m, 3α-H), and 5.3 (m, 6-H), (Found: C, 68.8; H, 8.4; N, 3.4, $C_{23}H_{33}NO_5$ requires C, 68.4; H, 8.2; N, 3.5%).

Conversion of the hydroxamic acid (228) to the lactam (235). Reduction and acetylation of the crude photolysate from the 17β-nitro-$-\Delta^5$-compound (10) (100 mg) as for that from the 17β-nitro-compound (221) and crystallisation of the resultant residue (100 mg) from methanol afforded 3β-acetoxy-17a-aza-D-homoandrost-5-en-17-one (229) (65 mg) (68%), m.p. 298-300°C (lit.,[76] m.p. 295-298°C). No evidence of any other lactam component could be detected in the product by tlc and ^1H nmr spectrometry.

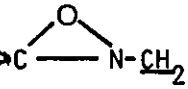
3β,17a-Diacetoxy-17a-aza-D-homo-5α,13α-androstan-17-one (238). The crude photolysate (100 mg) from the 17ξ-nitro-13α-compound (203) (100 mg) was acetylated as above and preparative tlc, eluting with benzene:ethyl acetate 3:1 gave three fractions. The most polar fraction (40 mg) was crystallised from methanol to afford the di-O-acetyl derivative (238) (30 mg) (27%), m.p. 195-196°C, $[\alpha]_D$ -47° (c, 5.0), ν_{max} ($CHCl_3$) 1790 (-CONROCOMe), 1735 (MeCOO), and 1670 (-CONROCOMe) cm^{-1}, δ 0.80 (s, 10β-Me), 1.3 (s, 13β-Me), 2.0 (s, 3-OAc), 2.15 (s, -NROAc), and 4.65 (m, 3α-H) (Found: C, 67.8; H, 8.7; N, 3.2 and $M^{+\cdot}$ 405.2513, $C_{23}H_{35}NO_5$ requires C, 68.1; H, 8.7; N, 3.5% and 405.2515). The least polar fraction was 3β-acetoxy-5α,13α-androstan-17-one (201) (20 mg), m.p. 129-131°C (lit.,[65] m.p. 133°C no depression of mixed m.p.).

An intermediate fraction (25 mg) was a mixture of the 13β ketone (183) δ 0.82 (brs, 10β- abd 13β-Me) and the 13α-ketone (201) δ 0.64 (s, 10β-Me) and 0.93 (s, 13β-Me). Tlc on authentic materials confirmed the ketones (183) and (201) have similar R_f values.

N-Butyl-17-spiro-oxaziridine (293).

A solution of the 17-ketone (183) (250 mg) in benzene (50 ml) containing para-toluene sulphonic acid (PTSA) (20 mg) and N-butylamine (20 ml) was heated under reflux overnight using a Dean and Stark trap. The solution was allowed to cool, washed with saturated sodium bicarbonate solution and water, dried and evaporated under vacuum to give the crude N-butyl imine (292), as a pale yellow gum (280 mg, 90%), γ max. ($CHCl_3$) 1730 (MeCOO) and 1675 ($\geq C = N$) cm^{-1}, δ 0.80 (s, 10β-Me), 0.86 (s, 13β-Me), 1.95 (s, 3β-oAc), 3.2 (t, J7Hz, $= N-\underline{CH_2}-CH_2R$) and 4.5 (m, 3α-H). Found: M^+ 387 ($C_{25}H_{41}NO_2$ requires M^+ 387). The freshly prepared N-butyl imine (292), was taken without further purificiation, and dissolved in benzene (25 ml) cooled to 5°C and ethanol (3 ml) added. A solution of MCPBA (110 mg) in benzene (5 ml) was added and the reaction mixture stirred in the dark for 2 hours after which it was washed with saturated sodium sulphite solution, saturated sodium bicarbonate solution and water and then dried. Removal of the solvent gave a pale yellow gum (200 mg) which was subjected to preparative tlc, eluting with toluene : ethyl acetate 3:1, and afforded the N-butyl spiro-oxaziridine (293) (145 mg, 70%), γ max. ($CHCH_3$) 1735 (MeCOO) cm^{-1}, δ 0.82 (brs, 10β-Me and 13β-Me) 2.02 (s, 3β-oAc), 2.7 (t, J7Hz  Pr) and 4.7 (m, 3α-H). (Found M^+ 403.3101, $C_{25}H_{41}NO_3$ requires 403.3086). Also obtained was the 17-ketone (183) 25 mg, 15%) m.pt 94-96, (lit[101] m.pt 94-96°C).

