Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
Edited by Saul Patai
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Supplement F

The chemistry of **amino, nitroso and nitro compounds and their derivatives** Part 1

Edited by
SAUL PATAI
The Hebrew University, Jerusalem

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Foreword

The present Supplement F includes material on nitrogen-containing functional groups such as amino, nitroso and nitro groups. In the main volumes of the Chemistry of the Functional Groups Series, these groups have been treated in the following books:

The Chemistry of the Amino Group (1968);
The Chemistry of the Nitro and Nitroso Groups, Part 1 (1969) and Part 2 (1970).

In addition, several functional groups which have not been treated in the main volumes have also been included, such as nitrones, nitronic acids, nitroxides, nitrosamines, nitrosoimines, enamines and ynamines.

With the exception of a chapter on 'Ipso-attacks involving NO_2 groups', all chapters planned for this Supplementary Volume actually materialized.

The editor will be very grateful to readers who would communicate to him omissions or mistakes relating to this volume as well as to other volumes in the series.

Jerusalem, July 1981 SAUL PATAI

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of deter-

mination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*two volumes*)
The Chemistry of the Carbonyl Group (*two volumes*)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (*two parts*)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (*two parts*)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (*two parts*)
The Chemistry of Quinonoid Compounds (*two parts*)
The Chemistry of the Thiol Group (*two parts*)
The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*two parts*)
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
The Chemistry of Diazonium and Diazo Groups (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)

Supplement B: The Chemistry of Acid Derivatives (*two parts*)
The Chemistry of Ketenes, Allenes and Related Compounds (*two parts*)
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues (*two parts*)
The Chemistry of the Sulphonium Group (*two parts*)
Supplement F: The Chemistry of Amino, Nitroso and Nitro Groups and their Derivatives (*two parts*)

Titles in press:

The Chemistry of Peroxides
The Chemistry of Organometallic Compounds
Supplement C: The Chemistry of Triple-bonded Functional Groups
Supplement D: The Chemistry of Halides and Pseudo-halides

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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CHAPTER 1

Structural chemistry

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I. INTRODUCTION

There has been a growing interest in finding relationships between the chemical and/or biological behaviour of chemical compounds and their molecular structure in

all fields of chemical research. This has meant that there has been ever-increasing application of physical techniques capable of providing such information, even if often qualitative and referring to only one state of matter – the solid state – rather than to the solution or gas states, in which most chemical and biological reactions occur.

Interest in structure now goes beyond merely knowing positions within the molecule. In favourable cases it is possible to extract information on the types of bond present and the valence electron distribution in the molecule.

This chapter reviews the structural properties characterizing the title functional groups and the more important molecules containing them. In addition an attempt will be made to outline the changes undergone by these groups in the presence of others in the same molecule.

The treatment is directed not only to workers involved in structural problems, but also to those in other scientific disciplines. We therefore think it useful to comment briefly on the reliability of the results reported, most of which have been obtained by X-ray and neutron diffraction techniques. Although microwave spectroscopy gives extremely accurate results, it has not been widely utilized because of the limitation that only simple molecules in the gas phase can be studied.

In many respects, X-ray diffraction and neutron diffraction are complementary techniques. The former involves (almost exclusively) the internal and valence electrons of the molecules, whereas in the latter the nuclei are responsible for the diffraction. Consequently, discrepancy in the charge density maps obtained via the two techniques occurs for atoms in which the centre of gravity of the electron density does not coincide with the nucleus. The extreme case is represented by the hydrogen atom, for which X-rays give bond distances up to 0.1 Å shorter than the true ones. In this respect, there is no doubt that the neutron diffraction technique is to be preferred because it allows the position of both very small atoms and high atomic weight atoms to be determined to the same accuracy.

Nevertheless, neutron diffraction also presents some anomalies. For example, at high angles atomic vibrations cause a decrease in intensity of the diffracted radiation.

Finally, both techniques necessitate work at low temperatures because of the effects of thermal motion.

Most of the disadvantages can now be overcome using more intense sources of radiation or, when available, more computer time. The use of more intense sources means that relatively smaller crystals may be used so that problems arising from multiple reflections, absorption and extinction become less important.

An excellent review on the subject has recently appeared[1]; it covers theoretical, experimental and computational aspects and also in part traces some future lines of development.

Two 'rule of thumb' criteria must be kept in mind when judging the 'quality' of a structure. The first is that the agreement between the observed structure factor amplitudes (F_o) and the calculated ones (F_c) must be of the same order of magnitude as the experimental accuracy to which the F_os are found. The second criterion is based on the reliability index (R); the lower is R, the more reliable are the results reported. R values ranging from 0.08 to 0.03 (8 and 3%) are now obtained and it is possible to go as low as 0.02.

However, caution must still be exercised in using R because it merely measures the extent to which the model chosen for calculation of the structure fits the experimental results. To make the calculated structure factors agree with the observed ones is, of course, a necessary condition for a good crystallographic

analysis. However, it is not a sufficient condition because several circumstances come to mind in which entirely erroneous results may be given, with excellent R results.

A. List of Abbreviations

av	Average
ED	Electron diffraction
e.s.d.	Estimated standard deviation; it is shown in parentheses and refers to the last digit
G	Gas phase
MW	Microwave spectroscopy
ND	Neutron diffraction
S	Solid state
XD	X-ray diffraction

II. THE AMINO GROUP

A. The Structure of Ammonia

From the point of view of the molecular structure, amines are often treated as derivatives of ammonia in which one or more hydrogen atoms have been substituted by alkyl and/or aryl groups. Although substitution may lead to different structural properties, especially when aryl groups are involved, we think it useful to briefly comment on the structure of ammonia because this molecule is often used for comparison purposes by various authors, particularly in the case of alkylamines.

Various lines of evidence, mostly of a spectroscopic nature, show that ammonia is a symmetric top molecule having a pyramidal structure (C_{3v}) with nitrogen at the apex of the pyramid and a hydrogen atom at each corner of the triangular base.

Molecular orbital treatments are in agreement with this configuration. In ammonia, the nitrogen atom utilizes sp^3-orbitals having a tetrahedral structure. Three of these orbitals are involved in the bonds to hydrogen, whilst the fourth is free and occupied by a lone pair of electrons.

Structural parameters obtained via various methods are in good agreement

TABLE 1. Structural parameters[a] of the ammonia molecule and some of its isotopic species

Species	N—H	N—D	$H\hat{N}H$	$D\hat{N}D$	Reference
NH_3	1.015		106.6		2
NH_3	1.014		106.8		3
NH_3	1.016		107.4		4
NH_3	1.008		107.3		5
NH_2D	1.014		107.1		6
NHD_2	1.014		107.2		6
NH_3	1.0124		106.67		7
NH_3	1.0173		107.78		7
ND_3		1.0108		106.70	7
ND_3		1.055		107.59	7
NH_3	1.011		106.7		8
NH_3	1.013		107.03		9

[a]In the gas phase; bond distances in Å and angles in degrees.

(Table 1). It is known that ammonia undergoes an inversion motion coupled to the rotation, with an inversion barrier[10] of 5.8 kcal mol^{-1}.

B. Aliphatic Amines

1. Free amines

In broad terms, aliphatic amines retain the same configuration and electronic structure as ammonia. For instance, ammonia has two harmonic frequencies at 3506 and 3577 cm^{-1} which lie in the same region as the N—H stretching vibrations in aliphatic amines. In fact, in carbon tetrachloride (dilute solution) primary aliphatic amines show two bands near 3400 and 3500 cm^{-1} (symmetrical and asymmetrical vibrations). In addition, the N—H infrared stretching absorptions of secondary aliphatic amines lie in this region (3400–3500 cm^{-1}).

Table 2 gives a summary of the more important structural parameters common to various homologues of the series. From this table it may be seen that there is good agreement as regards the C—N bond length [1.470(5) Å], the largest differences arising for dimethylamine [1.455(2) Å][17] and trimethylamine [1.454(2)[17] and 1.451(3)[19] Å]. However, a distance of 1.472(8) Å has also been reported for the latter molecule[18]. Although comparisons between bond lengths in individual molecules obviously have little meaning, there is, nevertheless, an undeniable shortening of the C—N bond as methyl groups are substituted for the hydrogen atoms of the amino group in methylamine.

Parameters in acceptable agreement are also available for the N—H bond, keeping experimental errors in mind. Only that for ethylenediamine [N—H = 0.86–0.87(3) Å, by X-ray crystallography][25] is significantly lower than the average value. As mentioned above, this is not structurally significant because the discrepancy is due to the fact that X-rays are diffracted mainly by electrons. Consequently, a bond distance shorter than the true one is given when atoms having the negative charge centre far from the nucleus are involved.

The H—N—H and H—N—C bond angles are in good agreement with that found for ammonia [105.8(2)° in methylamine compared to 106.6–107.3(2) in ammonia]. The decrease of this angle passing from ammonia to methylamine is very probably due to the steric hindrance of the methyl group. In fact the value of the C—N—H angle [112.0(2)°] is greater than the H—N—H angle in ammonia (106.6–107.8°). Steric hindrance is also responsible for a decrease in the C—N—C angle passing from dimethylamine to trimethylamine and in the latter there is a flattening of the pyramidal structure.

In the following pages we will examine several results which do not readily fall into Table 2, and which illustrate the molecular structure of these simple aliphatic amines.

(i) Methylamine, CH_5N. The structure of this molecule has been determined several times (Table 2) both in the gas phase and in the solid state.

In the gas phase, the molecule shows an internal rotation axis (or, more strictly, a torsional axis) about the C—N bond, as is evident from even a summary analysis of the microwave spectrum. The height (m kcal mol^{-1}) of this torsional barrier is: CH_3NH_2 1.95[32], 1.96[13], 1.97[11]; CH_3ND_2 and CD_3ND_2 1.94 and 1.92, respectively[32]. The rotational spectrum also provides evidence for the presence of an inversion mode of the $—NH_2$ ($—ND_2$) group, in phase with the torsional mode. Indeed, in order to restore the initial configurational situation, the inversion must be accompanied by a partial internal rotation (otherwise the presence of two conformers would have shown up in the MW spectrum). The barrier height of this

TABLE 2. Dimensions[a] of the amino group in some aliphatic amines

Compound	N—H	N—C	HNH	HNC	CNC	Method	State	Reference
Methylamine	1.014[b]	1.474(5)	105.8(2)	112.2(2)		MW	G	11, 12
Methylamine	1.011[c]	1.474	105.8	112.0		MW	G	13
Methylamine		1.4667(21)				ED	G	14
Methylamine		1.48(1)				XD	S[d]	15
CD_3ND_2		1.4679(21)				ED	G	14
Dimethylamine	1.022(7)[e]	1.466(5)		108.8(3)	112.2(2)	MW	G	16
Dimethylamine	1.00(2)	1.455(2)		107	111.8(6)	ED	G	17
Trimethylamine		1.454(2)			110.6(6)	ED	G	17
Trimethylamine		1.472(8)			108.7(10)	MW	G	18
Trimethylamine		1.451(3)			110.9(6)	MW	G	19
Trifluoroethylamine	1.01(2)	1.474[b]	110.5(10)	110		MW	G	21
Methyldichloroamine		1.47[b]			109(1)[f]	ED	G	21
Dimethylchloroamine		1.47(2)			107(2)[f]	ED	G	21
Perfluorotrimethylamine		1.43(3)			114(3)	ED	G	22
Aminoethanol	1.017(4)	1.475(23)	109.8(5)	$110.8(8)_{av.}$		MW	G	23
Ethylenediamine		1.469(4)				ED	G	24
Ethylenediamine	0.87(13)	1.47(1)	102(6)	104–9(4)		XD	S[g]	25
Hexamethylenediamine		1.51(3)				XD	S	26
Triethylenediamine		1.46(1)			$108.6(8)_{av.}$	XD	S	27
Triethylenediamine	1.11(1)	1.472(7)			108.7(4)	ED	G	28
Nitroguanidine		1.34(2)				XD	S	29
Tribenzylamine		$1.472(15)_{av.}$				XD	S	30
Vinylamine[h]	1.002	1.401(40)	120			MW	G	31
Vinylamine[i]	1.010	1.397(40)	114			MW	G	31

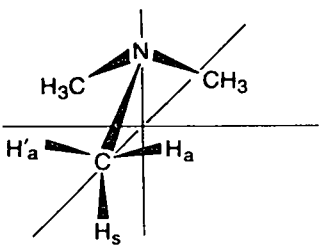
[a]Bond distances in Å and angles in degrees. .
[b]Assumed.
[c]Calculated from CH_3NH_2 and CD_3ND_2. The uncertainty in the hydrogen distances and angles is probably about 1%, while the C—N distance and the location of the N atom are believed to be somewhat more accurate.
[d]At −150°C.
[e]From 12 isotopic species of dimethylamine.
[f]C—N—Cl angle.
[g]At −60°C.
[h]Planar $C—NH_2$.
[i]Pyramidal $C—NH_2$. The spectral evidence suggests that vinylamine has a nonplanar equilibrium structure.

inversion is[33] 4.8 kcal mol^{-1}. Other relevant parameters not given in Table 2 are: C—H 1.093 Å (assumed)[11–13], H—C—H 109.5(10)°[11] and 109.5° (assumed)[13]. The angle between the $-CH_3$ axis and the C—N bond is 3.5(3)°[11,12] with the $-CH_3$ axis passing through the $-NH_2$ triangle[11–13].

In the solid state (at −150°C) methylamine forms hydrogen bonds with N . . . N distances of 3.18 and 3.27 Å, in sheets approximately parallel with each other. The structure[15] (determined using X-rays, with $R = 0.138$) shows that the methyl group is staggered with respect to the hydrogen bonds. A phase transition is observed at −172°C; this consists merely of a contraction in volume, probably involving the methyl group.

(ii) Dimethylamine, C_2H_7N. In the gaseous state this molecule has several internal degrees of freedom, such as the rotation of the two methyl groups and the inversion of the amino hydrogen. The barrier of the latter[16] is 4.4 kcal mol^{-1}. The difference in results for the molecular dimensions obtained from microwave spectroscopy[16] and electron diffraction[17] lie within experimental errors. In the equilibrium configuration the two methyl groups are arranged in such a way that a C—H bond of each group lies in the CNC plane. The angle between the CNC plane and the N—H bond[16] is 54.6–55.6(4)°.

(iii) Trimethylamine, C_3H_9N. This molecule has C_{3v} geometry in the gas phase[17–19]. The parameters obtained from microwave spectroscopy[19] are reported for (**1**), together with the equilibrium conformation of the methyl groups. H_a and H'_a indicate the two equivalent out-of-plane hydrogen positions on the same methyl group; H_s lies on a symmetry plane.



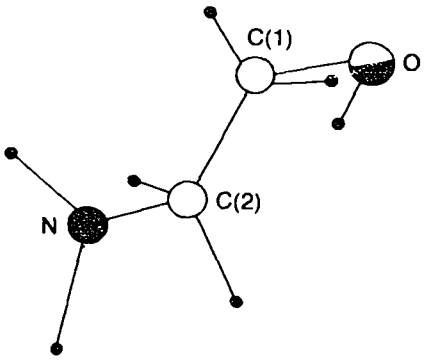
(**1**)

C—N	1.451(3) Å	N—C—H_s	111.7(4)°
C—H_s	1.109(8) Å	H_a—C—H_s	108.1(7)°
C—H_a	1.088(8) Å	H_a—C—H'_a	108.6(8)°
		N—C—H_a	110.1(5)°

In theory, the methyl group may be either eclipsed or staggered with respect to the other two C—N bonds. Calculations using substitution coordinates[34] and van der Waals' atomic radii favour[19] a staggered configuration (**1**), in which the methyl groups are tilted by 1.3° towards the nitrogen lone pair.

(iv) 2-Aminoethanol, C_2H_7NO (**2**)[23]. The structure of this molecule, found using microwaves[23,35], is conditioned by the presence of an intramolecular hydrogen bond of the O—H···N type, which stabilizes the *gauche* configuration. The overall structure of the amino group seems little affected by the presence of this bond. Conversely, there is a certain deformation with respect to the minimum energy structure, of 30° about the C—O bond and 20° about the C—N bond, which thus brings the hydroxyl proton close to the lone pair of the nitrogen. Note that r_s values for the O—H bond (1.139 Å) and the C—O—H angle (103.7°) become 1.00 Å and 108°, respectively, when the error caused by O···N 'shrinkage' upon deuteration is taken into account[35].

There is no substantial difference between 2-aminoethanol[23,35] and dimethylaminoethanol[36]. For the latter, microwave results are again consistent with a *gauche* OCCN configuration and an O—H···N type hydrogen bond. The central



N—C	1.475(3) Å	H—N—H	109.8(5)°
O—H	1.139(1) Å	C—C—O	112.1(1)°
N—H	1.017(5) Å	C—C—N	108.1(20)°
C—O	1.396(10) Å	C—O—H	103.7(2)°
C—C	1.526(16) Å	C—N—H′	110.4(8)°
		C—N—H″	113.1(8)°

(2)

C—N configuration is distorted by approximately 23° from the staggered conformation.

An analogous conformational problem arises in the case of trifluoroethylamine[20], the configuration of which will be inferred starting from that of ethylamine.

For the latter molecule, in the gas phase, infrared spectra[37,38] reveal that both *trans* and *gauche* configurations exist, in the ratio 2:1 (Figure 1). Now, if the *gauche* form were also present in the same ratio in the fluoro derivative, it should give spectral lines even more intense than those of the *trans* conformer because of the difference in the dipole moment components of the two isomers. Consequently, the absence of any lines for the *gauche* form in this derivative is an indication that the *trans* form alone is present, very probably stabilized and favoured thermodynamically by the formation of one, or two, hydrogen bonds, N—F···F. It is not clear whether such bonds are indeed formed or if the interaction involved is simply electrostatic. The uncertainty arises because the N—H distance is essentially the same as that observed for unsubstituted amines (1.007 Å vs. 1.015) and the H···F bond (2.65 Å) is 0.10 Å longer than the sum of the van der Waals' atomic radii for hydrogen and fluorine.

(v) Ethylenediamine, $C_2H_8N_2$ **(3)**. This molecule has different configurations in gas, liquid and solid state. This is due to the fact that the presence of internal rotation about the C—C bond can give rise to *cis* (C_{2v} symmetry), *trans* (C_{2h} symmetry) and *gauche* (C_2 symmetry) forms **(3)**.

The electron diffraction spectra[24] in the gaseous phase are compatible only with a

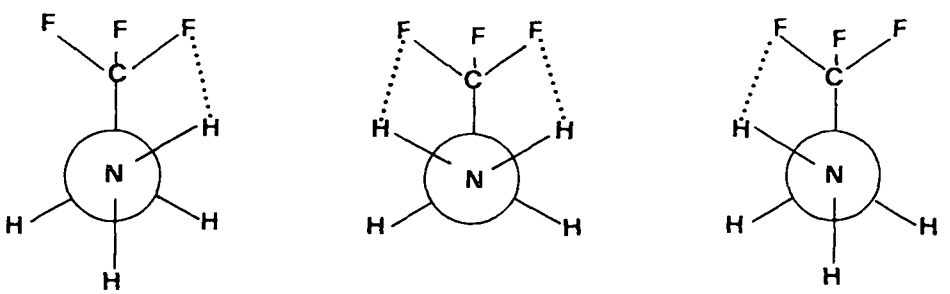
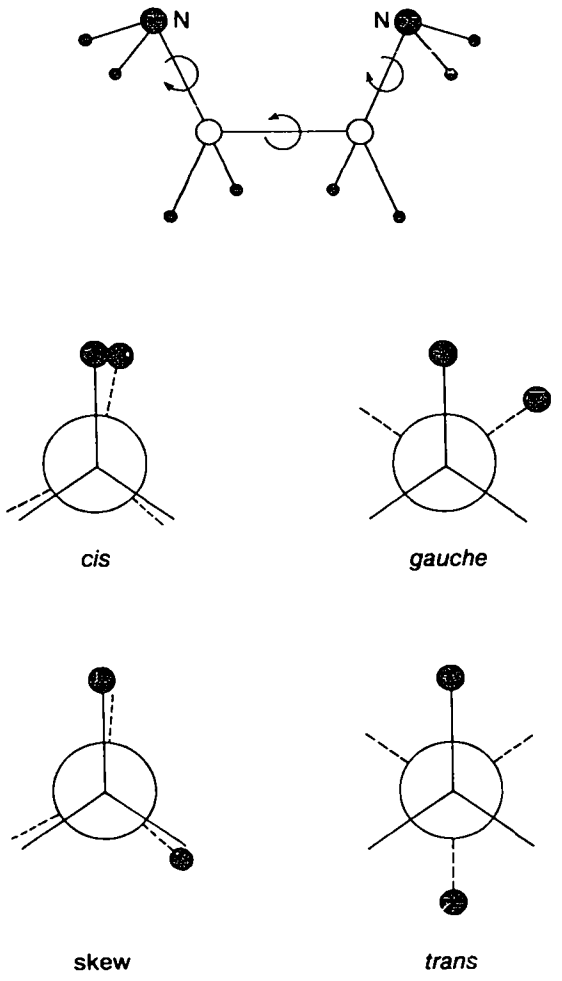


FIGURE 1. The two staggered rotamers in trifluoroethylamine, viewed along the C—N bond. Dotted lines indicate possible intramolecular hydrogen bonds.

gauche conformation between 50 and 120°C. Any other conformer can be present in no more than 5%, if at all. Semiempirical CNDO/2 calculations predict an energy minimum for the *cis* conformer, as well as for the *gauche* and *trans* ones.

The infrared and Raman spectra in liquid and solid were interpreted on the basis



(3)

	ED[24]	XD[25] (uncorr.)		ED[24]	XD[25] (uncorr.)
C—N (Å)	1.469(4)	1.47(1)	H—C—H (°)	112.7 (85)	108(6)
C—C (Å)	1.545 (8)	1.51(2)	N—C—H (°)		107–113(4)
N—H (Å)		0.86(13)	C—N—H (°)		104–109(4)
C—H (Å)	1.10(1)	1.04–0.99(13)	H—N—H (°)		102(6)
C—C—N (°)	110.2(7)	114.5(10)	N—C—C—N (°)[a]	64.0(4.5)	
C—C—H (°)	111.9(46)	104–110(4)			

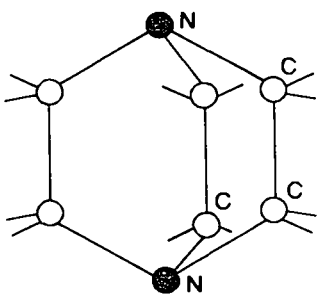
[a]This dihedral angle is measured from the *cis* position.

of the existence of the *cis* conformation alone[39]. However, for the solid state at −60°C, spectral measurements suggested[40] that a *trans* structure is present. A change of phase occurring at a much lower temperature has been interpreted as indicating the presence of a rotation about the C—C bond and hence a change to the *gauche* form.

The latter conclusions are in agreement with the results obtained from X-ray measurements at −60°C, according to which the *trans* configuration alone is present.

The structural parameters determined from three-dimensional single-crystal data ($R = 0.09$)[25] are not readily comparable with those for the gas phase obtained via electron diffraction. In fact, the only result in agreement is that for the C—N bond length [1.469(4) vs. 1.47(2) Å].

(vi) Triethylenediamine, $C_6H_{16}N_2$ **(4)**. The structure and the intramolecular and overall motions of this molecule have been investigated by several methods[27,28,41–46]. The parameters shown for **4** have been obtained via electron diffraction[28] and X-ray diffraction[27] ($R = 0.17$–0.18). A comparison with the molecule bicyclo[2.2.2]octane shows that the structural parameters involving the same atoms of this molecule are virtually the same as those of triethylamine, in both gaseous and solid states. This might indicate that they are little influenced by intermolecular interactions (which may be present in the solid state).



(4)

	ED[28]	XD[27] (uncorr.)
N—C (Å)	1.472(7)	1.46(1.46)$_{av.}^{a}$
C—C (Å)	1.562(9)	1.57(1.54)$_{av.}$
C—H (Å)	1.11(1)	
N—C—C (°)	110.2(4)	110.0(109.5)$_{av.}$
C—N—C (°)	108.7(4)	108.9(108.2)
H—C—H (°)	111.5(56)	

[a]For parameters obtained by X-rays, those outside parentheses refer to the centric structure $P6_3/m$ and the others to the acentric structure $P6_3$. The estimated standard deviations are 0.014 Å and 1.0°.

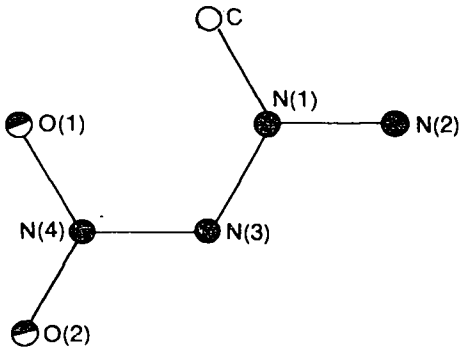
(vii) Nitroguanidine, $CH_4N_4O_2$ **(5)**[29]. Two structures were proposed for this molecule: $O_2N—N(NH_2)CNH_2$ and $O_2N—NH(NH_2)CNH$. The X-ray measurements ($R = 0.11$) indicate that the structure present is the former one, considered to be resonating among several valence bond structures. A strong hydrogen bond exists between the atoms O(1) and N(1).

2. Ammonium compounds

Table 3 lists C—N bond distances for some molecules of relatively simple structure, in which secondary effects arising from other groups present in the molecule might presumably be reduced to the minimum.

From this table (and comparison with Table 2) it may be seen that it is not possible to rationalize these results because accurate measurements of structural parameters of simple amine salts are lacking in the literature.

For the few cases in which both free amines and their salts have been studied,



(5)

Uncorrected values			
C—N(1)	1.34(2) Å	N(1)—C—N(2)	118°
C—N(2)	1.34(1) Å	N(2)—C—N(3)	112°
C—N(3)	1.35(2) Å	N(1)—C—N(3)	129°
N(3)—N(4)	1.35(2) Å	C—N(3)—N(4)	118°
N(4)—O(1)	1.22(2) Å	N(3)—N(4)—O(1)	124°
N(4)—O(2)	1.23(2) Å	N(3)—N(4)—O(2)	115°
		O(1)—N(4)—O(2)	121°

TABLE 3. Value of the C—N bond length (Å) in some ammonium compounds

Compound	C—N	Reference
Methylammonium chloride	1.465(10)	47
Methylammonium perchlorate	1.51(2) and 1.52(2)	48
n-Dodecylammonium bromide	1.482(17)	49
Methylammonium bromide	1.48	50
2,2′,2″-Triaminotriethylamine trihydrochloride	1.47(2)	51
2,2′,2″-Triaminotriethylamine trihydrochloride	1.457(5) and 1.474(2)[a]	52
Dimethylammonium chloride	1.455(8)	53
Trimethylammonium chloride	1.466(8) and 1.487(7)	54
Trimethylammonium iodide	1.45(6) and 1.46(4)	55
N-*t*-Butylpropylamine hydrochloride	1.51(3)	56
Tetramethylammonium hexahydrohexaborate	1.48(1)	57
Tetramethylammonium perchlorate	1.47(4)	58
Tetramethylammonium dichloroiodide	1.47(3)	59
Ethylenediammonium sulphate	1.49	60
Ethylenediammonium chloride	1.49	61
Trimethylenediammonium chloride	1.491	62
Tetramethylenediammonium chloride	1.50	63
β-Phenylethylamine hydrochloride	1.48(2)	64

[a]Corrected for riding motion. The two values for the distance between tertiary nitrogen and carbon are: 1.474(4) (uncorrected) and 1.492 Å (corrected).

the C—N bond distance seems to be almost the same in both compounds when the anion is simple – see the following examples: methylamine 1.470(5) Å and methylammonium chloride 1.465(10) Å; dimethylamine 1.460(5) Å and dimethylammonium chloride 1.455 Å; trimethylamine 1.452(2) Å and trimethylammonium chloride 1.466(8) Å and 1.487(7) Å. On the other hand, the C—N bond length is 1.470(5) Å in methylamine and 1.51(2) and 1.52(2) Å in monomethylammonium perchlorate.

In each case it is clear that the formal charge on the nitrogen atom does not give rise to a shortening of the C—N bond length below its normal covalence value.

It is of interest to recall that there is generally a significant increase in the C—N—C angle in the salts compared to that in the free amine analogues. This may be due to the fact that a lone pair exerts a greater repulsion than a bonding pair, rather than to the charged electron situation around the nitrogen atom.

Indirect information on the configuration of the N—H bonds around the nitrogen might be extracted from the arrangement of the halogen atoms with which the N—H bonds should form hydrogen bonds. However, at the present stage the information would be uncertain because of the various factors that condition the arrangement of the molecule in the solid state.

As regards the hydrogen bond in ammonium and alkylammonium halides NH_4Cl, RNH_3Cl, R_2NH_2Cl and R_3NHCl, it appears that there is a relationship between the coordination number of the nitrogen and the chlorine and the distance N—H···Cl. This may be explained on the basis of the two effects which are particularly important in influencing the coordinate bond length.

The first is the difference in electronegativity between substrate and substituent. Taking ammonium chloride as the parent molecule for obtaining the other salts, in the present case the hydrogen is substituted by a methyl group. Consequently we expect little change because the methyl group and hydrogen probably have comparable electronegativities.

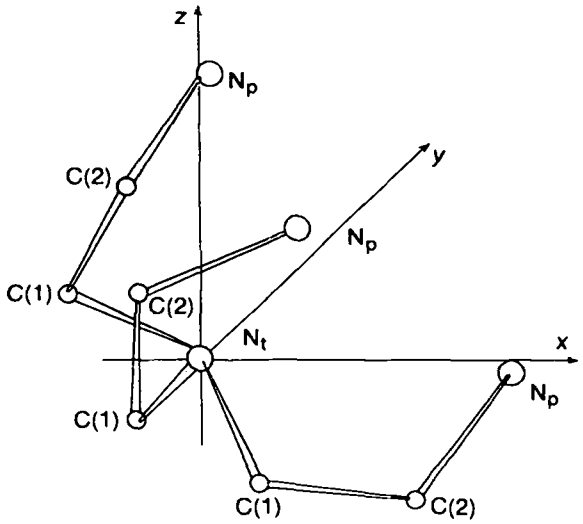
As for all coordinate bonds, the other effect is connected with the coordination number; in our case this changes along the series. This effect seems to be the most important in ammonium compounds as it may be seen from the following observed structural parameters.

In NH_4Cl with a CsCl-type structure, the nitrogen and the chlorine each have coordination number equal to 8 and the N—H···Cl distance is 3.35 Å, whilst in NH_4Cl with a NaCl-type structure the coordination number of both these atoms is 6 and the N—H···Cl distance is 3.26 Å. In CH_3NH_3Cl the nitrogen, bonded to a methyl group and four chlorine atoms, has coordination number 5 and the chlorine coordination number is 4, with a N—H···Cl distance of 3.11 Å. Finally, in $(CH_3)_3NHCl$ the coordination number of the nitrogen is 4 and that of the chlorine 1, with a hydrogen bond distance of 3.00 Å.

This regular decrease in the N—H···Cl bond length, which can only partially be ascribed to the fact that a hydrogen has been substituted by a methyl group, has been suggested using infrared spectroscopy (although this point remains to be clarified both experimentally and theoretically). Thus, from the general relationship between the A—H stretching frequency and the A—H···B distance[65], the regular decrease in this frequency along the series mono-, di-, and tri-methylammonium chloride[66] may be interpreted as an indication that there is a decrease in the hydrogen-bond length in the same sense.

We now report three accurate and comparable structures of salts of simple amines to give an idea of the structural situation present in these molecules.

(i) 2,2′,2″-Triaminotriethylamine trihydrochloride, $C_6H_{21}N_4Cl_3$ **(6)**[52]. The structure of this molecule has been determined from three-dimensional X-ray data,



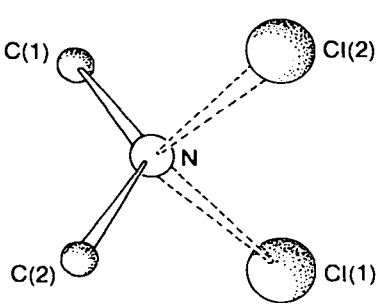
(6)

Uncorrected values			
$C(1)—N_t$	1.474(4) Å	$C(1)—N_t—C(1)$	108.8(9)°
$C(2)—N_p$	1.457(5) Å	$N_t—C(1)—C(2)$	113.3(9)°
C(1)—C(2)	1.495(5) Å	$C(1)—C(2)—N_p$	112.6(9)°
$N_p—H(1)$	0.889(38) Å		
$N_p—H(2)$	0.911(44) Å		
$N_p—H(3)$	0.978(45) Å		

with $R = 0.0476$. The bond distances are normal and very similar to those in methylamine. The following values corrected for riding motion have been obtained: $C(1)—N_t$ 1.492(4) Å; $C(2)—N_p$ 1.474(5) Å; C(1)—C(2) 1.495(5) Å.

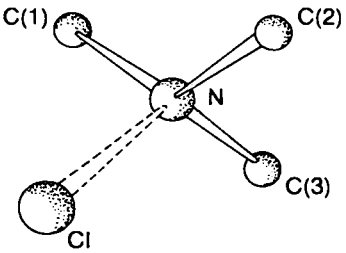
(ii) Dimethylammonium chloride, C_2H_8ClN **(7)**[53]. The structure three-dimensional X-ray data, with $R = 0.082$) at room temperature consists of infinite planar sheets of nitrogen and chlorine atoms linked by hydrogen bonds of length 3.12 and 3.09 Å.

(iii) Trimethylammonium chloride, $C_3H_{10}ClN$ **(8)**[54]. The structure has been determined from three-dimensional X-ray data, with $R = 0.064$, at room



(7)

Uncorrected values			
N—C(1)	1.455(8) Å	C(1)—N—C(2)	113.8(8)°
N—C(2)	1.455(8) Å	Cl(1)···N—C(1,2)	109.0(4)°
N···Cl(1)	3.126(7) Å	Cl(2)···N—C(1,2)	111.1(4)°
N···Cl(2)	3.091(8) Å	Cl(1)···N···Cl(2)	103.0(2)°



(8)

Uncorrected values			
N—C(1)	1.466(8) Å	C(1)—N—C(2,3)	110.2(3)°
N—C(2,3)	1.487(7) Å	C(2)—N—C(3)	112.1(6)°
N···Cl	3.005(5) Å	Cl···N—C(1)	111.3(4)°
		Cl···N—C(2,3)	106.5(3)°

temperature. It consists of neutral $(CH_3)_3NHCl$ units in which the trimethylammonium ion is bonded to the chloride ion via a hydrogen bond (3.00 Å).

C. Aromatic Amines

The structures of these very important compounds have been the object of much study over the years.

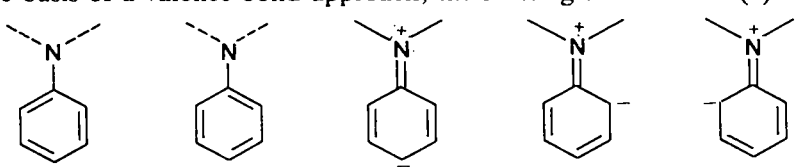
When discussing their structures the accent will be placed on the salient properties of these compounds, i.e., on the changes undergone by the amino group as a function of the substituents in the phenyl ring and vice versa. This aspect is closely related to the behaviour of anilines in organic syntheses.

After an analysis of the results on some derivatives, we shall attempt to provide an outline of the general behaviour of the functional group.

1. *Aniline*

The facility with which this compound is substituted in the *ortho* and *para* positions by electrophilic reagents is commonly explained by assuming that the structure is characterized by conjugation between the lone pair of the nitrogen and the π-system of the phenyl ring.

On the basis of a valence bond approach, the limiting structures in (**9**) have been

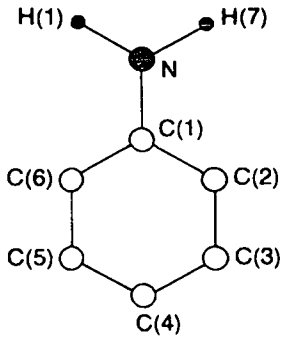


(**9**)

suggested. From the purely structural point of view, these forms may be divided into two groups. The first group (I, II) is compatible with an almost tetrahedral configuration at the nitrogen atom, whilst the other (III–V) requires a planar structure and a shorter C—N bond than exists in aliphatic amines.

The equilibrium configuration of aniline, in which a certain amount of delocalization between the nitrogen lone pair and the phenyl π-system has been established, is not planar. There is both direct and indirect evidence to support this.

Direct evidence is available from the structure in the gas phase[67,68] determined between −10 and 25°C by microwave spectroscopy of thirteen isotopic modifications (**10**). The accuracies in bond distances and angles are 0.002–0.004 Å



(**10**)

C(1)—N	1.402 Å	H(1)—N—H(7)	113.1°
N—H(1)	1.001 Å	C(6)—C(1)—C(2)	119.5°
C(1)—C(2)	1.397 Å	C(1)—C(2)—C(3)	120.1°
C(2)—C(3)	1.394 Å	H(2)—C(2)—C(3)	120.0°
C(3)—C(4)	1.396 Å	C(2)—C(3)—C(4)	120.7°
C—H	1.082 Å	H(3)—C(3)—C(2)	119.4°
		C(3)—C(4)—C(5)	118.9°

and 0.1–0.2°, respectively, apart from those for the N—H bond (0.01 Å) and H(1)—N—H(7) (2°). In this structure the plane of the $-NH_2$ group is out of the phenyl plane by 37.5(2.0)°.

Measurements of the same type[69] on $PhNH_2$ and $PhND_2$ are in agreement with these results; the angle between the two planes is ca. 38°.

Previous vibrational measurements[70] (Raman in the liquid phase; infrared in vapour, solution and liquid, on $PhNH_2$, PhNHD and $PhND_2$) as well as electronic spectra[71] have also been interpreted on the basis of a noncoplanar structure.

As in the aliphatic amines, the amino group undergoes an inversion mode and a rotation about the C—N bond. A value of 4.5 kcal mol^{-1} (at least) for the former and a value of 3.54 kcal mol^{-1} for the latter have been found from vibrational studies[70]. The value of 3.54 kcal mol^{-1}, for the rotation around the C—N bond, may be compared with the values of 1.92–1.97 kcal mol^{-1} observed[11,13,32] for various methylamine isotopic species.

The C—N bond [1.402(2) Å] is significantly shorter than that in aliphatic amines [1.475(5) Å]. Although it is not certain that this shortening is entirely due to the contribution of extreme planar forms (**9**, III–V) this possibility (at least in part) appears likely if evidence of a chemical nature is taken into account. On the other hand, if we attribute this bond-shortening as arising (in part) from the hybridization type of carbon, an analogous effect should be observed on going from nitromethane (C—N bond length 1.490 Å)[72] to nitrobenzene (1.492 Å)[73], which is obviously not the case. However, the difference in C—C bond distances between aniline and benzene[74] is too small and cannot be used as an evidence.

Indirect evidence of the noncoplanarity of the amino group and the phenyl is also forthcoming from the characteristics of the ultraviolet spectra of substituted anilines[75] and from the fact that the dipole moment of *N,N'*-tetramethyl-*p*-phenylenediamine (1.2 D)[76] is not zero, as would be expected for complete planarity.

2. *Phenyl derivatives*

a. General. Ideally, treatment of these molecules should allow the behaviour of the amine group to be clearly traced with change in the characteristics (electron-donor and electron-acceptor power) of the phenyl substituents and their position in the phenyl ring.

Unfortunately, literature data mainly refer to derivatives with electron-acceptor properties and in compounds with not readily rationalizable behaviour. Consequently a review of the phenyl derivatives can only underline the general properties common to all of them.

In Table 4 are reported the structural parameters of the amino group in some aniline derivatives. From this table it is seen that the C—N distance is strongly dependent on the characteristics of the substituents in the phenyl ring, their number and their position. In general, a distinct decrease in this distance is observed in the presence of clearly electron-attracting groups such as nitro or carbonyl. Thus, the C—N bond length goes from 1.406(11) Å in 3-nitroaniline to values of 1.371(7) and 1.353(7) Å in 4-nitroaniline, falling to 1.340(6) Å in 2,4,6-trinitroaniline and 1.312(6) Å in 2,3,4,6-tetranitroaniline.

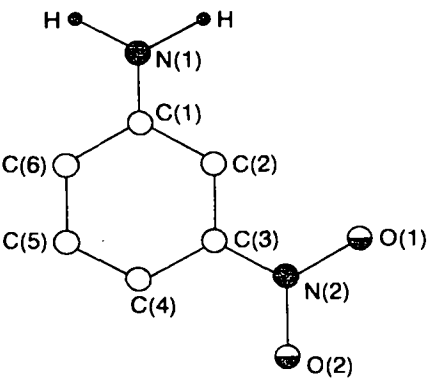
The behaviour of aminobenzoic acids[94–96] is interesting. For all three compounds two structurally distinct molecules were observed, but with closely similar structure parameters. As regards the amino group, the average C—N distance (1.370–1.380 Å, for the two structures determined from three-dimensional X-ray data) is shorter than that in aniline [1.402(2) Å] and is of the same order as that in nitroanilines (Table 4). This suggests that there are contributions from extreme forms of the quinonoid type, more or less of the same weight for all three molecules. The effects induced by electron-donor substituents, are not obvious from inspection of Table 4.

In general, with respect to aniline, the presence of electron donors decreases the contribution of structures I, II of (**9**), whilst electron-attracting substituents increase that of types III–V. This demonstrates the mobility of the electron density in aniline, which makes itself felt in the delocalization between the nitrogen lone pair and the π-electrons of the phenyl ring.

On this basis, it seems reasonable[82] to expect that this delocalization influences the dimensions of the phenyl ring, especially the C(1)—C(2) and C(1)—C(6) distances, as it is illustrated in Table 5. From this table it is seen that as the C—N bond length decreases, there is a clear tendency for the average C—C bond length to increase.

Below are reported some interesting comparable structures with the aim of developing structural aspects specific to each type of aniline derivatives.

b. Nitroanilines. (i) 3-Nitroaniline, $C_6H_6N_2O_2$ (**11**)[77]. The molecular structure



(**11**)

Uncorrected values			
C(1)—N(1)	1.406 Å	C(2)—C(1)—C(6)	119.6°
C(3)—N(2)	1.440 Å	C(2)—C(1)—N(1)	121.3°
C(1)—C(2)	1.366 Å	C(6)—C(1)—N(1)	119.1°
C(2)—C(3)	1.381 Å	C(1)—C(2)—C(3)	119.3°
C(3)—C(4)	1.409 Å	C(2)—C(3)—C(4)	122.3°
C(4)—C(5)	1.348 Å	C(2)—C(3)—N(2)	119.3°
C(5)—C(6)	1.380 Å	C(4)—C(3)—N(2)	118.3°
C(6)—C(1)	1.419 Å	C(3)—C(4)—C(5)	116.7°
N(2)—O(1)	1.242 Å	C(4)—C(5)—C(6)	123.4°
N(2)—O(2)	1.211 Å	C(5)—C(6)—C(1)	118.5°
		C(3)—N(2)—O(1)	119.5°
		O(1)—N(2)—O(2)	120.5°

(determined from three-dimensional X-ray data, with $R = 0.084$ and e.s.d.s of 0.011–0.016 Å and 0.7–1.0°), is almost perfectly planar. The position of amino hydrogens is not determined. The intermolecular distances indicate a very weak interaction between pairs of molecules.

(ii) 4-Nitroaniline, $C_6H_6N_2O_2$ (**12**)[79]. The structure of this molecule has been determined several times[78,79,97]. The results reported here have been refined[79]

TABLE 4. Dimensions[a] of the amino group in some phenyl-substituted anilines

Compound	N—*H*	N—C	$\widehat{HNH}$	$\widehat{CNH}$	Reference
3-Nitroaniline		1.406(11)			77
4-Nitroaniline		1.37(7)		120	78
4-Nitroaniline	0.75, 0.96(6)	1.371(7)[b]			79
		1.353(7)		118, 130(5)	
1,3,5-Triamino-2,4,6-trinitrobenzene	0.86, 1.06(9)	1.312(7)[c]	124(6)	116, 118(4)	80
		1.322(7)[c]	116(7)	121, 122(6)	
		1.314(7)[c]	123(7)	117, 119(5)	
1,3-Diamino-2,4,6-trinitrobenzene[d]		1.32(2)			81
		1.32(2)			
2,4,6-Trinitroaniline		1.340(6)	126.9(3)	113.1, 119(3)	82
2,3,4,6-Tetranitroaniline	0.95, 0.97	1.312(6)	120(4)	119, 120(4)	83
2-Chloro-4-nitroaniline		1.386(12)[e]			84
		1.382(12)			
2-Chloro-4-nitroaniline		1.358			85
4-Chloroaniline		1.40(1)			86
4-Chloroaniline		1.386(25)[e]			87
		1.381(15)	137(8)	111(8)	
2,5-Dichloroaniline		1.407(16)[e]			88
		1.395(16)			

2,4,6-Tribromoaniline	0.99, 1.03(9)	1.426(20)	141.3(98)	103.1, 104.0 (57)	89
4-Aminoacetophenone	0.91, 0.93(4)	1.376(4)	114(4)	113(2), 119(3)	90
2,2'-Dichlorobenzidine		1.40(2)			91
3-Tolidine		1.44(5)			92
4-Aminophenol		1.39			93
2-Amino-3-methylbenzoic acid	0.88, 0.91	1.367(18)	124	116, 119	94
3,5-Dibromo-4-aminobenzoic acid		1.311(60)[f]			95
		1.403(60)[g]			
		1.435(33)[h]			
		1.372(33)[i]			
4-Aminobenzoic acid	0.89, 0.94(6)	1.378(6)[k]	114(4)	118, 119(4)	96
	0.85, 0.94(6)	1.381(6)	114(4)	116, 121(4)	

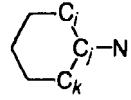
[a]Bond lengths in Å and angles in degrees.
[b]Corrected for librational and torsional effects.
[c]From spherical refinement. The values obtained from nonspherical refinement are very close to these.
[d]Form I. Two crystalline polymorphs have been observed from X-ray powder diffraction. Form I is stable from room temperature to 217°C and form II from 217 to its melting point.
[e]Corrected for librational effects.
[f]3,5-Dibromo-4-aminobenzoic acid in the solid state consists of two independent sets of molecules, one basic molecule (A) having mirror-image symmetry and the other (B) having a diad symmetry.
[g]Form A, at −150°C.
[h]Form B, at 25°C.
[i]Form B, at −150°C.
[k]There are two structurally distinct molecules in the asymmetric unit.

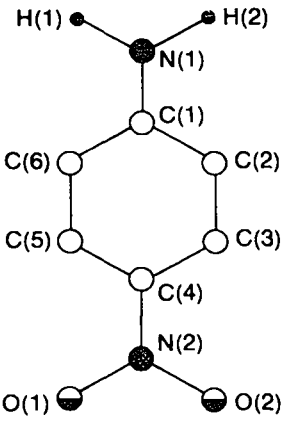
TABLE 5. Dimensions[a] of adjacent C—NH_2 and C—C bonds in some anilines

Compound	C_j—N	*i*	*j*	*k*	C_i—C_j	C_j—C_k	C—C[b]	Reference
2,4,6-Tribromoaniline	1.426	6	1	2	1.365	1.386	1.375	89
3-Nitroaniline	1.406	6	1	2	1.366	1.419	1.393	77
Aniline	1.402	6	1	2		1.397	1.397	68
2,5-Dichloroaniline	1.395	6	1	2	1.398	1.423	1.410	88
4-Aminophenol	1.39	3	4	5	1.39	1.40	1.395	93
2-Chloro-4-nitroaniline	1.382	6	1	2	1.420	1.394	1.407	84
4-Chloroaniline	1.381	6	1	2			1.418	87
4-Aminobenzoic acid	1.381	3	4	5	1.396	1.403	1.400	96
4-Aminoacetophenone	1.376	3	4	5	1.399	1.397	1.398	90
2-Amino-3-methylbenzoic acid	1.367	1	2	3	1.415	1.421	1.418	94
2,6-Dichloro-4-nitroaniline	1.358	6	1	2	1.408	1.420	1.414	85
4-Nitroaniline	1.353	6	1	2	1.405	1.412	1.409	79
2,4,6-Trinitroaniline	1.340	6	1	2	1.430	1.427	1.429	82
1,3-Diamino-2,4,6-trinitroaniline	1.32	6	1	2	1.39	1.47	1.43	81
	1.32	2	3	4	1.47	1.39	1.43	
2,3,4,6-Tetranitroaniline	1.312	6	1	2	1.428	1.434	1.431	83
1,3,5-Triamino-2,4,6-trinitrobenzene	1.312	6	1	2	1.433	1.443	1.438	80
	1.327	2	3	4	1.437	1.447	1.442	
	1.314	4	5	6	1.438	1.446	1.442	

[a]Bond lengths in Å.

[b]This is the average value between C_i—C_j and C_j—C_k bond distances. Symbols have the following meaning:





(12)

	Uncorr.	Corr.		
C(1)—N(1)	1.353 Å	1.371	C(2)—C(1)—N(1)	121.2°
C(4)—N(2)	1.454 Å	1.460	C(6)—C(1)—C(2)	118.9°
C(1)—C(2)	1.405 Å	1.408	C(1)—C(2)—C(3)	120.8°
C(2)—C(3)	1.374 Å	1.377	C(2)—C(3)—C(4)	119.2°
C(3)—C(4)	1.387 Å	1.390	C(3)—C(4)—C(5)	121.1°
C(4)—C(5)	1.392 Å	1.395	C(4)—C(5)—C(6)	119.8°
C(5)—C(6)	1.370 Å	1.373	C(5)—C(6)—C(1)	120.1°
C(6)—C(1)	1.412 Å	1.415	C(3)—C(4)—N(2)	120.4°
N(2)—O(1)	1.227 Å	1.246	C(4)—N(2)—O(1)	117.7°
N(2)—O(2)	1.229 Å	1.247	C(4)—N(2)—O(2)	119.0°
N(1)—H(1)	0.96 Å		O(1)—N(2)—O(2)	123.3°
N(1)—H(2)	0.75 Å		C(1)—N(1)—H(1)	118°
			C(1)—N(1)—H(2)	130°

three-dimensionally with visually estimated Cu $K\alpha$ data; $R = 0.095$ and e.s.d.s are 0.006–0.007 Å and 0.4°. E.s.d.s for bond lengths and angles involving hydrogen atoms are 0.06–0.07 Å and 5°, respectively.

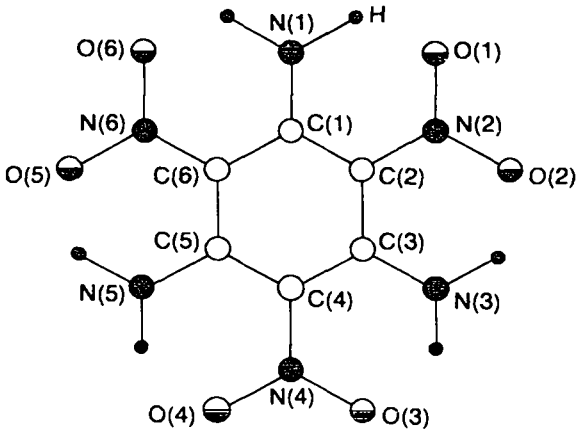
On the basis of the structural parameters, the presence of major contributions by quinonoid limiting forms when compared to aniline may be suggested, as may be deduced from the length of the bonds C(1)—N(1) and C—C. Nevertheless, the amino group interacts more extensively with the phenyl ring than does the nitro group.

According to some authors[84], the 2-chloro-4-nitroaniline molecule gives bond distances and angles different from those in 4-nitroaniline whereas others[85] assign virtually the same parameters to both molecules.

(iii) 1,3,5-Triamino-2,4,6-trinitrobenzene, $C_6H_6N_6O_6$ **(13)**[80]. The structure has been determined from three-dimensional X-ray data to $R = 0.053$, and refined with both spherical and nonspherical atomic scattering factors. We have reported only the values calculated using the first refinement. (Those obtained using nonspherical factors differ by 0.005 Å and 0.3–0.6° for nonhydrogen parameters and 0.02–0.04 Å and 1.0–3.0° for hydrogen ones). Estimated standard deviations are 0.006–0.007 Å and 0.4–0.5° for nonhydrogen atoms and 0.06–0.09 Å and 4.0–7.0° for others.

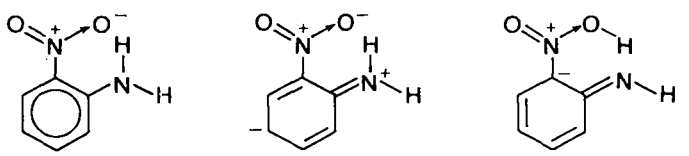
This molecule has several features in common with other nitroanilines, such as the extremely long phenyl C—C bonds and rather short C—NH_2 bonds. The molecule is planar. Consequently, since all ring positions are occupied, the ring distortion must consist of a symmetrical expansion.

Bond-order calculations were made[98] using the following bond lengths corrected for librational effects: C—C 1.444 Å; C—NH_2 1.319 Å; C—NO_2 1.426 Å; N—O 1.243 Å. The bond order obtained is: C—C 1.23, C—NH_2 1.46; C—NO_2 1.02; N—O 1.52. According to these results and because of the presence of six bifurcated hydrogen bonds, in a valence-bond description, contributions from several extreme forms, such as **(14)** for example, have been suggested[80]. We do not entirely agree with the result regarding C—N (nitro). In fact, taking into account the shortening of the C—N (nitro) bond in the present molecule [mean value 1.420(7) Å] with respect to the nitrobenzene and nitromesitylene [1.486(20) and 1.476(17) Å, respectively; see the section below on aromatic nitro compounds] contributions of extreme forms with a C—N (nitro) double bond must be suggested.



(13)

Uncorrected values					
C(1)—N(1)	1.312 Å	C(4)—N(4)	1.425 Å	C(6)—C(1)—C(2)	118.0°
C(2)—N(2)	1.421 Å	C(5)—N(5)	1.322 Å	C(6)—C(1)—N(1)	120.4°
C(3)—N(3)	1.314 Å	C(6)—N(6)	1.419 Å	C(1)—C(2)—C(3)	122.2°
C(1)—C(2)	1.438 Å	C(4)—C(5)	1.447 Å	C(1)—C(2)—N(2)	119.0°
C(2)—C(3)	1.446 Å	C(5)—C(6)	1.438 Å	C(2)—C(3)—C(4)	117.6°
C(3)—C(4)	1.433 Å	C(6)—C(1)	1.443 Å	C(2)—C(3)—N(3)	121.6°
N(2)—O(1)	1.233 Å	N(4)—O(4)	1.241 Å	C(3)—C(4)—C(5)	122.2°
N(2)—O(2)	1.243 Å	N(6)—O(5)	1.238 Å	C(3)—C(4)—N(4)	119.4°
N(4)—O(3)	1.246 Å	N(6)—O(6)	1.254 Å	C(4)—C(5)—C(6)	118.0°
N—H	0.80–1.06 Å			C(4)—C(5)—N(5)	120.4°
				C(5)—C(6)—C(1)	121.7°
				C(5)—C(6)—N(6)	118.8°

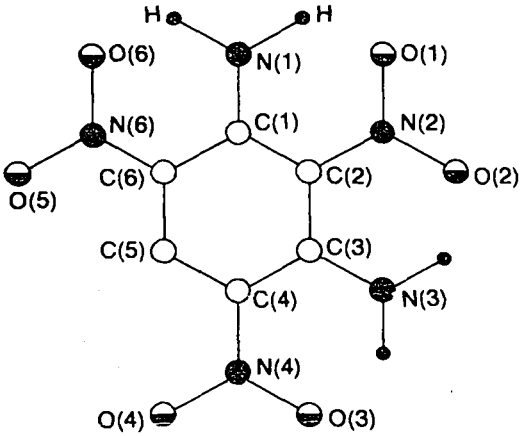


(14)

(iv) 1,3-Diamino-2,4,6-trinitrobenzene (form I) $C_6H_5N_5O_6$ (**15**)[81]. Two crystalline polymorphs of the present compound have been identified by X-ray diffraction. Form I is stable from room temperature to 217°C and form II from 217°C to its melting point (286°C).

The present structure has been determined from three-dimensional X-ray data with $R = 0.103$ and e.s.d.s are 0.019–0.023 Å and 1.3–1.6°. We report only bond lengths.

There is a certain distortion in the benzene ring with respect to the molecular plane, rather than a rotation of the nitro groups outside this plane. Thus, the C—C bond lengths on either side of the unoccupied ring position are 1.37–1.39 Å, whilst both distances on the crowded side are 1.47 Å. As for 1,3,5-triamino-2,4,6-

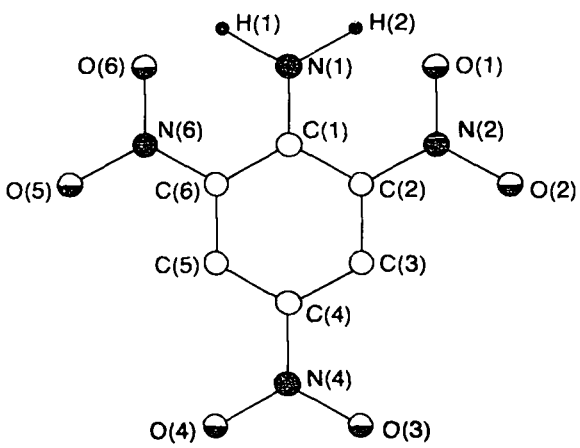


(15)

Uncorrected values			
C(1)—N(1)	1.32 Å	N(6)—O(5)	1.18 Å
C(3)—N(3)	1.32 Å	N(6)—O(6)	1.24 Å
C(2)—N(2)	1.42 Å	C(1)—C(2)	1.47 Å
C(4)—N(4)	1.43 Å	C(2)—C(3)	1.47 Å
C(6)—N(6)	1.51 Å	C(3)—C(4)	1.39 Å
N(2)—O(1)	1.26 Å	C(4)—C(5)	1.38 Å
N(2)—O(2)	1.24 Å	C(5)—C(6)	1.37 Å
N(4)—O(3)	1.26 Å	C(6)—C(1)	1.39 Å
N(4)—O(4)	1.22 Å		

trinitrobenzene, intra- and inter-molecular hydrogen bonds are present. As concerns the conjugation between amino and nitro groups, C—N bond distances clearly indicate a delocalization from the former to the latter, as it has been found for 1,3,5-triamino-2,4,6-trinitrobenzene.

(v) 2,4,6-Trinitroaniline, $C_6H_4N_4O_6$ **(16)**[82]. The structure (from three-



(16)

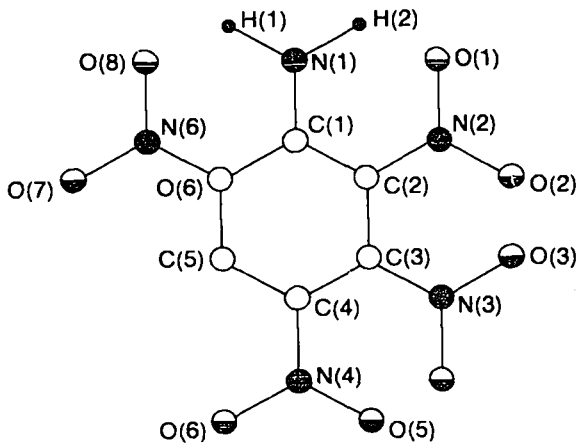
Uncorrected values					
C(1)—N(1)	1.340 Å	N(6)—O(5)	1.203 Å	C(1)—N(1)—H(1)	113.1(2.2)°
C(2)—N(2)	1.474 Å	N(6)—O(6)	1.230 Å	C(1)—N(1)—H(2)	119.8(2.2)°
C(4)—N(4)	1.468 Å	C(1)—C(2)	1.429 Å	H(1)—N(1)—H(2)	126.9(2.9)°
C(6)—N(6)	1.462 Å	C(2)—C(3)	1.372 Å		
N(2)—O(1)	1.220 Å	C(3)—C(4)	1.381 Å		
N(2)—O(2)	1.215 Å	C(4)—C(5)	1.372 Å		
N(4)—O(3)	1.224 Å	C(5)—C(6)	1.376 Å		
N(4)—O(4)	1.223 Å	C(6)—C(1)	1.427 Å		
N(1)—H(1)	0.92 Å	N(1)—H(2)	0.88 Å		

dimensional X-ray data) has been refined to a R value of 0.084; e.s.d. = 0.004–0.006 Å. For this compound, as well as for many others in the present review, we report only the bond lengths and the amino group bond angles, even though the other angle values have been determined accurately.

From the bond lengths a certain conjugation between the amino and nitro groups may be inferred. Of course, the effect of this delocalization is greater on the former group than on the latter one.

From the sum of the amino group bond angles it has been deduced[82] that the phenyl–amino group must be virtually planar, within the limits of the experimental errors. However, given the uncertainty in the bond angles involving hydrogen atoms this conclusion must be taken with caution.

(vi) 2,3,4,6-Tetranitroaniline, $C_6H_3N_5O_8$ **(17)**[83]. The structure of this molecule, which completes our information on nitroanilines, has been obtained from three-dimensional X-ray data, with $R = 0.08$ and e.s.d.s of 0.007 Å and 0.44° for nonhydrogen bonds and angles. As for the previous molecules, only bond distances are reported here, apart from the bond angles for the amino group.



(17)

Uncorrected values

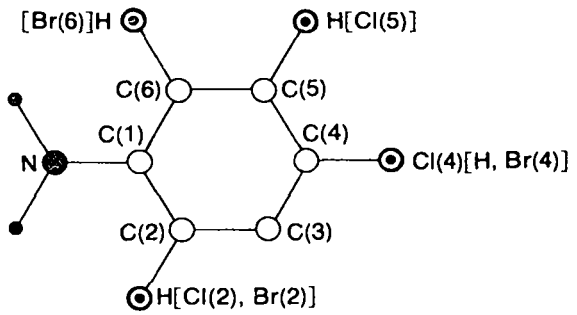
C(1)—N(1)	1.312 Å	N(6)—O(7)	1.222 Å	C(1)—N(1)—H(1)	120°
C(2)—N(2)	1.467 Å	N(6)—O(8)	1.215 Å	C(1)—N(1)—H(2)	119°
C(3)—N(3)	1.487 Å	C(1)—C(2)	1.434 Å	H(1)—N(1)—H(2)	120°
C(4)—N(4)	1.447 Å	C(2)—C(3)	1.361 Å		
C(6)—N(6)	1.461 Å	C(3)—C(4)	1.384 Å		
N(2)—O(1)	1.218 Å	C(4)—C(5)	1.377 Å		
N(2)—O(2)	1.218 Å	C(5)—C(6)	1.367 Å		
N(3)—O(3)	1.211 Å	C(6)—C(1)	1.428 Å		
N(3)—O(4)	1.207 Å	N(1)—H(1)	0.97 Å		
N(4)—O(5)	1.221 Å	N(1)—H(2)	0.95 Å		
N(4)—O(6)	1.227 Å				

This molecule is strictly related to the previous ones. In fact, the C—NH_2 bond distance is 1.312 Å, about the same reported for 1,3-di- and 1,3,5-tri-amino-2,4,6-trinitrobenzene, but significantly shorter than the value

observed for 4-nitroaniline. By way of contrast, the C—NO_2 bond distances are just below the value observed for nitrobenzene.

The sum of the bond angles at the amino group is 359° and each value is ca. 120°. This might indicate a trigonal hybridization of the nitrogen. Unfortunately, the errors in these angles are quite large (ca. 4°), making this conclusion uncertain.

c. Haloanilines. The structures of some chloro and bromo derivatives of aniline without other substituents in the ring have been determined[86–89]. They are reported together (see structure **18**) (only bond distances given here) because they have many things in common. These parameters have been calculated from three-dimensional X-ray data, with the following R values: 0.063[86] and 0.11[87] (4-chloroaniline)[99], 0.126[88] (2,5-dichloroaniline) and 0.555[89] (2,4,6-tribromoaniline).



(18)

	4-Chloroaniline		2,5-Dichloroaniline	2,4,6-Tribromoaniline
	Uncorr.[86]	Corr.[87]	Corr.[88]	Uncorr.[89]
C(1)—N (Å)	1.40(1)	1.386(25)	1.407(16)	1.426(20)
C(1)—C(2) C(6)—C(1) (Å)	1.40	1.424(21)	1.411(17)	1.376(22)
C(2)—C(3) C(5)—C(6) (Å)	1.41	1.394(18)	1.374(17)	1.393(23)
C(3)—C(4) C(4)—C(5) (Å)	1.37	1.400(20)	1.389(17)	1.381(22)
N—H(1) N—H(2) (Å)	0.94			1.01(9)
C(4)—Cl(4) (Å)	1.75	1.749(20)		
C(2)—Cl(2) (Å)			1.744(12)	
C(5)—Cl(5) (Å)			1.743(12)	
C(2)—Br(2) (Å)				1.886(16)
C(4)—Br(4) (Å)				1.891(16)
C(6)—Br(6) (Å)				1.896(16)
C(1)—N—H(1) (°)		111(8)		103.6(5.7)
C(1)—N—H(2) (°)				
H(1)—N—H(2) (°)		137(8)		141.7(9.8)

It is seen that the bond distances are similar to those observed for aniline, within the limits of the relevant experimental errors. The C—N bond length changes from 1.402(2) Å (aniline) to 1.40(1)–1.386(25) (monochloro derivative), to 1.407(16) (dichloro derivative) and to 1.426(2) (tribromo derivative). The C—Cl bond

distance [1.736(12)–1.750(2) Å] is very close to that observed for other aromatic chloro compounds[100], as is the average C—Br bond length [1.891(9) Å] to that [1.896(18) Å][101] observed for 1,2,4,5-tetrabromobenzene.

Despite the uncertainty in the structural parameters, very probably the rough agreement observed above (indicating an overall weak electron effect between halogens and amino group) is significant if we take into account experimental results of other types. In fact, a virtually zero interaction between halogen p-electrons and π-p system of the phenylamine group was also suggested on the basis of the observed nuclear quadruple constant data[102,103]. According to these results in 1,3,5-tribromobenzene (solid) the double-bond character in the three C—Br bonds is 0.03, 0.03 and 0.045 electrons and 0.035, 0.02 and 0.03 electrons in 2,4,6-tribromoaniline.

In our opinion these structures should be redetermined with the aim of comparing the behaviour of the various halogens.

3. *Heterocyclic amines*

These constitute a rather interesting class of compounds because they allow the behaviour of the amine group to be studied in the presence of an electron attractor in which problems connected with planarity do not arise.

We have chosen some representative examples, the structures of which have been determined quite recently.

The microwave spectrum of 2-aminopyridine in gas[104] consists of pairs of lines of comparable intensity, rather than a single series of decreasing intensity. This fact may be interpreted in terms of the presence of low-lying vibrational states. From the conformational point of view this is in agreement with the presence of an inversion mode for the $-NH_2$ group, as found for aniline and aliphatic amines (again in the gas phase).

The amino group is not coplanar with the pyridine ring, having the two hydrogen atoms approximately 0.25 and 0.32 Å out of the plane of the heterocycle, and on the same side. If we assume[67] an N—H bond length of 0.998 Å, the angle ϕ (between the bisector of the H—N—H angle and its projection in the ring plane) is found to be 31.6°. This value is sensibly smaller than that found in aniline (39°)[67], in agreement with the fact that in aminopyridine there is a greater contribution from quinonoid forms than in aniline.

The structure of 2-aminopyridine in the solid state has been determined using three-dimensional X-ray data[105], as well as those of 3-aminopyridine ($R = 0.039$)[106] and 4-aminopyridine ($R = 0.049$)[107].

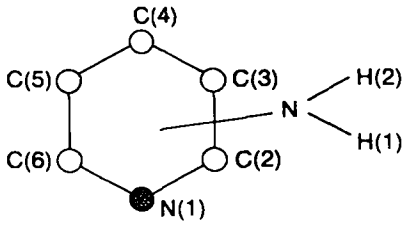
The structural parameters are reported (**19**) together with those for the pyridine molecule (from microwave spectroscopy)[108] for comparison purposes.

From these values it is seen that the C—N—C angle is little affected by the amino substituent and does not depend on the position in the heterocycle. A constant decrease in the endocyclic bond angles having as vertex the carbon atom bonded to the amino nitrogen is also observed.

The difference in $C—N_{sp^2}$ distances between the pyridine and aminopyridines is, in part, as expected on the basis of a p–π conjugation (2- and 4-isomers). In agreement with this the $C—NH_2$ bond length in 4-aminopyridine [1.363(3) Å] is about midway between the bond distance in 2- and 3-aminopyridine [1.351(2) and 1.384(4) Å, respectively].

The structures of other heterocyclic amines have been determined (Table 6), the behaviour of which is very similar to that of unsubstituted amino compounds.

In all these heterocyclic amines the $C(n + 1)—N—C(n)$ angle is sensibly lower



(19)

	Uncorrected values[a]			
	Pd	2-APd	3-APd	4-APd
C—N (Å)		1.351(2)	1.384(4)	1.363(3)
N(1)—C(2) (Å)	1.3376(4)	1.345(2)	1.336(4)	1.352(3)
N(1)—C(6) (Å)	1.3376(4)	1.340(2)	1.331(5)	1.338(3)
N—H(1) (Å)		0.88(2)	0.91(3)	0.94(3)
N—H(2) (Å)		0.89(2)	0.92(3)	0.91(3)
C(2)—C(3) (Å)	1.3938(5)	1.405(2)	1.399(4)	1.370(3)
C(3)—C(4) (Å)	1.3916(4)	1.364(2)	1.391(4)	1.406(3)
C(4)—C(5) (Å)	1.3916(4)	1.380(3)	1.376(4)	1.401(3)
C(5)—C(6) (Å)	1.3938(5)	1.367(3)	1.372(4)	1.374(3)
C—N—H(1) (°)		121(2)	118(2)	119(2)
C—N—H(2) (°)		120(2)	114(2)	120(2)
H(1)—N—H(2) (°)		117(2)	116(3)	116(3)
C(6)—N(1)—C(2) (°)	116.94(3)	117.7(1)	117.5(3)	115.0(2)
N(1)—C(2)—C(3) (°)	123.80(3)	121.6(1)	123.9(3)	124.7(2)
C(2)—C(3)—C(4) (°)	118.53(3)	118.6(2)	116.7(3)	119.4(2)
C(3)—C(4)—C(5) (°)	118.40(3)	120.2(2)	119.5(3)	116.4(2)
C(4)—C(5)—C(6) (°)	118.53(3)	117.8(2)	119.3(3)	119.4(2)
C(5)—C(6)—N(1) (°)	123.80(3)	124.2(2)	123.3(3)	125.5(2)

[a]Pd = pyridine, 2-APd = 2-aminopyridine, 3-APd = 3-aminopyridine, 4-APd = 4-aminopyridine.

TABLE 6. Relevant bond distances (Å) in some heterocyclic amines

Compound	C—NH_2	C(6)—N_{sp^2}	C(2)—N_{sp^2}	Reference
2-Aminopyridine	1.351(2)	1.340(2)	1.345(2)	105
2-Amino-3-nitropyridine	1.336(3)	1.364(3)	1.326(3)	109
2-Amino-4-methylpyridine	1.363(2)	1.348(2)	1.347(2)	110
2-Amino-5-methylpyridine	1.364(2)	1.347(2)	1.338(2)	111
2-Amino-5-chloropyridine	1.355(2)	1.342(2)	1.341(2)	112
2-Amino-5-chloropyridine[a]	1.357(1)	1.340(1)	1.341(1)	113
2-Aminopyrimidine	1.342(2)	1.348(2)	1.331(2)	114
Aminopyrazine	1.341(1)	1.336(1)	1.330(1)	115
2-Amino-3-chloropyrazine	1.366(7)	1.360(8)	1.332(7)	116
Pyrazine		1.314(3)	1.314(3)	117

[a]From neutron diffraction.

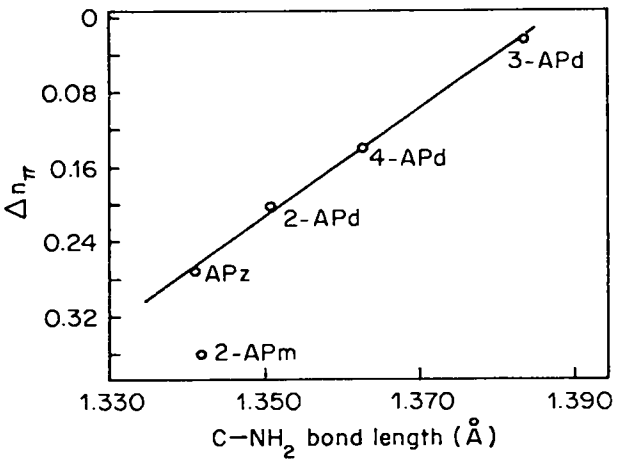


FIGURE 2. Plot of the increase in the ring π-population, Δn_π, vs. the C—NH_2 bond length. Δn_π is derived from the nuclear quadrupole resonance data and is given in units of the electron charge. The line represents a least-squares fit of the points, omitting 2-APm (2-aminopyrimidine); APd = aminopyridine, APz = aminopyrazine. Reproduced with permission from M. Chao and E. Schempp, *Acta Cryst.*, **B33**, 1557 (1977).

than 120°, going from 117.7° for 2-aminopyridine to 115.0° for 4-aminopyridine and 115.7° for 2-aminopyrimidine. This fact is characteristic of the heterocyclic ring and not a consequence of the presence of the amino group.

In general, as above, a strong conjugation is observed between the amino group (in the *ortho* and *para* positions) and the heterocyclic ring. Further evidence for this p–π delocalization is obtained from nuclear quadrupole resonance and nuclear magnetic resonance data[118–124]. In Figure 2 is shown the plot of the increase of n_π in the aminopyridines (APd) over n_π in unsubstituted pyridine [i.e. $\Delta n_\pi = (n_\pi)_{APd} - (n_\pi)_{Pd}$] vs. the C—$NH_2$ bond lengths. It can be seen from Figure 2 that the amino group behaves as deduced from the structural data.

There is a relation between the C—N bond length and both the angle ϕ (between the amino and phenyl groups) and the sum of the angles around the amino nitrogen. This interesting aspect will be treated at the end of this section because it is common to other aromatic amines.

4. N-*Alkylanilines*

Structural characteristics of any note are not expected in these molecules, at least not in the simpler ones.

Since the methyl group exerts only a low $+I$ inductive effect compared to hydrogen, in these molecules we can expect to find little evidence for a greater tendency of the nitrogen lone pair to conjugate with the phenyl group than is the case for the corresponding unsubstituted anilines.

Other differences may become particularly important for the solid state. Firstly, problems of a steric nature arise in the presence of a methyl group. Secondly, the

TABLE 7. Bond lengths (Å) involving the amino nitrogen in some *N*-alkylanilines

Compound	C_{sp^2}—N	C_{sp^3}—N[a]	Reference
3-Nitro-*N,N*-dimethylaniline	1.404(9)	1.476(10)	125
4-Nitro-*N,N*-dimethylaniline	1.358(16)[b]	1.484(22)[b]	126
4-Bromo-3-nitro-*N*-methylaniline	1.362(17)	1.460(21)	127
4-Methyl-3-nitro-*N*-methylaniline	1.377(6)	1.443(7)	127
N,3-Dimethyl-4-bromo-2,6-dinitroaniline	1.370(8)	1.426(8)	128
N-Methyl-*N*,2,4,6-tetranitroaniline	1.497(4)	1.466(4)	129
N,N-Difluoro-2,4,6-trinitroaniline	1.461(4)		130
N,N-Dimethylanthranilic acid	1.467(10)[b]	1.513(8)[b]	131
N,N,N',N'-Tetramethyl-1,5-diamino-4-nitrosobenzene	1.357(2)[a,b]	1.459(2)[a,b]	132
N,N-Dimethyl-4-nitrosoaniline	1.343(15)[a]	1.440(15)[a]	133
N,N-Diethyl-4-nitrosoaniline	1.351(4)[a]	1.478(4)[a]	134
N,N-Dimethyl-2,6-dichloro-4-nitroaniline	1.41(1)	1.46(1)	135
N,N-Di-*n*-propyl-2,6-dinitro-4-chloroaniline	1.368(6)	1.460(7)	136
N,N-Dimethyl-2-fluoro-4-nitroaniline	1.34(1)		137

[a]Average.
[b]Corrected.

amine hydrogen may form intra- and inter-molecular hydrogen bonds, which, of course, a methyl group cannot do.

We have chosen some cases to illustrate the behaviour of *N*-alkylanilines (Table 7). These results show that the C—N distance does not change significantly when the amine hydrogens are substituted by methyl groups. Thus, in 4-nitro-*N,N*-dimethylaniline a value of 1.404(9) Å is obtained vs. 1.406(11) in 3-nitroaniline, as expected; but we have also 1.358(16) for 4-nitro-*N,N*-dimethylaniline vs. 1.353(6) found for 4-nitroaniline. However, the problem merits further exploration.

These results exclude the presence of any hyperconjugation between the methyl group and nitrogen. In other words, the C—N bond retains the same characteristics as in the corresponding anilines which are not methylated at the nitrogen, and it is influenced by benzene-ring substituents in the same way.

As for nonmethylated anilines, the angle having the carbon atom bonded to the amino nitrogen as vertex is always smaller than 120°.

5. *Anilinium compounds*

In Table 8 we report bond lengths and angles involving the $-NH_3^+$ substituent. From this table it is seen that C—N bond lengths remain in the range 1.445–1.465 Å, with the more frequent value about 1.460 Å. This distance is equal to that for *o*-aminobenzenesulphonic acid [1.469(5) Å][146] and for simple aliphatic amines [1.470(5) Å].

There is in the C—N bond length no difference between monohydrochloride and dihydrochloride compounds. This indicates that the lone pair of the amino nitrogen conjugates with the π-system of the phenyl ring only when an electron-attractor group is present in the *ortho* or *para* positions which acts by means of a $-M$ electronic effect. This evidence is important in interpreting the results obtained on nitroanilines and other phenyl-substituted aromatic nitro compounds. The angles around the nitrogen are almost 107°, indicating that this atom is sp^3-hybridized.

The agreement in bond lengths found for the three aminobenzenesulphonic acids

TABLE 8. Bond lengths (Å) and angles (deg.) involving the $-NH_3^+$ group in some anilinium compounds

Compound	C—N	N—H	$\widehat{HNH}$	$\widehat{CNH}$	Reference
o-Diaminobenzene monohydrochloride	1.476(3)				138
o-Diaminobenzene monohydrochloride[a]	1.460(3)	1.042(5)	109.3(3)	111.0(3)	139
		1.042(5)		112.5(3)	
		1.037(5)			
o-Diaminobenzene dihydrochloride	1.457(2)	0.90(2)	106(2)	110(1)	140
		0.90(2)	108(2)	111(1)	
		0.86(2)	109(2)	112(1)	
p-Diaminobenzene dihydrochloride	1.49	0.90		109.1	141
		1.15		111.2	
		0.94		112.7	
p-Diaminobenzene dihydrochloride	1.462(2)	0.90(3)	106(3)	109(2)	142
		0.91(3)	110(3)	110(2)	
		0.92(2)	111(2)	112(2)	
o-Diaminobenzene dihydrobromide	1.445(1)				143
m-Aminobenzoic acid hydrochloride[b]	1.461(4)	0.95(4)	101(4)	108(1.7)	144
		1.00(4)	113(4)	108(1.7)	
		1.01(4)	116(4)	110(1.7)	
m-Aminobenzoic acid hydrochloride	1.458(10)	0.89	107	111(2.5)	144
		0.89	107	111(2.5)	
		0.91	110	110(2.5)	
Anilinium tetrachlorocuprate(II)	1.468(3)	0.84(3)			145
		0.90(3)			
		1.00(5)			
o-Aminobenzenesulphonic acid	1.469(5)[c]				146
	1.466(5)				
m-Aminobenzenesulphonic acid	1.44(1)				147
p-Aminobenzenesulphonic acid monohydrate	1.49(3)				148
o-Aminophenol hydrochloride	1.474(9)				149

[a]From neutron diffraction.
[b]The structure of this molecule has been determined independently in two different laboratories.
[c]Corrected.

is probably due to the high uncertainty in the values derived from the two dimensional sets of data (*para* isomer); consequently, it is not possible to carry out any extended discussion on the molecular structure or on the mutual effects involving the amino and sulphonic groups. The only thing it is possible to say is that the structure is zwitterionic. In fact, the C—N bond length [1.469(5) Å] is the same as that observed for anilinium compounds.

D. Conclusions

From the discussion above, it appears that the structural characteristics of the amino group in aliphatic compounds are very similar to that found for ammonia, with some minor modifications regarding especially the bond angles, due to the steric effect of the alkyl group(s).

In the aromatic amines, owing to the possible p–π conjugation between the nitrogen lone pair and the phenyl ring there is a regular variation of some structural parameters depending on the nature (and number) of the ring-substituents. These parameters are the C—N bond distance, the angle between the planes of the amino group and the phenyl ring and the sum (Σ) of the angles around the nitrogen (when these angles are not too different).

From Table 9 it is seen that the shorter the C—N bond the smaller the dihedral angle between the two planes. This correlation is shown in Figure 3, with a slope of

TABLE 9. Structural parameters of the amino group in some aromatic amines[a]

Compound	C—N	$\widehat{HNH}$ $\widehat{CNH}$	Σ^b	ϕ^c	Method	Reference
Aniline	1.402(2)	113.1(20)[d]		37.5	MW	67
1,3,5-Triamino-2,4,6-trinitrobenzene	1.314(7)	123(7) 117(5) 119(5)	359		XD	80
	1.322(7)	116(7) 122(6) 121(4)	359			
	1.312(7)	124(6) 118(4) 116(4)	358			
2,4,6-Trinitroaniline	1.340	126.9(38) 119.5(25) 113.1(25)	360		XD	82
2,3,4,6-Tetranitroaniline	1.312(6)	120 119 120	359		XD	83
4-Aminoacetophenone	1.376(4)	114(4) 113(2) 119(3)	346		XD	90
4-Aminobenzoic acid	1.376(6)	114(4) 118(4) 119(4)	351		XD	96
2-Aminopyridine				31.6	XD	104
2-Aminopyridine	1.351(2)	117(2) 120(2) 121(2)	358	15	XD	105

TABLE 9. *continued*

Compound	C—N	$\widehat{HNH}$ $C\widehat{N}H$	Σ^b	ϕ^c	Method	Reference
2-Amino-3-nitropyridine	1.336(3)	122(2) 117(2) 120(2)	359		XD	109
2-Amino-4-methylpyridine	1.363(2)	124(2) 115(1) 118(1)	357		XD	110
2-Amino-5-methylpyridine	1.364(2)	114(3) 121(2) 118(2)	353		XD	111
2-Amino-5-chloropyridine	1.355(2)	121.1(2) 118(1) 120.4(1)	360		XD	112
2-Amino-5-chloropyridine	1.357(1)	121.1(2) 118.5(1) 120.4(1)	360		ND	113
3-Aminopyridine	1.384(4)	116(3) 114(2) 118(2)	348	32	XD	106
4-Aminopyridine	1.363(3)	116(3) 120(2) 119(2)	355	21	XD	107
2-Aminopyrimidine	1.342(2)	119(1) 121(1) 115(1)	355	22	XD	114
Aminopyrazine	1.341(1)	124(1) 119.1(8) 116.6(8)	360	6	XD	115

[a]Bond distances in Å and angles in degrees.
[b]Sum of the angles around the amino nitrogen.
[c]Angle between the planes of the amino group and the phenyl ring
[d]Value of the $H\widehat{N}H$ angle. For the other molecules the first value reported refers to the $H\widehat{N}H$ angle and the other two to the $C\widehat{N}H$ angles.

4.4°/0.01 Å. The other correlation, between the difference $(360° - \Sigma)$ and the C—N distance is shown in Figure 4.

The present results must be interpreted with due caution, owing to the uncertainty in bond angles involving hydrogen atoms. In fact, only in the case of 2-amino-5-chloropyridine, the structure of which has been determined from neutron diffraction (with e.s.d. = 0.1–0.2°), can an almost coplanarity of the two groups be accepted and a sp^2-hybridization suggested for nitrogen. If we take into account the fact that this coplanarity has been observed with a C—N bond length equal to 1.357(1) Å and assuming that in the present molecules the geometry is determined by the p-π conjugation and not by the hydrogen bonding, we must deduce that some of the dihedral angles reported in Figure 3 are overestimated.

On the basis of the results obtained for 2-amino-5-chloropyridine from neutron diffraction, it may be concluded that a trigonal (or quasi) hybridization might also be present for other compounds in Table 9, for example, 1,3,5-triamino-2,4,6-trinitrobenzene, 2,3,4,6-tetranitroaniline, 2-amino-3-nitropyridine and aminopyrazine.

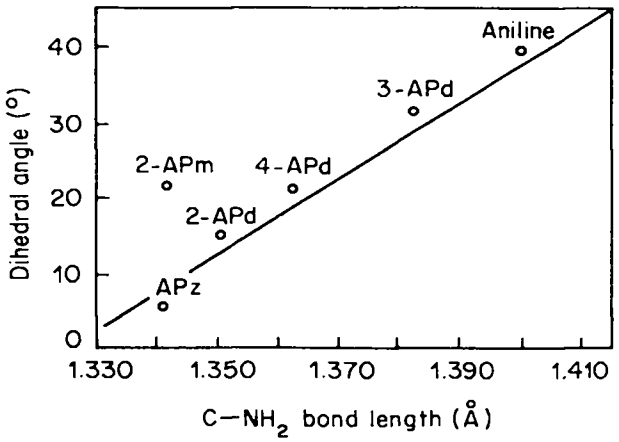


FIGURE 3. Correlation of the dihedral angle ϕ (between the phenyl and NH_2 planes) vs. the C—NH_2 bond distance. The least-squares straight line was fitted without including 2-APm (2-aminopyrimidine); APd = aminopyridine, APz = aminopyrazine. Reproduced with permission from M. Chao and E. Schempp, *Acta Cryst.*, **B33**, 1557 (1977).

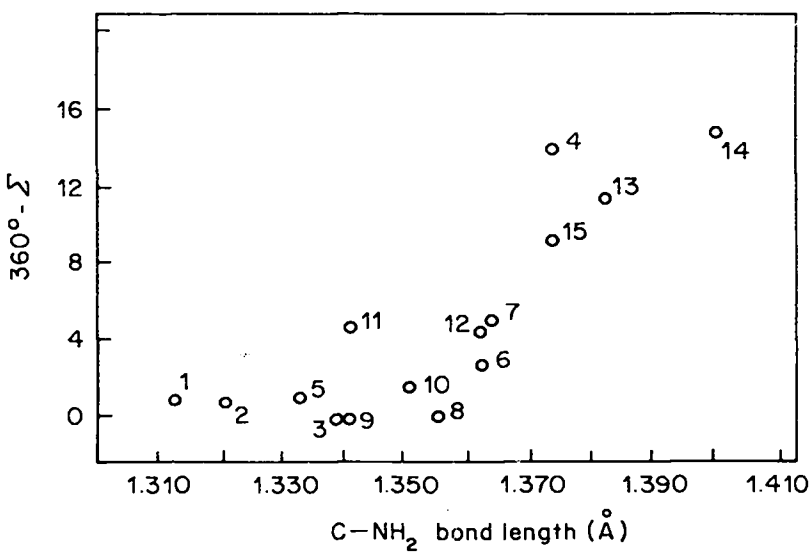


FIGURE 4. Correlation between the deviation from planarity of the amino group and the C—NH_2 bond length. Σ is the sum of the bond angles around the amino nitrogen. The estimated standard deviations have not been reported because of overlapping. The numbers indicate the following compounds: (1) 1,3,5-triamino-2,4,6-trinitrobenzene and 2,3,4,6-tetranitroaniline; (2) 1,3,5-triamino-2,4,6-trinitrobenzene; (3) 2,4,6-trinitroaniline; (4) 4-aminoacetophenone; (5) 2-amino-3-nitropyridine; (6) 2-amino-4-methylpyridine; (7) 2-amino-5-methylpyridine; (8) 2-amino-5-chloropyridine (from XD and ND); (9) aminopyrazine; (10) 2-aminopyridine; (11) 2-aminopyrimidine; (12) 4-aminopyridine; (13) 3-aminopyridine; (14) aniline; (15) 4-aminobenzoic acid.

A further question concerns the deformation of the phenyl ring with respect to both the bond lengths and angles. The problem is common to other groups and, consequently, will be treated at the end of the chapter.

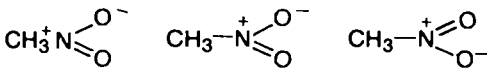
III. THE NITRO GROUP

A. Aliphatic Compounds

The structures of many compounds containing one or more nitro groups bonded to an aliphatic chain have been determined. Unfortunately, most of them are complex compounds or organometallics in which the function and, especially, the structural identity of the nitro group is probably modified and not rationalizable.

Conversely, very few structures are known of relatively simple molecules in which it is possible to isolate the rôle of the nitro group and the mutual influence between this group and other groups or atoms present in the same molecule.

The simplest aliphatic nitro compound is nitromethane (CH_3NO_2). Various nitromethane derivatives having a halogen and/or a nitro group in place of hydrogen have been studied (Table 10). The first comment to make after inspecting this table is that in nitromethane the C—N bond [1.489(5)–1.499(2) Å] is a little longer than the average value found for a single C—N bond (e.g. in aliphatic amines, the C—N bond length is about 1.470 Å). Consequently, these results do not provide evidence for contributions from extreme forms with a double bond between the carbon and nitrogen. Given this fact, in a valence bond description both the rather small O—N—O angle (125.3°) and the long N—O bond (1.224 Å) may be explained in terms of the presence of substantial contributions from forms of the type (**20**, I) in addition to (**20**, II and III). Recall the proviso that changes in structure parameters cannot be explained in terms of resonance alone.



II III

(**20**)

As regards the possible limiting structures participating in resonance in nitromethane, it is interesting that in this molecule the quadrupole coupling constants[158] may be explained by a valence bond description in which 'nitrite ion' type structures (**20**, I) contribute by ca. 20%.

The C—N bond length ranges from 1.494 Å (nitromethane) to 1.50 (fluoropicrin) and 1.59 (chloropicrin and bromopicrin). According to some authors[153,155], this difference in C—N distance together with the fact that the configuration of the nitro group is very similar to that in free NO_2, may be explained by some decomposition in halopicrins. Indeed, it is known that these molecules decompose very rapidly on heating. However, the fluctuations in the C—N distance do not appear to be mirrored in changes in N—O bond length, which are very small.

A further observation concerns the fact that the O—N—O angle is not constant along the series reported in Table 10. In compounds containing the NO_2 group, of the type RNO_2 (both organic and inorganic) a certain qualitative correlation was observed[150] between the electronegativity of the atom of R directly bonded to the nitrogen (Pauling scale) and this angle; increase in the former leads to an increase in the latter. In the light of the present results it is not unreasonable to suggest that

TABLE 10. Structural parameters for some aliphatic nitro compounds[a]

Compounds	C—N	N—O[b]	C—H	C—Hal	$O\hat{N}O$[b]	$H\hat{C}N$[b]	$Hal\hat{C}N$[b]	Reference
CH_3NO_2[c]	1.489(5)	1.224(5)	1.088[d]		125.3(5)	107.2(5)		150
CH_3NO_2	1.499(2)	1.225(1)	1.080(9)		125.0(2)	109.0(30)		151
$ClCH_2NO_2$	1.493(10)	1.230(2)	1.095[d]	1.765(9)	128(2)	111[d]	114(1)	152
CF_3NO_2	1.56(2)	1.21(1)		1.325(5)	132		109	153
CCl_3NO_2	1.59(3)	1.21		1.75(1)	127[e]			154
CCl_3NO_2	1.594(20)	1.190(2)		1.726(5)	131.7(27)		106.0(11)	155
CBr_3NO_2	1.59(2)	1.22(1)		1.920(7)	134		108.2	153
$CH(NO_2)_3$	1.505(5)	1.219(2)	1.13[d]		128.6(3)	108.6(6)		156
$CCl(NO_2)_3$	1.513(3)	1.213(1)		1.712(4)	128.3(5)		112.1(5)	153
$Cl(NO_2)_3$	1.44(6)	1.22(6)			122.5(15)		112.6(15)	157

[a]Bond distances in Å and angles in degrees. All dimensions have been determined from ED, except for CH_3NO_2[150] (MW) and $Cl(NO_2)_3$ (X-ray).
[b]Average.
[c]These parameters have been calculated from the MW spectrum obtained from the $m = 0$ levels, which is typical of an almost rigid asymmetric rotor.
[d]Assumed.
[e]Values calculated assuming CNO_2 coplanar.

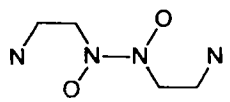
the overall electronegativity of the group R might be involved in this correlation, not only that of the atom bonded to the nitro nitrogen (which would also cover cases where R does not consist of a single atom). However it would be of interest to investigate this problem further.

Conformational aspects of these molecules are directly related to their electronic structures. The mononitro derivatives generally exhibit internal rotation about the C—N bond. In some polynitro derivatives listed in Table 10, this rotation is probably hindered by the interaction between the oxygen atoms of different nitro groups. For nitromethane, the height of this barrier is 6.03(3) kcal mol^{-1} (from microwave spectroscopy)[159,160], for chloropicrin 2.70–3.35 kcal mol^{-1} (from electron diffraction)[155], and for fluoropicrin 74.4(5) cal mol^{-1} (from microwave spectroscopy)[161].

The $-CNO_2$ group is not planar in halopicrins and the molecules adopt a staggered configuration, similar to that found in ethane derivatives (with one position vacant).

The structures of several salts are known (e.g. potassium trinitromethane and rubidium trinitromethane)[162] although not very accurately. The average C—N bond length is 1.40(4) Å and the N—O length 1.22 Å.

In the *trans* dimer of 2-nitronitrosoethane (**21**), obtained by reaction of ethylene



(**21**)

and N_2O_3 and identified by a three-dimensional X-ray data[163], the following values have been found for the nitro group: C—N 1.485(5) Å; $(N—O)_{av}$ 1.196(4) Å; O—N—O 123.2(4)°.

Finally from microwave spectroscopy it has been found that nitroethylene has a planar molecular structure[164–166] with C—N and C—O bond lengths, respectively, of 1.470 and 1.218 Å. The barrier to internal rotation about the C—N bond is 6.510 kcal mol^{-1} (infrared measurements). A value of 3.70(3) D for the dipole moment has been calculated from the Stark effect.

B. Aromatic Compounds

There are several aspects of the structure of aromatic nitro compounds which merit some attention. Among others, these are: (1) the structure of the nitro group and its dependence on the electronic properties of the other substituents in the aromatic ring; (2) the overall arrangement of the nitro group with respect to the benzene ring; (3) the changes undergone by the benzene ring on substitution of one or more hydrogen atoms by a nitro group.

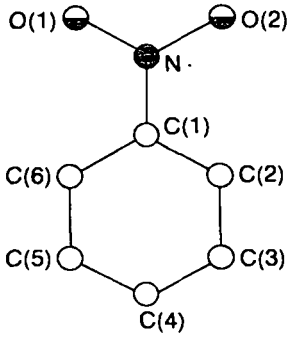
Directly related to these points is the question of the rôle played by resonance and hybridization in relation to the variations in bond lengths and angles as a function of electron-donor and electron-acceptor properties of the phenyl substituents.

1. Nitrobenzene

On the basis of the parameters obtained for the inertial defect[167,168] (microwave spectroscopy) some authors[169,170] have assigned a nonplanar structure to this molecule in the gas phase. More recently, others[171] have assigned a completely

planar geometry, again from microwave spectra, with a barrier to internal rotation of 2.85 ± 1.42 kcal mol^{-1}.

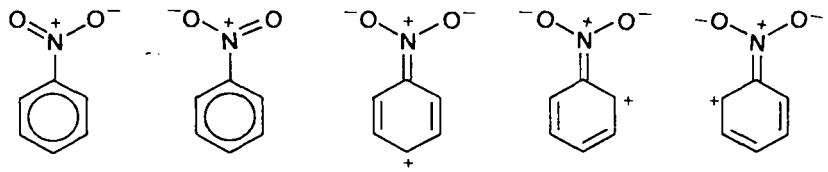
In the solid state at −30°C (X-rays, three-dimensional data, to $R = 0.169$)[172] the molecule is strictly planar, within the limits of experimental errors (**22**).



(**22**)

Uncorrected values			
C(1)—N	1.486(20) Å	C(1)—N—O	118°
$(N—O)_{av.}$	1.208(14) Å	O(1)—N—O(2)	124°
C(1)—C(2) C(6)—C(1)	1.367(14) Å	C(2)—C(1)—N C(6)—C(1)—C(2)	117° 125°
C(2)—C(3) C(5)—C(6)	1.426(14) Å	C(1)—C(2)—C(3) C(5)—C(6)—C(1)	116°
C(3)—C(4) C(4)—C(5)	1.363(14) Å	C(2)—C(3)—C(4) C(4)—C(5)—C(6)	121°
		C(3)—C(4)—C(5)	121°

At first sight, the structural results do not appear to be in agreement with the valence bond description of this molecule (**23**). In fact, if ionic structures participate



(**23**)

in some way in the resonance of the molecule, there should be a shortening of the C(2)—C(3) and C(5)—C(6) bond lengths and lengthening of the other four C—C bonds, as well as a decrease in the C—N bond compared with that in nitroalkanes (1.490 Å). Actually, there is virtually no variation in the latter and for the C—C bonds the variations (which are significant, on the basis of the standard deviations) go in the opposite sense to that expected if there were ionic structures contributing significantly to the resonance in nitrobenzene. This leads us to the conclusion that, in this case at least, resonance alone is unable to account for changes in bond lengths and angles and that other causes must be looked into.

The suggestion has been made[173] that the greater effect in operation is a change in hybridization of the carbon σ-orbitals, i.e. in a different contribution of the p- and s-orbitals compared to that in benzene. In the present case this would mean a decrease in p-contribution and increase in s-orbital contribution. This would also explain, qualitatively at least, the fact that the angles formed by the bonds shorter than those in benzene (1.392 Å) are also greater than 120° in nitrobenzene.

The problem regarding the bond-length distribution within the phenyl ring and the influence of the nature of the substituents on its geometry will be discussed after we have examined the structure of the groups.

Nitrobenzene has a dipole moment of 3.96[174] and 4.04[175] D (in benzene, at 25°C, assuming the atomic polarization to be zero). This is higher than that of nitromethane in the same conditions (3.12[176] and 3.45[177] D). This fact might suggest that there are contributions from ionic forms, although on the basis of the structural results, other factors (polarizability, induced moment, different

hybridization of the carbon atom bonded to the nitro group) must also be taken into account.

In terms of the structure, a comparison may be made between the bond lengths of nitrobenzene and those of nitromesitylene (XD, $R = 0.172$)[178] and *p*-nitrotoluene (XD, $R = 0.107$)[179].

The following values have been obtained, respectively, for these three molecules, in that order: C(1)—N 1.486(20), 1.476(17) and 1.482(7) Å; $(N—O)_{av}$ 1.208(14), 1.216(15) and 1.213(7) Å; C(1)—C(2) and C(6)—C(1) 1.367(8), 1.365(18) and 1.379(7) Å; C(2)—C(3) and C(5)—C(6) 1.426(18), 1.414(18) and 1.383(8) Å; C(3)—C(4) and C(4)—C(5) 1.363(14), 1.365(18) and 1.369(8) Å. From these values it may be inferred that the molecules are very similar in their electronic effects. This is not the case with regard to the angles, which are quite different. In addition, the nitro group is coplanar with the phenyl in nitrobenzene and is rotated by 66° (about the C—N bond) with respect to this plane in nitromesitylene.

2. *Mononitrobenzene derivatives*

This section aims to elucidate the mutual influence exerted on the nitro group by other ring substituents.

Table 11 lists the structural parameters for the nitro group in several nitrobenzenes. From this table it can be seen that nitrobenzene gives the longest C—N bond [1.486(20) Å]. In agreement with prediction, this bond lies in a small range [1.466(9)–1.480(7) Å] in all derivatives with electron-attracting substituents in the ring whatever their position.

Conversely, for derivatives with electron-donor substituents, there appears to be a shortening of the C—N bond length which, in valence bond terms, suggests that there is a major contribution by extreme ionic forms (**23**) compared to the nitrobenzene. Nevertheless, taking into account that in *p*-nitroaniline the C—NH_2 bond is 0.049 Å shorter than that in aniline and that the C—NO_2 bond is 0.012 Å shorter than that in nitrobenzene, it may be concluded that resonance alone is not sufficient to describe these variations.

The behaviour of *m*-nitroaniline [C—NO_2 bond length 1.440(16) Å] is unusual when compared to that of *N,N*-dimethylaniline [C—NO_2 1.492(11) Å], *p*-nitroaniline [C—NO_2 1.460(7) Å] and nitrophenols.

Also the comparison between the C—N bond lengths in *N,N*-dimethyl-*p*-nitroaniline [C—NO_2 1.405(16) Å] and *p*-nitroaniline [1.460(7) Å] indicates that very probably the value observed for the former is lower than that expected. This might be due to the fact that the parameters for the dimethyl derivative are less accurate. Unfortunately, on the basis of the estimated standard deviations most of the bond length variations in the six-membered ring of this molecule cannot really be significant. Further, the uncorrected C—NH_2 bond lengths are almost identical (1.353 and 1.358 Å, respectively, in *p*-nitroaniline and in its *N,N*-dimethyl derivative).

The behaviour of the average N—O bond lengths appears to be similar to that of the C—N bond; all are a little higher than that observed for nitrobenzene and lie in a restricted and significant small range. This is shown in the following (corrected) values for the N—O bond length: *p*-nitroaniline, 1.246(7) Å; *N,N*-dimethyl-*p*-nitroaniline, 1.249(19); *p*-nitrophenol (β-modification), 1.242(3); *p*-nitrotoluene, 1.243(7); *o*-nitrobenzaldehyde, 1.245(2); *m*-nitrobenzoic acid, 1.240(8); *p*-nitrobenzoic acid, 1.238(6).

Table 11 indicates that the O—N—O angle has a tendency to increase passing from nitro derivatives with electron-donor substituents to those with electron

TABLE 11. Structural parameters of the nitro group in some mononitrobenzenes[a]

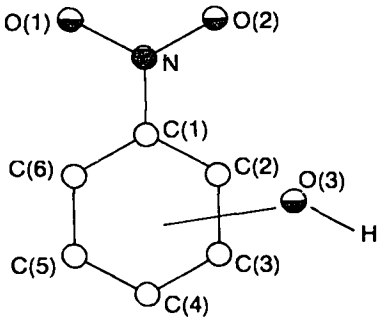
Compound	C—N	N—O[b]	$\widehat{ONO}$	ϕ[c]	Reference
N,N-Dimethyl-*p*-nitroaniline	1.400(16)	1.231(19)	121.4(12)	2.8	126
	1.405(16)[d]	1.249(19)[d]			
p-Nitroaniline	1.458(7)	1.228(7)	123.3(4)	1.9	79
	1.460(7)[d]	1.246(7)[d]			
o-Nitroaniline[e] (γ-modification)	1.490(20)	1.220(18)	125.7(14)		180
	1.429(19)	1.235(18)	120.6(12)		
N,N-Dimethyl-*m*-nitroaniline	1.492(11)	1.241(9)	122.3(7)	10	125
m-Nitroaniline	1.440(16)	1.227(10)	120.5(10)	2	77
p-Methyl-*m*-nitro-*N*-methylaniline	1.474(6)	1.216(5)	122.0(4)	3.1	127
p-Bromo-*m*-nitro-*N*-methylaniline	1.437(15)	1.131(22)	115.5(15)	13	127
p-Nitrophenol (α-modification)	1.442(6)	1.234(6)	122.0(4)	1.3	181
p-Nitrophenol (β-modification)	1.446(6)	1.226(3)	122.0	7.9	182
	1.450(6)[d]	1.242(3)[d]			
o-Nitrophenol	1.456(7)	1.219(7)	123.6(5)	1.6	183
	1.464(7)[d]	1.223(7)[d]			
m-Nitrophenol[f]	1.480(3)	1.216(3)	123.7(2)	0.6	184
	1.474(2)	1.217(2)	123.2(1)	0.5	
m-Nitro-*p*-chlorophenol	1.442(7)	1.220(6)	122.0(5)	0.4	185
o-Chloro-*p*-nitroaniline	1.466(13)	1.235(13)	123.0(1)	4.3	84
	1.471(13)[d]	1.240(13)[d]			
Nitromesitylene	1.476(17)	1.216(15)	117	66.4	178
p-Nitrotoluene	1.477(7)	1.214(7)	122.8(4)	3	179
	1.482(7)[d]	1.243(7)[d]			
Nitrobenzene	1.486(20)	1.208(14)	124	0	172
p-Nitrobiphenyl	1.465(5)	1.216(5)	122.7(3)	2	186
o-Nitrobenzaldehyde	1.468(8)	1.230(8)	125.0(6)	27.5	187
o-Nitrobenzaldehyde[g]	1.474(2)[d]	1.245(2)[d]	125.0(2)		188
p-Nitroacetophenone	1.466(4)	1.219(4)	123.3(3)	3.6	189
m-Nitrobenzoic acid[e]	1.470(8)	1.226(8)	123.4(5)	21.7	190
	1.474(8)[d]	1.241(8)[d]			
	1.476(8)	1.218(8)	124.0(6)	5.3	
	1.485(8)[d]	1.238(8)[d]			
o-Nitrobenzoic acid	1.466(9)	1.219(8)	123.6(6)	54.7	191
o-Nitrobenzoic acid	1.478(13)	1.209(13)	124.3(9)	54.3	192
p-Nitrobenzoic acid	1.480(7)	1.216(6)	124.1(14)	13.7	193
p-Nitrobenzoic acid	1.479(6)	1.222(6)	124.2(4)	13.8	194
	1.485(6)[d]	1.238(6)[d]			
p-Nitrobenzoic acid	1.476(2)	1.221(2)	124.2(1)	13.7	195
o-Nitroperoxybenzoic acid	1.478(7)	1.225(7)	124.8(5)	28	196
p-Nitrobenzonitrile	1.483(10)	1.214(10)	123.8(10)	10.3	197

[a]Bond lengths in Å and angles in degrees.
[b]Average.
[c]Dihedral angle between the planes of the nitro group and phenyl ring.
[d]Corrected.
[e]The asymmetric unit in the structure consists of two crystallographically independent molecules.
[f]Two sets of intensities were collected for crystals grown respectively from melt and from benzene.
[g]From neutron diffraction.

acceptors. We shall return to the meaning of the O—N—O angle in our conclusions as well as to the possible relation between the C—N distance and the angle by which the plane of the nitro group is rotated with respect to the phenyl ring.

Below are reported some comparable structures. The structural parameters of some nitroanilines have been listed above (Section II.C.2.b).

(i) Nitrophenols (**24**). The structure of these compounds has been determined from X-ray measurements ($R = 0.071$ for *o*-nitrophenol[183], 0.083 for the α-modification of *p*-nitrophenol[181], 0.069 for the β-modification of *p*-nitrophenol[182], and 0.036 for *m*-nitrophenol[184]). For the last molecule two refinements were carried out on data collected with two different crystals, from benzene (reported here) and from melt ($R = 0.041$).



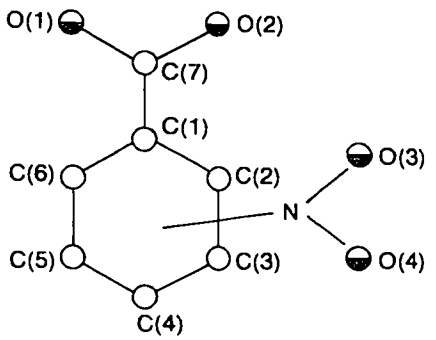
(**24**)

o-NP = *o*-nitrophenol (corrected)[183]
α-*p*-NP = α-*p*-nitrophenol (uncorrected)[181]
β-*p*-NP = β-*p*-nitrophenol (corrected)[182]
m-NP = *m*-nitrophenol (corrected)[184]

	o-NP	α-*p*-NP	β-*p*-NP	*m*-NP
C(1)—N (Å)	1.464(7)	1.442(6)	1.450(3)	1.474(2)
N—O(1) (Å)	1.240(6)	1.232(6)	1.243(5)	1.223(3)
N—O(2) (Å)	1.207(7)	1.236(6)	1.241(5)	1.209(3)
C—O(3) (Å)	1.343(7)	1.351(6)	1.361(3)	1.366(3)
C(1)—C(2) (Å)	1.408(7)	1.388(6)	1.394(3)	1.390(3)
C(2)—C(3) (Å)	1.389(8)	1.377(6)	1.378(3)	1.375(3)
C(3)—C(4) (Å)	1.360(9)	1.387(6)	1.399(3)	1.381(3)
C(4)—C(5) (Å)	1.380(9)	1.393(6)	1.396(3)	1.382(3)
C(5)—C(6) (Å)	1.370(9)	1.380(6)	1.382(3)	1.366(3)
C(6)—C(1) (Å)	1.400(8)	1.383(6)	1.393(3)	1.377(3)
C(1)—N—O(1) (°)	117.7(4)	119.3(4)	119.1	117.4(2)
O(1)—N—O(2) (°)	123.6(5)	122.0(4)	122.8	123.7(2)
C(1)—N—O(2) (°)	118.8(5)	118.8(4)	118.6	119.0(2)
C(6)—C(1)—C(2) (°)	120.7(5)	122.3(4)	122.0	117.7(2)
C(1)—C(2)—C(3) (°)	117.7(5)	118.6(4)	118.8	119.8(2)
C(2)—C(3)—C(4) (°)	120.8(6)	121.1(4)	120.0	120.8(2)
C(3)—C(4)—C(5) (°)	121.8(6)	120.9(4)	120.5	120.3(2)
C(4)—C(5)—C(6) (°)	119.1(6)	119.4(4)	120.0	117.7(2)
C(5)—C(6)—C(1) (°)	119.9(4)	118.9(4)	118.7	123.7(2)
C′—C—O(3) (°)	124.6(5)	122.4(4)	123.0	124.1(2)
C″—C—O(3) (°)	117.6(5)	116.8(4)	116.5	116.1(2)

As regards the structure of the nitro group the present results are consistent. For *o*- and *p*-nitrophenols contributions from quinonoid resonance structures may not be suggested from a comparison between the values of some bond distances (C—N and C—C) observed for these two molecules and those for the *meta* isomer.

(ii) Nitrobenzoic acids (NBA) (**25**). The structures of *o*-[192], *m*-[190], and *p*-nitrobenzoic[195] acids have been determined (*R* is 0.104, 0.118 and 0.040, respectively), with very accurate results only for the last molecule. The structural parameters reported are not corrected for thermal motion.



(25)

	o-NBA	*p*-NBA	*m*-NBA
C—N (Å)	1.478(13)	1.476(2)	1.470(8)
N—O(3) (Å)	1.221(13)	1.224(2)	1.237(7)
N—O(4) (Å)	1.198(13)	1.219(2)	1.216(8)
C(1)—C(7) (Å)	1.501(13)	1.486(2)	1.494(9)
C(7)—O(1) (Å)	1.290(13)	1.302(2)	1.282(8)
C(7)—O(2) (Å)	1.225(13)	1.234(2)	1.251(7)
C(1)—C(2) (Å)	1.390(13)	1.394(2)	1.384(9)
C(2)—C(3) (Å)	1.375(13)	1.387(2)	1.387(9)
C(3)—C(4) (Å)	1.370(13)	1.380(2)	1.380(9)
C(4)—C(5) (Å)	1.356(13)	1.379(2)	1.381(10)
C(5)—C(6) (Å)	1.417(13)	1.390(2)	1.403(9)
C(6)—C(1) (Å)	1.367(13)	1.391(2)	1.394(9)
C—N—O(3) (Å)	118.7(9)	118.3(1)	118.8(5)
C—N—O(4) (Å)	116.9(9)	117.5(1)	117.7(5)
O(3)—N—O(4) (°)	124.3(9)	124.2(1)	123.4(5)
C(1)—C(7)—O(1) (°)	116.2(9)	115.6(1)	115.7(5)
C(1)—C(7)—O(2) (°)	121.9(9)	121.3(1)	120.4(5)
C(6)—C(1)—C(7) (°)	118.7(9)	118.8(1)	120.8(6)
C(6)—C(1)—C(2) (°)	116.2(9)	120.4(1)	120.3(6)
C(1)—C(2)—C(3) (°)	123.7(9)	120.2(1)	117.8(6)
C(2)—C(3)—C(4) (°)	118.4(9)	117.9(1)	123.4(6)
C(3)—C(4)—C(5) (°)	120.6(9)	123.3(1)	118.3(6)
C(4)—C(5)—C(6) (°)	119.8(9)	118.2(1)	119.9(6)
C(6)—C(5)—C(1) (°)	121.2(9)	119.8(1)	120.2(6)

The structure of *m*-nitrobenzoic acid consists of dimeric units, with two crystallographically independent molecules. The maximum difference between the observed lengths of the equivalent bonds (not involving hydrogen atoms) in these two molecules is 0.011 Å (average scatter 0.004 Å).

A comparison of the molecular dimensions of these three isomers indicates that the structures are similar, especially as regards the nitro groups. Also for the N—O bond length is there no significant difference between the *ortho* and the other two

isomers. The angle between the phenyl ring and the plane of the nitro group is 54.3, 13.7 and 21.7° (5.3 in the other molecule in the dimeric unit), respectively, in *o*-, *p*-, and *m*-nitrobenzoic acid in which, however, the C—N bond length is 1.478(13), 1.476(2) and 1.470(8) Å [1.476(8)], in that order.

3. Polynitrobenzenes

In Table 12 are reported structural parameters to give the reader an orientative immediate idea of the behaviour of nitro group in these molecules. Of course, these results must be interpreted with caution, taking into account both the type of compound and the possible interactions between the nitro group and other phenyl substituents.

In spite of these limitations, two comments may be made. Firstly, in the presence of electron-withdrawing group the C—N bond distance is the same as that observed in mononitrobenzenes (1.470–1.485 Å), while in the presence of electron donors there is a tendency to shortening of the C—N bond length. This may be seen from the following examples: 1,3,5-trinitrobenzene, 1.479(7) Å; 2,4,6-trinitroaniline, 1.468(6) Å; 2,3,4,6-tetranitroaniline, 1.465(7) Å; 1,3,5-triamino-2,4,6-trinitrobenzene, 1.419(7) Å; 2,4-dinitrophenol, 1.445(7) and 1.461(7) Å. Secondly, a rough relation might be obtained between the N—O and C—N bond lengths.

The case of 1,3,5-triamino-2,4,6-trinitrobenzene is interesting when compared to nitrobenzene. In fact we have for the C—N bond length 1.418(5) vs. 1.486(20) Å, and for the N—O distance 1.243(5) vs. 1.203(14) Å, respectively, in this molecule and in nitrobenzene.

The structures of other interesting polynitrobenzenes have been determined, the results of which are not necessary to our treatment, for example, 1,3-diamino-2,4,6-trinitrobenzene[81], 1,3-dichloro-2,4,6-trinitrobenzene[211], 2,4,6-trinitrodiphenylamine[212], hexanitrobenzene[213], *m*-dinitrobenzene[214], *p*-dinitrobenzene[214], 2-(2′,4′-dinitrobenzyl)pyridine[215], ethyl 2,4-dinitrobenzoate[216], 2,4-dinitrophenol[217] and 9:10-dinitroanthracene[218]. The results obtained for the last molecule are to be compared with those for 9-nitroanthracene[219]. (For polynitroanilines see also Section II.C.2.b.)

C. Conclusions

Drawing a comparison between the values reported in Tables 10 and 11, it may be seen that the dimensions of the nitro group in aromatic derivatives are close to those in aliphatic ones, within the limits of experimental error. On the contrary, there is a significant difference between the C—NH_2 distance in aliphatic compounds and aromatic ones. This indicates that the conjugation between the nitro group and the phenyl ring is very small, if present.

Unfortunately, the dimensions of nitromethane and nitrobenzene refer to different states of matter (gas and solid, respectively) and have been obtained by two different techniques. In addition, the uncertainty in the nitrobenzene structural parameters is high (0.014–0.020 Å) and very probably of the same order as the difference one would expect to observe between aliphatic and aromatic nitro compounds. However, it is noteworthy that in molecules very similar to nitrobenzene, i.e. in nitromesitylene and *p*-nitrotoluene, the C—N bond distance does not change significantly [1.476(17) and 1.482(7) Å (corrected), respectively] compared to nitromethane and nitrobenzene [1.495(5) and 1.482(20) Å, respectively].

For aromatic nitro compounds many results are available that allow some

TABLE 12. Structural parameters of the nitro group in some polynitrobenzenes[a]

Compound	C—N	N—O[b]	$\widehat{ONO}$	ϕ[c]	Reference
1,3,5-Triamino-2,4,6-trinitrobenzene	1.421(7)	1.238(6)	118.1(4)	3.7	80
	1.419(7)	1.243(6)	117.9(4)	3.3	
	1.425(7)	1.246(6)	117.7(4)	1.6	
2,4,6-Trinitroaniline	1.474(6)	1.218(6)	123.9(4)	22.5	82
	1.468(6)	1.223(6)	124.5(4)	4.0	
	1.462(6)	1.217(6)	122.2(4)	8.5	
2,4-Dinitrophenol	1.445(7)	1.215(7)	122.7(5)	2.2	198
	1.461(7)	1.214(7)	123.1(5)	4.9	
2,6-Dinitrophenol	1.476(9)[d]	1.218(9)[d]	123.4(6)	13.1	199
	1.461(9)[d]	1.228(9)[d]	122.4(6)	2.7	
2-Chloro-4,6-dinitrophenol	1.472(7)	1.215(7)	124.0(4)	4.0	200
	1.464(7)	1.216(7)	123.4(4)	5.0	
2-Bromo-4,6-dinitrophenol	1.478(6)	1.211(7)	124.0(5)	5.0	201
	1.451(7)	1.224(7)	122.3(6)	9.4	
Picric acid[e]	1.455(7)	1.214(7)	122.4(5)	7.4	202
	1.455(9)	1.215(5)	123.8(6)	0.6	
	1.477(6)	1.192(9)	120.8(6)	17.2	
2,4,6-Trinitrophenetole	1.462(8)	1.220(10)	123.6(7)	31.8	203
	1.467(8)	1.219(10)	124.4(7)	3.8	
	1.479(8)	1.200(10)	123.9(7)	61.3	
Picryl chloride	1.468(5)	1.178(6)	122.9	33	204
	1.471(4)	1.211(5)	124.4	13	
	1.478(6)	1.204(4)	125.0	81	
2,3,4,6-Tetranitroaniline	1.467(7)	1.218(7)	124.0(4)	45	83
	1.487(7)	1.209(7)	128.0(4)	64	
	1.447(7)	1.224(7)	124.0(4)	19	
	1.461(7)	1.218(7)	123.0(4)	3	
2,4,6-Trinitro-*m*-xylene	1.475(4)	1.221(4)	125.1(3)	35.7	205
	1.480(4)	1.212(4)	125.2(3)	75.2	

TABLE 12. *continued*

Compound	C—N	N—O[b]	$\widehat{ONO}$	ϕ[c]	Reference
1,3-Dinitrobenzene	1.493(6)[b]	1.248(6)	125.8(4)	13	206
1,3,5-Trinitrobenzene[f]	1.493(7)	1.226(10)	127.1(7)	3	207
	1.475(7)	1.198(9)	124.7(7)	28	
	1.471(6)	1.199(8)	125.4(7)	8	
	1.480(6)	1.215(7)	124.1(6)	10	
	1.500(7)	1.209(9)	127.1(7)	10	
	1.442(7)	1.197(10)	121.9(8)	5	
3,5-Dinitro-4-methylbenzoic acid	1.471(9)	1.222(9)	124.2(6)	47.5	208
	1.491(8)	1.229(9)	125.1(6)	38.9	
3,5-Dinitropyridine	1.468(3)	1.216(4)	124.7(2)	7	209
2,2′,4,4′,6,6′-Hexanitroazobenzene (form I)[g]	1.482(5)	1.215(5)	125(0.4)	50	210
	1.472(5)	1.229(5)	125(0.6)	15	
	1.487(5)	1.219(5)	125(0.4)	39	
2,2′,4,4′,6,6′-Hexanitroazobenzene (form II)	1.481(5)	1.214(5)	125(0.4)	29	
	1.483(5)	1.213(5)	126(0.4)	1	
	1.481(5)	1.198(5)	125(0.4)	86	
	1.482(5)	1.208(5)	126(0.4)	53	
	1.490(5)	1.217(5)	126(0.4)	22	
	1.473(5)	1.219(5)	126(0.4)	37	

[a]Bond lengths in Å and angles in degrees.
[b]Average.
[c]Angle between the planes of the nitro and phenyl groups.
[d]Corrected. The uncorrected values are very close to the corrected ones.
[e]There are two crystallographically independent molecules in the asymmetric unit. There are no significant differences in bond lengths and angles between the two molecules.
[f]From neutron diffraction. There are two crystallographically independent molecules in an asymmetric unit.
[g]For form I only these values have been reported.

structural aspects to be examined thoroughly. In connection with this, several attempts have been made to determine possible relationships between various parameters of the nitro group, in order to draw conclusions as to its electronic structure.

These relationships are: (*i*) between N—O and C—N bond lengths[220]; (*ii*) between the O—N—O angle and the C—N distance[221]; (*iii*) between the dihedral angle ϕ (formed by the nitro group and phenyl planes) and the C—N bond length[185]. We shall attempt to examine each of these separately.

(i) Correlation between N—O and C—N bond lengths. From Tables 11 and 12 we have chosen the bond distances (17 nitro groups) corrected for thermal motion and with an accuracy equal or better than 0.008 Å. The least-squares plot of the N—O vs. C—N distances by means of a computer gave a correlation coefficient of −0.4. Even if this plot compares favourably with that found previously[220] using different aromatic nitro compounds, still no valid conclusions can be drawn and the qualitative evidence needs further research.

(ii) Correlation between the O—N—O angle and the C—N distance. From the values of Tables 11 and 12 (53 nitro groups with an accuracy equal or better than 0.007 Å in the bond distances and 0.6° in angles), we have calculated by means of the least-squares method a slope of 101.9° Å and a correlation coefficient of 0.88 for the plot of the O—N—O angle vs. the C—N distance. This result is in agreement with that obtained previously[221] and may in part be explained on the basis of a hard-sphere model in which, as a result of intramolecular repulsion, the atomic positions are governed by the size of spherical atoms packed around a given atom[222].

(iii) Correlation between the dihedral angle ϕ and the C—N bond length. In a study[185] of the dihedral angle ϕ (by which the nitro group plane is rotated with respect to the phenyl plane about the C—N bond) of 68 nitro groups in nitrobenzenes against the C—N distance, no remarkable increase was found in this angle at bond distances smaller than 1.467 Å, which is close to the $C(sp^2)$—$N(sp^2)$ bond length of 0% double-bond character[223]. We have examined this correlation using some values from Tables 11 and 12 (30 nitro groups having a C—N bond length greater than (or equal to) 1.470 Å and an e.s.d. of 0.007 Å and have found no correlation between these two parameters.

IV. THE NITROSO GROUP

C-Nitroso compounds make up a class of substances which are very interesting from a theoretical point of view. Unfortunately, due to the facility by which these molecules dimerize (especially the aliphatic ones), only a few structures have been reported for the monomeric forms. In addition, the results obtained regarding the parent molecules are sometimes uncertain and do not allow information on the electronic structure to be extracted from them.

It is desirable that several of these structures be redetermined because low-temperature equipment, more intense sources and much computer time are now available.

A. Monomeric Compounds

Table 13 lists the structural parameters of the nitroso group in some monomeric *C*-nitroso compounds.

From this table, except for trifluoronitrosomethane, a sharp difference is obvious between the alkyl and aryl nitroso compounds both in bond distances and angles.

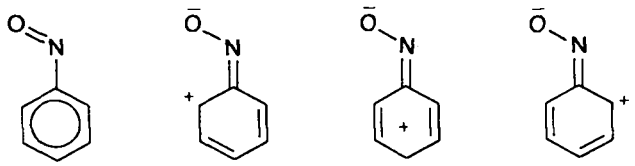
TABLE 13. Structural parameters of the nitroso group in some monomeric *C*-nitroso compounds[a]

Compound	C—N	N—O	$\widehat{CNO}$	Reference
Nitrosomethane	1.49	1.22	112.6	224
Nitrosomethane	1.480	1.213	113.2	225
Trifluoronitrosomethane	1.555	1.171	124	226
(+)-10-Bromo-2-chloro-2-nitrosocamphane[b]	1.48	1.19	118	227
Nitrosobenzene[c]	1.44	1.24	118	228
	1.47	1.21	116	
	1.51	1.17	114	
4-Iodonitrosobenzene	1.28	1.24	125	229
N,N-Dimethyl-4-nitrosoaniline[d]	1.445		116.4	133
	1.390		126.2	
N,N-Diethyl-4-nitrosoaniline[e]	1.38(1)	1.27(1)	112.6(6)	134
	1.435(19)	1.221(14)		
N,N,N',N'-Tetramethyl-1,5-diamino-4-nitrosobenzene	1.373(2)	1.277(2)	116(1)	132

[a]Bond lengths in Å and angles in degrees.
[b]The two crystallographically independent molecules appear to be identical chemically.
[c]These three sets of values have been obtained assuming the following N—O distances in this order: 1.24, 1.21 and 1.17 Å.
[d]Owing to the disorder observed in crystals, two structural refinements were carried out with crystals grown in different ways.
[e]Two molecules have been observed which are slightly different as to the conformation in the diethylamino groups. Slight disorder in the nitroso group allows only mean values for N—O bond lengths to be reported.

The C—N bond length is greater in the former, whilst the N—O distance is greater in the latter. At the same time, the angle C—N—O increases from the aliphatic to the aromatic compounds.

This evidence suggests the presence of conjugation between the nitroso group and the phenyl ring; the greater this delocalization the greater the C—N—O angle, according to the extreme forms **26**. Electric dipole moment measurements seem to be in agreement with this.



(26)

The presence of π–p delocalization between the phenyl ring and the nitroso group may be demonstrated by the dimensions found for *N,N*-dimethyl- and *N,N*-diethyl-4-nitrosoaniline compared to those obtained for dialkylaniline and nitrosobenzene. In fact, there is a decrease in the C—N(amino) bond length going from alkylanilines to their *p*-nitroso derivatives and a decrease in C—NO bond length from nitrosobenzene to its *p*-dialkylamino derivatives. In agreement with this evidence, the C—C bond distances support the presence of a significant contribution from extreme quinonoid forms. The following average values have been found for *N,N*-dimethyl- and *N,N*-diethyl-4-nitrosoanilines C(1)—C(2), 1.393(10) and 1.422(5) Å; C(2)—C(3), 1.348(10) and 1.375(5) Å; C(3)—C(4), 1.414(10) and 1.390(5) Å.

The behaviour of trifluoronitrosomethane is also quite interesting. In this molecule the C—N bond length is significantly greater than in nitrosomethane (1.555 and 1.49 Å, respectively) and the N—O bond length is smaller (1.17 vs. 1.22 Å). Considering this evidence and the fact that the observed dipole moment is much lower than the value predicted by addition of the bond moments, it has been suggested that contributions from an extreme ionic form $(N{=}O)^+CF_3^-$ must be present. Such behaviour has also been observed in halopicrins (Hal_3CNO_2) and explained in the same manner.

B. Dimeric Compounds

These compounds have been reviewed in a previous volume[230] of this series, which reports results till 1974. Since then no other relevant structural data have been published on these substances.

V. RING DEFORMATIONS

In the sections above, the few structures reported in full show that substitution of a hydrogen atom in benzene by a functional group or a different atom causes a modification of both the ring bond lengths and angles.

As regards the present groups, the angle having C—NH_2 as vertex is always smaller than 120°, whereas the corresponding angles with C—NO_2 and C—NO are greater than 120°. We have also seen that in aromatic amines there is a correlation between the C—N bond distance and the value of the adjacent C—C bond lengths in the phenyl.

In general the effect of the substituents on the geometry of the phenyl ring has been recognized by various authors[231] and explored accurately[231–233]. In the case of the C—C bond lengths of the phenyl ring in almost all the molecules examined up until now a rationalization cannot be made because accurate structure determinations are lacking due to thermal motion. In addition, for some molecules these variations in bond length are too small to be structurally significant when compared to those in benzene.

Conversely, for endocyclic angles accurate values are available which allow a study of the ring modifications to be made. This is interesting because it may be useful for an approach to the problem already mentioned in connection with the discussion of aniline and nitrobenzene structures. In particular we have noticed that very often bond distances and angles when compared to those in benzene cannot be explained purely on the basis of an electron delocalization between the phenyl ring and the substituent.

Various interpretations of the ring deformations have been made. They are based on: (1) the intramolecular nonbonded interactions[222,234,235]; (2) the coulombic interaction between formally charged atoms[231]; (3) the hybridization effects at the carbon atom to which the substituent is bonded[236,237]; (4) the valence-shell electron-pair repulsions[238–243]. The experimental results in general seem to be better explained on the basis of either of the two latter interpretations. Geminal intramolecular interactions may also contribute to the ring deformations to a lesser degree. The direction of the deformations depends on the nature of the phenyl substituents.

The overall deformation of the phenyl ring due to the presence of an electron-attracting substituent consists of: (1) a shortening of the adjacent C—C bonds; (2) an increase in the endocyclic bond angle opposite to the functional group; (3) a minor decrease in the two adjacent endocyclic angles. Generally the other structural parameters of the phenyl ring are not significantly influenced. The opposite occurs with electron-donor substituents.

The presence of a second substituent in the phenyl ring does not cause a substantial deformation of the opposite part of the phenyl ring as long as the electronic characteristics of the substituents do not change with respect to the monosubstituted derivatives.

In the presence of *ortho* and *meta* derivatives the situation is not rationalizable because the various effects overlap each other.

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CHAPTER **2**

Stereochemistry and conformations

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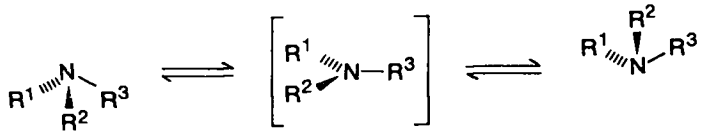
I. STEREOCHEMISTRY AT TRIVALENT NITROGEN

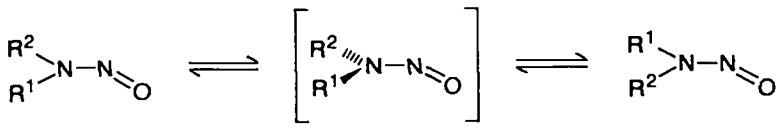
The stereochemistry of trivalent nitrogen compounds differs very considerably from the stereochemistry of carbon compounds since the configurational units associated with nitrogen are usually stereolabile in contrast to the stereostability of the asymmetric carbon atom and the configurational unit associated with the carbon–carbon double bond. As a consequence, stereochemistry of carbon compounds focuses on configurational assignments and stereomutation is generally associated with the making and breaking of bonds (mainly σ-bonds). On the other hand, the stereochemistry of trivalent nitrogen focuses on restrictions to geometry changes. These geometry changes can conveniently be grouped into two categories: (*A*) changes in bond angles and (*B*) changes in dihedral or torsion angles. The former category includes inversion of the nitrogen pyramid in amines (**1a** ⇌ **1c**) which requires a change in the RNR bond angle from ca. 109° (in the ground state) to ca. 120° (in the transition state **1b**), as well as the inversion mechanism for



(1a) (1b) (1c)

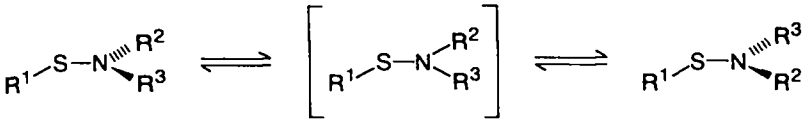
stereomutation of imines[1] (in-plane shift) in which the C=N—R angle must change from ca. 120° to 180°.

The latter category can be further subdivided into (*Bd*) those cases in which slow torsion about double bonds (or partial double bonds) leads to *E–Z* (*cis–trans* or *syn–anti*) isomerism or topomerism (*vide infra*) and (*Bs*) those cases in which slow torsion about formal single bonds gives rise to chirality. Class *Bd* includes the very extensively studied amides[2], many of which have relatively high barriers to torsion about the C—N partial double bond, in some cases high enough to permit the isolation of *syn* and *anti* isomers[3]. This class also includes a number of nitroso derivatives such as the nitrosamines **2** which can exist in *E* and *Z* configurations (**2a** and **2c**) and which can interconvert by torsion about the N—N partial double bond.



(2a) (2b) (2c)

Category *Bs* includes a number of systems in which trivalent nitrogen is bonded to a heteroatom (including N, O, S or P) which bears a lone pair of electrons. Typical of this class are the sulphenamides which exist in a chiral conformation and can interconvert with their enantiomers (**3a** ⇌ **3c**) by torsion about the S—N formal single bond via a transition state which is achiral (**3b**).



(3a) (3b) (3c)

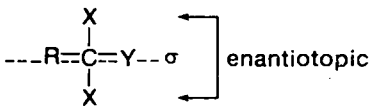
There is overlap between categories *A* and *Bs* for two reasons. In both cases we deal with restrictions to conformation change that result in chirality. Also, the presence of heteroatoms bonded to nitrogen could lead to enhanced barriers to nitrogen inversion as well as torsional barriers. Consequently, distinguishing between these two categories experimentally can present problems. In addition to these three categories we shall also consider the much lower barriers which result in conformational restrictions in simple systems and cases in which steric bulk can hinder conformational changes.

II. ISOMERISM AND TOPOMERISM

In most cases configurational units associated with trivalent nitrogen are stereolabile and undergo stereomutation at rates which are fast on the isolation time-scale. Such stereomutations have half-lives shorter than hours at normal temperatures and correspond to energies of activation below about 25 kcal/mol. As

a consequence, much of the experimental work on these systems has been carried out using the methodology of dynamic nuclear magnetic resonance spectroscopy (DNMR). Such studies often focus on the stereochemical relations between groups in the same molecule, rather than only the stereochemical relationships between different molecules. These stereochemical relationships are between paired groups whose environments can be indistinguishable, enantiomeric or diastereomeric and such paired groups are described as homotopic, enantiotopic or diastereotopic groups respectively.

The application of this nomenclature[4] to systems in categories *A* and *Bs* can be understood by reference to the relationship between the two X groups in molecules of the form $R—CX_2Y$. A substituent of the form $—CX_2Y$, for example, benzyl, isopropyl, ethyl, 2,2-dimethylpropyl or 2-methoxymethyl-2-propyl, contains a prochiral carbon atom and can serve as a probe for the chirality of the remainder of the molecule, R. If the R moiety is achiral, the molecule **4** possesses a plane of symmetry (σ-plane) which can interchange the two X groups, which as a consequence are enantiotopic and must have the same NMR chemical shifts. On the other hand, if R is chiral, as in **5**, the symmetry plane cannot be present and



R is achiral

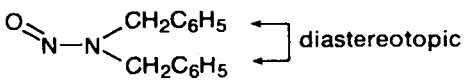
(4)

R is chiral

(5)

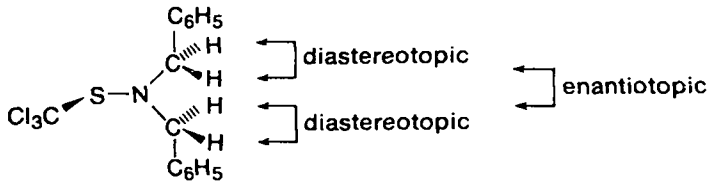
the two X groups must be diastereotopic and in principle should exhibit chemical-shift nonequivalence in NMR spectra. The observation of such nonequivalence provides direct evidence for the presence of a chiral unit within the molecule. The absence of observable nonequivalence is not conclusive, however, since the magnitude of the difference in chemical shifts can be small enough that the separate resonances are not resolved. For this reason more than one of the probe groups may be incorporated in a molecule in order to increase the probability that one of them will exhibit nonequivalence which is large enough to be observed.

The observation of chemical-shift nonequivalence of diastereotopic groups can also be used to demonstrate the presence of the achiral (or proachiral) stereochemical unit associated with category *Bd*, although the stereochemical differences between the two kinds of situations permit an easy differentiation. As an example, we may consider the dibenzylamino group in *N*-nitrosodibenzylamine (**6**)[5] which belongs in category *Bd*. The two benzyl groups taken as wholes are



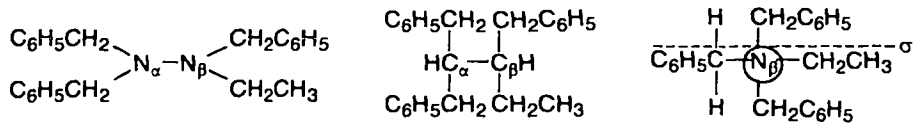
(6)

diastereotopic, while the two hydrogens within a single methylene group are enantiotopic. As a result two singlets are observed for the benzyl methylene protons[5]. On the other hand *N,N*-dibenzyltrichloromethanesulphenamide (**7**) belongs to category *Bs*. There, the two benzyl groups, taken as a whole, are enantiotopic, while the two hydrogens within each benzyl group are diastereotopic. Since the diastereotopic relationship is between two hydrogens which can couple with each other, an *AB* quartet is observed[6]. Since the two benzyl groups taken as wholes are enantiotopic, only a single *AB* quartet is observed.



(7)

Tribenzylethylhydrazine (**8**)[7] presents another interesting application of a symmetry argument. Here, it is used to distinguish between class *A* and class *Bs*. If inversion were slow at both nitrogen atoms in **8**, it would have the same symmetry (and topomeric relationships) as the carbon analogue **9**. In this case we



(8) (9) (10)

note that, because of the chirality at C_β, the two benzyl groups attached to C_α must be diastereotopic. Further, the pairs of methylene hydrogens within each methylene group are diastereotopic. Thus we expect to observe three *AB* quartets for the six diastereotopic benzyl methylene protons of **9** or, by extension, of **8** if it belonged to class *A*. If nitrogen inversion were rapid but rotation about the N—N bond were slow (class *Bs*) we could represent the molecule by the averaged structure **10** which has planar nitrogen atoms. It is clear that **10** is achiral and has a symmetry plane which passes through N_β and its three attached ligands. As a result, the two benzyl groups attached to N_α, as well as the two methylene protons in the benzyl group at N_β, will be enantiotopic. This symmetry plane lies between and does not pass through the two benzyl groups at N_α. Thus, while the two benzyl groups, as a whole, are enantiotopic, the two methylene protons within each group are diastereotopic. In this case, we expect to observe a singlet for the benzyl group at N_β and one *AB* quartet for the two benzyl groups at N_α. The latter pattern was observed experimentally[7] and the system assigned to class *Bs* rather than class *A*.

The coalescence phenomena observed in these cases of stereolabile units can also be conveniently described using this nomenclature. Again we consider a chiral molecule of the form $R—CX_2Y$ which can undergo reversible conversion with its enantiomer ($R_+—CX_2Y \rightleftharpoons R_-—CX_2Y$) a process we may refer to as *degenerate racemization*[6]. When this interconversion is slow on the NMR time-scale the two X atoms (or groups) are diastereotopic. When degenerate racemization becomes fast on the NMR time-scale the R group becomes achiral on time-average and the two X atoms become enantiotopic on time-average. Since the relationship between the two X atoms changes, we refer to the transformation of the NMR spectrum from an *AB* quartet to a singlet as the result of a *topomerization*[4b]. The first-order rate constant required for coalescence, as the result of topomerization, to be observed is proportional to the chemical-shift difference and usually in the order of 10–100 s^{-1}. This allows barriers of about 5–25 kcal/mol to be determined over the usually accessible temperature range for NMR spectroscopy.

III. EFFECTS ON TORSIONAL AND INVERSIONAL BARRIERS

A variety of effects on *A*, *Bs* and *Bd* barriers have been discussed in the literature[8]. These include steric effects, inductive effects and conjugation effects. This section

will examine the expected effects and their use in distinguishing between barriers of different classes. The experimental observations are deferred to the succeeding sections where the different systems are treated separately.

A. Steric and Inductive Effects

The effect of steric hindrance on all three classes is easily understood by consideration of the differential effect of steric interactions in ground and transition states. In class *A*, bond angles at nitrogen are increased in going from the ground state to the transition state. Thus when the size of the ligands at nitrogen is increased, more steric hindrance is present in the ground state than in the transition state, leading to lower barriers (steric acceleration). This steric acceleration has been experimentally observed in a number of systems[8c].

Steric acceleration is similarly observed in class Bd^2. Here, the ground state is characterized by smaller dihedral angles between ligands than is the transition state. As a consequence torsion via a transition state with a greater dihedral angle leads to relief of steric strain. The reverse situation applies to barriers in class *Bs*. Here the ground state is characterized by a larger dihedral angle and bulky groups must pass by each other in a transition state which is characterized by closer contact between groups attached to the ends of the bond in question. Here, increased steric bulk should lead to greater transition-state destabilizing action and higher barriers (steric deceleration)[8].

Since different steric effects are predicted for class *A* and class *Bs* the examination of a series of compounds with groups of different steric bulk at nitrogen can provide a diagnostic tool for differentiating between the two classes. Indeed there have been a number of investigations where the effect of changing alkyl ligands (primary, secondary and tertiary) has been examined. However, in evaluating these studies we must keep in mind that this series of ligands represents one in which inductive effects can also be operative and that it is important to inquire whether the observed trends might be due to an inductive effect.

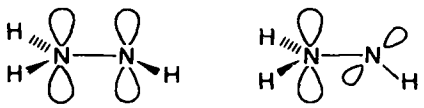
The inductive effect in class *A* is related to the hybridization changes which are associated with bond-angle changes. Inversion of the nitrogen pyramid involves an increase in the p-character of the lone-pair orbital and an increase in the s-character of the hybrid orbitals used in bonding to the ligands in going from the ground state to the transition state. Thus, electronegative elements at nitrogen should result in more p-character in the σ-bonding orbitals and less p-character in the lone-pair orbital in the ground state and should lead to increases in the inversion barriers. There has been both experimental and theoretical support for this proposition, although disentangling this effect from others has not always been straightforward[8]. It is clear that the attachment of electronegative elements to nitrogen (especially oxygen and the halogens) is associated with increased barriers to nitrogen inversion[8c]. However, it is not entirely clear how much of the barrier increase is due to the inductive effect and how much is due to the four electron interaction which is discussed in Section III.B. Similarly, electropositive elements (especially sulphur, silicon and germanium) result in lowered barriers to inversion and the inductive effect is the most likely factor in the trends observed[9]. Although, some earlier workers had suggested the p–d π-bonding might be important, more recent experimental[10,11] and theoretical[12,13] results tend to rule out this explanation.

It may be noted that heteroatom substitution in the β-position to nitrogen (R_2NCH_2X) can give rise to a two-electron interaction which can *lower* the barrier to inversion[11]. This type of polar substituent effect as well as the polar substituent effects on barriers to torsion (in classes *Bs* and *Bd*) are best discussed in molecular orbital terms (Section III.B).

B. Molecular Orbital Considerations

The analysis of molecular orbital differences in different geometries can be useful in understanding the distinctions between the two types of systems in classes *Bs* and *Bd* as well as some substituent effects in the two systems. As an example of the relationship between the two classes we may consider the hydrazyl species, H_2NNH^+ and H_2NNH^-, which as we shall see belong to classes *Bd* and *Bs* respectively.

In discussing the torsional barriers in both the hydrazyl cation and anion we focus attention on two conformers **11** and **12** in which, for convenience, the NH_2



(11) (12)

group is taken to be planar. Conformation **11**, in which the HNNH dihedral angle is 0°, involves a maximum interaction between the two p-orbitals on the two nitrogen atoms. In conformation **12** the HNNH dihedral angle is 90° and the two orbitals are mutually orthogonal. The interaction between the two atomic orbitals in **11** leads to bonding (π) and antibonding (π^*) combinations (Figure 1). In the hydrazyl cation only the bonding level is populated and the orbital interaction leads to multiple bonding and net stabilization. As a result geometry **11** which involves this interaction is the ground state for the cation, while **12** represents the torsional transition state. This behaviour is characteristic of class *Bd*.

In the hydrazyl anion both energy levels are populated. Since the increase in energy of the antibonding level is greater than the stabilization of the bonding level, net destabilization results. Thus, for the hydrazyl anion, **11** represents the torsional transition state, while **12**, in which the interaction is absent, is the ground state[14]. This behaviour is characteristic of class *Bs*.

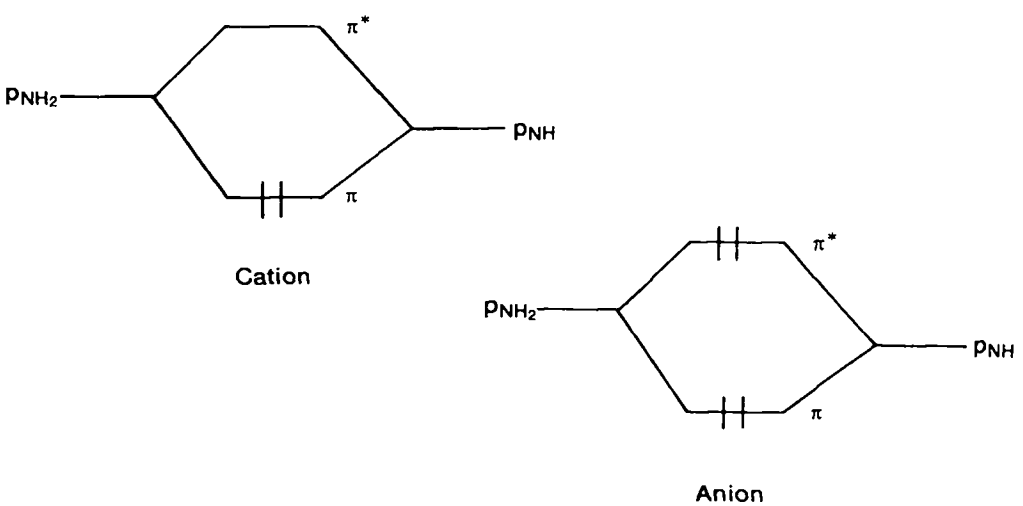


FIGURE 1. Orbital populations in the planar conformation of the hydrazyl cation and anion.

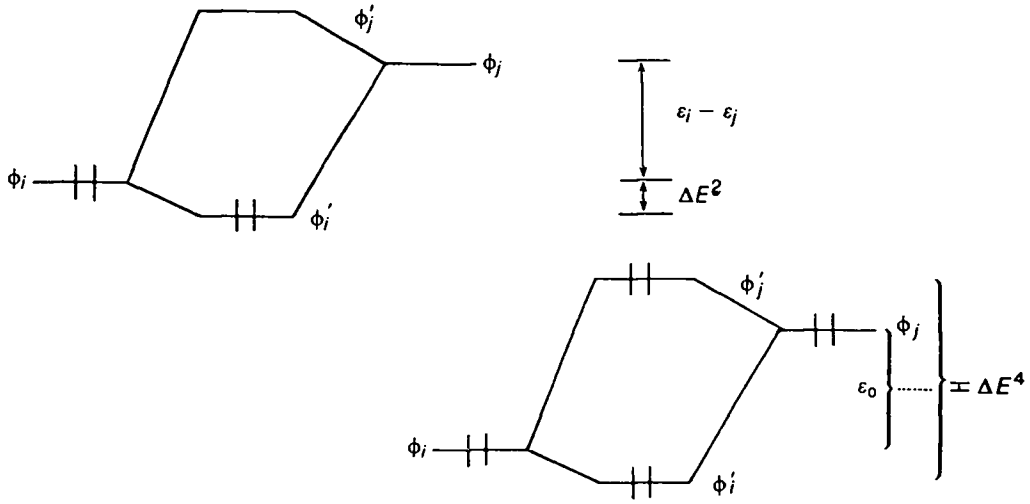


FIGURE 2 Two-electron (upper) and four-electron (lower) interactions.

These two situations correspond closely to the two-electron and four-electron interactions of perturbational MO theory[15] (Figure 2). The net stabilization energy (ΔE^2) of the two-electron interaction, which occurs when a doubly occupied molecular orbital ϕ_i interacts with a vacant nondegenerate MO ϕ_j, is directly proportional to the square of the resonance integral (H_{ij}) and inversely proportional to the energy difference between them (equation 1). This interaction,

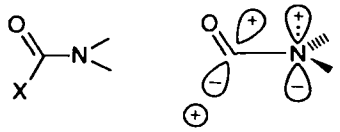
$$\Delta E^2 = \frac{2H_{ij}^2}{\varepsilon_i - \varepsilon_j} \tag{1}$$

which is important for class *Bd*, will occur when the nitrogen lone-pair atomic orbital can overlap with a low-lying vacant antibonding orbital. This is the interaction which is responsible for the preferred planar geometries and torsional barriers in amide-type systems has been examined by Kost[16a,c] and Sandström[16b]. In have low-lying π^*-orbitals. This framework thus accounts for the behaviour of the amides and *N*-nitroso compounds as members of class *Bd*. The nitro group has a similarly low-lying π^*-level and it too would give rise to the same behaviour if its symmetry did not preclude *E*–*Z* isomerism.

As indicated by equation (1) the magnitude of the two-electron interaction is increased when the vacant antibonding level is closer in energy to that of the nitrogen lone pair. Thus, substituents which lower the antibonding level or raise the level of the lone-pair orbital can be expected to increase the magnitude of the two-electron interaction and raise the torsional barrier. For the same reason, higher energy antibonding orbitals do not lead to two-electron effects of appreciable magnitude. Thus, the interactions between the lone-pair p-orbital and the N—H σ^* in geometry **12** can usually be neglected.

The effect of substituents on the two-electron interactions which lead to *Bd*-type barriers in amide-type systems has been examined by Kost[16a,c] and Sandström[16b]. In these systems halogen atoms or alkoxy groups attached to the carbonyl carbon atom lower the barrier. Two kinds of two-electron interactions involving the nitrogen lone pair were considered as responsible for barrier-lowering. In the

ground state, **13**, the lone-pair orbital interacts with π^*_{CO} and in the transition state, **14**, interaction with the σ^*_{C-X}-orbital is possible. The latter interaction could



(13) **(14)**

account for the barrier decrease if the σ^*_{C-X}-orbital were low enough to provide significant transition-state stabilization. The effect of X substituents on the interaction with the π^*_{CO}-orbital can also account for the barrier-lowering. Since these substituents also have nonbonding electrons (n_X) they can also be involved in two-electron interactions with the carbonyl π-system. The effect of the $n_X-\pi^*$ interaction is to raise the energy of the π*-level (ϕ_j' in Figure 2). When the π*-level is raised the interaction with the nitrogen lone pair is diminished and the barrier is lowered. Examination of key compounds and correlation with ionization potentials allowed both Kost and Sandström to conclude that the n–σ* two-electron interaction in the transition state was not an important factor in the barrier decrease. This accords well with the view that two-electron interactions with lower lying π*-orbitals should be much more important than those with σ*-orbitals.

The destabilization energy of the four-electron interaction, which results from the overlap of two doubly occupied MOs increases as the mean of their energies (ε_0) increases (equation 2). Thus, this interaction is much more substantial when the two orbitals involved are nonbonding orbitals than when either orbital is a lower energy bonding orbital. It is also clear from equation (2) that when overlap (S_{ij}) is neglected the interaction goes to zero.

$$\Delta E^4 = \frac{4(\varepsilon_0 S_{ij}^2 - H_{ij}S_{ij})}{1 - S_{ij}^2} \tag{2}$$

The four-electron interaction is characteristic of class *Bs* and can be expected to be important when a nitrogen atom with a lone pair of electrons is bonded to another atom (e.g. N, O, P, S) which also has a lone pair. Since this interaction is destabilizing, it contributes to the barrier by raising the energy of the transition state (geometry **11**) rather than stabilizing the ground state.

The two-electron interactions can also affect *Bs* torsional barriers. The two-electron interactions across the central bonds of *Bs* systems would involve n–σ* interactions. Thus in the *Bs* ground state, **12**, the important interactions might be interaction of either of the filled nitrogen lone-pair orbitals with the σ*-orbitals associated with N—H bonds on the adjacent nitrogen atoms. While the σ*-orbitals in the hydrazyl anion are high in energy, so that two-electron interactions in this system are expected to be of negligible importance, they have been adduced to account for some experimentally observed properties in systems containing polarized bonds.[17,26]

Barriers to nitrogen inversion (class *A*) are affected by both two-electron and four-electron interactions. These two types of interaction affect the barriers in opposite ways. Two-electron interactions are responsible for the lowered barriers in *N*-arylaziridines which decrease further when electron-withdrawing groups are substituted in the aromatic nucleus[18], i.e. when the lowest unoccupied molecular orbital (LUMO) level of the aromatic ring is lowered. The two-electron interaction

has also been invoked to account for the lowered barriers when there is an electronegative group β to nitrogen although this has been less precedented[11,19].

The increase in barriers to nitrogen inversion in compounds with bonds between nitrogen and halogen, oxygen or nitrogen is well documented[8]. Indeed, the *N*-haloaziridines and the oxaziridines exhibit barriers to nitrogen inversion high enough to permit separation of invertomers. However, two different effects are possible – four-electron interactions and the electronegativity effect on hybridization (cf. Section III.A). Both seem to be of importance although the relative importance of the two is not easy to assess. However, comparisons of barriers in cyclic and acyclic hydrazines and hydroxylamines indicate that the four-electron interaction plays a significant role. In cyclic hydrazines and hydroxylamines the four-electron interaction is greater than in their acyclic counterparts since the acyclic compounds can (and do) adopt conformations like that of **12** with nitrogen–heteroatom torsion angles such that the interaction between the two filled (nonbonding) orbitals is minimized. The cyclic compounds, by contrast, are more or less constrained to a conformation like that of **11** in which there is significant interaction. The inversion barriers in the acyclic compounds are substantially lower than in the cyclic compounds, indicating that the four-electron interaction is a major factor causing the higher barriers in the latter compounds[20].

The inductive (hybridization) and conjugative (two-electron and four-electron interaction) effects on nitrogen inversion barriers have been summarized by Lehn[8d] as shown in Figure 3. As the figure illustrates, groups which are inductively withdrawing and those which are conjugative donors (in four-electron interactions) increase barriers, while those which are inductively donating and those which are conjugative acceptors (in two-electron interactions) lead to lowered barriers.

The interplay between the two- and four-electron interactions and their effects on torsion and inversion barriers are well illustrated in the calculated (CNDO/2) geometries and barriers in the hydrazyl cation and anion[14]. The cation exhibits a planar ground-state geometry like that of **11**. The two-electron interaction is responsible not only for the eclipsed geometry but also for the planarity of the trisubstituted nitrogen. The difference between the two geometries is large, 38 kcal/mol, reflecting the magnitude of the two-electron interaction and suggesting a high torsional barrier. The anion on the other hand not only adopts a staggered geometry to minimize the four-electron interaction but the ground state differs from **12** in that the NH_2 group prefers a pyramidal geometry with a barrier to inversion at nitrogen. The torsional barrier is substantially smaller, 7 kcal/mol, indicating the general smaller magnitude of class *Bs* barriers[14].

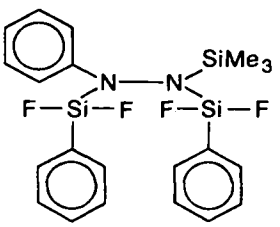
Since the four-electron interaction is maximized in the torsion transition state it is not surprising that the calculated nitrogen inversion barrier is higher at the torsion transition state than in the torsion ground state. This effect is more dramatically illustrated by *ab initio* calculations on aminophosphines which indicate planar geometry at nitrogen in the torsional ground state but pyramidal geometry at the torsional transition state[21]. This phenomenon is also related to the differences in the inversion barriers between cyclic and acyclic hydrazines and hydroxylamines discussed above

Increased barriers Decreased barriers

FIGURE 3. Inductive (↔) and conjugative (⇝) effects on nitrogen inversion barriers.

One final group of two-electron interactions deserves special mention, i.e. those involving d-orbitals on second row elements as the unoccupied orbitals. The early experimental literature on both nitrogen inversion barriers and torsional barriers contains references to the supposed importance of p–d π-bonding (i.e. two-electron interactions) in lowering inversion barriers or enhancing torsional barriers[8]. However, theoretical studies (*ab initio* molecular orbital calculations)[12,13] have invariably indicated that the effect of d-orbital conjugation is minimal and this has been borne out in more recent experimental work[10,11]. At the present time it seems to us that there is no well-documented case which argues convincingly for a substantial effect due to p–d π-bonding between nitrogen and a second-row element. When an alternate explanation is available it should be preferred to one based upon p–d π-bonding.

As an example we may consider the topomerization of the two constitutionally nonequivalent geminal pairs of fluorine atoms in **15**, both of which appear as *AB*



(15)

quartets. While this was ascribed to a substantial barrier to torsion about the Si—N bond[22], these results can be better accommodated within the framework of a class *Bs* barrier to torsion about the N—N bond which has a great deal of precedent even in similar *N*-silylhydrazines.

C. Molecular Orbital Calculations

The use of both semiempirical and *ab initio* SCF molecular orbital calculations has provided many of the insights into structural factors affecting torsion and inversion barriers which were discussed in the previous section. In many but not all cases, calculated barriers have been in reasonable agreement with experiments. The use of MO calculations has been especially valuable in the interpretation of photoelectron spectra (PES).

This area of research has been extensive and fruitful and it is not possible to cover it adequately here. However several of the reviews on rotation and inversion barriers stress theoretical methods and results[8c,d,h]. In addition, a selection of recent work is collected in Table 1.

IV. TORSIONAL BARRIERS IN NITROSO AND NITRO COMPOUNDS

A. Nitroso Compounds

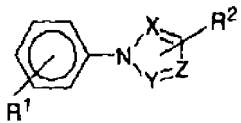
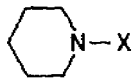
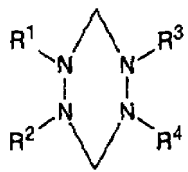
The nitroso functional group has associated with it an accessible π* antibonding orbital. The attachment of a moiety, D, with a high-energy doubly occupied orbital (an n- or π-orbital) which can overlap with it can give rise to partial double bonding and a configurational unit of class *Bd* as expressed in canonical structures **16** and **17**. The donor groups which have been studied include ones which have

TABLE 1. Molecular orbital calculations

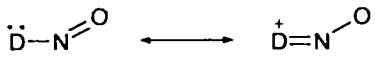
Molecule	MO method[a]	Barrier type[b]	Geometry optimization[c]	Calculation of barriers	Remarks	Reference
NR_3 (R = H, Me) NH_2OH NH_2CHO	MINDO/2′	*A*	PO	Yes	Comparison between MINDO/2′ and CNDO/2 and INDO inversion barriers	23
NR_3 (R = H, Me) NCl_3 $NClR_2$ (R = H, Me)	PCILO	*A*	S	Yes	Comparison of bond angles and inversion barriers to *ab initio* and CNDO/INDO calculations	24
NCl_3	*Ab initio*, various basis sets	*A*	S, PO	Yes	Non-optimized ground state, optimized transition state	13
$NH_3{\cdot}NH_3$	*Ab initio*	*A*	E	Yes	Influence of the hydrogen bond on the inversion barrier in an ammonia dimer	25
Me_2NOH	CNDO/2, CNDO Mislow, INDO	*A*, *Bs*	PO	Yes	The effect of the torsional RN—OH angle on the inversion barrier, as a model for cyclic hydroxylamines	20
NH_2NH_2 NH_2PH_2 PH_2PH_2	*Ab initio*, 4-31G	*A*, *Bs*	O	Yes	PMO analysis, conformational consequences of stabilizing and destabilizing orbital interactions	21
NH_2CH_2F NH_2NHF NH_2OF NH_2OH NHFOH	INDO, SCF, MO, LCBO	*Bs*	S	Yes	Importance of two-electron interaction on torsional potential [vicinal (lone-pair) n–(electronegative substituent)σ^* interactions]	26
Methyl- and fluoro-substituted amines, hydroxylamines, hydrazines	*Ab initio*, 4-31G	*Bs*	S	Yes	Fourier decomposition of the torsional potential functions	27
$MeNH_2$	*Ab initio*, STO-3G	*Bs*	O	No	PMO analysis	28

TABLE 1. *continued*

Molecule	MO method[a]	Barrier type[b]	Geometry optimization[c]	Calculation of barriers	Remarks	Reference
MeNH·NHMe	*Ab initio*, 4-31G	*Bs*	O	No	Calculated structural parameters used as constraints needed to interpret gas electron-diffraction data	29
$H_2NCH_2CO_2H$	*Ab initio*, 4-21G	*A*	O	No	Ground-state structure of glycine	30
$H_2NCH_2CO_2H$ $N^+H_3CH_2CO_2^-$	*Ab initio*, 4-31G	*A*	O	No	Energy differences of glycine and its zwitterion	31
$NH_2CH(Me)CO_2H$	*Ab initio*, 4-21G	*A*	O	No	Ground-state structure of alanine	32
$CH_2{=}CH{-}NH_2$	PRDDO	*A*, *Bd*	O	Yes	Rotational and inversional barriers	33
$CH_2{=}CH{-}NH_2$	PRDDO	*A*, *Bd*	O	Yes	Improved inversional barrier by fitting PRDDO calculations to microwave data	34
$C_6H_5NH_2$	CNDO/2	*A*, *Bd*	S, O	Yes	Rotation and inversion barriers for standard and optimized geometries, comparison to *ab initio* STO-3G and experimental data	35
$C_6H_5NH_2$	INDO, CNDO/S	*A*, *Bd*	S	Yes	Rotational and inversional barriers in aniline, interpretation of UV spectra	36
$Ar{-}NMe_2$ (Ar = aromatic or heteroaromatic)	CNDO/2	*Bd*	S	Yes	The rotational behaviour of the planar dimethylamino group in 19 different neutral compounds and six protonated heteroaromatic compounds, comparison to EHT, STO-3G, INDO, PCILO	37

	EHT	*Bd*	S	Yes	Rotational barriers in 8 related *N*-arylazoles	38
NH_2NO_2 NMe_2NO_2	*Ab initio*	*A*	PO	Yes		39
NH_2Cl NH_2Cl^+	*Ab initio*, STO-3G, STO-4G	*A*			Interpretation of PES spectra	40
Me_2NX (X = Cl, Br)	SPINDO	*A*			Interpretation of PES spectra	41
						
(X = H, Cl, Br)	SPINDO	*A*			Conformational behaviour from PES spectra	42
	MINDO/2	*A*, *Bs*			Conformational behaviour from PES spectra	43

[a]Details of the various methods can be found in the original references.
[b]For barrier classification, see Section I.
[c]O = optimized, PO = partially optimized, S = standard geometries, E = experimental geometries.

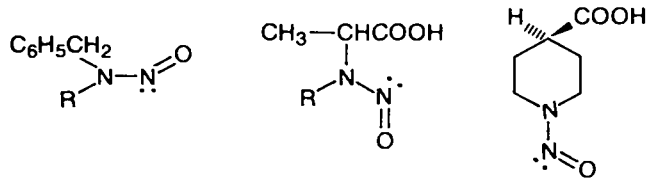


(16) (17)

atoms with lone pairs of electrons O and N (nitrous acid, nitrites and nitrosamines) and moieties with available π-electrons. The system most extensively studied has been that of the nitrosamines.

1. Nitrosamines

The pioneering work by Looney, Phillips and Reilly[44] demonstrated that the isomerism and topomerism in nitrosamines could be conveniently studied by variable temperature NMR spectroscopy and that the torsional barriers (ca. 19–24 kcal/mol) are within the range for determination by DNMR methods. Subsequent studies on this problem have utilized for the most part, ^{1}H-NMR spectroscopy, although ^{13}C-NMR[45], IR[44], PES and UV[46] techniques have also been employed. In some cases, barriers have been high enough to permit isolation of *Z* or *E* isomers. Compounds **18** and **19** have been separated (or partially separated) into their *E,Z* isomers and **20**, which exhibits geometric enantiomerism, was resolved. Measurements of the rate of stereomutation by NMR for **18**[47], mutarotation for **19**[48] and racemization for **20**[49] have confirmed the general magnitude of the torsional barriers in this system which have been measured for the most part using DNMR techniques.

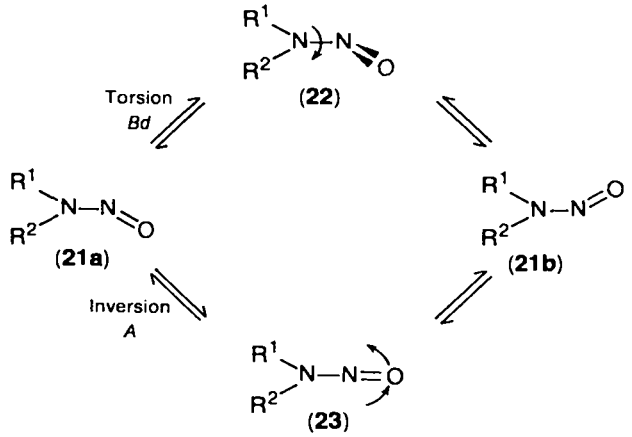


(18) (19) (20)

(**a**) R = 2, 6-xylyl
(**b**) R = *i*-Pr

(**a**) R = Me
(**b**) R = Et
(**c**) R = Pr

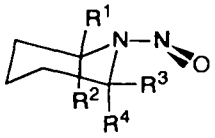
The interconversion of *E* and *Z* isomers (**21a** and **21b**) of nitrosamines (and other D̈—N=O compounds) could involve a *Bd* mechanism (via transition state **22**) or an *A* mechanism (via transition state **23**). Since either pathway can effect



(22) (21a) (21b) (23)

topomerization or isomerization, the experimentally observed barrier must correspond to stereomutation via the lower energy transition state. Almost invariably the assumption has been made that the *Bd* mechanism provides the lower energy pathway for *E,Z* isomerism and the possibility of stereomutation occurring via inversion has been rarely discussed. There are good reasons to suppose that transition state **23** should be very high in energy. In general, inversion at an sp^2-hybridized atom, as in the present case, involves a much higher activation energy than inversion at an sp^3-hybridized atom. In addition, the presence of the electronegative oxygen atom should also lead to a barrier increase because of the hybridization and four-electron interaction effects discussed in Section III. Semiempirical calculations (CNDO/2) on dimethylnitrosamine have given support to this view and suggested that the activation energy for inversion would be very much greater than that for *Bd* torsion (73 kcal/mol vs. 18 kcal/mol)[46]. The inversion mechanism has been suggested to account for the large negative entropies of activation measured for mutarotation of **19** in water[48]. In view of the limited information available and the difficulty in determining and interpreting entropies of activation this suggestion must be regarded as highly speculative.

Barriers in compounds **18–20** and other representative nitrosamines have been collected into Table 2. Comparisons between various compounds can lead to some generalizations about barriers in this system. Thus aromatic nitrosamines exhibit lower barriers than their aliphatic counterparts, in accord with the expected decrease in the two-electron interaction upon lowering of the energy level of the donor orbital. Ground-state destabilization might have been expected to lead to lower barriers if the steric bulk of the substituents on the amino nitrogen were increased. However, the barriers in dimethylnitrosamine, diethylnitrosamine and diisopropylnitrosamine are not very different, suggesting that steric interactions are not very substantial in this system. However, steric inhibition of resonance is observed in the *N*-nitrosopyrimidine system **24**[50]. The torsional barrier in the tetramethyl derivative **24c** is lowered by 3.1 kcal/mol relative to the parent compound **24a**, presumably as the result of steric interactions between the nitroso group and the equatorial methyls R^1 and R^3. The *cis*-2,6-dimethyl analogue is said to adopt a diaxial conformation **24b** in order to avoid methyl–nitroso interactions[51,52] although the barrier observed is the same as that in **24c** consistent with conformation **24d**.



(24)

(a) $R^1 = R^2 = R^3 = R^4 = H$
(b) $R^1 = R^3 = H$; $R^2 = R^4 = Me$
(c) $R^1 = R^2 = R^3 = R^4 = Me$
(d) $R^1 = R^3 = Me$; $R^2 = R^4 = H$

Relatively little has been done to probe the effect of solvent on nitrosamine torsional barriers. Cooney and coworkers[53] have shown, in two cases, that increased solvent polarity leads to higher barriers in accord with the greater solvation expected in the ground state in which the polar canonical structure **17** is important.

Steric factors seem to play a role in determining *E/Z* ratios also. This is illustrated by the series of *N*-methyl-*N*-alkylnitrosamines **25** (Table 2). All of the

TABLE 2. Torsional barriers and configurational preferences in substituted nitrosamines, R^1R^2NNO

Compound	R^1 (or structure)	R^2	E/Z Ratio (T, °C)	$\Delta G^{\circ}_{E \rightleftarrows Z}$ (kcal/mol)	$\Delta G_c^{\neq a}$ (kcal/mol)	T_c (°C)[b]	Solvent[c]	Method	Reference
	Me	Me			23.0	*d*	$PhNO_2$	^{1}H-NMR	50
	Me	Me			23.0	180	Neat	^{1}H-NMR	44
	Me	Me			25 ± 5[a]	*d*	Neat	^{1}H-NMR	56
	Me	Me			22.9[a]		Neat	Spin-echo off resonance	57
	Me	Me			21.9[a]		Neat	Spin-echo on resonance	57
	Me	Me			21.1	158	Gas phase	^{1}H-NMR	58
	Et	Et			23.2	*d*	$PhNO_2$	^{1}H-NMR	50
	Pr	Pr			22.5	170	Neat	^{1}H-NMR	54
	i-Pr	*i*-Pr			23.5	*d*	$PhNO_2$	^{1}H-NMR	62
	Ph	Ph			19.1	*d*	DMSO-d_6	^{13}C-NMR	45
	4-$BrCH_4$	4-BrC_6H_4			18.8	*d*	DMSO-d_6	^{13}C-NMR	45
	R^1R^2 = carbazole				16.8	*d*	DMSO-d_6	^{13}C-NMR	45
	Me	CH_2CN	*d*		20.3[e] $E \rightarrow Z$ 20.4 $Z \rightarrow E$	139	HCA	^{1}H-NMR	59
	Et	CH_2Ph	*d*		22.9 $E \rightarrow Z$ / $Z \rightarrow E$	174	Neat	^{1}H-NMR	54
18b	*i*-Pr	CH_2Ph	*d*		23.2 $E \rightarrow Z$ 22.3 $Z \rightarrow E$	(36.5)	CCl_4	Equilibration	47
	Et	CH_2CH_2OH	*d*		23.2 $E \rightarrow Z$ / $Z \rightarrow E$	173	Neat	^{1}H-NMR	54
19a	Me	$CH(Me)CO_2H$	2.3 (27)	0.5	23.7 $E \rightarrow Z$ 23.2 $Z \rightarrow E$	(27)	H_2O	Mutarotation	48
19b	Et	$CH(Me)CO_2H$	0.61 (27)	−0.3	23.7 $E \rightarrow Z$ 24.0 $Z \rightarrow E$	(27)	H_2O	Mutarotation	48
19c	Pr	$CH(Me)CO_2H$	0.45 (27)	−0.5	23.8 $E \rightarrow Z$ 24.3 $Z \rightarrow E$	(27)	H_2O	Mutarotation	48
18a	$PhCH_2$	2,6-xylyl	1.67 (36.5)	0.3	24.2 $E \rightarrow Z$ 23.9 $Z \rightarrow E$	(36.5)	CCl_4	Equilibration	47
25a	Me	CH_2Ph	3.0 (20)	0.6			*d*	^{1}H-NMR	44
25b	Me	Pr	3.6 (35)	0.8			CCl_4	^{1}H-NMR	60

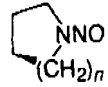
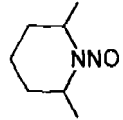
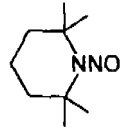
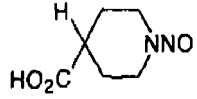
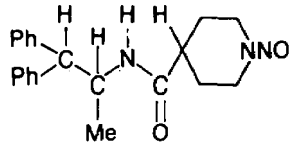
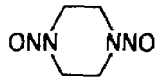
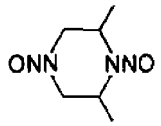
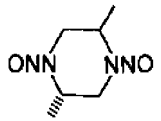
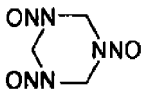
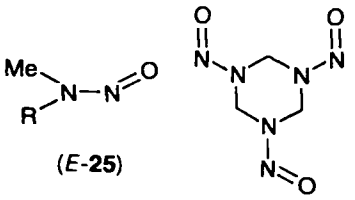
25c	Me	*i*-Pr	8.4 (35)	1.3			*d*	^{1}H-NMR	60
25d	Me	*s*-Bu	11.0 (35)	1.4			Neat	^{1}H-NMR	60
25e	Me	Ph	104.0 (35)	2.8			*d*	^{1}H-NMR	60
									
24a		$n = 1$			22.8	190	Neat	^{1}H-NMR	53
		$n = 2$			22.7	180	Neat	^{1}H-NMR	53
		$n = 3$			>23.3	>200	Neat	^{1}H-NMR	53
		$n = 4$			>23.5	>200	Neat	^{1}H-NMR	53
		$n = 5$			>23.4	>195	Neat	^{1}H-NMR	53
					25.9[f]	>175 (25)	oDCB	^{1}H-NMR	53
					25.1[f]	~195 (25)	DPE	^{1}H-NMR	53
			1.0		~23.9[g]	>175	oDCB	^{1}H-NMR	53
					24.5[f]	185(25)	DPE	^{1}H-NMR	53
24b					19.6	*d*	$PhNO_2$	^{1}H-NMR	50
					19.4	*d*	oDCB	^{1}H-NMR	51
24c					19.6	*d*	C_2Cl_4	^{1}H-NMR	50
20					22.3	(22)	MeOH	Racemization	49
					22.9	(22)	MeCN	Racemization	49

TABLE 2. *continued*

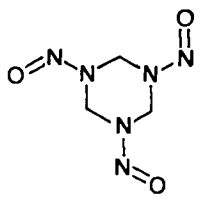
Compound	R^1 R^2 (or structure)	E/Z Ratio (T, °C)	$\Delta G^{\circ}_{E \rightleftarrows Z}$ (kcal/mol)	$\Delta G_c^{\neq a}$ (kcal/mol)	T_c (°C)[b]	Solvent[c]	Method	Reference
				22.4	(22)	MeOH	Mutarotation	49
				22.3	(127)	DMF-d_7	^{1}H-NMR	55
				18.3[h]	(127)	PCB/PhH (2:1)	^{1}H-NMR	55
		*d* (127)	0.590 0.358	23.7 *E,Z* → *Z,Z* 21.7 *E,Z* → *E,E*	(127)	DMF-d_7	^{1}H-NMR	55
		*d* (127)	0.979	18.4[i] **26a** → **26b** 18.2 **26a** → **26a** 18.0 **26a** → **26a**	(67)	DMF-d_7	^{1}H-NMR	55

[a]Barriers expressed as energies of activation (E_a) are indicated with the footnote *a*.
[b]Temperatures corresponding to the free energy of activation which are not coalescence temperatures are enclosed in parentheses.
[c]DMSO-d_6 = perdeuterodimethyl sulphoxide; HCA = hexachloroacetone; oDCB = *o*-dichlorobenzene; DPE = diphenyl ether; PCB = perchloro-1,3-butadiene; DMF-d_7 = perdeuterodimethylformamide.
[d]Not specified.
[e]Calculated from literature data.
[f]The free energy of activation at 25°C was calculated from $\Delta H^{\neq}$ and $\Delta S^{\neq}$ obtained from line shape analysis. The free energy of activation at the coalescence point was not measured.
[g]Estimated.
[h]The barrier given is for the nitroso group at N-1. The barrier for the nitroso group at N-2 was much greater.
[i]The free energies of activation given are for torsion of the three distinguishable nitroso groups of **26a**.



(*E*-**25**)

(**26a**)



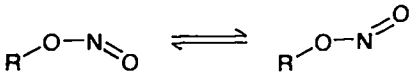
(**26b**)

(**a**) R = CH_2Ph
(**b**) R = *n*-Pr
(**c**) R = *i*-Pr
(**d**) R = s-Bu
(**e**) R = Ph

members of this series prefer the *E* configuration with the more bulky alkyl group *anti* to the nitroso oxygen and with increased equilibrium constants as the size of the alkyl group is increased. The chemical-shift assignments in this and other nitrosamines accord with the generalization that the methyl or alkyl group, α-hydrogens and α-carbons, *syn* to the nitroso oxygen, appear upfield relative to those *anti* to the nitroso oxygen[52,54]. The assignments in 1,3,5-trinitroso-hexahydro-*s*-triazine **26** can be easily made on symmetry grounds. Here, the less symmetrical isomer **26a** is preferred, as would be expected on the basis of entropy, although a study of the change in equilibrium constant in the range of 25–27°C suggested that an enthalpic preference for **26a** was dominant[55].

2. *Nitric acid and nitrite esters*

The *E,Z* isomerism of nitric acid and nitrite esters was first demonstrated using infrared spectroscopy[61] and later confirmed (for the alkyl nitrites) using NMR spectroscopy[62]. The relationship between torsional barriers in nitrites and nitrosamines parallels that between esters and amides[8,63]. Thus, while the barriers in simple dialkyl nitrosamines are in the neighbourhood of 25 kcal/mol, free energies of activation of about 10–11 kcal/mol can be calculated[64] from the data given for **27b–f**[65]: **27b**, 10.7 kcal/mol; **27c**, 10.6 kcal/mol; **27d**, 10.6 kcal/mol; **27e**, 11.0 kcal/mol; **27f**, 10.1 kcal/mol. Surprisingly, the experimental barriers accord well with the estimate of 10 kcal/mol obtained using a simple HMO calculation[66].



(*Z*-**27**) (*E*-**27**)

(**a**) R = H
(**b**) R = Me
(**c**) R = Et
(**d**) R = *n*-Pr
(**e**) R = *i*-Pr
(**f**) R = *i*-Bu
(**g**) R = Cl

While NMR spectroscopy has been useful in providing isomer ratios and barriers in these systems, dipole moment studies and microwave spectroscopy have proved

more useful in making configurational assignments and have resulted in the reversal of early assignments based upon NMR chemical shifts[60]. Nitric acid and methyl nitrite are more stable in the *Z* configuration by 0.4 and 0.8 kcal/mol, respectively[67,68]. However, when the alkyl group is made secondary or tertiary, the preference is reversed; isopropyl nitrite and *t*-butyl nitrite prefer the *E* configuration by a few hundred calories[66]. Compound **27g** appears to have a great preference for the *Z* configuration. This was the only form that could be detected in a microwave study[68].

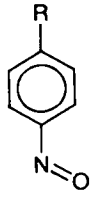
Both steric and electronic factors have been invoked to explain the configurational preferences. Dipolar stabilization has been used to explain the stability of the *Z* configuration of nitric acid[67] and methyl nitrite[66], while steric factors are said to be responsible for the reversal in the secondary and tertiary alkyl nitrites[60,66]. The preference in **27g**, however, is not easily explained within this framework[68].

3. *Aromatic nitroso compounds*

An aromatic π-system is a poorer donor than either a nitrogen or oxygen lone pair, and while nitrosobenzene exhibits a *Bd* barrier it is somewhat lower (7.7 kcal/mol)[69] than the barriers in nitrites and substantially lower than nitrosoamine barriers. The barriers in *p*-substituted nitrosobenzenes which have been measured by ^{1}H- or ^{13}C-NMR spectroscopy[69,70] correlate with Hammett σ_p constants (Table 3)[69]. The highest barriers correspond to those with the strongly electron-donating groups, amino and methoxy, which can be regarded as vinylogous nitrosamine or vinylogous nitrite. The substituent dependence of the substituted nitrosobenzenes is greater than that reported for *p*-substituted benzaldehydes[71] and acetophenones[72].

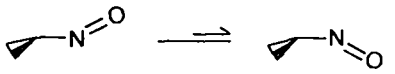
The importance of mesomerism in these compounds has been corroborated by X-ray crystallographic investigations of several substituted nitrosobenzenes which exhibit not only coplanarity of the aromatic and nitroso π-systems but also shortened C—N bonds[73]. While the analogy between the barriers in nitrosobenzenes and nitrosamines is well founded it may be noted that the solvent effects on torsional barriers which have been noted for nitrosamines are not seen in the nitrosobenzene system[74].

TABLE 3. Torsional barriers in *p*-substituted nitrosobenzenes[69]



R	Solvent	$\Delta G^{\neq}_{298}$ (kcal/mol)
NH_2	CD_3SOCD_3	13.9
NMe_2	CD_3SOCD_3	13.0
OMe	CD_3SOCD_3	10.3
Me	CD_3COCD_3	8.2
H	CD_3COCD_3	7.7
Cl	CD_3COCD_3	7.5

The high-energy filled orbital of the cyclopropane system can also act as a π-donor and the structure of nitrosocyclopropane indicates such overlap. The microwave spectrum provides evidence for an equilibrium mixture of bisected conformations, with the *S-trans* form **28a** predominating over the *S-cis*[75]. *Ab initio*



(28a) **(28b)**

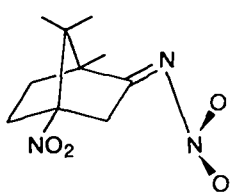
MO calculations (4-21G) carried out on this system accord with the experimental results[76]. By contrast the torsional barriers in simple nitrosoalkanes as obtained by microwave or IR techniques indicate very small V_6 barriers, e.g. CH_3NO, 1.13 kcal/mol[77]; CD_3NO, 1.09 kcal/mol[77]; CF_3NO, 0.77 kcal/mol[78]. It may be noted that the barrier obtained by microwave spectroscopy for nitrosobenzene (3.9 ± 1 kcal/mol)[78] is substantially lower than the more reliable value obtained by NMR spectroscopy.

B. Nitro Compounds

Like the nitroso group the nitro group can act as a π-acceptor group due to its accessible π*-orbital. However, because of the symmetry of the nitro group isomerism is not possible and the torsional barrier cannot be measured by NMR techniques (at least, not without using oxygen isotopes). Nevertheless other techniques have provided ample evidence for interactions with π-donor systems.

Structures obtained by X-ray crystallography have indicated that nitro aromatic compounds are planar in the absence of *ortho* substituents[79]. When *ortho* substituents are present the twist of the nitro group can be observed in structures obtained by X-ray crystallography[79] or deduced from UV absorption data[80]. A gas-phase electron diffraction study of dimethylnitramine indicated that the molecule was planar but with a longer N—N bond length (1.382 Å) than that in dimethylnitrosamine (1.344 Å), suggesting less double-bond character for the N—N bond in the former compound[81]. This is in accord with the microwave results which indicate that the torsional barrier in nitrobenzene is somewhat lower than that in nitrosobenzene[78].

A recent X-ray crystallographic study[82] of the *N*-nitroimine **29** indicated that the π-system of the imino nitro group was perpendicular to that of the imine. This conformation precludes a conjugated system between the nitro and imino groups and is in contrast with the results obtained for nitroethylene[83] (in the gas phase) and *E*-phenylnitroethylene (in the solid state)[84]. The bond lengths in **29** were



(29)

characteristic of a C=N double bond and an N—N single bond. The small CNN angle (113.8°) suggests that conjugation of the nitro group is not a major factor.

V. TORSIONAL AND INVERSIONAL BARRIERS IN AMINO COMPOUNDS

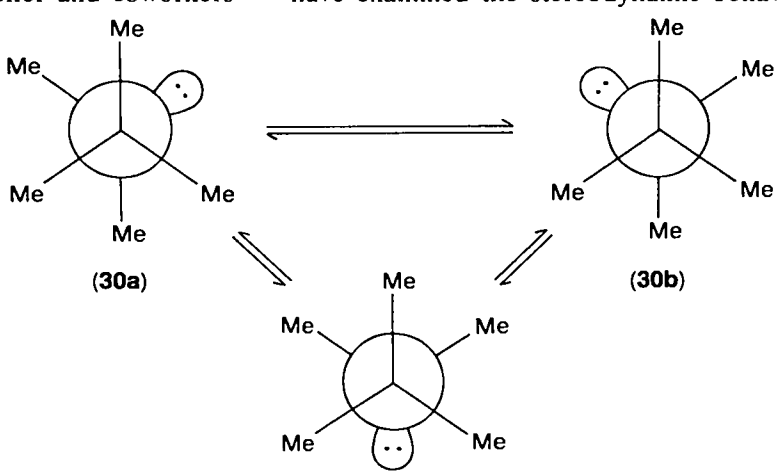
The study of barriers to inversion at trivalent nitrogen in amines and amino compounds and of barriers to torsion about nitrogen–heteroatom bonds has given rise to a very extensive literature over the past decade. There are a number of excellent reviews in this area, covering the general field or a subsection of it[8]. Since exhaustive coverage is beyond the purview of this chapter and since the literature has been reviewed elsewhere, we have limited discussion to some specific topics.

A. Simple Amines

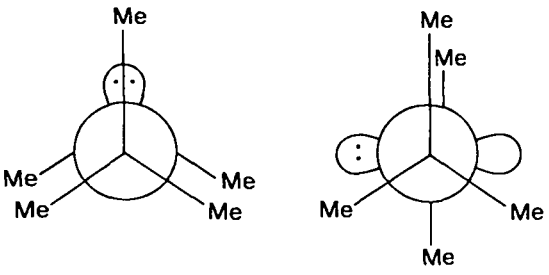
The barriers to nitrogen inversion in a number of simple trialkylamines have been measured by DNMR spectroscopy. Aside from the barriers in *N*-alkylaziridines, which are in the range of 17–20 kcal/mol, the observed topomerization barriers in simple cyclic and acyclic trialkylamines are a good deal lower (6–9 kcal/mol) but are well within the accessible range of DNMR spectroscopy, for example: 1,2,2-trimethylaziridine[85], $\Delta G_c^{\neq} = 18.5$ kcal/mol; 1,3,3-trimethylazetidine[86], $\Delta G_c^{\neq} = 8.2$ kcal/mol; 1,3,3-trimethylpyrrolidine[87], $\Delta G_c^{\neq} = 8.7$ kcal/mol; *N*-methylhomopiperidine[88], $\Delta G_c^{\neq} = 7.3$ kcal/mol; dibenzylmethylamine[89], $\Delta G_c^{\neq} = 6.6$ kcal/mol; *N*-*t*-butyl-*N*,*N*-dimethylamine[90], $\Delta G_c^{\neq} = 6.2$ kcal/mol; *N*-benzyl-*N*-*t*-butyl-*N*-methylamine[90], $\Delta G_c^{\neq} = 6.3$ kcal/mol.

The nitrogen inversion barriers for acyclic tertiary amines are close to the range of barriers for rotation about single bonds, and in some cases it is possible to effect topomerization either by nitrogen inversion or by torsion about C—N single bonds. As an example we may consider the behaviour of *N*,*N*-dimethyl-*t*-butylamine (**30**). At low temperatures the spectrum features two singlet resonances for the *t*-butyl group in a ratio of 2:1. This indicates that equilibration of the three topomers **30a–c** has become slow on the NMR time-scale. This topomerization could be envisioned as one which involves torsion about the N—C bond to the *t*-butyl group (three-fold barrier). This process would take place via a transition state, **31-T**, with pyramidal nitrogen. Alternatively, topomerization could occur via transition state **31-I**, *i.e.* involving inversion of the nitrogen pyramid.

Bushweller and coworkers[90,91] have examined the stereodynamic behaviour of a



(30a) (30b) (30c)



(31-T) (31-I)

number of systems of this sort using both low-temperature NMR methods and semiempirical molecular orbital (INDO) calculations. In the case of **30**, they have been able to conclude that the transition state for topomerization is **31-I** rather than **31-T** and that the proposed topomerization itinerary involves coordinated changes in both C—N torsion angles and bond angles at nitrogen and was described as a rotation–inversion process.

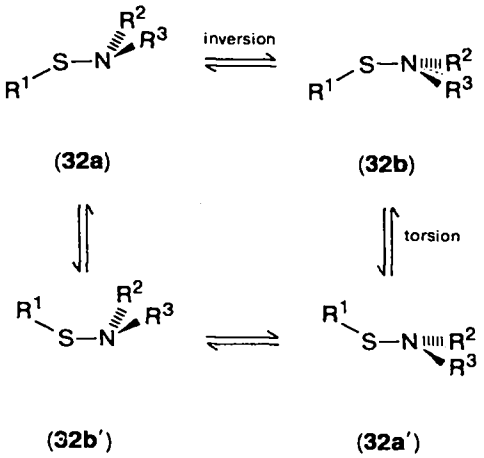
On the other hand, attachment of a halogen atom increases the barrier to nitrogen inversion, and the behaviour of *N*-chloro-*N*-ethyl-*t*-butylamine is different[91]. In this molecule a prochiral probe, the methylene group, is present which can be used to monitor nitrogen inversion since rapid inversion of the nitrogen pyramid can render the methylene protons enantiotopic on time-average but torsion about C—N single bonds cannot. In this compound, the observed barrier for topomerization of the *t*-butyl group ($\Delta G^{\neq}$ = 8.9 kcal/mol) is somewhat lower than that for the methylene group ($\Delta G^{\neq}$ = 9.7 kcal/mol). The lower barrier corresponds to torsion about a C—N single bond (with a transition state analogous to **31-T**) while the higher barrier corresponds to nitrogen inversion via a transition state like **31-I**.

In general, when the torsional barrier is lower than the inversion barrier, as in the chloroamine, topomerization of the *t*-butyl group occurs by torsion, while when the inversion barrier is lowered, the lowest barrier itinerary involves inversion of the nitrogen pyramid. It may be noted that the MO calculations for systems such as **30** indicate that the C—N torsional barrier is dramatically lowered at the inversion transition state as the torsional barrier changes from a three-fold barrier to a six-fold barrier[90].

B. Acyclic Compounds with Nitrogen–Heteroatom Bonds

The torsion–inversion dichotomy has also been the subject of inquiry in compounds which bear a heteroatom (especially N, O, P or S), which bears nonbonded electrons, attached to the nitrogen atom. However, the relationship between the two processes is very different from that in the tertiary amines and haloamines discussed in Section V.A above. Examples in the hydroxylamine and sulphenamide areas can illustrate the problems involved and the techniques which have been used to try to assign the probable mechanisms involved in topomerization.

The sulphenamides ($R^1SNR^2R^3$) present a useful system for discussion since it has been demonstrated that some compounds undergo topomerization via transition states that correspond to inversion while in other cases the transition state for topomerization involves torsion about the N—S bond. The topomerization of sulphenamides (the interconversion of a chiral sulphenamide molecule **32a** with its



(32a) (32b)

(32b') (32a')

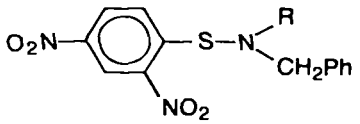
enantiomer 32a') requires both processes, inversion of the pyramid and torsion about the N—S bond. We may classify sulphenamides into class *A* or class *Bs* as the rate-determining step involves inversion or torsion respectively.

This situation is quite different from that of the simple acyclic amines discussed in Section V.A above since we have good grounds for supposing that inversion and torsion are sequential and that the combined process of torsion and inversion would require a higher energy transition state. Since four-electron interactions are thought to play a role in both barriers (Section III.B) we may consider whether the effect is exalted or diminished if inversion and torsion occur simultaneously. At the transition state for inversion the nitrogen lone pair of electrons is in a pure p-orbital and better able to overlap with the lone-pair orbital on the heteroatom. Since such overlap raises the energy of the torsional transitional state we may expect the torsional barrier to be enhanced at the inversion transition state. Similarly, the four-electron contribution to the inversion barrier should be enhanced at the torsional transition state since the torsion angle is then at or near the optimum value for overlap. These suppositions have been borne out in MO calculations[12,20] on the energy surfaces for torsion and inversion in hydroxylamines and sulphenamide analogues which indicate that topomerization is sequential. These conclusions are in accord with the observations, discussed in Section III.B, that inversion barriers are higher in systems in which the nitrogen and heteroatom are contained within a relatively small (3- or 4-membered) ring.

The acyclic sulphenamides have been assigned to class *Bs* on several grounds which are discussed below. However, incorporation of the nitrogen atom into a three-membered ring raises the nitrogen inversion barrier so that these compounds fall into class *A*. Thus the two systems exhibit different characteristics which can be used as diagnostics to assign the barrier type. Steric effects in the two systems have been noted. In the acyclic sulphenamides change of substituents at nitrogen from methyl to primary, secondary and tertiary alkyl results in a monotonic increase in the topomerization barrier consistent with the steric deceleration predicted for S—N torsion[6]. On the other hand, *N*-sulphenylaziridines exhibit steric acceleration characteristic of a nitrogen inversion barrier, when the substituent at sulphur is made more bulky[11,92]. The difference in the minimum barrier itineraries in the two systems is also illustrated by the difference in electronic effects in *p*-substituted benzenesulphenylaziridines and acyclic *p*-substituted benzenesulphenamides[10,11].

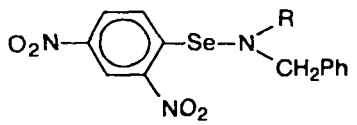
A second useful criterion is the effect of conjugation of the nitrogen lone pair. The predicted lowering of the nitrogen inversion barrier by conjugative withdrawal

has been well documented in the aziridine systems[18]. However, the barriers to torsion about N—S bonds do not exhibit this dramatic barrier-lowering. Thus, comparable barriers are observed for the *N*-isopropyl and *N*-phenyl sulphenamides **33a** and **33b**, $\Delta G_c^{\neq}$ = 16.5 kcal/mol and 17.8 kcal/mol, respectively. The selenamide system exhibits similar results with comparable barriers for **34a** and **34b**: **34a**, 15.2 kcal/mol; **34b**, 15.8 kcal/mol[93]. In the hydroxylamine system a substantial barrier is observed for **35**, $\Delta G_c^{\neq}$ = 8.5 ± 0.2 kcal/mol, although it is somewhat smaller than



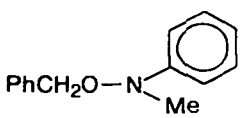
(33)

(a) R = *i*-Pr
(b) R = Ph



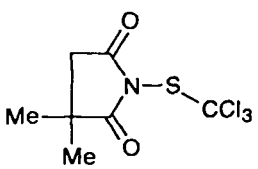
(34)

(a) R = *i*-Pr
(b) R = Ph

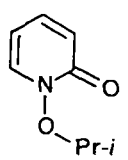


(35)

those observed for trialkylhydroxylamines ($\Delta G^{\neq}$ = 12–13 kcal/mol)[94]. The latter barriers are now thought to be inversion barriers on the basis of several lines of evidence[20,95]. Substantial torsional barriers are also observed in acyl derivatives, e.g. **36** and **37**, in which the nitrogen must be planar or nearly so.



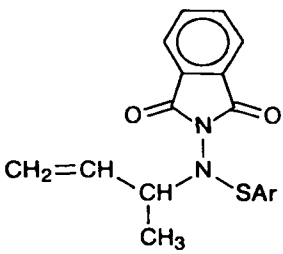
(36)



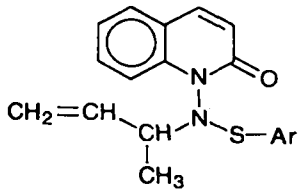
(37)

The use of symmetry arguments has been useful in recognizing and distinguishing torsional and inversional barriers in substituted hydrazines as discussed above in Section II. This approach has also been ingeniously used to distinguish between the N—N and N—S (*Bs*) barriers in **38** and **39**[96]. Thus in **38** the symmetrical substitution of the phthalimide nitrogen precludes observation of an N—N barrier and allows the observed barrier to be assigned to the N—S bond. Comparisons between the two systems indicate that the higher barrier in **39** is associated with torsion about the N—N bond.

Solvent effects have also been used as a criterion for distinguishing between torsion and inversion although their use is probably not completely reliable. While hydrogen-bonding solvents do appear to raise nitrogen inversion barriers by better solvation of the pyramidal ground state, the effect is not a large one and solvent effects on torsional barriers may not always be predictable[8d].



(38)



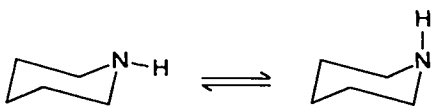
(39)

Ar = *o*-chlorophenyl, 2,4-dinitrophenyl

C. Saturated Nitrogen Heterocycles

The conformational problems involving torsion (ring-reversal) and inversional processes in saturated nitrogen heterocycles have generated a number of controversies in recent years. These areas of controversy have included the position of equilibria (axial and equatorial) in six-membered ring nitrogen heterocycles, distinguishing between nitrogen inversion and ring-reversal (which involves torsional barriers) in nitrogen-containing heterocycles and the assignment of various solvent and substituent effects. While in some areas controversy remains, in others the very considerable amount of experimental work appears to have brought resolution.

The conformational equilibrium in piperidine, **40e** ⇌ **40a**, has generated, very considerable controversy over a long period of time[8i,j]. Much of the early work in



(40e) (40a)

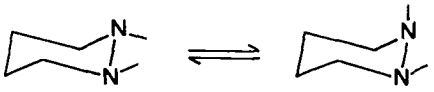
85% 15%

this area was misguidedly founded upon the supposition that the issue at hand concerned the size of the lone pair of electrons on nitrogen and that the position of the equilibrium was determined by steric factors. While the importance of other factors was recognized by 1975, conflicting review articles appeared[8i,j] one of which supported[8i] the predominance of the equatorial isomer while the other concluded[8j] that the axial isomer was favoured.

Recent ^{1}H- and ^{13}C-NMR spectra at very low temperature seem to have finally resolved this issue as well as to have provided the barrier to inversion, $\Delta G^{\neq} = 6.1$ kcal/mol[97]. The spectra in the range of $-140°$ to $-174°$ indicate the presence of two isomers in a ratio of 85:15 (at $-172°$, $\Delta G^0 = 0.36$ kcal/mol). Examination of the ^{1}H-NMR signal due to the axial hydrogen vicinal to the N—H indicates *gauche* vicinal coupling in the major isomer consistent with structure **40e** as the major form.

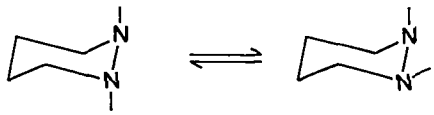
While the barrier to nitrogen inversion in piperidine (6.1 kcal/mol) is much lower than that for ring reversal[98] (10.4 kcal/mol), this is not true for the heterocycles containing nitrogen–heteroatom bonds such as the perhydro *N*-alkylpyridazines and

oxazines. In these compounds both barriers to nitrogen inversion and ring-reversal are enhanced. As a result the assignment of the slow step in topomerization to one or another of these processes is often difficult and sometimes controversial. In some cases assignments can be made by comparisons between related compounds using solvent effects and by observation of more than one barrier. As an example, 1,2-dimethylhexahydropyridazine (**41**) can exhibit a variety of barriers[8k]. Thus **41ee** ⇌ **41ea** and **41aa** ⇌ **41ea** represent barriers to nitrogen inversion. The former



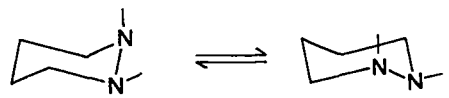
high N-inversion

(**41ee**) (**41ea**)



low N-inversion

(**41aa**) (**41ea**)

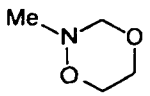


ring-reversal

(**41ea**) (**41ae**)

barrier which involves eclipsed *N*-methyl groups ('passing interaction') at or near the transition state is higher than the latter barrier which does not. The topomerization **41ea** ⇌ **41ae** is a ring-reversal process which also involves a passing interaction. By examination of low-temperature spectra of **41** as well as related compounds, estimates of all three of these barriers have been obtained[8k]: high nitrogen inversion barrier, $\Delta G^{\neq} = 12.7$ kcal/mol; low nitrogen inversion barrier, $\Delta G^{\neq} = 7.6$ kcal/mol; ring-reversal (passing) barrier, $\Delta G^{\neq} = 11.6$ kcal/mol. Similar passing and nonpassing barriers have been observed in 1,2,4-triazcyclohexanes[99].

In other cases, only one barrier can be observed for which assignment cannot be easily made. This is the case in the tetrahydrooxazine and related compounds[100–103]. Riddell and coworkers have described evidence which indicates that ring-reversal corresponds to a lower free energy of activation than does nitrogen inversion in these systems although the barriers are not very different. For example, in 2-methyl-1,4,2-dioxazine (**42**) free energies of activation of 11.4 kcal/mol and 10.9 kcal/mol were assigned to nitrogen inversion and ring-reversal respectively[100].



(**42**)

Comprehensive analysis of ring-reversal and nitrogen inversion in a variety of systems can lead to a determination of substituent effects on the various barriers.

However, the choice of model parameters is not always straightforward and two recent schemes[104,105] came to very different conclusions, differing, for example, as to whether the observed barrier in *N*-methyltetrahydrooxazine should be assigned to ring-reversal or nitrogen inversion. A recent attempt at synthesis of the two schemes has focused attention on the problems involved and pointed out that confusions can result unless the barriers in unsymmetrical systems are distinguished as energy differences between equatorial ground states and transition states (eq → ts barriers) on the one hand, and axial ground states and transition states (ax → ts barriers) on the other[106].

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **3**

The chemistry of ionized amino, nitroso and nitro compounds in the gas phase

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I. INTRODUCTION

The electron-impact-induced decomposition reactions of the radical cations from simple amino, nitroso and nitro compounds have been studied extensively during the past 20 years and are well documented both in the primary and secondary literature[1]. Thus, these results are only discussed in this paper if necessary for a better understanding of more complex reactions.

More 'complex reactions' are for instance caused by the presence of a second functional group in the molecule. It is the interaction of both functional groups which leads to reactions which are more or less unknown in compounds with a single functional group. Examples of such interactions are the elimination of small saturated neutrals via neighbouring-group effects, H-transfer reactions, cyclization processes or redox reactions. In addition to these reaction types isomerization processes (i.e. the rearrangement $R—NO_2^{\cdot+} \rightleftarrows RO—NO^{\cdot+}$) will be discussed in view of more recent experimental results. Moreover, the interesting chemistry of radical anions, in particular from aromatic nitro compounds, will be treated in detail. Ion/molecule reactions in the gas phase will only be mentioned in some special cases to demonstrate differences in the reactivity of 'open' and 'closed-shell' ions. The basicity/acidity of amines which has been studied extensively during the last few years will not be referred to in this paper as this subject is treated in a separate chapter. Furthermore, a detailed treatment of methodical developments and discussion of the more fundamental physicochemical aspects of the ionization process and the unimolecular or bimolecular chemistry of gaseous ions has to be omitted. The reader is here referred to the relevant literature. The central part of this chapter will be the 'chemistry' of those naked ions which contain the functional groups NH_2, NO or NO_2.

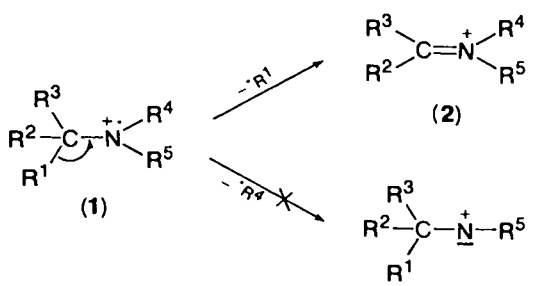
A. List of Abbreviations

AE	Appearance energy
CA	Collisional activation
CI	Chemical ionization
CICA	Chemical ionization collisional activation mass spectrometry
EI	Electron impact
ICR	Ion cyclotron resonance
PA	Proton affinity
TIC	Total ion current

II. AMINES

A. Neighbouring-group Effects in Functionalized Aliphatic Amines

Cleavage of the α-bond is the dominating fragmentation route in radical cations of aliphatic amines (Scheme 1). This cleavage is so facile that the molecular ion generated by electron impact (EI) is observed with low abundance or not at all. It has been shown by McLafferty[2] as early as 1962 that among the substituents at the α-carbon atom (R^1, R^2, R^3) the largest (e.g. R^1) will be lost preferentially. Cleavage of the C—N bond or loss of a substituent bound directly to the nitrogen, e.g. R^4,

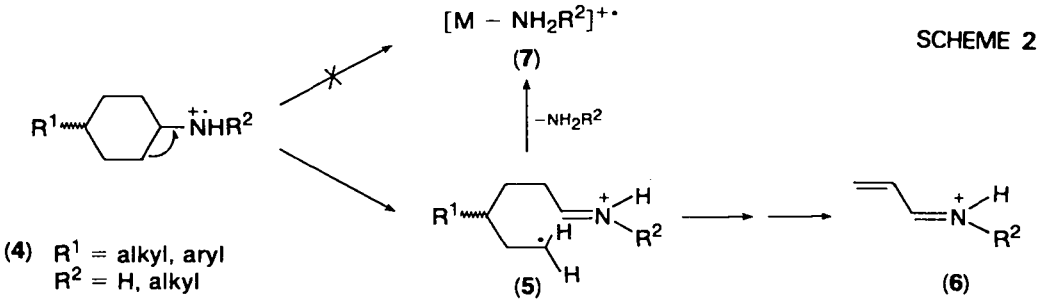


SCHEME 1

leading to the formation of a nitrene cation **3** (or an isomer thereof), is unimportant. This observation and additional thermochemical data lead to the conclusion that the formation of an immonium ion **2** via α-cleavage greatly outweighs energetically all competing reactions.

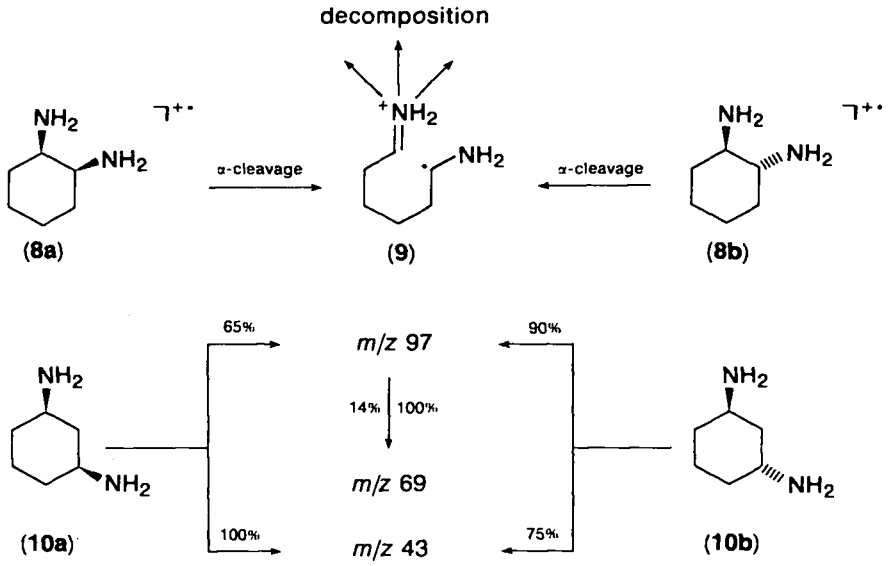
The fast α-cleavage explains why no stereospecific fragmentation is observed with the diastereomeric *cis/trans*-cyclohexylamines (**4**)[3]. While with the 3- and 4-substituted cyclohexanols not only the relative abundance of the $[M-H_2O]^{+\cdot}$ ions, but also the elimination mechanism, is determined by the *relative stereochemistry* of the two substituents[4], this is not the case with the corresponding amines (Scheme 2). The elimination of NH_3 or NH_2R from $M^{+\cdot}$ is of very minor importance (which is probably in general the case if a second functional group is missing[5]); furthermore, it appears that the reaction mechanism is not influenced by the relative stereochemistry of the intact six-membered ring. Both observations as well as energetic data[3] point to a rapid isomerization of the molecular ion **4** to **5** via α-cleavage. The activation energies, ε_0, for α-cleavages (under simultaneous formation of immonium ions) appear to be *lower* than those for the corresponding reactions in oxygen-containing compounds by 10–15 kcal/mol[3]; **5** is the precursor of all important consecutive fragmentations such as those leading to **6**. Moreover, all stereochemical relations of **4** are apparently levelled off in **5**. (Note that **5** still has diastereomers.) Thus identical fragments (such as **7**) with almost the same intensity ratios are formed from both isomers.

SCHEME 2



If the fragmentation behaviour of cyclohexylamines, such as **4**, is determined by fast ring-opening processes it is not surprising if the two stereoisomeric 1,2-cyclohexanediamines behave similarly as they indeed do. The mass spectra of the *cis/trans* isomers of 1,2-cyclohexanediamine (**8**) are almost indistinguishable[6]. This is rationalized assuming a *common* intermediate **9** for all decomposition pathways. It is, however, remarkable that in the case of 1,3- and 1,4-isomers (**10** and **11**) not only the two constitutional isomers yield distinct mass spectra (as expected); significant differences are also observed between the spectra of the stereoisomers. This will be demonstrated using the 1,3-isomer (**10**) as an example (Scheme 3). The *cis*-diamine **10a** yields *m/z* 43 as base peak, while the NH_3 elimination from $M^{+\cdot}$ (*m/z* 97) and the consecutive C_2H_4 loss (*m/z* 69) are observed with abundances of 65% and 14% (relative to the base peak = 100%). In the case of the *trans*-diamine **10b** the sequence $M^{+\cdot} \rightarrow m/z\ 97 \rightarrow m/z\ 69$ is clearly dominating with 100% and 90%, respectively, while *m/z* 43 is observed with an abundance of 75% (Scheme 3). Similar differences are also observed for the two stereoisomeric 1,4-cyclohexyldiamines (**11**).

It is not possible to decide unequivocally whether the observed phenomena result from the fact that in contrast to **4** and **8** the radical cations **10** and **11** do not undergo a ring-opening or whether the stereochemical differences of the ring-opened molecular ions are still so pronounced that sterically controlled

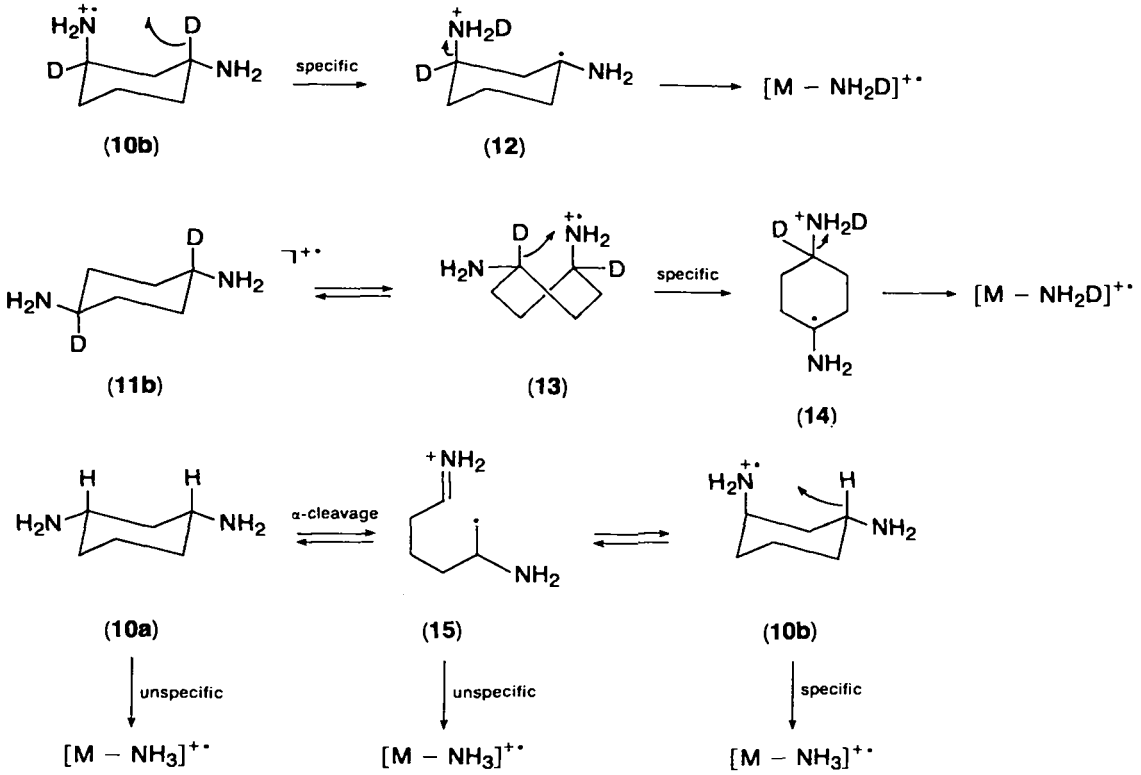


SCHEME 3

fragmentations are possible. However, the fact that the NH_3 elimination from the *trans* isomers **10b** and **11b** occurs stereospecifically with participation of the activated hydrogen at C(3) or C(4) (Scheme 4) points to intact ring-systems. It is, however, surprising that the NH_3 elimination from the *cis*-diamines **10a** and **11a** also largely occurs as 1,3- or 1,4-elimination. This result only makes sense if the *cis* compounds isomerize to the *trans*-diamines *prior* to decomposition (Scheme 4). There is no satisfactory explanation for this behaviour at present, but it is certain that the remarkably strong NH_3 elimination from diamines is induced by the presence of a second functional group.

The fragmentation of the radical cations of di(aminomethyl)cyclohexane isomers is also governed by pronounced stereochemical effects which result from the interaction of the two functional groups[6]. Thus ^2H-labelling studies demonstrate that in the case of the NH_3 elimination from, for example, the 1,3-*cis* isomers **16a** (Scheme 5), the necessary third hydrogen originates to 60% from the second aminomethyl group (**16a** → **17**). NH_3 elimination assisted by a S_Ni reaction[7] gives rise to the bicyclic ammonium ion **18** from which no further NH_3 can be eliminated. An analogous reaction sequence (**16a** → **19** → **20**) with participation of the C—H bond from C(5) is responsible for the remaining 40% of the ions. A second NH_3 elimination from $M^{+\cdot}$ is only observed for one of the two possible reaction paths of the *trans* isomer **16b** (**16b** → **23** → **24** → **25**). In this case the first NH_3 elimination is not the result of a cyclization via a S_Ni reaction, but occurs via intramolecular base-induced H-transfer after ring-inversion (**23** → **24**). In contrast to the $[M—NH_3]^{+\cdot}$ ions **18**, **20** and **22** the resulting ion **25** has a NH_3 group which can be eliminated.