N-Butyl-20-oxaziridine (315)

By the same procedure the 20-ketone (242) (250 mg) was heated under reflux with N-butylamine (2 ml), benzene (50 ml) and PTSA (20 mg) to give the 20-imine (314), as a pale yellow gum (300 mg, 100%) υ max. ($CHCl_3$) 1735 (MeCOO) and 1650 ($\rangle C{=}N$-R) cm^{-1} δ 0.75 (s, 13β-Me), 3.1 (t, J7Hz $\rangle C{=}N$-$\underline{CH_2}$-R), 4.7 (m, 3α-H). Treatment of the 20-imine (314) (150 mg), without further purification, at 5°C with MCPBA (180 mg), ethanol (3 ml) and benzene (20 ml) for two hours gave after normal work up the crude oxaziridine (315)(180mg) which was subjected to preparative tlc, eluting with toluene : ethyl acetate 3:1, to give the N-butyl-20-oxaziridine (315) (60 mg, 40%) γ max. ($CHCl_3$) 1735 (MeCOO) cm^{-1}, δ 0.7 (s, 13-β-Me), 0.82 (s, 10β-Me) 1.95 (s, 3β-OAc), 2.75 (t, J7Hz ), 4.7 (m 3α-H). Found: M^+= 431.3402, $C_{27}H_{45}NO_3$) requires 431.3399 and the 20-ketone (242) (50mg) m.pt 192 - 194 (lit m.p 194°C)

Photolysis of the N-butyl-17-spiro-oxaziridine (293)

The oxaziridine (293) (120 mg) in ethanol (100 ml) was photolysed using a medium pressure mercury arc lamp for 3 hours, after which time no starting material could be detected as judged by tlc. Removal of the solvent and preparative tlc of the residue, eluting with toluene : ethyl toluene : ethyl acetate 5:1, afforded 3β-acetoxy-17-butyl-17-aza-D-homo-5α-androstan-17a-one (300) (70 mg). Recrystallisation from methanol gave a pure sample (60 mg, 50%) m.pt 121 - 122°C υ max. $CHCl_3$ 1735 (MeCOO), and 1620 (R_2NCO) cm^{-1} δ 0.80 (s, 10β-Me), 1.06 (13β-Me), 2.00 (s, 3β-oAc), 3.25 (m, 16-CH_2 and N-CH_2-R) and 4.65 (m, 3α-H). Found: C 74.4%; H 10.6%; N 3.57 and M^+ 403.3092. $C_{25}H_{41}NO_3$ requires C 74.4%; H 10.2%; N 3.5% and M^+ 403.3087.

A second minor fraction was identified as the 17-ketone (183) (25 mg, 30%) m.pt 96 - 98, (lit m.p 95 - 97°C).

Photolysis of N-butyl-20-oxaziridine (315)

The N-butyl-20-oxaziridine (315) (100 mg) in ethanol (100 ml) was photolysed using a low pressure mercury arc lamp for 20 hours. Removal of the solvent and preparative tlc of the residue (90 mg), eluting with toluene : ethyl acetate 5:1 afforded the 20-ketone (242) (45mg) m.p 192-194° (lit[104] 194°) and the 20a-aza-compound (316) (15 mg, 15%) υ max. $CHCL_3$ 1735 (MeCOO) and 1625 (R_2NCO) cm^{-1}, δ 0.75 (s, 13β-Me), 0.85 (s, 10β-Me), 2.00 (s, 3β-oAc) and 2.9 (m, C_{21}-Me) and 4.7 (m, 3αH). Found: M^+ 431.3397, $C_{27}H_{45}N_1O_3$ requires 431.3399.

3β-acetoxy-17a-butyl-17a aza-D-homo-5α-androstan-17-one (309)

The lactam (307) (300 mg) was converted under standard conditions to give the tetrahydropyranyl ether (308) which, without purification was dissolved in DMF (20 ml) to which NaH (90 mg) was added. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 1 hour, after which freshly distilled butyl iodide (1 ml) was added. After stirring for a further 24 hours, methanol was added to destroy excess NaH and the mixture diluted with water and the product extracted with ether (x 2). The combined ether extracts were washed with water, dried and evaporated to give the crude N-butyl lactam (309) (200 mg). Successive treatment of this with methanol and PTSA under reflux and acetic anhydride and pyridine at room temperature afforded, after work up and preparative tlc, eluting with toluene : ethyl acetate 3:1, the N-butyl-lactam (299) as a gum (105 mg, 30%) υ max. $CHCl_3$ 1735 (MeCOO) and 1620 (R_2NCO) cm^{-1}, δ 0.80 (s, 10β-Me),

1.12 (s, 13β-Me), 2.02 (s, 3β-oAc), 2.4 (m, 16-CH_2) 2.9 and 3.5 (2 x 1 Hm, N-CH_2) and 4.65 (m, 3α-H). Found: M^+ 403.3083, $C_{25}H_{41}NO_3$ requires 403.3087.

3-ketonitrone (321)

The 3, 17-diketone (320) (250 mg) N-methylhydroxylamine hydrochloride (85 mg), sodium bicarbonate (0.35g) and ethanol (50 ml) were heated together under reflux, and in the dark with no starting material could be detected by tlc. The solution was cooled to room temperature, filtered and the solvent removed to give a yellow gum (200 mg). Preparative tlc using toluene/ethyl acetate/acetic acid 90:10:1 yielded the 3-methyl nitrone (321) (140 mg, 50%) γ $CHCH_3$ 1735 17C = O; ^{1}H.n.m.r. δ 3.3 (S $\overset{O}{\overset{\uparrow}{N}}$—Me) m.pt 149 - 152 (lit value[90] 150 - 152°C).

Photolysis of 3-methyl nitrone

The 3-methyl nitrone (321) (100 mg) was photolysed in ethanol using a medium pressure mercury arc lamp for 6 hours after which time no starting material could be detected by tlc. Removal of solvent gave a pale yellow gum which was recrystallised from ethanol to give the 3, 17-diketone (320) 85 mg, 90%).

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