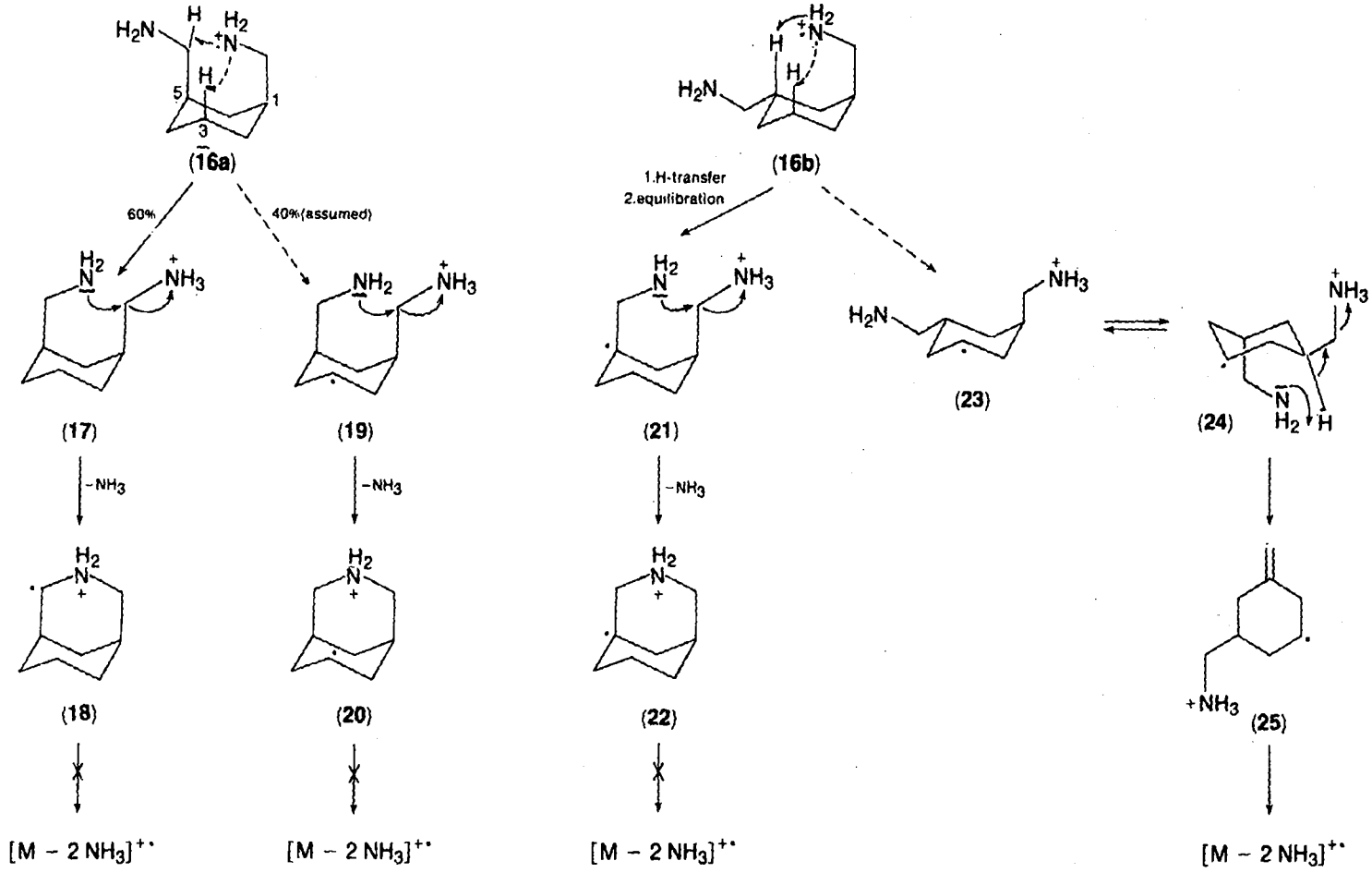
Moreover, neighbouring-group effects should also be responsible for the NH_3 elimination from acyclic diamines and ω-functionalized amines $[X—(CH_2)_n—NH_2]$. Here not only the number of methylene groups, n, which separate the functional groups (conformation effect), but also the nature of the second functional group X determines the extent of NH_3 and HX elimination and the regioselectivity of the H-transfer onto NH_2 and X. For 1,3-propanediamines **26** (R^1, R^2, R^3 = H, alkyl)



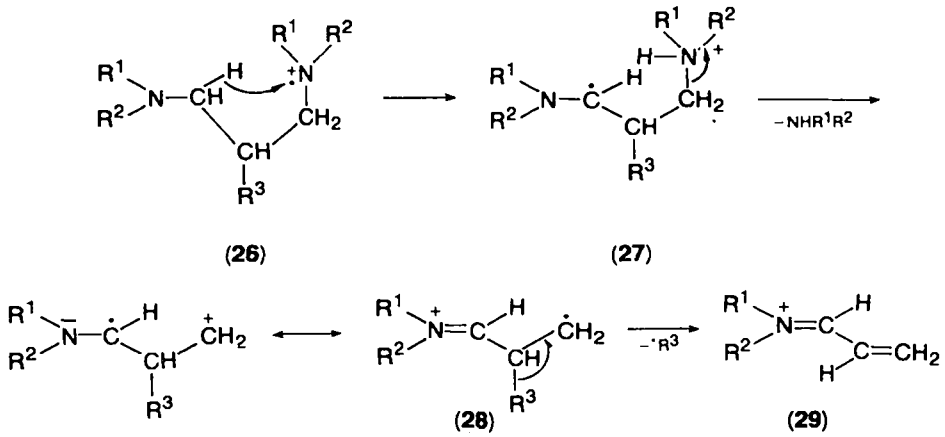
SCHEME 4

labelling experiments point to the reaction sequence shown in Scheme 6[8]. Here a hydrogen atom of an activated CH group is transferred to the ionized nitrogen in an almost regiospecific reaction (**26** → **27**). The heterolytic bond cleavage (**27** → **28**) is followed by an elimination of R^3 leading to the vinyl-substituted immonium ion **29**. The mass spectral behaviour of 1,4-diaminobutane (**30**) can also be rationalized by hydrogen-transfer reactions specifically induced by the NH_2 group[9]. With **30** the NH_3 elimination following the H-transfer (**30** → **31**) leads to a cyclic radical cation **32** via a S_Ni reaction which is the main difference from the 1,3-diaminopropanes **26** (Scheme 6). Loss of H• from **32** leads to **33** or **34** (Scheme 7). The cyclic structure of the primary product **32** is indirectly inferred from the dependence of the $[M - NH_3]^{+\bullet}$ intensity on the chain length of the diamines. Although such conclusions are justified in many instances[7,10], caution should be exercised if the diamines of alkanes are considered. Thus it should be noted that in many cases no cyclic species are apparently formed (e.g. **26**). Moreover, with higher homologues the reaction cannot be described by a single mechanism (see below). Thus a correlation of ion intensities with product stabilities (e.g. the ring size) is not justified in this case.

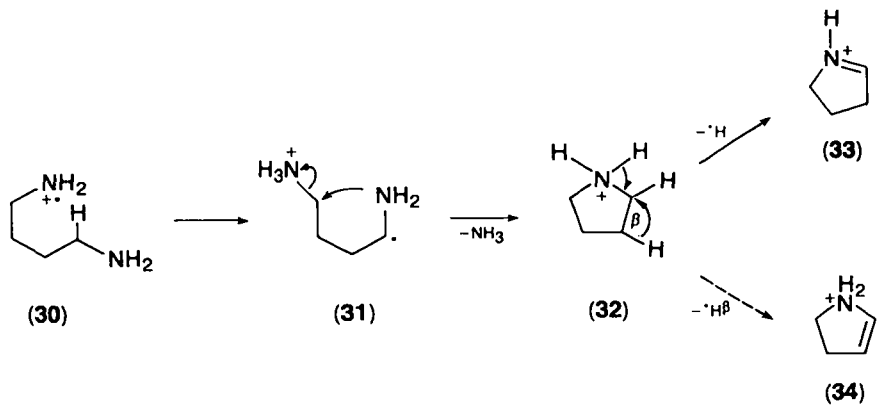
The complexity of neighbouring-group effects in the case of apparently simple NH_3 elimination will be demonstrated using the 1,6-diaminohexane **35** as an example. ^2H-labelling in every position of the molecule leads for the NH_3 elimination to a distribution shown in Scheme 8 which was simulated with a computer model[11]. The results demonstrate unambiguously that beginning from a certain chain length abundant H-exchange processes precede the elimination. The


(16a)
60%
40%(assumed)
(17)
(19)
-NH3
-NH3
(18)
(20)
[M – 2 NH3]+•
[M – 2 NH3]+•
(16b)
1.H-transfer
2.equilibration
(21)
(23)
(24)
-NH3
(22)
(25)
[M – 2 NH3]+•
[M – 2 NH3]+•

SCHEME 5



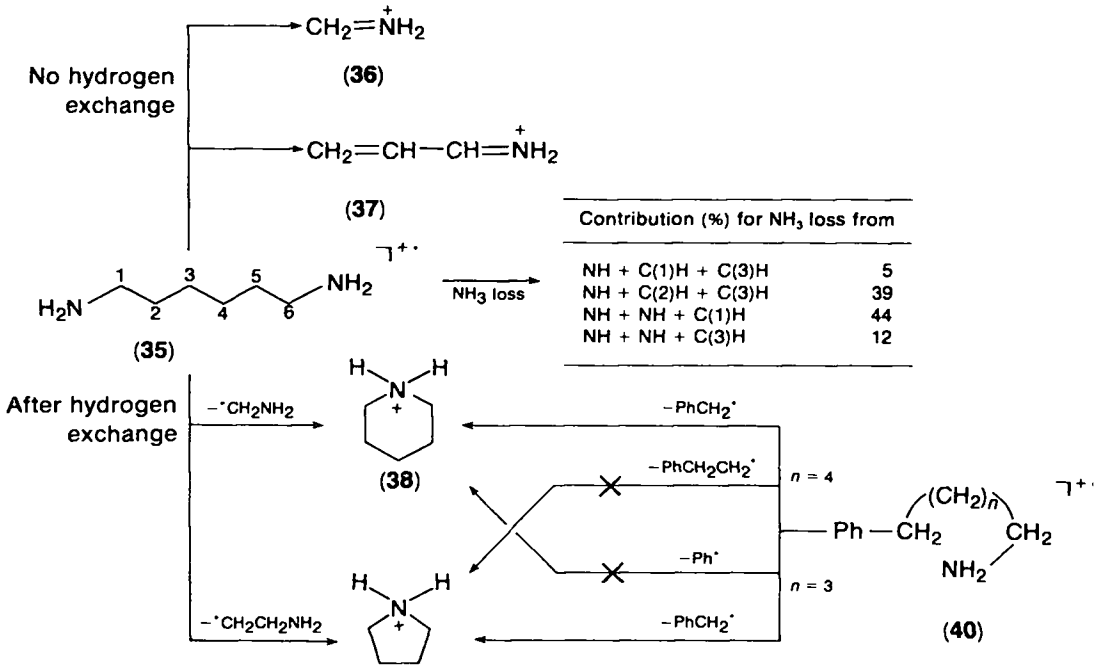
SCHEME 6



SCHEME 7

structures of the participating transition states or the resulting products (such as $[M - NH_3]^{+\bullet}$) are not known. It appears impossible – at least in this case – to describe the reaction using the concept of a simple S_Ni reaction. The exchange processes are especially pronounced for **33** and are encountered in all decomposition reactions (except the formation of **36** and **37**) including the elimination of $^{\bullet}CH_2NH_2$ and $^{\bullet}CH_2CH_2NH_2$ which only formally lead to the cyclic products **38** and **39** via S_Ni.

The question of the stability of cyclic ammonium ions (such as **38** and **39**) has been repeatedly discussed in the literature[12]. The fact that *n*-alkylamines preferably yield **38** has been rationalized assuming **38** to be more stable than **39**[12]. Appearance energy measurements[13] and proton affinity (PA) determinations[14] show that **38** is more stable than **39** by 8 kcal/mol. However, this does not permit the conclusion to be drawn that **38** is always formed at the cost of **39**. If suitable functionalized molecules, such as ω-phenylalkylamines (**40**) are considered, the stability of the radicals $Ph^{\bullet}$, $PhCH_2^{\bullet}$ or $PhCH_2CH_2^{\bullet}$ formed via an S_Ni reaction is so extremely different that it is the neutral *radical* which determines for a given chain length whether **38** or **39** is generated[14]. Thus in the case of the ω-phenylpentylamine **40a** ($n = 3$) almost exclusive elimination of $PhCH_2^{\bullet}$ with formation of **39** is observed,

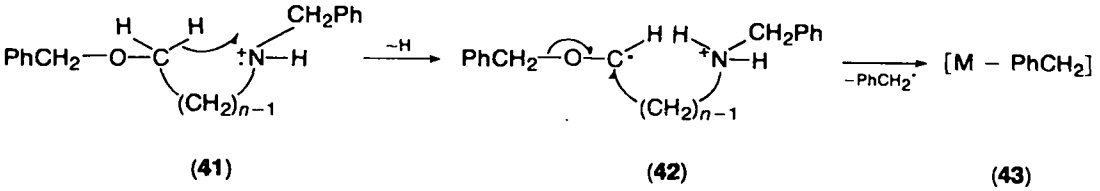


SCHEME 8

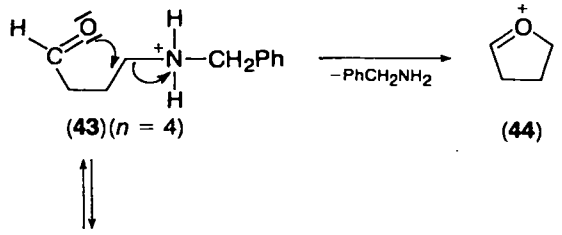
while the homologous ω-phenylhexylamine **40b** (n = 4) generates exclusively **38**. It is obvious that the formation of the products is determined by the special stabilization of the benzyl radical (as compared to the homologous phenyl and β-phenylethyl radical) and not by the stability of **38** and **39**[14].

Amine elimination via S_Ni reaction is also of importance with the radical cations of α-benzylamino-ω-benzyloxyalkanes (**41**) (Scheme 9)[15]. If the H-transfer can occur via *five-*, *six-* or *seven*-membered transition states (**41** → **42**) the benzyl elimination (**42** → **43**) is followed by a cyclization to **44** if n = 4. In competition with the $PhCH_2NH_2$ elimination (**43** → **44**) $PhCH_2OH$ can be lost via the sequence **43** → **45** → **46** → **33**. **41** exemplifies how reactions unknown in monofunctional compounds can be induced by the interaction of two functional groups.

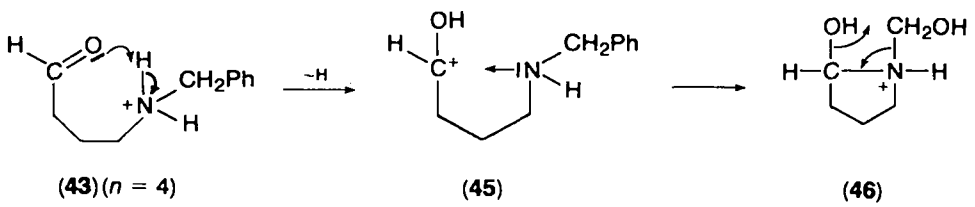
The theoretically[16] predicted existence of a protonated aziridine **48** was confirmed experimentally by Levsen and coworkers[17]. S_Ni reaction of β-phenoxyethylamine (**47**) gave **48** (Scheme 10) which was identified as a stable species by its collisional activation (CA) spectrum[18]. **48** was separated from the isomers **49** and **50** by significant potential barriers. Earlier CA studies[19] had already demonstrated that **49** and **50** also exist in potential minima. The isomerization **48** → **49** requires an activation energy of about 65 kcal/mol and is consequently only possible for sufficiently excited ions. If this condition is met, then the immonium ions **49**, generated from **48**, eliminate C_2H_2 as the barrier for isomerization **48** → **49** is above that of the transition state for the fragmentation **49** → C_2H_2 + NH_4^+. In addition, there are subtle arguments in favour of a 1,3-hydrogen migration[20] (**49** → **52**). Furthermore, it has been concluded indirectly that the transition state for the actual dissociation step (**52** → C_2H_2 + NH_4^+) has a ΔH_f^0 of *less* than 235 kcal/mol[17]. Figure 1 represents a simplified potential energy



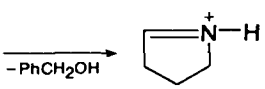
(41) (42) (43)



(43)(*n* = 4) (44)

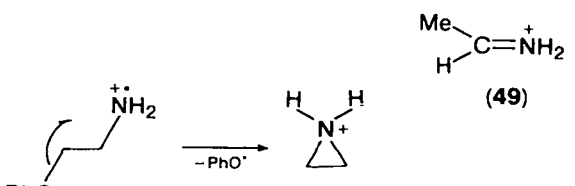


(43)(*n* = 4) (45) (46)



(33)

SCHEME 9



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

SCHEME 10

diagram for **48**, **49** and NH_4^+ formation from **49**. Earlier assumptions[21] that **48** does not exist in a potential minimum but acts only as transition state for the isomerization **49** → **50** could not be corroborated.

The gas-phase chemistry of $C_3H_8N^+$ ions has been studied using various techniques[19,22,23]. Thus CA spectra demonstrate that **53** and **54** exist in potential

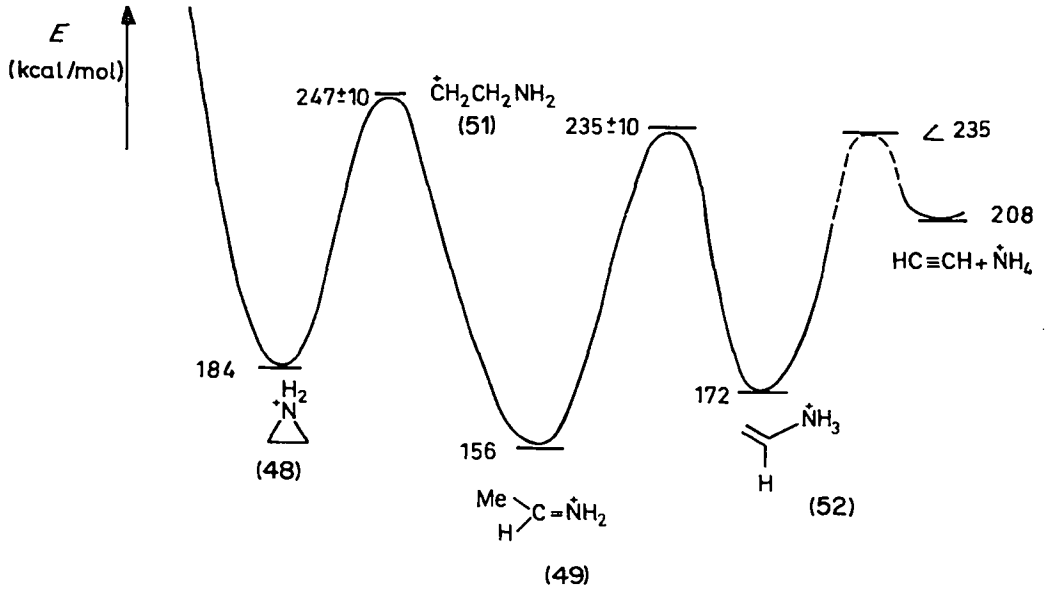
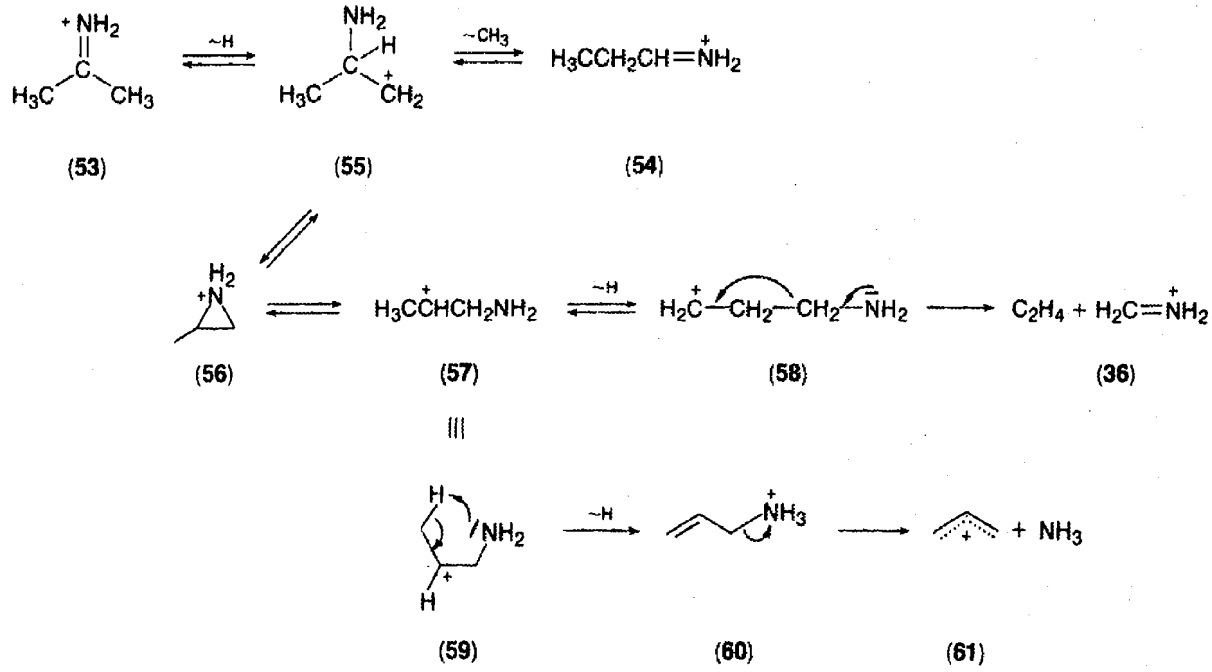


FIGURE 1.

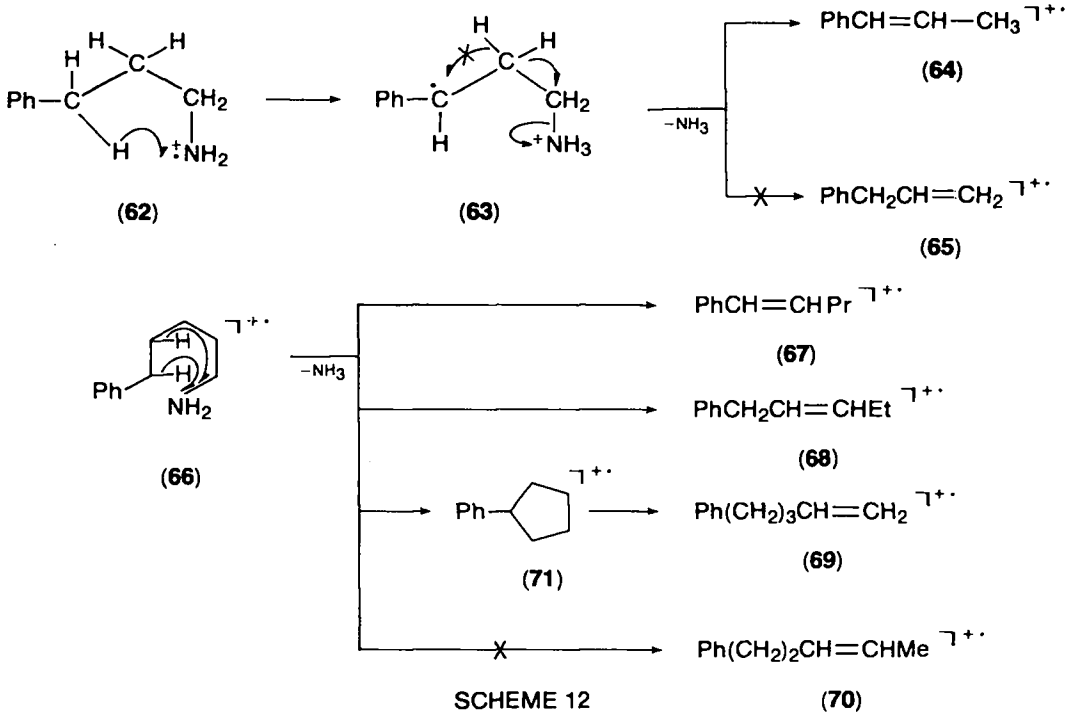
minima; if excited ions are considered, partial isomerization occurs via a sequence of 1,2-migrations as shown by ^2H- and ^{13}C-labelling. Moreover, cyclization reactions to the methyl-substituted aziridinium ion (**56**) can occur, from which C_2H_4 (by Grob elimination[24]) and NH_3 are finally eliminated after prior ring-opening and hydride shift (Scheme 11).

NH_3 loss from ω-phenyl-substituted amines **62** and **66** is also the result of functional-group interaction. The reaction sequence was analysed by a combination of isotopic labelling and collisional activation[14,25]. Ionized β-methylstyrene (**64**) is exclusively generated from **62**, while **67**, **68** and **69** are formed from the homologous 5-phenylpentylamine (**66**). The existence of **70** could not be demonstrated. While the formation of **67** and **68** presumably occurs via bicyclic transition states, **69** is most probably generated from the intermediate **71** (Scheme 12). All three $[M - NH_3]^{+\cdot}$ products have in common that the additional hydrogen lost as neutral NH_3 originates from the benzylic and homobenzylic positions, respectively. These observations have been considered as an indication that not necessarily conformational effects (concept of 'internal solvation'[26]), but in certain cases the activation of distinct C—H bonds, are responsible for H-transfer.

The examples shown in Figure 1 and Schemes 9 and 11 have already indicated that neighbouring-group effects are not restricted to 'open-shell' systems. The contrary is the case; they are often typical for 'closed-shell' ions, an observation which is well known in condensed-phase chemistry[27]. Protonation of a functional group X in the gas phase (e.g. by chemical ionization, CI[28]) sometimes leads to a loss of HX. This process is facilitated considerably by intramolecular interaction with a second functional group. A few examples have been selected to demonstrate this effect. While protonated α-amino acids do not generally lose H_2O and NH_3[29] these reactions are of high intensity with ω-amino and diamino acids[30]. From the numerous data available one can conclude that (1) the elimination of HX (X = OH, NH_2) is not determined by the original location of the proton


+NH2
H3C
CH3
(53)
~H
NH2
H
H3C
+CH2
(55)
~CH3
H3CCH2CH=+NH2
(54)
+H2N
(56)
H3C+CHCH2NH2
(57)
~H
H2C+—CH2—CH2—=NH2
(58)
C2H4 + H2C=+NH2
(36)
H
NH2
+
H
(59)
~H
+NH3
(60)
+
+ NH3
(61)

SCHEME 11

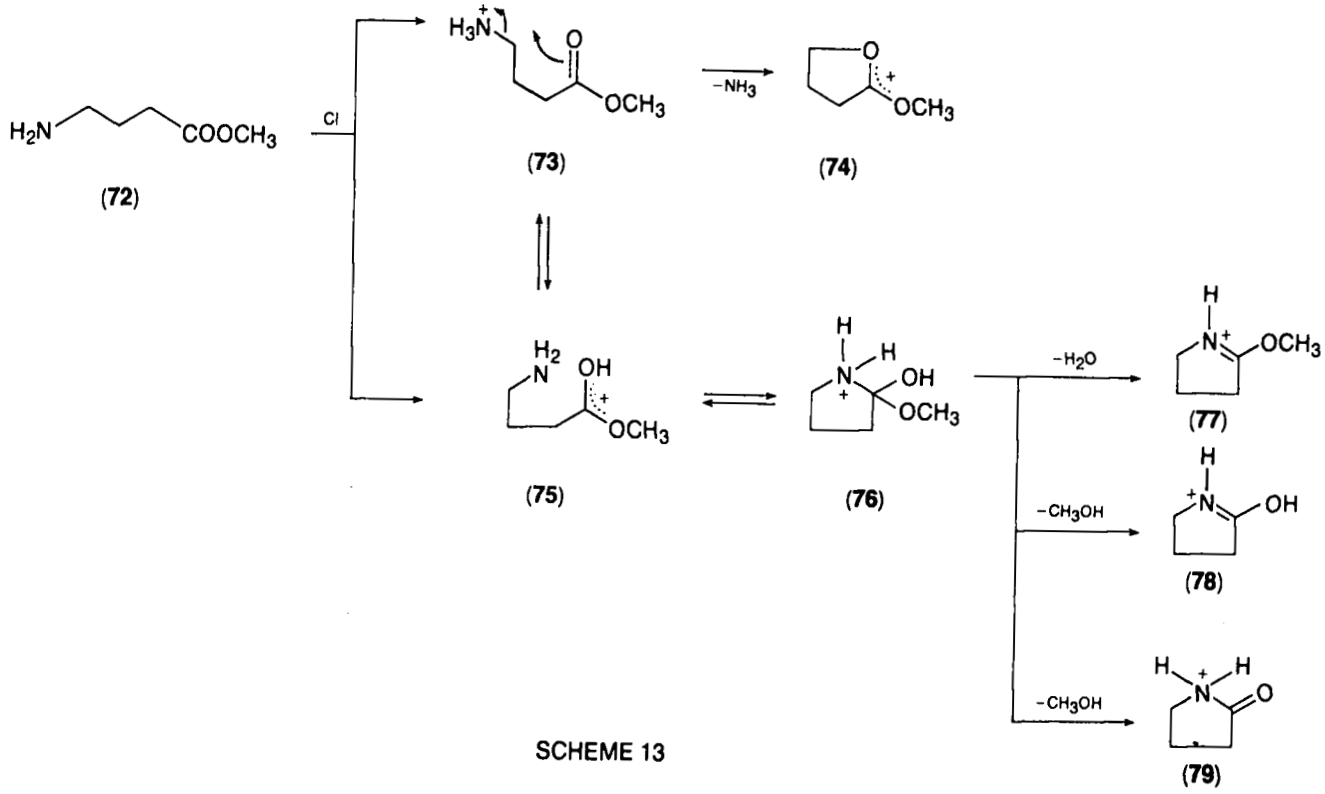


SCHEME 12

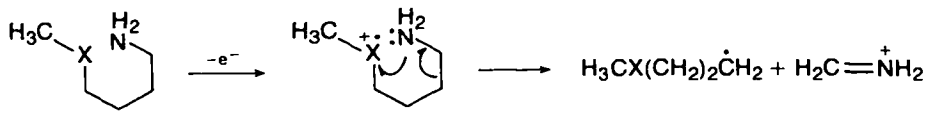
transferred, (2) extensive intramolecular H-exchange processes precede the decomposition and (3) the final reaction path of competing decomposition processes is exclusively determined by the product stabilities of the neutral and the ion. Neither the thermochemistry of the primary ion/molecule reaction (as reflected by the PA values), nor the stability of intermediate intramolecular hydrogen bridges are of importance for the reaction.

As examples of neighbouring-group effects in 'closed-shell' cations the elimination of NH_3, H_2O and ROH from protonated methyl ω-aminobutyrate (**72**)[30] is represented in Scheme 13. Whereas loss of NH_3 from **73** is assisted by a S_Ni reaction, the other decompositions shown in Scheme 13 are believed to occur via the tetrahedral intermediate **76**.

Finally, a special neighbouring-group effect in ω-functionalized amines should be mentioned briefly[32] as it has been used to probe the concept of charge localization[31]. It can be demonstrated for the case of Se- and S-substituted aliphatic amines[32] that for a given chain length (and thus conformation) *intramolecular charge transfer* through space occurs. Independently of the chain length, the primary ionization occurs predominantly at the functional group with the lowest ionization potential (in this case: S, Se). However, formation of the fragment **36** from **80** does not occur by α-cleavage of the original radical cation, but only after intramolecular electron transfer ($N \rightarrow S^{+\cdot}$ or $N \rightarrow Se^{+\cdot}$). Such processes are characterized by a significant effect of the chain length on the activation energies for the formation of **36** from the homologues of **80** (Scheme 14). If $n = 4$ the AE (**36**) corresponds more or less to the IP of the S or Se functional group while the AE is *significantly* higher with the other homologous compounds as well as with simple aliphatic amines.


H2N
COOCH3
(72)
CI
H3N+
O
OCH3
(73)
-NH3
O
+
OCH3
(74)
H2
N
OH
+
OCH3
(75)
H
N+
H
OH
OCH3
(76)
-H2O
H
N+
OCH3
(77)
-CH3OH
H
N+
OH
(78)
-CH3OH
H
N+
H
O
(79)

SCHEME 13



(80) (81) (82) (36)

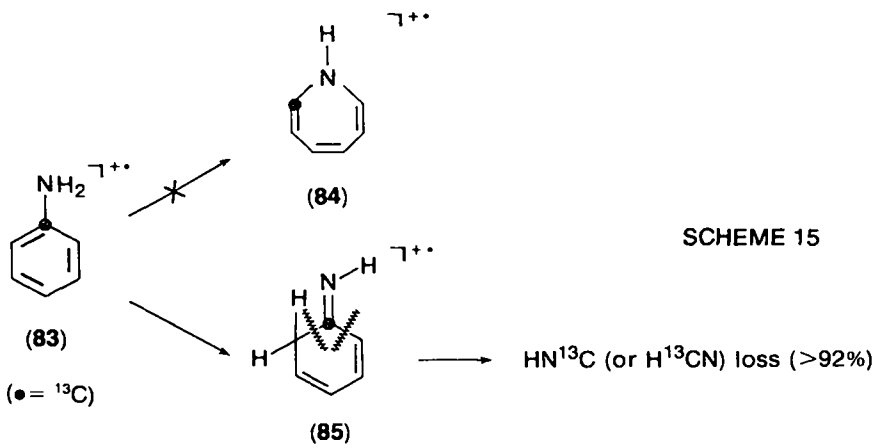
X = Se, S

SCHEME 14

B. Aromatic Amines

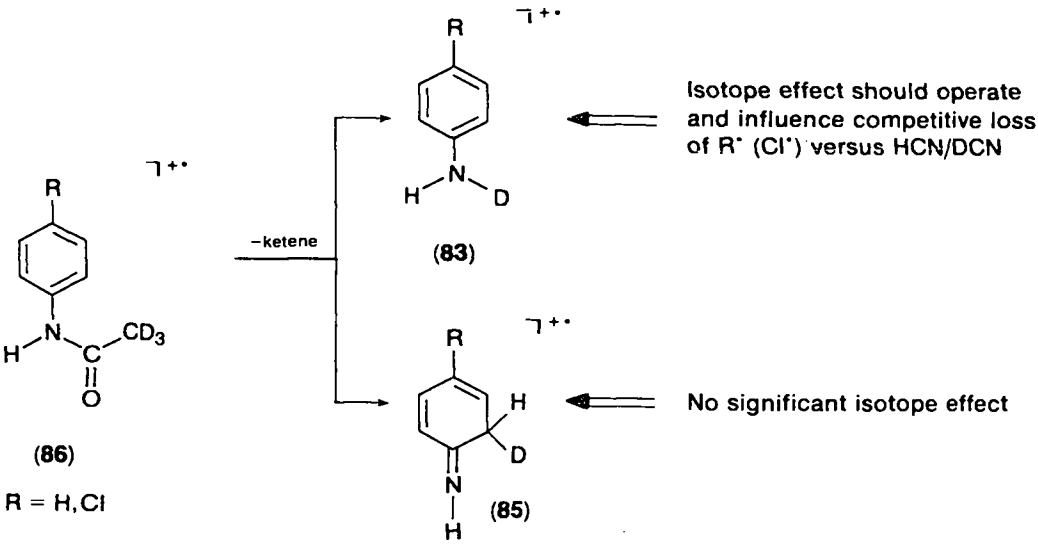
1. Aniline and benzylamine

In contrast to aliphatic amines, aromatic amines such as aniline (**83**) give rise to abundant molecular ions under electron impact conditions. Elimination of NH_2 is only a side-reaction; the main decomposition process corresponds to loss of HCN[1]. ^{13}C-labelling of aniline (**83**) leads to loss of HCN (or HNC) which contains at least 92% of the labelling[33]. This demonstrates that ring-enlargement of **83** to the azepinium ion (**84**) does *not* precede HCN loss. Instead it is assumed that prior to HCN loss an isomerization of **83** to **85** occurs via 1,3-hydrogen migration (Scheme 15).



SCHEME 15

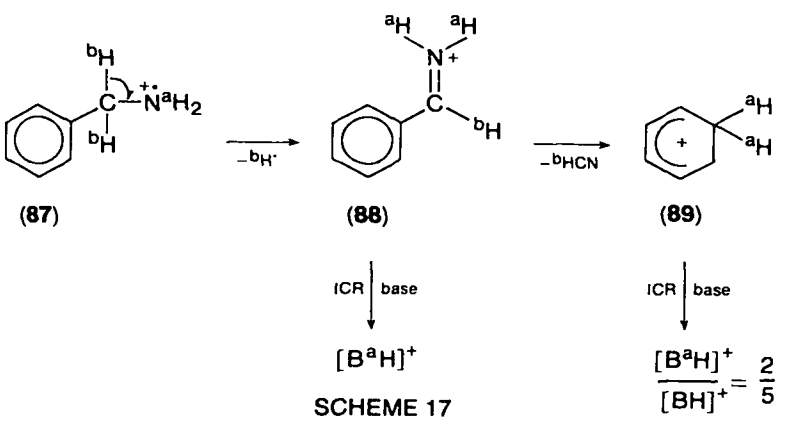
The mechanism of ketene elimination from the radical cation of acetanilide (**86**; R = H) has been discussed extensively[34,35]. The hydrogen migration which precedes this elimination may lead either to ionized aniline (**83**) or via a *six*-membered transition state directly to **85** (Scheme 16)[34,35]. Using an elegant experiment it can be demonstrated unequivocally that H-transfer from **86** occurs via a *four*-membered transition state leading to the ^2H-isotopomer of **83**. If this is indeed the case the competing secondary reactions of metastable $[M - \text{ketene}]^{+\cdot}$ ions should show a less significant HCN/DCN loss as compared to $Cl^{\cdot}$ loss, as a primary kinetic isotope effect operates during the isomerization but not during $Cl^{\cdot}$ loss. On the other hand, the direct transfer of a deuterium atom (**86** → **85**) should lead to no significant change in the relative abundance of $Cl^{\cdot}$ versus HCN/DCN loss. The analysis of seven deuterated isotopomers of **86** (R = Cl) and **83** demonstrates that a kinetic isotope effect, $k_H/k_D \simeq 2.2$, is observed for the decomposition of metastable ions in the second field-free region. Moreover, the relative abundance of HCN/DCN loss



SCHEME 16

(as compared to Cl• loss) decreases drastically in the case of **86** (R = Cl). Finally, the study of Williams[35] demonstrates that the 1,3-hydrogen migration (**83** → **85**) is at least partially reversible.

HCN elimination is observed as a secondary reaction in the mass spectrum of benzylamine (**87**)[36]. HCN elimination follows the specific loss of H• from the benzylic position. ^{2}H-labelling experiments show that *both* NH_2 hydrogens are transferred onto the phenyl ring (**88** → **89**). The result of ion/molecule reactions



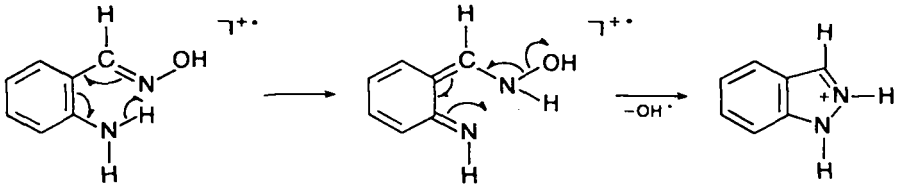
SCHEME 17

studied under ion cyclotron resonance (ICR) conditions is remarkable. While an ion/molecule reaction of **88** leads to a specific transfer of H^+ from the NH_2 position onto a suitable base, a complete equilibration of all seven hydrogens is observed in the case of protonated benzene. So far the mechanistic details of the double hydrogen transfer (**88** → **89**) has not been elucidated.

2. 'Ortho' effects

Mass spectrometric *'ortho'* effects have been reviewed in detail[37]. It is obvious that NH_2 groups can also act as ideal H-donors in such reactions if suitable acceptors are available in the *ortho* position. It is hardly possible to record the numerous examples for such rearrangements which usually involve *six*-membered transition states and lead to a loss of a neutral molecule. In this context only two reactions will be mentioned where direct bond cleavage seems to occur while in reality the reactions are induced by interaction with an *ortho* NH_2 group.

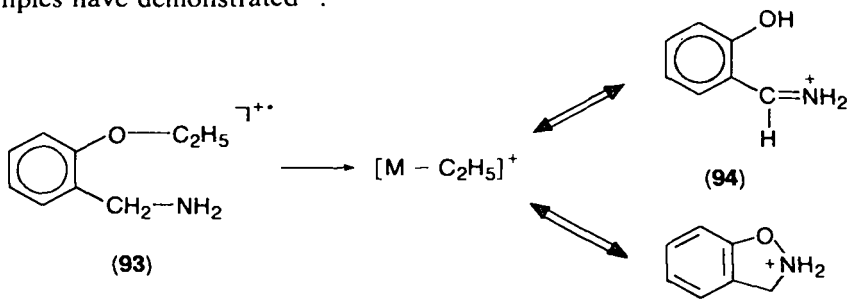
The first example represents the $OH^{\bullet}$ elimination from *ortho*-substituted benzaldoximes (**90**)[38]. Here a specific H-migration (**90** → **91**) precedes the $OH^{\bullet}$ loss as shown by the observation of isotope effects and the peak-shape analysis of metastable ions[39]. Rearomatization with concomitant cyclization (**91** → **92**) leads to the $OH^{\bullet}$ elimination (Scheme 18). This reaction type is not restricted to NH_2 groups as H-donors, but is also observed if CH_3 or OH are the *ortho* substituents.



(**90**) (**91**) (**92**)

SCHEME 18

Cleavage of the O—C bond in **93**[40] does not represent a simple dissociation. As the reaction is not observed with the *meta* and *para* isomers one has to conclude that the $C_2H_5^{\bullet}$ elimination from **93** is influenced in a specific way by the *'ortho'* substituent. With regard to both the structure of the $[M - C_2H_5]^+$ ion from **93** and the mechanism of its formation, there is so far no conclusive evidence as to whether a simultaneous elimination of $C_2H_5^{\bullet}$ and H-transfer (leading to **94**) or (less probable) an S_Ni reaction (leading to **95**) are operative. In any case, a cleavage of the O—C bond with charge localization at the oxygen atom (oxenium ion) is energetically very unfavourable and thus probably not realizable, as many recent examples have demonstrated[41].



(**93**) (**94**) (**95**)

SCHEME 19

III. NITROSO COMPOUNDS

References to the gas-phase chemistry of the radical cations of nitroso compounds are rarely encountered in the literature. The 70 eV mass spectrum of nitrosomethane[42a] contains, apart from the signal of $M^{+\bullet}$ (*m/z* 45) and NO^+ (*m/z*

30), an intense signal at m/z 90, which demonstrates that in the gas phase the radical cations of CH_3NO exist as dimers. The ion chemistry of trifluoronitrosomethane, CF_3NO, has been studied in detail[42b]. Dissociative ionization with cleavage of the relatively weak C—N bond is the dominant process in this case also. Ion/molecule reactions of CF_3NO in the gas phase lead to charge exchange followed by dissociation of $CF_3NO^{+\cdot}$ if hydrogen-free reactant gases are used. On the other hand, Brönsted acids yield $[MH]^+$ ions which, depending on the exothermicity of the proton transfer, may also decompose. The proton affinity (PA) of CF_3NO lies between that of HCN (173 kcal/mol) and H_2O (169 kcal/mol).

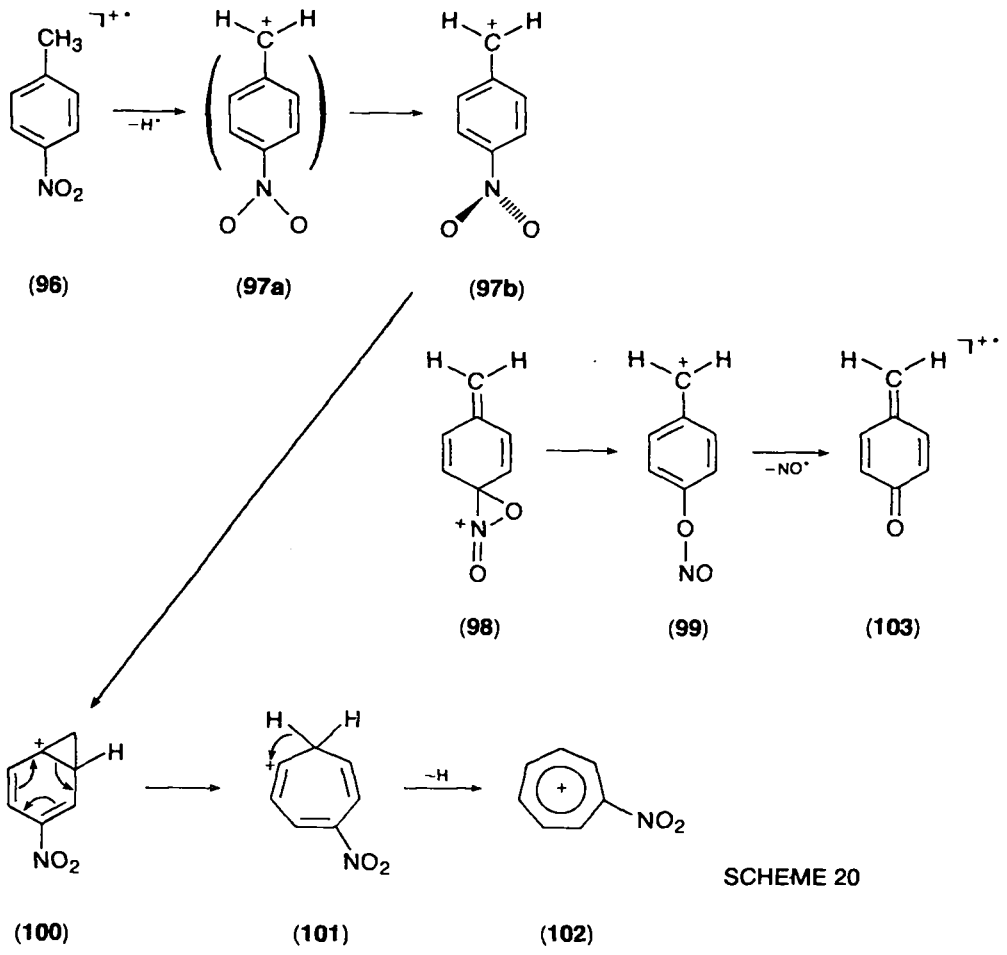
There are no indications of dimer formation in the mass spectrum of nitrosobenzene[43]. The spectrum is dominated by three signals: m/z 107 ($M^{+\cdot}$, 65%), m/z 77 ($[M - NO]^+$, 100%) and m/z 51 ($[M - NO - C_2H_2]^+$, 34%). The spectrum of the 3,5-$^2H_2$-isotopomer of nitrosobenzene displays a group of signals at m/z 53–51, the distribution of which reveals that the H/D atoms have become equivalent in the $[M - NO]^+$ fragment. Loss of the NO group is also the dominating reaction in the spectra of *o*-nitrosotoluene and *o*-nitrosobenzoic acid[42a]. The mass spectrum of 2-nitrosophenol was reported recently[110].

IV. NITRO COMPOUNDS

A. Isomerization $RNO_2^{+\cdot} \rightleftarrows RONO^{+\cdot}$

With the exception of nitromethane, aliphatic nitro compounds yield no, or only minor, molecular ions under electron impact conditions[44,45]. Thus, for analytical purposes (such as the qualitative and quantitative analysis of explosives) alternative ionization modes such as field desorption[46] or chemical ionization[47] have been tested and proved to be of value in practical applications. A suitable choice of experimental conditions leads either to abundant $[MH]^+$ ions or to structure-specific fragments. This is not possible if the classical 70 eV electron impact method is employed. Here aliphatic nitro derivatives and especially polynitro compounds lead to spectra with numerous fragments. For a long time it appeared that many decomposition channels of the $RNO_2^{+\cdot}$ ions proceeded from the isomeric $RONO^{+\cdot}$ form. However, detailed investigations demonstrated that this was not or only partially the case in aliphatic compounds[48]. For aromatic nitro compounds there have been many indications that, for example, the NO elimination is preceded by a nitro → nitrite rearrangement[49]. Moreover, the $[M - H]^+$ ions, which are surprisingly abundant in the spectrum of *p*-nitrotoluene (**96**)[50], owe their stability to the nitrite form **99**[50b]. If the NO_2 and $CH_2^{+\cdot}$ group in the nitro form **97a** were arranged in a planar conformation the NO_2 substituent would considerably destabilize the cationic centre. Detailed MINDO/3 calculations[51] give evidence that **97a** eludes this unfavourable situation by an orthogonal conformation **97b**. However, the decisive stabilization is achieved if **97b** isomerizes to **99** via **98**, a process which requires only 4 kcal/mol. According to MINDO/3 the nitrite-substituted benzyl cation **99** is more stable than the nitrobenzyl cation **97b** by approximately 40 kcal/mol. Isomerization of **97b** to the nitrotropylium ion **102**, which according to MINDO/3 is more stable than **97b** by 15 kcal/mol, proceeds via valence isomerization (**97b** → **100** → **101** → **102**) with a total activation energy of 33 kcal/mol (Scheme 20). Finally NO elimination occurs from **99** which leads to the quinonoid form **103**.

Cooks and coworkers[52] have studied the NO$^\cdot$ elimination from the radical cations of aromatic nitro compounds **104** by peak-shape analysis of decomposing metastable ions. Substituent effects and energetic data prove that NO$^\cdot$ elimination from $M^{+\cdot}$ proceeds by two competing processes. Electron-donating substituents

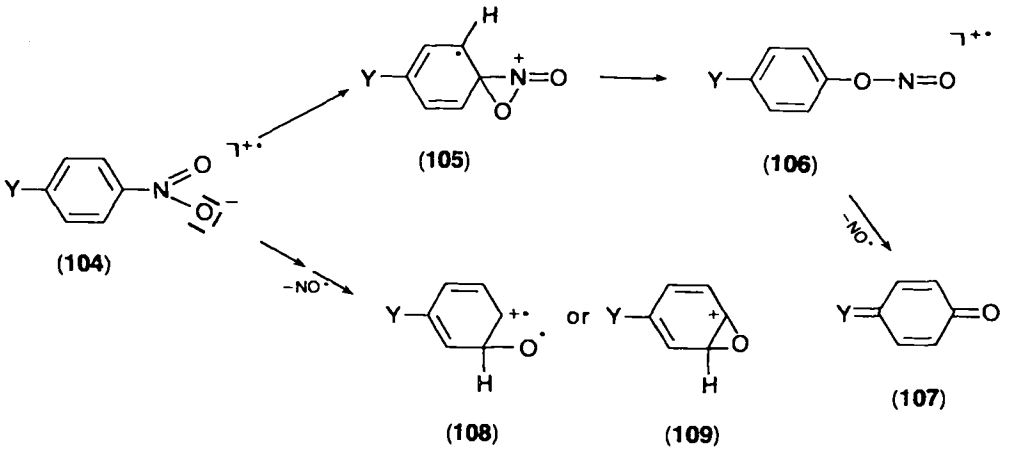


SCHEME 20

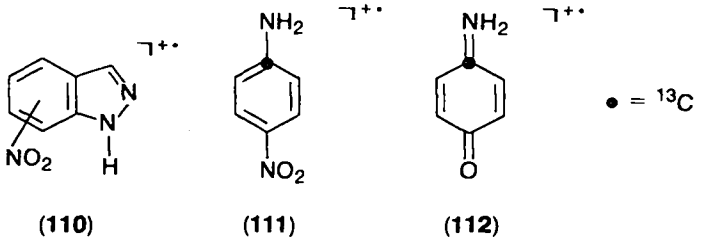
(Y = NH_2, OH, Me) favour the reaction path **104** → **107**, while with electron acceptors (Y = CHO) a different decomposition path prevails, which probably leads to **108** or **109** although this assumption has not been proven unambiguously (Scheme 21).

Peak-shape analysis for NO· elimination from aromatic nitro compounds has also been used to differentiate between isomeric nitroindazols (**110**). It is remarkable that the 70 eV mass spectra of the five isomers of **110** are almost identical, while the translational energy, T, released upon the unimolecular decomposition of $M^{+\cdot}_{110} \rightarrow [M - NO]^+$ is characteristically different for each isomer[53].

CO elimination from the $[M - NO]^+$ ions is a characteristic secondary decomposition of aromatic nitro compounds[1,49,50] (see also redox reactions in Section IV.B). The available data indicate that this reaction is very complex from a mechanistic point of view. It has been shown[33b] that the $[M - NO]^+$ ions (**112**) of *p*-nitroaniline (**111**) do indeed lose carbon monoxide (Scheme 22). However, not only ^{12}CO, but $^{12}CO/^{13}CO$ is lost in a ratio of 5:1. As no C-scrambling is observed in the molecular ions of **111**[33b] equilibration of carbon atoms presumably occurs in the $[M - NO]^+$ ions.



SCHEME 21



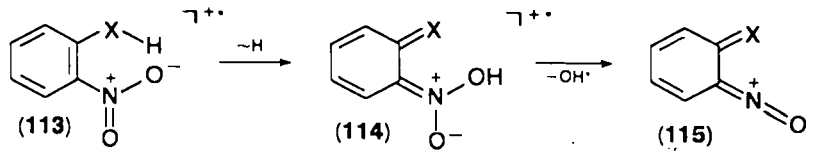
SCHEME 22

B. Redox Reactions of Aromatic Nitro Compounds

1. Hydrogen transfer

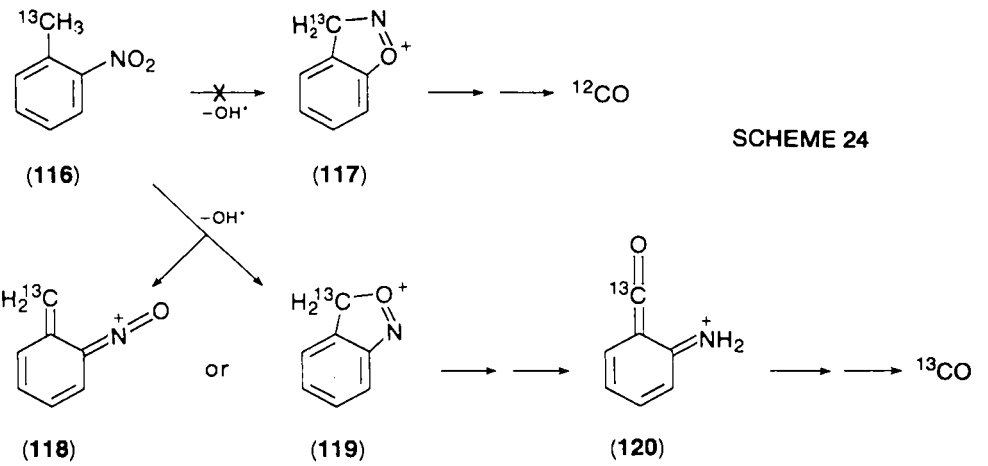
The unimolecular chemistry of radical cations is *inter alia* characterized by hydrogen-transfer reactions onto the NO_2 group followed by secondary decompositions[1]. H-transfer is particularly facile if (1) the hydrogen atom originates from an activated X—H bond, (2) the transition state is six-membered and (3) the H-donor (X—H) and acceptor (NO_2) are geometrically fixed as a result of the constitution of the compound. These conditions are ideally fulfilled for *ortho*-substituted aromatic nitro compounds. Thus it is not surprising that for **113** pronounced H-transfers are frequently observed[1,37]. Thus one observes abundant signals for OH• elimination, for example, for X = CH_2[49d,54], CHPh[55], NH[56], C=NAr[57] or CHN(alkyl)$_2$[58] (Scheme 23). The detailed mechanisms for H-transfer and OH• elimination (**113** → **115**) are determined by the nature of the substituent X. Thus depending on X the reaction probably proceeds via different mechanisms.

In the case of *o*-nitrotoluene (**116**) the reaction sequence can be elucidated, at least partially, using ^{2}H- and ^{13}C-labelled isotopomers[49d]. The $[M - OH]^+$ fragment loses exclusively ^{13}CO and no ^{12}CO, which leads to the conclusion that the OH•



SCHEME 23

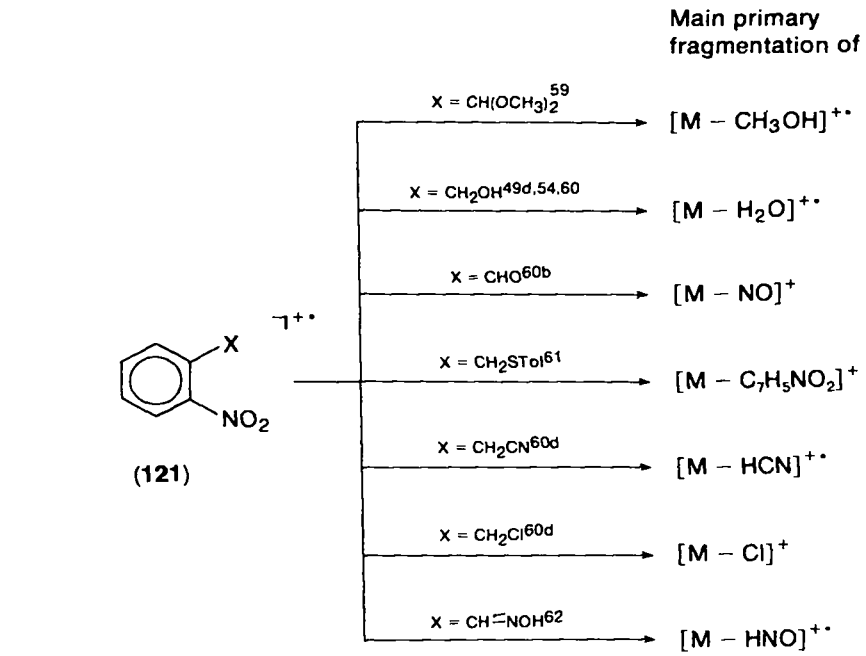
elimination does not proceed via **117** (**117** could be formed *inter alia* if the molecular ions **116** undergo an isomerization $RNO_2^{+\bullet} \rightarrow RONO^{+\bullet}$). Rather, it is assumed that $OH^{\bullet}$ loss leads to **118/119**. Although the mechanism is not fully understood **120** can be generated from these primary fragments. From **120** specific ^{13}CO elimination is possible[49d] (Scheme 24).



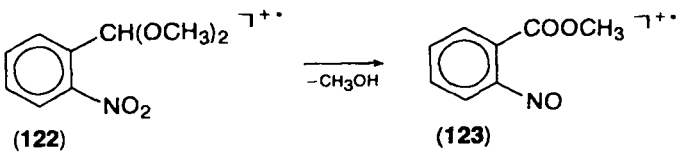
SCHEME 24

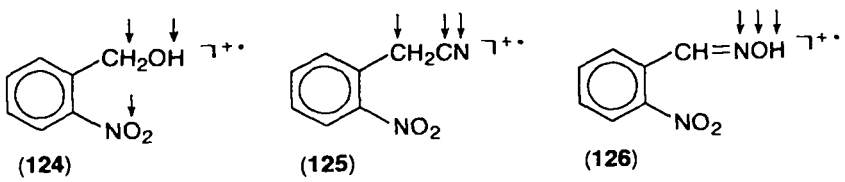
The complex and unpredictable influence of X on the details of the H-transfer and the consecutive reaction is reflected in Scheme 25, in which the main decomposition processes of some *ortho*-substituted aromatic nitro compounds are summarized. In spite of the fact that all substituents have an activated X—H bond, the very different products reveal the manifold chemical reactions. It is obvious that other processes outweigh the expected $OH^{\bullet}$ elimination, although these other processes are in part also induced by the primary H-transfer onto the NO_2 group.

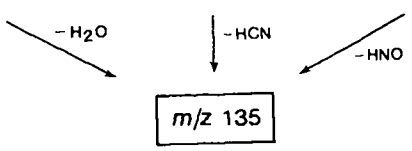
In spite of the employment of sophisticated experimental methods and the use of labelled compounds the reaction mechanisms and the ion structures involved in the majority of the processes listed in Scheme 25 are still not known. Only the product ions formed by elimination of CH_3OH, H_2O, HCN or HNO from **121** can be elucidated in part[62b] using CA spectroscopy[18]. Thus it can be demonstrated that analogously to the photochemical process[63] CH_3OH elimination from **122** leads to *o*-nitrosobenzoic acid methyl ester (**123**) (Scheme 26). In contrast to earlier postulates it can, however, be demonstrated that the remaining reactions do *not* lead to the radical cation of *o*-nitrosobenzaldehyde (**127**), but to the ionized 2.1-benzisoxazolinone-(3) (**128**). However, a mutual rearrangement of **128**, **129** and **130** as observed under thermal[64] or photochemical[65] conditions for the neutral molecules was not found for the radical cations[62b]. Partial isomerization of these species occurs only if the internal energy is raised[62a]. Although the structure of the primary fragments *m/z* 135 from **124**, **125** and **126** has been assigned unequivocally and the origin of the neutrals (indicated by arrows in Scheme 26) has been determined, one has to admit that the mechanistic details of the H-transfer, the



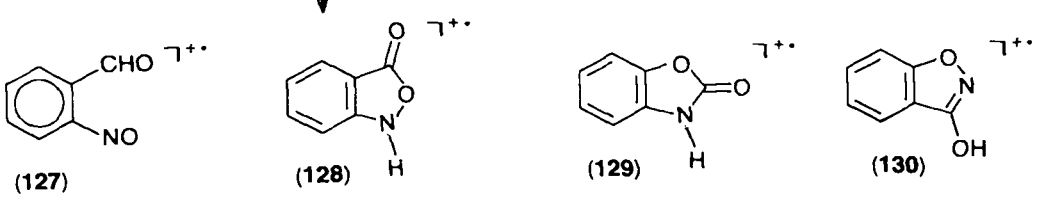
SCHEME 25





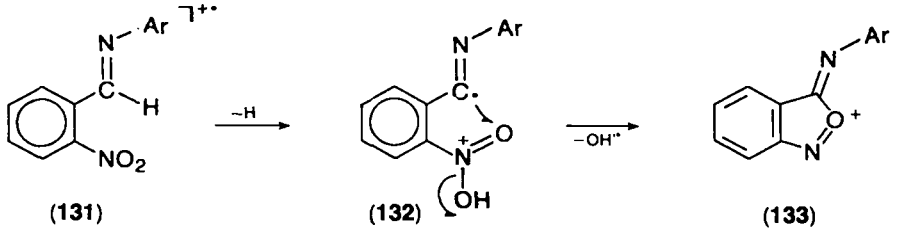


SCHEME 26



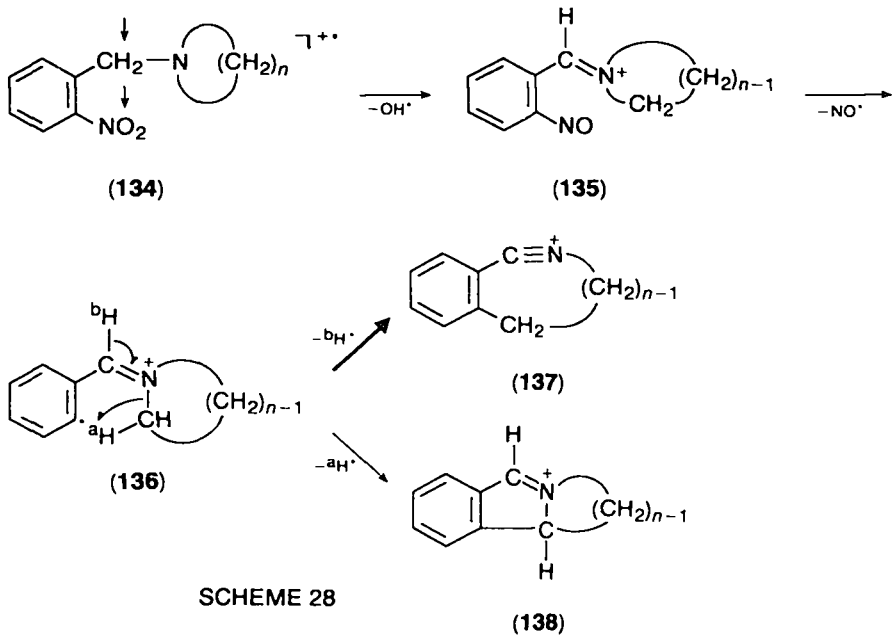
elimination of the neutrals and the structural reorganization of the ionic fragment are still not fully understood. Only a negative statement is possible: the processes outlined in Scheme 25 and 26 *cannot* be classified as 1,1-eliminations (cheletropic processes)[66]. Rather, these eliminations can be viewed as intramolecular redox processes with participation of *hydrogen* and *oxygen* rearrangements.

H-transfer in *o*-nitro-substituted aromatic cations, followed by OH$^{\bullet}$ elimination and cyclization, has also been observed for a variety of other compounds. Thus **133** is generated from the anilide of the *o*-nitrobenzaldehyde (**131**) via **132** by cyclization[57] (Scheme 27).



SCHEME 27

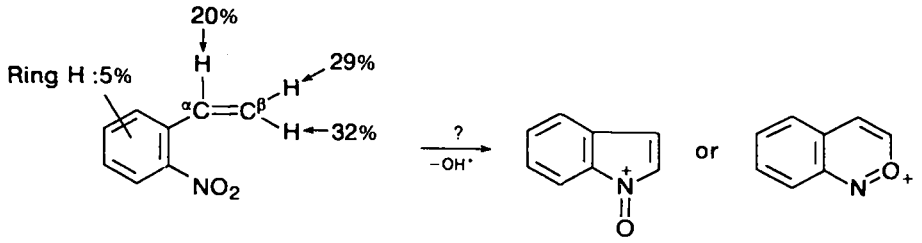
The molecular ions of the *N*-(*o*-nitrobenzyl)amine **134** (n = 4, 5, or derivatives of the dimethylamines) expel OH$^{\bullet}$ in a regiospecific fashion[58]. The consecutive NO$^{\bullet}$ elimination is followed by a rarely encountered radical-induced cyclization coupled with a Grob fragmentation[24] (**135** → **136** → **137**). The alternative reaction (**136** → **138**) is of little significance[58] (Scheme 28).



SCHEME 28

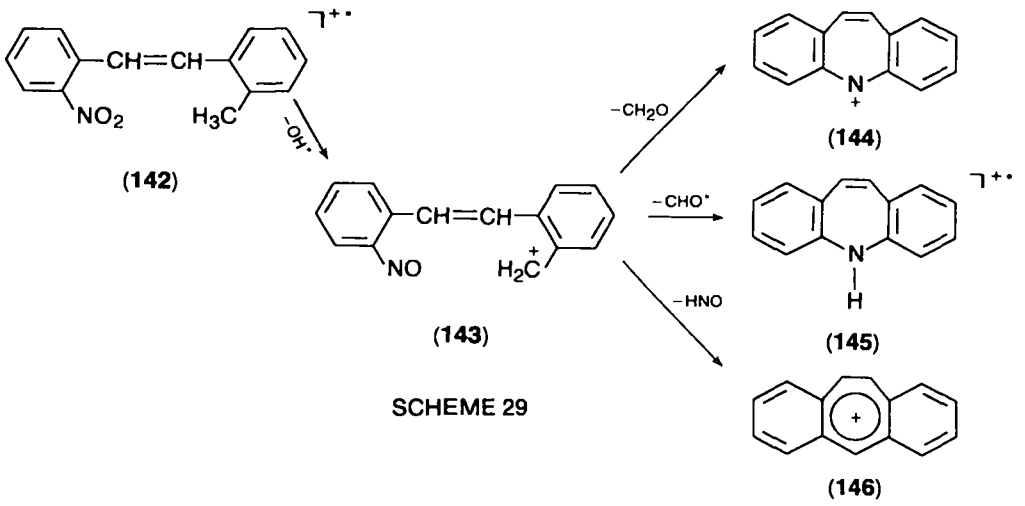
Combined ^{2}H- and ^{13}C-labelling has been used to study the OH$^{\bullet}$ elimination from *o*-nitrostyrene (**139**)[67,68]. ^{2}H-labelling reveals that the hydrogen of the hydroxy radical originates from *all* C—H bonds of the vinyl group. Surprisingly, hydrogen atoms of the phenyl ring also participate to the extent of 5% in the formation of

the neutral[68]. The CO loss from the $[M - OH]^+$ ion does *not* involve the β-carbon atom[67] thus excluding a simple cyclization of **139** to **140** or **141**.



(139) **(140)** **(141)**

It is likely that the hydroxyl elimination from the 2,2′-disubstituted stilbene **142** and the consecutive processes (elimination of CH_2O, CHO or HNO) are considerably more complex than suggested by the authors[69] (Scheme 29).

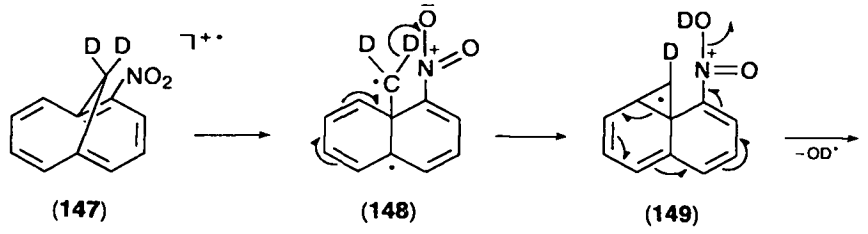


(142) **(143)** **(144)** **(145)** **(146)**

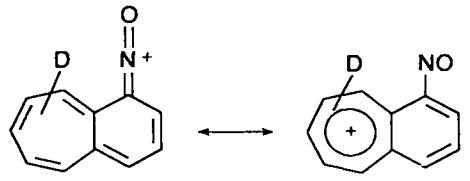
SCHEME 29

OH· elimination from the radical cation of the 2-nitro-substituted [1.6]-methanoannulene (**147**)[70] occurs surprisingly specifically. ^{2}H-labelling reveals that the hydrogen does not originate from the CH-perimeter, but exclusively from the methano bridge. The reaction sequence proposed in Scheme 30 is consistent with the experimental results (Scheme 30).

In this context it is necessary to mention that the OH· elimination from substituted aromatic nitro compounds is not restricted to the *ortho* compound. While OH· loss from **151** can be rationalized assuming that a ring-enlargement (**151** → **152**) and a migration of the substituent precedes the elimination[71], the hydroxyl loss from *p*-nitro-substituted aromatic cations **153**[72,73a] cannot be elucidated unequivocally in spite of extensive labelling experiments[73a]. It can only be ascertained that the OH· elimination from **153** is not a consequence of substituent migration (**153** → **154**). The CA spectra of the $[M - OH]^+$ ions from **153** and **154**, respectively, show pronounced differences, so that a common structure of the daughter ions and therefore also of the molecular ions can be ruled out[73a] (Scheme 31). The mechanism of the OH· elimination from nonvicinal NO_2-substituted aromatic compounds has been studied in detail by Cooks and coworkers[73b] and Baldwin[73c], although a safe conclusion could not be reached.

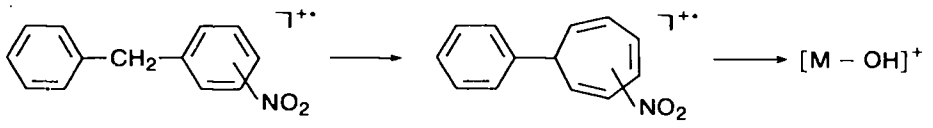


(147) (148) (149)

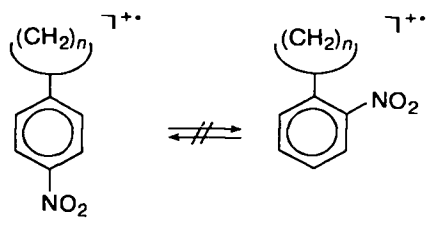


(150)

SCHEME 30



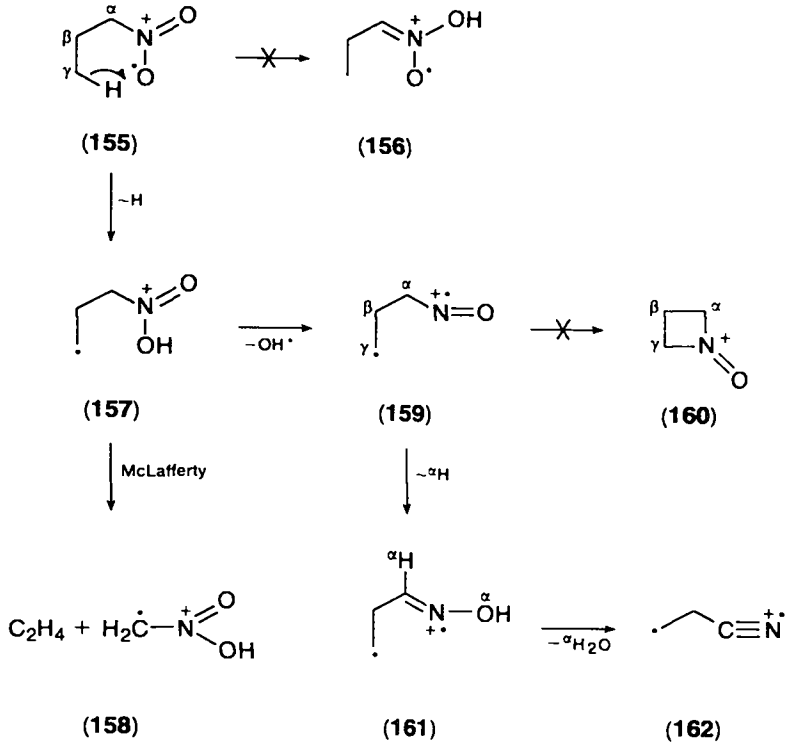
(151) (152)



(153) n = 2,3,4,5 (154)

SCHEME 31

Finally, H-transfer in *aliphatic* nitro compounds will be briefly discussed, restricted to those examples for which the reaction sequence has been ascertained by labelling experiments. Nibbering and coworkers[74] have elucidated the most important decomposition processes of 1-nitropropane (**155**) using ^{2}H-labelling. The authors have demonstrated that the radical cations from **155** do *not* decompose through the *aci* form (**156**); the main decomposition pathway from **155** is NO_2 elimination. In addition one observes an ethylene elimination via a McLafferty rearrangement (**155** → **157** → **158**) and loss of OH$^\bullet$. Both reactions proceed from the primary hydrogen rearrangement product **157**. Both hydrogen atoms involved in the H_2O loss from the $[M - OH]^+$ ion originate from the α-CH_2 group, demonstrating that cyclization of **159** to **160** does not occur, as the α/γ-CH_2 groups in the cyclic ion are indistinguishable. Instead of a cyclization the authors propose an isomerization **159** → **161** with subsequent H_2O loss to give **162** (Scheme 32).



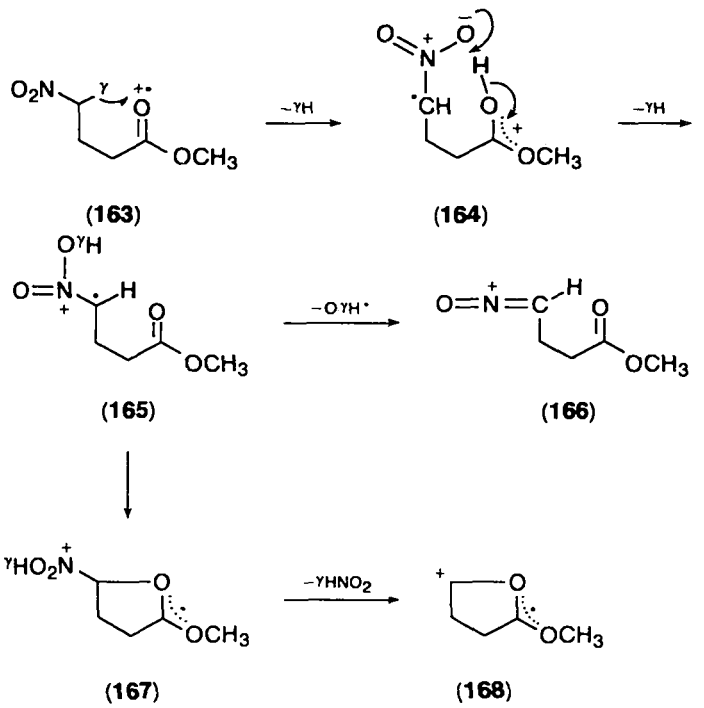
SCHEME 32

OH• elimination from ionized nitroalkanes is significantly influenced by the presence of a second substituent. In the case of methyl γ-nitrobutyrate (**163**) the hydrogen of the neutral originates exclusively from the γ-CH_2 group. It is assumed that this process is catalysed by the ester group. The primary transfer of a hydrogen onto the $COOCH_3$ group (**163** → **164**) is followed by a further transfer onto the NO_2 group. The resulting species **165** either eliminates OH• (**166**) or a cyclization (**165** → **167**) with loss of HNO_2 is observed. Formally speaking the HNO_2 elimination represents a 1,1-elimination. However, from a mechanistic point of view this elimination is the result of a neighbouring-group effect of the $COOCH_3$ functional group[75] (Scheme 33).

A completely different mechanism is found for the OH• elimination from ω-nitro amides (**169**)[76]. Depending on the chain length, $(CH_2)_n$, and the structure of the amino moiety (acyclic, cyclic, ring-size) various CH_2 groups act as H-donors. With all amides the oxygen of the neutral particle originates exclusively from the NO_2 group. Primary CH_3 groups as encountered with amides with acyclic amino moieties never act as H-donors. Besides this the situation is rather complicated as shown in Scheme 34 and cannot at present be rationalized in a simple manner. The carbonyl group probably acts as H-acceptor/donor catalyst in this case also.

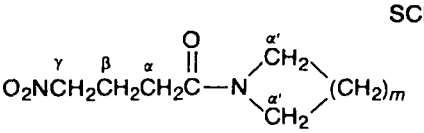
2. *Oxygen migration*

Intramolecular oxygen migrations in radical cations as described for the first time by Seibl[72,77] have been investigated extensively in recent years[37,38]. Thus, the use of high-resolution mass spectrometry, the study of labelled compounds and the analysis of metastable transitions have led to the elucidation of these complex

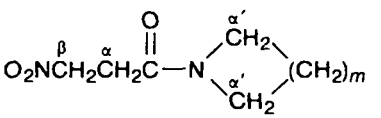


(163) (164) (165) (166) (167) (168)

SCHEME 33



(169)



(170)

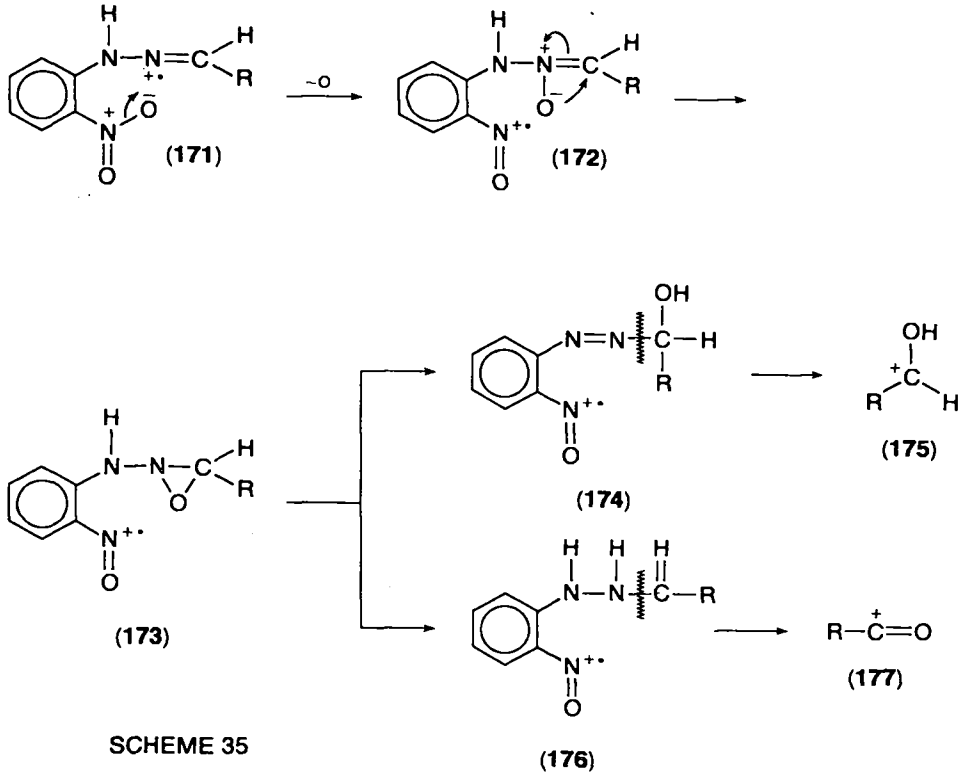
m	Hydrogen source		
	α′	α	γ
1	—	—	100
2	35	34	30
3	70	19	5

m	Hydrogen source		
	α′	α	β
1	—	40	30
2	100	—	—
3	100	—	—

SCHEME 34

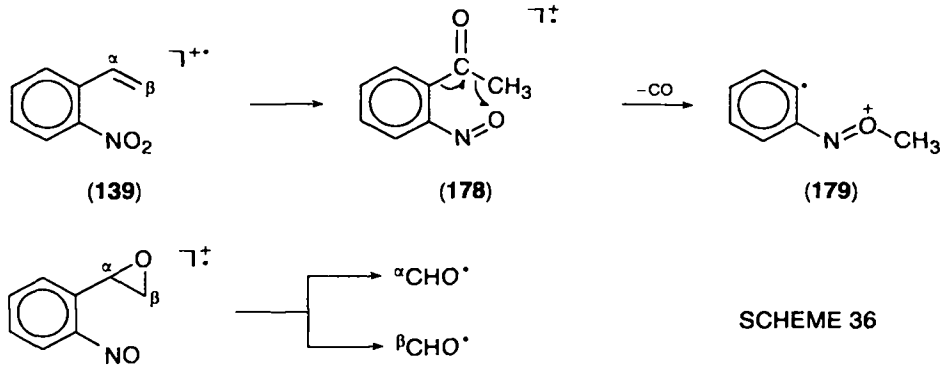
redox reactions for *o*-nitrophenylhydrazones (**171**) of aromatic aldehydes and ketones. The important step is the oxygen transfer from the nitro group to the N=C double bond (**171** → **172**) followed by a series of rearrangements. The reaction is completed by a heterolytic bond rupture leading to the structure-specific fragments **175** and **177**[72,77] (Scheme 35). Related processes have also been observed with nitrostilbene[79].

The complexity of such redox reactions is illustrated by the detailed investigation of Middleton[67]. The investigation of ^{13}C- and ^{2}H-labelled *o*-nitrostyrene (**139**) suggests that, for example, the CO elimination proceeds from the nitrosoacetophenone form **178** (**178** → **179**), while HCO loss occurs via the epoxide



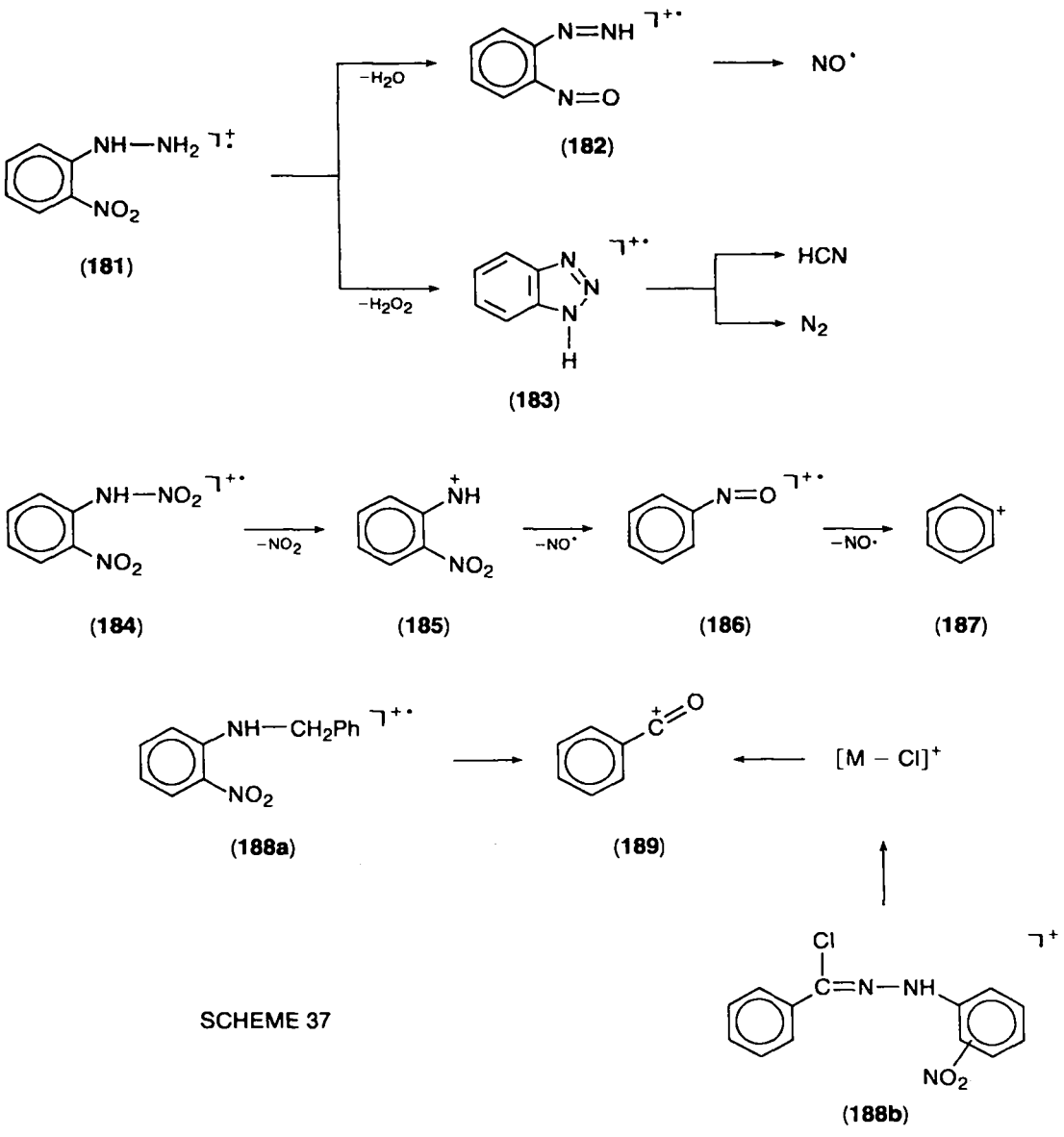
SCHEME 35

180. Both the α- and the β-carbon atoms are involved with equal probability in the HCO formation. It is assumed that the reaction proceeds via the well-known epoxide rearrangement[80] (Scheme 36).



SCHEME 36

Rather uncommon reactions are observed if a heteroatom-containing substituent (preferably with N, S or P) is in the position *ortho* to the NO_2 group. Holmes[81] reports that **181** eliminates unimolecularly not only H_2O but also H_2O_2 (!); Hammerum[82] has found that NO_2 elimination from **184** is followed by a double NO elimination (**184** → **185** → **186** → **187**). Moreover, the formation of Ph—$\overset{+}{C}$O from **188** must also be interpreted as intramolecular oxygen transfer[83a] (Scheme 37); *m/z*

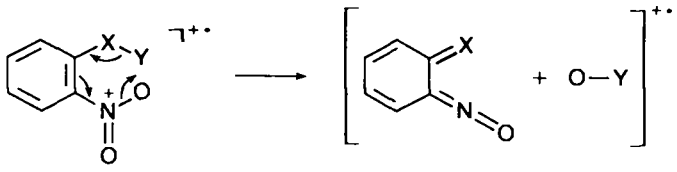


SCHEME 37

189 is also generated from the $[M - Cl]^+$ ions of hydrazonyl chlorides of type **188b**. It is noteworthy that this process is observed for all *three* constitutional isomers indicating that in this case a migration of the substituent occurs[83b].

The extent and ease of oxygen transfer processes in *N*-derivates of nitro compounds is probably influenced by the basicity of N and the electronic nature of X—Y (in **190**)[61]. Systematic investigations of the redox behaviour of radical cations with the general structure **190** were carried out in order to study the influence of the X—Y group on the reaction **190** → **191** + **192**. In contrast to the oxygen migrations observed by Seibl[72,77] this process is in direct analogy to the H-transfers

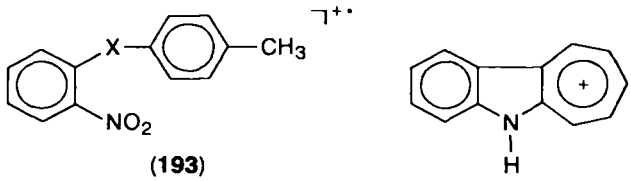
which occur by an *ortho* effect via six-membered transition states (Scheme 38). If X = CO (in **190**) intense fragments are found which result from an oxygen transfer if Y is nitrogen[82,84], sulphur[85], selenium[86], phosphorus[87] or carbon[88].



(190) **(191)** **(192)**

SCHEME 38

In several instances signals have been observed in the mass spectra of *ortho*-substituted aromatic nitro compounds which point to a *multiple* oxygen transfer[61,86]. While for the selenium compound **193** (X = Se) only a single oxygen transfer has been observed ($C_7H_7O^+$ = 7%; C_6H_4NOSe = 81%) the molecular ion of the corresponding sulphide (X = S) loses SO_2 (30%). Analogously only single oxygen transfer is observed if X = SeO while the sulphoxide (X = SO) expels both SO_2 and SO_3. Loss of SO_3 from **193** (X = SO) is followed by H$^\bullet$ elimination (100%) which presumably leads to **194**. The different behaviour of the Se/S compounds is probably due to the markedly different oxygen affinities of Se and S[61,86].



(193) **(194)**

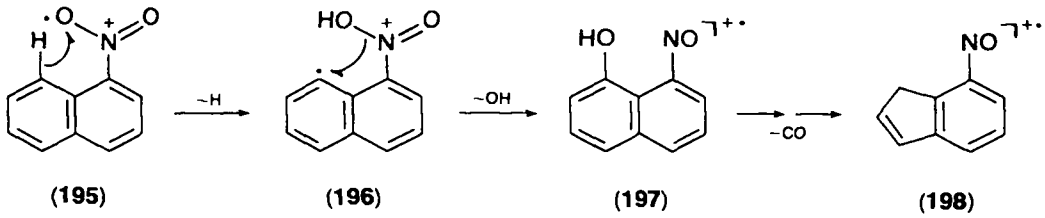
X = S, Se, SO, SeO

SCHEME 39

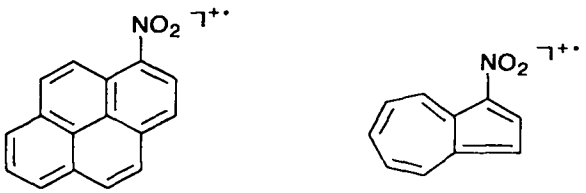
The fact that the molecular ions of 1-nitronaphthalene (**195**) lose CO (in contrast to the derivatives of nitrobenzene[1]) has been rationalized assuming an oxygen transfer[54,60b]. The reaction starts with hydrogen transfer from the *peri* position onto the NO_2 group. The following OH$^\bullet$ migration leads to a 'phenol' ion which after ketonization loses CO (Scheme 40). However, no loss of CO is observed for 1-nitropyrene (**199**) and 1-nitroazulene (**200**)[1d].

If the 8-position in 1-nitronaphthalene contains a substituent which can be eliminated (such as NO_2) $NO_2^\bullet$ elimination is observed (100%)[89]. From 10 investigated isomeric dinitronaphthalenes this reaction is only found for the 1,8-dinitro derivative (**201**). The elimination of NO_2 only occurs if the *peri* position carries a substituent which assists both sterically and electronically the cleavage of the C—N bond. The COOH group represents such a substituent. Thus the 1,8-disubstituted compound **203** displays an abundant NO_2 loss (95%) followed by twofold elimination of CO[90] (Scheme 41).

It seems that neighbouring-group-assisted NO_2 elimination is possible in largely different substrates. Thus intense signals for $[M - NO_2]^+$ are observed for the anthraquinone derivative **205**[91] or the azastilbene compound **207**[79]. The daughter ions are presumably cyclic (**206** and **208**). Moreover, the marked dependence of the intensity of the $[M - NO_2]^+$ ions on the chain length $(CH_2)_n$ in **209** (pronounced maximum for $n = 4$) can probably be rationalized assuming a cyclization (S_Ni

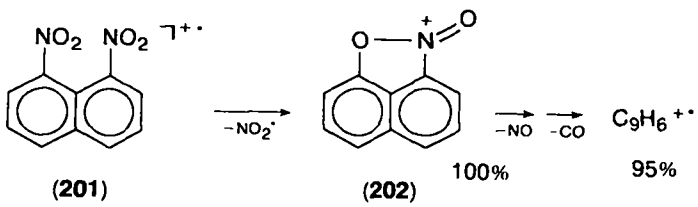


(195) (196) (197) (198)

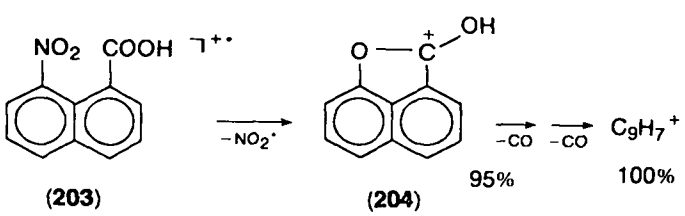


(199) (200)

SCHEME 40



(201) (202)

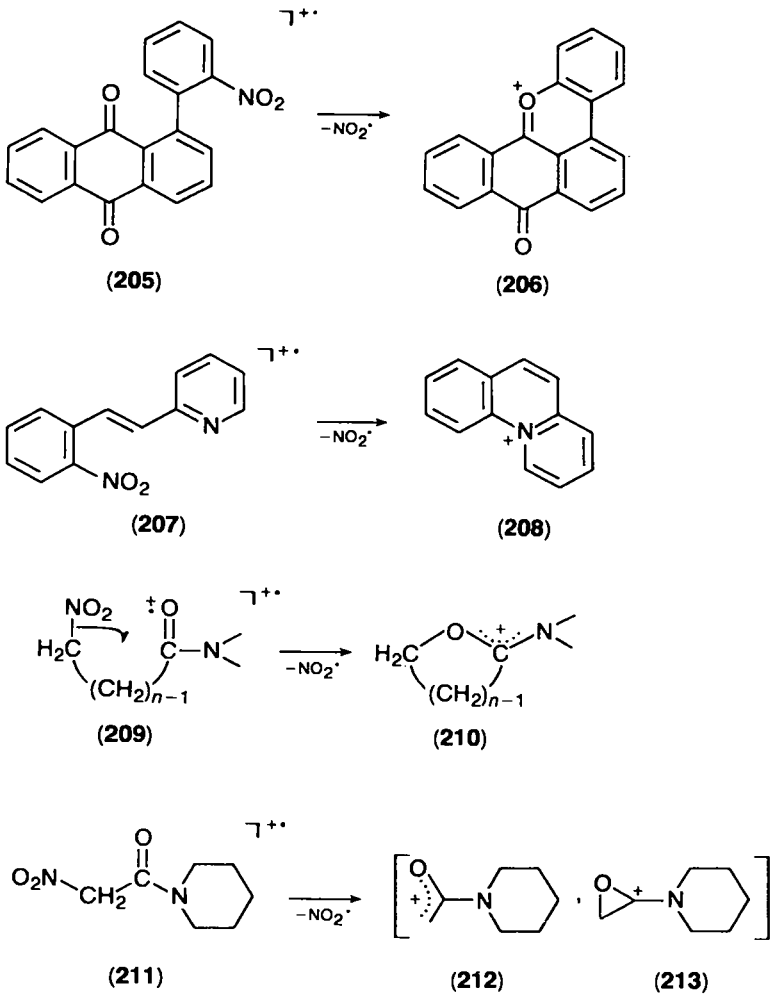


(203) (204)

SCHEME 41

reaction)[92]. Anomalous behaviour is, however, observed for the piperidide of nitroacetic acid (**211**). The $[M - NO_2]^+$ ion (25% TIC !) is the base peak in the spectrum. Further experiments and calculations are necessary to establish whether this surprising observation[92] can be explained by a particular stability of the resulting ion (**212**, **213** or isomers thereof) (Scheme 42).

It should be emphasized that redox processes according to Scheme 38 are not necessarily restricted to systems with a fixed conformation (such as **190**). If the

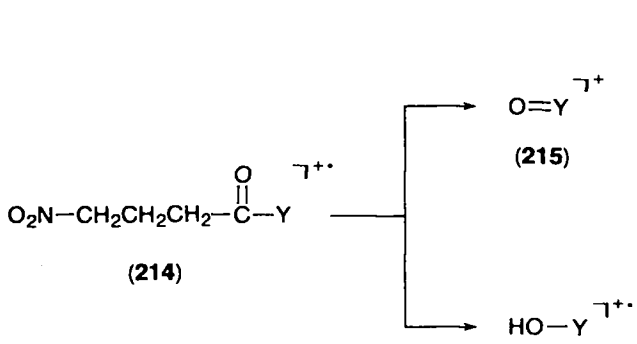


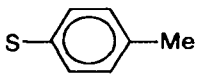
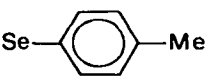
SCHEME 42

oxygen affinity of the structural unit X—Y (with X = CO) is sufficiently high, oxygen or hydroxy transfer onto Y is also observed in flexible molecular ions such as **214**[86,87].

C. Chemical Ionization of RNO_2

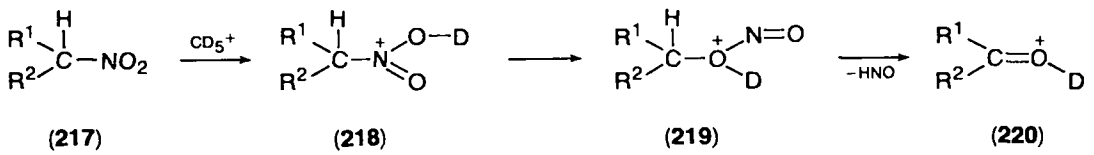
As mentioned above, chemical ionization is an important method for the mass spectrometric identification of nitro compounds[47]. This is particularly true for aliphatic nitro derivatives since the radical cations $RNO_2^{+\cdot}$, if produced by electron impact, are found, if at all, only with very low intensity. From a theoretical point of view this result is not surprising as according to MINDO/3 calculations the radical cations of aliphatic nitro compounds have no minimum on the potential energy surface[93]. They isomerize or decompose spontaneously. The situation is completely different if nitro compounds are transformed by ion/molecule reactions in the gas phase into 'closed-shell' cations RNO_2X^+ (X = H, C_2H_5, C_3H_5 etc.). Thus the CI



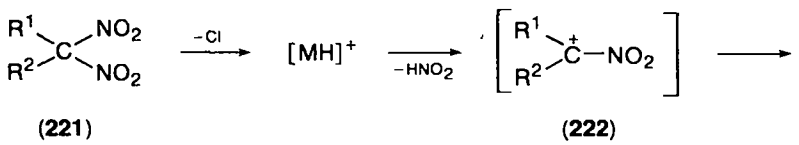
Y	Relative intensity (%) 215	216
	60	—
	—	47
	39	11

SCHEME 43

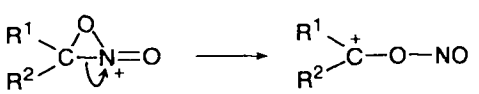
spectra do not show only signals due to fragment ions, but also signals for the cluster ions $[MX]^+$. The fragmentation pattern often reveals structure-specific details or allows the localization of the attachment of X^+ in polyfunctional molecules. Specific details of the decomposition of $[MH]^+$ in simple nitro compounds could be explained both by ^2H-labelling and MINDO/3 calculations[93]. Thus for secondary nitro compounds **217** ionization with CD_5^+ leads exclusively to loss of HNO (and not DNO) as shown in Scheme 44. The $[MH]^+$ ions of geminal



(217) (218) (219) (220)



(221) (222)

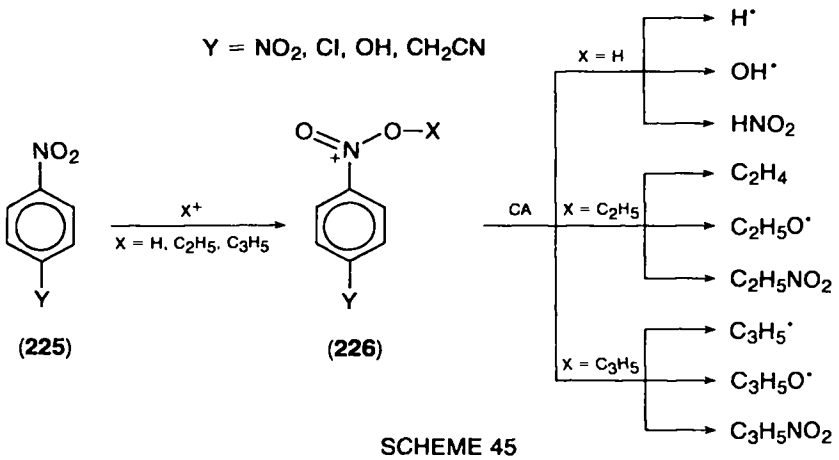


SCHEME 44 (223) (224)

disubstituted nitro compounds **221** eliminate HNO_2. This reaction does *not* lead to the α-nitro carbenium ion **222**, but via **223** to the nitrite-substituted cation **224** (Scheme 44; R^1, R^2 = alkyl, aryl). MINDO/3 calculations indicate that the isomerization **222** → **224** occurs without activation energy and that **224** is more stable than **222** by about 70 kcal/mol[93].

The unimolecular and collision-induced decompositions of cluster ions generated from substituted aromatic nitro compounds **225** have been investigated by Cooks

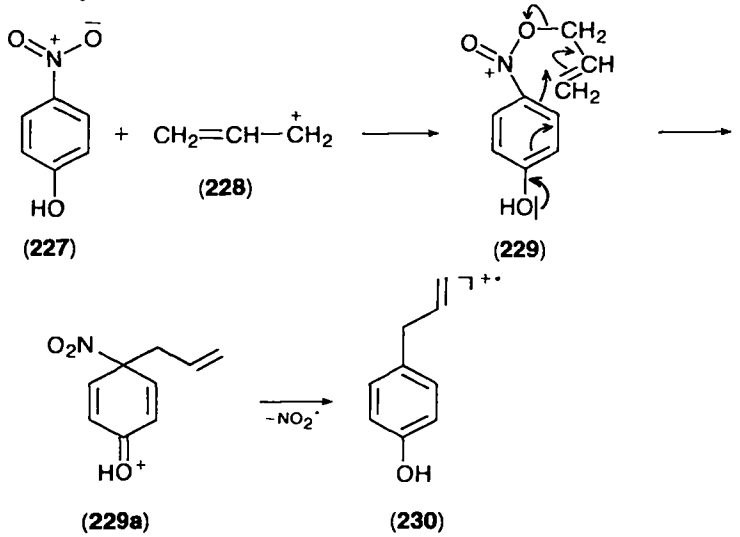
and coworkers[94]. The authors conclude that the protonation, ethylation or allylation of **225** occurs almost always at the nitro group (with the exception of Y = CH_2CN where both the nitro and nitrile group are protonated leading to the collision-induced loss of both HNO_2 and HCN). Similar conclusions have been reached by Liehr and McCloskey[95]. The collision-induced decompositions of $[MX]^+$ listed in Scheme 45 demonstrate that the electrophile X^+ indeed complexes the NO_2 group preferably.



(225) (226)

SCHEME 45

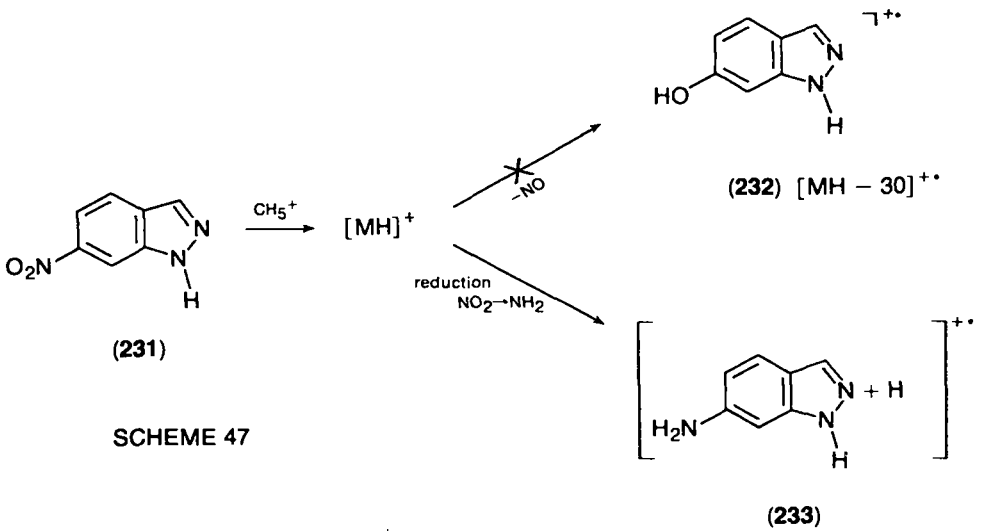
It is noteworthy that the allylation of **225** (Y = OH, X = C_3H_5) does not only occur according to the processes shown in Scheme 45. Here also an abundant NO_2 elimination is observed. The authors[94] interpret this result as indicating that the *reacting* $C_3H_5^+$ ion in ion-molecule reactions has the allyl structure **228**. The allyl cation is attached to the NO_2 group and NO_2 loss occurs after isomerization (**229** → **229a**) according to Scheme 46. It has been demonstrated in an independent CICA study that the nonreacting $C_3H_5^+$ ions in the CI (CH_4) plasma also have the structure of an allyl cation **228**[96].



(227) (228) (229) (229a) (230)

SCHEME 46

It should be mentioned that chemical ionization of nitro compounds cannot always be viewed as a simple acid–base interaction in the gas phase, as it sometimes leads to unexpected products. Thus the CI spectra of **231** do not only contain an $[MH]^+$ signal, but also an intense signal for $[MH - 30]^+$ which was originally explained as $[MH - NO]^+$. The CICA spectra of the $[MH - 30]^+$ from **231** and the protonated amine **233** are, however, identical[97]. Moreover, high-resolution mass spectrometry under CI conditions demonstrates, that the $[MH - 30]^+$ from **231** does not contain oxygen. Thus, one has to assume that under $CI(CH_4)$ conditions not only protonation, but also reduction of the NO_2 to the NH_2 group (**231** → **233**) occurs (see also References 111 and 112).

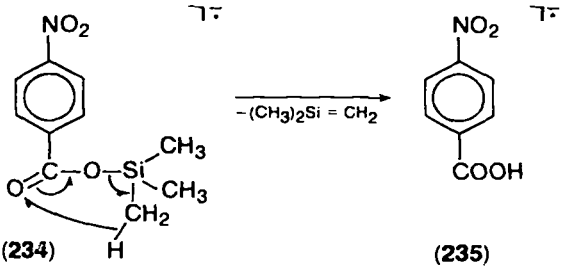


SCHEME 47

D. Radical Anions, $RNO_2^{\cdot -}$

An excellent review of the chemistry of anions in the gas phase has been published[98]. Thus, here only the chemistry of the radical anions of nitro groups will be treated. It is possible to generalize for this class of compounds that the formation of radical anions via electron attachment occurs easily as a result of the high electron affinity of the NO_2 group. The species formed by this process are usually more stable than the corresponding radical cations. This leads to more abundant signals of the molecular ions, which is sometimes of importance for analytical applications. However, depending on additional functional groups in the molecule and the excess energy of the $M^{-\cdot}$ ions, unimolecular decomposition also leads to structure-specific fragments.

A systematic comparison[99] of the reactivities of radical anions and cations of nitro-substituted aromatic esters, such as **234**, can be summarized as follows: The radical cations give only a weak molecular ion (5%); the base peak corresponds to the $CH_3^{\cdot}$ elimination which is typical for trimethylsilyl compounds. The situation is reversed for the radical anions. The $M^{-\cdot}$ represents the base peak while methyl elimination is almost not observed (1%). Besides the elimination of NO_2^- (45% for **234**) which is typical for NO_2 compounds, an unexpected process leads to loss of $(CH_3)_2Si{=}CH_2$ giving rise to **235**. Formally this process corresponds to the analogue of the McLafferty rearrangement in radical cations. However, there is no indication for such a process in the radical cation system of **234** (Scheme 48).

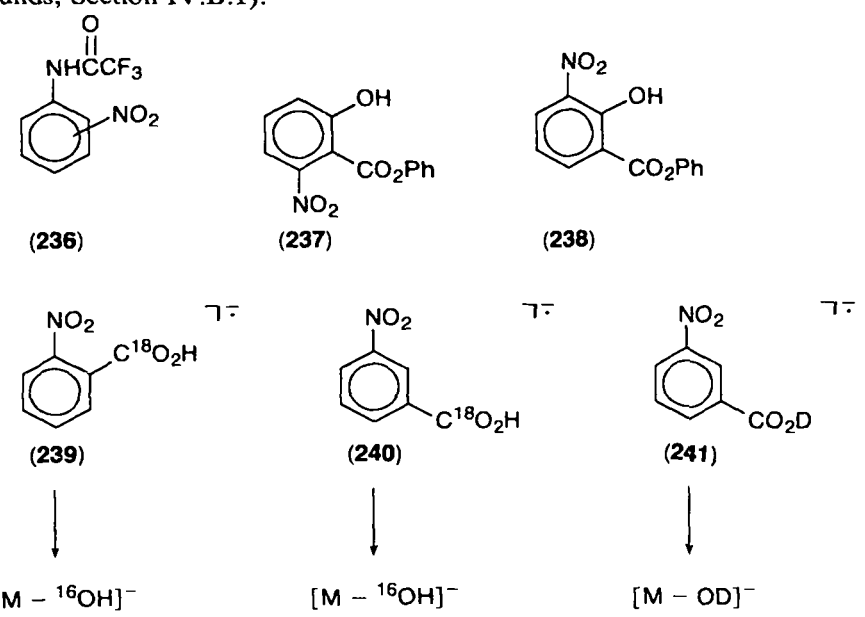


(234) (235)

SCHEME 48

A comparison of the $M^{+\cdot}$ and $M^{-\cdot}$ ions has been carried out for the *ortho*, *meta* and *para* isomers of **236**[100]. While the spectra of the $M^{+\cdot}$ ions of all three isomers are very similar, pronounced differences are observed for the anions, allowing a rapid identification of the isomers. Analogous results are observed for the constitutional isomers **237** and **238**. $M^{-\cdot}$ of **237** primarily loses PhO$^{\cdot}$ and PhOH (90 and 100%), while for **238** additional loss of OH$^{\cdot}$ and NO$^{\cdot}$ are found. Moreover, pronounced differences are observed for the abundance of the molecular anions of **237** and **238**[101]. These results are possibly explained by an *ortho* effect.

However, there are also examples of apparent *ortho* effects in radical anions[102]. The anion spectrum of **239** shows an intense signal for $[M - {}^{16}OH]^-$ which can be rationalized assuming that the neutral particle contains an oxygen from the NO_2 group and the carboxylic hydrogen (as shown by a study of the COOD compound). However, surprisingly, also the *meta* compound loses OH$^{\cdot}$, where OH$^{\cdot}$ is again formed out of the NO_2 group and the carboxyl group. Since a migration of the substituent can be excluded, this reaction must proceed via another, yet unknown, mechanism (see also OH$^{\cdot}$ loss from *para*-substituted cycloalkylaromatic nitro compounds, Section IV.B.1).

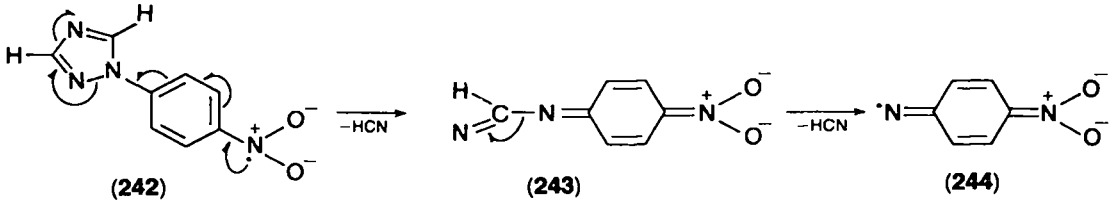


(236) (237) (238)

(239) (240) (241)

SCHEME 49

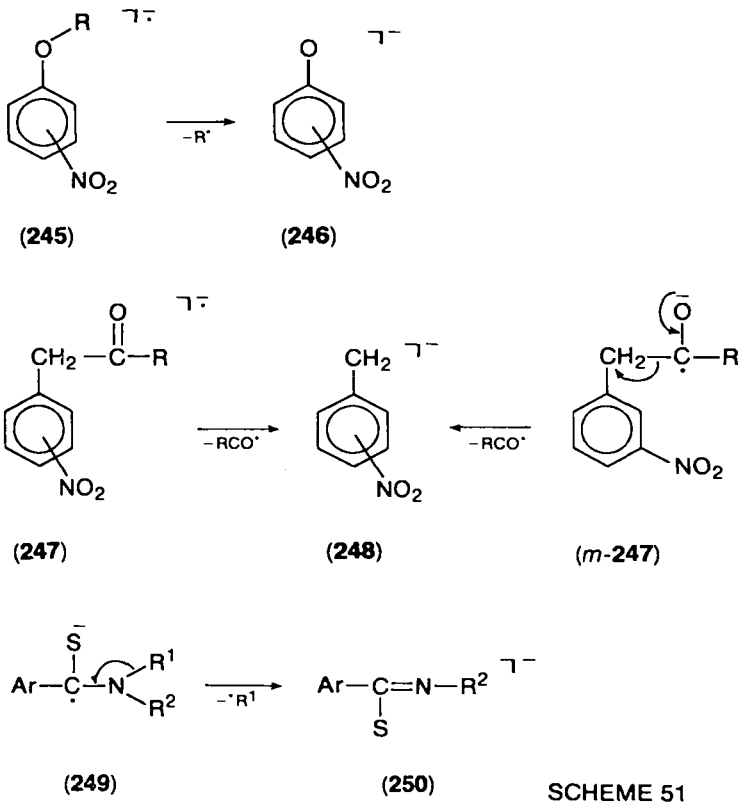
Many radical anions of nitro compounds, and in particular of *para*-substituted benzene derivatives, are characterized by the fact that the NO_2 group not only stabilizes the anion, but induces specific bond cleavages. Thus twofold HCN loss is only observed from the *para* isomer of the triazol derivative **242**[103] (Scheme 50) which is presumably induced by the radical site.



(242) **(243)** **(244)**

SCHEME 50

In analogous fashion the cleavage of the O—C bond in radical anions of the *para* isomer of **245** occurs[104]. A determination of the kinetic energy release, T, during unimolecular decomposition reveals that T decreases with increasing substituent R (R = alkyl). This observation is rationalized as follows: The increasing number of oscillators leads to the excitation of more vibrational states in the neutral particle R$^{\bullet}$. Thus a greater fraction of the reverse activation energy is stored as vibrational excitation. However, a quantitative correlation between the number of oscillators and T is not possible. It is noteworthy that the T values for the *ortho*, *meta* and *para* isomer show characteristic differences. Thus in this case also an isomerization

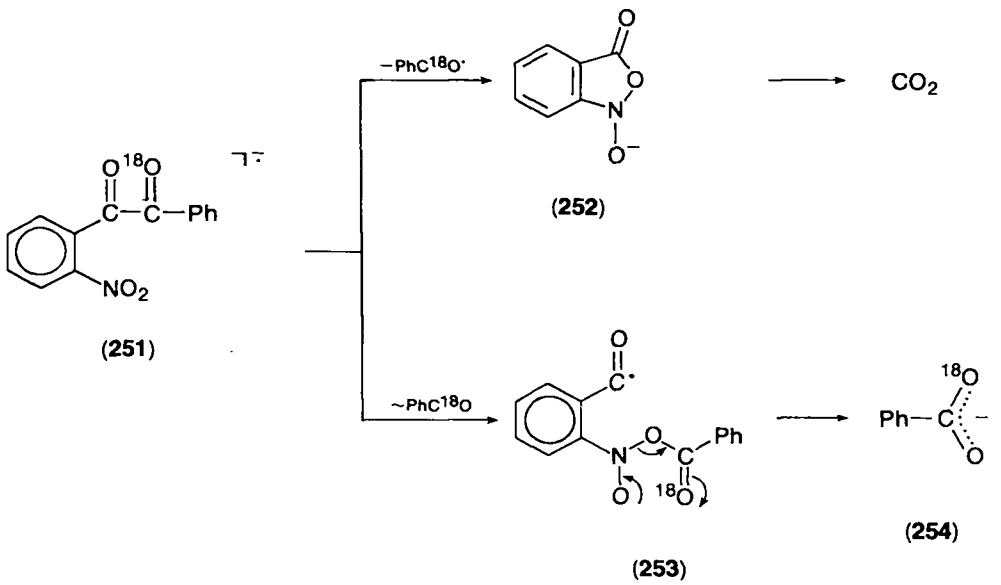


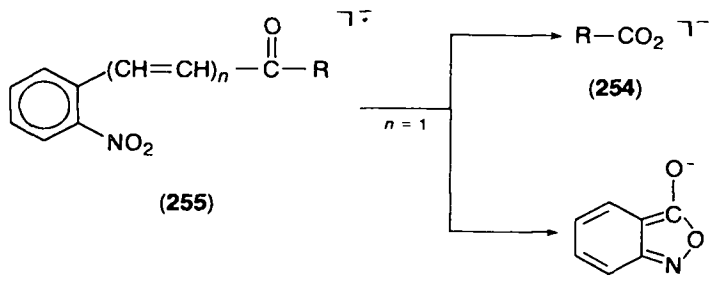
(245) **(246)** **(247)** **(248)** **(*m*-247)** **(249)** **(250)**

SCHEME 51

to a common intermediate can be ruled out. In the case of the *meta* isomers cleavage of the O—R bond in **245** and the C—C bond in **247** must proceed via a mechanism in which the NO_2 group does not participate in the fragment formation. A mechanism for *m*- **247** is outlined in Scheme 51[105]. A similar mechanism seems to explain the alkyl elimination from aryl-substituted thioamides **249**. Here always the largest substituent R (R = alkyl) is lost[106] (Scheme 51).

Finally, intramolecular oxygen migrations in the radical anions of *ortho*-substituted nitro aromatic compounds will be discussed. The hydrazone **171** is the best example for an oxygen transfer in radical cations (see Scheme 35). However, *no* products are identified in the anion spectrum which unequivocally point to such a process. The spectrum is dominated by a signal which can be explained by cleavage of the N—N bond (formal elimination of $R^1R^2C{=}N$; R^1, R^2 = H, alkyl). Oxygen transfer is, however, observed with other radical anions. Examples of such a process are the elimination of $Ph^{18}CO^{\cdot}$ from **251** (**251** → **252**) and the consecutive CO_2 loss or formation of $PhCO^{18}O^-$ from **251** (Scheme 52). **254** is also generated from **255** which again is the result of a rearrangement reaction. The fact that the ions RCO_2^- or $RCOCHO^{-\cdot}$ are generated from the vinylogous anions **255** (n = 1, 3) indicates that oxygen transfer is possible via *five*-,

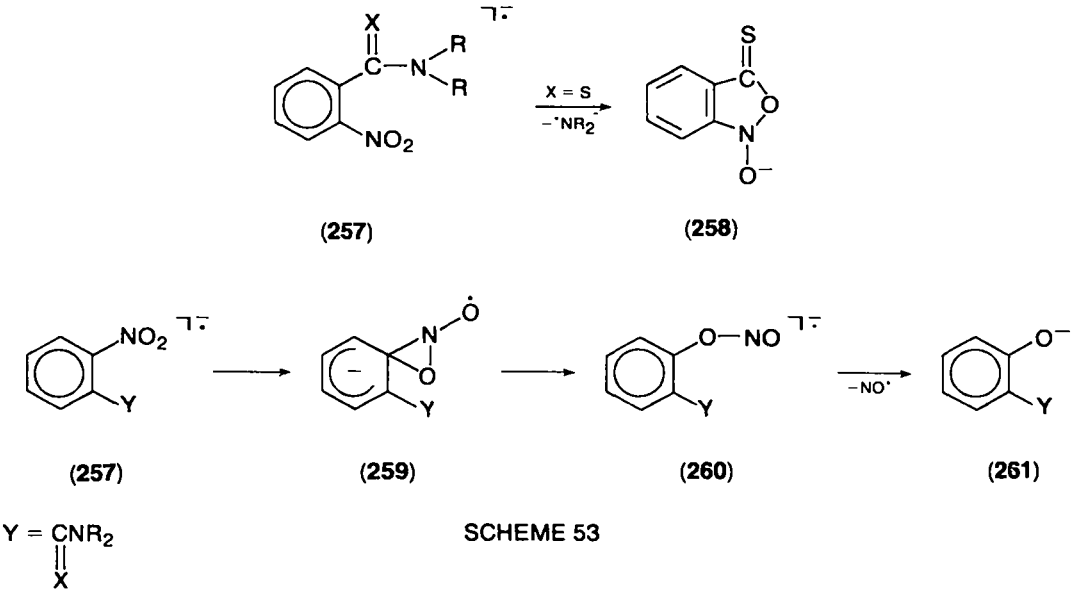




SCHEME 52

six- and *seven*-membered transition states. All oxygen migrations mentioned so far are suppressed if the NO_2 group is replaced by another substituent, such as COOR. Cyclization reactions (such as **251** → **252**) are also of importance for **255** (n = 1), (**255** → **256**)[107–109].

Analogously to the R$^\bullet$ elimination from **249** (Scheme 51) loss of $^\bullet NR_2$ is observed in aromatic nitro compounds such as **257**. In the case of the thioamide a cyclization reaction (**257** → **258**) is responsible for this process[106]. This reaction is suppressed in the analogous oxygen-containing compound (X = O). Here loss of NO$^\bullet$ and formation of NO_2^- are the main processes. An analysis of the peak-shape of decomposing metastable ions has been carried out for NO$^\bullet$ loss[106]. In correspondence to NO$^\bullet$ loss from the radical *cations* of nitro-substituted aromatic compounds (Scheme 21) a composite metastable peak is observed. The broad component of the peak probably corresponds to the isomerization **257** → **259** followed by NO$^\bullet$ loss (Scheme 53).



(**257**) (**258**)

(**257**) (**259**) (**260**) (**261**)

SCHEME 53

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CHAPTER **4**

Rearrangements involving nitroso and nitro compounds

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I. INTRODUCTION

The reactions to be discussed in this chapter are mainly restricted to those where actual rearrangement of the nitro or nitroso group occurs within a given molecule, although some reactions are considered where cross-nitration (sometimes called trans-nitration) or cross-nitrosation occurs to another molecule, i.e. where the nitro and nitroso compounds act directly as nitrating or nitrosating agents. In general the C—NO_2 and C—NO bond systems are relatively strong so that reactions of these involving C—N bond fission are limited to those taking place under extreme conditions, e.g. thermally and photochemically. Their *N*-nitro and *N*-nitroso counterparts are generally more reactive, both photochemically and also where heterolytic bond fission can occur, particularly in acid solution when protonation ensures a good leaving group. The same applies to *O*-nitroso and *O*-nitro compounds, i.e. alkyl nitrites and alkyl nitrates, although the latter will not be included in this chapter since another chapter in this volume is set aside for reactions of alkyl nitrates. By and large the aim has been to update previous volumes in this

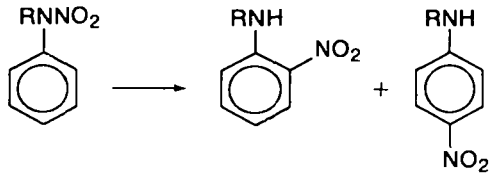
series, particularly sections of *The Chemistry of the Nitro and Nitroso Groups* and (for the *N*-nitro and *N*-nitroso compounds) sections of *The Chemistry of the Amino Group*. Consequently emphasis is laid on developments in the 1970s; the literature has been covered towards the end of 1979.

II. THE NITRAMINE REARRANGEMENT

A. The Acid-catalysed Reaction

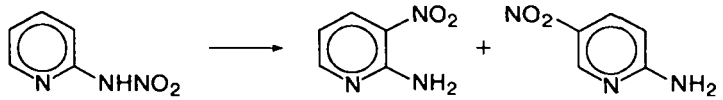
Aromatic and heterocyclic *N*-nitroamines readily undergo rearrangement giving *C*-nitro isomers, both under acid-catalysed conditions and thermally in the absence of a catalyst. The reaction has been known for some considerable time and is quite often used synthetically. Mechanistically the reaction was investigated quite thoroughly in the 1960s and early 1970s, but there is not complete agreement as to the mechanism of the rearrangement. The reaction has not been much studied very recently but has been reviewed by a number of authors[1–3].

The reaction is quite general, taking place readily in a variety of acid solvents to give *o*- and *p*-nitroaniline derivatives (equation 1). There is no apparent specificity



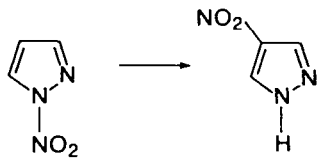
(1)

by hydrogen halide acids as is suggested in the Orton rearrangement of *N*-chloroanilides[4] and in the Fischer–Hepp rearrangement of *N*-nitrosoanilines (see Section III). Rearrangement also occurs in the heterocyclic series as typified by the rearrangement of 2-nitraminopyridine[5] (equation 2).



(2)

The rearrangement is also known for ring-*N*-nitro heterocyclics, e.g. the conversion of *N*-nitropyrazoles into 4-nitropyrazoles in sulphuric acid[6] (equation 3).

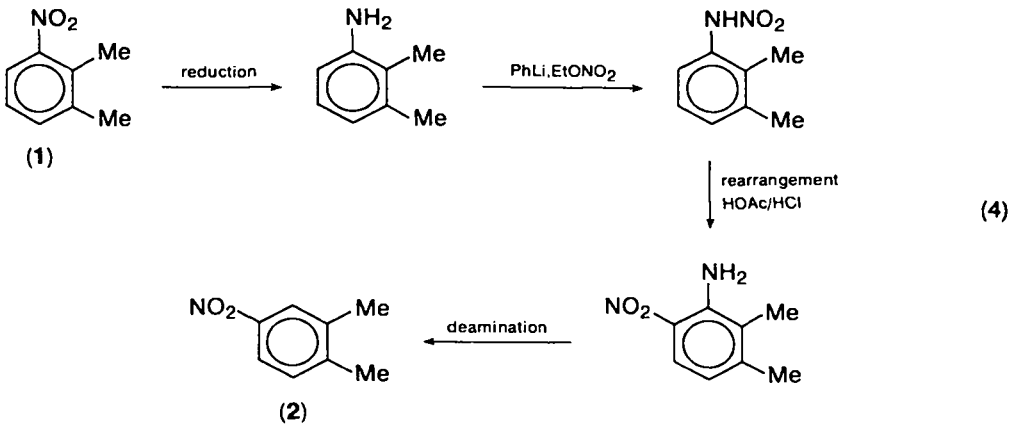


(3)

The rearrangement can also be brought about thermally and photochemically in *N*-nitroanilines, *N*-nitronaphthylamines[7] and *N*-nitropyrazoles[8]. Again this seems to be quite a general reaction.

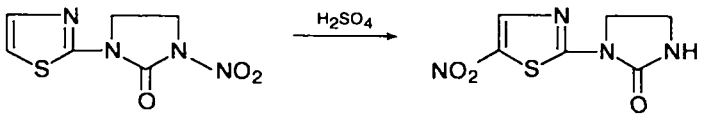
Before embarking on a discussion of the mechanistic aspects of the rearrangement it may be worth stressing its synthetic value. Bamberger[9], who pioneered much of the early work on this (and other) rearrangements considered the reaction as a good way of making aromatic *C*-nitro compounds. Generally *N*-nitroamines can be easily synthesized by reaction of the deprotonated form of the amine (formed using sodium, potassium or potassium ethoxide, in ether and other solvents) with an alkyl

nitrate such as ethyl nitrate[10,11]. A recent example[12] of the use of the nitramine rearrangement in synthesis occurs in the conversion of 3-nitro-*o*-xylene (1) to 4-nitro-*o*-xylene (2) as shown in equation (4).



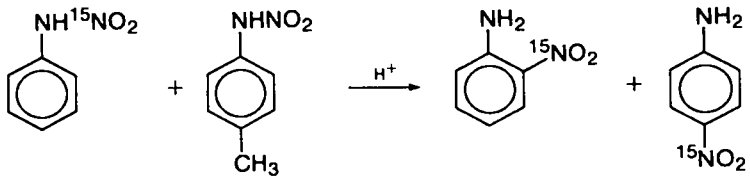
(1) (2) (4)

An example of the nitramine rearrangement occurs in the synthesis of a pesticide which is a 1-(5′-nitro-2′-thiazolyl)urea derivative. Thus 1-(5′-nitro-2′-thiazolyl)-2-oxo-tetrahydroimidazole (**4**) can be prepared[13] from 1-(2′-thiazolyl)-2-oxo-3-nitro-tetrahydroimidazole (**3**), by reaction in concentrated sulphuric acid (equation 5). This reaction has certain analogies with the rearrangement in the thiazole series[14].

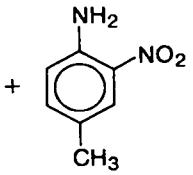


(3) (4) (5)

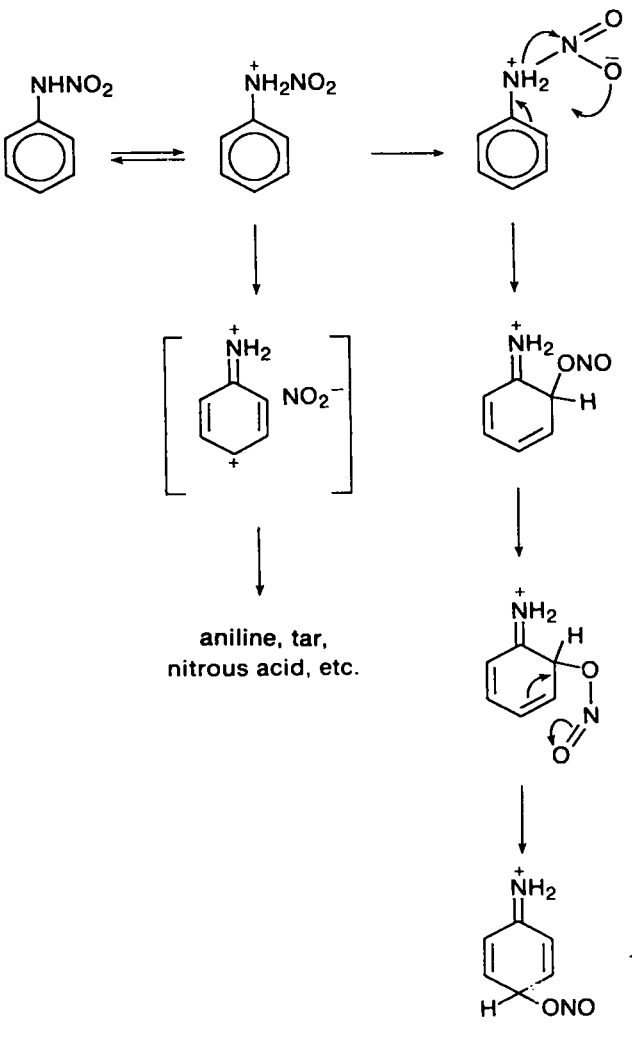
One of the main mechanistic questions regarding the nitramine rearrangement is the question of the intra- or inter-molecularity of the change. This has been probed by the ability or otherwise to transfer the nitro group to some other added reactive entity or by the use of labelling experiments. In studies of this kind it is important to know (1) whether the nitramine itself can act as a direct nitrating agent, and (2) whether reversible denitration of the nitramine can occur in parallel with an intramolecular rearrangement. Many of the experiments designed to establish the question of intramolecularity have not eliminated possibilities of this kind. The bulk of the evidence with ^{15}N labelling experiments argues in favour of an intramolecular mechanism. The rearrangement of *N*-nitroaniline itself in the presence of either [^{15}N] potassium nitrate, [^{15}N] nitric acid or [^{15}N] potassium nitrite gave[11,15] both *o*-and *p*-nitroaniline without excess ^{15}N. Similarly no incorporation of ^{15}N was found[16] in the rearrangement of *N*-nitro-1-naphthylamine and *N*-methyl-*N*-nitro-1-naphthylamine from experiments carried out over a range of acidity with added [^{15}N] NO_2^- and [^{15}N] NO_3^-. Labelling of the substrate showed the same result[17], thus when [^{15}N-NO_2]-labelled *N*-nitroaniline (**5**) was rearranged in the presence of normal *N*-nitrotoluidine (**6**), the nitrotoluidine product (**7**) did not contain excess ^{15}N (equation 6). ^{15}N labelling experiments in the pyridine series[5] were also taken to support an intramolecular mechanism. However experiments[18] with *N*-methyl-*N*-nitroaniline and *p*-fluoro-*N*-methyl-*N*-[^{15}N]nitroaniline were claimed to show that the reaction was in part intermolecular.


NH15NO2
NHNO2
H+
NH2
15NO2
NH2
15NO2
CH3

(5) (6) (6)


NH2
NO2
CH3

(7)

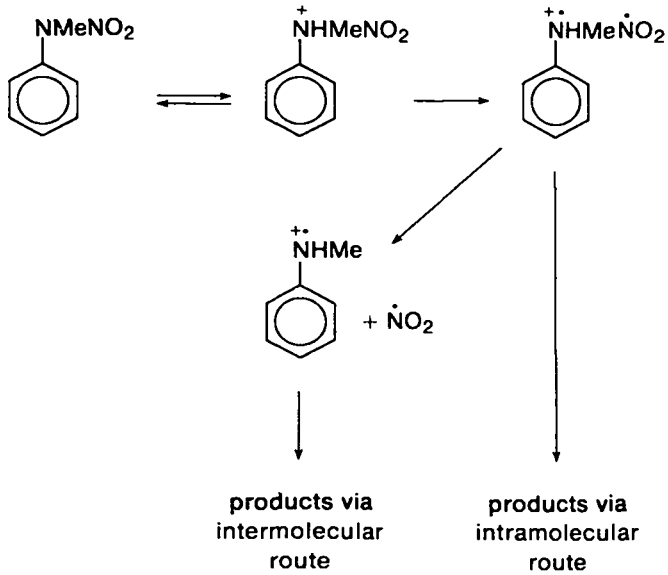

NHNO2
NH2NO2
NH2
NO2−
NH2
ONO
H
NH2
NO2
aniline, tar,
nitrous acid, etc.
NH2
H
O
N
O
NH2
H
ONO
NH2
NO2

(7)

It is conceivable that for the *N*-methylnitramine a different mechanism exists although it is equally possible that the ^{15}N exchange could arise by some reversible denitration.

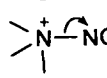
Banthorpe and coworkers[7,11,16] have proposed a cyclic transition-state mechanism (equation 7) which is based on the results of the ^{15}N experiments, the kinetic results and the results of product isomer distribution ratios. Attempts to identify radical intermediates by a number of different probes proved unsuccessful. Side-reactions were consistent with some heterolysis to give free nitrous acid.

White and coworkers[18–20] on the other hand prefer a mechanism involving caged-radical pairs. This is set out as equation (8) and involves the formation of a

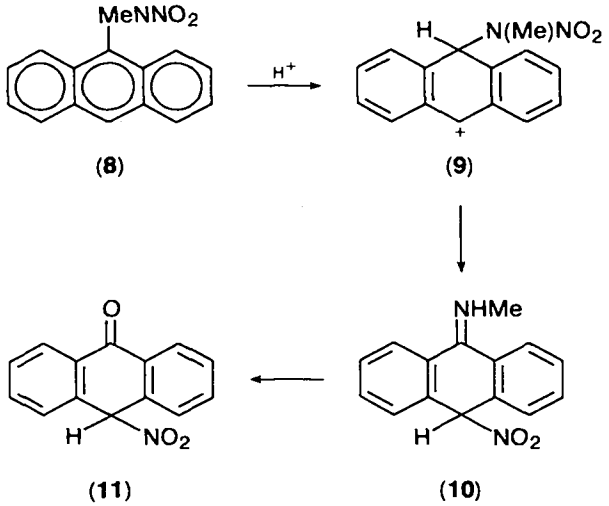


(8)

radical pair which is thought to combine either intramolecularly or which can dissociate fully and then react intermolecularly to give the products. *m*-Nitro compounds, which might be expected amongst the products, have never been found experimentally. More recent results[21] for the variation of the *ortho*:*para* ratio with the viscosity of the solution (using methanol–glycerol mixtures) have been taken to support the caged-radical mechanism.

It is clear, although there is no general agreement regarding the mechanism, that N–N bond fission occurs in the sense  rather than the reverse which would tend to favour nitronium ion formation. This is evident from rate measurement[20] with ring-substituted nitramines which gives a good correlation with σ^+ with a ρ value of -3.9. This eliminates an earlier mechanistic theory[22] based on π-complex formation involving the nitronium ion.

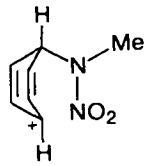
In an attempt to distinguish between the two main mechanisms, Banthrope and Winter[23] examined the rearrangement of *N*-methyl-*N*-nitro-9-aminoanthracene (**8**) (equation 9). It was expected that the presence of the benzo substituents would prevent the formation of the cyclic transition state, whereas these should not affect the formation of caged-radical pairs. In the event, 10-nitroanthrone (**11**) was formed in high yield by an intramolecular route (as shown by ^{15}N experiments) but the kinetic solvent isotope effect $k(D_2O)/k(H_2O)$ was 0.84. This compares with



(8) (9) (9)

(11) (10)

values of 2.5–3.3 found generally for all other nitramines studied[7,11,20]. The result was interpreted in terms of a mechanism where the first step is a rate-determining *C*-proton transfer to the 9-position to give **9**, which undergoes intramolecular rearrangement to **10**, giving the product by methylamine loss. It was believed that the actual rearrangement **9** → **10** could occur either via a bent boat-form transition state of the type **12**, or a tight ion-pair intermediate[11] or a radical-ion cage[19].



(12)

Transition states resembling **12** have been suggested[24] for a range of intramolecular aromatic rearrangements, but have not been generally accepted because of the lack of evidence for the necessary *C*-ring protonation.

In his original work Bamberger[25] believed that *C*-nitration of amines occured via *N*-nitration and intramolecular rearrangement. Later this was disputed since markedly different product isomer ratios were found for the two reactions[26]. However it is now known[27] that nitration of amines does in some cases involve direct reaction of the protonated form rather than the free base. Ridd and Scriven[28] have shown, using a much weaker base, 2,3-dinitroaniline (which undergoes nitration via the free base), that nitration does in fact occur at the amino nitrogen atom, and this is followed by intramolecular rearrangement. Similarly Russian workers[29] have obtained the same rate constants for the nitration of 2,4-dinitroaniline in HNO_3/H_2SO_4 and for the rearrangement of *N*,2,4-trinitroaniline, and have suggested that the nitramine is an intermediate in the *C*-nitration.

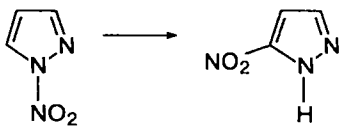
There has been a recent mechanistic investigation[30] into the nitraminopyridine rearrangement (equation 2). The main product here was the *p*-nitro isomer, contrasting with the phenyl series where generally the *o*-compound predominates. In 92% sulphuric acid only the rearrangement products were obtained. Product and

rate studies showed that complete dissociation of the nitramine occurred to give the amine and the nitronium ion, again contrasting with the phenyl series. The difference is believed to arise from the presence of the strongly electron-withdrawing influence of the ring nitrogen atom in the pyridine case. It was not possible to establish with certainty the mechanism of the subsequent reactions although substituent effects indicate that a direct *C*-nitration by the nitronium ion was unlikely.

B. The Thermal Reaction

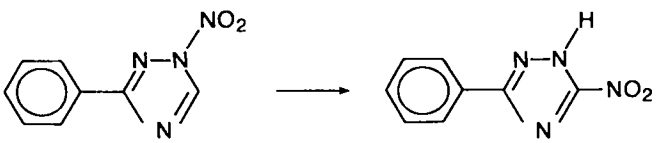
N-Methyl-*N*-nitro-1-naphthylamine rearranges rapidly at 100°C in a variety of solvents to give the 2- and 4-nitro isomers in ca. 40% yield[7]. The reaction is first order in the nitramine. No radicals are detected and a mechanism similar to that for the acid-catalysed process is envisaged.

In the heterocyclic field, *N*-nitropyrazole (**13**) (and methylnitropyrazoles) has been shown to undergo a thermal rearrangement to give 5-nitropyrazole (**14**) in



(**13**) (**14**)

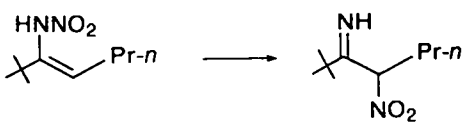
quantitative yield[8]. Similarly *N*-nitroindazoles[31] give the corresponding 3-nitro derivatives. Details of the mechanism have not been established, but reaction is believed to be an intramolecular [1,5]-sigmatropic rearrangement. Clearly the situation is different from the acid-catalysed case, where the 4-nitro isomer is obtained[6]. The thermal reaction seems to be a characteristic one for *N*-nitroazoles generally, since the *N*-nitrotriazoles (e.g. **15**) also give the 3-nitro isomers[32] (equation 10).



(10)

(**15**)

N-Nitroenamines have also been shown[33] to undergo a thermal rearrangement of the nitro group leading to α-nitroimines via a 1,3-rearrangement (equation 11).

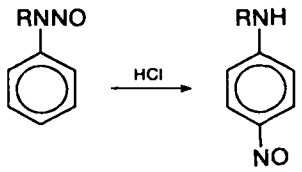


(11)

III. THE REARRANGEMENT OF *N*-NITROSAMINES

A. The Fischer–Hepp Rearrangement

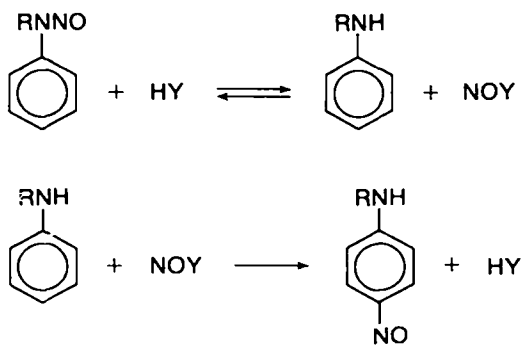
The rearrangement of aromatic *N*-nitrosamines proceeds readily in the presence of an acid catalyst (generally hydrogen chloride) in a variety of solvents to yield the corresponding *para* *C*-nitroso isomer (equation 12). There is no report of the



(12)

formation of the *ortho* isomer (other than from the 2-naphthyl derivative), indeed *o*-nitrosamines are barely known. The reaction often produces significant amounts of the corresponding denitrosated product, i.e. the secondary amine. The reaction has been used synthetically as one convenient way of synthesis of aromatic *C*-nitrosamines, since its discovery by Fisher and Hepp in 1886[34]. Use is made of this reaction industrially to prepare 4-nitrosodiphenylamine (from *N*-nitrosodiphenylamine), which is used to make Diafen FP, a rubber antioxidant. There is a large patent literature describing modifications of solvent and temperature in order to approach quantitative conversion of the *N*-nitrosamine. Typical conditions for the industrial process are 30% HCl in methanol/toluene at room temperature.

Early experiments by Fischer and Hepp[34] and later by Neber and Raucher[35] have been taken to support a suggested mechanism for the rearrangement given by Houben[36]. This is shown in equation (13) and involves denitrosation of the nitrosamine by the acid catalyst HY (e.g. HCl) to give the secondary amine and free NOY, which react in a conventional electrophilic substitution manner. This mechanism has been widely and generally uncritically accepted, and is reproduced in review articles[37] and organic textbooks[38], even though in fact the evidence, whilst being consistent with a mechanism based on equation (13) by no means specifically

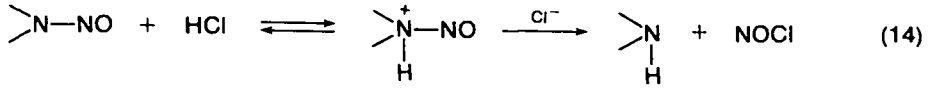


(13)

demands such a mechanism. Until 1968 the only known facts concerning the rearrangement were (*a*) that better yields were obtained using hydrogen chloride, than any other acid catalyst[35], (*b*) better yields were obtained with added sodium nitrite[36], (*c*) cross- or transfer-nitrosations of added amines and of an added alkene could be achieved[36], and (*d*) the reaction of *m*-nitro-*N*-methyl-*N*-nitrosoaniline in the presence of urea (a well-known trap for free nitrous acid derivaties) gave only denitrosation[39].

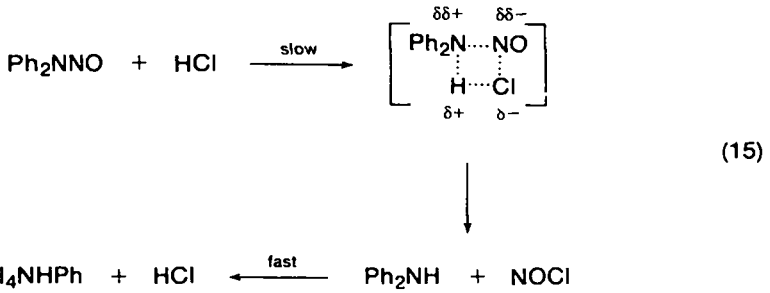
In 1968 Russian workers[40] found that rearrangement of a number of *meta*-substituted *N*-methyl-*N*-nitrosoanilines (*m*-OH,-OCH_3,-CH_3 and -H) occurred, at least to some extent, in the presence of quite large excesses of either urea or sulphamic acid, whereas it was reported that with *meta* electron-withdrawing groups (Cl, Br, COOH, NO_2) no rearrangement occurred. The suggestion was made that the rearrangement was in part intramolecular.

Baliga[41] reported the kinetics of the rearrangement of *N*-nitrosodiphenylamine for reaction in a methanol–toluene solvent containing hydrogen chloride. There was a first-order dependence upon both the nitrosamine and hydrogen chloride and the rate was almost independent of the concentration of added chloride ion. This result argues strongly against a mechanism (equation 14) where a rate-determining



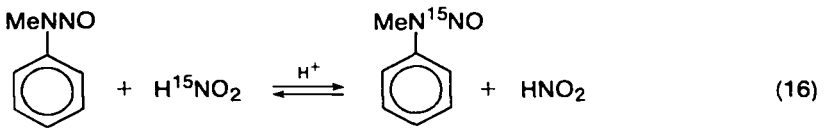
(14)

nucleophilic attack by chloride ion follows a rapid equilibrium proton transfer to the nitrosamine. Under these circumstances a rate dependence upon $[HCl]^2$ (and chloride ion catalysis by added chloride) is to be expected, such as has been found for the Orton rearrangement of *N*-chloroanilides[42]. An alternative mechanism for denitrosation was tentatively proposed (equation 15) involving a four-centred transition state.



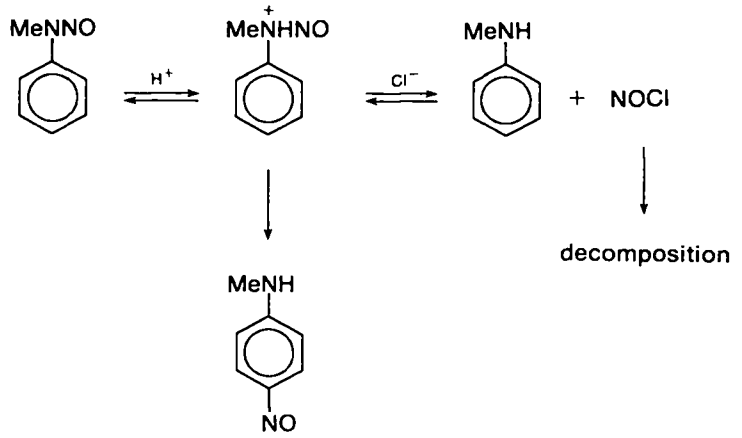
(15)

Attempts to distinguish inter- and intra-molecular pathways for the rearrangement were frustrated when it was shown[43] that, in the reaction of *N*-methyl-*N*-nitrosoaniline in the presence of added $H^{15}NO_2$, the reactant exchanged label with the nitrous acid at a rate much greater than that of the rearrangement (equation 16).



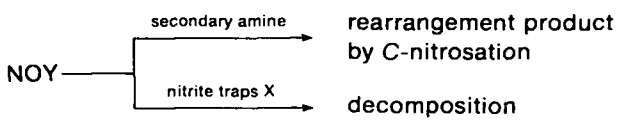
(16)

A series of papers has been presented aimed at establishing the mechanism of the Fischer–Hepp rearrangement in aqueous solution, using mainly kinetic methods. For the reaction of *N*-methyl-*N*-nitrosoaniline in hydrochloric acid it was found[44] that the reaction was first order in nitrosamine and approximately first order in the Hammett acidity function h_0. There was a solvent isotope effect $k(D_2O)/k(H_2O)$ of 2.1 and a ring deuterium isotope effect k_H/k_D of 1.7. Rearrangement occurred (together with denitrosation) even in the presence of urea. It was suggested that rearrangement occurred intramolecularly and concurrently with denitrosation as is set out in equation (17). Later it was possible to separate denitrosation from rearrangement[45,46] and to examine mechanistically both reactions in isolation. This was achieved (*a*) by carrying out the reaction in the presence of a large excess of the secondary amine product (*N*-methylaniline), which served to ensure the intial complete reversibility of denitrosation and allowed rearrangement only to occur, and (*b*) by adding an excess of a scavenger for nitrous acid (or NOCl) such as urea or sulphamic acid. This ensured that denitrosation was virtually *irreversible*. The ratio of the two products was then found to depend on



(17)

the concentration and reactivity of the nucleophile (e.g. Cl^-). The experiments which decided most clearly between the inter- and intra-molecular mechanisms (equations 13 and 17 respectively) were those[47] where the product ratio rearrangement:denitrosation was measured for reaction in the presence of a large excess of a nitrite trap X (sulphamic acid etc.). For a given acidity it can be seen (Table 1) that the % rearrangement is constant for a variety of nitrite trap concentrations and for different species X used as nitrite traps. In addition the observed first-order rate constant is constant for the series. Both of these results are consistent with two parallel first-order reactions deriving from a common intermediate, whereas they are not in agreement with a mechanism based on equation (13) where it is predicted that the yield of rearranged product should decrease to zero as the concentration and/or the reactivity of the nitrite trap is increased, since there is (as shown in equation 18) now a direct competition



(18)

between X and the secondary amine for the capture of the free nitrosating agent NOY. Further, a distinction can be made between the intra- and inter-molecular mechanism on the basis of the question of halide-ion catalysis. The detailed rate equation has been deduced[48] from a mechanism based on the intermolecular

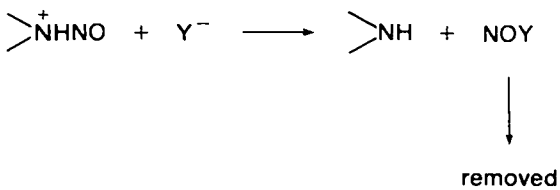
TABLE 1. The rearrangement product (%) and the observed rate constant as a function of added X

Added X	[X] (M)	$10^4 k_0$ (s^{-1})	Rearrangement (%)
HN_3	6.53×10^{-4}	0.65	21
HN_3	16.3×10^{-4}	0.67	21
NH_2SO_3H	3.1×10^{-3}	0.65	21
NH_2SO_3H	7.8×10^{-3}	0.64	22
$CO(NH_2)_2$	0.10	0.62	21
NH_2OH	2.58×10^{-3}	0.62	20
NH_2NH_2	1.56×10^{-3}	0.66	20

TABLE 2. The effect of halide ion on the rate constant for rearrangement

[Halide added]	$10^4 k_0$ (s^{-1})
0	1.75
0.24 M NaCl	1.79
0.10 M NaBr	1.77

mechanism (equation 13) which shows that there should always be a dependence of the observed first-order rate constant upon the halide ion present. Conversely in the intramolecular mechanism (equation 17) the pathway to rearrangement predicts no halide-ion catalysis. The results in Table 2 show clearly that under conditions of rearrangement only (in the presence of a large excess of the secondary amine *N*-methylaniline), the reaction is not subject to halide-ion catalysis. The denitrosation pathway, when studied in isolation free from rearrangement (i.e. in the presence of an excess of a nitrite trap X), showed by contrast a large dependence of rate constant upon the halide concentration (Table 3). Indeed the denitrosation reaction, which is regarded[46] as an example of rate-determining nucleophilic attack at the nitroso nitrogen atom of the protonated nitrosamine (equation 19), shows a large dependence upon the nature and concentration of the nucleophilic species for $Y^- = Cl^-$, Br^-, SCN^-, I^-, $SC(NH_2)_2$, RSH, RSR' etc.[49] and a remarkable correlation with the Pearson nucleophilicity parameter n for two nitrosamines[50].

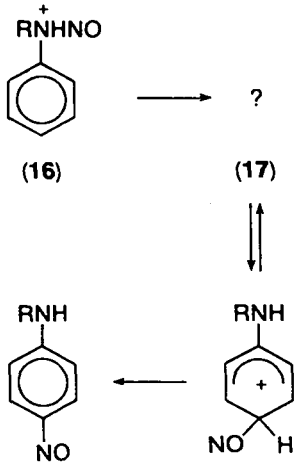


(19)

It is not easy to deduce the exact nature of the intramolecular rearrangement. It is likely that the protonated form of the nitrosamine **16** is an intermediate since the rearrangement is subject to acid catalysis[43]. Similarly the existence of the *p*-nitroso intermediate **18** is demonstrated by the presence of a significant ring deuterium isotope effect of 2.4 (k_H/k_D) for the rearrangement of **16** (R = Me) and of its *m*-OMe derivative[45]. Isotope effects of this magnitude are common in the *C*-nitrosation (mainly *para* substitution) of phenols and other aromatic substrates[51]. It seems unlikely, however, that the conversion **16** → **18** can occur in a single stage. Some intermediate (**17**) must be involved. It is merely conjecture to speculate as to the nature of **17**. Possible alternatives are the boat-form intermediate **19** suggested

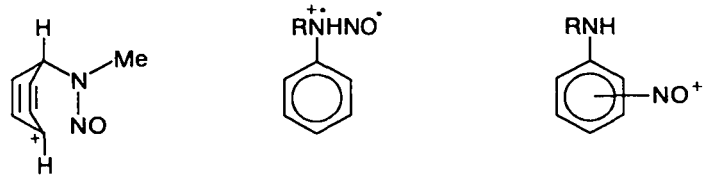
TABLE 3. The effect of halide ion on the rate constant for denitrosation

[Halide added]	$10^4 k_0$ (s^{-1})
0	16.3
0.25 M NaCl	41.7
0.10 M NaBr	75.1



(16) (17) (18) (20)

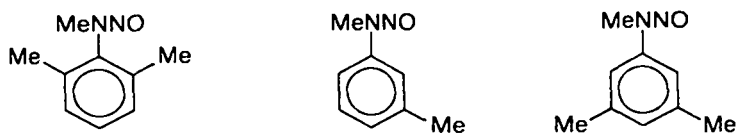
for this and other rearrangements of this type[24], a radical–radical-ion caged pair **20** (by analogy with White's mechanism[2] for the nitramine rearrangement), or possibly a π-complex **21**; other interpretations are also possible.



(19) (20) (21)

At very high acidities (>9.7M H_2SO_4) the rate constant for rearrangement levels off and decreases with increasing acidity[52]. This has been interpreted as involving virtually complete protonation of the nitrosamine and the decrease explained in terms of the rapidly decreasing activity of water at these acidities.

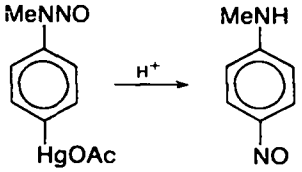
Rearrangements of the *N*-alkyl-*N*-nitrosoanilines occur[53] in sulphuric acid (in the presence of an excess of the secondary amine) with the expected rate sequence *N*-Me < *N*-Et < *N*-*i*-Pr. The *t*-butyl compound did rearrange (contrary to an early report[54]), but there were complicating features to the reaction. Electron-releasing substituents *meta* to the NRNO group increased the rate constant for rearrangement[45], whilst electron-attracting substituents decreased the rate constant. For the *m*-NO_2 compound, no rearrangement product was formed[55] (even in the absence of urea) which means that the early experiment of Macmillen and Reade[39] does not prove anything at all. 2,6,*N*-Trimethyl-*N*-nitrosoaniline (**22**) rearranged (and denitrosated) only extremely slowly. This was interpreted[56] in terms of steric



(22) (23) (24)

hindrance to solvation of the *N*-protonated intermediate. Whilst 3,*N*-dimethyl-*N*-nitrosoaniline (**23**) rearranged faster than in the absence of ring methyl substituent, the introduction of a further *meta* methyl substituent (**24**) resulted in a rate reduction, a result which could be interpreted in terms of a steric effect in the transfer of NO^+ from amino nitrogen to *para* carbon.

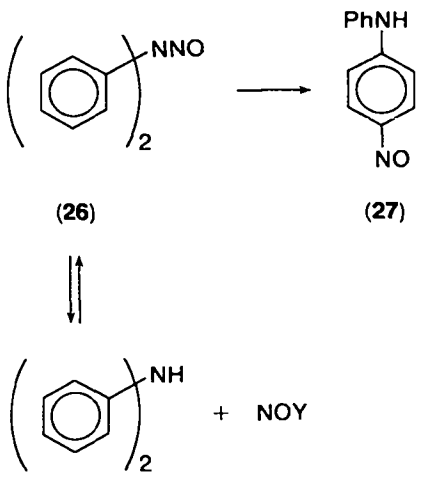
Generally when the *para* position is blocked no displacement of that group occurs and as has been noted no *ortho* product is ever formed. An exception to the former case was noted by Russian workers[57] who obtained the *p*-nitroso product from the mercurated *N*-nitrosoaniline **25** (equation 21).



(21)

(**25**)

In ethanol solution the rate constant for rearrangement of *N*-nitrosodiphenylamine (**26**) was measured[58] and found to be approximately the same as that measured for the formation of the *p*-nitroso product starting from diphenylamine, sodium nitrite and ethanolic hydrogen chloride, implying that the rate-determining stage is the same in both cases. When a nitrite trap was added to the reaction of **26** in ethanolic hydrogen chloride, no rearrangement product **27** was formed, but only the denitrosated product diphenylamine **28**. The rate constant for denitrosation was ca.



(**26**) (**27**)

(22)

(**28**)

700 times that of rearrangement. The results are consistent with a mechanism based on equation (22) but do not specifically demand an intramolecular rearrangement. Because of the large rate-constant difference between denitrosation and rearrangement for this nitrosamine in ethanol, it was not possible to make the mechanistic distinction as for the reaction of *N*-methyl-*N*-nitrosoaniline in water (Table 1 and equation 18).

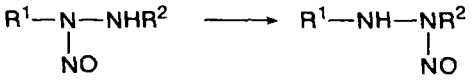
Recently, it has been shown[59] that the rearrangement of **26** occurs in each of eight

solvent systems and the rate constant correlated with three parameters relating to the solvent polarity, the solvent acidity and the solvent basicity.

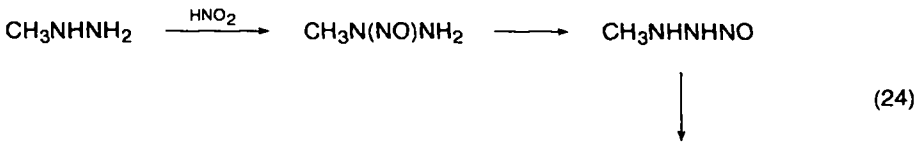
Whilst the considerable mechanistic effort in the 1970s on the Fischer–Hepp rearrangement has thrown light on many of its aspects, all questions have not yet been answered, e.g. (*a*) why is there no *o*-nitroso product and (*b*) what is the exact nature of the intermediates involved in the intramolecular rearrangement.

B. Other Rearrangements of *N*-Nitrosamines

It was suggested[60] in 1910 that 1,2-nitroso group rearrangement occurs (in acid solution) from one amino nitrogen atom to an adjacent amino nitrogen atom in hydrazine derivatives (see equation 23). It is believed[61] that a rearrangement of this type occurs in the nitrosation of methylhydrazine (equation 24) where the initial



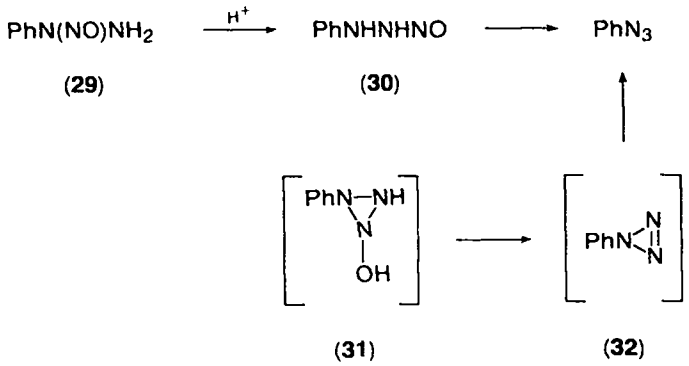
(23)



(24)

nitrosation is thought to occur at the methyl-substituted amino nitrogen followed by rate-determining rearrangement to the terminally substituted nitroso compound.

The decomposition of *N*-phenyl-*N*-nitrosohydrazine (**29**) to give phenyl azide is also thought[62] to involve acid-catalysed rearrangement to the isomer **30** (equation 25).

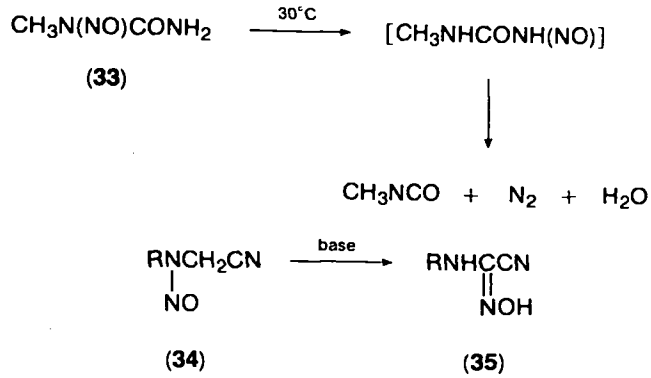


(25)

In this case, however, ^{15}N experiments show that some scrambling of the nitrogen atoms occurs, and the possible involvement of cyclic three-membered intermediates such as **31** and **32** was suggested as an alternative concurrent pathway.

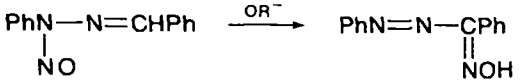
A 1,3-nitroso group rearrangement was suggested[63] for the decomposition of the nitrosoamide **33** (equation 26). Details of this and the preceding 1,2-rearrangements have not been established.

Both 1,2- and 1,3-rearrangements of the nitroso group have also been suggested to account for the observed products in base-catalysed reactions, although no mechanistic details have been established. The rearrangement of the *N*-nitroso cyano



(33) (34) (35) (26)

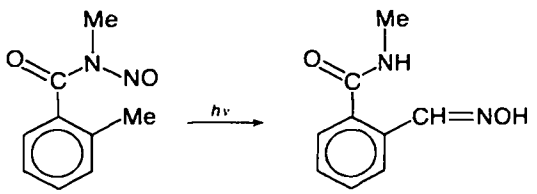
derivative **34** to give the oxime **35** must involve a 1,2-migration at some stage[64]. Similarly a 1,3-shift must occur in the base-catalysed isomerization[65] of *N*-nitrosohydrazones (equation 27).



(27)

It is known[48,49] that nitrosamines can transfer the nitroso group directly in an acid-catalysed reaction, to a variety of nucleophilic species, as shown in equation (19) earlier. Some nitrosocarbazoles are also known[66] to act as nitrosating agents towards, for example, secondary amines, by heating in organic solvents. The mechanism has not been established, but almost certainly involves homolysis to give NO which in turn is oxidized to NO_2 which effects the nitrosation possibly via N_2O_3.

Nitrosamines also react photochemically. One method of destroying carcinogenic nitrosamines is to expose them to ultraviolet light. In neutral solution it is believed that homolysis occurs to give nitric oxide and the corresponding amino radicals. Subsequent reaction depends upon the nature of the amino radical and the experimental conditions. In some cases the nitric oxide can attack another site in the amino radical resulting in an overall intermolecular rearrangement. For example[67] the photolysis of *N*-nitroso-*N*-methyl-*o*-toluamide (**36**) gives (by equation 28), in the absence of oxygen, the α-oxime **37**. In the presence of oxygen, the corresponding



(36) (37) (28)

nitrate ester was formed, presumably by some reaction of nitrogen dioxide. Similar results were found for the reaction of a more complex nitrosamide, *N*-nitroso-*N*-acetyldehydroabietylamine. Ring nitro products can also be obtained, particularly from diarylnitrosamines heated in the presence of oxygen[68]. In acid solution, it is believed[69] that photolysis of nitrosamines results in the formation of aminium radicals and nitric oxide (equation 29). Often a variety of products results which has been rationalized in terms of reactions of these aminium radicals, including the rearrangement reaction to give amidoximes (equation 30). Photoaddition of

$$R_2NNO + H^+ \xrightarrow{h\nu} R_2\dot{N}H^+ + NO \quad (29)$$

$$\begin{matrix} R^1 \\ \diagdown \\ R^2CH_2 \end{matrix}\!\!>NNO + H^+ \xrightarrow{h\nu} R^1NHC{=}NOH \quad (30)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R^2$$

nitrosamines to alkenes in acid solution gives *C*-nitroso products (or oximes) in a highly regiospecific manner[70] (see equation 31).

$$BuCH{=}CH_2 + Me_2NNO \xrightarrow[H^+]{h\nu} \left[\begin{matrix} BuCHCH_2NMe_2 \\ | \\ NO \end{matrix} \right] \quad (31)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \downarrow$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \begin{matrix} BuCCH_2NMe_2 \\ \| \\ NOH \end{matrix}$$

IV. REARRANGEMENTS INVOLVING ALKYL NITRITES

A. Thermal and Photochemical Reactions

Alkyl nitrites when heated can give a variety of products, all of which have been explained in terms of the initial homolytic fission of the O—N bond to give an alkoxy radical and nitric oxide (equation 32). In some cases the nitroso group can end up in

$$RONO \xrightarrow{heat} RO^{\bullet} + NO \quad (32)$$

a *C*-nitroso rearrangement product, particularly if R• is a tertiary alkyl group and also if a flow system is used so that the product is quickly removed from the reaction[71]. The sequence of reactions (equation 33) includes the break-up of the alkoxy radical

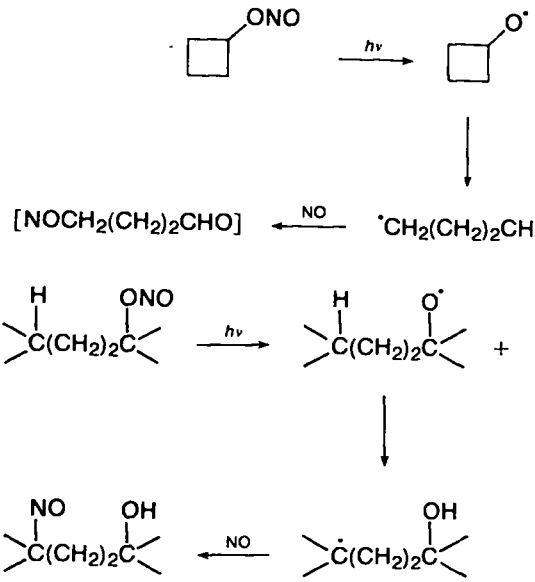
$$R_3CONO \xrightarrow{320°C} \begin{matrix} R_3CO^{\bullet} + NO \\ \downarrow \\ R_2CO + R^{\bullet} \end{matrix} \quad (33)$$

$$R^{\bullet} + NO \longrightarrow RNO$$

to give the carbonyl compound and the free radical R• which combines with the nitric oxide to give the *C*-nitroso product. A similar reaction has been reported for the photochemical reaction[72], when *t*-butyl nitrite gives acetone and nitrosomethane.

Cyclic nitrites can give ring-opened linear products (as *C*-nitroso dimers or oximes), again both thermally and photochemically. Thus[73] *c*-hexyl nitrite gives 6-nitrosohexanol when heated, and *c*-butyl, *c*-pentyl and *c*-hexyl nitrites yield the linear nitroso aldehyde derivatives[74], as typified by equation (34), from a photochemical reaction.

A 1,5-rearrangement of the nitroso group in alkyl nitrites from oxygen to carbon is a feature of the Barton reaction[75,76] A carbon chain of at least four atoms is necessary and the product is a 4-nitroso alcohol. The reaction is explained in terms of a rearrangement of the alkoxy radical, as shown in equation (35), followed by



(34)

(35)

reaction with nitric oxide. Again the product can be a nitroso dimer or an oxime. *c*-Alkyl nitrites also give the Barton reaction, but only if the ring size is greater than six[74]. Presumably a six-membered ring intermediate is necessary for the alkoxy radical rearrangement and also for the nitric oxide reaction which could well be simultaneous processes.

The Barton reaction has been used successfully in syntheses, particularly in the field of steroid chemistry where the products would be very difficult to obtain by other routes. Often side-reactions accompany oxime formation and can be rationalized in terms of the subsequent reactions of the radicals produced. A recent detailed analysis[77] of these side-reactions has enabled a clearer picture of the detailed mechanisms to be established. One interesting feature relevant to the nitroso rearrangement reaction is that the reaction in the presence of oxygen, which is known to yield nitrate ester products[78], is believed to involve peroxynitrites as intermediates.

B. Acid- and Base-catalysed Reactions

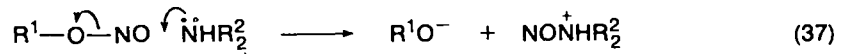
It is known that alkyl nitrites can act as nitrosating agents[79], both in acid- and base-catalysed reactions, although it has not always been established whether prior hydrolysis to give free nitrous acid is taking place. This hydrolysis is known to be a rapid process as is the reverse reaction, the *O*-nitrosation of alcohols. Very recently rate constants have been determined[80] (by stopped flow spectrophotometry) for the nitrosation of methanol and the reverse reaction the hydrolysis of methyl nitrite (equation 36). Both reactions are acid-catalysed and the rate constants at 25°C are

$$\text{MeOH} + \text{HNO}_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{MeONO} + \text{H}_2\text{O} \qquad (36)$$

$k_1/[\text{H}^+] = 700\ \text{l}^2\text{mol}^{-2}\text{s}^{-1}$ and $k_{-1}/[\text{H}^+] = 576\ \text{l mol}^{-1}\text{s}^{-1}$, showing that these reactions are indeed rapid processes so that any reaction of an alkyl nitrite in an aqueous acid medium almost certainly involves free nitrous acid. There is a report[81] that the *N*-nitrosation of sulphanilamide by *c*-hexyl nitrite and by nitrous acid involve

the same nitrosating agent. There appears to be no reference in the literature to a rearrangement reaction of an alkyl nitrite proceeding by an ionic mechanism analogous to the Barton reaction.

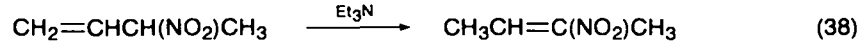
Recently it has been shown[82] that alkyl nitrites containing a β electron-withdrawing group react very rapidly with amines in basic solution to give nitrosamines. A kinetic study has also been reported[83] on the reaction of phenylethyl nitrite with a range of amines; the authors conclude that reaction involves a concerted displacement of RO^- by the amine (equation 37) as the rate-determining stage, rather than an addition–elimination mechanism.



(37)

V. THE REARRANGEMENT OF NITRO OLEFINS

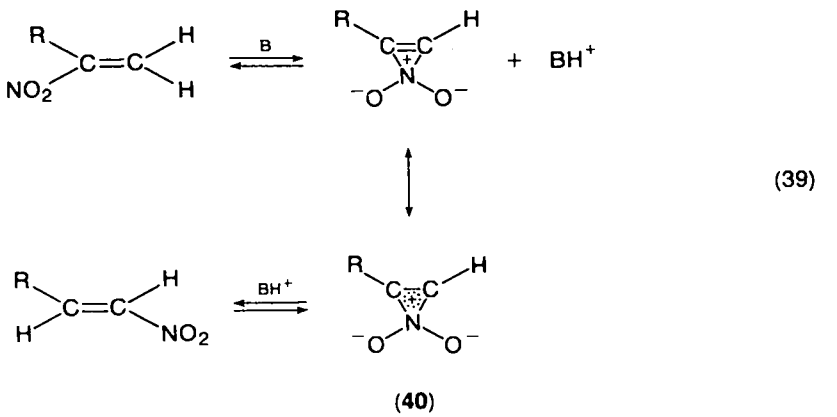
In the presence of bases nitro olefins readily undergo rearrangement in organic solvents. For example, 3-nitro-1-butene (**38**) gives[84] 87% 2-nitro-2-butene (**39**) on treatment with triethylamine in chloroform for 16 minutes (equation 38). This



(38)

(38) (39)

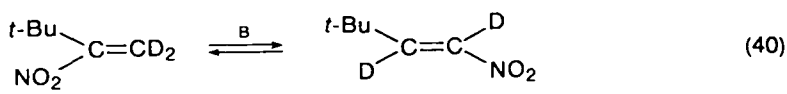
reaction has not been studied mechanistically and may well simply involve a prototropic shift. However a 1,2-nitro group shift is probable in the rearrangement of some conjugated nitro olefins. Mechanistic work has been carried out[85], noting the effects of solvent change, base strength and isotopic substitution upon the rates of the rearrangement. The authors take the results to support an earlier suggestion[86] that the mechanism involves proton abstraction to give a cyclic intermediate containing a three-membered ring (**40**) as shown in equation (39). The same equilibrium mixture



(39)

(40)

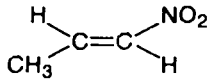
is obtained from both isomers. The rate constant increases with the polarity of the solvent suggesting that the transition state is more polar than the initial state. As expected the rate constant also increases with increasing base strength. The kinetic deuterium isotope effect (for equation 40) was found to be 6.20 at 40°C thus



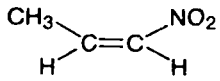
(40)

confirming the rate-determining proton transfer. No ^{15}N exchange with added [^{15}N] potassium nitrite was found, supporting an intramolecular rearrangement.

Each of the three nitropropenes **41**, **42** and **43** gave 2-nitropropene in a reversible



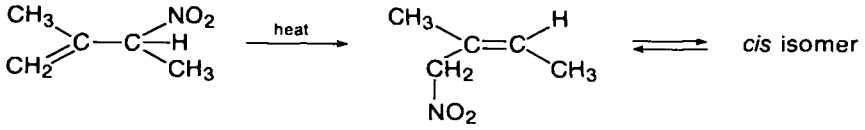
(**41**)



(**42**)

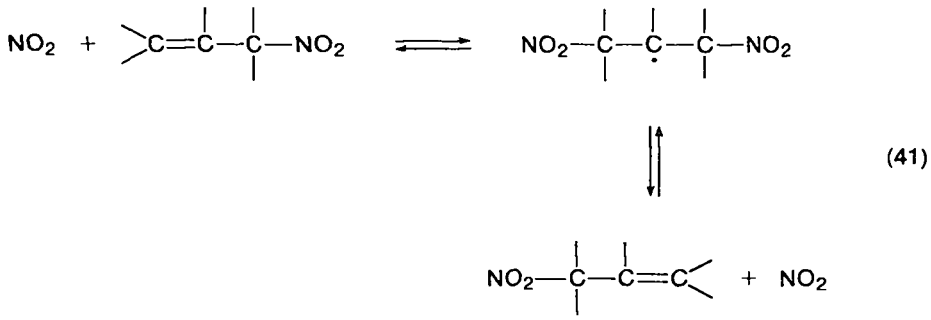
(**43**)

base-catalysed reaction[87]. Kinetic analysis however revealed that only *trans*-1-nitropropene (**41**) was directly converted to the product by a 1,2-NO_2 shift and vice versa for the reverse reaction. The same change was also accomplished photochemically. Heating 2-methyl-3-nitro-1-butene (**44**) resulted[88] in the formation of both *cis* and *trans* isomers of 1-nitro-2-methyl-2-butene (**45**). This is believed to



(**44**) (**45**)

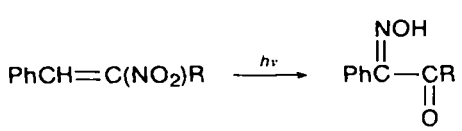
occur by a radical reaction of NO_2 formed in trace amounts through decomposition, followed by loss of the other nitro group as NO_2 (equation 41). This reaction



(41)

represents an example of a 1,3-rearrangement of the nitro group. Another example of this rearrangement has been reported earlier[89] from a reaction carried out in carbon tetrachloride containing added NO_2. Again the mechanism was presumed to involve reversible addition of NO_2 to the olefin forming the dinitroalkyl radical.

Some nitro olefins, when irradiated, undergo photorearrangements which appear to involve firstly isomerization to the nitrite form, followed by a 1,2 nitroso group rearrangement. Thus β-methyl-β-nitrostyrene (**46**, R = Me) gives[90] the α-oximinoketone **47** (equation 42). Later workers[91] showed that whilst this is the

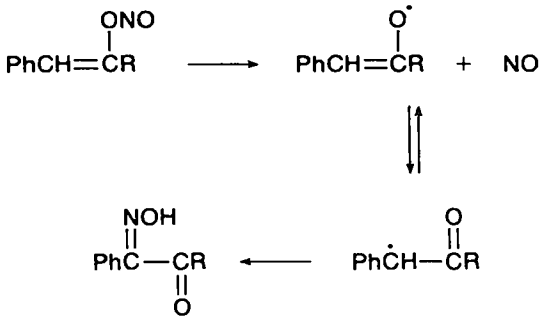


(42)

(**46**) (**47**)

main reaction, other products are found, particularly when using nitrostyrenes with electron-withdrawing substituents, which involves cyclization by the nitro group and

forms a *N*-oxide intermediate. The mechanism for the formation of **47** is thought to involve the nitro → nitrite isomerization, followed by homolysis to give NO which attacks the carbon atom as shown in equation (43) to give the α-oximinoketone

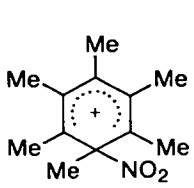


(43)

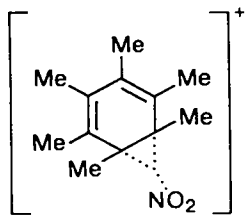
product. In the presence of oxygen this reaction does not occur, the intermediate radical now combining with oxygen to give the α-keto hydroperoxide which undergoes a normal cleavage reaction.

VI. AROMATIC NITRO GROUP REARRANGEMENTS IN ACID SOLUTION

Olah and coworkers[92] first demonstrated the mobility of the NO_2 group around the aromatic ring in the nitrohexamethylbenzenium ion (**48**). This was achieved by examining the NMR spectrum of hexamethylbenzene and nitronium fluoroborate in FSO_3H–SO_2 high-acid medium at −70°C. The spectrum was identified as that of **48**.



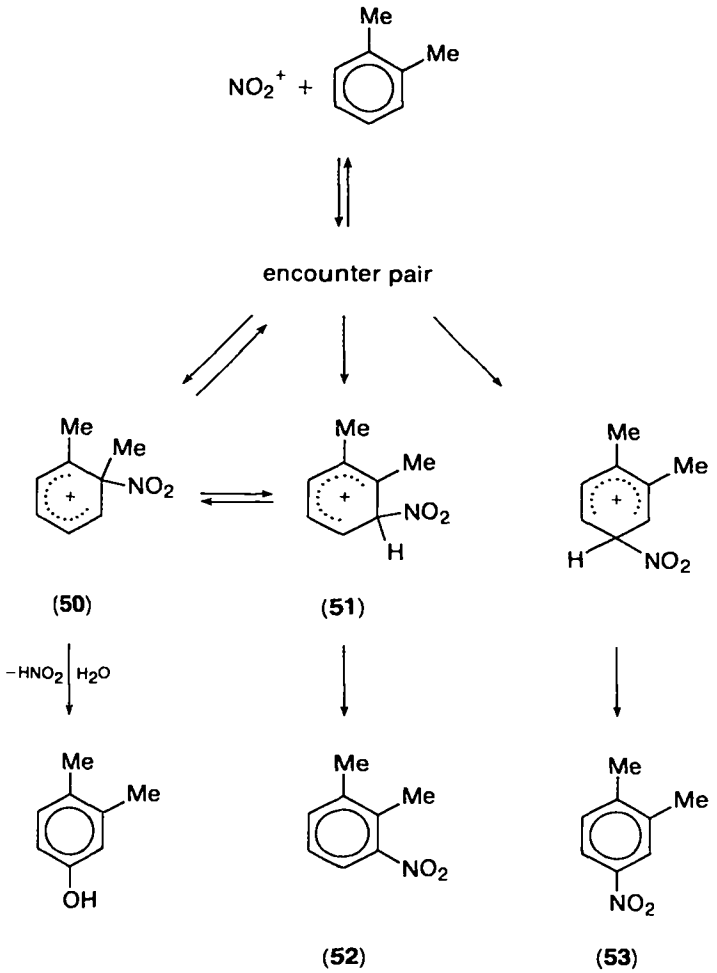
(48)



(49)

The change of the spectrum with temperature was consistent with continuous 1,2-intramolecular shifts of the nitro group and a transition state **49** was suggested involving three-centre bonds. Similar results were observed for the 1-nitro-2,6-difluorotetramethylbenzenium ion. Russian workers[93] have come to the same conclusion using the 'saturation label' method (double NMR and triple NMR). This equilibration reaction is not confined to nitro group shifts as the $-SO_3H$ group has also been shown[93,94] to migrate around the aromatic ring in this way.

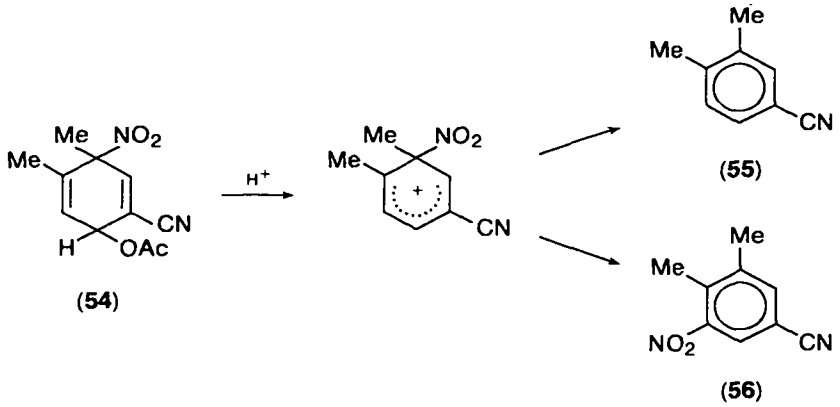
Myhre[95] was the first to recognize that 1,2 nitro group rearrangements could occur during aromatic nitration at high acidity. He introduced the mechanism (given in equation 44) to account for earlier results[96] giving the variation of the isomer ratios of the nitration products of *o*-xylene with the acid concentration. This topic is discussed more fully in another chapter in this volume, but it is included here as it does represent an example of a rearrangement clearly involving the shift of a nitro group. The ion formed by *ipso* attack (**50**) can either undergo hydrolysis to give a phenol group, return to reactants, or undergo a 1,2 nitro group shift to give the ion



(44)

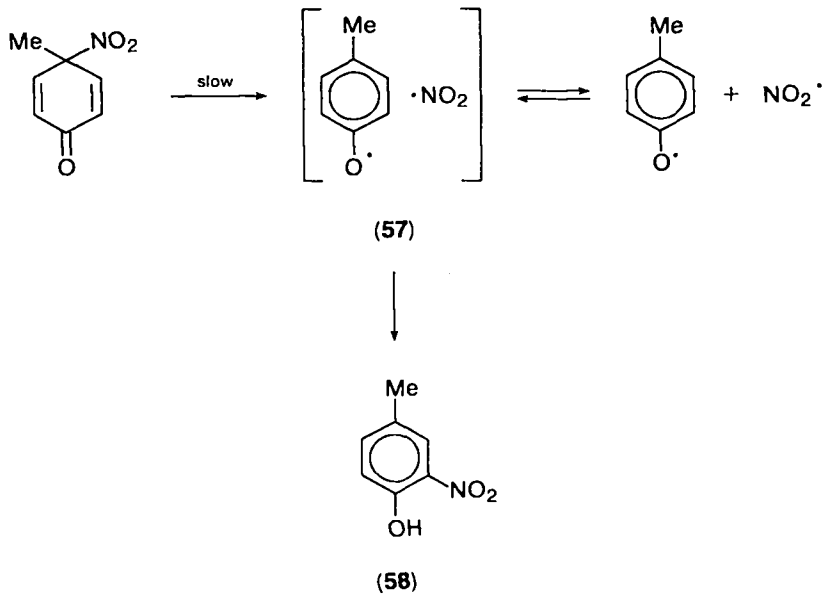
51 from which the 3-nitro-*o*-xylene product (**52**) is derived. This was confirmed by generating the ion **50** by solvolysis of 3,4-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate in high acid solution. In 85% sulphuric acid, 93% of **52** was formed; this dropped to 2% in 49% sulphuric acid. The change, and the change in the isomer ratios from the nitration are attributed to the competing parallel reactions of **50** to give hydrolysis product or rearrangement. The former reaction would be favoured at lower acidity. No **53** was found from the acetate hydrolysis experiment implying that **51** does not undergo a further 1,2 nitro group rearrangement. Subsequently a number of such rearrangements have been observed in nitration experiments[97] and *ipso* attack has been recognized as a major mechanistic pathway in aromatic nitration.

Formal 1,3 nitro group migrations are also known and are generally thought of as being repeated 1,2 nitro shifts[97], although their mechanisms have not been completely established. The adduct 2-cyano-4,5-dimethyl-4-nitrocyclohexa-2,5-dienyl acetate (**54**) (formed by nitration of 3,4-dimethylbenzonitrile in acetic anhydride) decomposes in acetic acid to give the original benzonitrile (**55**) and the 5-nitro isomer (**56**) as the major products[98] (equation 45).



(45)

More recently Barnes and Myhre[99] have suggested an alternative mechanism for the overall 1,3 nitro group rearrangement involving (equation 46) homolytic dissociation to give a radical pair (**57**), from which the product (**58**) is derived by

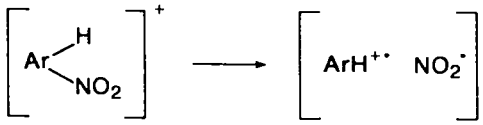


(46)

reaction within the solvent cage. The mechanism was supported by the evidence of substantial (but not complete) scrambling of isotopes in a double-labelling experiment involving [^{15}N]-NO_2 and 2,6-d_2-labelled reactant, which was allowed to react in the presence of an equimolar amount of the unlabelled reactant.

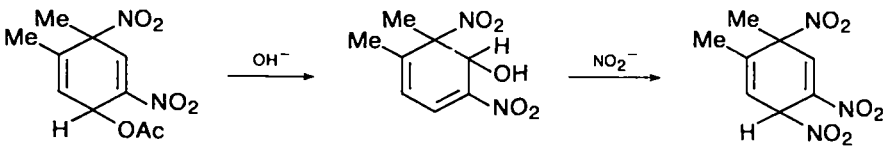
Earlier Perrin[100] explained the nitro group rearrangements accompanying rearomatization of *ipso* nitration products in terms of an intramolecular rearrangement (equation 47) involving the intermediacy of a radical–ion-radical pair analogous to that suggested by White[2] (equation 8 in Section II.A) for the mechanism of the nitramine rearrangement.

An overall 1,4 nitro group rearrangement has recently been observed[101] in the rearomatization of 4,5-dimethyl-2,4-dinitrocyclohexa-2,5-dienyl acetate (**59**) in the presence of various nucleophiles (e.g. OH^-). The rearrangement is explained in terms of a series of consecutive S_N2' substitutions as indicated in equation (48).



(47)

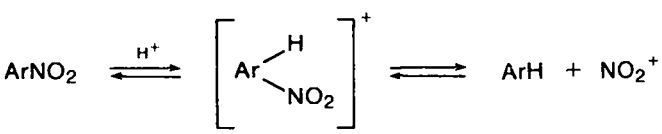
ring nitro products



(59)

(48)

Before the discovery of *ipso* attack and the resurgence of interest in aromatic nitration, it had been observed[102] that 2,3-dinitroaniline was converted (by heating in strong sulphuric acid for several hours) into 3,6-dinitroaniline (47%) and 3,4-dinitroaniline (24%). The mechanism was not established but a suggestion was made[103] that the rearrangements occurred by intermolecular reversible denitration and nitration (equation 49).

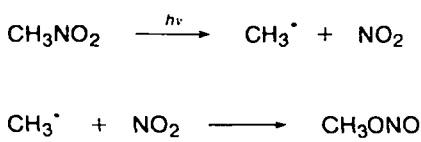


(49)

VII. REARRANGEMENTS OF C-NITRO COMPOUNDS TO C-NITRITES

Many reactions of *C*-nitro compounds generally brought about thermally or photochemically have been rationalized on the basis of an initial rearrangement to the nitrite form. The special case of nitro olefins has been discussed in Section V.

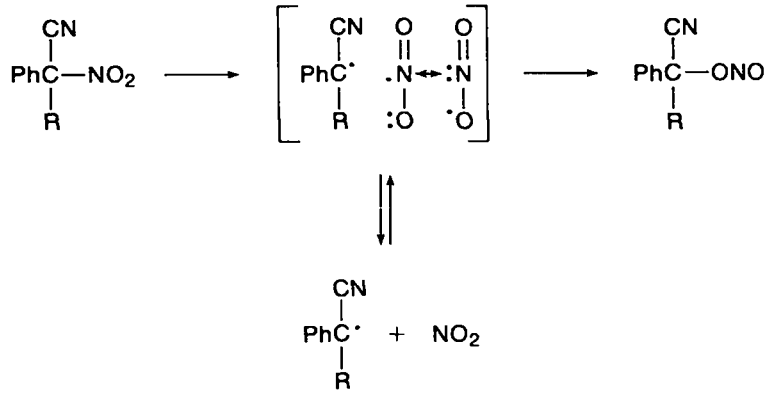
The photoisomerization of nitromethane[104] can be envisaged as a dissociation followed by a recombination (equation 50), although it is possible that the rearrangement is a completely intramolecular one. More complex schemes have also



(50)

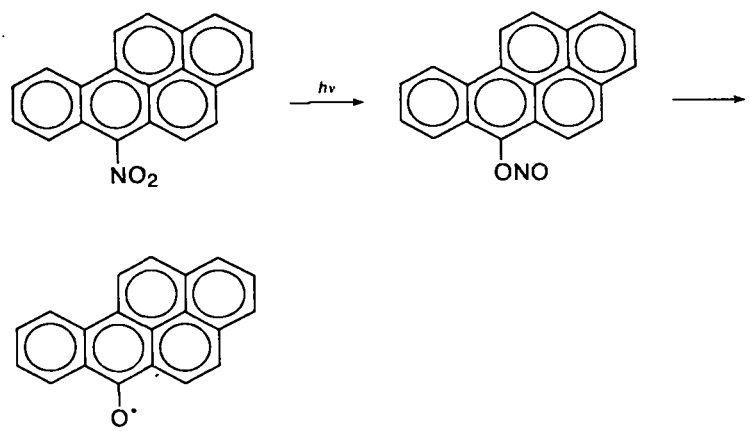
been advanced[105] which include the formation and participation of the methoxyl radical.

Recently kinetic and stereochemical evidence has been presented[106] in support of a mechanism involving homolytic fission and the formation of a radical-pair intermediate in the thermal isomerization of a nitroalkane to give the alkyl nitrite (equation 51).

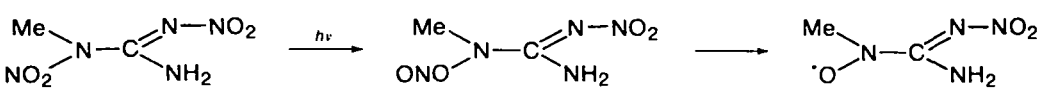


(51)

The ESR spectra have been recorded[107] of a number of alkoxy and aryloxy radicals derived from the photolysis of the corresponding nitro compound via, it is believed, the rearrangement to the corresponding nitrite, as is shown in equations (52) and (53). The spectra are identical with those obtained by formation of the oxy radicals by other routes.



(52)



(53)

The pyrolyses of methyl[108] and other nitrites have been investigated kinetically. The results are in accord with the homolytic dissociation to give RO• and nitric oxide.

Fission of the O—N bond is also thought to occur in the mass spectrometer when

nitrobenzene is believed[109] to isomerize to the nitrite form and thence lose NO which gives rise to the peak at *m/e* 30 (equation 54).

$$\begin{array}{ccccc} PhNO_2 & \xrightarrow{e^-} & [PhNO_2]^{\ddagger} & \longrightarrow & [PhONO]^{\ddagger} \\ & & & & \downarrow \\ & & & & [PhO]^+ + NO \end{array} \qquad (54)$$

Another interesting example[110] of the nitro–nitrite isomerization occurs in the photochemical reaction of the octahedral cobalt complex $[Co(NH_3)_5NO_2]^{2+}$ and more recently[111] in $Co(acac)_2pyNO_2$. Changes in both the vibrational and UV visible spectra are believed to be due to the $NO_2 \rightarrow ONO$ conversion.

Other photochemical rearrangements of *C*-nitro and *C*-nitroso compounds have been reviewed in an earlier volume in this series[112].

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CHAPTER **5**

The spectroscopy, photophysics and photochemistry of saturated amines

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I. INTRODUCTION

In considering the amine as a functional group, it readily becomes clear that the photochemical properties usually associated with the term 'amine' can be sorted into at least three main categories: (1) saturated amines in their excited states, (2)

unsaturated (including aromatic) amines in their excited states, and (3) both saturated and unsaturated amines in their ground states. In the third class, one usually views the amines as acting as reductive substrates towards some other, electronically excited, entity. The second category encompasses such a wide variety of unique cases that the coverage of their photochemical properties would easily require a separate volume. Thus, one would have to consider virtually as separate classes such cases as aromatic amines, heteroaromatic amines, and others. In the first category above, however, it is the amine functionality, *per se*, which determines the physical and chemical properties of the excited state. Thus, in order to expose, describe and attempt to explain the specific role of the nitrogen lone pair in molecular processes, this chapter is devoted to the excited state properties of the saturated amines. In particular, the spectroscopic and photophysical properties are emphasized. This is not only because of the author's particular research interests, but also because the photochemistry of these compounds was thoroughly reviewed recently by von Sonntag and Schuchmann (see Reference 94). Since the appearance of this work, relatively little has appeared in the literature concerning the photochemistry of saturated amines.

It is hoped that this chapter represents a successful attempt to unify the already complimentary domains of spectroscopy, photophysics and photochemistry. One at least learns that an understanding of one of these areas can only follow if one understands all three.

II. SPECTROSCOPY

A. Gas-phase Systems

1. Ammonia

The prototype molecule for considering the spectroscopy of saturated amines is, of course, ammonia. This is a small molecule, a first-row hydride, and accordingly, a great deal of attention has been given to all aspects of the spectroscopy of this fundamentally important compound[1]. Probes of the electronic structure of ammonia include numerous (one-photon) electronic absorption[2–6], photoelectron[7–8] and electron impact studies[9–11].

Ammonia vapour begins to absorb ultraviolet radiation at 2167.8 Å; this wavelength represents the O—O band of the lowest lying (singlet) transition ($\tilde{A} \leftarrow \tilde{X}$). It also marks the origin of a long series of vibronic bands (a progression) having a spacing of 870 cm^{-1} which is assigned as the out-of-plane symmetric bending vibratrion ($\tilde{\nu}_2'$) of the excited state. The maximum of this rich vibronic display appears at about 1947 Å, and corresponds to about six quanta of $\tilde{\nu}_2'$. This electronic transition is assigned as the promotion of an electron from the nitrogen atom nonbonding orbital (n_N) to the nitrogen atom 3s atomic-like orbital (i.e. $n_N \rightarrow 3s$). This is an example of a Rydberg transition, which by definition involves an excited state built up of atomic orbitals characterized by a higher principal quantum number than those which are used to describe the ground-state orbital configuration.

It is important to recognize that the equilibrium geometry of the excited state of ammonia is planar and symmetrical (i.e. belonging to the D_{3h} point group). This fact has significant consequences with respect to the photophysical properties of the saturated amines, and will be described below. This geometry assignment is made not only of the lowest excited state (the $\tilde{A}$ state) of ammonia, but also of the higher lying states as well, and is based upon certain observations, two of which are summarized as follows:

(1) The vibronic transitions which originate from one quantum of the ground-state inversion mode, $\tilde{\nu}_2''$ (thus 'hot' bands), show a slight, but significant alternation, or 'staggering' in the spacing. This would occur if the symmetrical bending mode in the excited state did not possess inversion components and this, in turn, would follow from a planar configuration. The alternation in the vibronic bands arises from the fact that in the pyramidal ground state, the $\nu_2' = 1$ inversion mode is split by 36 cm^{-1} (inversion doubling) into states of opposite symmetry, and thus optical transitions from this pair of states to the unsplit vibrational levels of the excited state are governed by symmetry considerations[2,12].

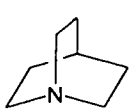
(2) The rotational analysis of the vibronic bands of the spectrum of ND_3 has been made by Douglas and shows details which are only consistent with a planar upper state belonging to symmetry species A_2'' [13].

The higher excited states of ammonia have also been assigned as planar Rydberg states involving the promotion of an electron chiefly from the n_N orbital. The details of these states and their assignments have been summarized by Herzberg[14] and Robin[15]. The $\tilde{A}$, $\tilde{D}$ and $\tilde{E}$ upper states are assigned as Rydberg 3s, 4s and 5s states, respectively, and the $\tilde{B}$ and $\tilde{C}$ states are denoted as being $3p_{xy}$ states, respectively. Recently, Nieman and Colson[16], using multiphoton ionization spectroscopy, have identified a new state in the vicinity of the (n_N, $3p_z$) state (the $\tilde{C}$ state) near 1565 Å, and have suggested that this state ($\tilde{C}'$) corresponds to an ($n_N \rightarrow 3d$) excitation.

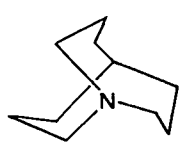
All of the upper states of ammonia are strongly predissociated, which means that there is strong coupling to a continuum of states based upon the bond-scission fragments, NH_2 and H. Thus, for ammonia and deuterated ammonia, the vibronic bands of the $\tilde{A} \leftarrow \tilde{X}$ are broadened and show no rotational fine structure[2,13]. It is reasonable to speculate that an appreciable role must be played by the antibonding orbitals (i.e. σ^* N—H) in the upper states of ammonia. Robin[17] has pointed out that such an intravalence state can be constructed from the σ^* (N—H) orbitals which have the same symmetry (e.g. nodal) properties as the Rydberg state (e.g. the 3s orbital). These so-called conjugate states can then mix with the Rydberg state, and the extent to which this mixing occurs depends upon the overlap between the zero-order states and also upon the geometry of the molecular system. Thus, as one of the N—H bonds become elongated (and the system goes over to C_{2v} symmetry), the importance of the dissociative (n_N, σ^*) state increases.

2. *Alkylamines*

In the simple alkylated amines, i.e. methyl-, dimethyl-, and trimethyl-amine, the vibronic structure which characterizes the spectra of ammonia rapidly disappears as the degree of alkylation increases[18]. This is particularly true of the lowest-lying $n_N \rightarrow 3s$ transition. For example, in the case of trimethylamine, this transition appears as a structureless band with λ_{max} at ca. 228 nm. Recently, however, Matsumi and Obi[19] have reported that this absorption band possesses very weak vibrational structure having a frequency of ca. 380 cm^{-1} which, they suggest, corresponds to the upper-state out-of-plane symmetrical C—N—C bending vibration.



ABCO



ABCU

Similar behaviour, i.e. a significant diminution in the appearance of vibronic features, is observed in the amines having higher degrees of alkylation. Some notable and very interesting exceptions to this trend are observed in the class of structurally 'rigid' cage amines containing bridgehead nitrogen atoms. Two such compounds are ABCO (1-azabicyclo[2.2.2]octane) and ABCU (1-azabicyclo[3.3.3]undecane). The absorption spectra of ABCO and triethylamine are portrayed in Figure 1. This contains the near-ultraviolet spectra of these amines, and shows the first two distinct transitions in ABCO.

The complete vapour-phase absorption spectrum of ABCO reveals three electronic transitions[20]. The lowest-lying one possesses a O—O band at 2559 Å and several vibrational progressions, the most prominant of which is in a frequency of 625 cm^{-1}. The O—O bands of the second and third transitions are located at 2286 Å and 1886 Å respectively. All three of these transitions are richly endowed with vibronic structure, and progressions in 625 cm^{-1} dominate the entire electronic spectrum. In fact, 12–14 members of such a progression can be identified in each of the latter two ABCO transitions. The 625 cm^{-1} excited-state mode is believed to correlate with a ground-state vibration of 604 cm^{-1} which has been assigned to a cage-squashing or a 'pseudo-inversion' mode in which the nitrogen atom oscillates along the molecular C_3 axis[21]. Thus, the predominance of this vibrational excitation in the absorption spectra of ABCO is in quite strong analogy with the situation in ammonia itself.

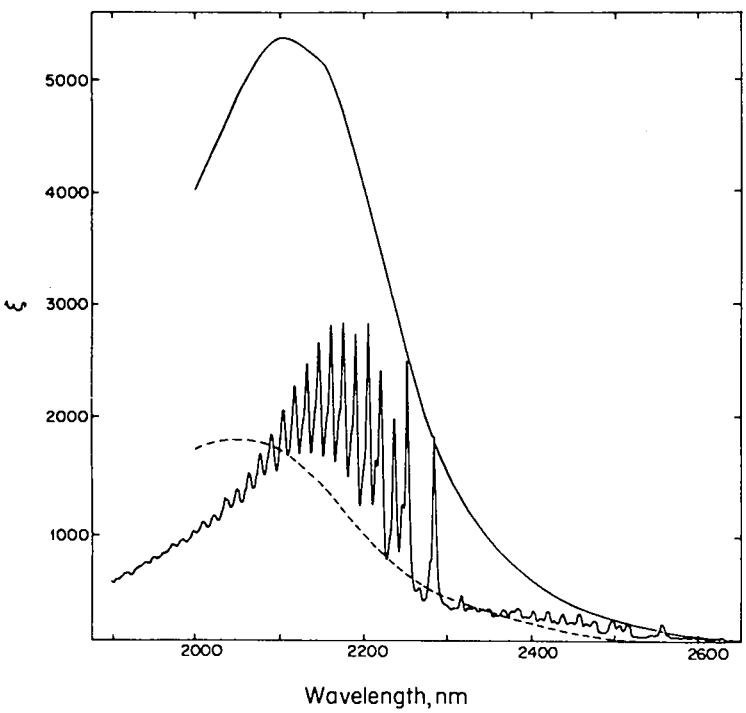


FIGURE 1. Solid, smooth curve: vapour-phase absorption spectrum of triethylamine; solid, structured curve: vapour-phase absorption spectrum of ABCO; dashed curve: absorption spectrum of ABCO in *n*-hexane solution. All spectra are taken under ambient temperature conditions.

These three electronic transitions in ABCO are assigned as $n_N \rightarrow$ 3s, 3p and 4p Rydberg states, respectively, on the basis of the term values, i.e. the difference between the ionization potential and the (adiabatic) transition energy. The photoelectron spectrum of ABCO also displays vibrational structure, and provides values of the adiabatic and vertical ionization potentials of 7.50 and 8.05 eV, respectively[22-23].

The vapour-phase absorption spectrum of another cage amine which is analogous to ABCO, namely, 1-azadamantane, also possesses remarkably sharp and extensive vibronic structure (see Figure 2)[99]. Because of the low vapour pressure of this amine at ambient temperatures (ca. 0.1 Torr at 25°C) the weak, low-lying $n_N \rightarrow$ 3s transition has not been observed. The stronger $n_N \rightarrow$ 3p transition, however, possesses even narrower vibronic bands than ABCO. The O—O band, for example, which appears at 2367 Å, has a half-width of (at most) ~15 cm^{-1} at 300 K. It is followed by many members of a progression in 620 cm^{-1} which presumably corresponds to the analogous cage-squashing mode observed in the spectrum of ABCO. Indeed, the absorption spectra of these rigid, symmetrical cage amines, with their profusion of sharp vibronic details, seems to be out of character for the large, polyatomic molecules which they are. It is as if the electronic absorption spectra of such compounds are more akin to the spectra of valence-state hybridized nitrogen atoms placed in an 'inert' hydrocarbon matrix.

Unlike ABCO, wherein the three ethylene bridges appear to impose no significant structural deformation of the bridgehead nitrogen atom, ABCU represents a case in which the transannular interactions between the hydrogens on the trimethylene bridges are large enough to constrain the nitrogen atom to assume a more planar configuration[24]. To wit, the C—N—C bond angles have been determined to be ca. 115°[25]. The spectroscopic consequences of this structural perturbation are dramatic. For example, in ABCU, the electronic absorption spectrum is dramatically red-shifted relative to ABCO. Four distinct transitions are observed in the vapour phase; the O—O positions of these bands are at: 2783, 2584, 2315 and 2088 Å[26]. The vibronic character of each of these transitions is distinctly different from the situation in ABCO in that a more 'vertical' transition is indicated. For example, in ABCU, the

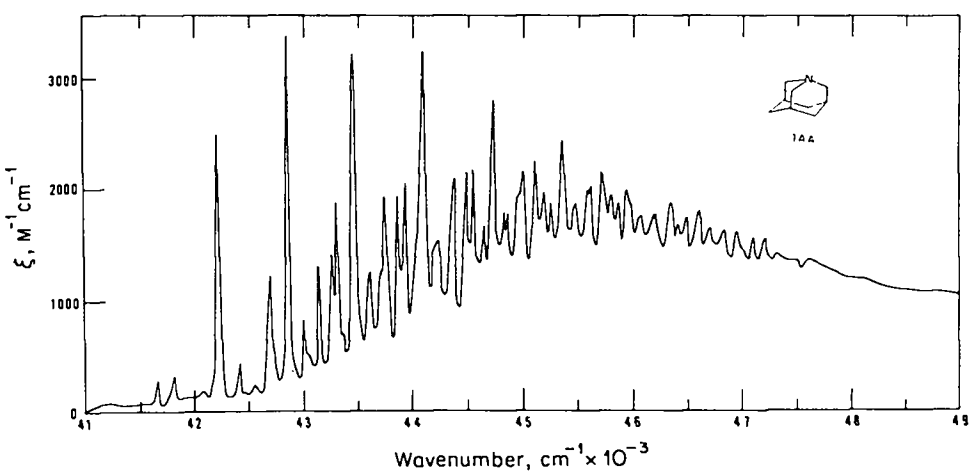
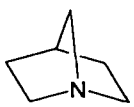


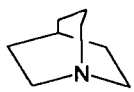
FIGURE 2. Vapour-phase absorption spectrum of 1-azaadamantane at 23°C. Taken from A. M. Halpern, *Mol. Photochem.*, 5, 517 (1973) and reproduced by permission of Marcel Dekker Journals.

most intense vibronic feature in each of these transitions is the O—O band, while in ABCO, the strongest band is represented by the excitation of four quanta of the symmetrical N—C stretching mode. As in ABCO, the electronic transitions in ABCU are all assigned as Rydberg transitions, and accordingly, the red-shift observed in these bands is a consequence of the lowered ionization potential (7.05 eV, adiabatic) due to the nitrogen atom flattening[27]. The first two transitions are assigned as n_N to 3s and 3p Rydberg states respectively. The third has been assigned as a promotion to either a 4s or a 3d state, and the fourth is interpreted as an excitation to a Rydberg 4p state.

The absorption spectra of two other nitrogen-bridgehead cage amines have been investigated and, like the situation in ABCO and ABCU, permit the location of the excited states to be made. In addition, similar, but more subtle, effects on C—N—C bond angles imposed by the cage bridges on the transition energies (and presumably, the ionization potentials) can be observed. These compounds are: 1-azabicyclo-[2.2.1]heptane (ABCH) and 1-azabicyclo[3.2.2]nonane (ABCN).



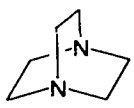
ABCH



ABCN

It should be noted that, as the C—N—C bond angle of the bridgehead nitrogen increases, the ionization potential decreases (i.e. the stability of the cation increases as the nitrogen atom centre is flattened) and as a consequence, the transition energies also decrease[28]. This information is summarized in Table 1.

Another bicyclic cage amine which deserved special comment is, 1,4-diazabicyclo[2.2.2]octane (DABCO). This amine, well known for its unusual



DABCO

quenching ability (because of its low ionization potential), also possesses a highly structured vapour-phase electronic absorption spectrum. Because of the relatively strong ground-state coupling between the two nitrogen atoms in DABCO, the highest-filled molecular orbital (represented by the in-phase, or symmetric, combination of n_N orbitals) lies about 0.5 eV higher relative to the n_N orbital energy of ABCO. (Actually, the splitting between the two n_N-based molecular orbitals in DABCO, i.e. $n_{\pm}$, is about 2.1 eV, as determined from photoelectron spectroscopy)[23,29,30].

Three electronic transitions have been observed in the vapour-phase spectrum of DABCO. The low-energy system will be described below. A very prominent O—O band marks the origin of the second transition at 2511 Å, and is followed by many vibronic features which belong to a complex superposition of progressions. The third transition commences with a O—O band at 2025 Å and is also associated with vibrational progressions. For both of these transitions, the most dominant upper-state vibrations which are coupled with the ground state are modes having frequencies of 875 cm^{-1} and 800 cm^{-1} [21].

The lowest-lying singlet electronic transition in DABCO is of particular interest because of its very weak nature. Because DABCO is a symmetric molecule (D_{3h}), one-photon transitions to upper states which have totally symmetrical wave

TABLE 1. Adiabatic ionization potentials and transition energies of cage amines

Amine	C—N—C (deg.)	(S_1, S_0) (Å)	Term value[a]	(S_2, S_0) (Å)	Term value[a]	(S_3, S_0) (Å)	Term value[a]	IP[b]
ABCH	101–103[c]	2316	24,580	2028	18,440	—	—	(8.4)[d]
ABCO	109	2556	23,150	2280	18,410	1886	9247	7.72[e]
ABCN	110–115[f]	2645	21,880	2399	18,000	1953	8485	(7.4)[d]
ABCU	115–116[g]	2783	20,690	2584	17,920	2315	13430[i]	7.02[h]
DABCO	109[j]	2794	22,530	2510	18,480	2025	8930	7.23[e]

[a]The term value, represented in cm^{-1}, is given as $E_{IP} - E_{trans}$.
[b]Values, where obtainable, refer to adiabatic IP, in eV.
[c]Structural data taken from norbornane.
[d]Based on the term value of the $S_2 \leftarrow S_0$ transition and assuming a quantum defect of 0.55 (see Refs. 15 and 20).
[e]Adiabatic IP taken from Ref. 30.
[f]Based on 3-azobicyclo[3.2.2]nonane[101].
[g]Ref. 25.
[h]Refs. 26 and 27.
[i]In ABCU, the $S_3 \leftarrow S_0$ transition, unlike the other amines, is not assigned as a $4p \leftarrow n_N$ transition, but rather to either a 3d or 4s Rydberg state. The $S_4 \leftarrow S_0$ transition has a term value of 8750 cm^{-1}.
[j]Ref. 102.

functions (i.e. A_1' or E) are forbidden. Such is the case with the lowest excited state in DABCO. The one-photon absorption spectrum, taken under conditions of high sensitivity, reveals this transition, but does not show presence of the O—O band[20,31–34]. Parker and Avouris have recently examined this system using multiphoton ionization spectroscopy[35]. In this approach, the lowest excited state is populated by an allowed two-photon absorption; detection via photoionization is then accomplished by subsequently absorbed photon(s). This technique allows the distinct identification of this transition, which is assigned as $A_1' \rightarrow A_1'$ with its O—O band at 2794 Å, along with many other well-defined features associated with progressions and sequences. The vibrational analysis of the vibronic bands of all of the DABCO electronic transitions (including the photoelectron spectrum) reveals that, like the situation in ABCO, the cage-squashing mode, in which the nitrogen atom oscillates along the C_3 axis, is most important in coupling the $n_N \rightarrow$ Rydberg (or ionic) states. Parker and Avouris assign the lowest excited state as being represented by the symmetric combination of 3s orbitals (an A_1' state) centred on the nitrogen atoms, and the second excited state as being described by the symmetric combination of the nitrogen-atom-based $3p_{xy}$ orbitals (E'). The symmetry assignment of these upper states was based by these authors upon the values of the fluorescence (and ionization current) polarization ratios.

It is quite interesting to note that in the related compound, 2-methyl-DABCO, the presence of the methyl substituent on the cage framework apparently represents enough of a perturbation to relax the (one-photon) forbiddenness of the lowest-lying electronic transition. To wit, the vapour phase absorption spectrum of 2-methyl-DABCO reveals a distinct transition in the region of ca. 36,000–40,000 cm^{-1} and in fact, clearly shows a O—O band at 35,790 cm^{-1} [32] (cf. 35,795 cm^{-1} for the reported O—O band location obtained from the two-photon absorption spectrum of DABCO)[35]. There is an analogous alteration in the fluorescence properties of this compound relative to DABCO (see below).

3. *The triplet state*

It is, of course, of considerable theoretical, and perhaps practical, interest to know the location and properties of the lowest triplet state in the simple amines. Estimates of the singlet–triplet energy difference (E_{ST}) in ammonia place the lowest triplet state about 0.2–0.4 eV (i.e. 4.6–9.0 kcal/mol) below the Rydberg $^1(n_N, 3s)$ state[36–39]. Attempts to observe the triplet state directly via optical excitation studies, even under conditions of long path lengths and high pressures have proved to be fruitless[13,40]. An indirect attempt to detect a long-lived metastable state in ammonia (>1 μs) by Auger detection subsequent to electron-beam excitation also failed to implicate a transition to a triplet state[41]. Moreover, Lassettre and coworkers were unable to find evidence of a low-lying triplet-state transition using electron impact excitation at 7° and 33 eV[11].

Subsequently, Compton and coworkers, using electron impact excitation and SF_6 scavenger detection in studies of NH_3 and ND_3, tentatively identified a transition in ammonia at ca. 4.4 eV as being due to the lowest triplet state[10]. Recently, however, Johnson and Lipsky, also using electron impact excitation, attributed this to an artifact[42]. Their observations, nevertheless, showed that based on the increased width of the 6.43 eV (vertical) $\tilde{A} \leftarrow \tilde{X}$ transition, observed at a scattering angle of 90° relative to 0°, a transition at 5.9 eV could be discerned. Johnson and Lipsky assign this 5.9 eV band to the triplet 3s Rydberg state of ammonia. This result, then, would provide an E_{ST} value of ca. 0.5 eV and thus place the triplet state of ammonia at about 2100 Å (47,800 cm^{-1} vertical).

Appropriate studies pertinent to locating the lowest triplet state of alkylated

amines have not been carried out. One might assume, however, in the absence of direct experimental evidence, that the E_{ST} values for alkyl-substituted amines should be similar to that for ammonia, i.e. a few tenths of an electron volt. One basis of support for this conclusion is the fact that the radiative rate constant (for fluorescence) for ammonia[43] is similar in value to that of trimethylamine, and other tertiary amines (see below)[44].

B Condensed-phase Spectra

According to Robin, one of the hallmarks of a Rydberg transition is its susceptibility to high-pressure effects[45]. Thus, the sharp vibronic details which so often characterize a Rydberg transition become markedly broadened and blue-shifted in the presence of a high pressure, ca. 100 atm or more of a nonreactive gas, such as hydrogen, argon, methane, helium, nitrogen, etc. This high-pressure condition induces a perturbation in the Rydberg upper states of molecules, as distinct from intravalence shell excited states, in which case such effects are generally minimal. For example, in benzene, the sharply structured 2500 Å transition [which is known to be an intravalence shell transition to a (π, π^*) state] remains essentially unchanged even in the presence of more than 1000 atm of a perturber gas[46,47]. The cause of this pressure effect on Rydberg states is that these upper states are significantly more spatially extensive than intravalence states, and accordingly, repulsive exchange forces are more significant in Rydberg upper states than in their ground states[48].

In the condensed phase, the nature of Rydberg states is more complex, and depends, in part, on the electron mobility of the medium[49]. As in the case of gas-phase pressure perturubation, however, one generally observed broadening in the vibronic features and an overall blue-shift in the spectrum of Rydberg transitions[50].

Based on the proposed Rydberg nature of the excited states of ammonia (and other amines), one would expect that the spectra of such compounds would demonstrate the high-pressure and medium effects described above. Indeed, Robin has observed that the presence of 136 atm of helium or nitrogen causes a broadening and a shift to higher frequencies of the lowest-lying ($\tilde{A} \leftarrow \tilde{X}$) transition in ammonia[51]. In *n*-hexane and diethyl ether[52] as solvents, the absorption spectrum of ammonia is completely structureless, and appears as a broad, smooth band. In *n*-hexane, the shape of this band appears to match the contour and absorption intensity of the minima of the vibronic features seen in the gas-phase spectrum[52]. Exactly the same type of behaviour is observed in the spectra of the 1-aza bicyclic cage amines discussed above. For example, the spectrum of ABCO in *n*-hexane appears as a completely unstructured band with λ_{max} at 208 nm[53] (see Figure 1). Likewise, the highly structured vapour-phase fluorescence spectra of these cage amines are replaced by structureless bands resembling the gas-phase Franck–Condon envelopes, and are also slightly blue-shifted[26,54]

III. PHOTOPHYSICS

A. Gas-phase Systems

1. *Ammonia*

Photophysics may be loosely defined as the study of the physical properties – structural and dynamical – which characterize the electronically excited state of a molecule. According to this description, then, photophysics represents an

intersection between the domains of spectroscopy and photochemistry, the former focusing mainly upon the electronic and geometrical structure of the excited state, and the latter upon the reactivity of the excited state vis-a-vis chemical bond disruption or rearrangement.

One of the most direct and straighforward ways in which the electronically excited state of a molecule can be probed is via luminescence or radiative relaxation. Thus, by monitoring the time dependence of fluorescence (or phosphorescence), the dynamical processes which characterize the relaxation of an excited state can be studied and measured. Since for most organic molecules in general, and the saturated amines in particular, radiative absorptive transitions from the (closed shell) singlet ground state directly produce excited singlet states, radiative relaxation from the initially formed excited state corresponds to fluorescence. Thus there is, in this case, no electron-spin multiplicity change.

As mentioned above, the upper states of ammonia and deuterated ammonias are strongly predissociated, and this has the result that the vibronic components of absorption spectra are broadened, and do not contain rotational fine structure. This implies that the excited state decays nonradiatively with a rate constant larger than ca. $10^{12}\ s^{-1}$ [54], making radiative relaxation extremely improbable ($\phi_f < 10^{-6}$). In the case of ND_3, however, rotational fine structure in the lower vibronic components of the $\tilde{A} \leftarrow \tilde{X}$ transition is well resolved[13]. On the basis of the rotational line-widths of the $\nu_2' = 0$ and 1 bands, the lifetimes of these states have been estimated to be ca. 2 and 7 ps, respectively[55].

Although Phillips and coworkers[56] were unable to detect fluorescence from ND_3 by exciting at 2062 Å (this populates the $\nu_2' = 3$ of the $\tilde{A}$ state), Koda and coworkers[57] have observed a structured emission from the compound by exciting at 2139 Å ($\nu_2' = 0$). The lifetime of this emission was estimated to be less than 10^{-10} s. Gregory and Lipsky[43] have since determined that the quantum efficiency for the fluorescence of ND_3, exicted at 2138.6 Å (into the $\nu_2' = 0$ level), is 8.3×10^{-5}. By estimating the lifetime of this state from the rotational line-width[13] (an observed line-width of $2.5\ cm^{-1}$ corresponds to an uncertainty-limited lifetime of 2.1 ps), a value for the Einstein A-coefficient (radiative rate constant) of $3.9 \times 10^7\ s^{-1}$ is calculated. Gregory and Lipsky also determined the A-coefficient from the emission intensity and the integrated absorption strength data for this particular vibronic transition in ND_3 and obtained a value of $3.3 \times 10^7\ s^{-1}$.

It is very interesting to note that if the A-coefficient for ND_3 is calculated using the well-known Strickler and Berg formulation[58] (wherein only a separation of the transition moment into electronic and nuclear parts is assumed), a value of $8.2 \times 10^7\ s^{-1}$ is obtained[43]. It is further suggested by Gregory and Lipsky that the origin of this discrepancy lies, in part, in the presence of an underlying continuum [perhaps due to the presence of a n_N,σ^*(N—H) state] in the wavelength region of the $\tilde{A} \leftarrow \tilde{X}$ transition[59].

2. *Primary and secondary amines*

Phillips and coworkers were also unable to detect fluorescence from simple primary and secondary amines (including several N-deuterated compounds) under their experimental conditions (λ_{ex} = 2062 Å)[56]. Their conclusion was that the rate of predissociation of the amine, presumably via tunnelling, was too rapid in order to allow the development of a sufficiently large emission probability. In view of the subsequently demonstrated emissivity of ND_3 (a consequence of the longer lifetime compared to ammonia) by Koda, Hackett and Back[57] and by Gregory and Lipsky[43], it seems probable that a weak emission should also be observable in the

deuterium-substituted primary and secondary amines if the amines are irradiated at sufficiently long wavelengths.

3. Tertiary amines

a. Trimethylamine and other simple amines. The most striking feature of the tertiary amines is that they are highly fluorescent. For example, Halpern and Gartman[44] have reported intrinsic fluorescence quantum efficiencies for trimethylamine and triethylamine of close to unity when the amines are excited at long wavelengths ($\lambda_{ex} > 240$ nm), taking into account self-quenching processes. The zero pressure limited fluorescence lifetimes of these two amines were measured to be 45 and 61 ns, respectively. It is interesting to note that the radiative rate constants for these tertiary amines, 2.1 and $1.6 \times 10^7\ s^{-1}$, respectively, are roughly comparable in value with that obtained for ND_3 by Gregory and Lipsky[43] of ca. $3.6 \times 10^7\ s^{-1}$.

Apparently, the high emissivity of the tertiary amines is a consequence of a significant reduction in the rate of the radiationless decay which dominates the upper-state dynamics of ammonia and ND_3. The explanation of this dramatic decrease in the radiationless decay rate is not clear, but will be discussed in further detail below in the Section IV.

One of the rather unusual aspects of the fluorescence of the tertiary amines is the very large Stokes shift which characterizes the emission spectra. Another is the appearance, or shape, of the fluorescence spectrum itself. These properties are clearly illustrated for trimethylamine, triethylamine and tri-*n*-propylamine in Figure 3. Considering first trimethylamine, it can be seen that the fluorescence spectrum, quite unlike the absorption spectrum, appears to indicate a substantially vertical (small geometry change) transition. The shoulder observed in the absorption spectrum at ca. 230 nm undoubtedly represents the lowest-lying singlet transition ($3s \leftarrow n_N$) and has a Franck–Condon envelope characteristic of the large geometry change (pyramidal → planar) discussed above in the case of ammonia (see also the

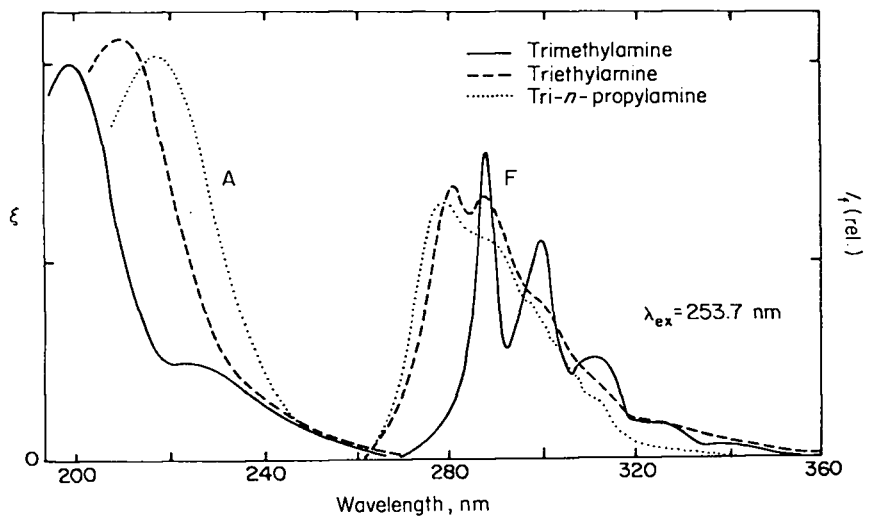


FIGURE 3. Vapour-phase absorption (A) and fluorescence (F) spectra of simple tertiary amines. Absorption units are arbitrary for each amine. See Reference 100.

spectrum of ABCO in Figure 1). The diffuse vibronic bands of the trimethylamine fluorescence spectrum can be analysed in terms of a progression of about 1350 cm^{-1}; in addition, a frequency of about 1100 cm^{-1} seems faintly superimposed upon the dominant structure. The 1350 cm^{-1} frequency may correspond to a combination band observed in the infrared spectrum at 1401 cm^{-1} which has been assigned by Gayles to $\tilde{\nu}_7 + \tilde{\nu}_{20}$[60]. These modes are assigned as the symmetrical out-of-plane bending (366 cm^{-1}) and the C—N stretching (1043 cm^{-1}) vibrations, respectively[60].

One possibility in explaining the rather vertical appearance of the emission spectrum of trimethylamine is that, assuming the transition originates from the equilibrated planar excited state, the transition terminates in the symmetrical component of an inversion doublet corresponding to a highly excited $\tilde{\nu}_7$ ground-state vibration (the out-of-plane bending mode). Such a vibrational state possesses a non-zero value of the vibrational distribution function at a point corresponding to the planar configuration (in the ground state)[61]. The energy difference between the (estimated) transition origin (40,000 cm^{-1}) and the prominent vibronic feature of the fluorescence spectrum (34,800 cm^{-1}) is ca. 5200 cm^{-1}, and implies a significant amount of excitation in the $\tilde{\nu}_7$ mode, and/or the involvement of another vibrational mode (or modes) in the $S_0 \leftarrow S_1$ transition.

Fletcher and coworkers have observed fluorescence from trimethylamine and triethylamine under conditions of electrical discharge excitation[62]. The emission spectra observed were considered to be identical to those obtained via optical excitation. At low amine pressures, or at high discharge frequencies, however, Fletcher and coworkers reported the appearance of a long-wavelength emission band at ca. 380 nm. Because the intensity of the 380 nm emission increased with time, and because the total pressure of the system also showed an increase, the origin of the 380 nm emission was associated with the formation of a reaction product. Attempts to observe lasing action in trimethylamine using xenon flash excitation and Tesla coil electrical discharge excitation were unsuccessful, presumably as a result of the photochemical lability of the amine and/or photoionization losses[62].

Using a tunable visible dye laser as an excitation source, Asscher and Haas have recently observed fluorescence from trimethylamine, triethylamine and tri-*i*-propylamine[63]. The excitation mode in this case is two-photon excitation of the amine. The spectra reported qualitatively resemble those depicted in Figure 3 and References 44 and 56 and are also presumed to be due to $S_1 \rightarrow S_0$ emission. They note a sharp decrease in the fluorescence lifetime of the amines with increasing photon energy (up to the equivalence of ca. 45,000 cm^{-1}), and suggest that the onset of this increase in $1/\tau_f$ (at about 43,000–44,000 cm^{-1}) corresponds to direct excitation into S_2, and is thus a consequence of direct or indirect photodissociation via C—N bond scission. Asscher and Haas have also determined that with respect to excitation at 248 nm (the wavelength corresponding to the output of the KF* 'excimer' laser), the lasing threshold energy values for trimethylamine and triethylamine are ca. 2.4 and 3.0 mJ, respectively (assuming 100 Torr pressure). This would require respective pumping powers of ca. 0.2 and 0.5 MW. Attempts to observe lasing action in trimethylamine by using KF* pumping have presumably failed as a result of multiphoton-induced ionization losses[64].

Very recently, Matsumi and Obi have measured the excitation wavelength dependence of the fluorescence lifetime and quantum efficiency of trimethylamine vapour[19]. They have examined the fluorescence spectrum at various wavelengths, and found that, while the general characteristics of the spectrum remain unchanged, the vibronic features (indicated in Figure 3) become more diffuse as the excitation energy increases, even at 220 nm, at which point appreciable direct excitation int S_2 occurs. No other emission at shorter wavelengths was observed, and it was therefore

concluded that excitation into S_2 results (at least in part) in internal conversion to S_1, and that fluorescence eminates from vibrationally excited levels of this state. They also found that although both the fluorescence lifetime and quantum efficiency are nearly excitation wavelength independent above ca. 240 nm, τ_f and ϕ_f decrease rapidly at shorter excitation wavelengths (down to 215 nm in their experiments). These observations pertain to 'collisionless' conditions because the trimethylamine pressures were between 40 and 100 mTorr. When analysed in terms of radiative (k_R) and nonradiative (k_{NR}) rate constants, these data indicate a slight decrease in k_R values over this wavelength range; for example, at 240 nm, $k_R = 2.46 \times 10^7\ s^{-1}$, while at 215 nm, $k_R = 1.48 \times 10^7\ s^{-1}$. This effect might be a manifestation of the dependence of the transition moment integral on the geometry of the excited and ground states; k_{NR} values, on the other hand, increase sharply and continuously in this region. In this respect, these observations are qualitatively consistent with the findings of Asscher and Haas for two-photon excitation of trimethylamine (at somewhat higher amine pressures)[63]. A plot of Matsumi and Obi's data for $\ln k_{NR}$ vs. excitation energy was shown to be linear, furnishing a slope of $1.5/1000\ cm^{-1}$. This value was considered to be consistent with radiationless decay associated with an internal conversion process between two widely separated potential surfaces (i.e. a large S_1–S_0 gap).

In further studies of the photophysics of vapour-phase trimethylamine, Obi and Matsumi have measured the self-quenching and vibrational relaxation rate constants. Their resulst show that trimethylamine itself is moderately efficient both as a vibrational relaxation agent ($k_{vr} = 6 \times 10^{10}\ M^{-1}\ s^{-1}$) and as a self-quencher ($k_{sq} = 2 \times 10^{10}\ M^{-1}\ s^{-1}$). The latter value is somewhat smaller than that reported by Halpern and Gartman (3.2×10^{10})[44]. The gas kinetic collision frequency for trimethylamine, expressed as a second-order rate constant, is approximately $2 \times 10^{11}\ M^{-1}\ s^{-1}$ (assuming a mean collision cross-section of 4 Å). Helium was found, as expected, to be relatively inefficient in promoting vibrational relaxation ($k_{vr} = 6 \times 10^8\ M^{-1}\ s^{-1}$). Electronic quenching by oxygen and nitric oxide took place at very high efficiency, as is reflected by the respective quenching rate constants, 3.6 and $2.8 \times 10^{11}\ M^{-1}\ s^{-1}$. The anomolously large values of k_q for these quenchers were interpreted in terms of an electron-transfer mechanism via an 'exciplex' intermediate.

The emission spectra of the higher alkylated amines, e.g. triethylamine and tri-*n*-propylamine, and others, appear at shorter wavelengths relative to trimethylamine (see Figure 3). Moreover, compared with trimethylamine, the absorption spectra of these amines are red-shifted, and thus it appears that the emission spectra of these compounds are characterized by a smaller Stokes' shift. This might indicate that the relaxed upper states of the more highly substituted tertiary amines do not completely achieve planarity. Furthermore, it is to be noted that the fluorescence spectra of these amines, unlike the corresponding absorption spectra, appear to be characteristic of vertical transistions, and this is reminiscent of the situation in trimethylamine. For example, in triethylamine, fluorescence commences sharply at ca. 270 nm, and rises to a maximum at 278 nm. A partially resolved shoulder appears at ca. 286 nm corresponding to a vibrational frequency of about $1000\ cm^{-1}$, which might be the C—N stretching mode. In tri-*n*-propylamine, the vibrational structure in the fluorescence spectrum becomes even more diffuse relative to triethylamine. The vapour-phase fluorescent lifetimes and efficiencies of these amines will be discussed in the section below.

b. Bridgehead cage amines. As mentioned above (Section II.A.2), the absorption spectra of this class of amines are usually characterized by a considerable degree of vibrational structure. The comparison, for example, between triethylamine and ABCO illustrates the point in Figure 1. Analogous observations can be made about

the emission spectra of the cage amines. Thus, the fluorescence spectra of ABCO, ABCU, ABCH and ABCN all possess well-resolved O—O bands along with various degrees of vibronic structure. The vapour-phase fluorescence spectra of ABCO and ABCU have been described by Halpern[26]. The spectrum of ABCO contains a O—O band at 2560 Å and in addition possesses a large number of vibronic features. Progressions in 600 and 965 cm^{-1} can be identified and compared with the observed ground-state vibrational frequencies 604 cm^{-1} and 965 cm^{-1}. These have been assigned by Brüesch and Günthard as the cage-squashing and C—N stretching modes, $\tilde{\nu}_{12}$ and $\tilde{\nu}_{33}$ respectively[66]. The Franck–Condon envelope of the fluorescence spectrum is indicative of a transition between states of differing geometries. It is also significant that the fluorescence lifetime of ABCO is considerably longer than that of triethylamine (e.g. 363 ns compared with 61 ns)[26,44]. The emission efficiencies of both amines are near unity. The much smaller radiative rate constant for ABCO compared to triethylamine may be a consequence of the apparently much larger geometry difference between the upper and lower states in these amines.

The general appearance of the fluorescence spectra of the cage amines ABCH and ABCN is similar to that of ABCO, while the energy (S_1–S_0) gaps which characterize the spectroscopy of these compounds are quite different (see Table 1). The vertical appearance of the absorption spectra of ABCU (also discussed above in Section II.A.2) prevails in the fluorescence spectrum. The lack of strict mirror symmetry in the $S_1 \leftrightarrow S_0$ spectra of ABCU has been pointed out and it was suggested that either a lowering in the C_3 symmetry in the upper state occurs, or that there is some degree of vibronic interaction in the upper state of this amine. Consistent with the smaller geometry change between the upper and lower states of ABCU is the fact that this amine has a shorter lifetime, 91 ns (O—O band excitation), and accordingly, a larger radiative rate constant. These data, along with the radiative rate constants for several simple tertiary amines are summarized in Table 2. The k_R values clearly illustrate the sensitivity of the radiative transition probability to changes in both the ground- and upper-state equilibrium geometries.

It is interesting to note that the agreement between the observed and calculated k_R values for ABCO is surprisingly good, while an unexpectedly large discrepancy is seen for the ABCU values. Halpern has suggested that the disagreement in the case of ABCU might be a result of a vibronic perturbation on the $S_1 \leftrightarrow S_0$ transition moments[26], and that in the case of ABCO, the success of the Strickler–Berg approach in predicting k_R might be, in part, fortuitous.

One of the particularly unique photophysical properties associated with bridgehead cage amines is intermolecular excimer emission in the vapour phase. An

TABLE 2. Fluorescence lifetimes, quantum efficiencies and radiative rate constants for some amines

Amine	τ_f (ns)	ϕ_f	k_R (obs.)	k_R (calc.)[a]
Trimethylamine	45[b]	0.97[b]	2.1×10^7	1×10^7[c]
Triethylamine	61[b]	0.98[b]	1.6×10^7	—
ABCO	363[d]	(1)[d]	2.75×10^6	2.9×10^6
ABCU	91[d]	1.0[d]	1.1×10^7	6.7×10^6

[a]Using the Strickler–Berg relation, see Ref. 58.
[b]Data taken from Ref. 44.
[c]Taken from Ref. 19; the $S_1 \leftarrow S_0$ and $S_2 \leftarrow S_0$ transitions are badly overlapped (see Figure 3).
[d]Taken from Ref. 26.

excimer can be defined as the species which results when (usually) two identical molecules, one being in an excited state, form a bound pair, a dimer. Radiative relaxation of the excimer leads directly to the dissociative ground-state dimer of the species. Excimer emission is well known in many aromatic molecules[67,68], but has only recently been reported for nonaromatic systems and, in particular, for the cage amine ABCO[53,69,70]. ABCO undergoes excimer formation and emission in both the vapour and condensed phase. At ambient temperatures, the vapour pressure of ABCO is sufficiently high (ca. 2 Torr) to allow for a large number of intermolecular interactions to take place during the excited state lifetime. Excimer fluorescence from ABCO appears as a very broad, structureless band maximizing at ca. 375 nm. The photophysical properties of this excimer system have been described by Halpern, who showed that the time dependence of the excimer fluorescence has the characteristic built-up feature, and that the monomer fluorescence decay has the expected two-component property[69]. A kinetic analysis of the ABCO system at different vapour pressures at 26°C was performed using the usual monomer/excimer kinetic scheme, and the rate constants for the pertinent processes were extracted[70]. The excimer decay constant, k_D, was found to be $2.27 \times 10^6\ s^{-1}$, and the formation constant, k_{DM}, was $3.1 \times 10^{10}\ M^{-1}\ s^{-1}$, which is about 0.2 that of the gas kinetic collision frequency. One of the most notable aspects of this system is that the excimer fluorescence intensity (observed with excitation into the monomer O—O band) increased considerably with the addition of *n*-hexane as a buffer gas. This illustrates that collisional stabilization of the excimer occurs, and implies that the initially formed excimer (a 42-atom molecule) does not dissipate its own formation energy (ca. 9 kcal/mol) very effectively as an intramolecular process.

The only other cage amine which exhibits excimer emission is ABCH. This excimer also emits at about 375 nm, but because of the higher energy of the monomer S_1 state (see Table 1), it appears that the binding energy of the ABCH excimer is larger than that of the ABCO excimer. The properties of these excimer-forming amines in the condensed phase will be discussed below.

c. Diamines. It is mentioned above (Section II.A.2) that because of the fixed and close proximity of the two nitrogen atoms in DABCO, appreciable ground coupling between the nitrogen n orbitals results. Consequently, the spectroscopy of DABCO and 2-methyl-DABCO is very much dominated by this interaction. The photophysics of these amines is, accordingly also unique relative to other monoamines. DABCO vapour is highly fluorescent; in fact, it was for DABCO vapour that saturated amine fluorescence was first reported[31]. It was also noted that the juxtaposition of the very weak, long-wavelength absorption with the emission spectrum clearly indicates an absence of a O—O band for the $S_1 \leftrightarrow S_0$ transitions[32]. Multiphoton ionization spectroscopy has since been used to probe this lowest excited state in DABCO (see above and Reference 35). Consistent with the fact that one-photon transitions between S_0 and S_1 are forbidden, the lifetime of the DABCO fluorescence is anomolously long, 1.04 μs. Another very interesting aspect of this system is that the presence of a methyl substituent on the cage appears to represent enough of a perturbation that the one-photon forbiddenness of the $S_1 \leftrightarrow S_0$ transitions is relaxed. Thus, in 2-methyl-DABCO, not only are the $S_1 \leftrightarrow S_0$ transitions distinctly observable (including the presence of a O—O band), but the fluorescence spectrum has a strikingly different Franck–Condon envelope (it also possesses a dominant O—O band)[32]. Nevertheless, the perturbation represented by the methyl group is apparently not sufficient to change the energetics of the S_0 and S_1 (and other) states; DABCO and 2-methyl-DABCO have nearly identical ionization potentials, and the O—O energy of the substituted amine is virtually the same ($35{,}790\ cm^{-1}$)[32] as that for DABCO ($35{,}790\ cm^{-1}$)[35]. It is also interesting that the presence of the methyl

group apparently also induces radiationless relaxation from S_1; i.e. τ_f and ϕ_f values for DABCO and 2-methyl-DABCO are, respectively, 1,040 ns, 0.9, and 133 ns, 0.3. Thus, there is nearly a 3-fold increase in k_R and a much larger, 55-fold, increase in k_{NR} between the two amines.

Another interesting and puzzling observation of the DABCO vapour system is that both k_R and k_{NR} increase as the pressure of a buffer gas (*n*-hexane) increases. The fluorescence lifetime and quantum efficiency both decrease as the *n*-hexane pressure is increased up to about 50–80 Torr, but remains nearly constant above this level[32]. It was suggested that both radiative and nonradiative relaxation processes are induced by collisions with a partner, perhaps because of a transient lowering in the effective chromophore symmetry which would occur. In other words, the photophysical properties of the highly symmetrical DABCO seem to carry over to those of 2-methyl-DABCO as a consequence of perturbing collisions.

Other symmetrical diamines possess unusual photophysical properties as well. For example, *N,N'*-dimethylpiperazine has a fluorescence spectrum which is considerably red-shifted (313 nm) relative to the monoamine, *N*-methylpiperidine (290 nm). In addition, the fluorescence lifetime of the diamine is strikingly longer than that of the monoamine, 770 ns as compared with 60 ns. Because of the lower fluorescence quantum efficiency of the diamine (0.23, as compared with the monoamine, 0.95), the radiative rate constants of the amines are widely disparate: $3.2 \times 10^5\ s^{-1}$ and $1.6 \times 10^7\ s^{-1}$, respectively. Thus, *N,N'*-dimethylpiperazine seems to be more akin to DABCO ($k_R = 8.6 \times 10^5\ s^{-1}$) as far as photophysical properties are concerned. It may be suggested, therefore, that either there is weak ground-state coupling between the nitrogen atoms in this diamine, giving rise to the same type of spectroscopic situation which characterizes DABCO, or that the excited state itself undergoes coupling (such as in an excimer), in which case the fluorescence properties would be based on a different species. Neither the absorption spectrum nor the photoelectron spectrum of the diamine provides evidence of ground-state N . . . N interaction; hence, it was suggested by Halpern and Gartman that an upper-state reorganization takes place in this compound[44].

Another symmetrical diamine, *N,N,N',N'*-tetramethyl-1,2-ethanediamine, also possesses anomalous photophysical properties relative to monoamines. For this compound, the fluorescence spectrum is slightly red-shifted (303 nm), but the lifetime and quantum efficiency values are quite different (71 ns and 0.23). Because the absorption and photoelectron spectra of this amine are typical of appropriate monoamines, it was suggested that upper-state coupling takes place. In studying the self-pressure dependence of both the fluorescence lifetime and quantum efficiency, Halpern and Chan have proposed a model in which a low-lying, emissive state is produced by the initially formed, nonemissive state[71]. In addition to self-quenching of both of these states and the inclusion of vibrational relaxation, the model contains a step in which collisions with ground-state amine enhance the radiative transition probability. Thus, k_R was separated into a unimolecular part ($3.2 \times 10^6\ s^{-1}$) and a bimolecular component in which the 'pressure coefficient', k_{QR}, is $2.4 \times 10^9\ M^{-1}\ s^{-1}$. This pressure dependence of k_R was noted earlier with respect to DABCO. The pressure dependence of the fluorescence lifetime and quantum efficiency of trimethylamine failed, on the other hand, to reveal a pressure-dependent k_R[72].

In a related linear-chain diamine, *N,N,N'N'*-tetramethyl-1,3-propanediamine, dual fluorescence was observed in the vapour phase[71]. This was interpreted in terms of separate monomer (uncoupled) and excimer (coupled) emission. The monomer band was seen as a shoulder at 290 nm, and the main emission at 365 nm was associated with the excimer. The ratio of the excimer to monomer intensities decreased with increasing excitation energy at an amine pressure of 5 Torr. This was analysed in

terms of vibrational relaxation in the excimer manifold and consequent fluorescence enhancement. The predominance of excimer fluorescence in this amine is an example of the Hirayama $n = 3$ rule as applied to the saturated amines[73,74]. This 'rule' states that moieties separated by a trimethylene linkage have a very high probability of interacting in such a way so as to favour excimer stabilization and emission.

B. Tertiary Amines in Solution

1. Nonpolar solvents

a. Fluorescence spectra and lifetimes. As mentioned above, the effect of the condensed medium on the Rydberg upper states of the amines changes the absorption spectrum so that (1) the vibrational structure is blurred or even obliterated, and (2) the spectrum is shifted to higher energies. The response of the absorption spectrum of ABCO has been discussed and pointed out in Figure 1. In the case of trimethylamine, the absorption spectrum in *n*-hexane solution also responds according to the prediction for a Rydberg state. No vibrational structure is observed under these conditions, and the shoulder observed at 225 nm in the vapour-phase spectrum (which is probably due to the $S_1 \leftrightarrow S_0$ transition) is shifted to ca. 220 nm. The absorption maximum cannot be located with accuracy because of competitive solvent absorption and/or the limitation of an air-path spectrophotometer.

The fluorescence spectrum of ABCO in this medium is likewise devoid of the rich vibronic features seen in the vapour phase. The Franck–Condon envelope, nevertheless, resembles that of the vapour spectrum, and has a maximum at ca. 272 nm. This is a relatively high energy for the fluorescence maximum of a saturated amine, and is a reflection of the inability of ABCO to achieve maximum stability (planarity) in the excited state.

The fluorescence spectrum of trimethylamine in *n*-hexane solution nevertheless still reveals the general vibrational pattern seen in the vapour spectrum, except that these features are considerably more diffuse. It is interesting to note, however, that the entire spectrum is slightly red-shifted in this condensed phase; the most prominent feature appears at 290 nm (cf. 287.4 in the vapour) and the vibronic band at ca. 300 nm (cf. 299 nm in the vapour). Thus the vibrational spacing implied by these data is slightly smaller, 1150 cm^{-1}. The small red-shift (ca. 300 cm^{-1}) is presumably a result of the increased polarizibility of the *n*-hexane medium relative to the vapour state.

The quantum efficiency and lifetime of trimethylamine in this solvent are 0.75 and 17.6 ns, respectively, and thus the k_R value is $4.3 \times 10^7\ s^{-1}$; this compares with a value of $2.1 \times 10^7\ s^{-1}$ for the vapour phase. The solvent medium thus enhances both the radiative and nonradiative transition probabilities. The role of the solvent can be thought of as a nonspecific perturbation of the Rydberg state in which the 'excited' electron is 'scattered' from the spatially extensive Rydberg orbital.

The photophysical properties of the higher substituted amines in *n*-hexane solution show similar trends relative to trimethylamine. Thus, for triethylamine, there is also a slight red-shift in the emission spectrum (282 nm relative to 278 nm in the vapour). The lifetime and quantum efficiencies are likwise smaller than those in the vapour phase, with τ_f and ϕ_f equal to 31 ns and 0.69, respectively; k_R is thus $2.2 \times 10^7\ s^{-1}$. As the three alkyl chains are extended, the fluorescence quantum efficiency seems to hold constant at about 0.70 while the lifetime gradually increases; for example, τ_f for tri-*n*-dodecylamine is 38.0 ns.

It is also interesting that the fluorescence spectra of methyl-substituted amines

TABLE 3. Fluorescence quenching constants for *N,N*-diethylmethylamine in *n*-hexane

Quencher	k_Q (10^{10} M^{-1} s^{-1})
N,N-Dimethylmethylamine	0.70
Dimethylformamide	4.9
Acetic acid	1.8
Ethyl acetate	0.65
Acetonitrile	2.4
2-Butyne	0.014
Dimethylsulphoxide	2.4
Acetone	3.2
Tetramethylethylene	0.001
Benzene	2.1
Perfluorocyclohexane	0.13
Ethanol	0.4
n-Propyl bromide	2.9
Oxygen	6.0

have maxima at ca. 290 nm, while the spectra of other tertiary amines have maxima at 282 nm. This distinction may be useful for characterizing the nature of *N*-alkylation.

b. Quenching reactions. While the tertiary amines are all highly fluorescent, they appear to be highly susceptible to quenching reactions with a large variety of other molecules. Some of these data are summarized in Table 3 which lists quenching constants for the fluorescence of a prototype amine, *N,N*-diethylmethylamine in *n*-hexane solution (3×10^{-4} M).

It is apparent that, considering the wide variety of molecules listed in Table 3, saturated amines must undergo fluorescence quenching via a number of different processes. One mechanism which would be expected to be common is electron transfer, perhaps with accompanying exciplex emission. While there are many quenchers which would act as effective electron acceptors (e.g. oxygen, acetonitrile, dimethylformamide, dimethylsulphoxide, perfluorocyclohexane, etc.), intermolecular exciplex emission has not been observed for the saturated amines. Intramolecular exciplex emission with the phenyl moiety has been observed, and intra and intermolecular excimer emission have also been reported. These systems will be described below.

c. Energy-transfer reactions. Another mechanism which one might anticipate is energy transfer. This has indeed been observed in the cases of the intermolecular quenching of amines by saturated ketones and by benzene. In the case of the ketones, it should be noted that there is considerable overlap between the amine fluorescence band and the ketone absorption spectrum. Moreover, the ketone absorption spectrum typically possesses a 'window' at about 220 nm, at which point the amine absorption intensity is appreciable (see Figure 1). Thus relatively selective amine or ketone excitation can be accomplished by the appropriate choice of the excitation wavelength.

Halpern and Lyons have shown that a consequence of the intermolecular fluorescence quenching of *N*-methylpiperidine by adamantanone is sensitized ketone fluorescence[75]. The overall quenching constant was measured to be 3.2×10^{10} M^{-1} s^{-1} in *n*-hexane solution, which is consistent with a diffusion-controlled process. Intramolecular amine fluorescence quenching was also observed in a number of β-aminoketones; in addition, ketone fluorescence was apparently quenched by the

amino moiety in these bichromophoric compounds. This is consistent with the fact that amines intermolecularly quench the fluorescence of ketones with moderate efficiency[76]. For example, adamantanone fluorescence is quenched by *N*-methylpiperidine with a rate constant of 5.9×10^8 M^{-1} s^{-1} [75]. Presumably, the mechanism of this quenching reaction involves electron transfer from the amine to the excited ketone, while electron transfer in the opposite sense is most likely important in the quenching of the excited amine by ketone.

In another aminoketone, 3-quinuclidinone, Halpern and Walter noted that the amine-type fluorescence (i.e. characteristic of ABCO) could not be observed, and that excitation into (primarily) the amine transition resulted in ketone-like fluorescence[77]. The efficiency of this intramolecular energy transfer was estimated to be ca. 0.5. The vapour-phase absorption spectrum of this compound shows vibrational structure which, when compared with that of ABCO, indicates that the energy levels of the amine chromophore are (apparently) unperturbed.

Another example of fluorescence quenching which takes place via an energy-transfer mechanism is the amine/benzene system. Like the ketones, benzene and its derivatives have an absorption spectrum which has a 'window' in the 220–225 nm region. Hence, selective excitation into the amine chromophore (ca. 220 nm) vis-a-vis the aryl chromophore (ca. 265 nm) can be accomplished. In a nonpolar solvent such as *n*-hexane, both a saturated amine (e.g. a simple trialkylamine) and benzene (or an alkyl derivative) fluoresce in the same region (280–290 nm). Thus amine fluorescence quenching cannot be easily measured via steady-state measurements. Fluorescence decay curves of amine/benzene mixtures, however, clearly reveal two components, one associated with the quenched amine emission, and the other with the benzene fluorescence[78].

Fluorescence decay studies of the system, benzene/*N,N*-diethylmethylamine, show that this amine is quenched by benzene at the diffusion-controlled rate in *n*-hexane solution (see Table 3). Moreover, it appears that, even taking into account the fact that benzene weakly absorbs at the excitation wavelength (220 nm) and that some of the benzene fluorescence can result from direct excitation, there is an appreciable extent to which sensitized benzene fluorescence takes place. This process occurs with nearly unit efficiency[78].

Interestingly, energy transfer in the reverse direction also takes place in this system; thus irradiation of benzene (262 nm) in the presence of the amine results in both sensitized and directly produced amine fluorescence[79–81]. This process appears to occur with somewhat lower efficiency than the forward energy-transfer step mentioned above[81].

d. Exciplex and excimer fluorescence. As noted above, one of the most likely processes by which the excited state of saturated amines are quenched is via an electron-transfer process. If the extent to which electron transfer occurs is only moderate, then the polar intermediate exciplex might have a sufficiently long lifetime to allow fluorescence to be observed. In fact, fluorescence from an *inter*molecularly formed exciplex has not been observed to date, although fluorescence from amines in polar solvents might represent an example (see below). Under favourable circumstances, however, *intra*molecular exciplex fluorescence can be observed in a nonpolar solvent between the amine and aryl groups. For example, Bryce-Smith and coworkers have reported the fluorescence of the intramolecular exciplex in the series $Ph—(CH_2)_n—NMe_2$ for $n = 2$, 3 and 4[82]. The aryl group was photoexcited. In another study, it was implied that the exciplex might be an intermediate in the 1,4-photoaddition of tertiary amines to benzene (again, aryl excitation)[83]. Recently, Davidson and coworkers have compared the emission properties of $n = 4$, above, and 1-dimethylamino-4-phenylbicyclo[2.2.2]octane[84]. They have found that the

former compound exhibits exciplex emission in a variety of solvents, and that the latter compound shows amine-type fluorescence in methylcyclohexane under the condition that most of the light is absorbed by the phenyl moiety. This was interpreted as energy transfer from the aryl to the amine group.

More recently, another investigation of the α,ω-phenyldimethylaminoalkanes (n = 3 and 4, above) was undertaken by De Schryver and coworkers[85]. Their studies of the fluorescence spectra of these compounds were also interpreted as exciplex emission. Moreover, from the solvent polarity dependence of the fluorescence spectrum of the exciplexes, the dipole moments were estimated. For the n = 3 and 4 compounds, excited-state dipole moments of ca. 14.5 and 15.4 D, respectively were assigned. It was suggested that the larger dipole moment of the n = 4 compound was caused by a larger separation between the ionic components in that exciplex. Presumably this situation is the result of the structural constraints imposed upon the exciplex geometry by the intervening polymethylene chain. From the temperature dependence of the emission spectrum of the n = 3 compound in isopentane solution, they estimated the formation enthalpy of the exciplex to be ca. −3.7 kcal/mol.

Interestingly, Shizuka and coworkers have recently reported the results of a study of the intramolecular quenching of amine fluorescence in primary amine analogues of the above series[86]. No evidence of intramolecular emission is reported for these compounds. Thus, the presence of an N—H bond apparently results in very rapid radiationless decay of the exciplex, and in this respect is reminiscent of the situation regarding the fluorescence efficiencies of the amines themselves. The effect of the length of the polymethylene chain on the amine quenching was studied as a function of temperature in several solvents. In nonpolar (or weakly polar) solvents, they have interpreted the results in terms of a static mechanism involving an (exciplex-like) intermediate for n = 3. In more polar solvents, a dynamic quenching mechanism is involved; electron transfer (as the quenching step) is correlated with the efficiency of rotational diffusion.

e. Excimer formation. As mentioned above, intramolecular excimer fluorescence from the saturated amine moiety is observed in a few specific cases. In the series, $(Me)_2N(CH_2)_n(Me)_2$, diamines n = 1, 2, 3 and 4 reveal anomalous fluorescence spectra. The spectra of n = 1 and 2 are red-shifted relative to dimethylethylamine, and the spectra of n = 3 and 4 show two components, one associated with monomer emission, and the other (at longer wavelengths) with intramolecular excimer emission[71,87]. The fluorescence decay curves of n = 1 and 2 are exponential, implying that monomer–excimer equilibration occurs rapidly relative to fluorescence decay. For n = 3 and 4, however, nonexponential decay is observed, which does not appear to be readily analysed into the two-component terms associated with monomer–excimer dynamics. This may be a result of the 'transient' effect on the very fast monomer decay component. From the temperature dependence of the emission spectrum of the n = 3 compound in n-hexane solution, a binding energy of ca. 2.2 kcal is estimated[71]. Interestingly, no evidence of intermolecular excimer (for a dimethylalkylamine) or intermolecular exciplex (with benzene as the partner) has been found. This illustrates the ability of the intervening trimethylene linkage to affect certain unique physical (and perhaps chemical) interactions[74].

One of the particularly interesting aspects of saturated amine photophysics is the fact that certain amines exhibit intermolecular excimer fluorescence. The unusual strength and specificity with which these excimers are formed is particularly noteworthy. For example, of the many different types of saturated amines which have been studied and reported to date, it is only the ABCO-type of amine which exhibits excimer fluorescence. Excimer formation and emission in the vapour phase of ABCO is discussed above. In n-hexane solution, 1-azaadamantane (which

possesses the intrinsic ABCO-like structure) also forms a rather tightly bound excimer (ca. 10.2 kcal/mol)[53]. The only other saturated amine, not strictly possessing the bicyclooctane nucleus, which undergoes excimer formation, is 1-azabicyclo[2.2.1]heptane. This amine, presumably because of the smaller C—N—C bond angles, has higher $S_n \leftarrow S_0$ transition energies (see Table 1). In addition, perhaps as a result of this elevation in the $S_n - S_0$ energies, the binding energy of the excimer (as determined from the temperature dependence of the fluorescence spectrum in *n*-hexadecane solution) is considerably larger than that for ABCO, i.e. ca. 15 kcal/mol[28].

Not all 1-azabicyclic cage amines exhibit excimer fluorescence. For example, the homologue of ABCO, 1-azabicyclo[3.2.2]nonane, 1-azabicyclo[3.3.3]undecane and DABCO all possess concentration-independent fluorescence spectra. Nevertheless, these amines undergo self-quenching with widely different efficiencies ($K_q = 8 \times 10^9$, 2.0×10^{10} and ca. 10^7 $M^{-1}s^{-1}$ respectively).

It has been proposed that the structure of the excimer involves the approach of the two amines such that the nitrogen atoms face each other[53]. Thus, steric interference of the approach of the nitrogen-bearing portions of the amines cannot be an overriding criterion regarding excimer formation and stabilization. Since the amines mentioned above (as well as many other acyclic amines) undergo self-quenching, it can be suggested that some of these quenching processes involve the existence of a 'nonemissive' excimer intermediate. Thus, the question regarding excimer stabilization might ultimately concern the nature of chemical interaction between excited and ground-state amines, or the ability of a transient excimer to undergo internal conversion.

An interesting application of excimer formation and self-quenching in the saturated amines has been reported by Halpern and coworkers in the investigation of the photophysical properties of members of the α,ω-bis(dimethylamino)alkane series[87]. The fluorescence characteristics of members $n = 1$–4 are mentioned above in the context of intramolecular excimer formation. For higher members of this series, however, intramolecular excimer emission is not observed, and consequently, the fluorescence spectra of such diamines appear to be identical to dimethylalkylamines. Nevertheless, interaction between the amino functionalities still takes place, as evidenced by the fact that the fluorescence lifetimes of such compounds (n = 5–13, 16, 18 and 20) are all shorter than corresponding monoamines. This was interpreted as intramolecular self-quenching, the rates of which being dependent upon the nature of the end-to-end distribution functions of the linear chains. Since the decay curves of these compounds were observed to be exponential (with the exception of $n = 18$), the interaction frequencies of the amino units was considered to be a manifestation of the differences in the static conformational distribution functions of the diamines. Moreover, the dependence of the intramolecular self-quenching rate constant on the chain length was found to parallel qualitatively the analogous reaction rates of lactone formation in α,ω-bromocarboxylic acids[88]. The rates of forming medium-sized rings (n = 7–9) were slowest.

f. Temperature dependence. Halpern and Wong have investigated the temperature dependence of the fluorescence lifetimes and quantum intensities of a variety of saturated amines in alkane solvents[89]. They have found that, while the fluorescence lifetime of an amine (in a dilute solution) is nearly invariant with temperature (over the range of ca. −20 to 100°C), the fluorescence intensity, however, increases monotonically between ca. −100 and 100°C. For example, for *N*,*N*-dimethylethylamine, τ_f increased from 24.1 ns at −16°C to 27.5 ns at 100°C. This change was attributed, in part, to the decrease in the refractive index of the

medium. Between −100 and 100°C, I_f was found to increase by a factor of ca. 77. No change in the shape or location of the emission spectrum was observed.

Because no change in the absorption spectrum was detected, the origin of this thermal enhancement of the fluorescence intensity was ascribed to an upper-state process in which the initially formed and relaxed (planar) states are separated by an energy barrier. A value of 2.6 kcal/mol was estimated for this barrier for *N,N*-dimethylethylamine. Support for this hypothesis was provided by the observations that (1) the activation energy increased with increasing solvent viscosity, and (2) the thermal enhancement of fluorescence was apparently absent (or very slight) for 'rigid' amines such as ABCO and ABCU.

Because the optical densities of the amine solutions studied were quite small at the excitation wavelengths used, it is nevertheless possible that part of the effect reported above, might be a consequence of ground-state involvement through 'hot' transitions.

2. *Polar solvents*

As mentioned above, the excited states of saturated amines are quite generally susceptible to quenching reactions with a wide variety of molecules. Hence, the number of solvent media in which appreciable saturated amine fluorescence can be sustained is small. Two general types of solvents can nevertheless be readily identified: saturated hydrocarbons and ethers. The fluorescence properties of the amines in hydrocarbons were discussed above. In the weakly polar saturated ethers such as diethyl ether and tetrahydrofuran, amines still retain reasonably strong emissivity; for example, in these solvents, the quantum efficiencies of *N,N*-diethylmethylamine are 0.55 and 0.14, respectively.

Significantly, there is a red-shift in the fluorescence spectrum of the amines in these solvents. This was first pointed out by Tsubomura and coworkers[38] who ascribed this solvent shift to the solvation of an ionic Rydberg state. The respective fluorescence maxima for *N,N*-diethylmethylamine in these solvents are 310 nm and 340 nm. Interestingly, also, is the fact that the fluorescence lifetimes of the amine *increase* in these media to 42 and 47 ns, respectively (cf. 26 ns in *n*-hexane). Thus, there is a decrease in the radiative rate constants in these weakly polar media.

The mechanism of this red-shift and lifetime enhancement is not clear. One possibility is that the amine forms an exciplex with the ethers in which the nonbonding electrons of the oxygen atom in the ethers associate with the quasi-radical cation of the excited amine. This hypothesis is not yet supported by direct evidence: the fluorescence spectra of the amine in mixed THF–hexane solvents gradually shift from 290 nm (hexane) to 340 nm (THF). Moreover, the decay curves of these systems do not reveal the build-up feature which would be expected for ordinary exciplex formation. In addition, the fluorescence spectra of amino ethers which contain an ether moiety separated from a nitrogen atom by three methylene units reveal entirely 'normal' fluoresence properties (in *n*-hexane solution). It would be expected that for these molecules, intramolecular exciplex formation would be greatly facilitated.

It is also possible that the effects mentioned above are the result of nonspecific interactions, that is, between the excited state of the amine and the bulk medium. The difficulty with this interpretation is that the relaxed upper state of the amines are presumed to be planar and thus nonpolar; hence dipole stabilization between the polar solvent and the excited amine would vanish. Quadrupole interactions would be expected to be too small to cause the observed spectral shifts.

IV. PHOTOCHEMISTRY

Early studies of the photolysis of gas-phase saturated amines were carried out by Bamford[90], Taylor and coworkers[91,92] and by Gesser and coworkers[93]. Since that time, many other photochemical investigations of the simple amines have been pursued. A comprehensive review of the photolysis of the saturated amines under a variety of conditions was recently presented by von Sonntag and Schuchmann, and will not be recounted here[94].

It has been mentioned above in connection with the photophysics of the amines, that the most significant mode of photolytic relaxation of ammonia and the primary and secondary amines is the dissociation of the N—H bond. Thus, while tertiary amines are highly emissive when excited at relatively long wavelengths at low pressures, the rate of nonradiative relaxation (in the 'isolated' molecule) increases very sharply at shorter wavelengths[19,63]. Because quantitative photochemical studies have not been carried out on the tertiary amines under these conditions, it is not clear whether this nonradiative dissipation involves an internal conversion to the ground state (with or without subsequend dissociation), or direct dissociation from S_1 or S_2.

Recently, several detailed studies of the photolysis of ammonia and ND_3 have been carried out by Back and coworkers at 2144, 2139, 2062 and 1850 Å[54,95,96], and by Donnelly and coworkers using an ArF* laser at 193 nm[97,98]. The results of these investigations have permitted models for the mechanism of the dissociation of ammonia to be articulated. By phtolysing NH_3 or ND_3 in the presence of propane and ethylene, Back and Koda were able to determine the excess translational energy of the photofragmented hydrogen atoms[54]. Their results show that with respect to excitation at 2139, 2062 and 1850 Å, the excess translational energy of the hydrogen atoms (or deuterium atoms) *decreases* with increasing photon energy. Moreover, in the photolyses of deuterated ammonias, the dissociation of hydrogen atoms is favoured by 2–3 relative to deuterium at shorter excitation wavelengths. At longer wavelengths, this factor is larger[93].

Back and Koda have interpreted these results by proposing that photodissociation of the ammonia could lead to NH_2 radicals in either its ground ($\tilde{X}^2B_1$) or excited ($\tilde{A}^2A_1$) state; the energy threshold for the formation of the $\tilde{A}$ state of NH_2 from the $\tilde{A}$ (S_1) state of ammonia lies between 2139 and 2062 Å (in fact, for ND_3 the dissociation limit is between the $v_2' = 1$ and $v_2' = 2$ vibrational levels). Thus, according to this picture, the decrease in the translational energy of the photofragments at shorter wavelengths results from the production of electronically excited NH_2 molecules.

Back and Koda point out, however, that for a planar (D_{3h}) configuration of the upper state of ammonia ($\tilde{A}^1A_2''$) the excited state of NH_2 ($^2A_1$) does not correlate with the A_2'' state, and thus in order for this hypothesis to hold, the dissociation process into $NH_2(\tilde{A}^2A_1)$ fragments must involve the nonpolar configuration. In this view, the ground state of ammonia correlates with the ground state of NH_2, as do the two respective upper states. Central to this point is the fact that, as mentioned above in connection with the spectroscopy of ammonia, the importance of the dissociative σ^* state (the conjugate intravalence state to the 3s Rydberg state) is strongly dependent upon the molecular geometry.

In a recent study of the 193 nm ArF* laser photolysis of NH_3, Donnelly and coworkers have confirmed the above hypothesis by observing fluorescence from the excited ($\tilde{A}^2A_1$) state of NH_2[97]. In addition, they were able to determine the relative amount of NH_2 produced in the ground ($\tilde{X}^2B_1$) state by detecting the visible dye laser-induced fluorescence from $(A^2A_1)NH_2$ produced by excitation of the ($\tilde{Z}^2B_1$)

state. Their results indicate that with 193 nm excitation of NH_3, the $^2A_1$ state of NH_2 is produced with a 2.5% yield relative to the $^2B_1$ state. Also, the rotational and vibrational populations of the photolytically-formed NH_2 fragments were discussed.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **6**

Photochemistry of nitro and nitroso compounds

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I. INTRODUCTION

The light-induced reactions of nitro, nitroso and carbonyl compounds probably attracted chemists' attention earlier than photoreactions of other compounds[1]. The synthetic and mechanistic studies of carbonyl photochemistry have matured in the last decades, to the stage that chemists can predict with reasonable confidence the physical and chemical processes after excitation[2]. In contrast, the early results in nitro and nitroso group photochemistry have been followed up with only sporadic interest until fairly recently; there has been a gradual upsurge activity in this field[3] since the early 1960s. It is, therefore, most opportune to bring up to date the last review[3] on photochemistry of nitro and nitroso compounds which appeared in 1969 in this series.

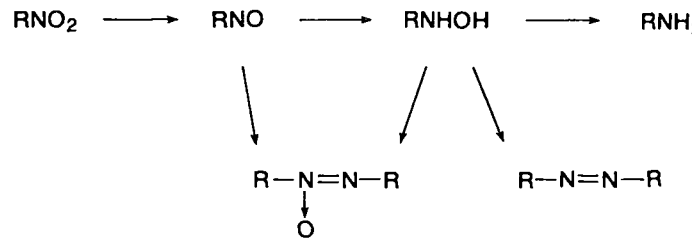
This chapter is organized according to the functional groups, e.g. the nitro and nitroso groups attached to carbon, oxygen or nitrogen. Inevitably such an arrangement results in some overlap in description and some repetition in mechanistic coverage. Wherever possible, the author has tried to avoid such repetitions by reference to the previous discussions. The photochemistry of nitro and nitroso compounds must be regarded as a developing field; their physical and chemical processes as the consequence of excitation are frequently not as clear and certain as those of carbonyl compounds and need further investigation with modern techniques. The mechanistic aspects of the photochemistry will no doubt be refined in the future. However, in the last ten years, sufficient information has accumulated to permit discussion of these mechanisms with a degree of confidence. Notably, it is gratifying to witness the good progress in the photochemistry of aromatic nitro compounds, nitrosoalkanes, nitrites, nitrosoamines and nitroamines, among others. It

is hoped that this review may serve to identify the areas of inadequacy in our understanding and to stimulate research in the phtotochemistry of nitro and nitroso compounds.

II. PHOTOCHEMISTRY OF AROMATIC NITRO COMPOUNDS

The upsurge in the investigation of photoreactions of aromatic nitro compounds[1] in the early 1960s was undoubtedly stimulated by the remarkable success in the mechanistic photochemical work on carbonyl compounds[2]. However, the resemblance is rather superficial; the intrinsically more complex physical, as well as chemical, behaviour of the excited and ground states of nitro compounds makes definitive results more difficult to achieve. Thus, disagreements among the investigators in this field are frequently encountered.

There are two main factors that contribute to the complexity of nitro compound photochemistry. Firstly, the photoreactions of a nitro group can involve variety in atomic reorganization and various reduction stages of reasonably stable, and often isolable, intermediates which may undergo dark reactions or secondary photoreactions (equation 1). Secondly, the excited states of nitro compounds



(1)

generally emit weakly, or more often show no emission, thereby depriving one of a powerful means of unravelling the mechanism of their excited-state reactions. Nevertheless, in the past ten years, various physical methods, such as conventional and laser-flash excitation, ESR spectroscopy, and chemically induced dynamic nuclear polarization (CIDNP), have become available for the study of the photochemical mechanisms of nitro compounds. One may expect rapid progress in this field in the next few years.

Electronically excited nitro compounds[3] may undergo C—NO_2 bond scission[4], rearrangement to nitrites[5], addition to π-bonds[6], abstraction of a hydrogen with subsequent reduction[7,8], and nucleophilic substitution at the aromatic nucleus[9–11]. The last two types of reaction[7–11] have been reviewed repeatedly in recent years.

A. Photoreduction

1. Under neutral conditions

a. General pattern. Nitrobenzene and 2-nitronaphthalene are photolytically reduced in *i*-propanol in low quantum yields ($\phi \sim 0.011$ and 0.037, respectively) to yield the hydroxylamines and acetone[12–15] (equations 2–4). It has also been shown that substituted nitrobenzens can be photolysed in solvents with various hydrogen-donating abilities to afford anilines with minor amounts of azo- and azoxy-benzenes depending on the conditions[16] (equations 5 and 6). Mechanistically, it is proposed that the primary photochemical act is hydrogen abstraction by the lowest triplet state of the nitro compound followed by a series of dark radical reactions leading directly to the hydroxylamine[12]. While it is reasonable to expect

$$^3(ArNO_2)^* + (CH_3)_2CHOH \longrightarrow ArNO_2H + (CH_3)_2\dot{C}OH \quad (2)$$

$$ArNO_2H + (CH_3)_2\dot{C}OH \longrightarrow ArN(OH)_2 + (CH_3)_2CO \quad (3)$$

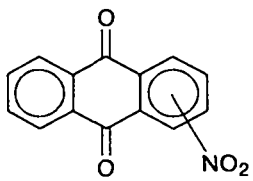
$$ArN(OH)_2 + (CH_3)_2CHOH \longrightarrow ArNHOH + (CH_3)_2CO + H_2O \quad (4)$$

$$ArNHOH \xrightarrow{red.} ArNH_2 \quad (5)$$

$$ArN(OH)_2 \longrightarrow ArNO + H_2O \quad (6)$$

that nitroso compounds are also formed as intermediates, and participate in coupling to yield the azoxy compound[17], their presence in the photolysis has not been proven[16]. The complexity of the proposed mechanism raises certain questions: e.g. whether the reactions of equations (3)–(6) involve another photoexcitation, direct or sensitized, or are merely dark radical processes.

The photoreductions of 1- and 2-nitroanthraquinone (**1**) in *i*-propanol have been reported to occur by three distinctly observable photoprocesses to give the corresponding aminoanthraquinones as in equation (7), though the intermediacy of



(1)

$$ArNO_2 \xrightarrow{h\nu} ArNO \xrightarrow{h\nu} ArNHOH \xrightarrow{h\nu} ArNH_2 \quad (7)$$

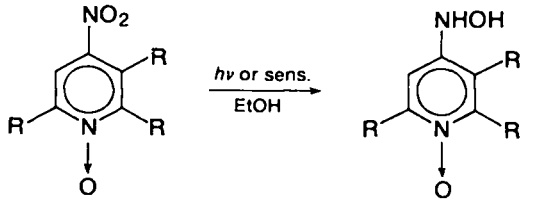
the nitroso intermediates is derived from indirect evidence[18,19]. The transformation of the hydroxylamines to the amines is sensitized by the nitro or nitroso compound but does not occur by direct photolysis[19]. Furthermore, anthraquinone sensitizes the whole photodecomposition much more efficiently than the direct photolysis[19].

Nitrobenzenes with *para* and *meta* substituents are photolytically reduced in *i*-propanol to give the corresponding anilines with quantum yields of 0.12–0.45 for those carrying electron-withdrawing groups and of 0.02–0.03 for those carrying electron-donating groups[20]. It has been shown that the quantum yields are linearly correlated with the Hammett σ constants[20]. It is also noteworthy that the photolysis of 4-nitroacetophenone preferentially reduces the nitro group[21] as shown in equation (8). The *N*-oxides of 4-nitropyridines (**2**) are photoreduced, directly[22] or by biacetyl

$$4\text{-}CH_3COC_6H_4NO_2 \xrightarrow[i\text{-PrOH}]{h\nu} CH_3COC_6H_4{-}N{=}N{-}C_6H_4COCH_3 \quad (8)$$

sensitization[23], to the corresponding hydroxylamines (**3**) in excellent yields (equation 9).

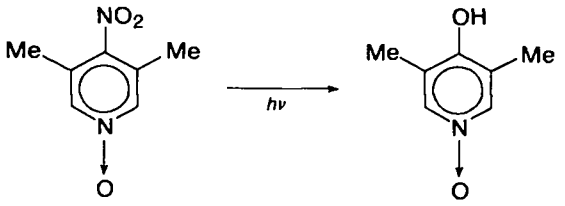
b. Mechanistic considerations. Photoreduction of substituted nitrobenzenes has been widely regarded to occur from their lowest triplet state on the basis of quenching by biacetyl ($E_T = 56.3$ kcal/mol) or by perfluoronaphthalene ($E_T = 56$ kcal/mol)[16]. Sensitization of 2,6-dimethyl-4-nitropyridine *N*-oxide (**4**, $E_T = 52$ kcal/mol) by biacetyl to yield the corresponding hydroxylamine is



(2) (3)

R = H, Me

(9)



(4) (5)

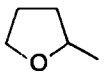
interpreted as a triplet reaction[23,24] since the direct photolysis gives pyridinol (5) as shown in equation (9). It is generally agreed, by analogy to carbonyl photochemistry, that hydrogen abstraction of nitro compounds is associated with the $n \rightarrow \pi^*$ character of the triplet states[15]. For example, the rate constant for hydrogen abstraction (k_H) by the triplet state of nitrobenzene from 2-propanol is as high as $10^6\,M^{-1}\,s^{-1}$ because of the $n \rightarrow \pi^*$ character[15], but those by the well-established triplet states of 1- and 2-nitronaphthalenes from alcohols are much lower ($1\text{–}5 \times 10^4\,M^{-1}\,s^{-1}$ as shown by nanosecond flash excitations[25,26]). In addition to other supporting data, it has been concluded that the excited states of the latter possess a high degree of intramolecular charge transfer (or $\pi \rightarrow \pi^*$) character in polar solvents.

The reluctance of *p*-nitrophenol and *p*-nitroaniline to undergo photoreduction has been ascribed to the charge-transfer character of their triplet state[20]; by flash photolysis the latter is shown to have a charge-transfer triplet state (T–T absorption at 595 nm)[27]. In contrast, the lowest triplet state of 4-nitro-*N*,*N*-dimethylnaphthylamine is likely to have $n \rightarrow \pi^*$ character because of the relative constancy of the triplet–triplet absorption maxima at 500–510 nm on changing solvent polarity as well as the high rate constant of hydrogen abstraction from 2-propanol ($k_H = 4 \times 10^7\,M^{-1}\,s^{-1}$)[28].

For 19 aromatic nitro compounds, the energies of the lowest triplet excited states (E_T) and their reduction potentials ($-E_{1/2}$) have been plotted to give three distinct groups of correlations[29]. It is claimed that compounds with a lowest triplet $n \rightarrow \pi^*$ state correlate linearly and undergo hydrogen or electron abstraction; those with a lowest triplet $\pi \rightarrow \pi^*$ state also correlate linearly and undergo nucleophilic photosubstitution. The nitro compounds with charge-transfer triplet states do not correlate systematically and are unreactive. Such correlations would contribute significantly to the understanding of nitro compound photochemistry if they were improved by more accurate data and rigorous refinements.

Despite a number of ESR studies on the photoreduction of nitrobenzene in hydrogen-donating solvents, the key intermediate $C_6H_5NO_2H^{\bullet}$ has eluded detection so far. In every case the radicals (**6**) derived from solvent radical attachment to aromatic nitro compounds (equation 10) are detected on irradiation[30,31]. Whether radicals **6**

$$ArNO_2 + R^{\cdot} \longrightarrow ArNO_2R^{\cdot} \quad (6) \qquad (10)$$

R =  Me_2COH, $EtSi-$

play a role in photoreduction is not clear; no doubt relatively slow decomposition allows them to accumulate to a certain concentration during the irradiation. The low pseudo-first-order rate constants[31] of $ArNO_2SiEt^{\cdot}{}_3$ decomposition suggest that the pathway may be a minor one in the overall reaction.

During irradiation of substituted nitrobenzenes and dinitrobenzenes in the presence of 2,6-di-*t*-butylphenol or 2,6-di-*t*-butyl-4-methylphenol, the nuclear polarizations of the *para* hydrogen or *para*methyl group are observed. This indicates that the triplet state of aromatic nitro compounds with $E_T > 56$ kcal/mol abstract phenolic hydrogen reversibly to give the radical pair ($^3Ar^1NO_2H^{\cdot} + Ar^2O^{\cdot}$); the ESR signals of the corresponding phenoxy radical are also observed[32].

Benzylic C—H bonds with a *p*-methoxy substituent can be oxidized to the corresponding benzyl alcohols and carbonyl compounds[33] by excited-state nitrobenzenes in good yield as in equation (11). The nuclear polarizations of the

$$p\text{-}MeOC_6H_4\underset{\displaystyle H}{\overset{\displaystyle R^1}{\underset{|}{\overset{|}{C}}}}-R^2 + XC_6H_4NO_4 \xrightarrow{h\nu} p\text{-}MeOC_6H_4\underset{\displaystyle R^1}{\overset{\displaystyle R^1}{\underset{|}{\overset{|}{C}}}}-OH + p\text{-}MeOC_6H_4\overset{\displaystyle O}{\overset{\|}{C}}R^1 \qquad (11)$$

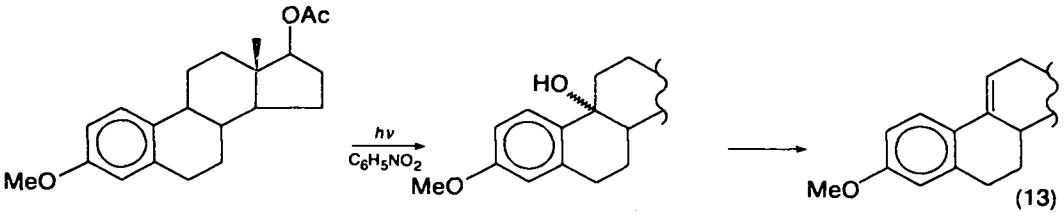
$R^1, R^2 = -[CH_2]_5-$ X = H
R^1 = Et, R^2 = H X = *o*-NO_2
$R^1 = R^2$ = H X = *p*-NO_2

benzylic and aromatic protons are observed when 4-methylanisole and 2-dinitrobenzene are irradiated in acetonitrile. Since tolune, ethylbenzene and cyclohexylbenzene are neither photooxidized by nitrobenzenes nor give rise to CIDNP effects under similar conditions, the oxidation must be initiated by electron transfer to the triplet state of nitrobenzenes[33] as in equation (12). The polarization as

$$\begin{array}{l} ArNO_2 + MeOC_6H_4CH_3 \xrightarrow{h\nu} (ArNO_2^{\cdot -} + MeOC_6H_4CH_3^{\cdot +}) \\ \qquad\qquad\qquad\qquad \searrow \\ (ArNO_2H^{\cdot} + MeOC_6H_4\dot{C}H_2) \longrightarrow ArNO + MeOC_6H_4CH_2OH \end{array} \qquad (12)$$

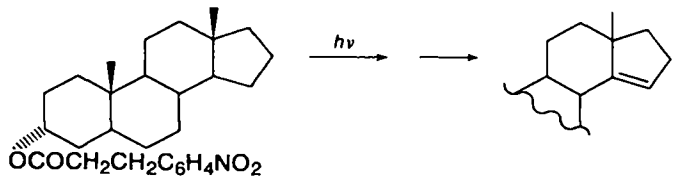
well as the photooxidation of 4-methoxybenzyl compounds are efficiently curtailed by the presence of *i*-propanol or H_2SO_4; the observations support the proposed mechanism.

c. Concurrent photooxidation of substrates. While photoreduction of aromatic nitro compounds has been extensively investigated, concurrent oxidation of substrates as a synthetic tool, such as shown in equation (11), has not attracted much attention. On the same principle as in equation (12), estratriene (**7**) can be oxidized at the benzylic position by photoexcited nitrobenzene[34] to give alcohol **8** and the olefin **9** (equation 13). A nitrobenzene moiety attached to a rigid molecular framework can be photoexcited to oxidize a specific remote position as controlled by stereochemical factors as demonstrated in the formation of the C_{14}-olefin[35] in

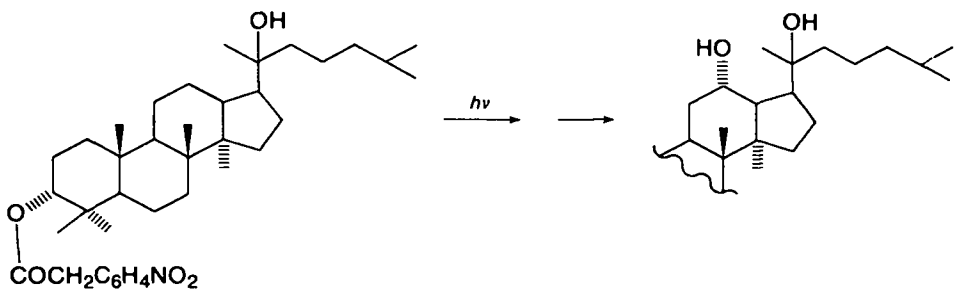


(7) (8) (9) (13)

equation (14) and of damarene diol derivatives[36] in equation (15). Incorporation of oxidized solvent moieties, mostly ethers and alcohols, into the aromatic amines as the result of photoreaction is also reported[37,38].



(14)



(15)

2. *Under acidic conditions*

Monosubstituted nitrobenzenes are photoreduced in 12N aqueous hydrochloric acid to give chlorinated aniline derivatives; an example is shown in equation (16)[39].

$$C_6H_5NO_2 \xrightarrow[HCl-H_2O]{h\nu} \underset{44\text{–}61\%}{2,4,6\text{-}Cl_3C_6H_2NH_2} + \underset{\sim 10\%}{2,4\text{-}Cl_2C_6H_3NH_2} + \underset{\sim 3\%}{2,3,4,6\text{-}Cl_4C_6HNH_2} \quad (16)$$

It is also observed that the rate of nitrobenzene photoreduction in aqueous 2-propanol is considerably enhanced by addition of hydrochloric acid[13,40]. The fact that both phenylhydroxylamine and nitrosobenzene are converted to chlorinated anilines and/or coupling products in the presence of hydrochloric acid under similar conditions or in the dark indicates that these two compounds can be regarded as intermediates in the photoreaction[40,41]. Under similar irradiation conditions, 4-nitropyridine is converted in an excellent quantum yield to 4-hydroxylaminopyridine[42,43] and 5-nitroquinoline is converted to 5-amino-6,8-dichloroquinoline[44].

The effect of acidity on the enhancement is dependent on the nature of the aromatic nitro compound; the quantum yield of disappearance of nitrobenzene[41] is 0.15 in the acid concentration range of 0.05–6M but those of 4-nitropyridine[43] and

5-nitroquinoline[44] reach the maximum value of 0.6 and 0.054 at 2M and 1M hydrochloric acid concentration, respectively. The presence of chloride ion is essential since the use of sulphuric acid does not enhance the photoreduction significantly. This has led to the proposal of an electron transfer as the primary process in the photoreaction[41] as shown in equations (17)–(22) in which *i*-propanol is oxidized to acetone.

$$^3(C_6H_5NO_2)^* + Cl^- \longrightarrow C_6H_5NO_2^{\cdot-} + Cl^{\cdot} \quad (17)$$

$$C_6H_5NO^{\cdot-} + H^+ \rightleftharpoons C_6H_5NO_2H^{\cdot} \ (pK_a\ 3.2) \quad (18)$$

$$Cl^{\cdot} + (CH_3)_2CHOH \longrightarrow HCl + (CH_3)_2COH^{\cdot} \quad (19)$$

$$(CH_3)_2COH^{\cdot} + C_6H_5NO_2 \longrightarrow (CH_3)_2CO + C_6H_5NO_2H^{\cdot} \quad (20)$$

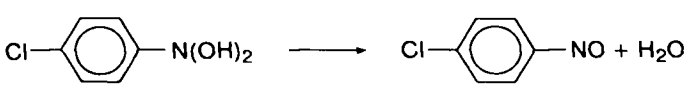
$$2\ C_6H_5NO_2H^{\cdot} \longrightarrow C_6H_5NO_2 + C_6H_5N(OH)_2 \quad (21)$$

$$C_6H_5N(OH)_2 \longrightarrow C_6H_5NO + H_2O \quad (22)$$

In aqueous hydrochloric acid, inevitably HCl has to serve as the reducing agent and the addition–rearrangement sequence as shown in equations (23)–(25) has been

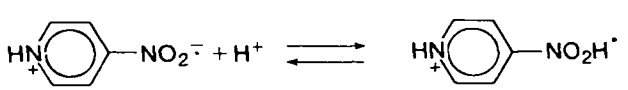
(23)

(24)



(25)

suggested as a possible mechanism[39]. By flash excitation spectroscopy, the anion radical **10** of 4-nitropyridinium ion and the conjugated acid **11** are detected in 50%



(10) **(11)**

λ_{max} = 480 nm, τ ~1 ms — λ_{max} = 430 nm, τ ~1 ms

aqueous *i*-propanol containing various concentrations of hydrochloric acid[45]. The anion radical (λ_{max} 550 nm, τ 5 ms) of 5-nitroquinoline[46] and the $C_6H_5NO_2H^{\cdot}$ radical (λ_{max} 440 nm, τ 2.7 ms) of nitrobenzene[45] are also observed under similar conditions. These support the electron-transfer process as the primary photochemical act.

3. *Under basic conditions*

Two types of basic conditions have been utilized in the photoreduction of aromatic nitro compounds, namely, amine or aqueous amine solutions or methanol containing sodium methoxide or hydroxide. It has been reported[16] that various aromatic nitro compounds are photoreduced more smoothly in diethyl- and triethyl-amine than in alcohol or ether, and, in the former photoreduction, more coupling products, such as azoxy- and azo-benzenes, are produced at the expense of the yields of aromatic amines. These coupling products are shown to arise from the base-catalysed condensation of nitroso and hydroxylamine derivatives, the intermediates formed during photoreduction. The fact that 1-nitronaphthalene can be smoothly photoreduced in diethylamine[16] and in *N,N*-dimethylaniline (or *N*-alkylanilines)[47] as in equation (26), in contrast to the resistance to do so in *i*-propanol[19], indicates that

$$C_{10}H_7NO_2 + C_6H_5N(CH_3)_2 \xrightarrow[\text{benzene}]{h\nu} C_6H_5NHCH_3 + C_6H_5N(CH_3)CHO + C_6H_5NHCHO + C_{10}H_7NH_2 \quad (26)$$

other mechanisms different from hydrogen abstraction must be operating in the former. By analogy to the fast quenching of the triplet states of benzophenone and other aromatic ketones by aliphatic and aromatic amines by an electron-transfer mechanism[48], it is now generally regarded[7,8] that the primary photochemical process in this system is the electron transfer generating nitro compound anion radicals and aminium radicals as in equation (27); the involvement of an exciplex and/or a radical pair is a matter for future investigation. The suggested ensuing pathways are shown in equations (27)–(32).

$$^3(ArNO_2)^* + R^1_2NCH_2R \longrightarrow ArNO_2^{\cdot-} + R^1_2NCH_2R^{\cdot+} \quad (27)$$

$$ArNO_2^{\cdot-} + R^1_2NCH_2R^{\cdot+} \longrightarrow ArNO_2H^{\cdot} + R^1_2\overset{+}{N}{=}CHR^{\cdot} \quad (28)$$

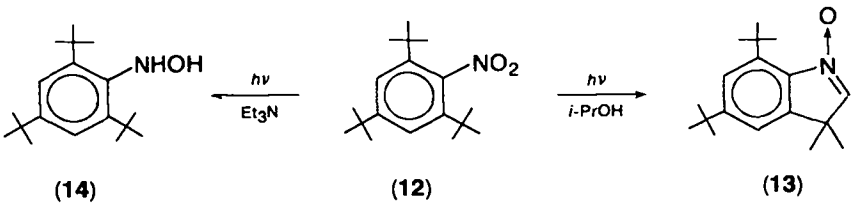
$$R^1_2NCHR^{\cdot} + ArNO_2 \longrightarrow R^1_2\overset{+}{N}{=}CHR + ArNO_2^{\cdot-} \quad (29)$$

$$R^1_2\overset{+}{N}{=}CHR + H_2O \longrightarrow R^1_2NH + RCHO + H^+ \quad (30)$$

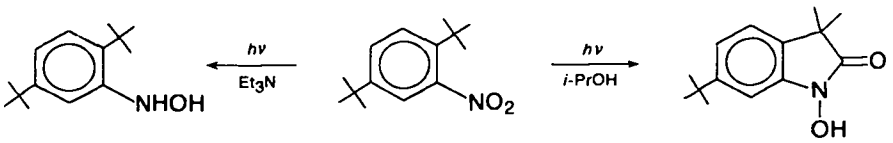
$$R^1_2\overset{+}{N}{=}CHR \xrightarrow{\text{ox.}} R^1_2NCOR \quad (31)$$

$$ArNO_2H^{\cdot} \xrightarrow{\text{red.}} ArNO \xrightarrow{\text{red.}} ArNHOH \quad (32)$$

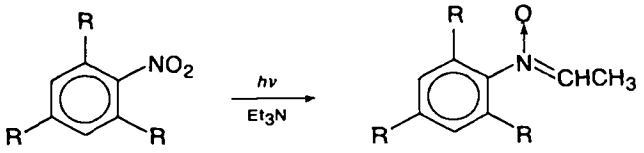
Fast quenching of the triplet states of aromatic nitro compounds (probably by the electron-transfer process if energetics are favourable) occurs during intermolecular photoreduction in competition with intramolecular processes. Photolyses of hindered nitrobenzenes **12** and **15** (equations 33 and 34) in *i*-propanol, other alcohols, ether or hydrocarbon solvents, give exclusively intramolecular redox products[49–52] **13** and **16.** **13** may be further photolysed or oxidized under these conditions to other isolated products. For the photolyses in triethyl- or diethyl-amine[49–52], however, the intramolecular processes are effectively (completely in **12**) quenched and the intermolecular reduction dominates the reaction to give hydroxylamines **14** and **17** as the identifiable intermediates. The latter may react further under these conditions to give the corresponding nitroso, amino, azo and azoxy derivatives, among others. Another example of preferential intermolecular photoreaction over the intramolecular mode is the photolysis of 2,4,6-trisubstituted nitrobenzenes **18** in



(14) (12) (13) (33)



(17) (15) (16) (34)



(18) (35)

R = Me, Et, *i*-Pr

triethylamine (equation 35). The nitrone products are probably formed from the corresponding hydroxylamines and acetaldehyde derived from the oxidation of triethylamine[53]. A direct proof of the electron transfer is still lacking, but nanosecond flash photolysis and CIDNP experiments might be able to demonstrate the presence of radical ions in the photolysis.

In 1963, it was demonstrated[54,55] that photolysis of nitrobenzene in ethanol or methanol containing sodium alkoxide or sodium hydroxide generates the ESR signal of the corresponding anion radical in significant yields. Russell and Geels[54] have suggested that the anion radical is formed by hydrogen abstraction–deprotonation and other secondary processes. It is also reasonable to formulate the direct electron transfer and hydrogen transfer as in equations (36)–(38) to account for the

$$^3(C_6H_5NO_2)^* + CH_3O^- \longrightarrow C_6H_5NO_2^{\cdot-} + CH_3O^{\cdot} \quad (36)$$

$$C_6H_5NO_2 + CH_3O^{\cdot} \longrightarrow C_6H_5NO_2H^{\cdot} + CH_2O \quad (37)$$

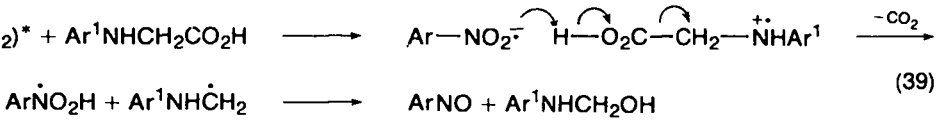
$$C_6H_5NO_2H^{\cdot} + CH_3O^- \longrightarrow C_6H_5NO_2^{\cdot-} + CH_3OH \quad (38)$$

observation. Later, Russian investigators reported that the quantum efficiency of the photoreduction of substituted nitrobenzenes is greatly enhanced in the presence of sodium methoxide (in methanol) or sodium hydroxide (in 50% aqueous methanol)[56,57]. For example, 1,3-dinitrobenzene is converted in the latter medium to the corresponding azoxy- (44%) and azo-benzenes (20%) and 4-nitrotoluene to 4-toluidine (62%) in addition to other minor reduction products. The corresponding hydroxylamine is one of the intermediates and in some cases can be isolated when the photoreduction is run in a HCO_2H–Na_2HPO_3 buffer solution.

The quantum yields of the disappearance of these nitrobenzenes in methanol without alkali are in the order of 10^{-3}–10^{-4}. In 1,3-dinitrobenzene and 4,4′-dinitrobiphenyl photoreductions, $1/\phi$ is linearly correlated with $1/[CH_3O^-]$ indicating the participation of methoxide ion in the photoreaction[57,58]. The enhancement of the photoreduction by other alkoxide ions is also demonstrated and the order of effectiveness is i-$PrO^- > EtO^- > MeO^-$, namely, the same as the order of their oxidation potential[58]. The deuterium isotope effect, k_H/k_D, of this photoreaction in 50% methanol–water and the deuterated solvent is ~2.6, but that in the presence of sodium hydroxide is unity in the same solvent systems[58]. Taken together, the electron transfer from methoxide to the triplet excited state of 4-dinitrobenzene, similar to equation (36), has been proposed to account for the enhanced photoreduction. However, the ensuing reactions remain to be clarified. Enhanced quantum yields, promoted by methoxide ion in methanol, are also observed in the photoreduction of 1- and 2-nitroanthraquinones[18,19] shown in equation (7).

It is pertinent to mention that various substituted nitrobenzenes are photoreduced in 50% aqueous methanol with HCO_2H–Na_2HPO_4 buffer to give the corresponding hydroxylamines, or decomposition products thereof. In this reaction, the formate anion is shown to be the reducing species, and it is suggested it acts in the same role as played by alkoxide anions[57].

In the presence of various nitrobenzenes or 1-nitronaphthalene, *N*-(2-chlorophenyl)glycine is efficiently photodecomposed and a similar mechanism as shown in equation (39) has been formulated to explain the formation of

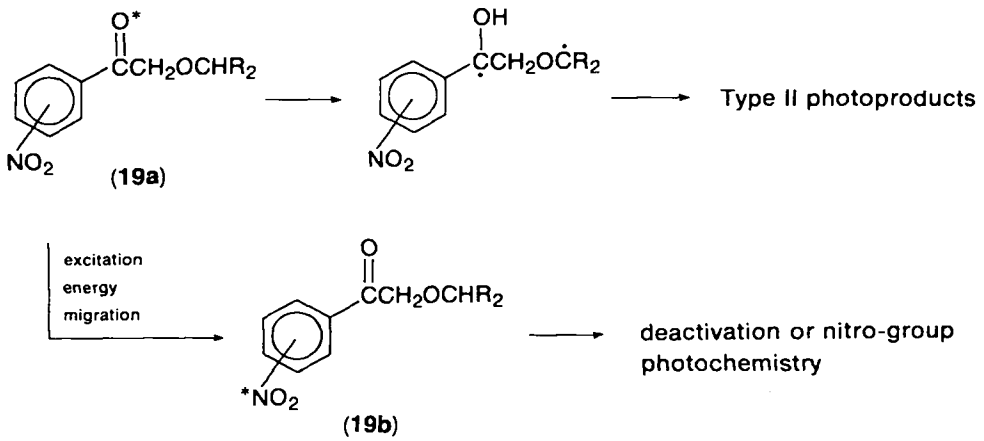


(39)

$Ar^1 = 2\text{-}ClC_6H_4^-$

2-chloroaniline (20–50%) and carbon dioxide (37–68%)[59]. The photoinduced decarboxylation of phenylthioacetic acid in the presence of aromatic nitro compounds under similar conditions yields carbon dioxide and thiophenol by an analogous mechanism[59].

By virtue of the well-investigated and better understood photochemistry of carbonyl groups[5], the photoreaction of alkanophenones substituted with a nitro group has been studied to provide some insight into the photochemical process of aromatic nitro compounds. Whereas an electron-withdrawing group enhances the intramolecular γ-hydrogen abstraction, 3-nitrobutyrophenone and 4-nitrovalerophenone are photochemically insert in benzene solution giving Type II quantum yields[60] of less than 1.3×10^{-4}. However, 4-nitro-substituted α-alkoxyacetophenones (**19a**, R = Me or H) are photolysed to give low but dramatically increased Type II quantum yields ranging from 0.015–0.035 depending on the ease of the γ-hydrogen abstraction by the carbonyl group. It is hypothesized[60] that the initial carbonyl-localized excited state ($n \rightarrow \pi^*$ triplet as in **19a**) transmutes to an energetically lower nitro-localized excited state ($n \rightarrow \pi^*$ triplet as in **19b**) from which rapid deactivation occurs as has been suggested in the photochemistry of nitroaromatics[15]. Obviously, a δ-alkoxy hydrogen provides better opportunity for the intramolecular hydrogen transfer in competition to the deactivation process. This assumption gains some support from the observation that 4-nitro-α-methoxyacetophenone (**19a**, R = H) is photoreduced in *i*-propanol with quantum efficiency comparable to that observed for carbonyl-substituted nitrobenzenes[20].

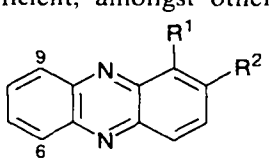


B. Nucleophilic Photosubstitution

Upon excitation, many substituted benzenes, naphthalenes, and heteroaromatics undergo nucleophilic substitution; aromatic nitro compounds compose a majority of these compounds studied to date. A detailed review of the subject has been given by the Havingsa–Cornelisse group in Leiden[9–11]. In addition, Döpp's review[7] also deals with photosubstitution of aromatic nitro compounds. Here, only a few recent developments will be added.

Photolysis of 3,5-dinitroanisole and hydroxide ion in 50% aqueous nitrile gives a clean formation of 3,5-dinitrophenol with a quantum yield[61,62] of 0.48. By flash excitation techniques. the triplet excited state of the dinitroanisole is shown to have $\tau \sim 12$ nanosecond (λ_{max} 475 nm) which reacts with hydroxide to give a transient (a complex?) with $\tau \sim 400$ nanosecond (λ_{max} 550–570 nm). The latter transient decays either to 3,5-dinitrophenol directly or to the anion radical as shown by UV spectroscopy. The anion radical was shown by UV and ESR spectroscopy to possess a lifetime (τ 40 ms), which is obviously too long to be the phenol precursor; it is suggested that the anion radical follows a reduction pathway. While the results clearly demonstrate the interface of photoreduction and photosubstitution, certain discrepancies need to be reconciled. For example, it has been reported that 4-nitroanisole is photoreduced in diethylamine[16], but undergoes photosubstitution in 6% dimethylamine to give *N*,*N*-dimethyl-4-nitroaniline[63].

Photolysis of 2-nitrophenazines (**20**) and primary alkylamines (methyl, ethyl, *i*-propyl and *t*-butyl) in acetonitrile gives 6- and 9-alkylamino-2-nitrophenazine as the major products. A similar substitution pattern is observed on photolysis of 1-nitrophenazine (**21**)[64]. The fluorescence of 2-nitrophenazine-10-oxide is quenched by alkylamines and the *N*-oxide group is photoreduced by the amines to **20**. Triethylamine is the most efficient, amongst others, in quenching as well as in

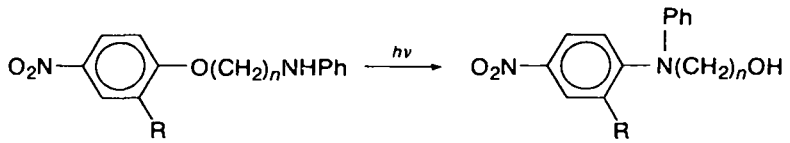


(**20**) $R^1 = H$; $R^2 = NO_2$
(**21**) $R^1 = NO_2$, $R^2 = H$

photoreduction; the electron transfer from either a singlet or a triplet excited state of the *N*-oxide is proposed as the primary photoprocess[65].

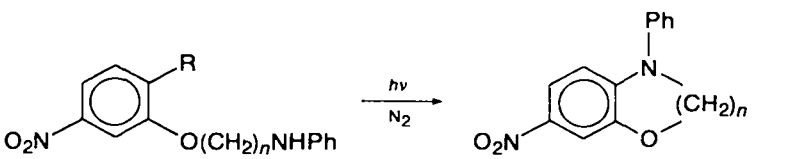
Recently, fluoro- and methoxy-substituted nitronaphthalenes were photolysed in the presence of methoxide, hydroxide or methylamines showing that the photosubstitution of the fluorine and methoxy group arises from activation by the nitro group; the *meta*-directing effect of nitro groups was reconfirmed[66]. The kinetics of photosubstitution of 1-fluoro- and 1-methoxy-2-nitronaphthalenes with hydroxide ions or methylamine were investigated by quenching experiments using 3,3,4,4-tetramethyldiazetidine dioxide ($E_T \sim 40$ kcal/mol) and fluorenone ($E_T \sim 53$ kcal/mol) as triplet quenchers. The higher quantum yields of the fluoro as compared with the methoxy compound are ascribed to the longer liftime of the former[67].

Photosubstitution in the intramolecular mode provides interesting comparisons with comparable intermolecular cases. The photolyses of *p*-nitrophenyl ethers **22** and **23** yield the rearranged products **24** and **25** in excellent conversions[68,69]. Similar photolyses of *m*-nitrophenyl ethers **26** and **27**, however, give cyclization products **28** and **29**. It is also shown that the N—H bond is required in **22**, that the *N*-Me



(41)

(**22**) R = H, n = 2–5 (**24**)
(**23**) R = OMe; n = 2–4 (**25**)



(42)

(**26**) R = H; n = 2, 3 (**28**)
(**27**) R = OMe; n = 2, 3 (**29**)

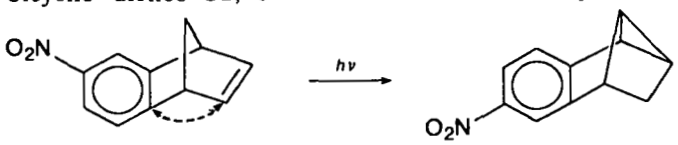
analogue of **26** (Ph = Me) does not cyclize, and that the homologues with chain length, n, longer than indicated do not undergo the photosubstitution. The photoconversion of **26** requires oxidation steps and is slow, but the oxidizing species is not known. In contrast to the well-established photosubstitution of 3-nitroanisole[70] and 3,4-dimethoxynitrobenzene[71] with methylamine at the *m*-methoxyl group, these intramolecular photosubstitutions do not exhibit the *meta*-directing effect of the nitro group even though option for a *meta* substitution is available. Further, the substitution patterns shown in equations (41) and (42) manifest the *para* activation effect of nitro groups, the effect of which is similar to that observed in the photoreaction of 4-nitroanisole[63].

Previously, the same group had demonstrated the presence of charge-transfer interactions for ethers **22** where n = 2 and 3, but not for those of n = 4 and 5, by fluorescence spectroscopy[72]. For this reason, a CT-complex or exciplex was regarded to be of minor importance and the Smiles-type rearrangement involving an amine anion **30** was proposed, as in equation (43), to explain the photosubstitution. It is obviously difficult to explain the photosubstitution of **26** by such a mechanism where oxidation steps have to be devised. More than one mechanism may be operating for the inter- and intra-molecular photosubstitutions.

$$Ar{-}O(CH_2)_nNHPh \xrightarrow[-H^+]{h\nu} Ar{-}O(CH_2)_n\bar{N}Ph \longrightarrow Ar{-}\underset{\displaystyle Ph}{\overset{\displaystyle |}{N}}(CH_2)_nOH \quad (43)$$

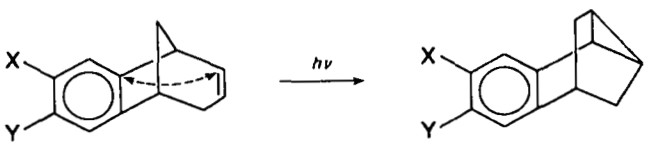
(30)

Photoinduced di-π-methane rearrangements (equations 44 and 45) of nitro-substituted bicyclic dienes **31**, **33** and **34** exhibit low quantum yields due to



(44)

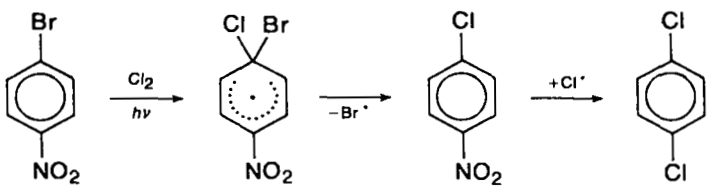
(31) (32)



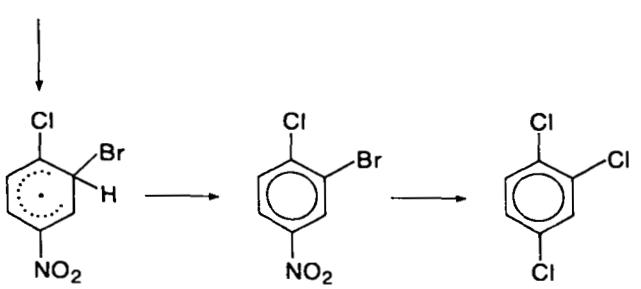
(45)

(33) X = H, Y = NO_2 (35)
(34) X = NO_2, Y = H (36)

inefficient singlet–triplet intersystem crossing and nitro-accelerated triplet decay, but are highly regiospecific in the bridging step, forming specifically the vinyl–aryl bridge *para* to the nitro group[73]. This is interpreted as an electrophilic radical attack by the vinyl group on the *para* position which is claimed to have higher electron density than the *meta* position in the excited state. **31** gives **32** exclusively; a mixture of **33** and **34** yields only **35** since the photorearrangement of **34** is very slow ($\phi < 0.0002$) owing to the unfavourable initial bridging at the position *meta* to the nitro group.



(37) (39) (40)



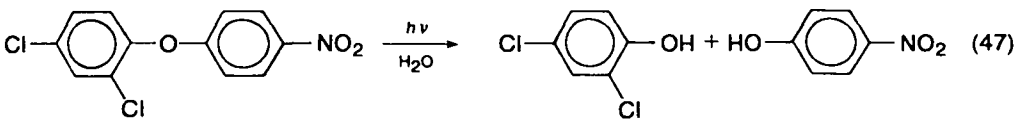
(46)

(38) (41) (42)

Photoinitiated free-radical substitution of 4-bromonitrobenzene is suggested to involve *ipso* intermediates, **37** and **38**, to account for a consecutive substitution pattern[74]. Though reaction is slow and may not involve direct excitation of the nitro group, mechanistically it is a fascinating reaction. The major product is **40** derived from another *ipso* substitution on **39**. The rearrangement of *ipso* intermediate **37** to **38** is indicated by the isolation of **41** and **42** as minor products. A similar photosubstitution of **39** also gives **40** as the major product with a small amount of **42**.

The photocyclization of hydrazones **87** described in equation (77) may be formally grouped with the substitution reactions. Such a decision is related to the overall mechanistic pattern of the fascinating rearrangements shown by this class of compounds (see Section II.D.1.e).

It is worth noting that 2,4-dichlorophenyl 4-nitro-phenyl ether, a herbicide called *nitrofen*, is photodecomposed in an aqueous suspension to give a complex mixture; the major and primary photolytic pathway is the substitution to yield 2,4-dichlorophenol and 4-nitrophenol[75] as in equation (47). A plethora of other

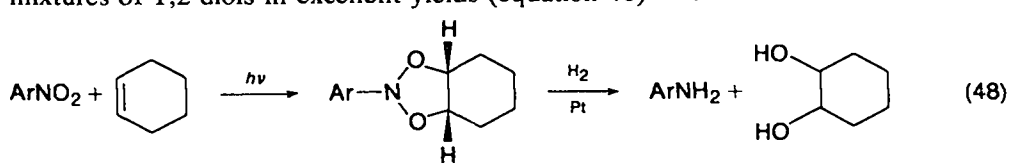


(47)

products have also been identified and are formed by the substitution of chlorine, hydrogen and nitro groups by a hydroxyl group and photoreduction of the nitro group.

C. Photoaddition

De Mayo and coworkers have published a definitive work on the photoaddition of aromatic nitro compounds to olefins in which the triplet excited nitrobenzenes are added by a stepwise radical mechanism to give the 'ozonide-like' intermediate **43**, which is successfully isolated at −70°C and can be hydrogenated to stereoisomeric mixtures of 1,2-diols in excellent yields (equation 48)[76,77].



(48)

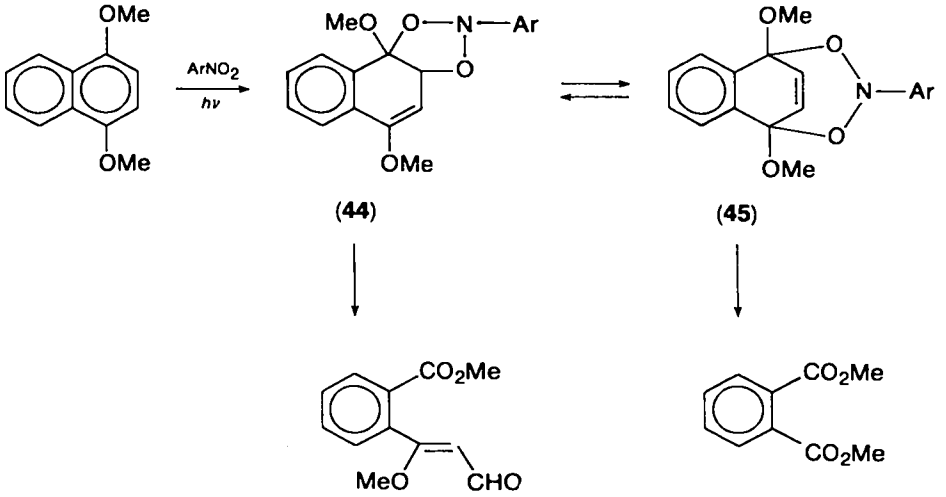
(43)

Ar = C_6H_5, 3-ClC_6H_4, 4-ClC_6H_4

Whereas 1-nitronaphthalene fails to add to olefins[77], this, as well as other aromatic nitro compounds, photolytically adds in aprotic solvents to methoxy-substituted benzenes[78] and naphthalenes[79], followed by cleavage reactions as shown by the example in equation (49). The proportions of intermediates **44** and **45** are influenced by temperature and solvent. Aromatic nitro compounds are presumably reduced to azo and amino derivatives by the intermediacy of arylnitrenes.

D. Photorearrangement

In this section photoinduced rearrangements of nitro groups attached to aromatic rings will be discussed. These include intramolecular redox reactions of



(49)

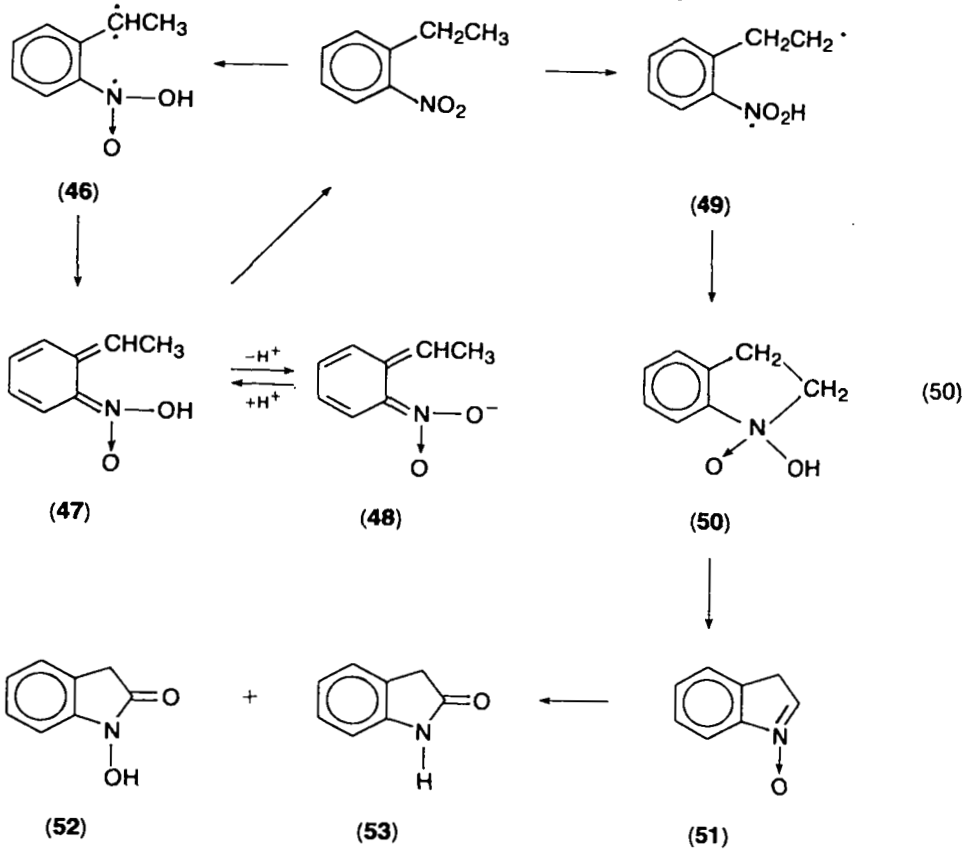
ortho-substituted nitrobenzenes, intramolecular additions of nitrobenzenes carrying *ortho*-substituted π-bond systems and the nitro–nitrite conversion.

1. *Intramolecular redox reactions*

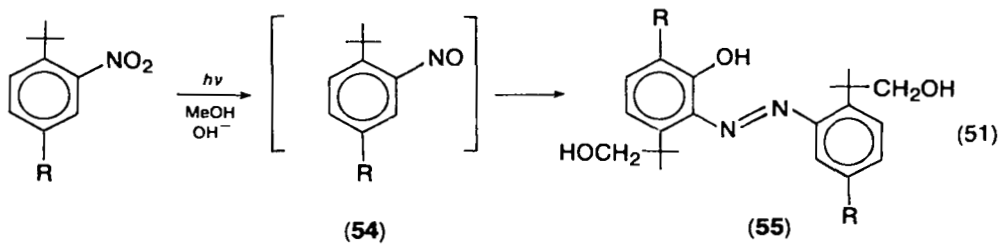
Photoinduced reactions between a nitro and the *ortho*-substituted group are among the earliest known photoreactions of aromatic nitro compounds; the early literature is reviewed by Morrison[3]. For convenience, this section will be divided, probably, somewhat arbitrarily, according to the nature of the *ortho* substituents, namely, alkyl, benzyl, π-bond and heteroatom.

a. o-*Alkylnitrobenzenes.* Photoreactions of mono- and poly-substituted nitrobenzenes with various degrees of steric crowding have been reviewed by Döpp[7] and related photochromic phenomena by Margerum and Miller[80]. The primary chemical process is generally regarded as a hydrogen abstraction from the *o*-alkyl group (equation 50). The abstraction of an α-hydrogen from the *o*-alkyl group is usually followed by collapse to, with certain exceptions[50], the *o*-quinoid *aci*-nitro form as in **46** → **47**. The *aci*-nitro compound **47**, being a strong acid (pK_a 3.7–1.1)[81], dissociates readily in weakly basic solvents to give the coloured *aci*-nitro anion **48**, which has the relatively long lifetime of milliseconds before reverting to the parent nitro compound[81–83]; this is the basis for the observed photochromism. The abstraction of a β-hydrogen leads directly to **50** from the diradical **49**; the dehydration of **50** gives the first observable intermediate[84,85], i.e. the nitrone **51**. The isolated products from this irreversible photoprocess are cyclic hydroxamic acid (**52**) and the lactam **53**, among others.

Such photochemical reactions have been investigated with 2-*t*-butylnitrobenzene[84] and its 5-substituted (e.g. *t*-Bu, Br, NO_2,NHAc) compounds[52], 2,4,6-tri-*t*-butylnitrobenzene[50,51], 4-substituted (e.g. Ac, NO_2, Me) 1-*t*-butyl-2,6-dinitro-3,5-dimethylbenzenes[85] and others[50]. The photolysis can be carried out in the solid state or in solution, without interference from solvents except in alkylamines where effective intermolecular reduction occurs as shown in equations (27)–(32), to give the corresponding cyclic hydroxamic acid **52** and other minor products in good yields, but low quantum efficiencies (0.01–0.02). Benzophenone sensitizes and 1,3-pentadiene can quench, although not very effectively, and oxygen shows no effect on the photorearrangement[50]. The photolyses of the less hindered



2-*t*-butylnitrobenzene[84] and its 5-substituted compounds[52] (equation 51) in methanolic sodium hydroxide also give small amounts of azo compounds **55** arising from the secondary photorearrangement of the corresponding azoxy compounds, which must be derived from an intermolecular reduction (see Section II.A.3). The

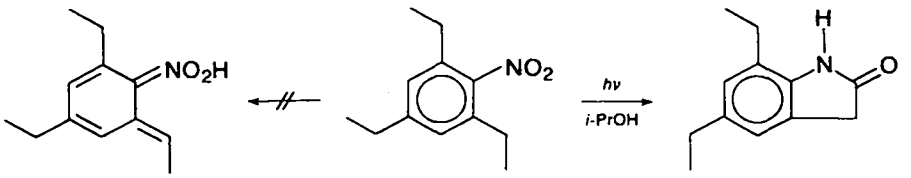


(51)

initial step of the photoreaction is obviously the intramolecular hydrogen abstraction leading to the oxidation of the *t*-butyl group; the proposed electron-transfer reaction[56,57] as shown in equation (36) is, therefore, not operating here. It may be concluded that if such electron-transfer processes operate at all in the photoreduction of aromatic nitro compounds, the efficiency is probably not as good as that observed in alkylamine solutions[52] (see equations 27–32).

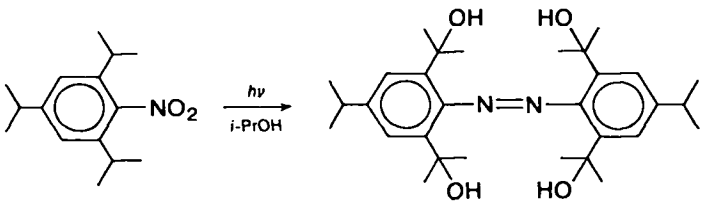
Whether an α- or β-hydrogen is abstracted in this photoreaction is very much dependent on the type of *o*-alkyl group. The photolysis of 2,4,6-triethylnitrobenzene (equation 52) in dioxane–D_2O gives no deuterium incorporation and in *i*-propanol

yields the lactam **56** (40%) indicating the operation of exclusive β-hydrogen abstraction. In contrast, the photolyses of 2,4,6-triisopropyl- (equation 53) and 2,3,5,6-tetraisopropyl-nitrobenzenes (equation 54) lead to exclusive α-hydrogen



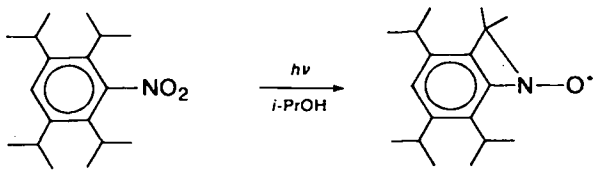
(52)

(56)



(53)

(57)



(54)

(58)

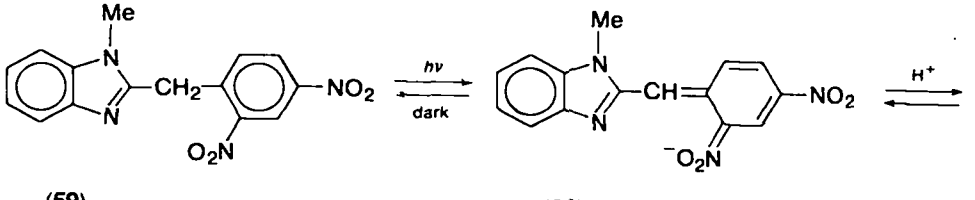
abstractions, yielding, respectively, azo compound **57** and stable nitroxide **58** in quantitative yields[50]. The different pathways may be controlled by the conformations of the *o*-alkyl groups in these sterically crowded molecules.

b. o-Nitrobenzyl derivatives. Using flash photolysis[86,87], imidazole derivative **59** is converted in buffered 50% ethanol solution to anion **60** at pH > 8.5 and to zwitterion **61** at pH < 6.5. The rate constant of reversion to **59** is pH-dependent, showing $3.5 \times 10^2\ s^{-1}$ at pH 3.7 and $5 \times 10^{-2}\ s^{-1}$ at pH 10.17. A slow irreversible reaction also occurs, but this has not been elucidated. The photochromism of the corresponding 2-pyridyl derivatives of **59** has also been reported[88].

Photoinduced cyclizations of 2,2′-dinitrodiphenylmethanes in *i*-propanol and in ethanol containing sulphuric acid (equation 56) are useful syntheses of heterocycles **62** and **63** which are obtained in 35–50% yield in addition to substantial amounts of other cyclization products[89]. However, the presence of triethylamine does not change the pattern of the photoreaction in the way shown in equations (27)–(32).

The photoreactions of *o*-nitrobenzyl derivatives can be interpreted as involving intramolecular hydrogen abstraction from the benzylic position, though no concrete proof is available. It is generally accepted that the ensuing redox processes take place by the sequence shown in equation (57), or a similar one, to yield *o*-nitrosobenzaldehyde as the primary product.

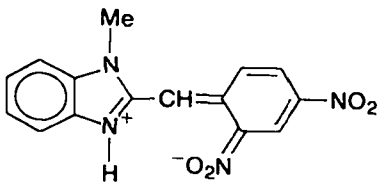
While there are no reports of kinetic and mechanistic studies, the redox products **64** and **66** have been identified (equations 58 and 59); the latter is assumed to be



(59) (60)

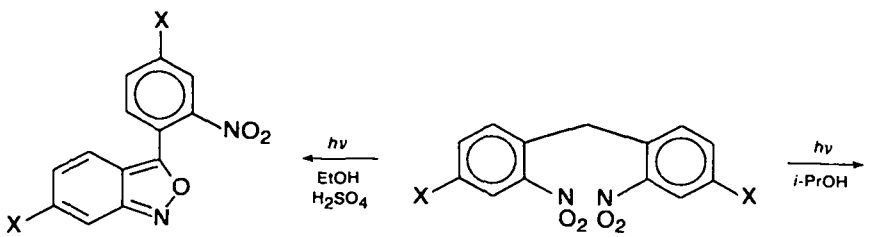
λ_{max} = 495, 645 nm

(55)

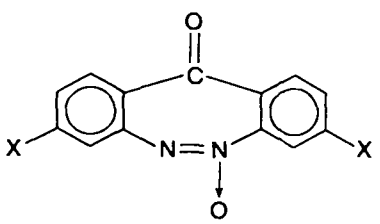


(61)

λ_{max} = 520 nm



(63)

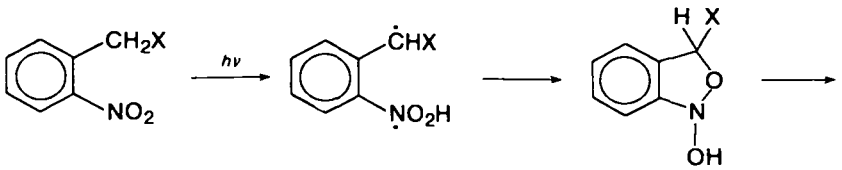


(62)

(56)

X = H, Cl and Br

derived from the corresponding *o*-nitrosobenzaldehyde **65** by secondary photolysis[90]. Regardless of the mechanistic ambiguity, *o*-nitrobenzyl derivatives have been successfully and elegantly utilized as a photosensitive protecting group in various syntheses of peptides, glycosides, nucleotides and others, which are sensitive to varied reagents under conventional conditions. In these complex chemical transformations *o*-nitrobenzyl-protected functional groups can withstand fairly well a variety of reagents and reaction conditions, until they are photoactivated for removal



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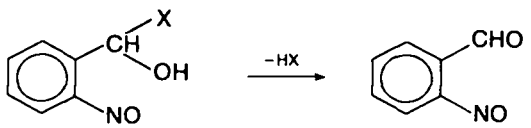
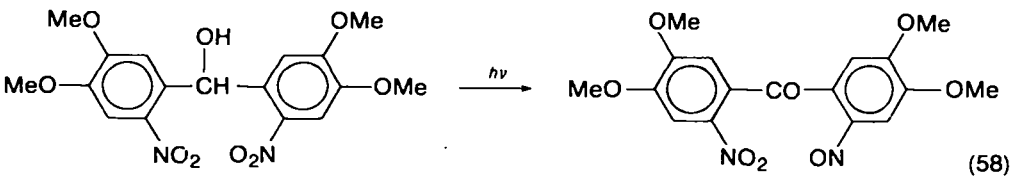
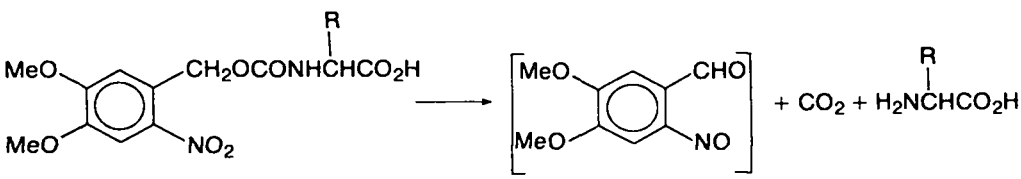




(58)

(64)



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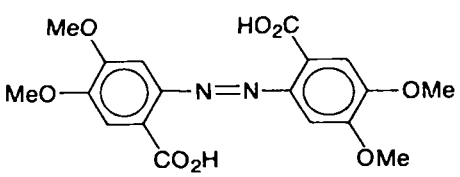
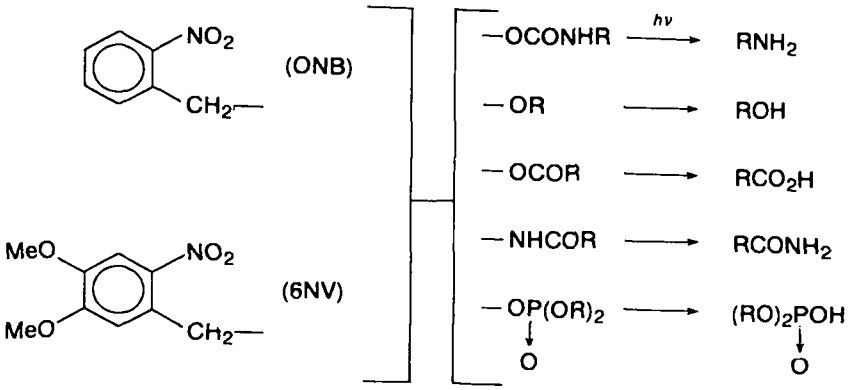


(66)

under mild conditions. Applications of *o*-nitrobenzyl protecting groups have been reviewed as a part of the general practice of photosensitive protecting groups[91,92]. Both *o*-nitrobenzyl (ONB) and 6-nitroveratryl (6NV) moieties can be linked to various functionalities to form a variety of compounds liable to further modification of the R group by conventional methods, without affecting the protected entities, which are released in their integrality upon photolysis as shown in equation (60).

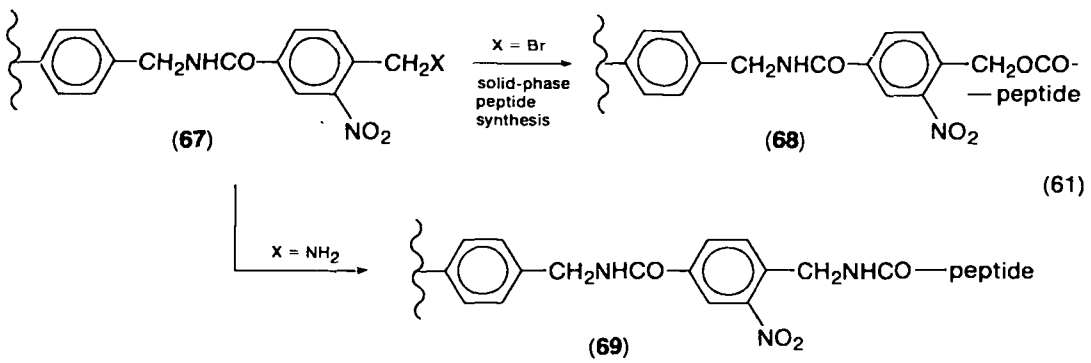
For various amino acids including the light-sensitive tryptophane, the amino groups protected as ONB- and 6NV-urethanes (equation 60) and the carboxyl groups protected as ONB esters are photolysed to regenerate the amino acids in virtually quantitative yields if 'aldehyde reagents' (hydrazine, hydroxylamine



(60)

hydrochloride, etc.) are added to scavenge *o*-nitrosobenzaldehyde[90,93]. Histidine protected by a ONB group on the imidazole side-chain is regenerated by photolysis without racemization[94].

An ONB moiety can be attached to a polystyrene resin and used in the synthesis of protected peptides at *C*-terminal carboxylic acid[95,96] or carboxamide[97] in the solid phase. The ONB bromide and ONB amine moiety incorporated in styrene resin (**67**) has been used in solid-phase peptide synthesis to yield **68** and **69** (equation 61),

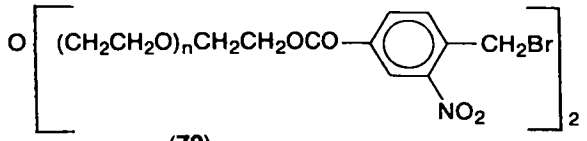


(61)

photolyses of which yield peptides, possessing free *C*-terminal carboxylic acid and carboxamide groups, respectively. By the latter method, a biologically active decapeptide 'luteinizing hormone-releasing hormone' has been synthesized[97]. Similarly, an ONB bromide group incorporated in polyethylene glycol support (**70**) is utilized in peptide synthesis in the liquid phase to give **71** (equation 62). Photolysis of **71** gives a tetrapeptide possessing a free *C*-terminal carboxyl group in 98% yield[98].

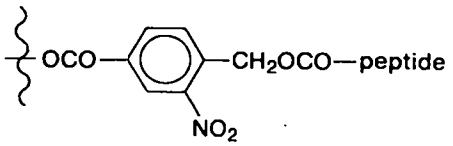
The protection of amino groups as ONB and 6NV urethanes and hydroxyl groups as their ethers has been utilized in syntheses of glycosides and amino sugars[99–101]. These protective linkages are fairly stable to acid hydrolysis but readily removed photolytically. A 6NV alcohol moiety built into a styrene–divinylbenzene copolymer (**72**) is used in a multi-step synthesis of the polymer-supported disaccharide **73** in the solid phase (equation 63). The 6NV ether linkage withstands basic and acidic treatment but photolytically cleaves to give benzylated isomaltose[102]. It has also been shown that ribonucleosides (adenosine, inosine, cytidine or uridine) with the 2′-OH protected as the ONB ether group can be photolysed to regenerate the ribonucleoside without affecting either the purine or pyrimidine bases[103].

The ONB moiety as a blocking group of phosphate function is shown in an example of mononucleotide synthesis[104] (equation 64): 3′-*O*-acetylthymidine

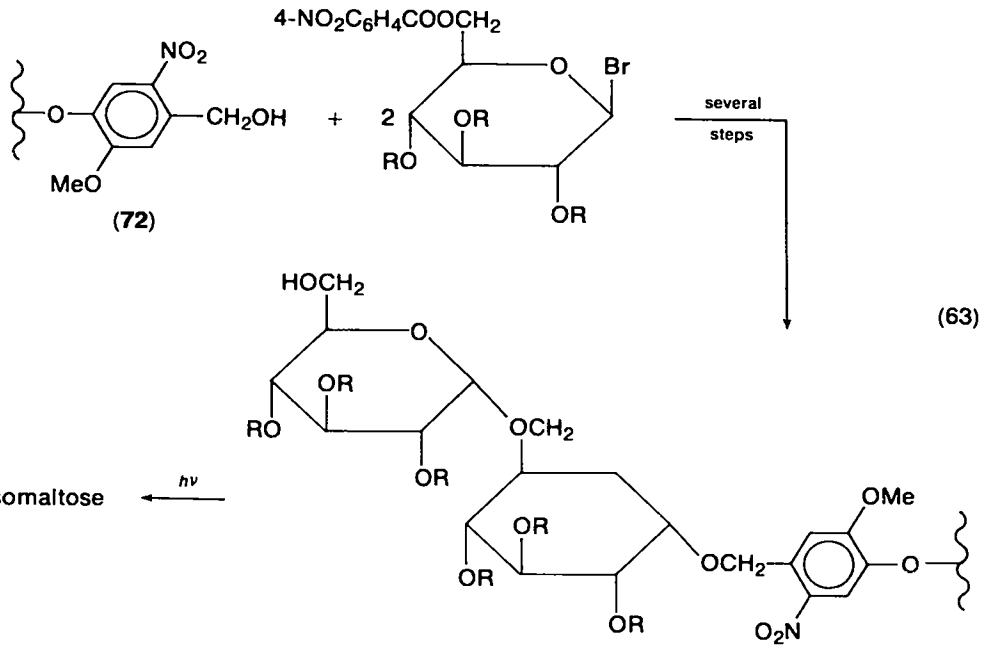


(70)

(62)



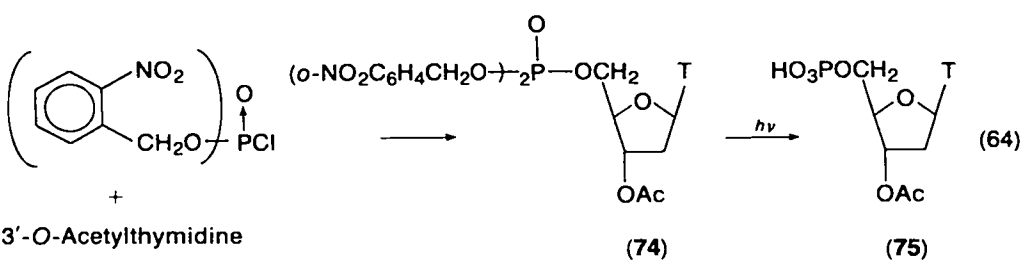
(71)



(72)

(73)

(63)



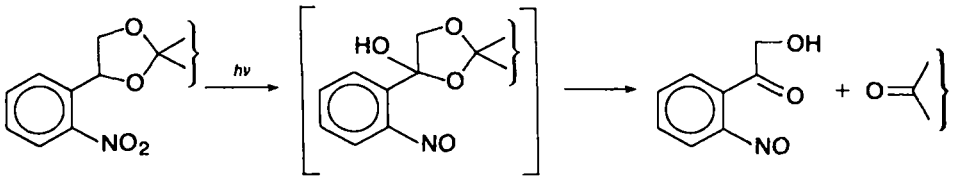
(74) (75)

(64)

T = thymine

phosphate (**75**) is obtained by photolysis of **74** in aqueous *t*-butanol in the presence of a polystyrene-bound semicarbazide to scavenge *o*-nitrosobenzaldehyde. The ONB ester of guanosine 3′-, 5′-phosphate is stable and transportable through membranes; after reaching a target the nucleotide can be released by photoloysis in a cell experiment[105].

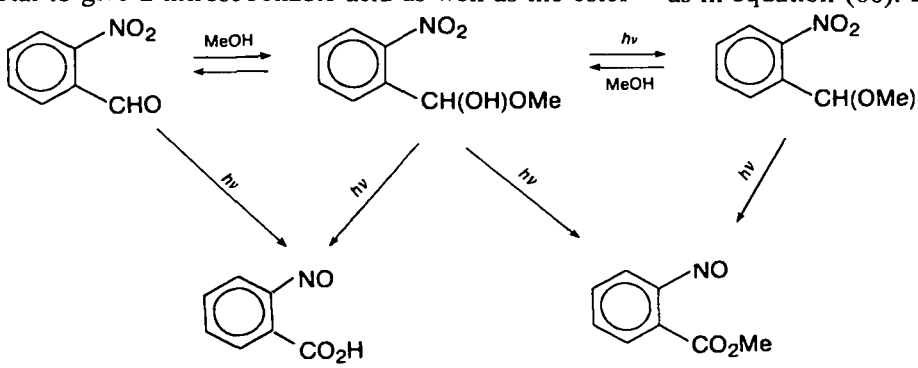
Some carbonyl groups in steroids can be protected as the acetal **76** and photolytically released via **77** (equation 65), though stability of the acetal linkage towards various reagents has not been demonstrated[106].



(65)

(**76**) (**77**)

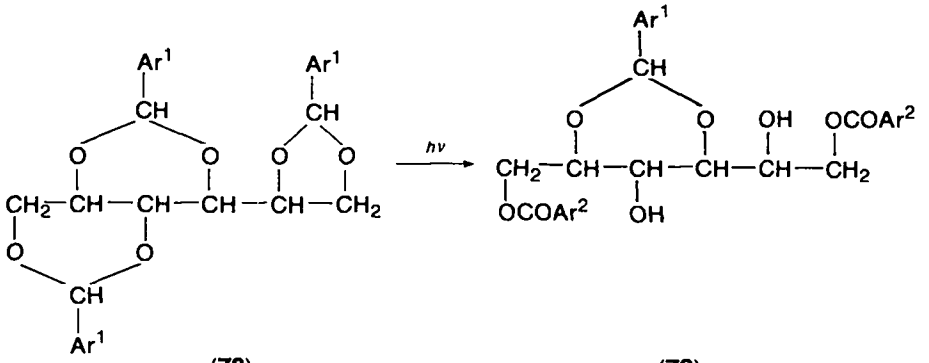
c. Nitrobenzenes with ortho *C=X bonds and their derivatives.* The photochemistry of 2-nitrobenzaldehyde has been studied for along time and been reviewed[3]. The primary photochemical act is shown to be the intramolecular hydrogen transfer in the triplet excited state[107]; the follow-up reactions are similar to those shown in equation (57) to give 2-nitrosobenzoic acid as the primary product. In alcoholic solutions, photorearrangement can also occur from the hemiacetal and acetal to give 2-nitrosobenzoic acid as well as the ester[108] as in equation (66). It has



(66)

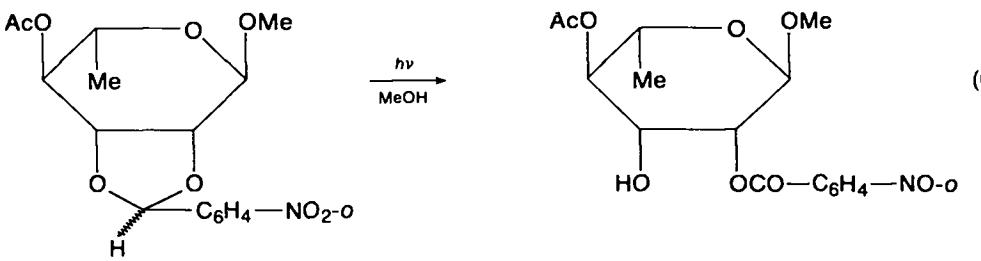
been suggested that the formation of the acetal is photocatalysed[109]. If this is the case, the photolysis is very efficient since in methanol the quantum yields of the disappearance of 2-nitrobenzaldehyde, and the formation of the acid and the methyl ester have been determined[107] to be 0.5, 0.25 and 0.25, respectively. An early ESR study on the photolysis of 2-nitrobenzaldehyde assigning the observed signal[109] to $2\text{-}NO_2C_6H_4\dot{C}HOMe$ has been disproved and it has been reassigned to the $2\text{-}HO_2CC_6H_4NH—O^{\bullet}$ radical[110,111].

From equation (66) it is clear that 2-nitrobenzaldehyde and polyhydroxy compounds can form acetals with a photosensitive protecting group. Applications of such a scheme in the protection of hydroxy groups in sugars have been extensively investigated by Tanasescu and coworkers[112,113]. For example, the *tris*-benzylidene derivative of 2,4-dinitrobenzaldehyde (Ar^1CHO in **78**) derived from D-glucitol is photolysed to give the 2-nitroso-4-nitrobenzoate ($AR^2CO_2—$ in **79**) without epimerization (equation 67). The light-induced removal of the 2-nitrobenzylidene moiety as a protecting group in glycosides also gives good results as shown by the phototransformation of the methyl L-rhamnoside derivative[114,115] in equation (68).



(67)

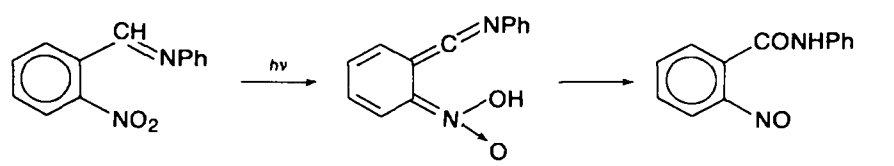
(78) (79)



(68)

While the photochemical reaction is clean and mild, the scheme suffers from two obvious difficulties, namely: (1) the cleavage of the C—O bond is not always highly regiospecific, and (2) the formation of benzylidene derivatives may generate a pair of epimers.

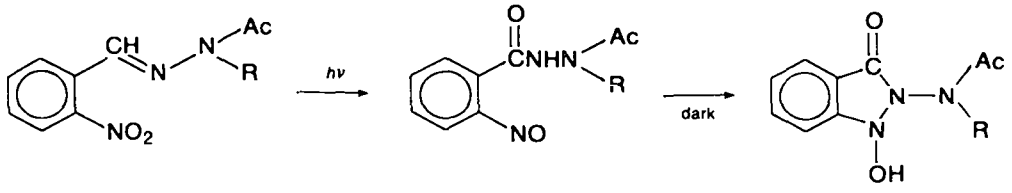
Photolysis of 2-nitrobenzylideneaniline (**80**) in solution or in the solid state was shown in as early as 1902 to give 2-nitrosobenzanilide (**82**)[116]. Recent studies using flash excitation[117] have assigned an observed transient ($\lambda_{max} \sim 460$ nm in benzene, $k \simeq 0.5\,s^{-1}$) to ketimine **81** (equation 69). Although no evidence is



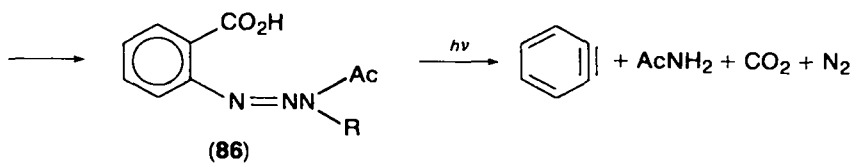
(69)

(80) (81) (82)

available yet, the formation is assumed to be initiated by intramolecular hydrogen abstraction. A similar mechanism[118,119] is assumed to operate in the photolysis in benzene of the corresponding *N*-acetyl-*N*-alkylhydrazones **83** to give hydrazides **84**; in methanol, or better by a brief treatment with alkali, **84** rapidly rearranges to triazenes **86** via **85**. The photolysis of **83** in methanol, however, yields benzyne, via **86** as in equation (70), which has been trapped with tetracyclone. The presence of the *N*-acyl group is required for the photoreaction since the corresponding methylhydrazone is stable to irradiation. It is surprising that hydrazones **87**, containing a N—H bond, are photolysed in alcohols to 1-substituted 5-nitrophthalazines (**89**) in 30–60% yields (equation 71), though the benzyne pathway of equation (70) also operates to a minor extent[120]. The presence of the



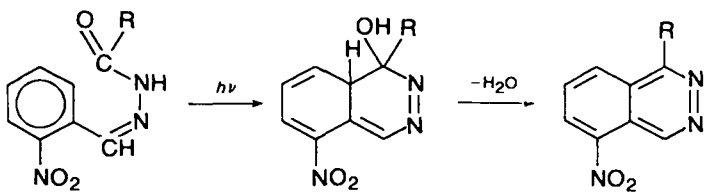
(83) (84) (85)



(86)

(70)

R = Me, Et, CH_2Ph



(87) (88) (89)

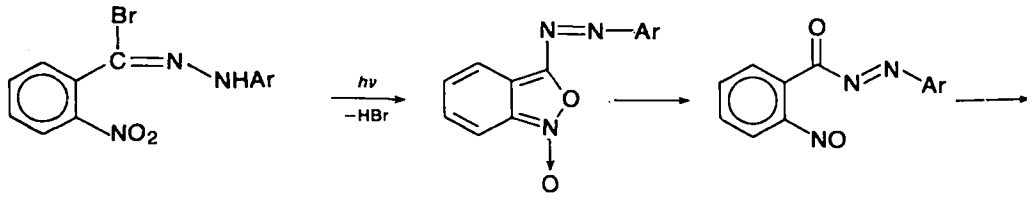
(71)

R = Me, Ph, CH_2Ph, 4-pyridyl

o-nitro group is required but its role in the photoreaction is yet to be defined. It has been suggested that **88** is the intermediate arising from a photochemical 6π electrocyclic reaction (equation 71).

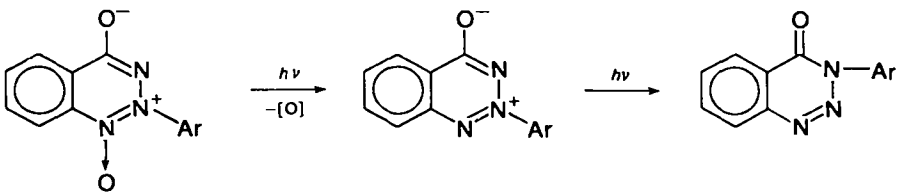
The photorearrangement of hydrazonoyl bromides **90** in acetonitrile to give triazinones **95** (40–55% yields) is explained[121] by the sequence shown in equation (72). The key intermediate, betaine *N*-oxide **93**, is isolable by short irradiation or by base treatment. This as well as betaine **94** can be photolysed to triazinone **95** under similar conditions in which an unknown deoxygenation step is involved. The primary photoprocess is not clear but must be very different from that of equations (69)–(71). In view of the photolability of the parent triazinone (**95**, Ar = Ph), it is remarkable that triazinones **95** are stable to irradiation.

The photorearrangements of 2-nitrostilbenes and 2-nitrotolan to 2-phenylisatogens have been discussed in detail[3]. These reactions have been postulated to occur by an intramolecular addition, similar to that demonstrated in the intermolecular addition (equation 48)[76,77], as the primary step. There is a growing tendency to use this mechanism to explain the primary photochemical acts of this type of *o*-nitroaromatic compound; however evidence concerning the postulated mechanism is still scarce. Isatogen formation appears to be, though the yields are generally low, a general reaction[122] of *o*-nitro derivatives of stilbenes and of 1,4-diphenyl-1,3-butadienes as in equation (73) and from nitro and acetylenic linkages placed in proximate positions on an aromatic nucleus as in equations (74) and (75). Although, the products are somewhat different, 1,3-dimethyl-5-nitro-6-styryluracils also undergo a related photorearrangement[123].



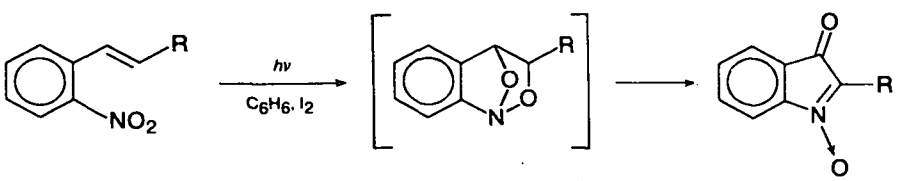
(90) (91) (92)

(72)

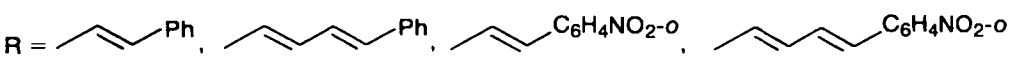


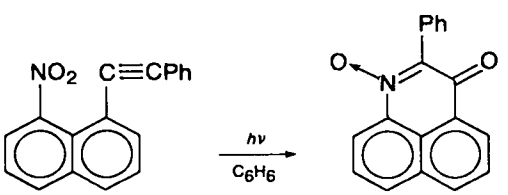
(93) (94) (95)

Ar = 4-$NO_2C_6H_4$, 2-Br-4-MeC_6H_3, 2,4-$Br_2C_6H_3$

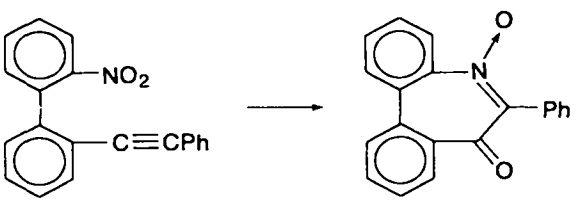


(73)



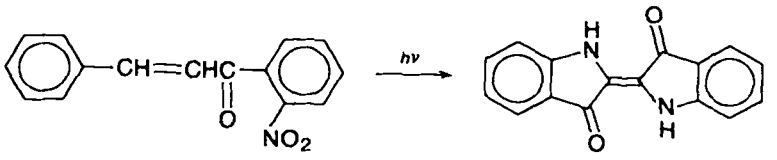


(74)



(75)

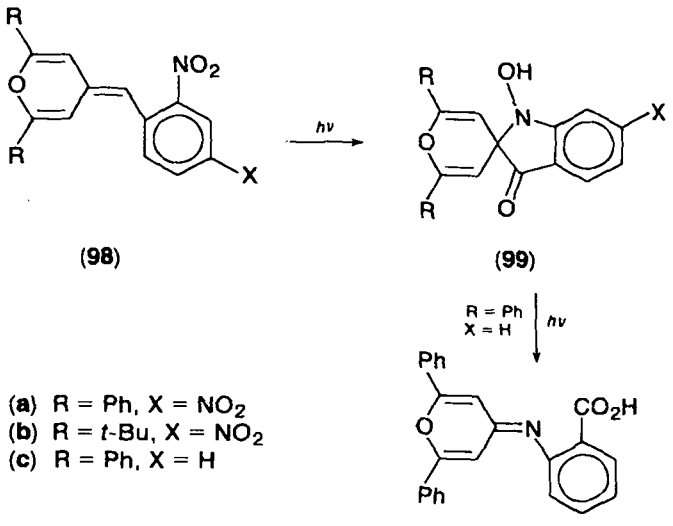
The formation of indigo (**96**) from 2′-nitrochalcone (**97**; equation 76) probably involves multi-step photolysis and dark reactions[124]; a mechanistic study is as yet unavailable. Irradiation of halogen-substituted chalcones **96** in the solid state shows



(96) (97) (76)

that the *s-trans* conformation is a necessary, but not a sufficient, condition[125] to give indigos **97** (equation 76).

The photocyclization[126] of 4-(2′-nitrobenzylidene)-4*H*-pyrans to the indolines **99** (equation 77) may be explained by an intramolecular photoaddition followed by



(98) (99) (77)

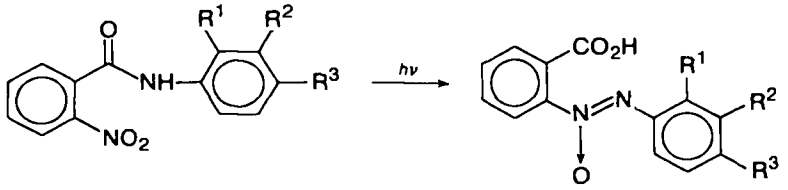
(a) R = Ph, X = NO_2
(b) R = *t*-Bu, X = NO_2
(c) R = Ph, X = H

(100)

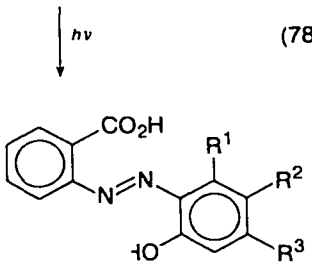
further rearrangements very similar to those involved in equation (73). The further light-induced rearrangement of **99c** to **100** resembles the redox reaction coupled with migration of the hydrazone group in equation (70).

The photorearrangement of 2-nitrobenzanilides (**101**) to azoxybenzene-2-carboxylic acids (**102**) and their subsequent photolysis to 2-hydroxyazobenzenes **103** (equation 78) is very much dependent on substituents on the aniline ring[127]. The azoxy–azo rearrangement step is a well-established photoreaction[128]. The anilides **101** carrying an electron-withdrawing group (e.g. R^1, R^2 or R^3 is NO_2 or CN) are stable to irradiation, and nor does *N*-alkyl-substituted 2-nitrobenzamide undergo the photorearrangement. This suggests that the rearrangement possesses a high degree of, if not completely ionic character. The first step, transformation to azoxy acids, does not formally involve a redox process, but has been suggested to occur by an unusual hydrogen atom abstraction from the N—H bond similar to the pathways shown in equations (50) and (57). Since nitro groups are good electron acceptors, it may be reasonable to consider an electron-transfer process as a possible initial step as in equation (79). Such a mechanism is somewhat similar to that of the photoreduction of nitrobenzenes in the presence of amines (see Section II.A.3) and can avoid the direct hydrogen atom abstraction step.

d. Nitrobenzenes with ortho *heteroatom substituents and their derivatives.* The stability of nitroanilines and nitronaphthylamines towards photoreduction and



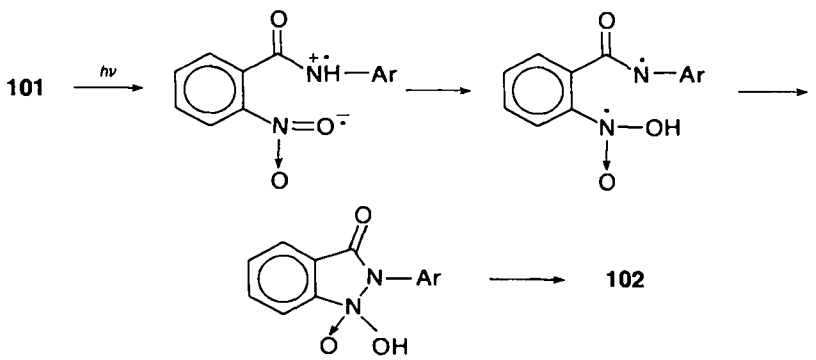
(101) (102)



(103)

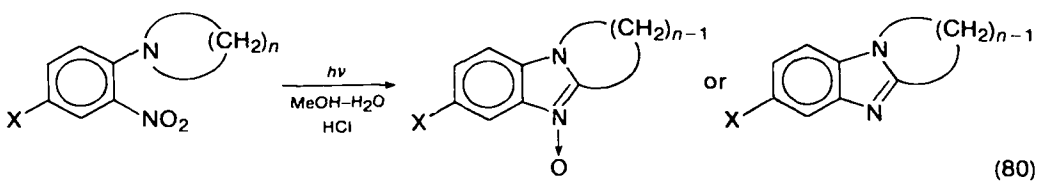
(78)

R^1, R^2, R^3 = H, Me or Cl



(79)

photosubstitution has been ascribed to the charge-transfer character of their lowest excited state[27,57]. However, photoreduction occurs with acylation of the amino group in nitroanilines[51,52]. In contrast, photolysis of *N*-alkylated 2-nitroanilines induces intramolecular redox reaction just as easily as in the photorearrangements described above. The photocyclization of 2-cycloaminonitrobenzenes (**104**) in aqueous acidic methanol gives either a benzimidazole **106** or its *N*-oxide **105** (but not both),

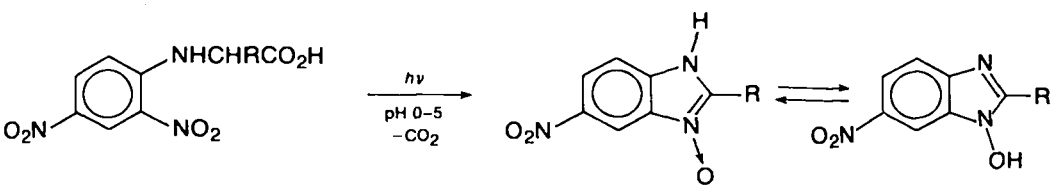


(104) (105) (106)

(80)

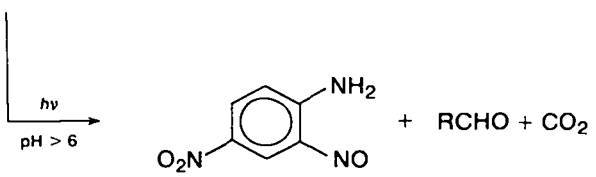
X = H or Cl
n = 4, 5, 6 or 10

depending on the structure[129]. Two independent but closely related mechanisms, e.g. the hydrogen abstraction (as in equation 50) and electron-transfer processes, are proposed to account for the formations of **105** and **106**, respectively, since **150** does not undergo photodeoxygenation under these conditions. The transformation can also be brought about by acid catalysis or reduction. Formally related to this reaction is the photoinduced decarboxylative cyclization of *N*-2,6-dinitrophenyl α-amino acids in aqueous solution[130–132]. The photorearrangement is pH-dependent[130] as shown in equation (81) and the yields of benzimidazole *N*-oxides



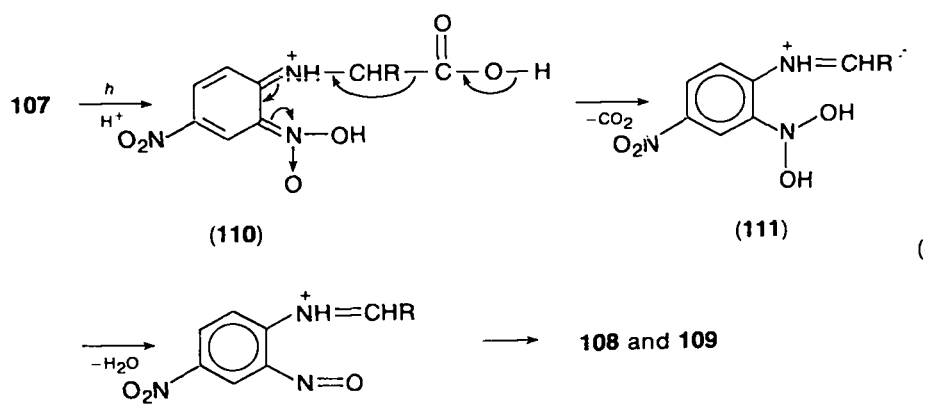
(107) (108)

(81)



(109)

108 are the highest at pH ~ 3 for all of the α-amino acids studied[131]. The role of acids in the photoreaction, particularly that in equation (80), is not clear but may be assumed to catalyse the cyclization of a redox intermediate, such as **111** or **112**. It has been shown that nitrosoaniline **109** reacts with aldehydes by acid catalysis to give benzimidazole *N*-oxides[130]. In principle, the cyclization reaction may be explained by a mechanism initiated by hydrogen atom abstraction similar to that shown in equation (50). If the proposal regarding the charge-transfer character of the lowest excited state of 4-nitroaniline[27] is accepted, an ionic mechanism as in equation (82)

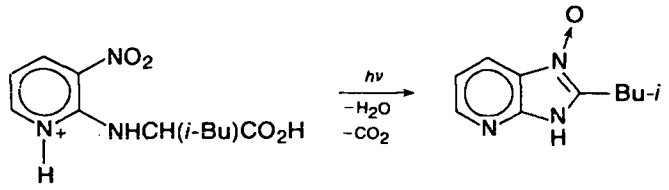


(110) (111) (112)

(82)

may be postulated to explain the decarboxylative cyclization of **107**. This mechanism bears a similarity to that of the decarboxylation of α-amino acids by photoexcitation

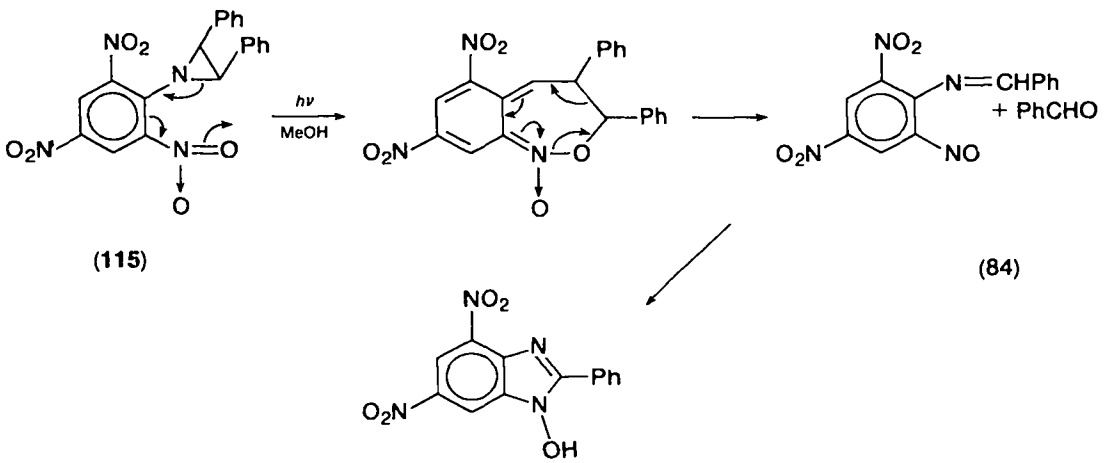
of aromatic nitro compounds (equation 39) where intermolecular electron transfer is involved[60]. Although no quantitative measurements have been made, the quantum efficiency of these photorearrangements appears to be better when more electron-withdrawing groups are attached to the aromatic ring. For example, photorearrangement of **113** to **114** is shown to occur primarily from the pyridine protonated species[132].



(83)

(113) **(114)**

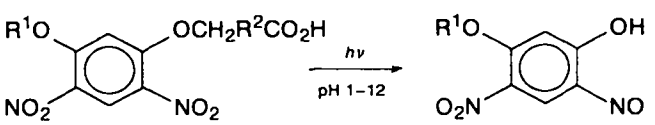
Since many polynitroaniline derivatives are used as drugs and herbicides and, also, shown to be photolabile, a better understanding of the mechanism of the above photorearrangement is greatly needed. The photochemistry of *cis*-1-(2,4,6-trinitrophenyl)-2,3-diphenylaziridine[133] **(115)** and a few *N*-alkylated 2,6-dinitroanilines[134–136] has been reported. While the photorearrangements of the latter herbicides give products predictable from the mechanisms discussed so far, that of the former has been explained by the mechanism[133] shown in equation (84).



(115) (84)

In connection with the decarboxylative photorearrangement of **107**, it is pertinent to mention that 4-nitrophenylvaline is shown to photolytically decompose to 4-nitroaniline and *i*-butylaldehyde[137] as in equation (85). The intermolecular redox process of equation (39) has been suggested to explain the product pattern[59].

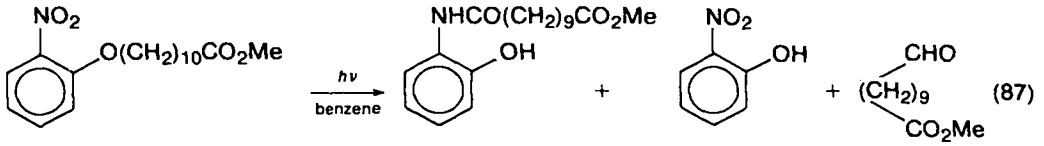
$$4\text{-}NO_2C_6H_4NHCH(i\text{-}Bu)CO_2H \xrightarrow{h\nu} 4\text{-}NO_2C_6H_4NH_2 + i\text{-}BuCHO + CO_2 \quad (85)$$



$$+ R^2CHO + CO_2 \quad (86)$$

(116)

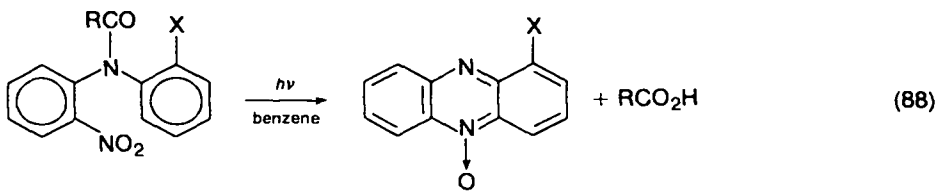
The photodecarboxylation of 5-alkoxy-2,4-dinitrophenoxyacetic acids (**116**)[138] is analogous to that shown in equation (81) although the mechanism may be quite different. The decarboxylation of the phenoxyacetic acid moiety occurs preferentially over the oxidation of 5-alkoxy moiety and the reaction is independent of acidity. Nevertheless, the 2-nitrophenyl ether of methyl undecanoate (**117**) in benzene is readily photorearranged to the products (equation 87)[139] reminiscent of those shown



(**117**)

in equation (81). The formation of 2-nitrophenol may not imply an intermolecular pathway, since an *o*-nitrosophenol can be photolytically oxidized by the parent nitro compound (see equation 93). It is also pertinent to question if the intramolecular redox mechanism is not partially responsible for the photolysis of 2-nitroanisole to 2-nitrophenol[11].

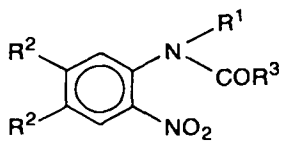
The photolysis of *N*-acyl-2-nitroanilines has been shown to release the acyl group as a carboxylic acid by intramolecular oxygen transfer with accompanying redox processes. Maki and coworkers[140] have demonstrated that the presence of an *N*-acyl group is mandatory for the photolytic rearrangement of 2-nitroanilides **118** to phenazine *N*-oxides **119**. The requirement for the X group is not critical for the



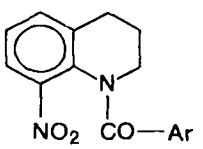
(**118**) (**119**)

R = Me, Ph; X = SMe, OMe, CO_2Me, Me, H

photorearrangement, but phenazine *N*-oxides **119** with X = H and Me are photosensitive and have not been isolated. Patchornik and coworkers[141,142] have irradiated 2-nitroanilides and 2-nitroveratramides **120** and *N*-acyl-8-nitrotetrahydroquinolines **121** to give excellent yields of the corresponding



(**120**)



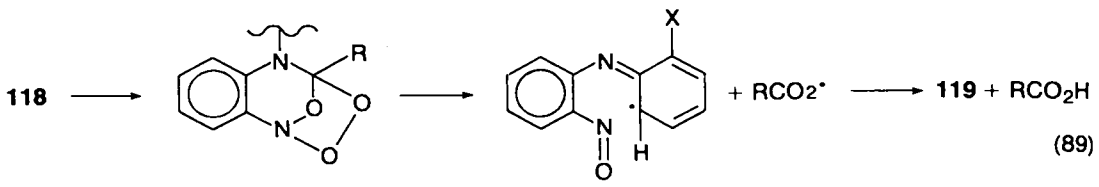
(**121**)

R^1 = alkyl, benzyl, phenyl
R^2 = H or OMe
R^3 = Me, Ph, 2-$C_{10}H_7$

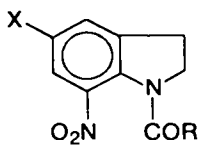
Ar = Ph, 3,4-$Cl_2C_6H_3$

carboxylic acids, R^3CO_2H and $ArCO_2H$, and claim that these amide moieties are excellent photosensitive protective groups for carboxylic acids. Though other

photoproducts have not been identified, it has been established that the secondary amide (**120**, R^1 = H) is stable to photolysis[141], that a nitro oxygen is transferred to the carboxylic acid by ^{18}O-labelling experiments[141], and that the carboxylic acid hydrogens can come from substrates **120** and **121** or from the solvent, whichever is the better hydrogen-donating source. Since the intramolecular hydrogen atom abstraction cannot operate in **118** and **121**, the reaction must be initiated by an intramolecular attack of the nitro group on the carbonyl group to give an intermediate[140] such as **122** as proposed in equation (89). While the ensuing steps are not clear, the acyloxy radical is proposed as an intermediate since a phenyl acylate has been isolated when the photorearrangement of **118** is run in benzene. It is extraordinary that the acyloxy radical can survive without decarboxylation in a wide variety of solvents to give the carboxylic acid in better than 80% yield.



(**122**)

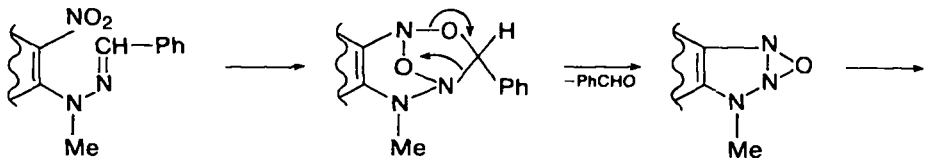


R = Ph, 4-$MeOC_6H_4$, 3,4-$Cl_2C_6H_3$, 2-$C_{10}H_7$, *n*-C_7H_{15} or 2-furyl
X = Br, NO_2

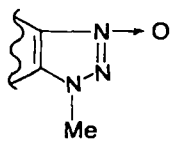
(**123**)

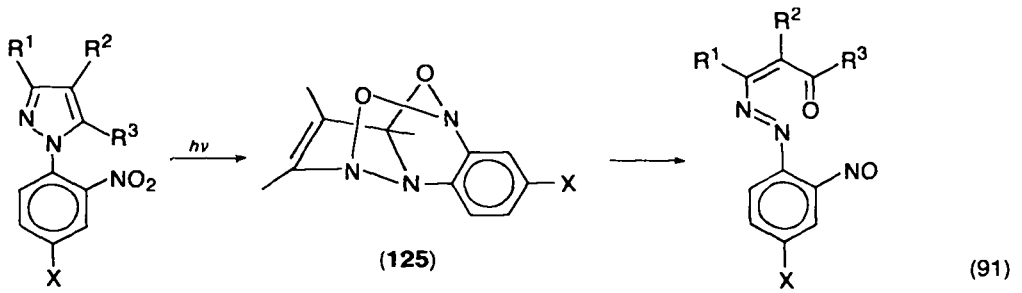
In contrast to the photoinitiated redox reactions observed above, 5-substituted 1-acyl-7-nitroindolines (**123**) are solvolysed by irradiation in the presence of water, alcohols, or ammonia, to give excellent yields of the corresponding carboxylic acids (RCO_2H) or their esters or amides and 5-substituted-7-nitroindolines[143]. The incorporation of solvents in the carboxylic acids (RCO_2H) and the isolation of 7-nitroindolines as the product leave no doubt that the photoreaction involves, not an intramolecular redox process, but a solvolysis. While the nitro group at the 7-position is a requirement, its reaction pattern, and therefore the mechanism, find no analogy in the photochemistry of other *o*-nitroaromatic compounds. The 3-nitrobenzamide derivative **123** (R = 3-$NO_2C_6H_4$) is photosolvolysed in the presence of water but photoreduced in alcohols; presumably photosubstitution may occur in the presence of ammonia.

Vicinal nitroarylidene hydrazone groups attached to a uracil aromatic or heteroaromatic nucleus are photolysed to give triazole *N*-oxides as the major product, and are explained by an intramolecular addition followed by rearrangement[144] as in equation (90). The extensive photorearrangement of *o*-nitrophenyl-substituted pyrazoles **124** has been interpreted as involving the 1,4-adduct **125**, or its equivalent, as the primary step followed by ring-opening, and reclosure to give benzotriazole 1-oxides[145] **127** as in equation (91). The intervention of a nitrosobenzene intermediate with an *ortho*-substituted π-bond system such as **126** is a plausible precursor to cyclization and has been proposed in many cases, e.g. equations (82), (84), (89), etc. in this section. Similar photorearrangements of



(90)

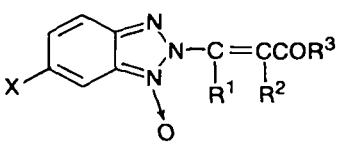




(124) (125) (126)

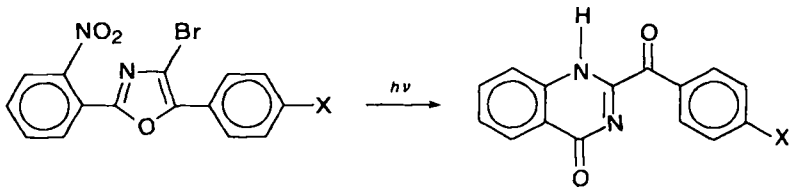
(91)

R^1, R^2, R^3 = H, Me, Ph, *t*-Bu, OMe or Br
X = H or NO_2



(127)

1-(2,4-dinitrophenyl)imidazoles with at least one phenyl substituent gives various benzimidazole derivatives and have been explained by similar mechanisms[145]. One can look forward to more interesting photorearrangements of 2-nitrophenyl-substituted heterocyclic compounds. An example shown in equation (92), though it may not properly belong here, may illustrate the point. The photorearrangement of oxazoles **128** to quinazolinones **129** involves the loss of the bromine at the 4-position and an oxygen atom: the bromine at the 4-position is



(92)

(128) (129)

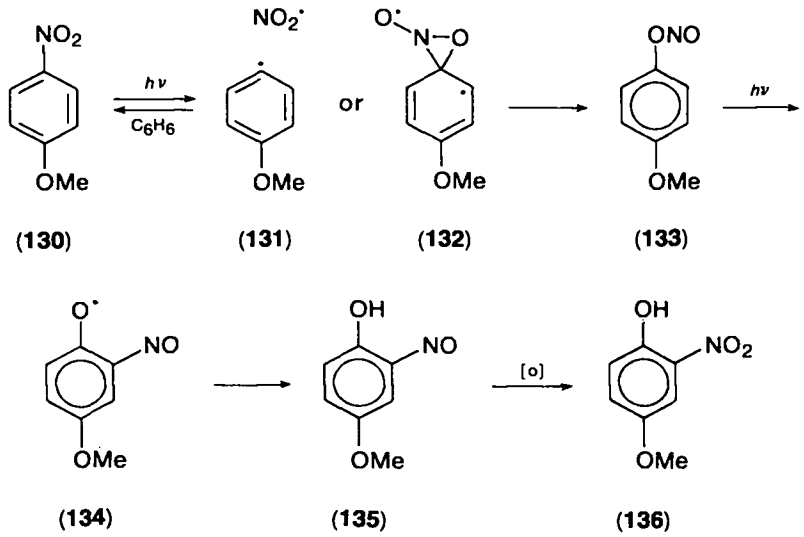
X = H or Br

required for the photoreaction to occur[146]. Mechanistically it is a challenging problem to ascertain whether the photorearrangement is initiated by the excitation of the nitro or the oxazole group.

In contrast to the facile and clean photodecomposition of the 2,4-dinitrophenyl derivatives of α-amino acids and glycolic acids as shown in equations (81), (82), (83) and (86) the photochemical behaviour of 2,4-dinitrophenylthioacetic acid and its α-alkyl analogues vary considerably depending on the α-substituent and conditions[147]. The complex reaction patterns are probably due to the ready oxidizability of the sulphide bond and other secondary photoprocesses. Nevertheless, the parent compound was photolysed to give 2,4-dinitrophenyl methyl sulphide in good yield. While 2-nitrodiphenyl sulphide is stable to irradiation, the corresponding sulphoxide and its 4′-substituted (Me, Cl or Ac) analogues are photolysed to give 2-nitrosodiphenyl sulphones[148].

2. *Nitro–nitrite rearrangement*

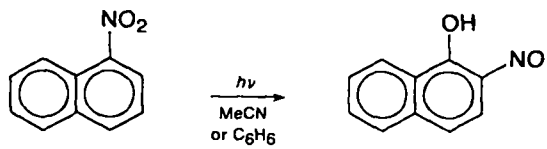
The photorearrangement of aromatic compounds involving an overall C—N bond cleavage and a C—O bond formation was observed in the photolysis of 9-nitroanthracene to anthraquinone monooxime, by, among others, Chapman and coworkers, who proposed the nitro–nitrite isomerization as the first step in the reaction[149]: the mechanism is shown in equation (93) using the photolysis of



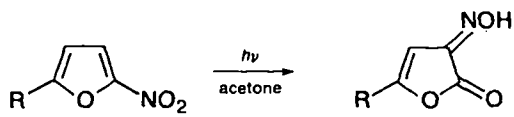
4-nitroanisole as a model[150]. This mechanism has been widely accepted and supported by evidence reported recently. The nitro group tumbling via diradical **132** was originally suggested by Chapman and coworkers[149] to accommodate the facile photolysis of compounds with noncoplanarity between the nitro and the aromatic moieties due to steric crowding. Alternatively, the radical pair **131**, from homolytic dissociation of an excited state of an aromatic nitro compound, has been proposed[151]. The intermediacy of such aryl radicals has been shown by the trapping of phenyl radicals in the photolysis of nitrobenzene. Though a nitrite such as **133** has never been identified directly, it is regarded as a logical intermediate and probably rearranges quickly to the nitrosophenol (e.g. **135**) via ionic and/or radical pathways under the photolysis conditions. The intermediacy of aryloxy radicals, such as **134**, is

confirmed by the presence of the respective ESR signals in the photolysis of 6-nitrobenz[*a*]pyrene, 9-nitroanthracene and 2,6-dimethylnitrobenzene[152]. Because of the high sensitivity of the ESR detection technique, the homolysis of nitrite **133** may not be necessary as a major pathway in the overall photorearrangement.

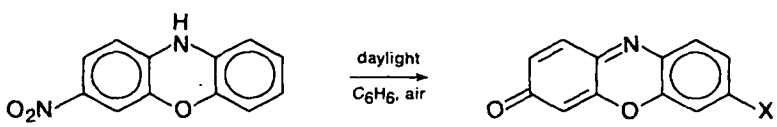
The final products in this photorearrangement vary considerably depending on structures and conditions. Nitroso compounds or their tautomers are obtained in certain cases[150,153] as in equations (94) and (95), but more often the nitroso compounds are susceptible to photooxidation to the corresponding nitro compounds by the parent nitro compounds (equation 93)[150] or by oxygen if not removed (equation 96)[151,154]. In equation (93), it has been established that the parent nitro compound **130** transfers an oxygen atom to the nitroso compound **135** under the photolysis conditions, and **130** is reduced to 2-nitrosoanisole in a corresponding amount[150]. The formation of phenols is generally assumed as a part of the aryloxy radical reaction[155]; indeed the presence of the 9-anthracenyloxy radical in the photolysis of 9-nitroanthracene[149] is indicated by the isolation of the coupling



(94)

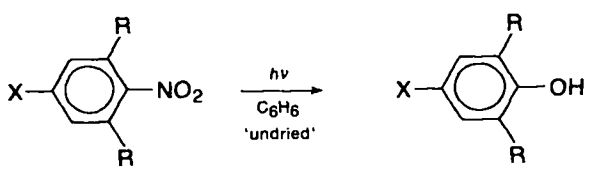


(95)



(96)

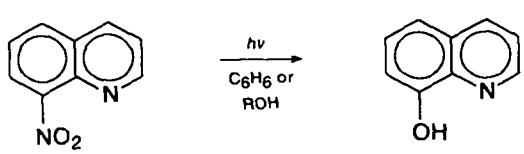
X = H or NO_2



(97)

(**137**) (**138**)

R = Cl, X = H; R = X = Me



(98)

(**139**) (**140**)

product, bianthrone. However, the observation that phenols are formed only in 'undried' benzene, and not in anhydrous benzene (equation 97)[50], suggests that the thermally or photolytically initiated hydrolysis of the corresponding nitrite may be the more probable pathway under the conditions.

Photorearrangement and the light-induced reduction and substitution constitutes the overall pattern of the photolysis of aromatic nitro compounds. Most of the photorearrangements have been suggested to occur from the lowest triplet excited state, and probably a $n \rightarrow \pi^*$ state, of the nitro group on the basis of sensitization (with, for example, benzophenone) or quenching by oxygen or nitric oxide. Within the limitation of the reliability of such photophysical processes, the intramolecular photoredox reaction in 2,4,6-trimethylnitrobenzene (**137**, deuterium exchange at the *o*-alkyl groups) has been suggested to occur from a singlet excited state[50] and the rearrangement of equation (96) from a triplet excited state[154]. By fluorescence quenching studies, photoexcitation of some aromatic nitro compounds is shown to undergo predissociation to aryl and NO_2 radicals, e.g., **131**, which may recombine to the parent nitro compounds (**130**) in a tight radical pair or to the nitrites (**133**) in a loose radical pair[151]. This could also account for the low quantum yields of the photorearrangement.

There is some evidence that the nitro–nitrite photorearrangement is less efficient than intra- and inter-molecular photoreduction and photosubstitution. As such, the rearrangement tends to be the sole or major process observed in poor hydrogen-donating and nucleophilic solvents, e.g., benzene, acetone, acetonitrile, etc. In 0.1N sodium hydroxide solution, 4-nitroanisole (**130**) is photolysed to give 4-methoxyphenol as the major product which is interpreted as substitution on the basis of the dependency of the quantum yields on hydroxide concentration ($\phi = 0.085$ at 0.6M sodium hydroxide)[63]. The quantum yield of the photorearrangement of **130** in benzene (equation 93) is about an order of magnitude lower[150]. However, 8-hydroxyquinoline is assumed to be formed from 8-nitroquinoline (equation 98) by the rearrangement pathway regardless of the photolysis in benzene or in aqueous alcohol[155]: this assumption may be justified since the quantum efficiency of the formation ($\phi \simeq 1 \times 10^{-3}$) does not change significantly up to 1M sodium hydroxide.

The originally suggested steric requirement in the nitro–nitrite photorearrangement[149] does not appear to be critical. Undoubtedly, steric crowding around a nitro group accelerates the departure and/or facilitates the oxaziridine ring-closure and thus, would contribute to the efficiency of the photorearrangement in competition with other processes. Evidence for such acceleration can be seen in the photolysis of the hindered nitro compound **137** in *i*-propanol[50] and **15** (equation 34) in alkylamines[52]; in both cases, minor amounts of the photorearrangement products are also obtained along with the major reduction products. The examples of photorearrangement as in equations (93)–(98) suggest that electronic effects must also operate in some way, though they have not been considered. It is worth noting that in contrast to the efficient photosubstitution of 3-nitroanisole in aqueous sodium hydroxide[156], the same compound is extremely stable to irradiation in benzene[150]; this behaviour is very different from that of **130**. Such considerations leave no doubt that much structure–reactivity research is needed in this area.

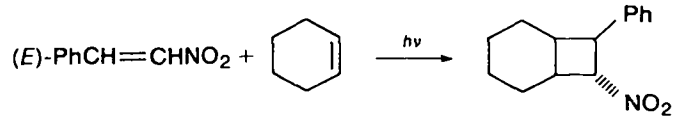
III. PHOTOCHEMISTRY OF α,β-UNSATURATED NITRO COMPOUNDS

Since the early 1960s, the photochemistry of nitroalkenes has attracted considerable attention; some of these reports are summarized in an earlier review[3]. From the accepted mechanistic interpretations, the photoreactions may be divided into three

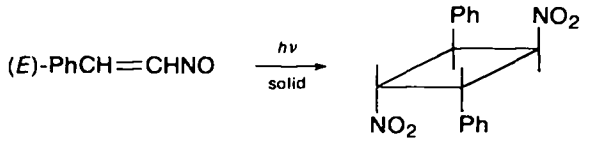
categories, namely, (1) the reaction involving only the π-bond, (2) reactions via the nitro–nitrite rearrangement, and (3) reactions via intramolecular addition.

A. Photoreaction of the Olefinic Bond

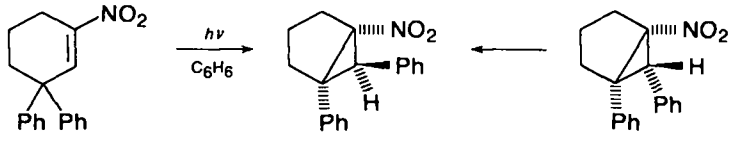
This first category includes a wide variety of typical phototransformations of the olefinic bond, e.g. *cis–trans* isomerization, cycloaddition[5] (equation 99) and cyclodimerization[157] (equation 100), skeletal rearrangement[158] (equation 101) and deconjugation to a β,γ-unsaturated nitro compound[159] (equation 102).



(99)

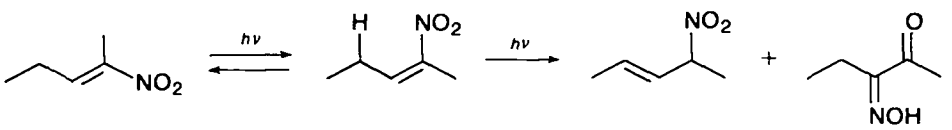


(100)



(101)

(141) (142) (143)



(102)

(144) (145) (146) (147)

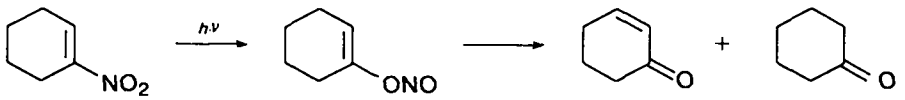
major

Although a systematic investigation of the *cis–trans* isomerization is still lacking, in some cases[160–163] such isomerizations are experimentally demonstrated in connection with the geometric requirements for photorearrangements of nitroalkenes. Regardless of overall reaction patterns, the ubiquitous occurrence of the *cis–trans* isomerization must be expected in all photolyses of acyclic nitroalkenes. Sensitized isomerizations indicate that high-energy sensitizers, e.g., acetophenone, favour the *trans*-nitroalkene formation[162]. The cycloaddition of nitroalkenes is a part of the general [2 + 2]cycloaddition of substituted olefins and is more aptly discussed in the photochemistry of alkenes elsewhere[164]. The photocyclodimerization of a heterocyclic nitroalkene in various states has been described recently[165].

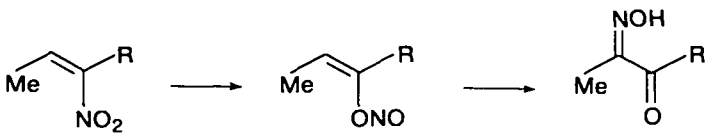
Nitroalkene **141** photolytically rearranges from its triplet $n \rightarrow \pi^*$ excited state to bicyclo nitro compounds **142**, either by direct photolysis or with a triplet sensitizer, in low quantum yields ($3 \sim 4.5 \times 10^{-4}$). A mechanism similar to that of the $n \rightarrow \pi^*$ triplet photorearrangement of 4,4-diphenylcyclohexenones is proposed to account for the analogous reaction pattern. The minor product, 3,3-diphenylcyclohexanone, is

assumed to arise from the nitro–nitrite rearrangement pathway (see equation 105). In *i*-propanol, **141** is mainly photoreduced to 3,3-diphenylcyclohexanone oxime.

In contrast, the photoinduced deconjugation of α,β-unsaturated nitro compounds has been demonstrated to involve an intramolecular hydrogen abstraction from the γ-position as the primary chemical process. This step is indicated by kinetic evidence that the *trans*-nitroalkene **144** rearranges to the β,γ-nitroalkene **146** via the intermediate *cis*-**145** where an intramolecular hydrogen abstraction can occur readily[162]. In other words, if such a hydrogen abstraction cannot occur for stereochemical reasons, as in 1-nitrocyclohexene (equation 103) and



(103)



(104)

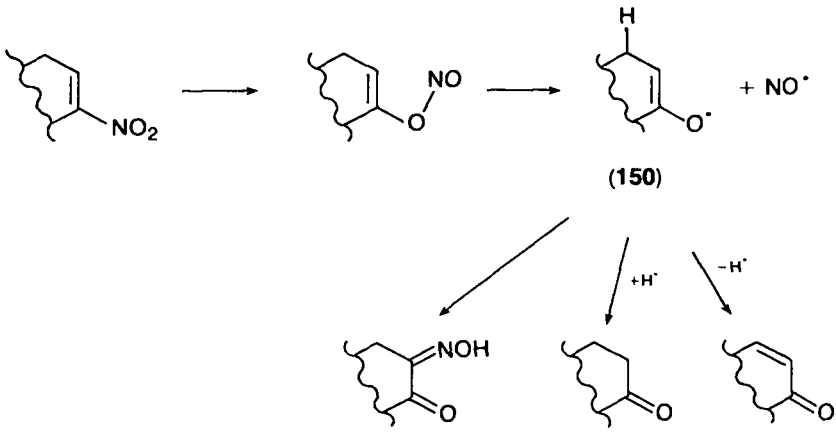
(148) **(149)**

R = Me, Et

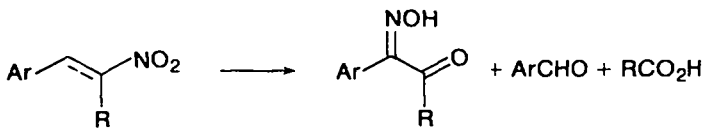
3-nitrocholest-2-ene (cf. equation 111), or is difficult to occur for energy reasons, as in nitroalkene **148**, an alternative pathway, e.g. nitro–nitrite rearrangement, dominates the reactions[159] (see Section II.D.2). On the other hand, *cis*-2-nitro-2-pentene (**145**), *cis*-1-nitrododecene[159], cyclohexylidenenitromethane[162] and the 6-nitro-cholest-5-enyl derivative (equation 112)[166–168] have the configurations suitable for such a hydrogen abstraction with low activation energy barriers; deconjugation operates extensively in competition with other photoprocesses. The mechanism of the deconjugation is, therefore, similar to that of the 2-alkylnitrobenzenes shown (**46** → **47** → **48**) in equation (50), except that a β,γ-unsaturated nitroalkene does not readily rearrange back to the α,β-isomer[162].

B. Nitro–Nitrite Rearrangement

The nitro–nitrite rearrangement (equation 93) is generally regarded as the primary chemical act in the photolysis of nitroalkenes such as **144** and **148** to α-oximinoketones **147** and **149**, respectively, and **141** and 1-nitrocyclohexene (equation 103) to the corresponding simple carbonyl compounds[158,159]. The overall reaction pattern is shown in equation (105). The enoloxy radical (**150**) may lose a γ-hydrogen to become the enone or gain a hydrogen intermolecularly to give the ketone. When such intra- and inter-molecular processes are inaccessible or demand a high energy barrier (e.g. hydrogen abstraction from solvents is retarded by steric crowding or by a poor hydrogen-donating ability), the formation of an α-oximinoketone appears to dominate the reaction. This supposition is derived, in part, from the excellent yields of α-oximinoketones obtained in the photorearrangements of 2-nitro-1-aryl-propenes or -butenes (**151**)[168–171]; the corresponding enoloxy radicals are relatively crowded and possess no γ-hydrogen. The photorearrangement of β-nitro-β-bromostyrene (**151**, R = Br) in ethanol to pyruvate ketoxime **152** (R = OEt) is an interesting variation. The presence of an



(105)



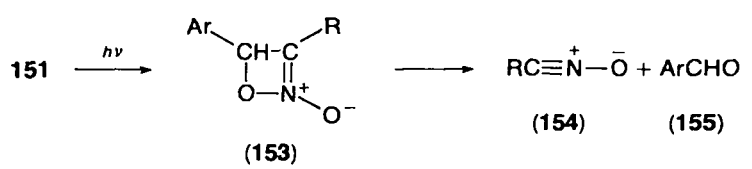
(106)

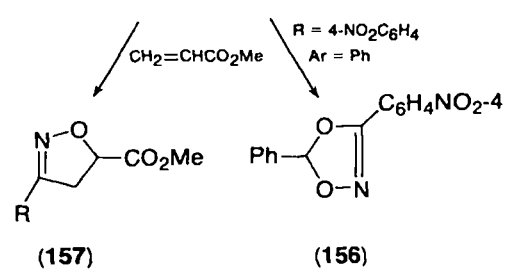
(151) (152)

major product

Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-pyridyl, 3-pyridyl
R = Me, Et, 4-$NO_2C_6H_4$

alkyl or aryl group at the carbon α to the nitro group (R in **151** and **148**, and others) appears to be a mandatory requirement for this rearrangement to occur[168]; this group may provide some steric acceleration. However, nitroalkenes **151** do not follow the nitro–nitrite photorearrangement pathway exclusively, but also undergo a cleavage reaction to yield ArCHO and RCO_2H, the extent of which is particularly considerable if the Ar group has an electron-withdrawing group[169] or if α-nitrostilbenes are involved[171] (see equation 107).





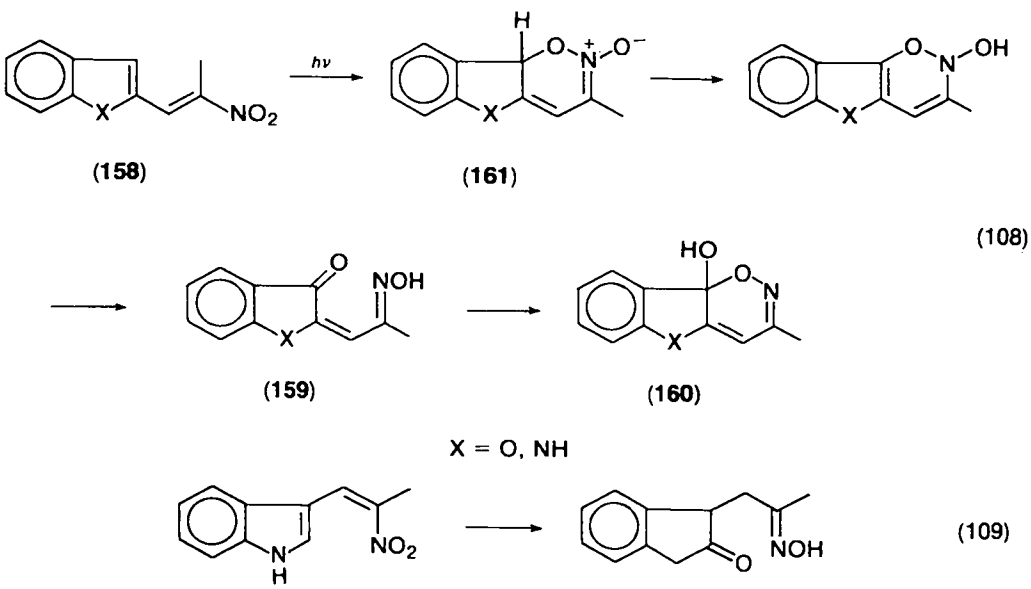
(107)

C. Intramolecular Photoaddition

Photoinitiated intramolecular addition of the nitro group in α-nitro-alkenes and -alkadienes is readily conceivable by analogy to that proposed in the photorearrangement of 2-nitrostyrene derivatives in equation (73). Although, differences in overall product patterns suggest that, after the addition, the two pathways are quite dissimilar due to structural features, they share a common feature in that the olefinic bonds are oxidized by an excited-state nitro group by oxygen transfer, i.e. in an intramolecular redox reaction.

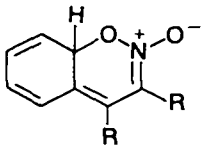
To explain the formation of dioxazole **156** in the photolysis of **151** (equation 107) and the cleavage products, benzaldehyde and 4-nitrobenzoic acid (ArCHO and RCO_2H in equation 106), Pinhey and Rizzardo[171] have proposed an *N*-oxide intermediate **153** (R = 4-$NO_2C_6H_4$, Ar = Ph) and its cleavage products, nitrile oxide (**154**) and benzaldehyde (**155**); a 1,3-dipolar addition between **154** and **155** to yield **156** has precedence and 4-nitrobenzoic acid may be considered as a hydrolysis product of **154** or photolysis product of **156**. Matsuura and coworkers[169] have provided a further proof by trapping acetonitrile oxide, formed in the photolysis of **151** (R = Me, Ar = 4-$NO_2C_6H_4$) in acetonitrile, with methyl acrylate to give isoxazole **157**. In these photolyses (equation 106), α-oximinoketones **152** are always the major products and aldehydes **155** are produced in considerable yields (~15%) when Ar carries an electron-withdrawing group such as chloro or nitro[169].

The photolysis of benzofurans and indoles containing a nitroalkene side-chain (**158**)[172] yields oxazines **160** via the intermediacy of oximes **159** (equation 108). The photorearrangement of the indolylnitroalkene to the known oxindole (equation 109)



(158) (161) (159) (160) (108) (109)

is also explained by the oxygen-transfer pathway[172] similar to that shown in equation (108). Obviously, a *cis–s–cis* geometry is required for the rearrangement to occur; such a geometry is not readily fulfilled in an acyclic α-nitroalkadiene. For example, 4-nitro-1-phenylpenta-1,3-diene dimerized readily even in photolysis of a dilute solution[172]. The *N*-oxide intermediate **161** assumed in equation (108) is analogous to the intermediate **162** identified by flash photolysis in the photochromism of certain *cis*-nitrostyrene derivatives[160,161].



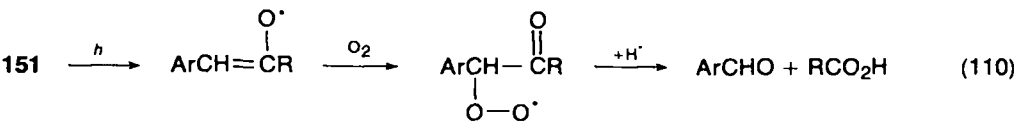
$\Delta E^* = 11–16$ kcal/mol
$\tau_{1/2} = 0.03–5$ ms at 15°C
$\lambda_{max} = 410–450$ nm

(162)

D. Interfaces of the Reaction Pathways

The photorearrangement of α-nitroalkenes can follow all or part of the various pathways described above; the product patterns are therefore controlled by the energy barriers of the competing pathways. Undoubtedly, the nitroalkene structure and the conditions of photolysis greatly influence the overall reaction patterns; most of them are complex – the photolysis of nitroalkenes **151** shown in equations (106) and (107) is a case in point. Even those reported to afford one major product clearly lack precise analysis to indicate that other products are not formed. Owing to the mixed reaction pathways and the ubiquitous presence of the *cis–trans* isomerization, mechanistic and kinetic studies of nitroalkene photorearrangements are relatively few and the interfaces of various pathways remain a qualitative guess.

In the photoreaction of **151**, the formation of ArCHO (**155**) via **153** (equation 107) can be sensitized by triphenylene and quenched by 1,3-pentadiene, but the formation of α-oximinoketone is not affected by either one. It has been concluded that the former photoprocess (**151** → **153**) is derived from the lowest triplet state and that of the latter nitro–nitrite rearrangement (equation 105) from a singlet or higher triplet state[169]. Oxygen obviously does not quench the photorearrangement of **151** → **153** since isoxazole **157** can be obtained in the presence of air. However, oxygen completely interrupts the formation of α-oximinoketones **152**, presumably by trapping the corresponding enoloxy radical, followed by the transformations shown in equation (110), to give ArCHO and RCO_2H in excellent yields. Thus, by

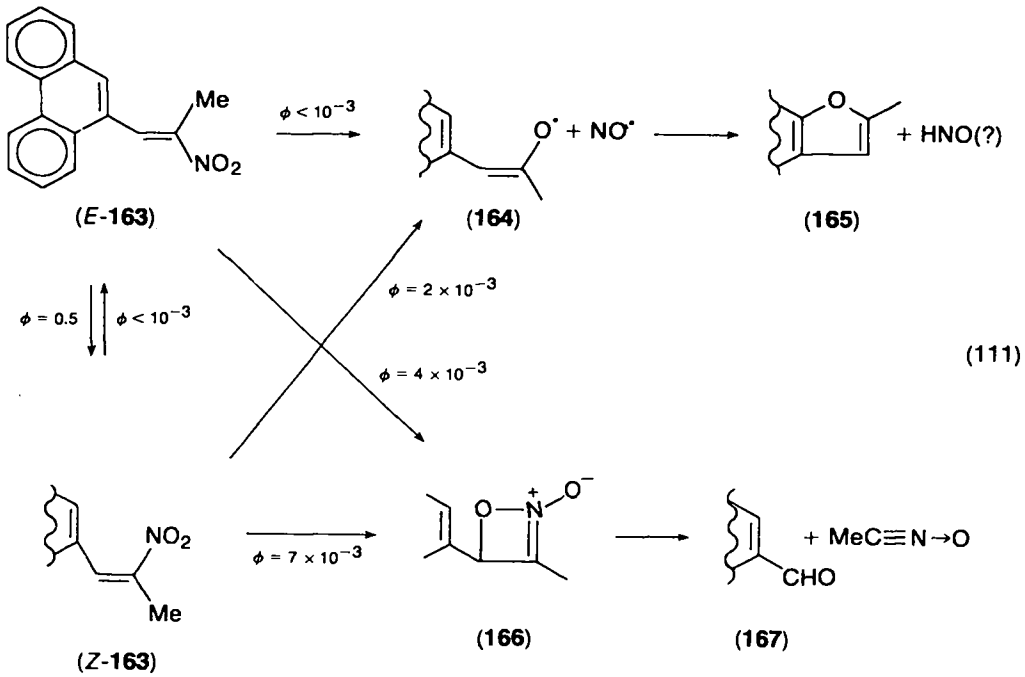


(110)

fortuitous coincidence, the photolysis under oxygen cleanly converts **151** to ArCHO and RCO_2H.

The photodecomposition pattern of *trans*-nitroalkene **163** is summarized in equation (111) with the quantum yields indicated[163]. From the heavy-atom effect of bromohexane and sensitization by camphoroquinone, it is concluded that the lowest triplet excited state of **163** decays to yield aldehyde **167**, but furan **165** is a singlet-state-derived product; this is in agreement with the conclusion reached in the photolysis of **151**. The cyclization of enoloxy radical **164** is a new pathway but not totally unexpected; the low quantum yields may arise from a low probability of the particular geometry required for the cyclization. By flash excitation, a transient can be obtained from *Z*-**163** but not from *E*-**163**, and has been assigned a structure similar to **162** on the basis of its physical properties (λ_{max} 405 nm, $\tau_{1/2}$ 6.1 s at 30°C in ethanol). The fate of this transient remains to be clarified.

The earlier controversy over the photorearrangement of 6-nitrocholest-5-ene derivatives[167,168] has been unravelled in a definitive report[169] which illustrates the sensitivity of the rearrangement pattern due to changes in reaction conditions. The rigid skeleton of **168** eliminates uncertainty arising from the *cis–trans* isomerization

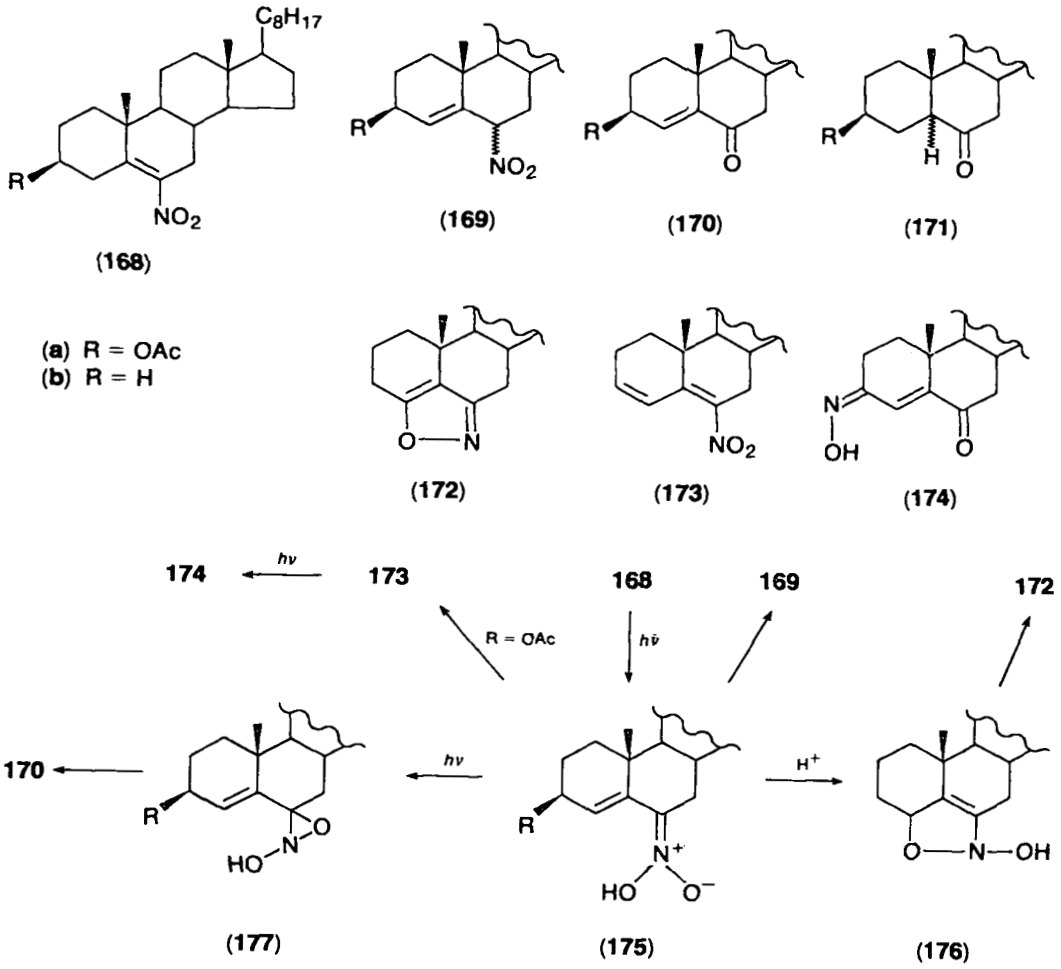


and also facilitates mechanistic interpretations with the benefit of stereochemical controls. Notwithstanding these advantages, the product patterns of the photorearrangement of **168b** shown in Table 1[169] provide a glimpse of the complexity of the reaction depending on conditions. The major products are either **169b** or isoxazole **172b**, both of which are thought to arise from intramolecular hydrogen abstraction. Since the photolysis of **168b** in *i*-propanol gives nearly the same product patterns as that in *t*-butanol, intermolecular redox processes are not operating significantly.

The key intermediate in the photolysis of **168** is the *aci*-nitro form **175** derived from intramolecular hydrogen abstraction as shown in equation (112) (for comparison, see **47** in equation 50). The *aci*-nitro form **175** is the precursor to **169** as indicated by its deuterium incorporation when photolysed in *t*-BuOD. The formation of isoxazole **172** may follow one of the oxygen-transfer mechanisms frequently proposed in the intramolecular oxidation of *ortho*-substituted nitrobenzenes, e.g. equations (50), (69), etc. However, in the latter photolyses, isoxazole formations are

TABLE 1. The product patterns of the photorearrangement of 6-nitro-cholest-5-ene **168b**

	Products (%)				
Conditions	**169b**	**172b**	**170b**	**171b**	Others
Hexane, reflux	55	0	8	0	—
t-BuOH, reflux	30	16	15	6.5	—
AcOH, r.t.	45	10	5	0	5
AcOH, reflux	0	38	2.8	10.5	2
Dioxane–D_2O	0	0	22	0	—

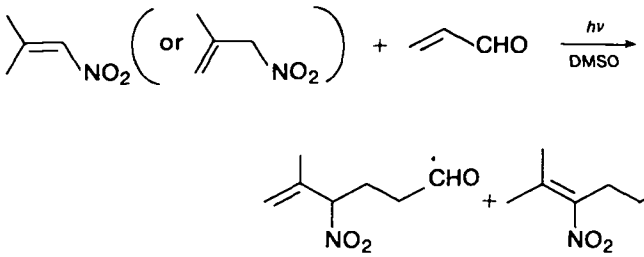


(112)

rarely observed except for that shown in equation (56). The pathway **175** → **176** → **172** is an economical representation of a number of alternative mechanisms for the formation of **172**. Obviously, the partition of the ground-state decay of **175** to **169** and **172** favours the latter in acidic conditions. While the mechanism outlined in equation (105) can adequately explain the formation of ketone **171** and enone **170**, the latter may be formed from the photolysis of **175** via assumed intermediate **177**, in analogy to the photolysis of *aci*-4-*t*-butyl-1-nitrocyclohexane[173].

The presence of the 3-acetoxy group in **168a** alters the photolysis pathway drastically in polar protic solvents, such as ethanol or dioxane–water, to give not **169a** but nitrodiene **173a** (13%) and oxime **174a** (49%); the former can be derived from deacetoxylation of **175a** and is shown to be photolytically converted to **174a** by the nitro–nitrite rearrangement[168]. This pathway appears to prevail if the R group in **168** is a good leaving group[167] such as CF_3CO_2 or Cl. However, photolysis of **168a** in a nonpolar solvent gives the deconjugated nitro compound **169a** as the major product with minor amounts of others.

The photoinduced Michael-type addition of α,β- and the corresponding β,γ-unsaturated nitroalkenes to α,β-unsaturated aldehydes is a potentially useful synthetic method in certain cases where other photorearrangements do not interfere seriously[162]; such an example is shown in equation (113). As the reaction also occurs



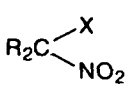
(113)

major product minor product

thermally, it may be interpreted as the addition of the common *aci*-nitro form, generated by irradiation, to acrolein in analogy to an enol reaction. It has also been demonstrated that a conjugated nitroalkene is photolytically transformed to the unconjugated nitroalkene which undergoes photoaddition to give the unconjugated product as the major product. Therefore, the efficiency of the *cis–trans* isomerization and deconjugation greatly affects that of the photoaddition of α,β-unsaturated nitroalkenes.

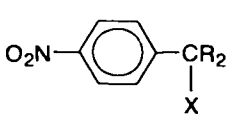
IV. PHOTOCHEMISTRY OF ALIPHATIC NITRO COMPOUNDS

Although the photolability of nitroalkanes has been recognized for a long period, investigations of the photoreactions in gas, liquid and solid phases combined together are not as extensive as those of aromatic nitro compounds. Photolyses of simple nitroalkanes have been primarily studies in the gas phase and are characterized by complex product patterns; the published data up to 1973 have been reviewed[4]. One of the remarkable developments in this field is the nucleophilic substitution at the α-carbon of the tertiary nitroalkenes **178** and 4-nitrobenzyl derivatives **179** by a radical chain mechanism, the so-called $S_{RN}1$ reaction[174,175]. These reactions are tremendously accelerated by light which is assumed to initiate the radical process by promoting an electron transfer, although the precise photophysical phenomena have



(178)

X = Cl, Br, NO_2, CN, CO_2-alkyl, COAr or SO_2-alkyl



(179)

R = Me or H; X = NO_2 or Cl

not been clarified, nor explained. The details of this reaction will be covered by Professor N. Kornblum in a separate chapter. Photochemistry of nitroalkanes often involves the corresponding nitrite, nitrosoalkane and/or, even, nitrate as intermediates. Thus, a part of this section may inadvertently deal with the photochemistry of these intermediates as secondary photoreactions.

A. Simple Nitroalkanes

The primary photochemical act of simple nitroalkanes by either continuous or flash photolysis has been generally accepted to be the homolysis of the C—N bond as in equation (114), although, in addition, a molecular elimination mechanism, such as equations (116) and (117), has also been suggested to occur[4]. The alkyl and $^{\bullet}NO_2$

$$R{-}NO_2 \xrightarrow{h\nu} R^{\bullet} + {}^{\bullet}NO_2 \qquad (114)$$

$$R^{\bullet} + {}^{\bullet}NO_2 \longrightarrow R{-}ONO \xrightarrow{h\nu} RO^{\bullet} + {}^{\bullet}NO \qquad (115)$$

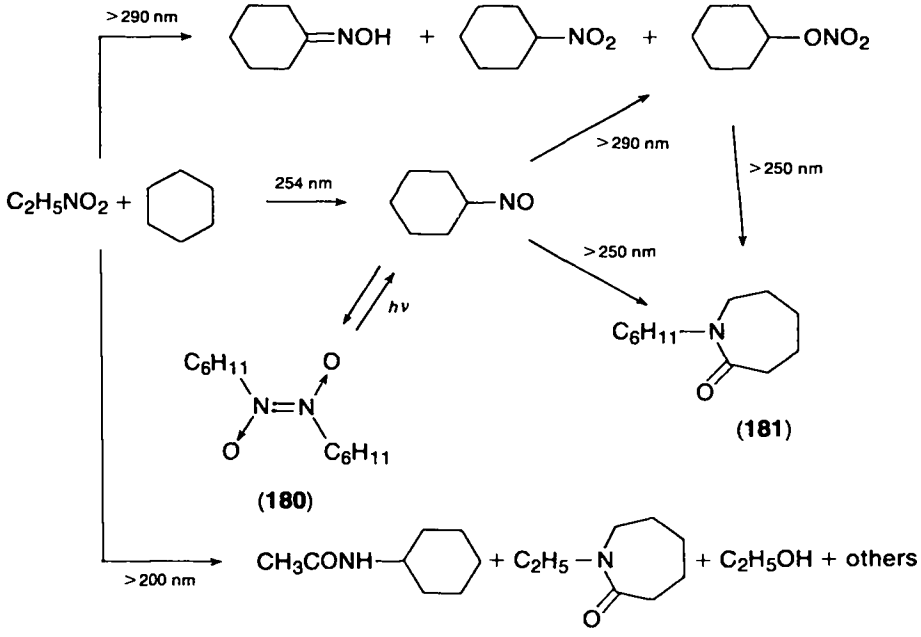
$$CH_3NO_2 \longrightarrow CH_2O + HNO \qquad (116)$$

$$CH_3CH(R)NO_2 \longrightarrow CH_2{=}CHR + HNO_2 \qquad (117)$$

radicals have been confirmed by ESR evidence in low-temperature irradiation[176] and shown to rapidly combine to give the corresponding alkyl nitrites if excess residual energy from the photoexcitation can be dissipated, e.g. in liquid or solid phase at a low temperature. However, in the gas phase at low pressure or in the liquid phase at higher temperatures, the alkyl nitrites are assumed to dissociate rapidly into alkoxy and nitric oxide radicals. Generally, the product patterns are complex due to ensueing reactions of the radicals and/or secondary photolysis of intermediates. In vacuum ultraviolet photolysis of 2-methyl-2-nitropropane (excitation at 147 and 123.6 nm) not only the rearranged nitrite dissociates extensively, but a number of secondary reactions arising from vibrationally excited species also occur vigorously to give a plethora of products[177]. Obviously, nitroalkane photochemistry considerably overlaps with the photochemistry of the corresponding alkyl nitrites.

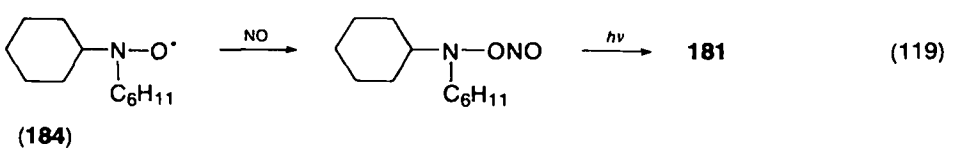
Recently, confirmation of the primary photochemical process as in equation (114) has been provided by other physical methods. Laser-induced photodissociation of nitromethane and 2-nitropropane has been shown to afford the vibrationally excited $NO_2^{\bullet}$ radical[178]. The results are interpreted in terms of migration of the localized energy at the NO_2 chromophore to the $R{-}NO_2$ bond within a singlet excited state manifold leading to an indirect predissociation (cf. Reference 151). By optoacoustic spectroscopy, continuous irradiation of nitromethane generates the signals $NO_2^{\bullet}$ at ~586 and 590 nm and also of nitromethane[179]. It is significant that methyl nitrite is not detected, hinting that this species may have only fleeting existence owing to excess vibrational energy.

In terms of preparative applications, the photochemistry of nitroalkanes had been scarcely investigated until the appearance of recent reports on the subject[180,181]. Remarkable wavelength dependence of the product patterns of the photolysis of nitroethane in cyclohexane under nitrogen, as an example, is shown in equation (118). Other nitroalkanes, such as nitrocyclohexane, 2-nitropentane, etc., also gave comparable results. The interesting features of this photolysis are the exclusive formation of nitrosocyclohexane with 254 nm light; this is most readily explained by the nitro–nitrite photorearrangement (equations 114 and 115) followed by the

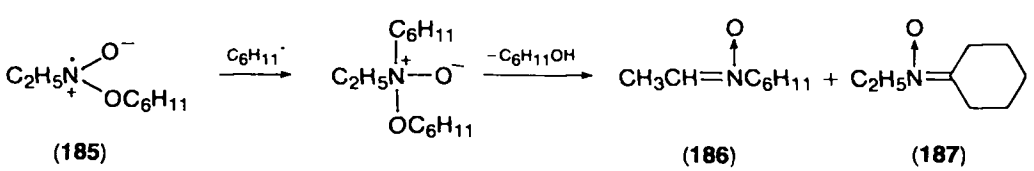


(118)

alkoxy radical mediated intermolecular hydrogen–nitroso group exchange reaction[181] (see Section VI.A.1). Secondly, facile photorearrangement of nitrosocyclohexane and cyclohexyl nitrate to caprolactam **181** occurs by irradiation with >250 nm light. Precise mechanisms for the formation of this as well as amides **182** and **183** are probably quite intricate but relatively stable nitroxide radicals, such as **184** and **185**, may be suggested as the intermediates which may undergo further transformation by, for example, processes such as equations (119) and (120) to give the final productions. Both the presence of radicals[30] such as **185** and the photorearrangement of nitrons[128] **186** and **187** to the respective amides **182** and **183** have ample precendents. Lastly, it is noteworthy that the product pattern is entirely different in irradiation with >200 nm light (quartz apparatus, and a medium pressure lamp)[180]; in addition to amide **182**, caprolactam **183** and ethanol, solvent oxidation products, e.g., cyclohexanone and cyclohexanol are obtained and may be accounted for as the by-products in the formation of **182** and **183** as in equation (120). The solvent oxidation with the complex pattern shown in equation (118) is



(184) (119)

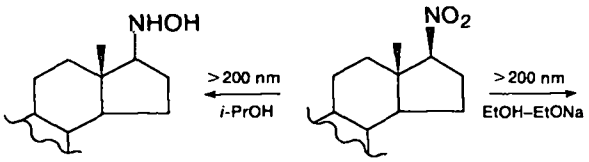


(185) (186) (187)

(120)

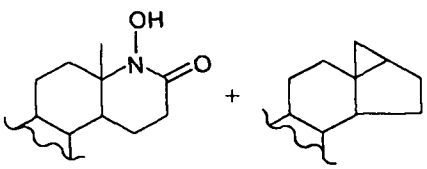
reminiscent of the photolysis of nitrosamides[182,183] and nitrites[184] published previously and may arise from the interactions of nitrogen oxides and alkyl radicals generated during primary and secondary photoprocesses.

The physical and chemical evidence encountered so far produces one noteworthy feature, that is, excited-state nitroalkanes generated either in gas or solid phases or in solution decay primarily by C—N bond fission and scarcely abstract a hydrogen intermolecularly from donors, as shown in these reactions. Further, intramolecular hydrogen abstraction similar to that of alkoxy radicals (see Section VI.A.5) is not observed in the photolysis of 2-nitropentane and 2-nitrooctane[180]. The excited-state reactivities of nitroalkanes exhibit remarkable contrast to those of aromatic nitro compounds. Such reactivity differences may have their origin in the nature and electronic configuration of the excited states of aromatic and aliphatic nitro compounds. However, recently, hydroxylamine **189** has been obtained in the photolysis of 3β-acetoxy-17β-nitro-5α-androstane (**188**) in *i*-propanol[185], in a process which is similar to the photoreduction of aromatic nitro groups by intermolecular hydrogen transfer (see Section II.A.1). Whereas irradiation of the *aci*-nitronate of **188** in ethanol/NaOEt gives quite different types of products, such as **190** and **191**, in ethanol alone the photolysis gives neither of these compounds[185].



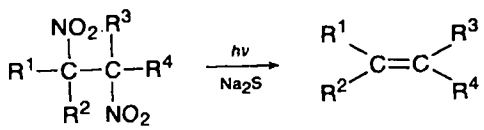
(**189**) (**188**)

(121)



(**190**) (**191**)

While photolyses of nitroalkanes in general are unpredictable, *vic*-dinitro compounds **192** are smoothly eliminated to tetrasubstituted olefins **193** in excellent



(122)

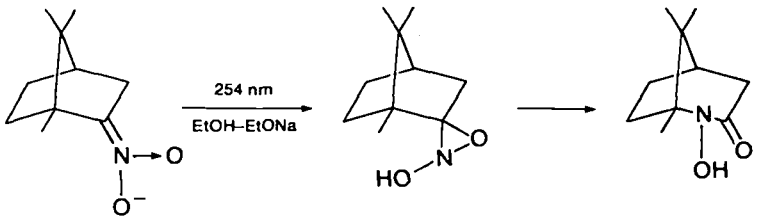
(**192**) (**193**)

R^1, R^2, R^3 and R^4 = alkyl, cycloalkyl or phenyl

yields by photolysis in the presence of sodium sulphide[186,187] (equation 122). Clearly the photoreaction is a radical chain process but a satisfactory pathway is yet to be defined.

B. *aci*-Nitronates

The anions of *aci*-nitro compounds exhibit UV maxima at about 240 nm and, when irradiated with >200 nm light or 254 nm light (low-pressure Hg resonance lamp) in ethanol, they rearrange to hydroxamic acids, such as **190** in equation (121)[185] and **196** in equation (123)[188], for which the *N*-hydroxyoxaziridine **195** or its



(123)

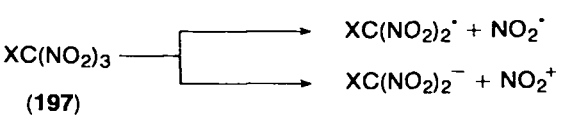
(194) **(195)** **(196)**

anion have been proposed as the intermediates. A wide variety of simple nitronates has been claimed to rearrange from their singlet excited states on the basis of the lack of oxygen quenching and by a sensitization pattern[188]. The regiospecificity of the rearrangement of **195** and equivalents to hydroxamic acids is no doubt related to the migratory aptitude of α-alkyl groups. This rearrangement may share a common pathway with the nitrite rearrangement in equation (105).

It is interesting that while the *aci*-nitronates of arylnitromethanes are photorearranged to the corresponding hydroxamic acids with 254 nm light, they are converted to benzaldehydes by irradiation with >200 nm light[188]. Whether a different pathway has superseded under the latter conditions is not clear. It has been shown that the pK_a of this *aci*-nitronate is decreased and its quantum yield increased significantly on addition of a cationic surfactant, hexadecyltrimethylammonium bromide, in a concentration higher than a certain critical value[189]. These phenomena have been interpreted as the stabilization of the *aci*-nitronate form with concomitant facilitation of the photodecomposition to benzaldehydes. Photolysis of the stable *aci*-nitro form of 4-*t*-butylnitrocyclohexane in benzene, on the other hand, gives the parent nitroalkane, and the corresponding ketone and oxime without the formation of the hydroxamic acid[173].

C. Geminally Substituted Nitroalkanes

Tetranitromethane photolysis has been shown to induce homolysis of a C—N bond[176] on the basis of the ESR signal of $NO_2^{\cdot}$ observed in the matrix at −77°C.



(124)

(197)

X = NO_2, Cl, F, Br

Pulsed photolysis of tetranitromethane in aqueous alcoholic solvents generates trinitromethyl anion (λ_{max} 350 nm) which accumulates by a rapid first-order reaction as well as by a slow complex reaction, without being affected by the presence of oxygen; the anion is not formed in aprotic solvents such as acetone, octane, carbon tetrachloride and acetonitrile[190]. These observations have led to the proposal of the photoinduced heterolysis of the C—N bond, the quantum yields of which are

determined to be 0.5 in methanol and 0.35 in ethanol[191]. However, the pulsed photolysis of trinitrohalomethanes **197** at low temperatures gives rise to the ESR signal of $XC(NO_2)_2^{\bullet}$ radicals by a first-order reaction[192].

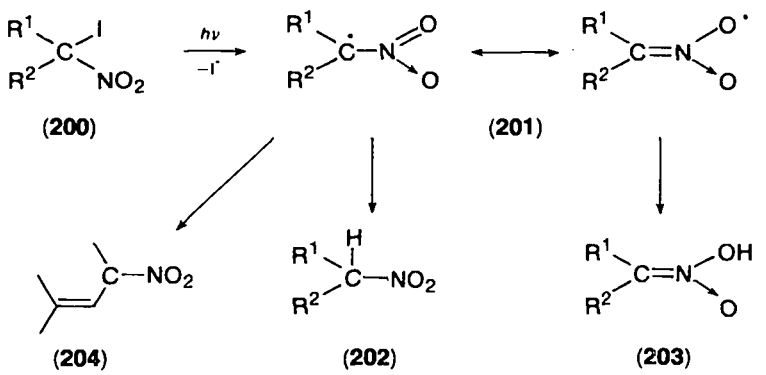
The generation of the $XC(NO_2)_2^{\bullet}$ radicals by the photolysis of **197** and, also, those of the $R^1R^2R^3C^{\bullet}$ radicals from **198** are well supported by radical trapping with phenyl-*t*-butylnitrone in which the corresponding nitroxides are observed[193,194]. In these experiments, benzoyl-*t*-butyl nitroxide, arising from the trapping of $NO_2^{\bullet}$, was also obtained. However, in contrast to the exclusive C—N bond scission in **197** and **198**, iodonitro compounds **199** photodissociate by C—I bond scission because of the

$R^1R^2R^3CNO_2$ (**198**) R^1, R^2, R^3 = Me and/or NO_2

$XC(NO_2)_2I$ (**199**) X = NO_2 or F

weaker C—I bond[194]. Such selectivity of homolytic scission in α-halonitroalkanes is a general trend regardless of photolysis conditions.

Excitation of dialkyliodonitromethanes **200** occurs via the $n \rightarrow \sigma^*$ transition ($\lambda_{max} \sim 300$ nm) giving, through homolysis, nitromethane radicals **201** (equation 125a) which can be trapped with 2-methyl-2-nitrosopropane to give ESR signals of the corresponding nitroxide[195,196]. In contrast, 1-bromonitrocyclohexane is stable to

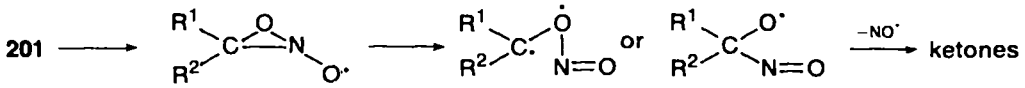


(125a)

R^1 and R^2 = Me, Me; —$(CH_2)_5$—; c-C_3H_5, Me; admantilydene; Ph, Me

photolysis in benzene. While **201** may behave as a *C*- or *O*- radical, nitroxides arising from *O*-radical attachment have not been detected. In spite of this observation, it has been suggested that the nitroadamantyl radical generated by photolysis of the corresponding iodonitro compound **200** in hydrogen-donating solvents abstracts a hydrogen atom from both radicals (**201**) to give nitroadamantane (**202**) and its *aci* form (**203**)[195]. To account for the failure of deuterium incorporation in **202** when photolysed in *i*-PrOD and cyclopentane/MeOD, it has been further assumed that the *aci*-form **203** rearranges exclusively to adamantanone and only feebly to nitroadamantane.

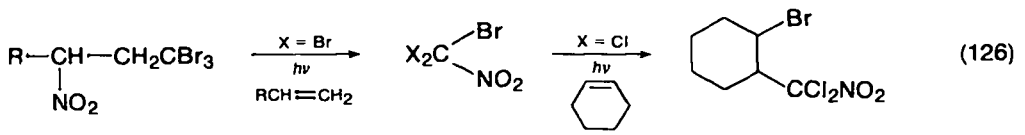
In the photolysis of iodonitromethane **200** in poor hydrogen-donating solvents, the product patterns are readily explained by intermediate radicals **201** in terms of elimination to nitroalkenes **204**, if there is a readily removable hydrogen at the β-position, and rearrangement to ketones as shown in equation (125b). Indeed, the thermal or photolytic rearrangement of nitronic acids, such as **203**, to ketones is known, but is generally accompanied by the formation of the corresponding oximes and nitro compounds[173]. It may be simpler to suggest that in the photolysis of iodonitromethanes **200**, the ketones are formed from radicals **201** by equation (125b)



(125b)

and the hydrogen abstraction of **201** does not occur from its *O*-radical. For delocalized amphoteric radicals, such lopsided behaviour by one radical site is also shown by amidyl radicals[197]. The intermediacy of radicals **201** is further supported by the formation of 5-iodo-2-nitro-2-pentene together with methyl cyclopropyl ketone in the photolysis of 1-cyclopropyl-1-iodonitroethane and the formation of 2,3-dinitro-2,3-diphenylbutane and acetophenone in that of 1-iodo-1-nitro-phenylethane[196].

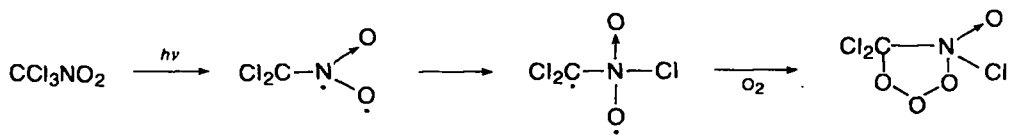
The photocatalysed addition of tribromonitromethane (**205**) to terminal olefins[198] yields the expected 1-tribromomethyl-2-nitro adducts **206** in accordance with *a priori* photodissociation of **205** (X = Br) to tribromomethyl and $NO_2^{\cdot}$ radicals. However, the reported photoaddition of bromodichloronitromethane (**205**) to cyclohexene[199] to give the bromo derivative **207** (equation 126) is evidently a deviation from the



(126)

(206) **(205)** **(207)**

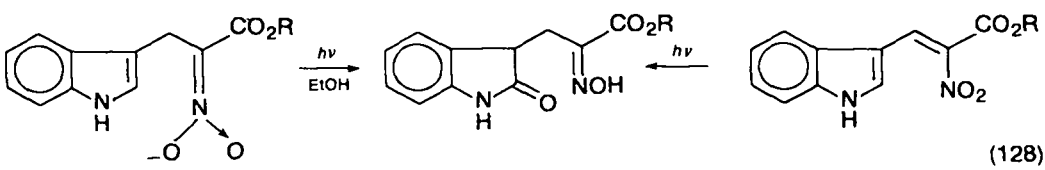
well-established cleavage pattern of halonitromethanes shown in equation (124). It is apparent that a different addition mechanism operates in this reaction. Trichloronitromethane, known as chloropicrin as an agricultural chemical, is photolysed under simulated environmental conditions to give phosgene and nitrosyl chloride as the primary photoproducts; the latter is further photolysed to various nitrogen oxides and chlorine[200]. The photolysis requires the presence of oxygen and $^{18}O_2$ is incorporated into phosgene; a trioxazole *N*-oxide is proposed as an intermediate (equation 127) to account for these observations.



(127)

$\longrightarrow$ $Cl_2CO + NOCl + O_2$

Photorearrangements of α-nitrocarbonyl compounds have been relatively little investigated. The photolysis of the ammonium salt of the α-nitrocarboxylic acid **208** gives isatin **209** (equation 128) which is also obtained in the photolysis of

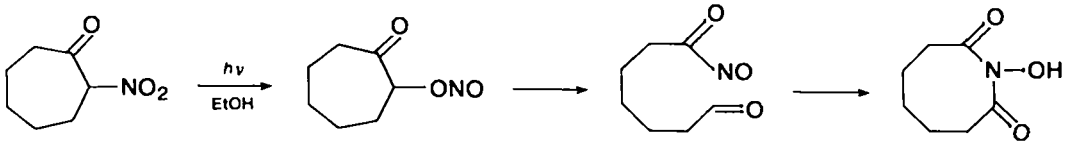


(128)

(208) NH_4^+ **(209)** **(210)**

R = Me, Et

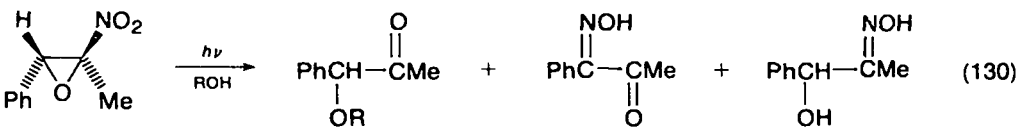
3-(3'-indolyl)-2-nitroacrylates (**210**)[201] (cf. equation 109). The former photo-transformation must involve an oxidation step, the mechanism of which has not yet been explained. The facile photorearrangement of 2-nitrocycloheptanone (**211**) or other α-nitroketones to *N*-hydroxyimide **214** has been interpreted by the sequence shown in equation (129)[202]. The transformation of nitrite **212** to *N*-hydroxyimide **214**



(**211**) (**212**) (**213**) (**214**) (129)

finds similarity in the photorearrangements of bornyl nitrite[203]. It is interesting to note that some of the α-nitrocycloalkanones also undergo acid-catalysed rearrangement to afford *N*-hydroxyimides such as **214**[204].

Photolysis of nitroepoxide **215** occurs in alcoholic solvent (equation 130) but not in *t*-butanol, benzene, acetonitrile or *n*-hexane[205]. The product distribution is very dependent on acidity and hydrogen-donating power of the solvents; in methanol, the alkoxyketone **216** is formed exclusively but in *i*-propanol both oximinoketone **217** and hydroxyoxime **218** are formed as the major products. A poor yield of **218** is also obtained in the photolysis of **215** in ether. It appears that the pathways to **216** and **217** are facilitated by the acidity of alcohols and the formation of **217** and **218** is related to the hydrogen-donating ability of the solvents. It is proposed that two basic pathways are operating on excitation of **215**. In one pathway the excitation energy on



(**215**) (**216**) (**217**) (**218**) (130)

the nitro group is transmitted to the epoxide ring, causing ionization of a C—O bond followed by a nitro group shift or HNO_2 elimination. The competing pathway is hydrogen abstraction by the excited nitro group leading to a variety of reduction stages; at a certain stage the epoxide ring may be opened with the aid of electronic interactions or by another photoexcitation. The photorearrangement of nitroepoxide **215** is suggested as occurring from the triplet excited state, but the corresponding nitroalkene is shown not to be an intermediate.

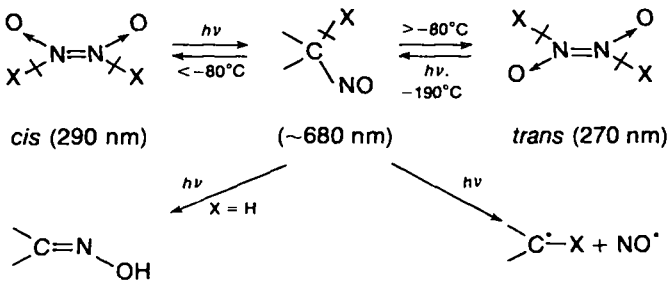
V. PHOTOCHEMISTRY OF C-NITROSO COMPOUNDS

The photochemistry of *C*-nitroso compounds overlaps extensively with those of nitro compounds since they are the intermediates in photoreduction (Section II.A) as well as photorearrangement (Section II.D) processes. *C*-Nitroso compounds are also intermediates in certain photoreactions of nitrites, nitrosamines and nitrosamides. Brief notes on the photolysis of *C*-nitroso compounds as the test of intermediacy have been reported in various articles[16,19,123]. In the photoreduction of aromatic nitro compounds, the nitroso intermediates are generally regarded to undergo dark reactions rather than secondary photoreactions[16], in spite of a claim to the

contrary[19]. Since nitroso compounds are the key intermediates in the photooximation of cycloalkanes with nitrosyl chloride (or the equivalent), an economically important process for the manufacture of polyamides[206–208], their photochemical behaviour plays an important part in that industry, and has attracted much attention recently. Significant progress has been made since the last review[3] covering the literature up to the late 1960s. In ambient conditions, blue-coloured *C*-nitroso compounds exist in equilibrium with their colourless dimers containing azodioxy linkages[209]; irradiation of such mixtures transforms the dimers to monomeric *C*-nitroso compounds from which photochemical reactions are observed by excitation of the $n \rightarrow \pi^*$ transition band at about 600–700 nm.

A. Simple Nitrosoalkanes

The basic photochemical processes of nitrosoalkanes are summarized[3] in equation (131). Photolysis of the dimers of nitrosoalkanes induces dissociation to the

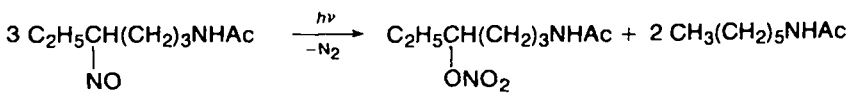


(131)

X = H, aryl, alkyl, Cl, NO_2, $OCOCH_3$, CN

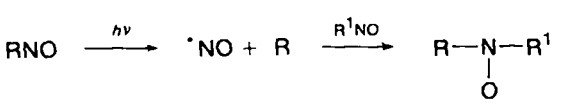
corresponding monomers which dimerize spontaneously in the dark to *cis*-azodioxy compounds below −80°C and to the *trans*-azodioxy compound above this temperature[184,210]. Excitation of the $n \rightarrow \pi^*$ transition band of nitrosoalkanes causes two competing chemical acts as established so far; one is irreversible tautomerization to oximes[184,210,211] for those with X = H and the other is homolysis of the C—N bond to give alkyl and nitric oxide radicals for all nitrosoalkanes[212]. Nitrosoalkanes (X = H) tautomerize readily in protic solvents; the process is catalysed by either acids or bases[209] but enormously accelerated by the excitation of the 680 nm band.

The photoinitiated homolysis of nitrosoalkanes was invoked to account for the light-induced disproportionation of nitrosamide **219** to nitrate **220** (see equations 134, 139 and 141 shown below)[189,211], and also for the observation of the ESR signals of nitroxide radicals in the photolysis of nitrosoalkanes[212,213] as in equation (133). As typified in equation (133), nitrosoalkanes have been used as a spin trap to



(132)

(219) **(220)**



(133)

convert transient radicals, such as alkyl[212], alkoxy[214], acyl[215] and possibly others, to relatively stable nitroxides, the ESR spectra of which can be observed relatively easily and analysed to provide information on the transient radicals. The stability of the nitroxide radicals is the key factor in the operation and is very much dependent on the structure of the R and R^1 groups: 2-nitroso-2-methylpropane is the most widely used spin-trapping agent amongst them. These nitroxides are obviously generated in minute amounts in the photolysis of nitrites[214,215], nitrosamides and nitrosamines[216] in solution, and can be studied by ESR spectroscopy even if not isolable.

Kinetic studies on the attachment of the photolytically generated *t*-butyl radical with 2-nitroso-2-butylpropane[217] and hindered nitrosoarenes in benzene at 300 K give the rate constant of 3.3×10^6 M^{-1} s^{-1}. The gas-phase photolysis of 2-nitroso-2-methylpropane at 700 nm or in the vacuum ultraviolet region (147 and 123 nm) also induces homolysis of the C—N bond; in the former case, nitroxide formation is a significant process[177], but in the latter case the *t*-butyl radical fragments extensively due to excess vibrational energy[213].

Recent studies on the photolysis of simple as well as α-substituted nitrosoalkanes in solution have shown that homolysis of the C—N bond as in equation (131) overwhelmingly dominates, the primary photochemical act, and that the HNO elimination and hydrogen abstraction are unimportant[184,218]. The ensuing dark reactions are mainly additions of the radicals to nitrosoalkanes followed by ionic or radical reactions of the adducts. In certain cases, one of the pathways among those shown below may proceed more rapidly than the others, e.g. the formation of nitrate **220** in the photolysis of **219** as in equation (132). On the basis of the product patterns, the proposed major processes[218] are summarized in equations (134)–(144);

$$RNO + 2NO^{\bullet} \longrightarrow \underset{\underset{N=O}{|}}{RNON=O} \longrightarrow RN=NONO_2 \qquad (134)$$

$$RNO + R^{\bullet} \longrightarrow R_2NO^{\bullet} \xrightarrow{R^{\bullet}} R_2NOR \qquad (135)$$

$$R_2NO^{\bullet} + NO^{\bullet} + R^1OH \longrightarrow R_2NOH + R^1ONO \qquad (136)$$

$$RN=NONO_2 \longrightarrow \text{alkenes} + N_2 + HNO_3 \qquad (137)$$

$$RN=NONO_2 + R^1OH \longrightarrow ROR^1 + N_2 + HNO_3 \qquad (138)$$

$$RN=NONO_2 \longrightarrow RONO_2 + N_2 \qquad (139)$$

$$\underset{\underset{N=O}{|}}{R-NONO=O} + R^1OH \longrightarrow \underset{\underset{N=O}{|}}{RNOH} + R^1ONO \qquad (140)$$

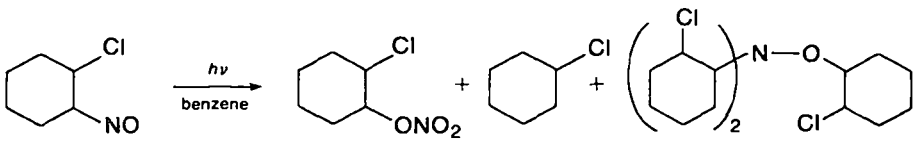
$$RN=NONO_2 \longrightarrow R^{\bullet} + NO_3 + N_2 \longrightarrow RONO_2 \qquad (141)$$

$$NO_3 + NO \longrightarrow 2NO_2 \qquad (142)$$

$$RNO + NO_2/NO_3 \longrightarrow RNO_2 + NO/NO_2 \qquad (143)$$

$$R^{\bullet} + NO_2 \longrightarrow RNO_2 + RONO \qquad (144)$$

these reactions may be formal representations of more intricate processes and have other variations. However, observed products from nitrosoalkane photolysis can be accounted for by combinations of equations (134)–(144). In alcoholic solution, intermediates are rapidly dissipated by solvolysis (equation 136), but in benzene processes other than solvolysis dominate the overall pattern. The nitrate formation (equations 132 and 145) follows equations (134), (139) and (141) and may occur wherever alkyl radicals and nitric oxide coexist in a system[219]. While the formation of ethers ROR^1 and nitrites R^1ONO is typical of the photolysis of **225–227** in alcohol,



(145)

(221) **(222)** **(223)** **(224)**

$(CH_3)_3CNO$ $C_6H_5(CH_3)_2CNO$ $C_6H_5CH_2(CH_3)_2CNO$

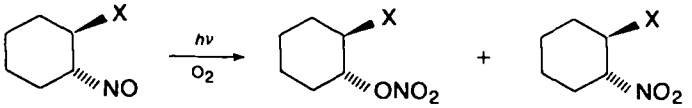
(225) **(226)** **(227)**

alkenes are always major products in alcohol or benzene and are more likely formed by elimination (equation 137). The ubiquitous formation of nitroxides can be shown by ESR spectroscopy, but trialkyl hydroxylamines, such as **224**, are isolated only in the photolysis of **221** and **225** in low yields. Nitro compounds, RNO_2, may be formed by the combination step (144) or the oxidation step (143) without scission of the C—N bond. The interplay of various processes depends on the nitrosoalkane structure and the reaction conditions and is reflected in wide variations in product patterns. For example, photolysis of the *trans* dimer of **221** preferentially isomerizes to the corresponding insoluble *cis* dimer even at room temperature in methanol or benzene, and the photodecomposition of the monomer to **222–224** occurs very slowly[184]. Nitrosoalkanes **225** and **227** are readily photodecomposed with >540 nm radiation to yield a variety of major and minor compounds[218] as shown in Table 2.

In the presence of oxygen the photolysis of nitrosoalkanes dramatically changes the product pattern to give the nitrates $RONO_2$ and /or nitro compounds RNO_2 in high yields[184,220,221] in addition to minor amounts[222] of the nitrites RONO and alcohols ROH. The ratio of $RONO_2$ to RNO_2 varies considerably; for example, the oxidative photolysis of nitrosoalkane **219** gives the nitrate **220** cleanly but that of **228** in benzene or methanol gives both nitrates **229** and nitro compounds **230** in which the yields of the latter are about equal to or more than those of the former. In the

TABLE 2. The product patterns of the photodecomposition of nitrosoalkanes (RNO) **225** and **227**

	Products (%)							
RNO	R_2NOR	Alkenes	ROMe	ROH	RNO_2	RONO	$RONO_2$	MeONO
225 (in MeOH)	16	16	20	9	<1	—	—	18
(in C_6H_6)	15	32	—	—	11	7	3	—
227 (in MeOH)	+	20	13	11	<1	—	—	14
(in C_6H_6)	+	56	—	—	11	8	—	—



(146)

(228) (229) (230)

X = Cl, $N(CH_2)_5$

photolysis of the nitrosoalkanes **225**, the ratio of $RONO_2$ to RNO_2 varies from 73/12 at a high concentration of oxygen to 47/33 at a low concentration[222,223]. However, the nitro compound RNO_2 has never been 'the exclusive product' as claimed before by the same group[222]. In the photolysis of **228**, the loss of stereochemical integrity in nitrate **229** and the maintenance of that in nitro compound **230** (X = Cl) suggests that the formation of the former involves a C—N bond scission but that of the latter does not necessarily. Whilst singlet oxygen has been shown not to be an oxidizing species in the photooxidation[220,222], simple straightforward oxidation by nitrogen oxides or other oxidizing species generated during the reaction merits consideration. Photoinduced oxidations of aromatic nitroso compounds to nitroaromatics are well-established reactions[16] (see equations 93 and 167), and nitrosoalkanes are known to be oxidized by NO_2 to nitroalkanes[224,225] (equation 143).

In the photolysis of 2-nitroso-2-methylpropane (**225**) with 540–800 nm radiation in the presence of $^{17}O_2$, *t*-butoxy *t*-butyl nitroxide (**233**) with the ^{17}O lable at the *t*-butoxy group has been detected by ESR spectroscopy[224]. Such alkoxy nitroxides have also been obtained by the photolysis of azoalkanes in the presence of oxygen and nitrosoalkane **225**. On the basis of these observations Pfab has proposed the mechanism as shown in equations (147)–(151) to account for the oxidative photolysis. Similar photolyses in the gas phase with a wide range of oxygen concentrations have also generated radicals $RO^{\bullet}$ and $NO_2^{\bullet}$ by equation (152) instead of leading to the pernitrite (**232**) or nitroxide (**231**). The complex product pattern in the gas-phase photolysis has been interpreted in terms of radical combinations and decompositions.

$$R + O_2 \longrightarrow R{-}O_2^{\bullet} \xrightarrow{R^1NO} R{-}O_2N(O^{\bullet})R^1 \quad \textbf{(231)} \tag{147}$$

$$\textbf{231} \longrightarrow RO^{\bullet} + R^1NO_2 \tag{148}$$

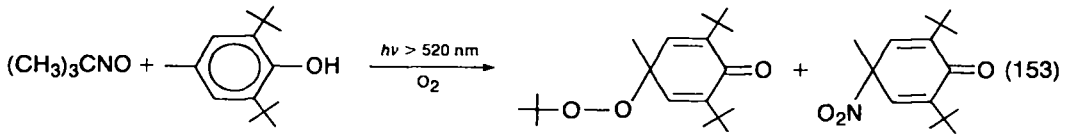
$$\textbf{231} \longrightarrow R^{1\bullet} + RO_2NO \longrightarrow RO^{\bullet} + NO_2^{\bullet} \longrightarrow RNO_3 \quad \textbf{(232)} \tag{149}$$

$$RO^{\bullet} + NO^{\bullet} \longrightarrow RONO \tag{150}$$

$$RO^{\bullet} + R^1NO \longrightarrow RON(O^{\bullet})R^1 \quad \textbf{(233)} \tag{151}$$

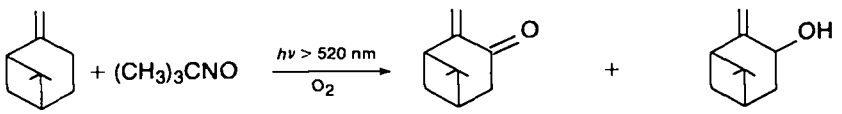
$$RO_2^{\bullet} + NO \xrightarrow{gas} RO^{\bullet} + NO_2^{\bullet} \tag{152}$$

Obviously peroxynitroxides **231** are too unstable to be detected even by ESR spectroscopy. However, alkylperoxy radicals $RO_2^{\bullet}$ and $NO_2^{\bullet}$ have been trapped as quinoid compounds **234** and **235** in a similar photolysis in the presence of 2,6-di-*t*-butyl-4-methylphenol[223] (equation 153).



(225) **(234)** **(235)**

In the oxidative photolysis (>520 nm) of **225** in solution, solvents with readily abstractable hydrogen or alkenes are also concurrently oxidized to give good yields of alcohols or carbonyl compounds[222]. Ethylbenzene is oxidized to give acetophenone and 1-phenylethyl alcohol in 40 and 21% yields, respectively, at a high concentration of **225**, and 17 and 68% at a low concentration. β-Pinene is photooxidized to ketone **236** and alcohol **237** (equation 154). It is simplest to assume



(236) **(237)**

that hydrogen abstraction from the substrates by *t*-butoxy radical ($RO^{\bullet}$ in equations 148 and 149) to generate the benzyl and allyl radicals as an essential step in this oxidation; under the reaction conditions these radicals are probably converted to the peroxy radicals and enter into the oxidation cycle shown in equations (147)–(151) or other similar pathways to give the observed products. Styrene is oxidized in the photolysis of **225** under oxygen at −70°C to give an unstable adduct which is reduced to phenylethylene glycol and decomposed at room temperature to benzaldehyde and formaldehyde; nitrosoalkane **225** is claimed to be concurrently oxidized to 2-nitro-2-methylpropane in 91% yield[222]. Since both the *t*-butoxy or *t*-butylperoxy radicals attack an olefin bond feebly, the identity of the electrophilic species initiating the addition is a key question for this interesting photooxidation.

B. Geminally Substituted Nitrosoalkanes

The excitation of α-substituted nitrosoalkanes (R_2CXNO; X = Cl, $\lambda_{max} \sim 650$ nm; X = NO_2, λ_{max} 650 nm; X = CN, $\lambda_{max} \sim 625$ nm) at the $n \rightarrow \pi^*$ transition band invariably causes homolysis of the C—NO bond to generate carbon radicals and nitric oxide. The photolysis of α-chloronitrosoalkanes has been studied most extensively[225–229] and previous suggestions of C—Cl bond scission[226] and hydrogen abstraction[226,227] from excited-state chloronitrosoalkanes are definitely disproved by a recent publication[228]. The photolysis of α-chloro- and α-nitro-nitrosoalkanes is characterized by drastically different product patterns in protic and nucleophilic solvents, such as alcohols, and in aprotic solvents such as benzene, chloroform, alkanes, etc. Photolysis of 1-chloronitrosocyclohexane (**238**, $R_2 = -(CH_2)_5-$) in methanol gives nearly 0.5 mole each of cyclohexanone oxime, its dimethyl acetal and methyl nitrite as the primary products, if the generated hydrogen chloride is scavenged by triethylamine[228]. In aprotic solvents, 1-chlorocyclohexene, 1,1-dichlorocyclohexane and cyclohexanone are the major products among many

other minor products. Similar irradiation of 2-chloro-2-nitrosoadamantane gives comparable results[227,229]. The mechanism shown in equations (155)–(160) has been

$$R_2ClCNO \rightleftharpoons R_2ClC^{\bullet} + NO^{\bullet} \quad (155)$$

(238)

$$R_2ClC^{\bullet} + R_2ClCNO \longrightarrow (R_2ClC)_2NO^{\bullet} \quad (156)$$

(239)

$$(R_2ClC)_2NO^{\bullet} + NO^{\bullet} \longrightarrow R_2C(Cl)-N(\rightarrow O)=CR_2 + NOCl \quad (157)$$

(240)

$$NOCl + MeOH \longrightarrow MeONO + HCl \quad (158)$$

$$\mathbf{240} + 2\,MeOH \longrightarrow R_2ClC-NHOH + R_2C(OMe)_2 \quad (159)$$

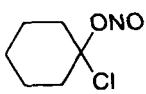
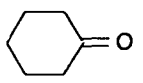
$$R_2ClC-NHOH \longrightarrow R_2C=NOH + HCl \quad (160)$$

proposed to account for the stoicheiometry observed in methanol. The key step is the elimination of the α-chlorine to form nitrone **240** and nitrosyl chloride as in equation (157) (cf. equation 136), both of which undergo solvolysis and elimination (equations 158–160) to give the observed products.

In aprotic solvents, the evolution of nitrogen suggests that the diazonium nitrate **241** ($R_2 = -(CH_2)_5-$) (cf. equation 134) is the key intermediate which may decompose as shown in equation (162) or by some similar processes. The formation of 1,1-dichlorocyclohexane is most simply accounted for by equation (163). The

$$R_2ClCNO + 2\,NO^{\bullet} \longrightarrow R_2ClC-N=N-ONO_2 \quad (161)$$

(241)

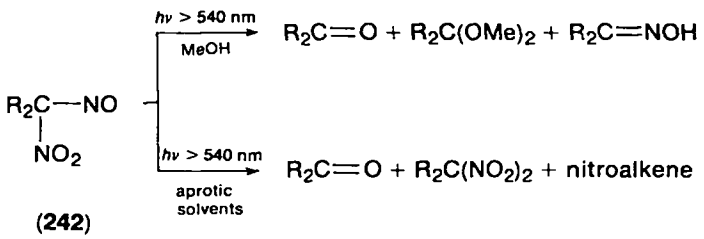
$$HNO_3 + \text{  } \xleftarrow{-N_2} \mathbf{241} \xrightarrow{-N_2} \text{  } \longrightarrow \text{  } + ClNO_2 \quad (162)$$

$$R_2ClC^{\bullet} + ClNO_2 \longrightarrow R_2C(Cl)_2 + NO_2^{\bullet} \quad (163)$$

$$R_2ClC^{\bullet} + NO_2 \longrightarrow R_2C(NO_2)Cl + R_2C(ONO)Cl \quad (164)$$

absence of cyclohexanone oxime and of chlorocyclohexane in aprotic solvents, indicates that hydrogen abstraction by an excited state of **225** or by the 2-chloropropyl radical are unimportant. By adding a trapping agent, such as NO_2 or bromine, the $R_2ClC^{\bullet}$ radical can be trapped to give good yields of *gem*-disubstituted alkanes (see equation 164); indeed, photolysis of various α-chloronitrosoalkanes in the presence of bromine affords excellent yields of α-bromochloroalkanes[230].

Photolysis of α-nitronitrosoalkanes (**242**) follows a pattern nearly identical to that in equations (155)–(164) except that N_2O_3 and nitrous acid are generated[231,232] instead of NOCl and HCl. Various points discussed above are applicable to this photolysis with the exception that N_2O_3 and HNO_2 or their equivalent forms make the reaction much more complex; they react with methanol to give a large quantity of methyl nitrite and generate nitrogen dioxide extensively in aprotic solvents. Photolysis of 2-nitro-2-nitrosopropane or 1-nitro-1-nitrosocyclohexane in methanol and in aprotic solvents such as benzene, chloroform, methylene chloride, etc., are summarized[231,232] in equation (165). The product pattern in methanol can be simply accounted for by the nitrone intermediate, such as **240** where Cl = NO_2. In aprotic solvents, the ketoximes are not formed and the presence of NO_2/N_2O_4 has been confirmed; this indicates the intermediacy of a diazonium nitrate, such as **241** where Cl = NO_2, and there is extensive NO_2 generation. Evidence indicating the stability of the $R_2(NO_2)C^{\bullet}$ radical may be gleaned from the isolation of the normal products, as shown in equation (165), in the photolysis of 1-nitro-1-nitroso-1-cyclopropylethane

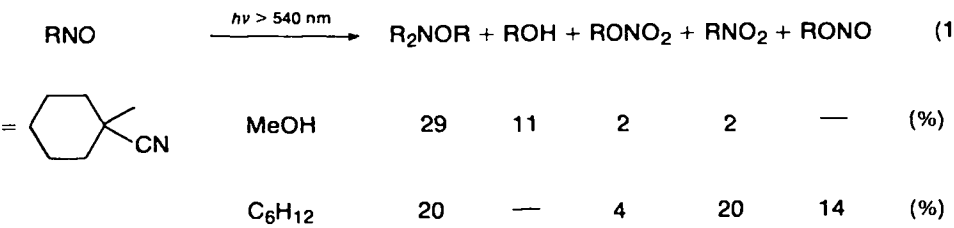


(165)

R_2 = CH_3, CH_3; cyclopropyl; —$(CH_2)_5$—

(**242**, R_2 = cyclopropyl) in which a cyclopropyl ring-scission product is not encountered[231]. This suggests the significant delocalization of the spin density into the nitro group retarding the ring-opening of the cyclopropylcarbinyl radical.

The product pattern of the photolysis of 1-nitroso-1-cyanocyclohexane in methanol and cyclohexane is summarized in equation (166); photolysis in other solvents or of



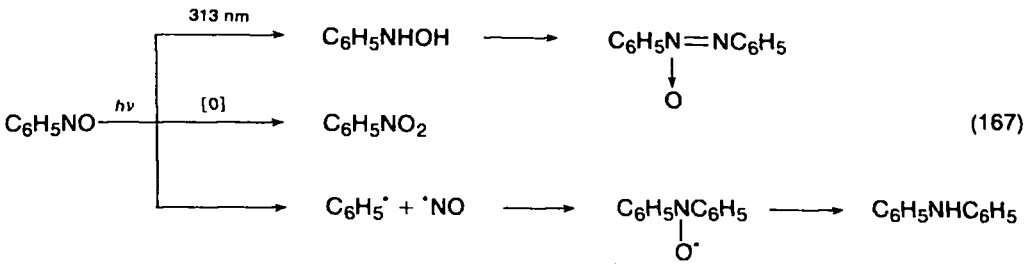
(166)

2-nitroso-2-cyanopropane gives comparable patterns and alkyl nitrites are formed in alcohol solvent[232]. The formation of trialkylhydroxylamine, R_2NOR, as the major product indicates that an α-cyanonitroxide is resistant to the elimination of the cyano group (cf. equation 157), and that in both types of solvent systems the reaction mechanisms are similar to those of simple nitrosoalkanes as shown in equations (134)–(144) and depart considerably from those shown in equations (154)–(164).

C. Aromatic Nitroso Compounds

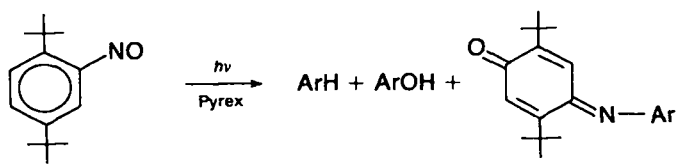
Nitrosobenzene is readily photoreduced to azoxybenzene under deoxygenated conditions or photooxidized to nitrobenzene in the presence of oxygen[16]. The spin-trapping of nitroso compounds was first demonstrated by Maruyama in the

photolysis of nitrosobenzene in which diphenyl nitroxide was detected by the ESR technique[233] and isolated later[234]. The photolysis of nitrosobenzene in ethanol under air yields diphenylamine and its nitrosated and nitrated compounds in addition to azoxybenzene[235]. This information proves the homolysis of the C—N bond as one of the primary photochemical processes shown in equation (167). This process is indeed

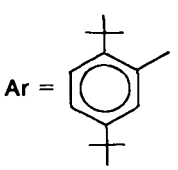


(167)

remarkable since homolytic dissociation of a substituent attached to an aryl ring is rarely observed. *N*-Nitrosodiphenylamine has been assumed to be an intermediate for the formation of diphenylamine and its 4-nitroso derivative[235]; indeed, the photolysis of the nitrosamine gives both compounds but at much slower rates[234]. Nitrosobenzene is also cleanly photoreduced in *i*-propanol to phenylhydroxylamine with 313 nm light. It is interesting to note that irradiation in the $n \rightarrow \pi^*$ transition band at 760 nm causes no reaction of nitrosobenzene[236] nor the formation of nitroxide[214]. This suggests that the primary photoprocess occurs from the second excited state, but not from the lowest one, of nitrosobenzene.



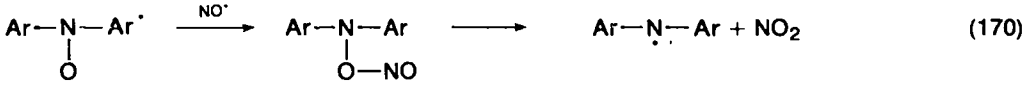
(243) **(244)** (168)



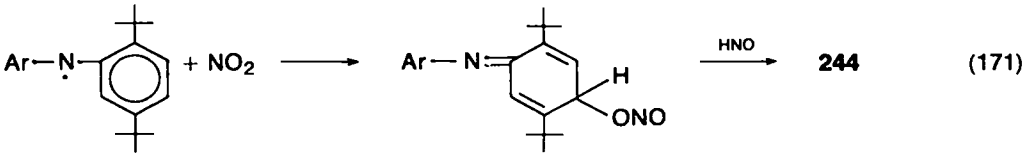
Photolysis of 2,5-di-*t*-butylnitrosobenzene (**243**) gives the ESR signal of the nitroxide $Ar_2NO^{\bullet}$ and, preparatively[237] gives the corresponding phenol and arene, and the quinonimine **244**. The formations of these amine-type compounds shown in equations (167) and (168) arise from intermolecular reduction and may be explained by the mechanism shown in equations (169)–(172). Diphenylamine[234,235], 1,4-di-*t*-butylbenzene and 2,5-di-*t*-butylphenol[237] can be obtained by hydrogen transfer to the respective radicals as indicated in equation (173).

In contrast, sterically crowded 2,4,6-tri-*t*-butylnitrosobenzene (**245**) is photorearranged via the phenyl radical **246** by an unusual intramolecular

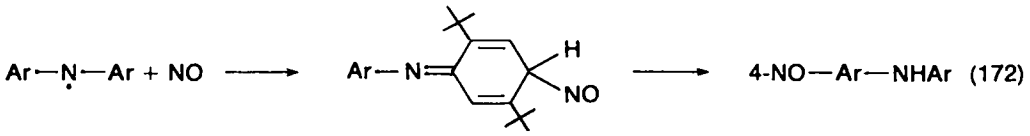
(169)



(170)

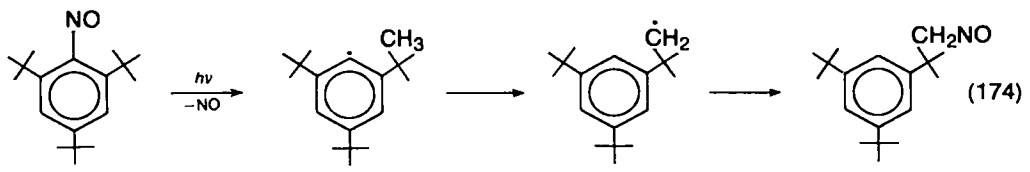


(171)



(172)

(173)



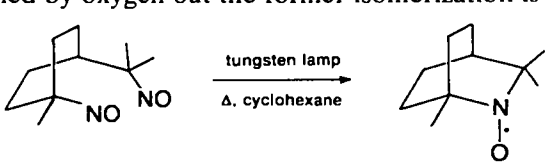
(174)

(245) **(246)** **(247)** **(248)**

hydrogen-transfer process to give nitrosoalkane **248** which is isolated as the *C*-nitroso dimer or oxime[237]. Irradiation of **245** in hydrocarbon solvent gave the ESR signal of ArNOH•, but not the usual diaryl nitroxide radical, due probably to the steric crowding around the radical centre. However, the intramolecular hydrogen transfer should be facilitated by both proximity and the same steric effects.

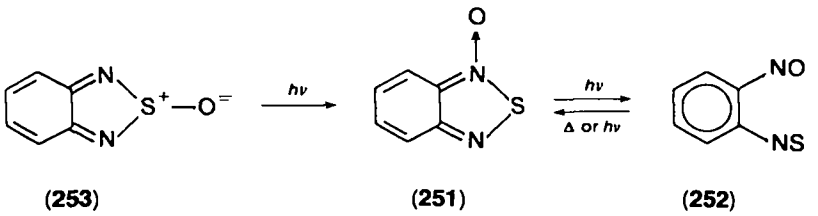
D. Other *C*-Nitroso Compounds

The facility of nitroxide formation is demonstrated by the irradiation of 1,8-dinitroso-*trans*-*p*-menthane (**249**) to afford nitroxide **250** in 72% yield[238] (equation 175). 2-Thionitrosonitrosobenzene (**252**) is stable at 85 K and can be generated by low-temperature photolysis of thiadiazole oxide[239] **251** (equation 176); **252** is converted to **251** photolytically at a low temperature or thermally at room temperature with the rate constant of $100\,s^{-1}$. However, excitation of thiadiazole oxide **251** leads to dual decay pathways; in addition to the reversible ring-opening to **252**, it also irreversibly rearranges to *S*-oxide **253** which hydrolysed rapidly at room temperature to give stable benz[*c*]-1,2,5-thiadiazoline 1,1-dioxide[239]. The latter process is quenched by oxygen but the former isomerization is not. The photolytic or



(175)

(249) **(250)**



(176)

(253) (251) (252)

λ_{max} 463 nm λ_{max} 493 nm

thermal isomerization of 1,2,5-oxadiazole 2-oxides (furoxanes) is generally assumed to occur by the intermediacy of 1,2-dinitroso compounds; low-temperature of flash photolysis has so far failed to reveal the dinitroso compounds[240].

The photolysis of heptafluoro-1-nitropropane[241] appears to cause homolysis of the C—N bond and produces 'dimers', $(n\text{-}C_3F_7)_2NONO$ and $(n\text{-}C_3F_7)_2NNO_2$, $(n\text{-}C_3F_7)_2NOC_3F_7\text{-}n$, $(n\text{-}C_3F_7)_3N$ and $(n\text{-}C_3F_7)_2NN(C_3F_7\text{-}n)_2$, by similar mechanisms proposed previously for trifluoronitromethane[3].

The C—N bond dissociation energy of nitrosyl cyanide has been found by electron impact methods to be as low as 29 kcal/mol[242] in comparison with 34–41 kcal/mol reported for D(C—NO) of nitrosoalkanes[225]. The gas-phase photolysis of nitrosyl cyanide with 589 nm radiation gives nitrogen, carbon monoxide, carbon dioxide and nitrous oxide in a ratio of 5:2:4:3 in addition to cyanogen isocyanate (NCNCO)[243]. The product pattern can be explained by homolysis of the C—N bond as the primary photochemical process followed by addition of the cyanide and nitrosyl radicals to the nitrosyl cyanide to generate the key intermediates $(CN)_2N—O^{\bullet}$ or $CN(NO)N—O^{\bullet}$. The ensuing reactions involve many possibilities. Since cyanogen, nitric oxide, nitrogen dioxide and oxygen have been shown to be absent, extensive redox reactions are assumed to occur to produce the observed products.

VI. PHOTOCHEMISTRY OF ALKYL NITRITES

The photolysis of organic nitrites constitutes an important part of the radical-mediated intramolecular exchange reactions of an alkly hydrogen atom with a functional group, such as a nitroso, chloro or bromo group, which is generally known as the Barton reaction. Mechanistically, it unveils a new chemical concept of selectively functionalizing an unactivated carbon atom, i.e. a chemical process mimicking enzyme processes. In terms of industrial application, the photolysis may rank as the most versatile and useful photochemical process ever devised. However, on photolysis, nitrites undergo other types of reaction as well. Their primary photoprocess in solution is the homolysis of the O—N bond, though other reactions may also occur in the gas phase. Thus, the photochemistry of organic nitrites in solution is essentially a study of photolytically generated alkoxyl radicals. Nitrites are also assumed to be intermediates in the photorearrangements of aromatic nitro compounds (equation 93, Section II.D.2), nitroalkenes (equation 105, Section III.B) and nitroalkanes (equation 115, Section IV.A). However, these nitrites may have only transient existence and decompose rapidly without a secondary photoexcitation. To date, aryl or alkenyl nitrites have not been isolated and characterized.

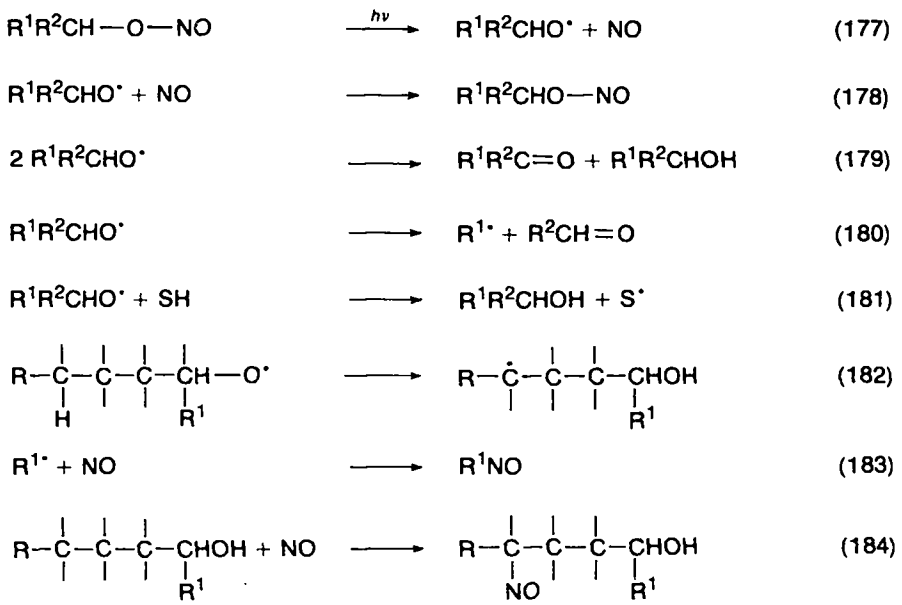
Photolyses of organic nitrites have been reviewed as a part of the Barton reaction[244–246], the last review[246] discussing the reaction in great detail with reference up to 1967. One obvious technical problem of nitrite photolysis is the secondary

photoreaction of nitrosoalkanes, the primary photoproducts, the reaction pattern of which has been discussed in Section V. Generally, nitrites are irradiated in hydrocarbon solutions with a Pyrex filter and a high-pressure mercury resonance lamp. Such a set-up also irradiates nitrosoalkane dimers and monomers; this may explain the low recovery and/or complex mixtures of the products in some nitrite photolyses.

A. Photolysis of Simple Alkyl Nitrites

1. Overall reaction pattern

The extensive literature on the photolysis of nitrites shows that the primary photoprocess in solution is exclusively the dissociation to alkoxyl and nitric oxide radicals as in equation (177). Since alkoxyl radicals are also generated by the homolysis of hypohalites, peroxides, hydroperoxides, peresters and alkyl nitrates (see Section V.II), these reactions share with the photolysis of alkyl nitrites certain pathways common to alkoxyl radical reactions; the generally accepted decay pathways of alkoxyl radicals are shown in equations (177)–(182). Depending on the substrate (SH) and conditions (e.g. photolysis or thermolysis, solution or gas phase, etc.), alkoxyl radicals may decay predominantly by one pathway, or by combinations of two or more competing ones (shown in equations 178–182), to give different product patterns[247].



In the photolysis of alkyl nitrites (or hypohalites), the intramolecular δ-hydrogen transfer of equation (182) generally requires a lower activation energy and occurs preferentially over others to generate the C-radical intermediates, the combination of which with nitric oxide *in the bulk*, as in equation (184), gives the nitrosoalkanes. There are variations in each discrete stage and in the secondary reactions of the nitrosoalkanes, but equations (177), (182) and (184) constitute the basic process of the Barton reaction[245,246] which will be discussed in detail later. The parent alcohols,

aldehydes and ketones are often the observed products from disproportionation (equation 179) and/or α-cleavage (equation 180). The $R^{1\bullet}$ radical generated in the latter is usually scavenged by nitric oxide to form nitrosoalkanes as in equation (183).

2. Recombination

It is pertinent to understand the nature and scope of each process of these competing processes. The quantum yields of the photodissociation of alkyl nitrites (reaction 177) have been shown to approach unity[248,249] in the gas phase, but are generally in the range[250] of 0.7–0.8, due to the recombination process of equation (178). In solution, the operation of the recombination process is supported by the increased quantum efficiency of *n*-octyl nitrite from 0.25 in benzene to 0.76 in heptane[251] and by the inefficient photodissociation of *t*-butyl nitrite ($\phi = 0.08$)[252,253]. A proof of the operation of equation (178) is also provided by the isotope dilution of the labelled ^{15}N in a nitrite when this is photolysed in the presence of a second unlabelled nitrite[245].

3. Disproportionation

Whereas direct evidence is lacking, disproportionation (equation 179) is often proposed to account for the isolation of carbonyl compounds and the parent alcohols from primary and secondary alkoxyl radicals. The oxidation of primary and secondary alkoxyl radicals formally corresponds to the elimination of an α-hydrogen atom, the occurrence of which is less likely for thermodynamic reasons. Because of the transient nature of alkoxyl radicals, it may be assumed that equation (179) operates to only a limited extent. Nevertheless, recently, in the irradiation of methyl nitrite with focused infrared multiphoton beams, the observed fluorescence from a vibrationally excited formaldehyde has led the author to conclude that equation (179) operates in this case[254]. In the photolysis of primary and secondary nitrites, the corresponding carbonyl group can be formed by equation (185). Such a process is well established in gas-phase photolysis[250] by the isolation of N_2O and is scarcely retarded by steric crowding of alkoxyl radicals. Naturally, the partition of the reactants between equations (178) and (185) is an interesting question for inquiry.

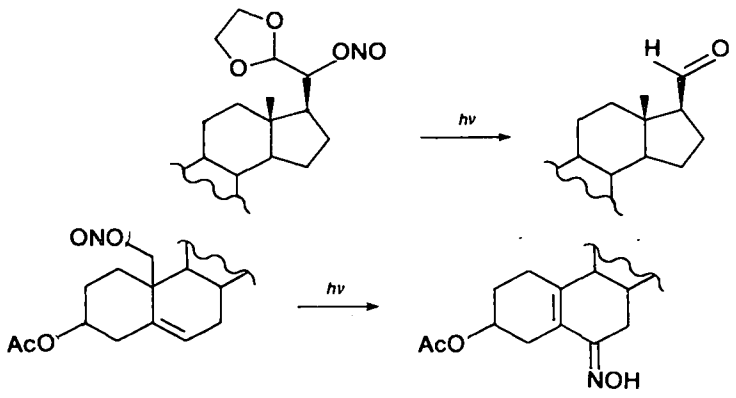
$$R^1R^2CHO^{\bullet} + NO \longrightarrow R^1R^2C{=}O + HNO \qquad (185)$$

$$N_2 + HNO_3 \xleftarrow{2\,NO} (HNO)_2 \longrightarrow H_2O + N_2O \qquad (186)$$

4. α-Cleavage reactions

There are a number of examples pertaining to the α-cleavage of equation (180) reported in the literature. Thermochemical calculations give the heat of reaction as only 1–2 kcal/mol for equation (180), indicating that it is a relatively facile process. Indeed, this reaction pathway is the most frequently observed diversion among the others in the Barton reaction, and occurs not only in the photolysis of nitrites and hypohalites[245,246], but also in the generation of alkoxyl radicals by lead tetraacetate and iodine[255]. The factors promoting the α-cleavage reaction of alkoxyl radicals are uniquely characteristic of radical reactions and many examples are documented in reviews[245,246]. Firstly, stabilization of the generated *C*-radical by delocalization with a π-bond system or heteroatomic substituents significantly promotes such a cleavage as

$$C_6H_5CH_2CH_2ONO \xrightarrow{h\nu} C_6H_5CH_2CH_2O^{\bullet} + NO \longrightarrow C_6H_5CH_2NO + CH_2O \quad (187)$$



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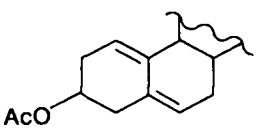
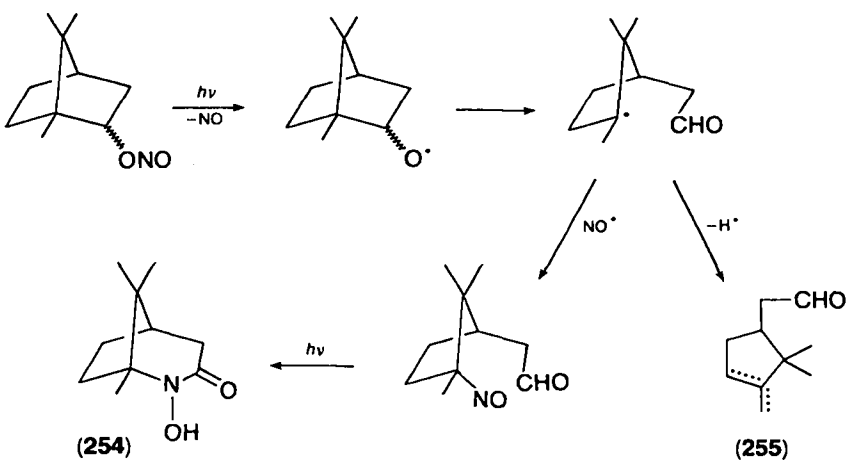


(189)

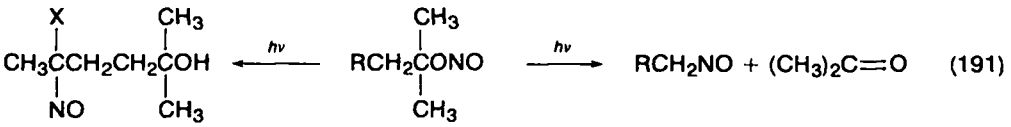
shown in equations (187–(189)[252,253,256]. Secondly, destabilization of the alkoxyl radical by steric strain or crowding tends to facilitate the cleavage in order to alleviate the steric energy; the ring-opening of cyclobutoxyl and cyclopropoxyl radicals and photolysis of bornyl and isobornyl nitrites to give the same products, hydroxamic acid **254** and aldehyde **255**, in similar proportions, are excellent examples of relief of steric strain[257] (equation 190, see also Section VI.D).



(190)

Since reaction (180) is one among many competitive pathways (equations 177–182) it may become important if other pathways, particularly hydrogen abstraction by inter- and intra-molecular modes, are retarded. Cyclopentoxyl radicals tend to undergo ring-opening reactions to give δ-substituted aldehydes[257]: excellent examples of such cleavage reactions will be discussed in Section VI.D.

Cyclohexyloxyl radicals require a high energy barrier to undergo the δ-hydrogen transfer, but generally undergo intermolecular hydrogen abstraction instead of α-cleavage. Cycloheptoxyl, cyclooctoxyl or higher cyclic alkoxyl radicals can undergo Barton-type reactions[257]. The photolysis of *t*-alkyl nitrates **256** (equation 191)



(191)

(257) **(256)**

For R = *n*-Pr, *s*-Bu For R = H, Me, Et

demonstrates that the α-cleavage pathway operates primarily, to give about equal amounts of nitrosoalkanes and acetones, if the Barton reaction or intermolecular hydrogen abstraction does not operate efficiently[252]. It is interesting to point out that in acyclic alkoxyl radicals, a primary hydrogen at the δ-position, as in the case of **256** where R = Et, is abstracted very sluggishly (Section VI.A.5).

5. *Hydrogen abstraction*

Hydrogen abstraction from alkoxyl radicals, either by intra- or inter-molecular modes, is well documented and exothermic by 8 kcal/mol[258] if it involves a secondary hydrogen. However, intramolecular hydrogen abstraction (equation 182) is expected to require much smaller negative entropy than intermolecular cases (equation 181): the former will be overwhelmingly favoured over the latter under comparable conditions. The stereochemical driving force has been most clearly revealed in rigid steroidal systems on which the Barton reaction was originally demonstrated. For example, in the photolysis of the 6β- or 11β-nitrite of a steroid in toluene, intramolecular hydrogen abstraction of the corresponding alkoxyl radical dominates the overall reaction[245]. Competition between the two hydrogen abstraction processes is demonstrated in the photolysis of *n*-octyl nitrite in *n*-heptane solution in which 4-nitroso-1-octanol and a mixture of nitrosohexanes are obtained in a 4.5:1 ratio[251]. However, the *t*-butoxyl radical preferentially undergoes intermolecular hydrogen abstraction rather than other decay processes when *t*-butyl nitrite is photolysed in alkanes and alkylbenzenes under controlled conditions to give excellent yields of the nitrosoalkanes and α-nitrosoalkylbenzenes[259, 260] The order of preferential nitrosation is tertiary > secondary > primary hydrogens of the substrates, in analogy to the hypochlorite halogenation of similar substrates[261]; in particular, isobutane and 2,3-dimethylbutane are nitrosated exclusively at the tertiary carbon[259]. Because of the photolability of nitrosoalkane monomers and dimers (Section V.A) irradiation must use ~400 nm light to give good yields. Without such precautions, the photoreactions of nitrosoalkanes described in equations (133)–(144) can complicate the overall reaction and retard the yields. Using ESR spectroscopy, dialkyl, alkoxyl, alkyl and acyl nitroxides, arising from secondary photoprocesses, have been detected[212–215].

6. *Gas-phase photolysis*

In the connection with air pollution in the urban atmosphere, gas-phase photolysis of low molecular weight alkyl nitrites has attracted renewed attention recently[249,250].

A pattern as shown in equations (177)–(186) has been generally accepted in addition to other probable reaction pathways[262,263] such as molecular elimination. In the gas phase, owing to long collision radii, certain mechanistic departures from the photochemistry in solution are expected. Irradiation of *t*-butyl, ethyl and *i*-propyl nitrites with 254 nm radiation is claimed to generate both the vibrationally excited and ground-state alkoxyl radicals, in which the former undergoes α-cleavage to the methyl radical and the carbonyl compound as in equation (180), while the latter recombines with nitric oxide to revert to the nitrites[249].

The focused irradiation of methyl nitrite with infrared multiphoton radiation reveals that both the *cis* and *trans* isomers react by the same pathways, e.g. equations (177)–(181), to give the same products in the same proportions[254]. The methoxy radical disproportionates (equation 179) to give fluorescing formaldehyde (at 3.54–3.99 μm) and methanol, but no fluorescence of nitric oxide and methyl nitrite is observed. The photodissociation spectrum of ethyl nitrite, generated by crossing a polarized laser beam at 347 nm with a molecular beam of the nitrite, shows that the excited $n \rightarrow \pi^*$ state has a lifetime of 2×10^{-13} s and decays to ethoxyl and nitric oxide radicals[264]. Such short lifetimes of excited states may be prevalent in nitro and nitroso compounds. Irradiation of *t*-butyl nitrite with 123 and 147 nm radiation (corresponding to 970 and 815 kJ/einstein) in the vacuum ultraviolet region generates the *t*-butoxyl radical and nitric oxide in their excited states; the latter emits intensely with the light corresponding to the nitric oxide γ-system ($A^2\Sigma^+ \rightarrow X^2\pi$)[177,265]. In this photolysis, the dissociation to *t*-butyl and nitrogen dioxide radicals is also a main pathway.

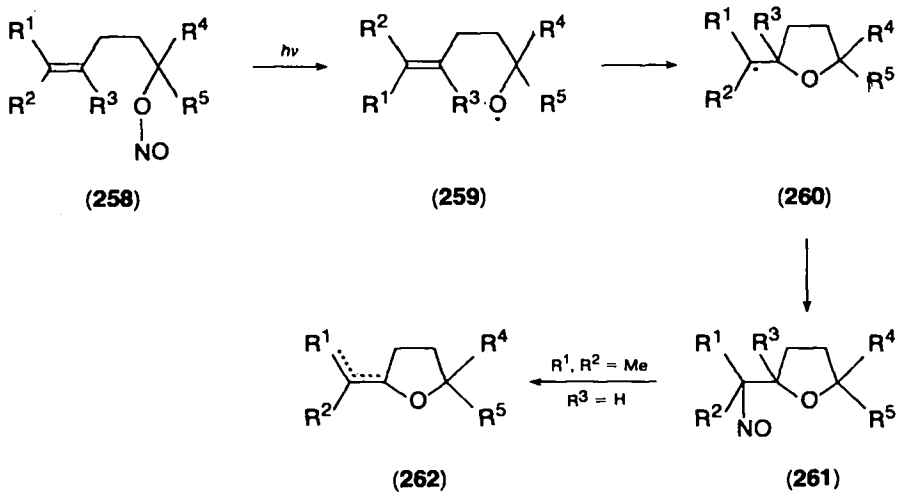
B. Photoaddition of Alkyl Nitrites

Alkoxyl radicals are assumed to react with olefins by the abstraction of an allylic hydrogen, except with styrene where no readily abstractable hydrogen is available[266]: *t*-butyl hypochlorite[267] and methyl hypobromite[268] add to styrene by a radical mechanism to give 1-phenyl-1-halo-2-alkoxyethanes. Methyl bromite[268] has been shown to react with 1-hexene primarily by allylic hydrogen abstraction to give the allyl bromides and, to a minor extent, by addition to give 1-methoxy-2-bromohexane under conditions favouring radical reactions, i.e. under the conditions where cyclohexane is also converted to bromocyclohexane. With alkynes, alkoxyl radicals generated from hypohalite have been shown to abstract an acetylenic hydrogen exclusively[267].

In contrast to the intermolecular reactivity of alkoxyl radicals heavily favouring hydrogen abstraction over addition to π-bonds, intramolecularly alkoxyl radicals behave in the opposite way and add to a suitably placed π-bond efficiently and exclusively rather than abstract an internal γ-hydrogen[269–272]. Photolyses of typical $\Delta^{4,5}$-alkenyl nitrites **258**, **263** and **266** are summarized in equations (192)–(194); in all these photoreactions, in addition to the products indicated, the parent alcohols and the corresponding ketones are always obtained, owing to the ubiquitous competing reactions shown in equations (179)–(181). The photocyclization of alkenyl nitrites **258** occurs efficiently to give the nitroso intermediates **261**, which are isolated in ca. 60% yields as the corresponding oximes or as olefins **262** if the tautomerization is blocked[269]. The alkoxyl radical **259** attacks the π-bond intramolecularly, at the 4-position exclusively, to generate the thermodynamically less stable *C*-radical **260**, the intermediacy of which has been demonstrated by the ESR detection of the symmetrical nitroxide[271] formed from **260** and **261**. The cyclization process is apparently kinetically controlled and irreversible, and extraordinarily regiospecific as shown by the exclusiveness of the formation of a 5-membered ring. Furthermore, the

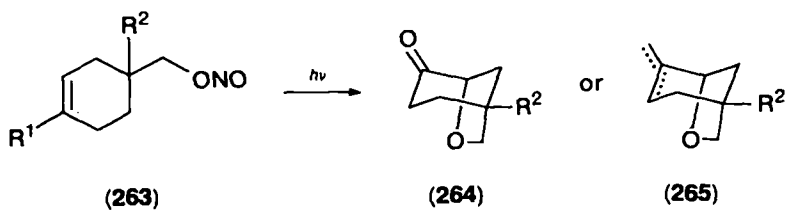
failure of 5-hexenyl nitrite and 3-butenyl nitrite to yield the cyclization product upon irradiation[269] attests to the stringent stereochemical requirements for the cyclization. The 3-butenoxyl radical from the latter might have preferentially undergone the cleavage reaction, but the products were not identified.

The photolysis of alkenyl nitrites **263** and **266** gives fair yields of the cyclization products and others but no products from the Barton reaction[269,270]. These results indicate that the corresponding alkoxyl radicals preferentially attack the π-bond at the 4-position rather than the δ-hydrogen. The photolysis of **263** where R is Me yields only olefins **265**, which might arise from secondary photolysis of the *t*-nitrosoalkane intermediate. In these reactions, the cyclization products have never exceeded 60% and are accompanied by quantities of polymeric materials. As the intermediates, nitrosoalkane monomers and dimers, are photolabilie, irradiation with ~400 nm band, as has been done in the preparation of nitrosoalkanes[259,260], might be needed to achieve better results.



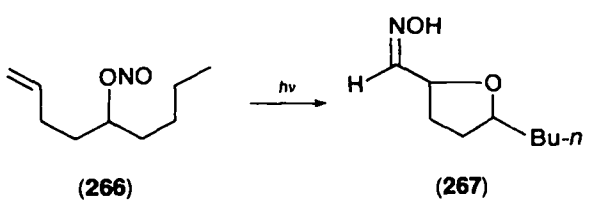
(192)

$R^1 - R^5$ = H or Me

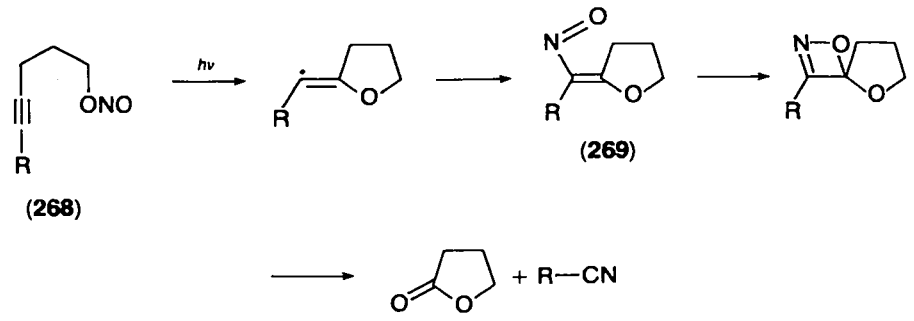


(193)

R^1, R^2 = H or Me



(194)

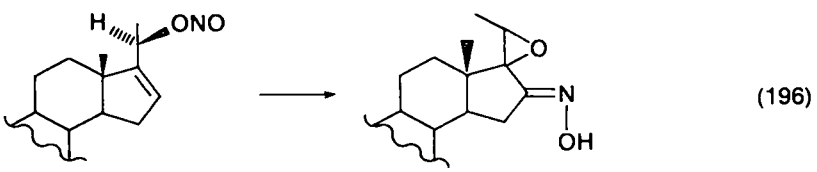


(268) (269) (195)

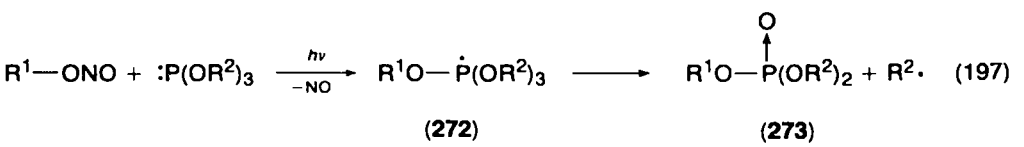
R = Me, Ph

The erroneous report[274] that 4-alkynyl nitrite **268** fails to photocyclize has been revised[273] by the identification of low yields of γ-butyrolactone and the nitriles that are interpreted to form by the cylization–cleavage pathways shown in equation (195). The unstable intermediates, nitrosoalkenes **269**, might have decomposed by other thermal or photolytic pathways, contributing to the low yields.

The formation of epoxide **271** in the photolysis of 20β-hydroxy-4,16-pregnadien-3-one nitrite (**270**) finds no analogy (equation 196); the corresponding alkoxyl radical undergoes intramolecular addition instead of the expected hydrogen abstraction from the C(18) methyl group[275]. The $\Delta^{16,17}$ double bond not only provides a π-receptor but also distorts the molecular geometry significantly (cf. Section VI.C) to hamper the hydrogen abstraction.



(270) (271) (196)



(272) (273) (197)

R^1 = 3β-cholestanyl, *s*-Bu, *c*-Hex

R^2 = Me, Et, *i*-Pr, $Ch_2C(CH_3)_3$, CH_2CF_3, Bz, *c*-Hex

The photoinduced reaction of alkyl nitrites with phosphites to synthesize phosphate **273** is a novel application of nitrite photolysis and has been interpreted, with good evidence, as indicating that alkoxyl radicals add to trivalent phosphites with the attendant valence expansion to generate phosphoranyl radicals **272** as the key step[276]. A smaller alkyl group in **272** appears to be preferentially ejected. As nitrite groups can be made selectively in a complex molecule, this method is applicable to the introduction of a phosphate group at a specific position: indeed, it has been applied to the preparation of a hindered phosphate.

C. Mechanism of the Barton Reaction

The Barton reaction is broadly defined as the intramolecular exchange of an unactivated δ-hydrogen and the X group through the intermediacy of a heteroatom radical[246] as in equation (198). While the articulation of the principle and

(198)

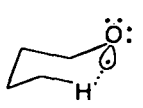
X = NO, Cl, Br or I; Y = O or N

experimental verifications are provided by the photolytic generation of alkoxyl radicals from alkyl nitrites and hypohalites[277], a wide range of radical ractions giving a similar overall reaction pattern may be covered under the principle; these related reactions have been enumerated in a previous review[246]. Nitrite photolysis, however, offers versatility in synthetic application and diversity in enunciating the basic mechanism.

The Barton rearrangement of alkyl nitrites (equation 198, Y—X = ONO) proceeds in discrete stages, each of which involves a finite radical intermediate of distinctive properties susceptible to a variety of competing side-reactions. Because of the advantages of the stereoelectronic disposition offered by rigid systems, its investigations have mainly utilized the nitrite derivatives of steroids, terpenes and alkaloids. Such complex molecules naturally pose frequent challenges in structural elucidation but stereochemical driving or retarding forces often provide rich and fascinating molecular reorganizations. Excellent discussions of the mechenism can be found in the previous review on the subject[246] and on the related oxidation of alcohols with lead acetate and iodine[255].

1. *Intramolecular hydrogen abstraction*

The hydrogen transfer step (equations 182 and 198) is the key step in the Barton reaction, the selectivity of which is determined primarily by the stereochemical factors applying to the transition state of the hydrogen transfer, but scarcely by thermochemical factors. For both cyclic and acyclic alkoxyl radicals generated in the photolysis of nitrites, the six-membered transition state with a chair conformation as in **274** possesses an activation energy low enough to compete favourably with α-cleavage or intermolecular hydrogen abstraction; a five- or seven-membered ring transition state cannot compete with other processes favourably unless geometrical constraint forces such a process. The transition state for the hydrogen transfer is largely deduced from the reaction of 6β-, 11β-, 20α- and 20β-alkoxyl radicals in rigid steroid skeletons as in **275**. Owing to geometric ambiguity in the transition state, the C . . . O distances from Dreiding models are used to correlate with the ease of the hydrogen transfer. It is concluded that the intramolecular hydrogen transfer occurs to the virtual exclusion of other processes if the C . . . O distance is in the range of



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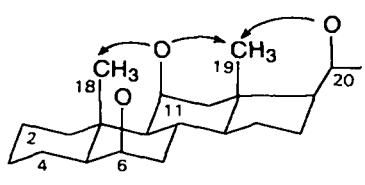
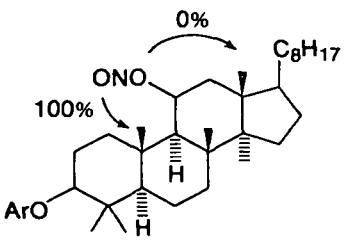


(275)

2.5–2.8 Å, and that if the C . . . O distance exceeds 2.8 Å up to 3.0 Å, intermolecular hydrogen abstraction and α-cleavage compete with this process[255].

In acyclic nitrite photolysis the stereochemical driving force for the δ-hydrogen transfer to the alkoxyl radical is an overriding factor, as can be seen in the photorearrangement of 5-phenylpentyl nitrite to 4-nitroso-5-phenylpentanol[252]. For semirigid cyclohexyloxyl and cycloheptyloxyl (or higher) radicals, the conformational energy required to achieve the transition state of **274** must be taken into consideration when assessing the feasibility of the transfer. Experimentally, it is observed that cyclohexyl nitrite and its 2-methyl-, 3-methyl- and 4-methyl-substituted analogues do not react by the Barton pathway on irradiation, but that cycloheptyl nitrite or higher homologues are more flexible and do undergo the normal Barton reaction[257].

The sensitivity of the transition state of the intramolecular δ-hydrogen abstraction to stereochemical controls is amply displayed by many significant differences in product pattern arising from subtle structural changes. The photolysis of 11β-nitrites **276–280** can functionalize both C(18) and C(19) methyl groups but the relative



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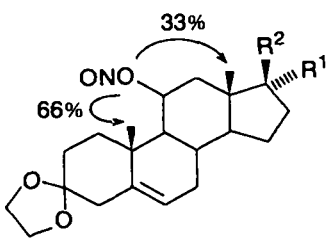

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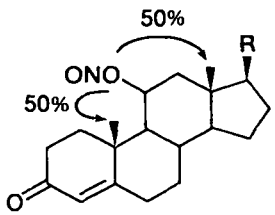

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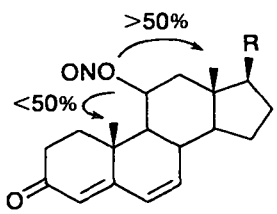

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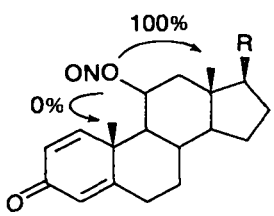
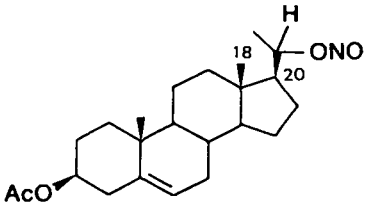


(280)

percentage varies considerably depending on the geometric shape of the *A*/*B* rings[246,278]. Obviously, as the *A*/*B* rings become flatter the C(19) methyl group separates further from the 11β-alkoxyl centre and the hydrogen abstraction from the C(19) methyl is progressively diminished. It has been consistently observed[245,246] that steroidal nitrites of the 20α-epimer give a much higher yield of 18-oximes than those of the 20β-epimer; more facile hydrogen abstraction by the 20α-alkoxyl radical with respect to other competing reactions may be explained by less steric crowding in this transition state as compared to that of the 20β-alkoxyl radical abstraction. Photolysis of the 20β-nitrite of pregnenyl acetate **281** gives the parent alcohol, the 20-ketone and the 18-oxime in 26, 13 and 44% yields, respectively, and that of 20α-nitrite in 14, 13 and 60% yields[279]. Photolysis of the 20α-nitrites of the etiojervene derivative[280] **283** and the lupane derivatives[281] **284** functionalizes the C(18) and



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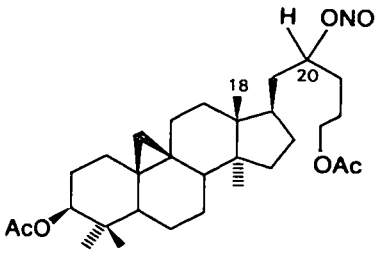

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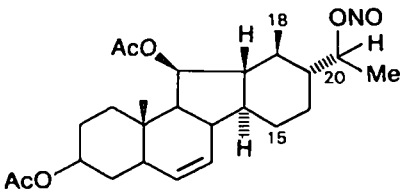

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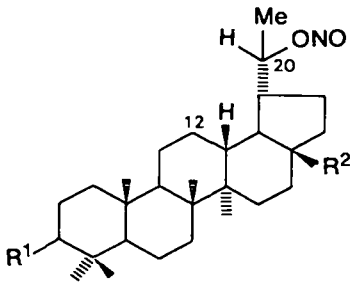
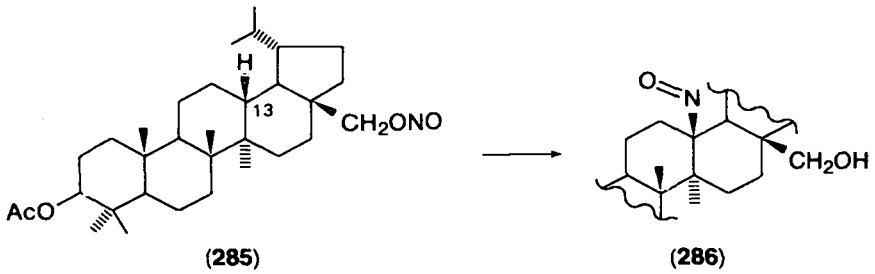


(284)

C(12) positons, respectively, and also yields the corresponding ketones and alcohols. However, the 20β-nitrites yield on photolysis complex mixtures containing none of the expected oximes. It is reported that the C(18) methyl group in cycloartenol derivatives **282** is functionalized in 50% yield regardless of irradiating the 20α- or 20β-nitrite[282]. The functionalization of **284** at the C(12)-position requires that the alkoxyl radical abstract the 12-hydrogen by a seven-membered ring transition state because of the geometric constraint in bringing the two centres in closer proximity. Such a seven-membered transition state has been observed in the photolysis of a diterpene nitrite[283] (see equation 202).

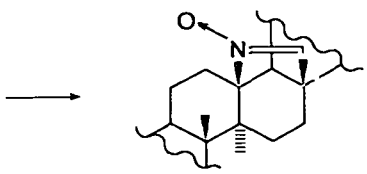
On the basis of the extensive data on the decomposition of long-chain tertiary hypochlorites, the relative reactivities of hydrogens toward intramolecular abstraction by alkoxyl radicals are determined to be primary < secondary < tertiary in the approximate ratio[284] of 1:9:47. The photolysis of 3β-acetoxy-28-nitrosoxylupane (**285**) gives a good yield of the 13-nitroso derivative arising from the preferential abstraction of the C(13) tertiary hydrogen over other hydrogens[285]. Nitroso compound **286** is isolated as nitron **287**, the conversion of which might involve photoexcitation of the nitroso group.

Functionalization of other unactivated positions with appropriately located nitrite groups in other steroidal systems by the Barton reaction have been published[286–289]. While photolyses of the nitrites of 4,4-dimethyl-6-β-hydroxycholestane[286], 21-chloro-20β-hydroxypregn-4-en-3-one[288] and 3β-acetoxylandrostan-7α-ol[289] give the expected oximes in good yields, irradiation of the 3β-nitrite **288** demonstrates the types of by-products[287] being persistently encountered in nitrite photolysis. Among these products *syn* and *anti*oximes **292**, nitrate **293** and ether **291** are derived from the primary photoproduct, the 5β-CH_2NO compound. The last two are most likely formed from the intermediacy of diazonium nitrate $RN{=}NONO_2$ (equations 134,

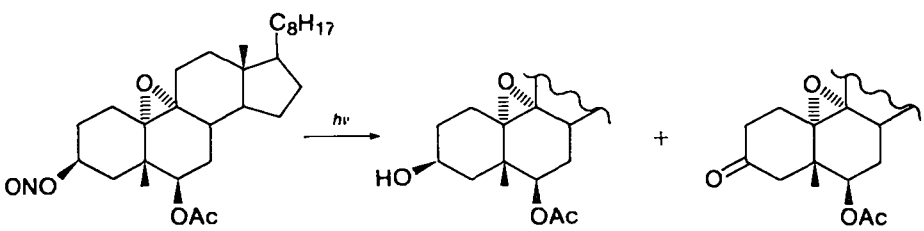


(285) (286)

(199)

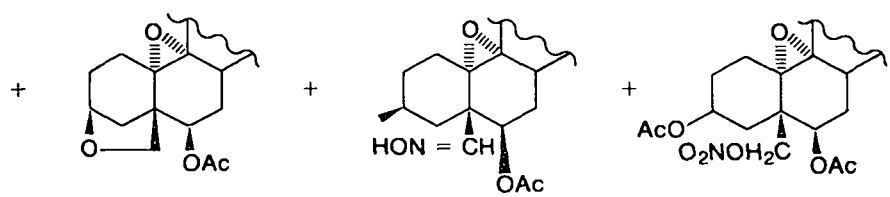


(287)



(288) (289) (290)

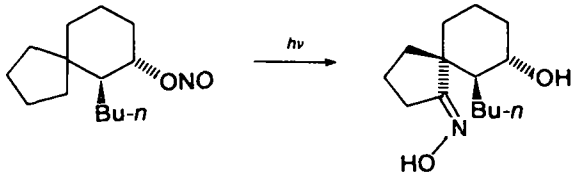
(200)



(291) (292) (293)

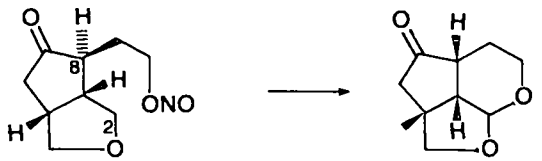
138 and 139 in Section V.A); In the photochemistry of complex alkyl nitrites in solution, both the alcohols and ketones, such as **289** and **290**, are persistently isolated as by-products. The disproportionation reaction of alkoxyl radicals (equation 179) obviously does not account for their formation in solution since the yields are concentration-independent. By showing the formation of hyponitrous acid, $H_2N_2O_2$, in the photolysis of a nitrite, the ketones such as **290** are shown to be formed[279] by equations (185) and (186). The parent alcohol **289** is commonly regarded as being formed by intermolecular hydrogen abstraction by the alkoxyl radical. However, it has also been claimed that hydrogen abstraction occurs from the corresponding *C*-radical rather than form the alkoxyl radical[279] (see Section VI.C.3).

The Barton reaction is a powerful synthetic technique which can functionalize a remotely located and unactivated alkyl carbon, not readily achieved by conventional methods. The nitrite phototransformation shown in equation (201) cleverly exploits



(201)

the orientation of the nitrite group to manoeuvre the oxime group on the right side of the ring in the synthesis of perhydrohistrionicotoxin[290]. Photoexcitation of nitrite **294** simultaneously epimerizes the C(8) position and functionalizes the C(12) position via a seven-membered transition state to give a precursor of tetrahydroanhydroaucubigenin (**295**)[291].

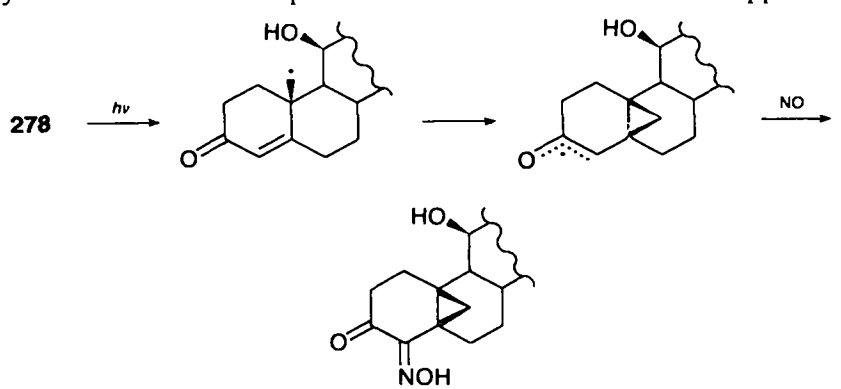


(202)

(294) **(295)**

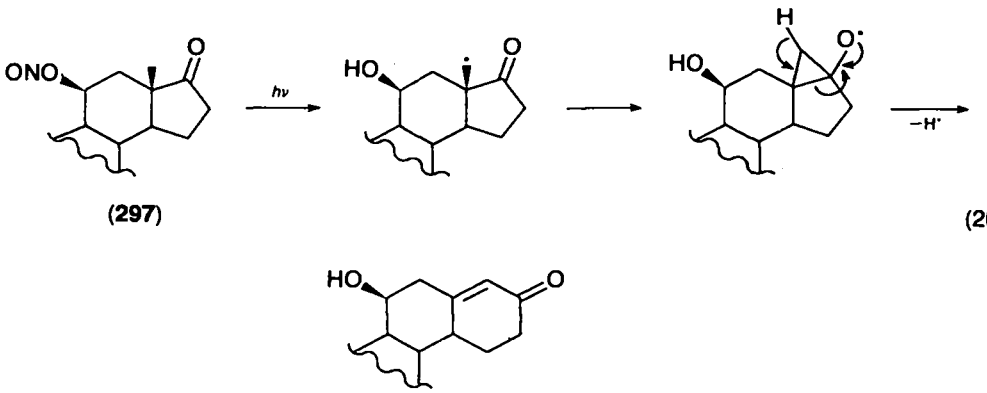
2. *Reactions of the alkyl radicals*

In comparison with carbonium ion rearrangements, alkyl radical rearrangements are relatively rare. However, when a *C*-radical centre is generated in a complex molecule, unexpected molecular reorganization may occur. Alkyl radicals can have a nucleophilic character[292] through a contribution from electron-transfer resonance. The intramolecular attacks of the *C*-radicals generated in the Barton reactions on electron-deficient centres have been discussed[245,246]. Two of them, as shown in equations (203) and (204), are noteworthy. The cyclopropyl oxime **296** obtained in the photolysis of nitrite **278** can be simply explained by the radical attack at the electrophilic β-carbon terminus of the α,β-unsaturated ketone[293]. The *D*-ring expansion in the photolysis of Δ-[1]-androsten-3,17-dione-11β-yl nitrite (**297**) has been interpreted by the addition–cleavage pathway[284] shown in equation (204), although other rearrangement pathways are also possible. Rearrangements initiated by an alkyl radical attack at a proximate electron-deficient centre appear to be fairly



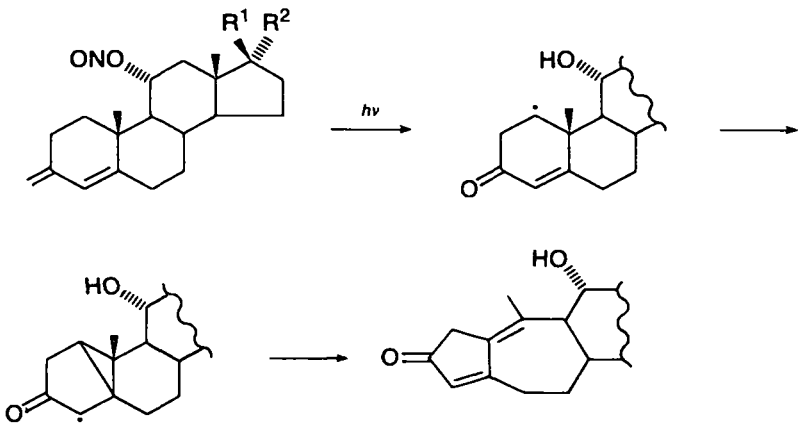
(203)

(296)

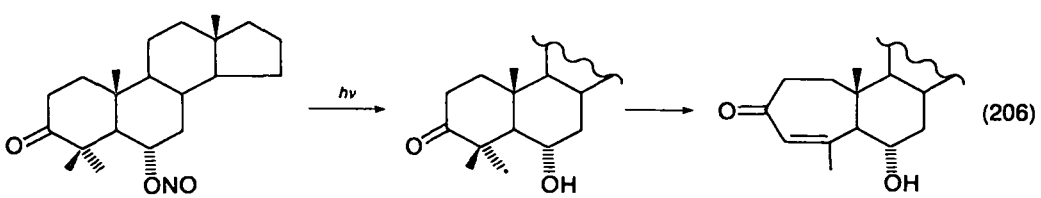


(297) (204)

general phenomena as demonstrated in two skeletal rearrangements[295,296] illustrated in equations (205) and (206). In both photolyses, since the expected oximes are also obtained as the major products, the alkyl radicals from the Barton sequence must be generated as the intermediates.

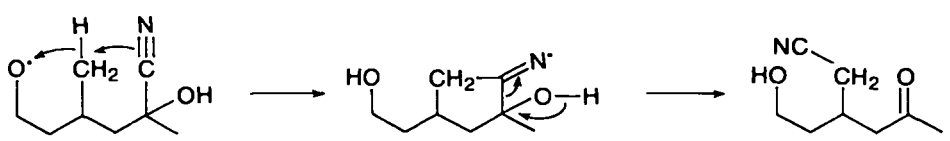


(205)



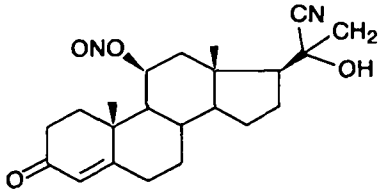
(206)

The basic mechanistic concept described above can be utilized to explain the radical-induced intramolecular migration of a cyano or formyl group described by Kalvoda and coworkers. The interesting reaction sequence shown in equation (207)

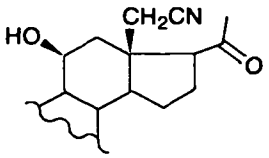


(298) (299) (207)

was proposed to explain the oxidative cyanohydrin–cyanoketone rearrangement induced with the iodine–lead tetraacetate reagent[255]. The photolysis of the 20-cyanohydrin of 11β-nitrosoxyprogesterone (**300**) proceeds in the expected manner to give cyanoketone **301** in 30% yield[297]. Similarly, the formylhydroxy analogue **302** is photolytically rearranged to ketone[298] **303**. The presence of the 20-hydroxyl group appears to be the key to this rearrangement in the sense that the proposed intermediate **298** is cleaved, in the manner indicated, to **299** with the participation of the 20-hydroxyl group.

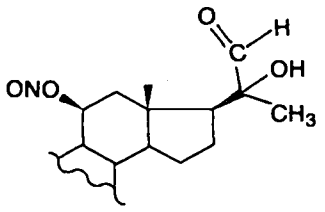


(300)

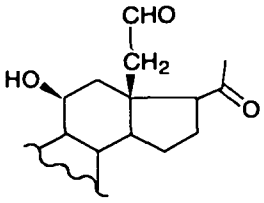


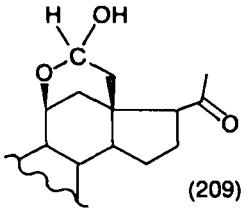
(301)

(208)



(302)





(303)

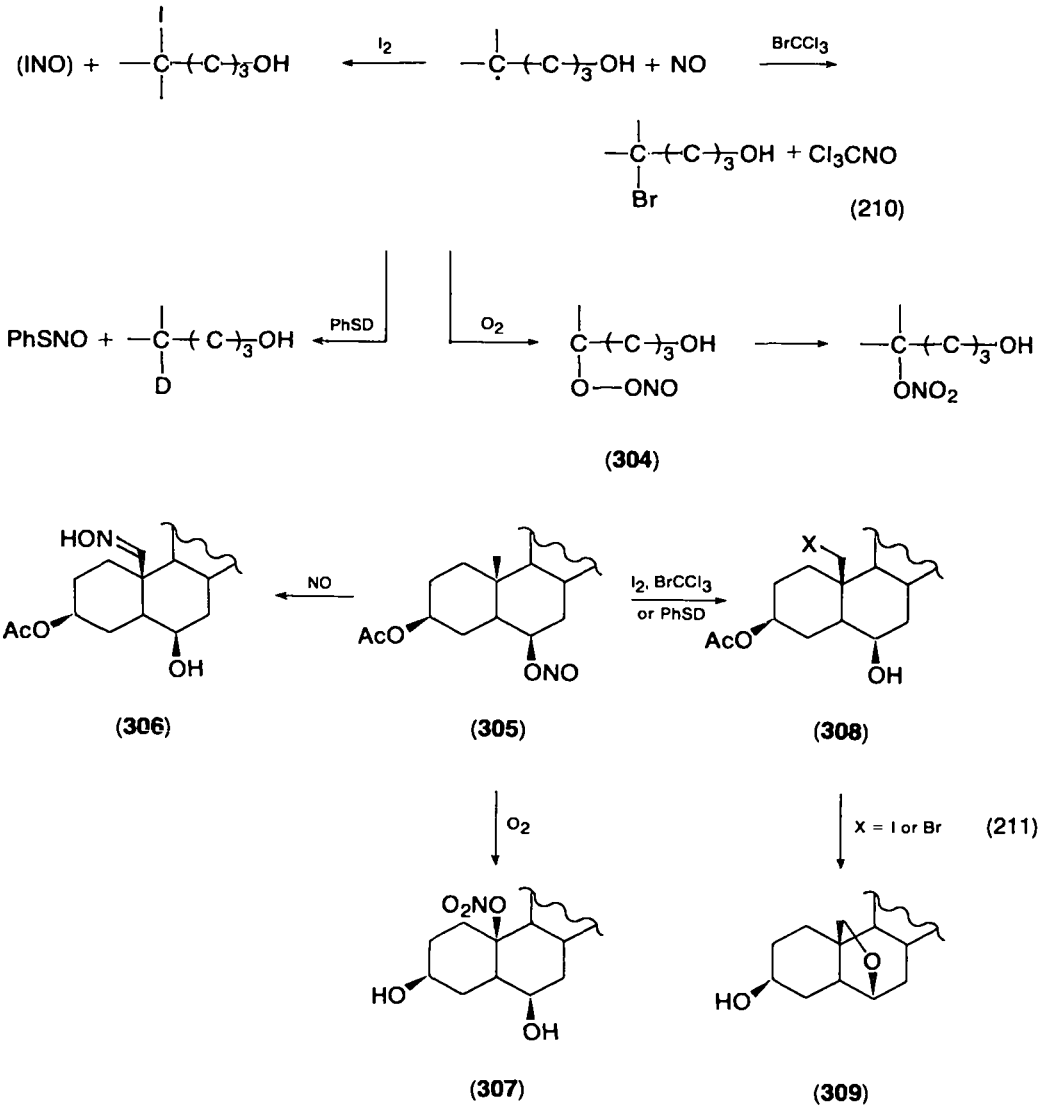
(209)

3. *Trapping of the alkyl radicals*

The Barton reaction, as illustrated in equations (182) and (184) or in equation (198), does not involve a caged intermediate of the alkyl radical and the nitric oxide; this is demonstrated by the extensive randomization of the ^{15}N label on 3β-acetoxycholeston-6β-yl nitrite (**305**) in the products of the photolysis of a mixture of this and another nitrite[299]. This is in contrast to the proposed caged reaction[279] of nitric oxide with alkoxyl radicals to form ketones as in equation (185). This explicitly indicates the discrete presence of the free *C*-radicals that may be captured with a spin-trapping agent; trapping by the nitrosoalkane formed *in situ* giving a stable nitroxide has been known for some time[259,260]. In effect, any trapping agent that can react with alkyl radicals with rates faster than the nitric oxide reaction (equation 183) may be applied to divert the final stage to the formation of new products. From the nature of the alkyl radicals[292] it is obvious that a trapping agent with electrophilic character would be the choice, and indeed, deuterated thiophenol, iodine, iodoform, bromotrichloromethane[300], and oxygen[221,301,302] have been shown to react with the alkyl radicals (equation 210). Among them, the scavenging with oxygen of alkyl radicals has been shown to be an excellent modification of the Barton reaction since the final products, alkyl nitrates, are stable to a variety of reagents[302] and >300 nm irradiation[221]. This oxidative photorearrangement was first demonstrated in the photolysis of 1-pentyl nitrite and menthyl nitrite in which the corresponding rearranged nitrates were obtained among other by-products[221]. In this photolysis, the primary photoproducts were most likely peroxynitrites **304** in analogy

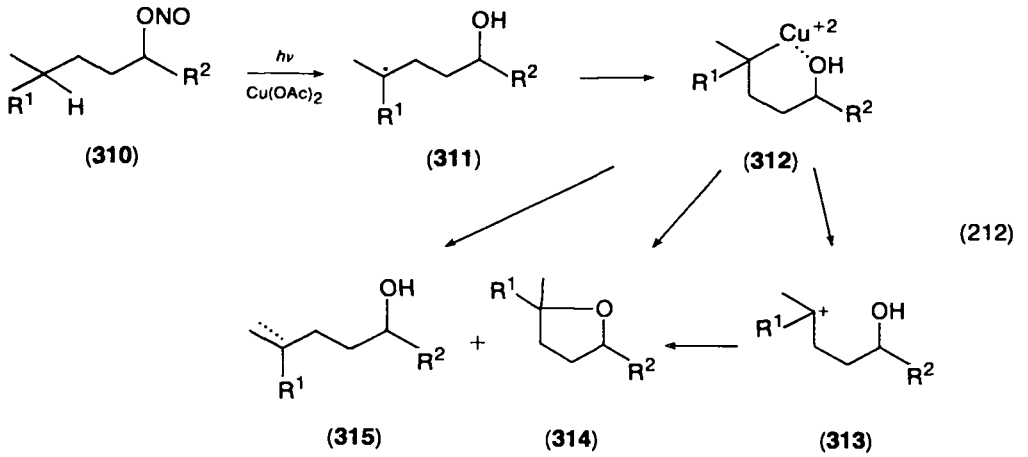
to the mechanistic pathways proposed for photooxidation of nitrosoalkanes as shown in equations (147)–(152). It was also shown that peroxynitrite **304** prepared *in situ* rearranged spontaneously to the nitrate esters[279].

Using cholestanyl 6β-nitrite **305** as a model compound, the observed trapping reactions of the corresponding alkyl radicals[279,300] are shown in equation (211). The incorporation of deuterium at the C(19) position in the alcohol **308** (X = D) in the presence of deuterated thiophenol constitutes good evidence that the alkyl radicals also abstract hydrogen intermolecularly. The intramolecular displacement in **308** (X = I) is spontaneous to give the ether **309** as the final product.



The photolysis of alkyl nitrites in the presence of cupric acetate[303] is most likely to involve the trapping of alkyl radicals **311** by the cupric ion to give copper alkyls **312** which decompose to a mixture of $\Delta^{4,5}$- and $\Delta^{3,4}$-alkenols **315** and tetrahydrofurans

314. The oxidative capture of alkyl radicals, such as **311**, has been proposed in the metal-catalysed decomposition of hydroperoxides[304,305]; the alkylcopper intermediate **312** is presumably stabilized by chelation as is often found in transition metal complexes. Since the $\Delta^{4,5}$-alkenols are consistently obtained in yields several times higher than the $\Delta^{3,4}$-alkenols, the alkenols are believed to be formed from alkylcopper **312** directly by the preferential elimination of a C(5) hydrogen.



(310) (311) (312) (315) (314) (313) (212)

R^1 = H, Me, Et, *n*-Pr; R^2 = H, Me

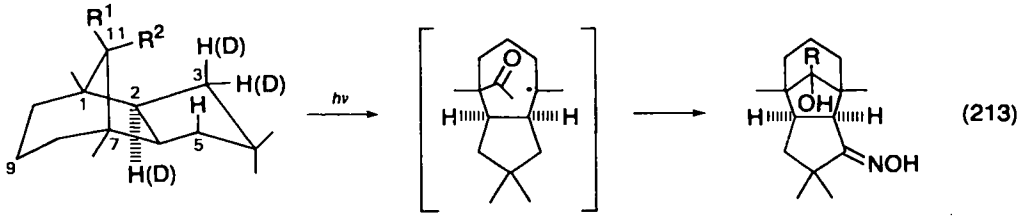
Tetrahydrofuran **314** could be formed directly from alkylcopper **312** or indirectly via carbonium ion **313**. As is common with other nitrite photolyses, the parent alcohols and the corresponding carbonyl compounds are also obtained in significant yields.

D. Interface of the Barton and the α-Cleavage Reactions

The factors influencing the cleavage and intramolecular hydrogen abstraction for alkoxyl radicals generated by nitrite photolysis have been discussed. Among various possible decomposition pathways of alkoxyl radicals, these two reactions and intramolecular addition proceed by first-order kinetics; the competition for these pathways is more meaningful when considered in terms of stereochemical controls in alkoxyl radical reactions.

In the photolysis of isobornyl nitrite (equation 190)[257], the exclusive α-cleavage of the corresponding alkoxyl radical typifies the propensity of cyclopentoxyl radical ring-opening reactions[246]. The absence of hydrogen abstraction from the C(7) methyl group may be attributed to the fact that the C···O distance is greater[306] than 3 Å. It is noteworthy that the product distributions from the photolysis of the two sterically dissimilar isobornyl and bornyl nitrites are the same and the yields of the parent alcohols and the ketone are only traces[257]; it suggests that both photolyses proceed from a common intermediate, probably an alkoxyl-like radical from a C—O bond inversion[255].

Such a C—O bond inversion has been observed unequivocally in the photolysis of apollan-*epi*-11-ol and apollan-11-ol nitrites (**316** and **317**) and their 11-methyl homologues, in which the oximes **319** are obtained regardless of which epimeric nitrite is irradiated[307,308]. To account for these observations, it has been suggested that the alkoxyl radical **317** (R^1 = O$^\cdot$) epimerizes via a ring-opened radical **318** to the alkoxyl



(213)

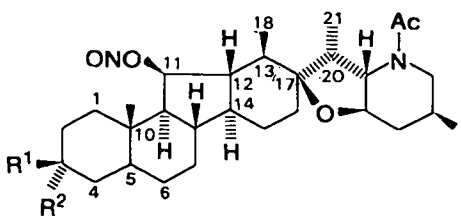
(316) R^1 = H, Me; R^2 = ONO
(317) R^1 = ONO; R^2 = H, Me

(318)

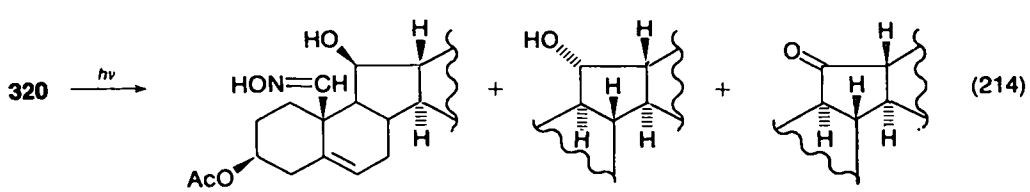
(319)
R = H, Me

radical **316** (R^2 = O•) and that this epimerized radical, without reverting to nitrite **316**, abstracts hydrogen from either the C(3) or C(5) position. Furthermore, its reactivity is identical with that of the alkoxyl radical generated from nitrite **316**, as shown by identical primary and secondary deuterium isotope effects in the photolysis of appropriately deuterated nitrites. Whatever the mechanistic details of the epimerization, it is clear that an electronically or vibrationally 'excited' alkoxyl radical is not required for hydrogen abstraction. The sensitivity of the transition state involved in the hydrogen abstraction (and also the α-cleavage reaction) is demonstrated by the low primary isotope effects (k_H/k_D = 1.1) for the tertiary nitrites (**316** and **317**, R^1 or R^2 = Me), as opposed to the k_H/k_D of 4.4 for the secondary nitrites (**316** and **317**, R^1 or R^2 = H), and also by high secondary isotope effects[307]. The photochemistry of this system is likely to throw more light on the mechanistic details of alkoxyl radical reactions.

The competition of alkoxyl radical reactions in the photolysis of complex nitrite esters has been shown in a series of interesting reports using nitrites derived from jervane[309,310], veratramine[311–314] and etiojervane[315] systems; in the photolyses of all these nitrites, except that of **337**, the corresponding alkoxyl radicals undergo the α-cleavage reaction in competition with other pathways. In particular, photolysis of nitrites **328** (and its 3,23-diketo analogue)[313], **329** and **330** result in the regiospecific

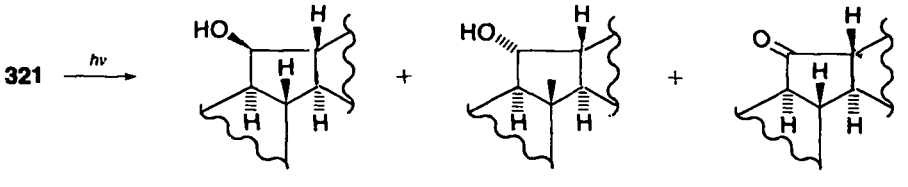


(**320**) R^1 = OAc, R^2 = H; $\Delta^{5,6}$
(**321**) R^1, R^2 = O; $\Delta^{4,5}$



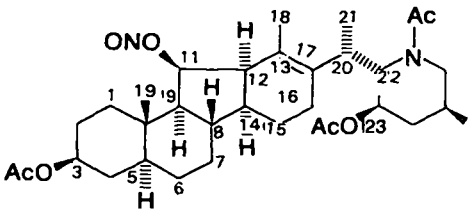
(214)

(**322**) 5%
(**323**) 27%
(**324**) 24%

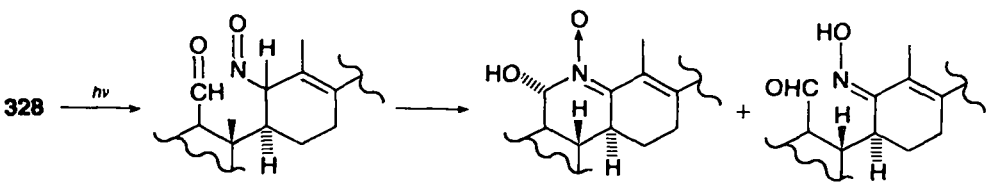


(325) 23%
(326) 2%
(327) 3%

(215)

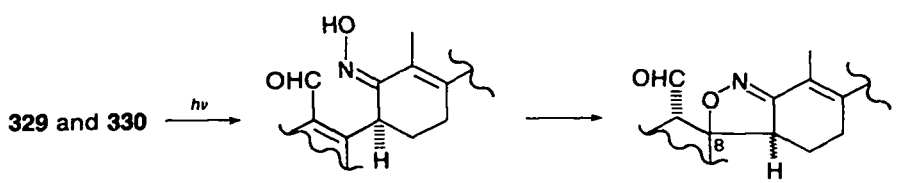


(328)
(329) $\Delta^{8,9}$
(330) $\Delta^{5,6;8,9}$



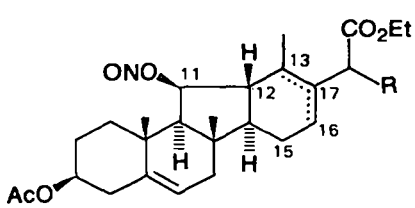
(331) (332) (333)

(216)



(334) (335)

(217)



(336) R = OAc; $\Delta^{13,17}$
(337) R = Ac; $\Delta^{16,17}$

cleavage of the C(11)–C(12) bond, predominantly because of the conjugative effect of the $\Delta^{13,17}$ double bond[311,314]. This occurs in spite of the fact that the C(18)–O distance is just abut 2.6 Å and that intramolecular addition of the alkoxyl radical to the $\Delta^{8,9}$ double bond is possible in **329** and **330**. The corresponding alcohols and ketones are not formed in any significant amounts. In both cases, the intermediates, nitroso aldehyde **331** and oximino aldehyde **334** can be identified and are shown to rearrange thermally, but not photolytically, to the final products, nitrone **332** and oxime **333** in the former and the epimers at C(8) of oxazoles **335** in the latter case. No doubt, the primary photoreaction is the homolysis of the nitrite group as shown by extensive scrambling of the ^{15}N labelling in the photolysis of ^{15}N-nitrite **328**; this proves that free alkoxyl radicals are discrete intermediates in these phototransformations.

The Barton reaction does occur in the photolysis of **320**, but only feebly in competition with the major α-cleavage pathway, if indeed the epimerization to 11α-alcohol **323** arises from the scission of an α-bond, i.e. the C(11)–C(12) or C(11)–C(9) bond[309,310]. Such an α-cleavage reaction does not seem to occur significantly in the photolysis of **321**. The poor material balances as well as the inconsistent product patterns in the two photolyses do not allow one to draw a conclusion. However, it is clear that configuration and conformation subtly control the reactivity of the alkoxyl radicals. As expected, the α-cleavage occurs in the photolysis of **336** to give the nitrone analogous to **332** in a low yield but it does not occur in that of **337**. In both cases, the Barton-type reaction products are not obtained.

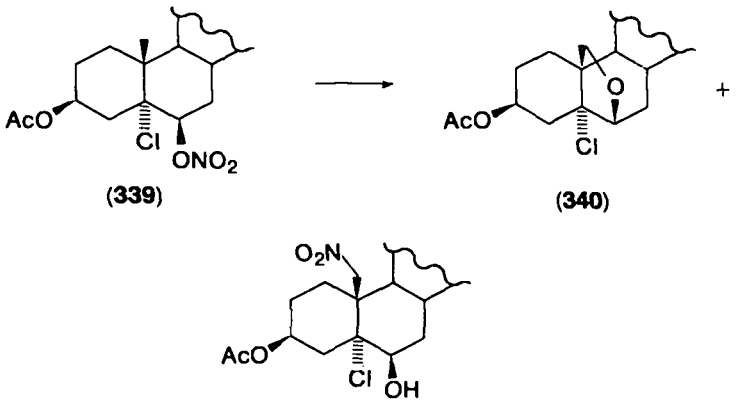
VII. PHOTOCHEMISTRY OF NITRATE ESTERS

Though aryl nitrate esters appear to be unknown, nitrate esters of simple alkanols are stable compounds. They show a weak (ε 12–37) $n \rightarrow \pi^*$ transition band at ca. 270 nm which is often submerged in the tailing of a much stronger $\pi \rightarrow \pi^*$ transition band[316,317] at ca. 190 nm. The photochemistry of alkyl nitrates has been scarcely investigated, partly because of problems of apparatus and side-reactions associated with higher energy irradiation. Early studies of the photolysis of simple alkyl nitrates[258,316,317] show that the primary photoprocess is the dissociation of the O—NO_2 bond to generate alkoxyl and nitrogen dioxide radicals; insofar as alkoxyl radicals are concerned, the photochemistry of nitrate esters resembles that of nitrites. However, nitrogen dioxide is much more reactive as a radical and as an oxidizing agent than nitric oxide. Photolysis of aralkyl nitrates (**338**) in benzene or ethanol has been shown to produce the carbonyl compounds (ArCHO) through the alkoxyl radicals by cleavage of the alkyl groups (equation 218); the benzene is converted to

$$\underset{\textbf{(338)}}{\mathrm{ArRCHONO_2}} \xrightarrow[\text{benzene}]{h\nu} \mathrm{ArRCHO^{\cdot}} \longrightarrow \mathrm{ArCH{=}O} + \mathrm{R^{\cdot}} \qquad (218)$$

2-nitrophenol and other nitroaromatics, and the ethanol is oxidized to acetaldehyde[317]. In contrast to nitrite photolysis, the ketones ArCOR are not obtained.

The Barton-type rearrangement can be observed in the photolysis of 3β-acetoxy-5α-chlorocholestan-6β-yl nitrate **339** producing small amounts of the ether **340** and the 19-nitro compound **341** together with the usual parent alcohol and ketone and many other unidentified compounds[317] (equation 219). The application of a nitrate group as a photolabile protecting group in carbohydrate chemistry has

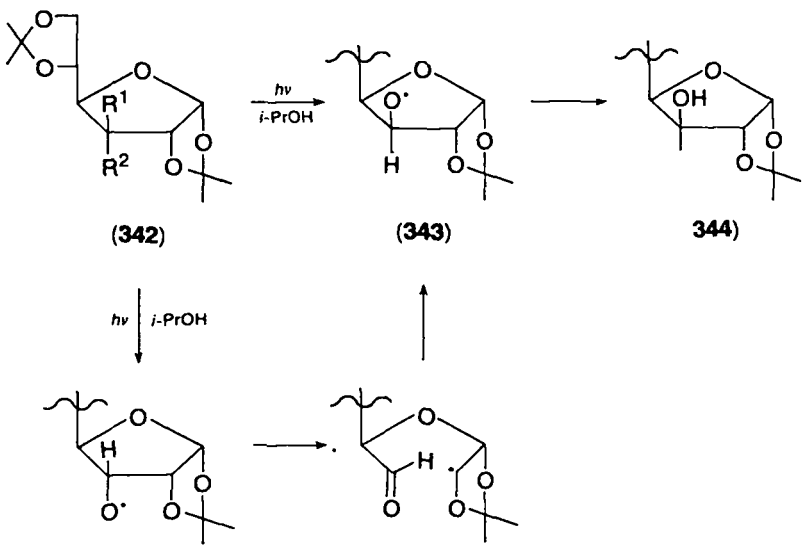


(339) (340) (219)

(341)

been demonstrated; the unusual C—O epimerization is observed (see Section VI.D, equations 213–215). Photolysis of some mononitrate esters of carbohydrates in *i*-propanol gives almost quantitative yields of the corresponding alcohol which can be explained by intermolecular hydrogen abstraction from *i*-propanol by the alkoxyl radicals[318] (see Section VI.A.5). Such efficient and clean denitration is a basis for using nitrate esters as a protecting group in synthesis, particularly in carbohydrates which generally contain no light-absorbing chromophore in the region above 200 nm.

Thus, photolysis of the 3β-nitrate **342** ($R^1 = ONO_2$, $R^2 = H$) gives the expected alcohol **344** in 92% yield via the alkoxyl radical **343**. Remarkably, the photolysis of the 3α-nitrate **342** ($R^1 = H$, $R^2 = ONO_2$) also gives the 3β-alcohol *quantitatively*, for which the inversion mechanism similar to that shown in equation (213) is proposed (see equation 220). While attempts to trap alkyl radical **346** have not been successful, the extraordinary feature is the complete regiospecificity in cleaving and reforming the C(2)–C(3) bond for which stereoelectronic factors have been invoked as possible explanations.



(342) (343) 344)

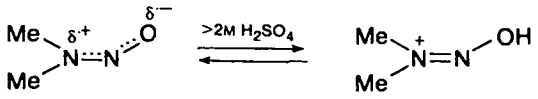
(345) (346) (220)

VIII. PHOTOCHEMISTRY OF *N*-NITRO AND *N*-NITROSO COMPOUNDS

Stimulated by the remarkable success in nitrite photochemistry, photochemical studies of *N*-nitroso compounds started to appear in 1964 and those of *N*-nitro compounds in the early 1970s. The development of photochemistry in this field coincides with the discovery of the carcinogenicity of *N*-nitroso compounds, which are present ubiquitously in low concentration in environmental samples, such as preserved meat and fish, cosmetics, beer, cheese, wine, tobacco smoke, just to mention a few[319]. Although carcinogenicity of *N*-nitro compounds is less well-established, their toxicity must be assumed since they can be reduced to N-nitroso compounds in biological systems. Considering the fact that some *N*-nitro and *N*-nitroso compounds are common propellants and explosives, their chemical and biological activities must be defined urgently. Because of the similarity in their primary photochemical acts, *N*-nitro and *N*-nitroso compounds are discussed in the same section.

A. Nitrosamines

Simple dialkylnitrosamines, e.g. *N*-nitrosodimethylamine (**347**), are extremely stable molecules. Their structure is a resonance hybrid of the canonical forms shown in equation (222). Such a resonance structure has been amply substantiated by



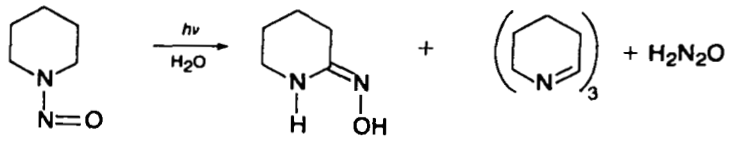
(347) (348) (221)

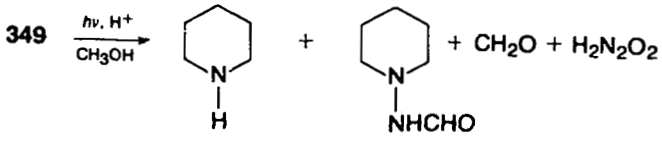
(222)

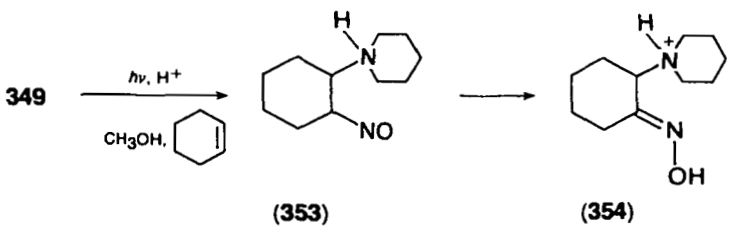
electron diffraction studies[320] of **347** and X-ray diffraction studies[321] of its cupric chloride complex, revealing the coplanarity of the C_2N_2O moiety and the partial double-bond character of the N—N bond. The latter gives rise to the magnetic nonequivalence of the two methyl signals in the NMR spectra, the temperature-dependent character of which provides for the activation energy for free rotation at the N—N bond[322,323] to be 23.4 kcal/mol. Because of the extensive contribution of the polar form (ca. 48% by SCF calculations)[324], high electron density resides at the oxygen atom but not at the amine nitrogen atom; thus protonation[325] in >2M H_2SO_4 solution or alkylation with a carbonium ion[321] occurs at the oxygen as in equation (221). Most simple dialkylnitrosamines exhibit the $n \rightarrow \pi^*$ transition band in the vicinity of 350 nm (ε ca. 100) and the $\pi \rightarrow \pi^*$ band[326] at 230 nm. The $n \rightarrow \pi^*$ band is bathochromically shifted with increased steric crowding at the α-position; e.g. *i*-Pr_2NNO absorbs at 370 nm. The photochemistry of nitrosamines was reviewed[327] in 1973.

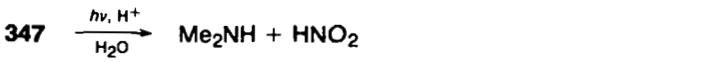
Irradiation of a dialkylnitrosamine in neutral solvents at the $n \rightarrow \pi^*$ transition band (in a Pyrex apparatus) causes almost no perceivable decrease of the absorption band. The decrease is slightly faster when irradiated at the $\pi \rightarrow \pi^*$ transition band but it is too slow for the practical purposes of photolysis[328–331]. In dilute acidic solution, e.g., 0.5–0.001N hydrochloric acid in alcohols or water[328,331], the photolysis of the nitrosamines under nitrogen proceeds efficiently with quantum yields of about

2.5. Using *N*-nitrosopiperidine (**349**) and **347** as model compounds, the typical photoreactions of nitrosamines under acidic conditions are summarized[331] in equations (223)–(226).





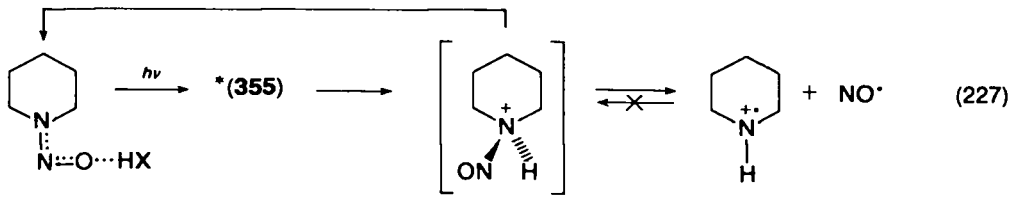




The photoelimination shown in equation (223) involves the elimination of HNO as the overall step but HNO may also attack the C=N double bond to give amidoxime **350**. This process occurs predominantly in a poor hydrogen-atom-donating solvent, such as water or acetic acid, and by the $n \rightarrow \pi^*$ excitation[331]. The photoreduction (equation 224) is favoured in good hydrogen-donating solvents and by excitation of the $\pi \rightarrow \pi^*$ band[331]. In the presence of an olefin[332,333], such as cyclohexene, the photoaddition as shown in equation (225) dominates the reaction to give the *C*-nitroso compound **353** which rearranges to 2-aminoketoximes **354**. In acidic aqueous solution, **347** photolytically hydrolyses to give dimethylamine and nitrous acid as shown in equation (226): the photohydrolysis is facilitated by the presence of nucleophiles such as guanidine and urea[334].

1. Primary photoprocesses

From UV spectroscopic studies[325], nitrosamines have been shown to associate with an acid in dilute acidic solution as shown in **355**. While neither neutral nitrosamine **347** nor the protonated **348** are photolabile, the acid complex **355** is assumed to be the species responsible for the observed photoreactions and has been suggested to undergo primary photochemical acts as shown in equation (227) to give



aminium radicals[327], e.g. the piperidinium radical **357**. The lowest singlet excited state of **355** is believed to decay to the ground-state *N*-nitrosoammonium ion **356** which decomposes to the piperidinium and nitric oxide radicals with the aid of residual vibrational energy or, even, by a second photon. The recombination of the radicals are retarded because **356** is a high-energy species and no low energy pathway is available to form **355**. The singlet-state reaction is derived from the failure of oxygen to quench the photoreaction (see Section VIII.A.4) and from the failure of triplet sensitization with carbonyl compounds; flash photolysis also shows that the precursor of the piperidinium radical[335] has a lifetime shorter than 10^{-7} s which is not likely to be a triplet state.

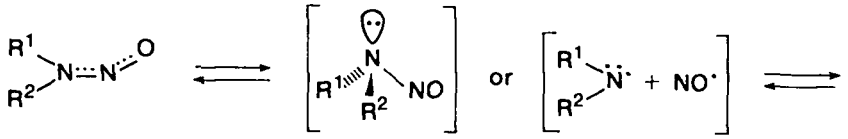
Flash excitation[335] of **349** in dilute acidic solution gives the piperidinium radical **357** as the observable transient which decays with the first-order rate constant of $8.3 \times 10^3\ s^{-1}$ in 0.01N aqueous H_2SO_4 solution, and reacts with various substrates with the second-order rate constants (k_2) shown in Table 3. It is noteworthy that the addition of the piperidinium radical **357** to cyclohexene and 1,3-pentadiene is faster by three orders of magnitude than its hydrogen abstraction from alcohols or dioxane. These kinetic data quantitatively reveal the relative importance of photoelimination, photoreduction, and photoaddition (equations 223–225).

While the presence of an acid for efficient photolysis is well-established, photolysis of nitrosamines in neutral solvents is also reported; for example, *N*-nitrosodiethylamine has been shown to photodecompose in methanol and cyclohexane[336] and **347** is photolysed at 77 K to give the ESR signal of the dimethylaminyl radical[337]. During the photolysis acids may be formed from the nitroso moiety, particularly by π–π^* irradiation, and may catalyse the photodecomposition. With low concentrations and small quantities of nitrosamines, such induced photolyses no doubt occur extensively. It is shown that various unsymmetrical nitrosamines can be reversibly and repeatedly photoisomerized (*E* to *Z* isomers or vice versa) in deuterated acetone, toluene, or acetonitrile without

TABLE 3. Second-order rate constants for the reaction of the piperidinium radical **357** with various substrates

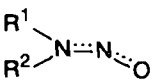
Substrate	k_2 ($M^{-1}\ s^{-1}$)
Methanol	$(2.4 \pm 0.3) \times 10^3$
Ethanol	$(1.4 \pm 0.2) \times 10^4$
i-Propanol	$(4.4 \pm 0.2) \times 10^4$
t-Butanol	$(3.6 \pm 0.5) \times 10^3$
Cyclohexene	$(2.4 \pm 0.1) \times 10^7$
1,3-Pentadiene	5.3×10^7
Benzene	$\leq 3 \times 10^2$
Dioxane	9.3×10^3

causing photodecomposition[338]. The isomerization may occur either via the intermediacy of the electron-localized tetrahedral amine configuration **358** (the



(358)

(228)

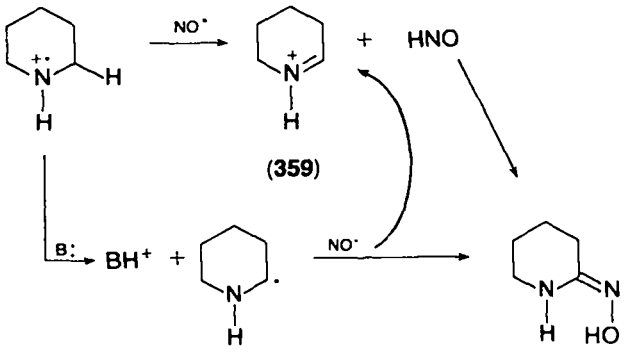


unprotonated analogue of **356**) as the consequence of the $n \rightarrow \pi^*$ excitation, or by homolysis to aminyl radicals and NO· followed by recombination. If the latter mechanism operates, the recombination process must be very fast, which may indeed be the case since no conceivable energy barrier exists for the recombination. However, the occurrence of nitrosamine photodecomposition in neutral solution depends on structure and conditions[336] and, without special structural reasons, can never be an efficient process (see Section VIII.A.5).

Photohydrolysis of nitrosamines is an important process in the destruction of these compounds in environmental samples. It is assumed to occur by the attack of a nucleophile at the nitroso group[334] of **356**.

2. Photoelimination

Mechanistically, this process[328–331] may be interpreted either as nitric oxide assisted hydrogen-atom detachment (cf. equations 185 and 186) or, alternatively, as deprotonation giving the α-amino radical **360** followed by electron transfer to nitric oxide (equation 229). Amidoximes may arise from radical combination of nitric

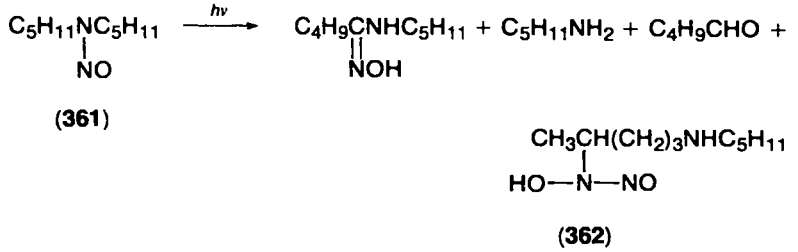


(359) (360) (350)

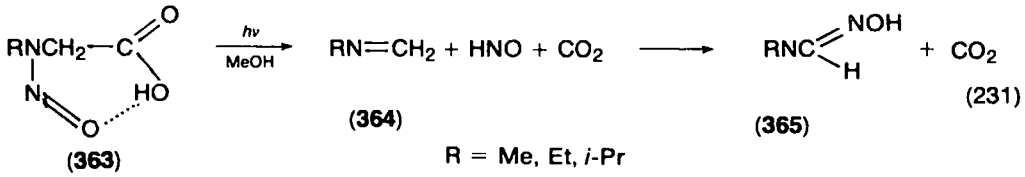
(229)

oxide with **360** or nucleophilic attack of HNO on **359**. Imonium ions **359** also undergo polymerization as shown in equation (223) or hydrolysis as indicated by the formation of pentanal and pentylamine in the photolysis of *N*-nitrosodipentylamine[331] (equation 230). A hydrogen atom of the more substituted α-carbon or of a benzyl carbon is always preferentially eliminated to form a more substituted or conjugated C=N bond. Thus, the photolysis of *N*-nitroso-*N*-methylcyclohexylamine yields large amounts of cyclohexanone and

methylamine, and that of *N*-nitroso-1,2,3,4-tetrahydroisoquinoline gives 87% of 1-oximino-1,2,3,4-tetrahydroisoquinoline[331].

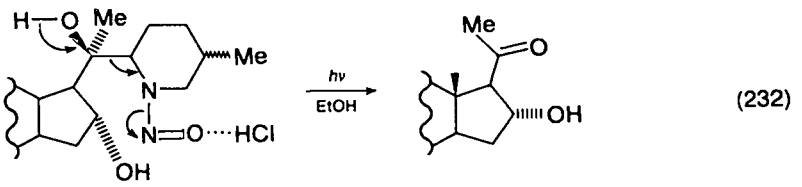


(361) (362) (230)



(363) (364) (365) (231)

R = Me, Et, *i*-Pr



(366) (367) (232)

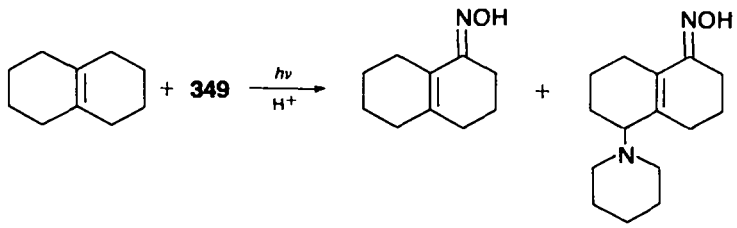
The photoeliminations of *N*-alkyl-*N*-nitrosoglycine[339,340] (**363**) and a nitroso derivative **366** of the cholestene series[341] give excellent yields of products **365** and **367**, respectively. The photolysis of **363** in methanol proceeds rapidly without the assistance of an external acid, obviously intramolecularly catalysed by the proximate carboxyl group[340]. Furthermore, in neutral solution *N*-nitrosopipecolinic acid is efficiently photodecomposed to **350** while *N*-nitrosonipecotic acid is photostable[340]. These results confirm the role played by acids in this photoreaction.

It is not certain that the corresponding aminium radicals act as intermediates in the photolysis of **363** (equation 231), since a concerted elimination mechanism can be easily written. Irradiation of *N*-nitroso-*N*-methylaniline at the $n \rightarrow \pi^*$ band in neutral or acidic solution causes sluggish decomposition due to the formation of highly coloured *N*-methyl-4-nitrosoaniline (see Section VIII.A.5)[328]. However, *N*-nitroso-*N*-phenylglycine (**363**, R = Ph) is readily photodecomposed to *N,N',N''*-triphenylhexahydrotriazine, a trimer of **364** (R = Ph)[340]. It should be added that photolysis of nitrosamine **363** in the presence of cyclohexene does not give the addition product as is obtained in equation (225) (see Section VIII.A.4).

3. Photoreduction

Hydrogen abstraction by aminium radicals is just as common as by alkoxy radicals; when it occurs intramolecularly, it is similar to the Hoffmann–Löffler reaction, the Barton reaction (Section VI.C) and nitrosamide photolysis (Section VIII.C). In the photolysis of *N*-nitrosodipentylamine (equation 230)[331], the functionalization at the

C(4) in **362** arises from intramolecular δ-hydrogen abstraction and a mechanism similar to that discussed in the Barton reaction (Section VI.C). The *N*-nitrosohydroxylamino group is derived from the reaction of the 4-nitroso derivative, the primary product, with HNO[342]. Owing to the propensity of aminium radicals to attack olefinic bonds, their intermolecular hydrogen abstraction involving allylic hydrogen does not occur to any significant extent unless a double bond is severely hindered[343] as shown in the oximation of $\Delta^{9(10)}$-octalin in equation (233).



(233)

The photolysis of nitrosamines in methanol (or other alcohols) causes reduction of the former and oxidation of the latter[331] as shown in equation (224); a likely mechanism is shown in equations (234)–(237). In ethanol solution, acetaldehyde and *N*-acetamidodialkylamines are obtained[342].

$$R_2NNO\cdots H^+ \xrightarrow{h\nu} R_2NH^{\ddagger} + NO^{\bullet} \quad (234)$$

$$R_2NH^{\ddagger} + CH_3OH \longrightarrow R_2NH_2^+ + {}^{\bullet}CH_2OH \quad (235)$$

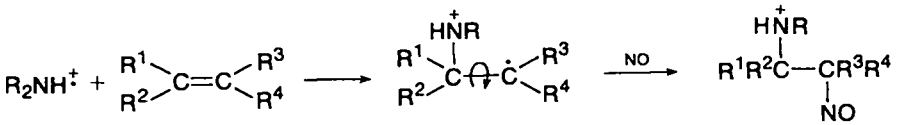
$$^{\bullet}CH_2OH + R_2NNO \longrightarrow R_2N{-}\underset{\underset{O^{\bullet}}{|}}{N}{-}CH_2OH \xrightarrow{NO^{\bullet}} R_2N{-}\underset{\underset{O{-}NO}{|}}{N}{-}CH_2OH \quad (236)$$

$$R_2N{-}\underset{\underset{O{-}NO}{|}}{N}{-}CH_2O{-}H \longrightarrow R_2N{-}NHCHO + HNO_2 \quad (237)$$

$$\text{or} \longrightarrow R_2NNO + CH_2O + HNO$$

4. *Photoaddition*

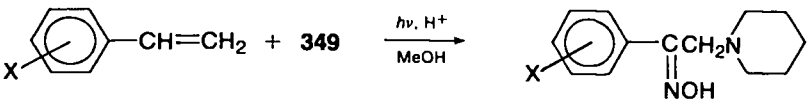
The nitrosamine photoaddition to olefins is a most efficient radical addition reaction to give excellent yields of 1:1 adducts and a potentially excellent reaction for preparing nitrogen-containing compounds from olefins. The success obviously hinges on the propensity of aminium radicals to electrophilically attack π-bonds by a stepwise radical addition[344] (equation 238) as indicated by the kinetic data (Section VIII.A.1). Because of the discrete stepwise addition mechanism, the intermediate *C*-radical **368** can be trapped by other radical-donating agents to give a variety of other derivatives[345]. The *C*-nitroso compounds **369** also undergo various thermal or photolytic secondary reactions which provide a glimpse of the scarcely



(368) (369) (238)

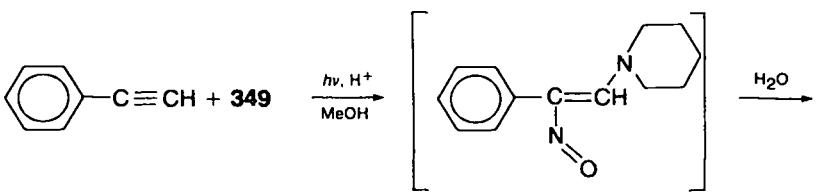
explored field of *C*-nitroso compound chemistry; the simplest one is the irreversible tautomerization to the corresponding oximes if R^3 and/or R^4 is hydrogen.

The photoaddition of nitrosamines to simple olefins is highly regiospecific in that aminium radical attack always leads to more stable radicals as controlled by electronic and steric factors[333] (*e.g.* equation 239). Photoaddition of nitrosamines to acetylenes[346] and conjugated dienes[347,348] also occurs; since the latter are very reactive substrates, the regiospecificity is slightly impaired (equation 241). The primary addition product of *N*-nitrosopiperidine to phenylacetylene[346], the β-nitrosoenamine **370**, is rapidly hydrolysed to give phenylglyoxal ketoxime (**371**) in solution; **371** tautomerizes reversibly to *C*-nitroso compound **372** and crystallizes as the dimer **373**. Other examples of photoadditions are described in the original



(239)

X = H, 4-OMe, 4-Me, 4-Cl, 4-CN, 3-Br, 3-OMe, 3-Me, 3-NHCOMe



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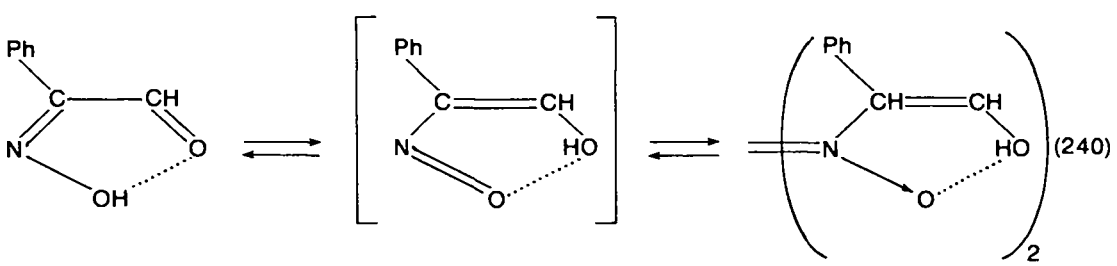
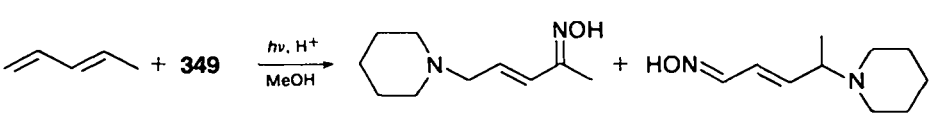


(240)

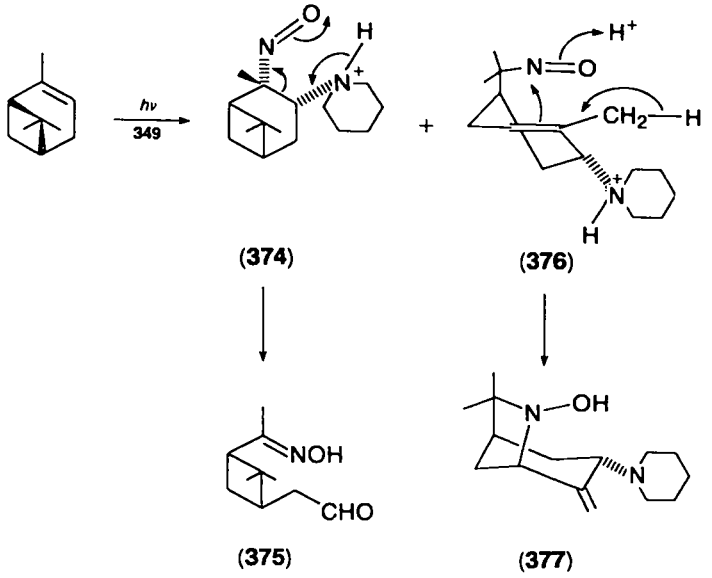
(371) (372) (373)



(241)

papers. The reactivity of olefins towards the nitrosamine photoaddition is in the decreasing order of $PhCH{=}CH_2$ > $RCH{=}CH_2$ > *cis*-$RCH{=}CHR$ > $Me_2C{=}CMe_2$ > *trans*-$RCH{=}CHR$ in which R is an alkyl group. The characteristically electrophilic nature of aminium radicals is demonstrated by a structure–reactivity correlation[349] using the photoaddition of **349** to substituted styrenes as in equation (239) to give a Hammett ρ value of -1.29. In agreement, it is also found that nitrosamines **347** or **349** do not photolytically add to electron-deficient π-bonds such as phenyl vinyl sulphone and methyl acrylate.

The photoaddition of nitrosamines is often accompanied by secondary reactions at various intermediate stages in equation (238). For example, photoaddition of **349** to α-pinene[350,351] gives *C*-nitroso compounds **374** and **376**, both of which undergo

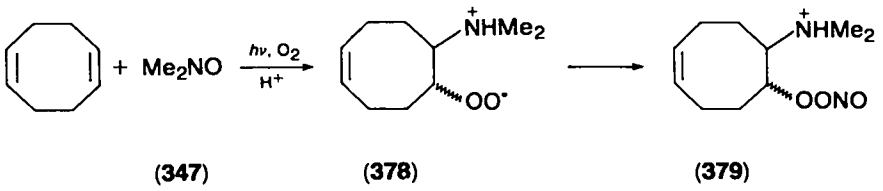


(242)

acid-catalysed rearrangements, (equation 242) to give the aldehyde **375** (and its methyl acetal) and the hydroxylamine **377**; the latter is readily air-oxidized to the stable nitroxide radical[351]. At −40°C, the formation of **375** and its congeners is favoured with excellent yields, but at room temperature or higher, the formation of **377** is favoured due to the thermally assisted cyclobutyl ring-scission from the *C*-radical intermediate such as **368**. The cleavage reaction of *C*-nitroso compounds **364** to **375** is facilitated by the *cis* configuration of the nitroso and ammonium groups and may occur by intramolecular proton transfer and electron reorganization as shown; such a cleavage reaction has been observed in the nitrosamine photoaddition to camphene, norbornene, α-methylstyrenes and β-pinene[350,352]. The cyclization of **376** to **377** occurs only when the nitroso and π-bonds are oriented in interacting proximity to provide some entropy gain. Similar reaction patterns are observed in the photoaddition to 1,5-cyclooctadiene and 5-methylen-2-norbornene[216,353].

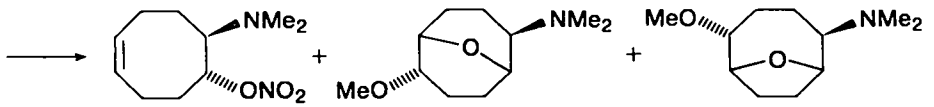
When the nitrosamine photoaddition to olefins is run in the presence of oxygen, the *C*-radical intermediate is trapped by oxygen to give nitrate esters, presumably via the intermediacy of pernitrites[345,354,355] as shown in equations (210) and (211) (see Section VI.C.3). Photoaddition of **347** under oxygen gives the *trans*-aminonitrate which is isolated, after reduction, as the *trans*-amino alcohol, in good yields; the *cis*-pernitrite rapidly reacts with the transannular π-bond to give **381** and **382** as the minor products[355]. The trapping of the *C*-radicals with bromotrichoromethane[356–358] affords the *endo*-bromo compound **386** as shown in the intramolecular photoaddition of nitrosamine **383** (equation 244); similar trapping experiments in the photolysis of nitrosamines **387** and **391** have been reported[357] (equations 245 and 246).

The intramolecular photoaddition of the nitrosamine **387** under oxygen affords good yields of unstable nitrate **388** which, after neutralization, rapidly undergoes a series of intramolecular reactions to give the amide **390** among other products[357]. The reactions involve the amino-group-assisted cleavage of the nitrate **388** to **389** followed by an intramolecular redox reaction, **389** → **390**[354]. Both rearrangements are facilitated by the stereoelectronic assistance of the lone-pair electrons of the amine centre, oriented antiperiplanar to the bonds being broken. A similar reaction



(347) (378) (379)

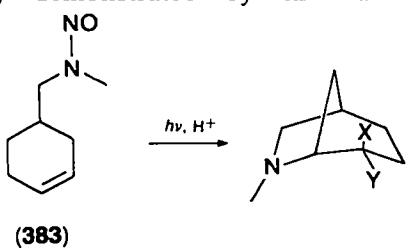
(243)



(380) (381) (382)

pattern prevails on oxidative photoysis of the nitrosamine **391** but the rearrangements occur more slowly; immediate reduction of the corresponding nitrate also affords the alcohol **393**[357].

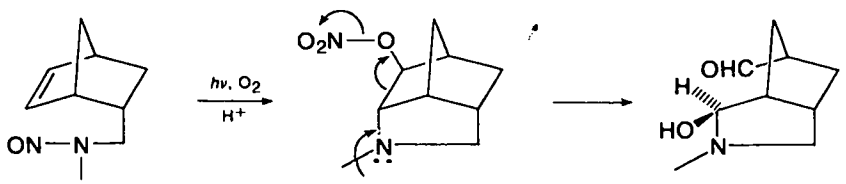
There are two noteworthy features in the intramolecular photoaddition of nitrosamines as shown in equations (244)–(246). Firstly, aminium radicals overwhelmingly attack intramolecularly the δ-position of the π-bond to give pyrrolidine derivatives to the exclusion of piperidine derivatives[356]. This is most strikingly demonstrated by the failure to produce the twisted azacyclic



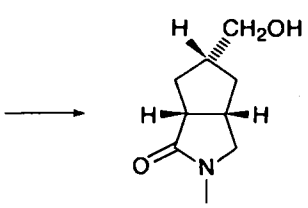
(383)

(**384**) X, Y = HON=
(**385**) X, Y = H, ONO_2
(**386**) X = H, Y = Br

(244)

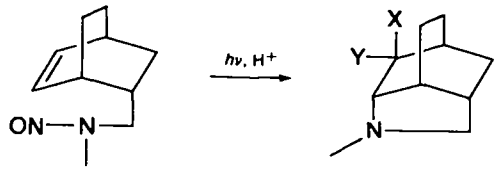


(387) (388) (389)



(390)

(245)



(391)

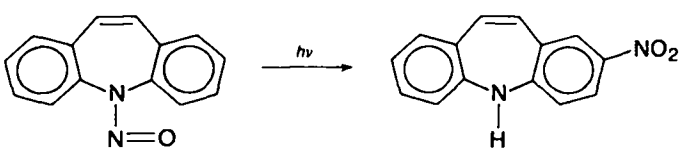
(392) X, Y = HON=
(393) X = OH, Y = H (246)

compound[357,358] in the photolysis of **391**. This regiospecific cyclization is believed to arise from better p-orbital overlap of the radical centre with the δ-position in the transition state. Secondly, aminium radicals preferentially attack (intramolecularly) a π-bond rather than abstracting an allylic hydrogen as shown in the photolysis of **383**: this reactivity pattern is similar to the intermolecular reaction of aminium radicals. In contrast, alkoxy radicals behave very differently in intermolecular and intramolecular reactions (see Section VI).

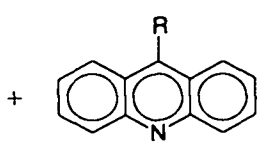
While both nitrosamines **347** and **349** fail to add photolytically to benzene, toluene, or anisole, they do so to condensed polynuclear aromatic compounds. Photolysis of these nitrosamines in the presence of anthracene gives good yields of 9-aminoanthrone oximes[359].

5. *Photolysis of other nitrosamines*

The photochemical behaviour of nitrosamines is very much affected by conditions and structure. Irradiation of *N*-nitroso-*N*-methylaniline at 254 nm causes reversible photochromism in water but rapid decomposition in alcohol[360]: with 313 nm light, this compound is photolysed slowly even in methanol. The photolysis in neutral solvent may largely depend on the stability of the generated aminyl radical which, with conjugative stabilization, may survive long enough to enter reactions other than recombination (see equation 228). Both 4-benzylnitrosamino-1,2,4-triazols[361] and *N*-nitroso-5*H*-dibenz[*b*,*f*]azepine (**394**)[362] are photolabile in methanol or benzene solution. The photolysis of **394** is efficient only in the presence of oxygen in which adventitious acids may have been formed; whatever the conditions, **394** undergoes an interesting photorearrangement as shown in equation (247). In both cases, the primary photoprocess is assumed to be homolysis of the N—N bond. However, the photodecomposition of the peroxynitrosamine[363] **398** may be triggered by

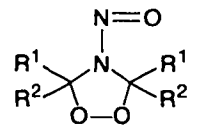


(394) (395) (247)



(396) R = H
(397) R = CHO

photoexcitation of the peroxy bond rather than the nitrosamino bond (equation 248).



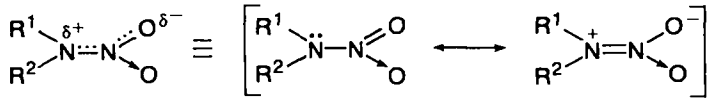
$$\xrightarrow{h\nu} R^1R^2C{=}O + N_2O \qquad (248)$$

(398)

R^1 and R^2 = Me, Et, $-(CH_2)_5-$

B. Nitramines

Simple dialkylnitramines undoubtedly possess structure **399** resulting from resonance as indicated by the short N—N bond distance (ca. 1.3 Å) determined by

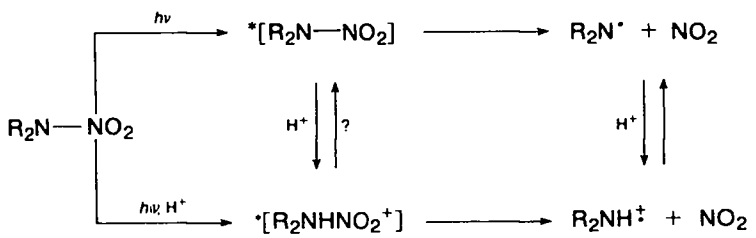


(249)

(399) (399a) (399b)

electron diffraction in *N*-nitrodimethylamine[364]. They exhibit a $\pi \rightarrow \pi^*$ transition band at ca. 240 nm (ε ca. 5000) without showing a $n \rightarrow \pi^*$ band[365,366]. In contrast to the photostability of nitrosamine in neutral solvents, nitramines can be photodecomposed in neutral solvents or in the solid state to afford nitrosamines as the sole or major products[367–369]. The ESR signals of the nitroxides are also detected in the photolysis of some cyclic nitramines[368]. In spite of the assertion of N—O bond scission in solid-state photolysis[369], the primary photoprocess of nitramines evidently occurs by N—N bond scission in analogy to nitramine thermolysis[370]. Photolysis of *N*-nitro-*N*-methyl-1-naphthylamine gives 2- and 4-nitro derivatives of *N*-methyl-1-naphthylamine and has been claimed to occur by a nonradical mechanism[371].

In recent studies[372,373], *N*-nitrodimethylamine and *N*-nitropiperidine are shown to photodecompose readily in neutral solvents, such as methanol, hexane, acetonitrile, or in dilute acid solution, e.g. methanol containing 0.1–0.05N hydrochloric acid, with quantum yields in the range 5–8. It is further shown that these nitramines add photolytically to olefins under acidic conditions but fail to do so under neutral conditions. Hence, it is proposed that photolysis generates aminium radicals under acidic conditions and aminyl radicals under neutral or basic conditions (equation 250). Since the acidity of excited-state nitramines is unknown, it is uncertain whether



(250)

(400) R, R = Me, Me

(401) R, R = $-(CH_2)_5-$

acid–base equilibrium is established upon excitation. Since the dimethylaminyl radical is shown[374] to have pK_a 6.5–7.5, the aminium radical must have been obtained in the acidic photolysis of nitramines.

Nitramines **400** and **401** are both photolysed in methanol under nitrogen to give the amines, dialkylformamides and a small amount of nitrosamines regardless of the presence or absence of olefins[372]. Under acidic conditions, the nitramines are photolysed to give the amines and formaldehyde *in the absence of an olefin*. The formation of these products may be interpreted by the reactions shown in equations (251)–(254), but each step may be explained by a variety of mechanisms. Both

$$R_2N^{\bullet} \text{ or } RNH^{\ddagger} + CH_3OH \longrightarrow R_2NH \text{ or } R_2NH^{+} + {}^{\bullet}CH_2OH \xrightarrow{-H^{\bullet}} CH_2{=}O \quad (251)$$

$$2\,NO_2 \rightleftharpoons N_2O_4 \quad (252)$$

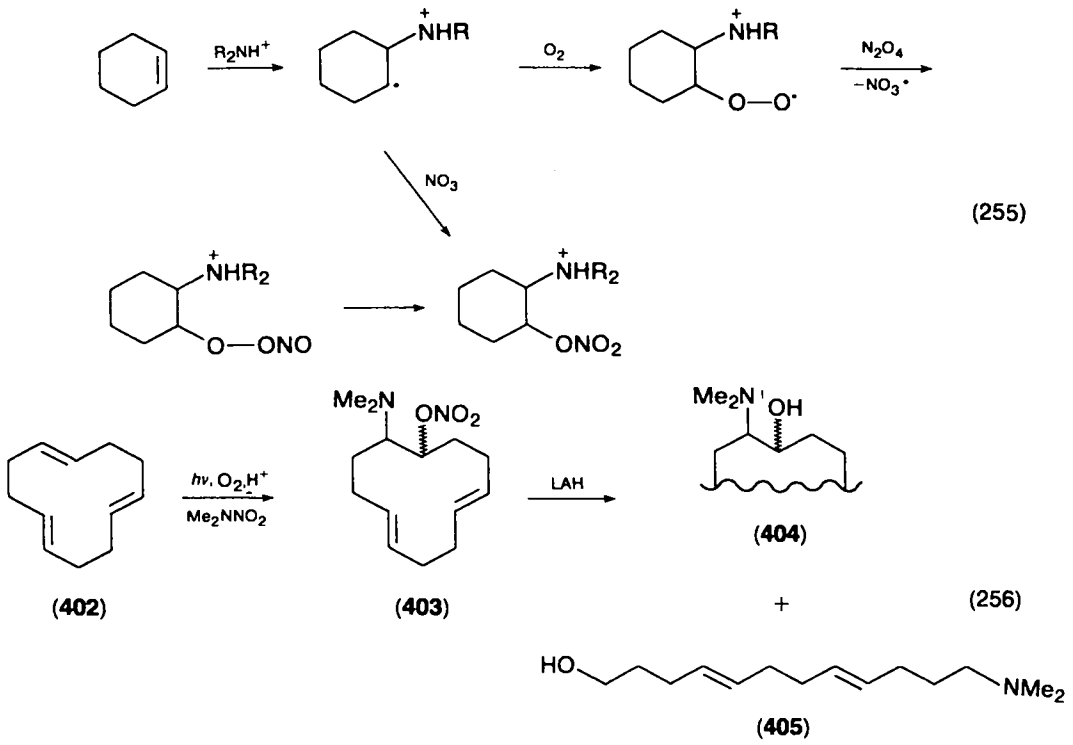
$$R_2NH + CH_2O \longrightarrow R_2NCH_2OH \xrightarrow{[o]} R_2NCHO \quad (253)$$

$$R_2NH + N_2O_4 \longrightarrow R_2NNO + HNO_3 \quad (254)$$

aminyl and aminium radicals are shown to abstract hydrogen[375,376] by which methanol is oxidized to formaldehyde. Nitrogen dioxide tends to dimerize to N_2O_4 which is a radical donor and an oxidizing and nitrosating agent[377]. That the nitrosamines are formed by the nitrosation of amines (equation 254) is shown by their high yields in the photolysis in the presence of sodium carbonate. The failure of the formation of the formamides and nitrosamines in acidic solution is due to the protanation of amine preventing the nucleophilic reactions in equations (253) and (254). In these photolyses, the products arising from α-elimination of aminium and aminyl radicals are also obtained, particularly in poor hydrogen-atom-donating solvents such as acetonitrile or *n*-hexane.

In *acidic solution under nitrogen*, nitramines **400** and **401** photolytically add to cyclohexene to give a complex mixture of addition products: e.g. 2-piperidinocyclohexanols, 2-piperidinocyclohexanone oxime, 1-nitro-2-piperidinocyclohexane, piperidinocyclohexenes and 1-methoxy-2-piperidinocyclohexane, etc. The plethora of products obviously arises from the fact that NO_2 can behave as an *O*- as well as a *N*-centred radical, that nitrite esters and *C*-nitroso compounds are formed and undergo secondary photolysis, and that N_2O_4 may react in more than one way[377]. This can be avoided when the photolysis is run under oxygen, in which 2-aminocyclohexanol nitrate esters are formed together with minor quantities of the corresponding cyclohexanols and cyclohexanones (equation 255); excellent yields of *cis*- and *trans*-2-aminocyclohexanols can be obtained after lithium aluminium hydride reduction. The mechanism depicted in equation (255) is similar to that of the oxidative photoaddition of nitrosamines shown in equation (243). The minor products, the cyclohexanones and cyclohexanols, are believed to be formed from the pernitrite by elimination and solvolysis. Indeed, photolysis of *N*-nitrodimethylamine and 1,5-cyclooctadiene under oxygen followed by a lithium aluminium hydride reduction also gives the same products, **380**, **381** and **382** in the same percentages[373] as those obtained in the nitrosamine photoaddition (equation 243).

Oxidative photoaddition of nitramine **400** to various olefins (e.g. 1-hexene, 3-hexene, *cis,trans*-1,5-cyclodecadiene, *endo*-dicyclopentadiene, etc.) and subsequent reduction have been shown to give similar results[373]. Oxidative photoaddition of **400** to *trans,trans,trans*-1,5,9-cyclododecadiene **(402)** gives the nitrate **403** and other



(255)

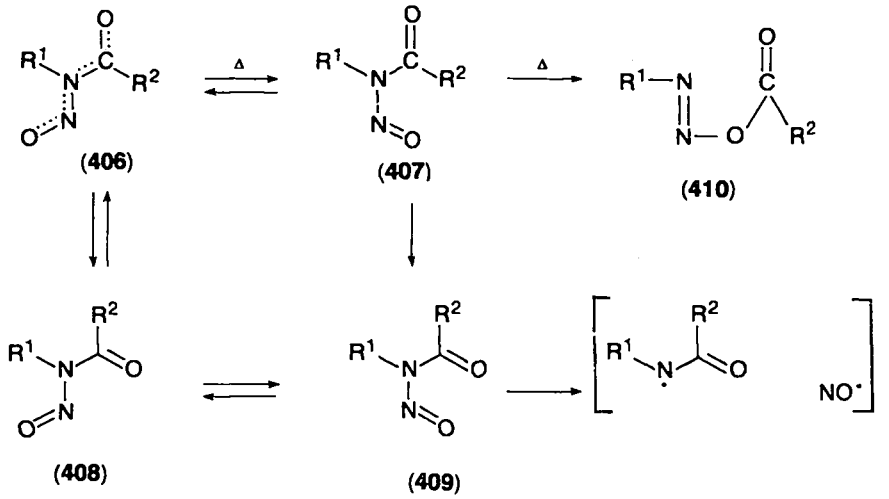
(256)

minor products. Surprisingly, lithium aluminium hydride reduction of **403** gives the open-chain amino alcohol **405** in 85% yield with only 15% of the corresponding alcohol **404**.

C. Nitrosamides

Alkylnitrosamides (**406**) show an orange–yellow colour and only one set of NMR signals for the alkyl groups; for example, *N*-nitroso-*N*-methylacetamide (**406**, $R^1 = R^2 = Me$) exhibits only two NMR singlets[378] indicating the lack of rotational isomerism commonly observable in the NMR spectra of amides and nitrosamines. Since a nitroso group is more electron-withdrawing than a carbonyl group, the delocalization of the electron pair at the amine centre with the nitroso outweighs that with the carbonyl as indicated by the carbonyl stretching absorption at 1730 cm^{-1}. In view of the dipole–dipole repulsion, the ground-state nitrosamides are considered to be preponderantly in conformation **406** among other conformers **407–409**.

Because of the biased delocalization, the N—CO bond in nitrosamides is weakened as shown by their facile rearrangement to diazo esters (**410**) at ambient temperatures. This fascinating thermal rearrangement is proposed to occur by the bond shifts from conformer **407** and is followed by the elimination of nitrogen to give deamination products; the reaction has been studied extensively[379]. Nitrosamides usually exhibit a $\pi \rightarrow \pi^*$ transition band at 240 nm (ε ca. 5000) and a series of peaks in the 390–430 nm region (ε ca. 100) for the $n \rightarrow \pi^*$ transition. In neutral solvents, polar or nonpolar, photolysis of nitrosamides causes scission of the N—NO bond to generate amidyl and nitric oxide radicals[182–184,211,378]: the ensuing chemical events are essentially those of amidyl and nitric oxide radicals, in a paired state or individually



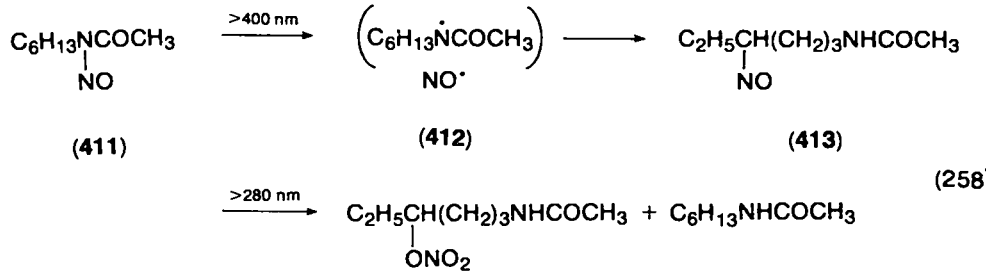
(257)

in the majority of solutions. Both the instability as well as the ready photodecomposition reveal the contrast between the behaviour of nitrosamides as compared to nitrosamines (cf. Section VIII.A).

1. *Pattern of nitrosamide photolysis*

Although amidyl radicals follow the general pattern of radical (e.g. alkoxy) reactions, the nitrosamide photolysis is complicated by the presence of a radical pair as shown in equation (257) and the disproportionation of nitric oxide arising from the secondary photolysis of *C*-nitroso intermediates. Photolysis of *N*-nitroso-*N*-hexylacetamide (**411**) with >400 nm light under nitrogen gives the δ-nitroso derivative **413** which is isolated as the *C*-nitroso dimer in good yields[345]. The reaction is essentially a δ-hydrogen nitroso group exchange and is mechanistically similar to the Barton reaction (Section VI.C). Photolysis with a Pyrex filter (>280 nm) under nitrogen yields nitrate **414** and hexylacetamide[183], which arise by disproportionation from the secondary photolysis of **413** by a similar mechanism[184] to that shown in equations (134) and (139). Photolysis of **411** in benzene solution saturated with nitric oxide (opaque up to 380 nm due to the presence of a trace of NO_2) does not affect the yield of *C*-nitroso compound **413**, nor does it result in the formation of nitrate **414**, indicating that external nitric oxide participates neither in the intramolecular hydrogen nitroso group exchange nor in the disproportionation reaction[211]. Therefore, it is proposed that the photolytically generated nitric oxide exists in pair with the amidyl radical as in **412** which collapses rapidly to give **413**.

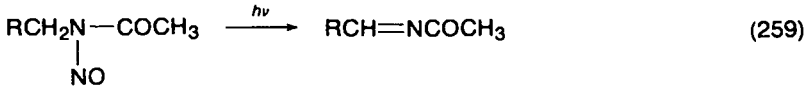
Irradiation of *N*-nitroso-*N*-hexanamide gives no intramolecular δ-hydrogen nitroso exchange product[183,380,381] due to unfavourable stereoelectronic factors in transferring a δ-hydrogen of the acyl chain to the amidyl radical centre[197] which is shown to have the π-radical configuration[382,383]. However, the photolysis yields the parent amide by intermolecular hydrogen abstraction and formylidenehexanamide (isolated as *N*,*N*′,*N*″-trihexanoylhexahydrotriazine) by α-elimination. When the Barton-type pathway is not available, amidyl radicals undergo these reactions: the former is favoured by good hydrogen-atom-donating substrates (e.g. mesitylene, toluene, cyclohexane, etc.) and the latter occurs extensively in poor hydrogen-donating solvents[182,183], particularly when such an elimination produces a



(411) (412) (413)

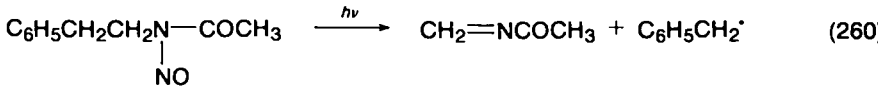
(258)

resonance-stabilized species such as the benzyl radical or benzylideneacetamide as in equations (259) and (260). Acylimines are generally converted by solvolysis or addition of nucleophiles to give the observed products, e.g. benzaldehyde, acetamide, $C_6H_5CH(NHCOCH_3)_2$, etc.



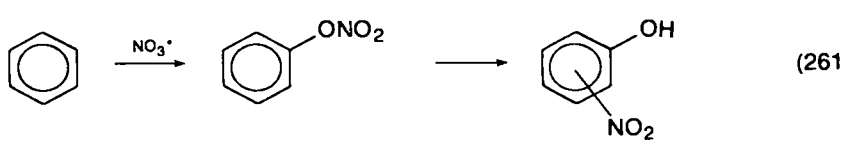
(259)

R = H or Ph

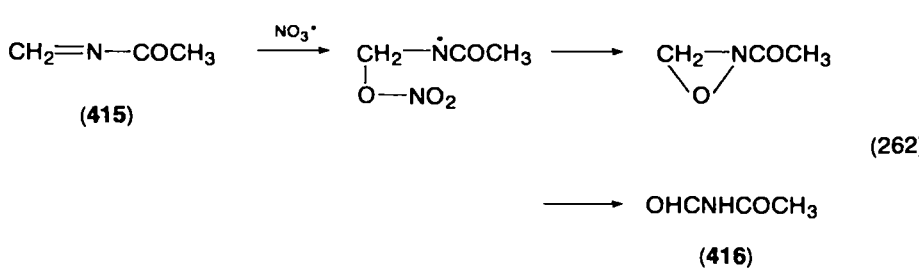


(260)

Photolysis of nitrosamides with a Pyrex filter always produces many minor side-products, such as nitrate esters or nitro compounds derived from solvents and nitroamides derived from the parent amides, suggesting the presence of $NO_3^{\bullet}$ in the reaction[182]. When benzene is used as the solvent, nitrobenzene and 2- and 4-nitrophenols are always obtained indicating the occurrence of radical reactions such as equation (261). Part of formylidene acetamide (**415**) is oxidized to *N*-formylacetamide (**416**) probably by the mechanism shown in equation (262).



(261)

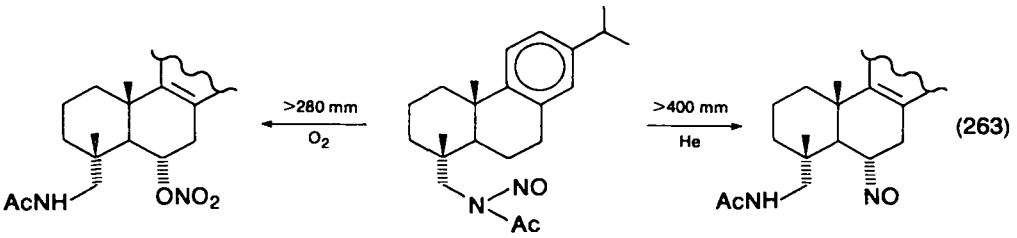


(415) (416)

(262)

Photolysis of *N*-nitroso-*N*-methylacetamide in the presence of cyclohexene or 1,3-pentadiene yields the products from intermolecular hydrogen nitroso exchange reaction but no addition product.

Irradiation of a benzene solution of nitrosamides, such as **411**, under oxygen with >280 nm or >400 nm light gives nitrate **414** in good yields and minor amounts of *N*-nitro-*N*-hexylacetamide, nitrobenzene and nitrophenols[345]. The oxidative photorearrangement obviously occurs by a mechanism similar to that shown for the oxidative rearrangement of nitrites (equation 210 Section VI.C.3). In view of the formation of nitrobenzene and nitrophenols, $NO_3^{\bullet}$ must also be generated by the combination of oxygen and nitric oxide. The combination of $NO_3^{\bullet}$ with *C*-radicals may also serve as a possible pathway for the nitrate formation. Such a nonoxidative or oxidative photorearrangement of *N*-nitroso-*N*-acetylabietylamine (**417**) gives the expected nitroso dimer of **418** or nitrate **419** in ca. 40% yields[384]. The clean

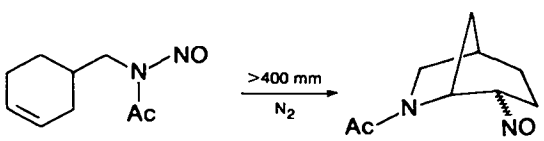


(263)

(419) (417) (418)

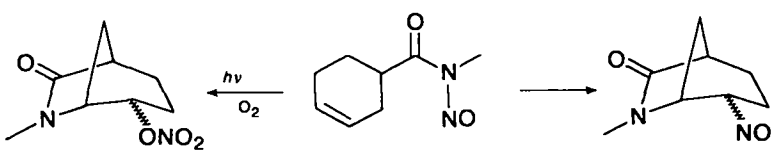
functionalization at the 6α-position arises from less hindrance for the approach of reactants at the α-side of the abietyl molecule.

In spite of the fact that intermolecularly amidyl radicals preferentially abstract an allylic hydrogen rather than add to an olefinic bond of cyclohexene or 1,3-pentadiene[211], the pattern of the reactivity is completely reversed in intramolecular cases[385,386] (equations 264 and 265). In these nitrosamide photolyses,



(264)

(420)



(265)

(422) (421) (423)

C-nitroso compounds **420** and **423** are isolated as the oximes. In analogy to the intramolecular reaction patterns of alkoxy (Section VI.B) and aminium (Section VIII.A.4) radicals, amidyl radicals predominantly attack the C(5) position of the π-bond even where an allylic hydrogen at the δ-position is available. Furthermore, intramolecularly, amidyl radicals attack a π-bond in the acyl side-chain just as easily as that in the alkyl side-chain, in contrast to the severe discrimination in intramolecular hydrogen abstraction.

2. Mechanism of nitrosamide photolysis

The quantum yields of nitrosamide photolyses vary from 0.8 to 2.5 depending on solvent and concentration (10^{-1}–10^{-3} M) because of a complex reaction pattern[387]. Owing to the lack of emission in *N*-nitroso-*N*-methylacetamide, $Ac(CH_3)NNO$, its lowest singlet-state energy (E_s) is estimated to be 67 kcal/mol from the absorption maximum and its lowest triplet-state energy (E_T) has been determined as 51 kcal/mol from quenching experiments. Upon excitation to the singlet state, a nitrosamide is believed to dissociate into radicals so rapidly that the probability of fluorescence and intersystem crossing to the triplet state are virtually none for the following reasons: Firstly, *trans*-stilbene (E_S 89 kcal/mol, E_T 49 kcal/mol) neither quenches the photoreaction of $Ac(CH_3)NNO$, nor itself undergoes isomerization. Secondly, oxygen does not quench the photoreaction but reacts with the precursor of the amidyl radical (see below).

Flash excitation, by direct photolysis (>400 nm) or acetone sensitization, of $Ac(CH_3)NNO$ in degassed benzene or water solution reveals the amidyl radical transient[387] exhibiting λ_{max} 335–350 nm. Oxygen reacts with the precursor of the amidyl radical from which the lifetime of the precursor is estimated to be ca. 10^{-9} s. Kinetic studies show that the amidyl radical decays with a first-order rate constant of $2.09\ (\pm 0.02) \times 10^4\ s^{-1}$ (equation 272) as well as with a second-order rate constant of $3.96\ (\pm 0.05) \times 10^6\ M^{-1}\ s^{-1}$ (equation 271), and that it reacts with cyclohexane and *trans*-1,3-pentadiene by second-order rate constants of 1.85×10^4 and $2.84 \times 10^5\ M^{-1}\ s^{-1}$, respectively. Interestingly, the precursor also reacts with these two substrates with very high rate constants of 1.87×10^8 and $4.04 \times 10^9\ M^{-1}\ s^{-1}$, respectively. The detailed mechanism of the photolysis of $Ac(CH_3)NNO$ is shown in equations (266)–(274).

$$Ac(CH_3)N{-}NO \xrightarrow{h\nu} {}^*[Ac(CH_3)N\cdots NO] \longrightarrow [Ac(CH_3)N^{\bullet} + NO] \quad (266)$$

$$[Ac(CH_3)N^{\bullet} + NO] \longrightarrow Ac\dot{N}CH_3 + NO^{\bullet} \quad (267)$$

$${}^*[Ac(CH_3)N\cdots NO] + O_2 \longrightarrow [Ac(CH_3)N\cdots NO_3] \longrightarrow \text{products} \quad (268)$$

$${}^*[Ac(CH_3)N\cdots NO] + SH \longrightarrow AcNHCH_3 + S^{\bullet} + NO \quad (269)$$

$$Ac\dot{N}CH_3 + SH \longrightarrow AcNHCH_3 + S^{\bullet} \quad (270)$$

$$Ac\dot{N}CH_3 + Ac(CH_3)N{-}NO \longrightarrow AcNHCH_3 + CH_2{=}NAc + NO \quad (271)$$

$$[Ac\dot{N}CH_3 + NO] \longrightarrow CH_2{=}NAc + HNO \quad (272)$$

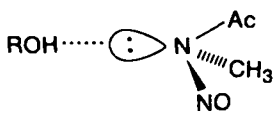
$$Ac(CH_3)N{-}NO + {}^3\text{sens.} \longrightarrow {}^3[Ac(CH_3)N{-}NO] + \text{sens.} \quad (273)$$

$${}^3[Ac(CH_3)N{-}NO] \longrightarrow Ac\dot{N}CH_3 + NO \quad (274)$$

As the precursor is an extraordinarily reactive species, it is tentatively assigned as either the vibronically or singlet excited nitrosamide in which the N—N bond is stretched to possess radical character. Physically, it is believed that the bonding

electrons are still within the interacting distance and the amido portion resembles the Σ electronic configuration[382]. It should be noted that a triplet state of $Ac(CH_3)NNO$ cannot be reached by intersystem crossing but is readily obtained by a triplet sensitization. This triplet state also dissociates to afford the amidyl radical. Indeed, benzophenone-sensitized nitrosamide photolysis exhibits the same product pattern as direct photolysis[211].

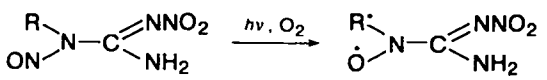
Low-temperature photolysis[388] of $Ac(CH_3)NNO$ at −150°C with 405 nm monochromatic light gives a frozen intermediate, exhibiting bathochromically shifted (by ca. 30 nm) uv absorptions for the n → π* transition bands and IR bands at 1712 and 1555 cm^{-1}. This intermediate decomposes irreversibly, to the amidyl and nitric oxide radicals, by a second photon at −150°C, but reverts to the original structure on warming to −90°C. A similar monochromatic photolysis of $Ac(CH_3)NNO$ at 25°C also causes irreversible dissociation indicating that the biphotonic process at −150°C has been changed to a monophotonic process. The intermediate is suggested to have the structure of valence tautomer **424** or the rotamers **408** and **409**. Thus, it is proposed that by photoexcitation and nonvertical relaxation during low-temperature photolysis, the nitrosamide is elevated to a higher energy configuration which cannot be reached by thermal excitation. At 25°C, the excited state of the nitrosamide is shifted to the dissociative hypersurface with assistance from the additional thermal energy and a monophotonic dissociation process prevails.



(424)

3. *Photolysis of other nitrosamides*

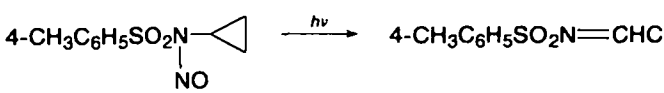
Photolysis of *N*-alkyl-*N*-nitroso-*N'*-nitroguanidine (**425**) in benzene solution saturated with oxygen generates nitroxide radicals **426** and is also interpreted as homolysis of the N—NO bond followed by oxidation of the amidyl radicals[389]. Photolysis of *N*-cyclopropyl-*N*-nitrosotoluene sulphonamide **427** causes complete ring-opening and rearrangement to give the *C*-nitroso compound **428**, isolated as the



(275)

(425) **(426)**

R = Me, Et, *n*-Pr, *n*-Bu



(276)

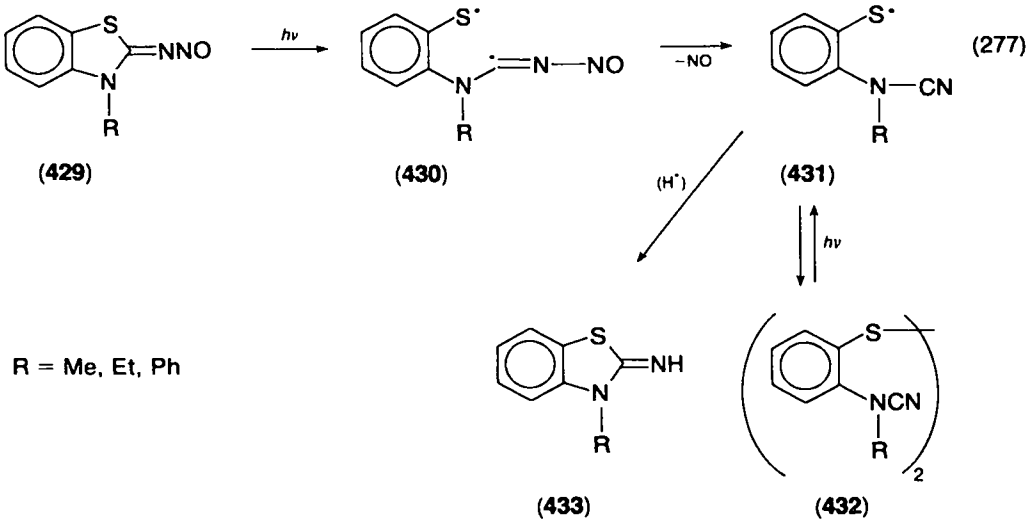
(427) **(428)**

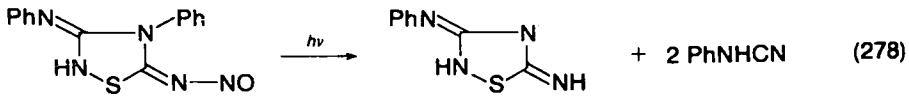
dimer, probably by a radical mechanism[390]. Similar nitrososulphonamides with primary or secondary alkyl groups (instead of cyclopropyl in **427**) attached to nitrogen are photolysed to give 4-toluene sulphonamide, nitrous oxide and the

corresponding carbonyl compounds derived from the alkyl groups in excellent yields. Interestingly, an intramolecular δ-hydrogen nitroso group exchange reaction (the Barton-type reaction; Section VI.C) has not been observed in the photolysis of *N*-hexyl-*N*-nitrosotoluene sulphonamide. If the corresponding sulphonamidyl radicals are formed from the photolysis, it must be assumed that these radicals abstract hydrogen feebly but preferentially undergo elimination.

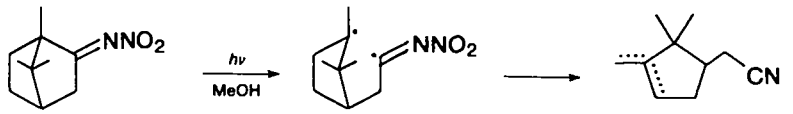
IX. PHOTOLYSIS OF *N*-NITROSIMINES AND *N*-NITROIMINES

Among several nitrosimines studied by photolysis, **429** and **434** have been shown to be photolabile by irradiation at their $\pi \rightarrow \pi^*$ transition band[391] (ca. 350 nm); nitrosimines are stable to irradiation at the $n \rightarrow \pi^*$ band. These nitrosimines rearrange cleanly by thermolysis to the corresponding ketones, which are not formed in the $\pi \rightarrow \pi^*$ band photolysis. Photolysis of nitrosimine **429** is interpreted as causing ring-scission followed by elimination of nitric oxide to give the disulphide **432** (major product) and the imine **433** via radicals **430** and **431**; because of the photosensitivity to $\pi \rightarrow \pi^*$ excitation, the reverse order of elimination is regarded as unlikely. Since imine **433** is formed as the major product at the expense of disulphide **432** on prolonged irradiation, a secondary photolysis of the latter may also occur. The primary photoprocess for nitrosimine **434** is also assumed to be ring-scission at the C—S bond to give imine **435** and phenyl cyanamide as the primary photoproducts.



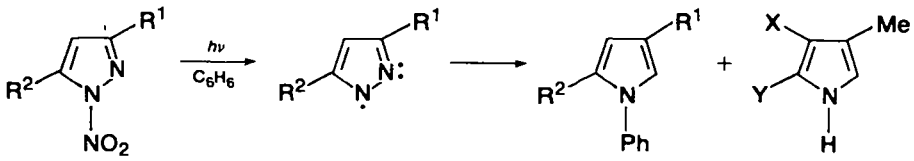


Thus, a nitrosimino group appears not to be photosensitive and the observed photolability generally arises from the reaction of the heterocyclic ring. It is not surprising, therefore, that many other heterocyclic nitrosimines are resistant to photodecomposition[391,392].



(279)

(436) (437) (438)



(280)

(439) R^1 = Me, R^2 = H (441) (443) (445)

(440) R^1 = H, R^2 = Me (442) (444) X, Y = H or NO_2

Photodecomposition of nitroimines generally proceeds slowly as shown by the limited work available. Camphor nitroimine (**436**) is photolysed to give cyano olefins **438** and a number of other minor products in which the ring-scission to **437** is proposed as the primary photoprocess[393]. Isomeric nitropyrazoles **439** and **440** are photolysed in benzene to give mainly **445** with a small amount of *N*-phenylpyrazoles (**443**:**444** = 4:1)[394], irrespective of starting from **439** or **440**. It is proposed that the pyrazole radicals generated from the excitation have the Σ configuration and can isomerize mutually from one to another; i.e. **441** ⇆ **442**.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **7**

Radiation chemistry of amines, nitro and nitroso compounds

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I. INTRODUCTION

Absorption of high-energy or ionizing radiation, including charged particles and electromagnetic waves, produces ionization and excitation of molecules within the absorbing material (Allen[5], Draganić and Draganić[28], Spinks and Woods[95]). Energies of the order of 30 eV or less are capable of ionizing all stable molecules. The resulting ionized and excited species are unstable and undergo very rapid chemical changes by fast reactions with neighbouring molecules. In many systems, the initial energy absorption, resulting in ionization and excitation, is rapidly transferred from the site of energy deposition to other molecules, leading ultimately to the formation of chemical damage at some distance from the incident site. In the case of aqueous solutions, with which this review is principally concerned, this energy-transfer process from ionized water to target amines, nitro or nitroso compounds is known as 'indirect action'. The initial ionization and excitation events are followed by ion-molecule reactions, charge neutralization and dissociation of molecules, giving rise, within nanoseconds, to the formation of reactive free-radical species. In the radiolysis of aqueous solutions, the principal primary reactive species are the hydrated electron (e^-_{aq}), which may be considered the ultimate nucleophile, and the hydroxyl free radical (·OH, the notation indicates the presence of an unpaired electron), a transient oxidizing agent with electrophilic properties[45,63].

In recent years, radiation chemists have made considerable progress in understanding the nature and reactivity of free radicals formed by the radiolysis of aqueous solutions, and the mechanisms involved in the resulting chemical damage. The advent of pulsed radiation sources including linear accelerators and Van de Graaff generators in the early 1960s, has led to the development of the pulse radiolysis technique (Matheson and Dorfman[65], Ebert and coworkers[32]), a kinetic spectrophotometric method by which absolute rate constants for free-radical reactions are measured directly. In addition, new analytical techniques have enabled the quantitative analysis of radiation products and their mechanism of formation to be achieved (Neta[80]). This review will consider the mechanistic aspects of the reaction kinetics of these free-radical species interacting with amines, nitro and nitroso compounds, and give an analysis of the resulting products.

The radiation chemistry of amines, nitro and nitroso compounds is becoming increasingly important, not only from a fundamental point of view, but also because of some of its important applications (Fendler and Fendler[38], Wardman[102,103]). In order to appreciate some of the diversity of applications of radiation chemistry today, a section at the end of this review will consider, briefly, some areas in biology and biochemistry in which studies are used, not simply to characterize the degree and extent of the radiation damage process, but to use this knowledge of radiation-induced free-radical kinetics to investigate such biological processes as drug toxicity and metabolism, carcinogen activation, improvements in cancer therapy, and the treatment of chemical waste.

In this chapter the symbol R is used for different aliphatic and aromatic groups, as indicated by the relevant parts of the text.

II. RADIATION CHEMISTRY

A. Energy Absorption

Figure 1 shows, schematically, the processes which may occur when an electron beam is incident on an aqueous solution[61]. High-energy electrons lose energy by elastic and inelastic collisions with molecules. Inelastic collisions, with bound

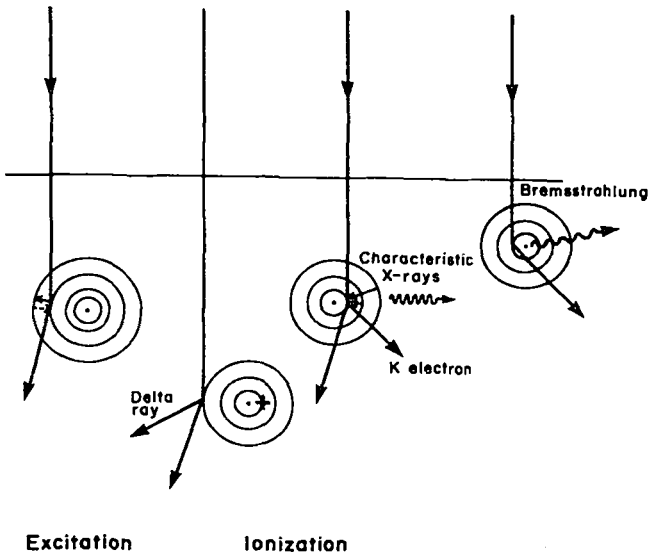


FIGURE 1. Electron tracks showing possible modes of interaction in solution. From H. E. Johns and J. R. Cunningham, *The Physics of Radiology*, 1969. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.

molecular electrons resulting in ionization of the molecule, predominate[34]. Below ~1 MeV, electrons lose energy predominantly through coulomb interactions with electrons in the sample. Much of the energy in excess of the ionization potential is carried by the ejected secondary electron. Inelastic collisons of high-energy electrons (≳1 MeV) with heavy nuclei produce X-rays (Bremsstrahlung). The rapid deceleration of an electron in the field of a nucleus results in the emission of a quantum of radiation.

Since the energy-loss process is stochastic, monoenergetic electrons show a statistically indefinite range, but from such a probabilistic number–distance curve, an extrapolated range can be estimated. Although the electron energy loss by excitation and ionization is defined precisely by the Bethe expression[14,60], for more practical purposes, two empirical formulae[62] may be used to estimate the range of monoenergetic electrons in materials of low atomic number:

$$\text{For energies } E \leq 2.5 \text{ MeV}, \quad \text{range (mg cm}^{-2}) = 412E^{n} \tag{1}$$

where $n = 1.265 - 0.0954 \ln E$

$$\text{For energies } E > 2.5 \text{ MeV}, \quad \text{range (mg cm}^{-2}) = 530E - 106 \tag{2}$$

For X-rays and γ-rays, energy loss occurs by collision between the photon and molecular electrons, producing ionizations and resulting in the scattering of the primary photon and the ejection of high-speed electrons. The fate of these high-speed electrons is described in the previous section. A schematic diagram showing the different interactions of high-energy photons with molecules in aqueous solutions is given in Figure 2.

There are three distinct processes whereby X-ray photons interact with absorbing material; the photoelectric effect, the Compton effect and pair production[60,61]. At low photon energies (≲ 0.1 MeV), the photoelectric effect predominates. Here

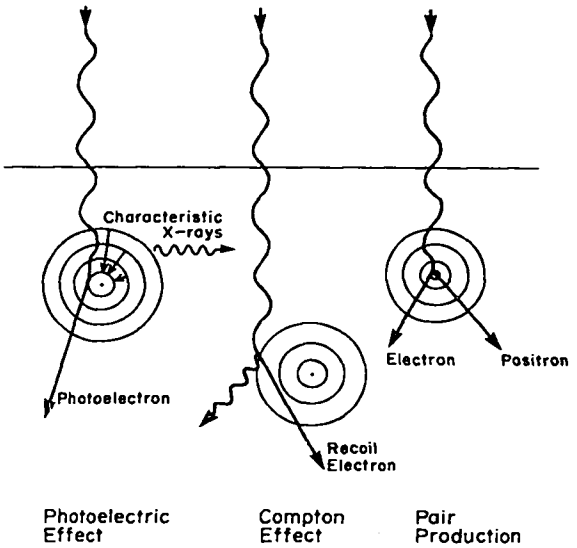


FIGURE 2. Photon tracks showing possible modes of interaction in solution.

photons collide with, and impart nearly all of their energy to, molecules, which causes the ejection of photoelectrons from the strongly bound inner K, L, M or N shells. Characteristic radiation arises from the subsequent cascade of electrons from outer electron orbitals to fill the vacancy left by the emitted photoelectron. At higher photon energies (0.1–10 MeV), Compton scattering predominates. Here the photon is deflected by colliding with an outer orbital electron, thereby losing part of its energy to the electron. The third process of energy absorption for photons is known as pair production, and refers to the interaction of a high-energy photon with an atomic nucleus, resulting in the production of an electron–positron pair. The threshold for pair production is 1.02 MeV, and this process only becomes important at very high energies ($\gtrsim$10 MeV). A graph showing the relative efficiencies of these three absorption processes for aqueous solutions, as a function of photon energy, is shown in Figure 3.

Electromagnetic radiation, unlike charged particles, loses a relatively large amount of energy at every collision, and this results in an exponential attenuation of the intensity (I) of a photon beam[61]:

$$I = I_0 e^{-\mu l} \tag{3}$$

where μ (cm^{-1}) is the total linear absorption coefficient and l(cm) is the thickness of the absorber. The half-value layer (HVL) is the thickness of the sample required to attenuate half the incident radiation:

$$\text{HVL (cm)} = \ln 2/\mu = 0.693/\mu \tag{4}$$

B. Early Events

The energy lost when high-energy radiation is slowed down and absorbed in solution gives rise to an inhomogenous distribution of ions and excited states along each primary radiation track. The average amount of energy lost per absorption

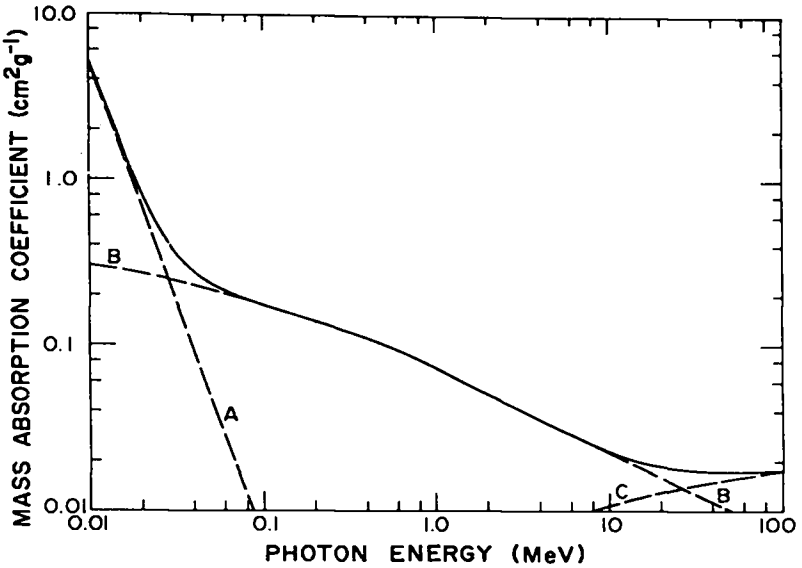


FIGURE 3. Total mass attenuation coefficient, μ/ρ (where ρ, g cm^{-3} is density), for water, showing the contribution of (A) photoelectric effect, (B) Compton scattering and (C) pair production. From H. E. Johns and J. R. Cunningham, *The Physics of Radiology*, 1969. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.

event is ~ 100 eV[93], which is sufficient to produce several pairs of ions and/or excited states. The sites of such clusters of reactive species are known as spurs, blobs or short tracks[19,73], depending upon the amount of energy deposited (see Figure 4). The extremely reactive ions and excited states are formed in close proximity within spurs, which have an estimated initial diameter of ~25 Å[89], and many react with one another, producing the stable molecular products H_2 and H_2O_2. Those ions and excited states which do not react in spurs undergo rapid

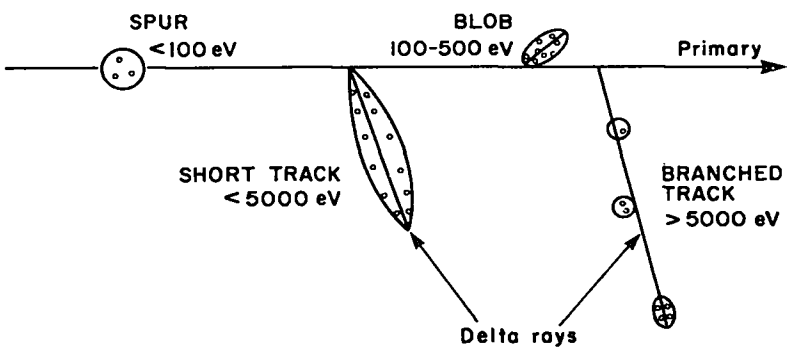


FIGURE 4. Distribution of ions and excited molecules in the track of a fast electron or high-energy photon (not to scale). The spurs, blobs and tracks contain positive ions (dots), as well as geminate electrons and excited species. From M. Burton, *Chem. Eng. News*, **46**, 86 (1969). Reproduced by permission of The American Chemical Society.

ion-molecule reactions with the solvent to form free-radical species, which diffuse into the surrounding liquid and engage in chemical reactions with stable molecules. The time-scale of such physical and chemical processes is as follows[95]:

Energy absorption event	10^{-18} s
Excitation and ionization	10^{-16}–10^{-15} s
Ion-molecule reactions	10^{-14} s
Electron and cation solvation	10^{-11} s
Free-radical formation and diffusion	10^{-10}–10^{-9} s
Production of chemical damage	10^{-8} s → s.

The radiolysis of water may be summarized as follows:

$$H_2O \rightsquigarrow \begin{matrix} H_2O^+ + e^- \\ H_2O^* \end{matrix} \quad (5)$$

$$H_2O^+ \xrightarrow{H_2O} H_3O^+ + \cdot OH \quad (6)$$

$$e^- \xrightarrow{H_2O} e^-_{aq} \quad (7)$$

$$H_2O^* \longrightarrow H\cdot + \cdot OH \quad (8)$$

$$e^-_{aq} + H_3O^+ \longrightarrow H\cdot + H_2O \quad (9)$$

In deaerated water:

$$e^-_{aq} + e^-_{aq} \longrightarrow H_2 + 2\,OH^- \quad (10)$$

$$H\cdot + H\cdot \longrightarrow H_2 \quad (11)$$

$$\cdot OH + \cdot OH \longrightarrow H_2O_2 \quad (12)$$

In aerated water:

$$e^-_{aq} + O_2 \longrightarrow O_2^{-\cdot} \quad (13)$$

$$H\cdot + O_2 \longrightarrow O_2^{-\cdot} + H^+ \quad (14)$$

$$O_2^{-\cdot} + O_2^{-\cdot} \xrightarrow{2\,H^+} H_2O_2 + O_2 \quad (15)$$

The major reactive species are e^-_{aq} and ·OH, potent reducing and oxidizing species, respectively, and the superoxide radical anion $O_2^{-\cdot}$. The molecular products H_2 and H_2O_2 arise principally from the reactions of the primary species H·, e^-_{aq} and ·OH in spurs. The yields of radiation products are expressed as G values, defined as the number of species formed by the absorption of 100 eV of energy in solution, and for the radiolysis of deoxygenated water, the primary yields[27,28] are: $G(e^-_{aq}) = 2.7$, $G(H\cdot) = 0.6$, $G(\cdot OH) = 2.8$, $G(H_2) = 0.45$ and $G(H_2O_2) = 0.7$.

C. Dosimetry

Ionizing radiation only produces chemical effects when it is absorbed. The official

unit of absorbed dose is the rad, which is equivalent to 100 erg g^{-1}. A recently adopted unit of absorbed dose, the Gray = 1 J kg^{-1} is equal to 100 rad.

G values for molecular radiation products (P), as a measure of solute radiosensitivity, are obtained from the following equation:

$$G(P) = \frac{[P]\,9.65 \times 10^5}{D\rho} \tag{16}$$

where [P] is the amount of product (mol l^{-1}) formed by a radiation absorbed dose D (krad) and ρ is the density (g cm^{-3}) of the irradiated solution. From this expression, it can be seen that the yield of ion pairs and of the primary species e^-_{aq} and $^{\cdot}OH$ in irradiated water is equivalent to 3.1 μ mol/krad.

D. Reaction Kinetics

1. *Free-radical reactions*

Organic compounds in dilute solution are damaged by radiation as a result of indirect action. Energy absorbed in the solvent is transformed into free radicals, ions and excited states. The primary solvent radiolysis species diffuse to and undergo chemical reactions with dissolved organic molecules. The study of the rate and mechanism of such reactions is known as chemical kinetics. In the simplest case, involving the reaction of a single reactive radical species (r·) with an organic substrate (S), the rate of the reaction is proportional to the concentration of the organic substrate, and the reaction is said to be 'first order':

$$S + r \longrightarrow P \tag{17}$$

$$-d[S]/dt = -d[r\cdot]/dt = d[P]/dt = k[S][r\cdot] \tag{18}$$

Upon integration, for $[S] \gg [r\cdot]$

$$-\log[r\cdot]/[r\cdot]_0 = k[S]t \tag{19}$$

In a first-order reaction, which is the one most frequently encountered in radiation chemistry, the reactive species decay exponentially with time, at a rate k' (s^{-1}) = $k[S]$ which is proportional to solute concentration.

When reactions between a solute (S) and a reactive species (r·) occur at every collision, as do many of the reactions of water radiolysis species with organic amines, nitro and nitroso compounds, diffusion[24] alone controls the reaction:

$$k_{diff} = 4\pi(r_S + r_{r\cdot})(D_S + D_{r\cdot})N/1000 \sim 10^{10}\ l\ mol^{-1}\ s^{-1} \tag{20}$$

where r_S and $r_{r\cdot}$ are the encounter radii of the two reactants, D_S and $D_{r\cdot}$ are their diffusion constants and N is Avagadro's number.

Occasionally, particularly at high dose-rates, as with pulse-irradiated solutions, reactive species may self-react or react with a solute of equivalent concentration by second-order kinetics:

$$r\cdot + r\cdot \longrightarrow P \tag{21}$$

$$-d[r\cdot]/dt = k[r\cdot]^2 \tag{22}$$

Upon integration

$$[r\cdot]^{-1} - [r\cdot]_0^{-1} = kt \tag{23}$$

In these reactions, the rate of decay $k' = k[r\cdot]$ varies continuously with time and inversely with radical concentration.

2. Radical scavenging

In the radiolysis of aqueous solutions, several primary reactive species are formed simultaneously and together, and it becomes difficult to resolve their individual contributions to the radiation damage. In order to clarify the reaction mechanisms, and to study the nature and kinetics of the reactions of a single reactive species with various solutes, radical scavengers are employed which, hopefully, will selectively react with and inactivate competing reactive species. For example, nitrous oxide (N_2O) in alkaline solution may be used to convert H· and e^-_{aq} to ·OH as follows, thereby generating a single radical system:

$$H\cdot \xrightarrow{OH^-} e^-_{aq} \tag{24}$$

$$e^-_{aq} + N_2O \xrightarrow{H_2O} N_2 + OH^- + \cdot OH \tag{25}$$

Alcohols, particularly *t*-butanol or formate, are often used as ·OH scavengers when studying electron-transfer or redox reactions involving e^-_{aq}, $CO_2^{\cdot-}$ or $O_2^{\cdot-}$:

$$\cdot OH(H\cdot) + (CH_3)_3COH \longrightarrow (CH_3)_2\dot{C}H_2COH + H_2O(H_2) \tag{26}$$

(inert)

$$\cdot OH(H\cdot) + HCO_2^- \longrightarrow CO_2^{\cdot-} + H_2O(H_2) \tag{27}$$

$$CO_2^{\cdot-} + O_2 \longrightarrow O_2^{\cdot-} + CO_2 \tag{28}$$

3. Pulse radiolysis

With the advent in the 1960s of high-intensity pulsed radiation sources and the development of sensitive detection methods, the ability to observe free radicals directly and to monitor their reactions became possible[32,65]. Typically, Van de Graaff generators, Febetron pulsed X-ray sources and microwave linear accelerators are today capable of delivering single microsecond or nanosecond pulses of high-energy (>3 MeV) electrons producing absorbed doses in the 0.1–10 krad/pulse range. Such absorbed doses will generate instantaneous micromolar concentrations of free radicals in the aqueous sample within the irradiation cell, well within the limit of detection of kinetic spectrophotometric, conductometric or polarographic analyses. A schematic diagram of a typical pulse radiolysis set-up[59] using optical detection is shown in Figure 5. Transient changes in light transmission resulting from radiolytic absorbing species formed in the sample cell are transported to a fast photomultiplier detector via a monochromator, using a light transport system of lenses and mirrors. The photomultiplier signal (Figure 6) may be displayed on an oscilloscope and the recording of the reaction sequences photographed with a Polaroid camera, or, as is becoming more common, it may be fed into and processed by a computer for on-line kinetic or spectroscopic analyses[81,99].

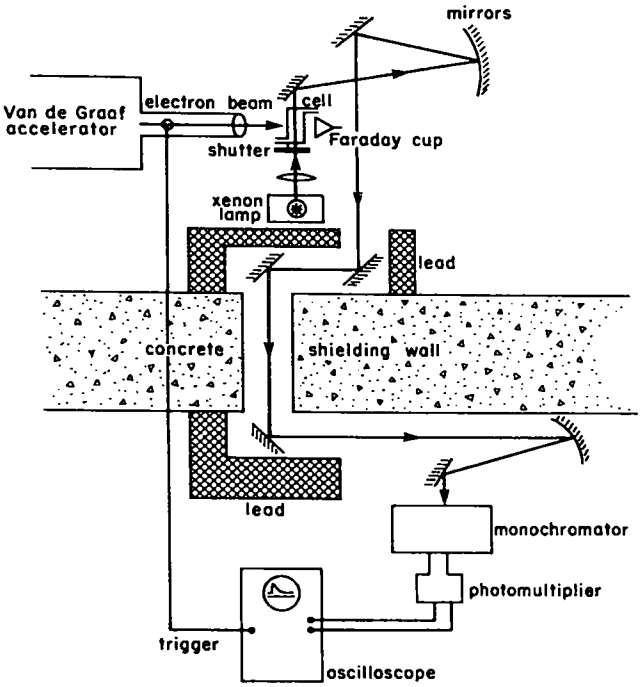


FIGURE 5. A schematic diagram of the nanosecond pulse radiolysis apparatus at the Whiteshell Nuclear Research Establishment. Transient species are detected using kinetic spectrophotometry.

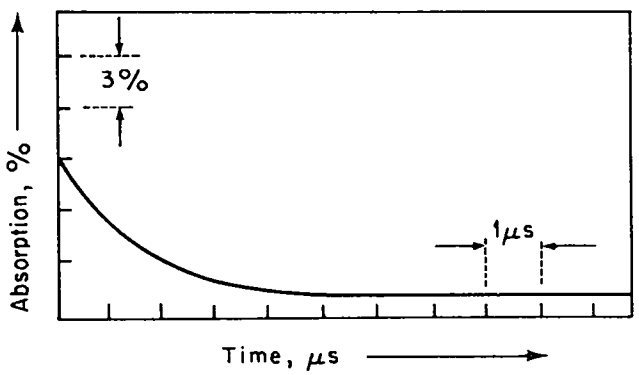


FIGURE 6. Graph drawn from a typical oscilloscope photograph illustrating the exponential decay of a transient absorbing species, as a function of time after the radiation pulse.

4. *Product analysis*

The ultimate effect of fast free-radical reactions between solvent reactive species and dissolved solute is to produce permanent chemical changes in the irradiate

solutions. The types and yields of different products can be determined by gross changes in the overall physical or chemical properties of the irradiated solutions. Changes in optical absorption of a solute chromophore are often used to determine the G value for total solute destruction, and liquid chromatography or scintillation spectrometry can help to unravel a complex reaction mechanism through a detailed analysis of the immediate radiation products and their by-products. As with pulse radiolysis, the careful design of steady-state radiolysis experiments using appropriate radical scavengers is important in the unambiguous determination of radiation damage mechanisms.

III. RADIOLYSIS OF AMINES

A. Aliphatic Amines

Aliphatic amines are relatively nonreactive ($<10^7$ l mol^{-1} s^{-1}) towards e^-_{aq} (Table 1)[7], although alkylammonium ions, formed by protonation of the amino group in acidic solution, show a higher reactivity[43]. Substituted aliphatic amines irradiated in aqueous solution show a selective radiosensitivity attributable to increased free-radical reactivity at the C—NH_2 site. Reductive deamination[72,74,75,92,106], which is initiated by an electron transfer to the amino group, is a direct indication of this reaction:

$$RCH_2NH_2 + e^-_{aq} \xrightarrow{H_2O} \cdot RCH_2 + NH_3 + OH^- \qquad (29)$$

TABLE 1. Rate constants for the reactions of e^-_{aq}, H· and ·OH with amines and amino acids[7,8,36]

Compound	Rate constants (1 mol^{-1} s^{-1})		
	k (e^-_{aq})	k (H·)	k (·OH)
Aliphatic amines and analogues			
Butyrate	—	10^7	2×10^9
2-Aminobutyrate	$<10^7$	$<10^6$	2×10^8
Ethanol	$<10^5$	10^7	2×10^9
2-Aminoethanol	—	3×10^6	—
Ethane	—	2.5×10^6	10^9
Ethylenediamine	$<10^6$	—	10^8
Allylamine	10^7	—	—
Methane	$<10^7$	$<10^4$	2×10^8
Methylamine	—	$<10^7$	2×10^8
β-Alanine	10^7	$<10^6$	5×10^7
Glycine	$\leq 10^7$	$<10^6$	5×10^7
Aromatic amines and analogues			
Benzene	$<10^7$	10^9	5×10^9
Aniline	$\sim 10^7$	3×10^9	8×10^9
Benzoate	3×10^9	10^9	4×10^9
4-Aminobenzoate	5×10^9	—	8×10^9
Toluene	10^7	2×10^9	3×10^9
Benzylamine	3.5×10^7	—	—

The rate of reductive attack of hydrogen atoms[8,76] on aliphatic amines is also low ($<10^7$ l mol^{-1} s^{-1}) (Table 1). For hydrogen atom reactions, unlike those of e_{aq}^-, there is no evidence for an electron-transfer process. The reaction of H· with aliphatic amines involves mainly a hydrogen abstraction from the aliphatic chain, at a rate which is determined by the substituent. The amino group enhances the rate of hydrogen abstraction from an adjacent C—H bond, whereas a protonated ammonium group retards it[43]:

$$\mathrm{H\cdot + RCH_2NH_2} \xrightarrow{\text{predominates}} \mathrm{\dot{C}HNH_2} \quad + \quad \mathrm{RCH_2\dot{N}H} \tag{30}$$

In degassed solution, the resulting radicals self-react with no release of ammonia. When oxygen is present, peroxy radicals are formed, leading to the formation of aldehydes, oximes and other oxidized products:

$$2\,\mathrm{R\dot{C}HNH_2} \longrightarrow \text{products} \tag{31}$$

$$2\,\mathrm{R\dot{C}H_2\dot{N}H} \longrightarrow \text{products} \tag{32}$$

$$\mathrm{R\dot{C}HNH_2 + O_2} \longrightarrow \mathrm{RCH(O_2\cdot)NH_2} \tag{33}$$

$$\mathrm{RCH(O_2\cdot)NH_2 + O_2^-(\cdot OH)} \longrightarrow \mathrm{RCOOH(RCHO) + NH_3 + O_2} \tag{34}$$

$$2\,\mathrm{RCH(O_2\cdot)NH_2} \longrightarrow \mathrm{NH_3} + \text{products} \tag{35}$$

Hydroxyl radicals, like hydrogen atoms, abstract hydrogen from alphatic amines, but the site of attack differs for the neutral and protonated forms, being predominantly from NH_2 and α-C positions for the free amines (reaction 36), but from β-C positions and sites remote from the NH_3^+ groups for protonated amines (reaction 37)[43]. Rate constants for ·OH attack on aliphatic amines[36] are shown in Table 1.

$$\mathrm{\cdot OH + R(H)CH_2NH_2} \longrightarrow \mathrm{R(H)\dot{C}HNH_2 + H_2O} \quad \text{or} \quad \mathrm{R(H)CH_2\dot{N}H + H_2O} \tag{36}$$

$$\mathrm{\cdot OH + R(H)CH_2NH_3^+} \longrightarrow \mathrm{\cdot RCH_2NH_3^+ + H_2O} \tag{37}$$

This shift in site of primary attack of ·OH is reflected in pH studies of electron-transfer oxidation of the resulting radicals by strong electron acceptors such as 2-methyl-1, 4-naphthoquinone or nitroaromatic compounds[69,84]. At neutral or alkaline pH a higher percentage of electron-transfer oxidation is observed than in acidic solutions of protonated amines, where a lower yield of readily oxidizable α-C radicals is produced[83].

In the absence of oxygen, the radicals formed by H· and ·OH attack decay by second-order processes (radical dimerization or disproportionation), but when oxygen is present they decay exponentially by reaction with oxygen, and the resulting species (peroxy radicals) undergo slow second-order decay forming the final products. The principal products formed in ethylamine irradiated in aerated, basic aqueous solution[29] are acetaldehyde, hydrogen peroxide and $CH_3CH{=}NOH$.

B. Aromatic Amines

The radiation chemistry of aromatic amines is dominated by radical attack on the electron-delocalized aromatic ring structure rather than the amino group[21]. This is reflected in the higher reactivity towards primary water radiolysis species[7,8,36], particularly H· and ·OH, of aromatic amines compared with aliphatic amines (Table 1).

Nevertheless, a major product of the reaction of e_{aq}^- with aromatic amines is ammonia[72]:

$$RC_6H_4NH_2 + e_{aq}^- \xrightarrow{H_2O} RC_6H_4\cdot + NH_3 + OH^- \quad (38)$$

The other radiolytic reducing species, H·, on the other hand, primarily abstracts hydrogen atoms from the benzene ring without subsequent release of ammonia:

$$RC_6H_4NH_2 + H\cdot \longrightarrow RC_6\dot{H}_3NH_2 + H_2 \quad (39)$$

Hydroxyl radicals can react with aromatic amines, either at the NH_2 group, or by reaction with the conjugated aromatic ring; predominantly via ·OH addition. For aromatic systems, there is a higher probability of ·OH attack at the benzene ring, and ·OH addition will be favoured, resulting in the formation of hydroxycyclohexadienyl radicals:

$$\begin{aligned} RC_6H_4NH_2 + \cdot OH &\longrightarrow R\dot{C}_6H_4(OH)NH_2 \\ &\longrightarrow R\dot{C}_6H_3NH_2 + H_2O \\ &\longrightarrow RC_6H_4\dot{N}H + H_2O \end{aligned} \quad (40)$$

The percentage of hydroxy-cyclohexadienyl radicals formed may be inferred from electron-transfer studies, since such radicals are readily oxidized by suitable electron acceptors. The efficiency of such reactions is monitored spectrophotometrically, using pulse radiolysis, by following the extent and rate of electron-adduct formation on the acceptor molecule. Approximately 25% of ·OH attack on aniline forms the OH adduct to the aromatic ring, which donates electrons to 2-methyl-1,4-naphthoquinone as electron acceptor[84].

In addition, there is evidence to suggest that ·OH adducts are unstable, and readily eliminate water to form anilino radicals or radical cations[21,39,40,78,84]:

$$\begin{aligned} R\dot{C}_6H_4(OH)NH_2 &\longrightarrow RC_6H_4\dot{N}H + H_2O \\ &\longrightarrow RC_6H_4NH_2^+ + OH^- \end{aligned} \quad (41)$$

There is some evidence to suggest that anilino radicals can undergo ionic disproportionation to form an anion–cation charge-transfer complex. Reaction of the cationic species with OH^- may lead to the formation of a hydroxylamine[78].

IV. RADIOLYSIS OF AMINO ACIDS

There is a vast literature on the radiation chemistry of aliphatic and aromatic amino acids[39,40] whose general structure is $NH_2CH(R)COOH$. In neutral solution, the predominant form of amino acids is the zwitterion $NH_3^+CH(R)COO^-$. A brief summary of the radiation chemistry of the simplest amino acid, glycine[67,68,91,105], reveals the importance of the amino group in determining the radiation damage

pathways, and, therefore, the similarity of amino acid and amine radiation chemistry. The principal reactions of the three primary water radiolysis species, e_{aq}, H· and ·OH, with glycine, whose rate constants are listed in Table 1, are as follows:

$$e_{aq}^- + NH_3^+CH_2COO^- \longrightarrow NH_3 + \cdot CH_2COO^- \quad (42)$$

$$H\cdot + NH_3^+CH_2COO^- \longrightarrow H_2 + NH_3^+\dot{C}HCOO^- \quad (43)$$

$$\cdot OH + NH_3^+CH_2COO^- \longrightarrow H_2O + NH_3^+\dot{C}HCOO^- \quad (44)$$

In the absence of oxygen (Table 2), the secondary radicals undergo disproportionation reactions to form acetic acid, glyoxylic acid and ammonia[39,40]:

$$2\,NH_3^+\dot{C}HCOO^- \longrightarrow NH_2^+{=}CHCOO^- + NH_3^+CH_2COO^- \quad (45)$$

$$NH_2^+{=}CHCOO^- + H_2O \longrightarrow NH_4^+ + HCOCOO^- \quad (46)$$

$$NH_3^+\dot{C}HCOO^- + \cdot CH_2COO^- \longrightarrow NH_2^+{=}CH\dot{C}OO^- + CH_3COO^- \quad (47)$$

Small quantities of CO_2 and HCHO are formed also, possibly as hydrolysis products of iminoacetic acid:

$$NH_2^+{=}CHCOO^- + H_2O \longrightarrow NH_3 + HCHO + CO_2 \quad (48)$$

The negligible yield of hydrogen peroxide suggests that it is consumed by radical reactions:

$$H_2O_2 + NH_3^+\dot{C}HCOO^- \longrightarrow NH_2^+{=}CHCOO^- + H_2O + \cdot OH \quad (49)$$

In the presence of oxygen, the reducing species e_{aq}^- and H· are converted to the relatively unreactive species $O_2^{\cdot-}$. In addition, oxygen will react with the ·OH-induced glycyl radicals to form unstable peroxy radicals which give ammonia and glyoxylic acid as breakdown products (Table 2). A probable reaction sequence is given below:

$$NH_3^+\dot{C}HCOO^- + O_2 \longrightarrow NH_3^+\,CH(O_2\cdot)COO^- \longrightarrow$$

$$NH_4^+ + CHOCOO^- + HO_2\cdot \quad (50)$$

TABLE 2. Product yields in the radiolysis of neutral aqueous glycine solutions[67,68,105]

	G values	
Product	Oxygenated solutions	Deoxygenated solutions
H_2		2.0
H_2O_2	3.6	—
NH_3	4.3	4.0
CO_2		0.9
HCHO	1.1	0.5
HCOOH		0.1
CH_3NH_2	0.15	0.2
CH_3COOH		1.2
OHCCOOH	3.4	2.1

$$HO_2\cdot + NH_3^+ CH(O_2\cdot)COO^- \longrightarrow NH_3^+ CH(OOH)COO^- + O_2 \quad (51)$$

$$NH_3^+ CH(OOH)COO^- \xrightarrow{H_2O} NH_3 + CHOCOOH + H_2O_2 \quad (52)$$

$$\longrightarrow NH_3 + HCHO + H_2O_2 + CO_2 \quad (53)$$

The hydrate electron reacts readily with amino acids[7]. However, the reactivity is generally associated with the substituent R, being greatest for the disulphide, sulphydryl, imidazole and aromatic side-chains. Reductive deamination (reaction 42) is a general reaction of e_{aq}^- with aliphatic and aromatic amino acids[39,72,74,75,92,106]. Product analysis of steady-state radiolysis results indicates that deamination arises as a consequence of the initial e_{aq}^- attachment to the carbonyl group:

$$e_{aq}^- + NH_3^+ CH(R)COO^- \longrightarrow NH_3^+ CH(R)\dot{C}OO^{2-} \longrightarrow NH_3 + \cdot CH(R)COO^- \quad (54)$$

Evidence for an unstable intermediate which decays to the presumed deamination radical at room temperature, has been obtained using ESR at 77 K[90]. Farraggi and Tal[35] have observed a proposed deamination free radical by pulse radiolysis of diglycine, which is similar spectroscopically to that formed by reductive dehalogenation of *N*-chloroacetylglycine:

$$e_{aq}^- + NH_3^+ CH_2CONHCH_2COO^- \longrightarrow NH_3 + \cdot CH_2CONHCH_2COO^- \quad (55)$$

$$e_{aq}^- + ClCH_2CONHCH_2COO^- \longrightarrow Cl^- + \cdot CH_2CONHCH_2COO^- \quad (56)$$

The yield of deaminated radicals decreases in polypeptides of increasing chain length due to the decreased probability of reductive deamination from the *N*-terminal amino acid in competition with e_{aq}^- attack at the other carbonyl sites.

The hydroxyl free radical is a good oxidant, as well as hydroxylating agent, and hydrogen atom abstraction predominates in ·OH attack of aliphatic amino acids. The reaction is rapid, and results in ultraviolet absorbing radical products which may be readily detected using pulse radiolysis[57]. Both ·OH and H· undergo hydrogen abstraction reactions with amino acids, predominantly at the α-C position, leading via subsequent disproportionation reactions, to the formation of oxidation products and some oxidative deamination.

V. RADIOLYSIS OF NITRO AND NITROSO COMPOUNDS

A. Aliphatic Nitro Compounds

Hydrated electrons react at diffusion-controlled rates with aliphatic nitro[10,11,82], and presumably nitroso compounds (Table 3):

$$e_{aq}^- + RCH_2NO_2 \longrightarrow RCH_2NO_2^{\cdot-} \quad (57)$$

Only one aliphatic nitro compound has been studied in any detail, tetranitromethane, TNM[10,82]. Because of its high electron affinity, TNM is readily reduced by any radiolytic reducing species, including e_{aq}^-, H·, $O_2^{\cdot-}$, $HO_2\cdot$, α-C radicals, $CO_2^{\cdot-}$ etc. In all cases, the result of the reaction is to form a stable, highly coloured nitroform ion, with the concomitant release of NO_2:

TABLE 3. Rate constants for the reactions of e_{aq}^-, H· and ·OH with nitro and nitroso compounds[7,8,36]

Compound	Rate constants ($l\ mol^{-1}\ s^{-1}$)		
	$k(e_{aq}^-)$	$k(H\cdot)$	$k(\cdot OH)$
Aliphatic nitro compounds			
Ethane	—	2.5×10^6	10^9
Nitroethane	3×10^{10}	7×10^7	—
Methane	$<10^7$	$<10^4$	2×10^8
Nitromethane	2×10^{10}	4×10^7	3×10^8
Tetranitromethane	5×10^{10}	5×10^8	—
Aromatic nitro compounds			
Benzene	$<10^7$	10^9	5×10^9
Nitrobenzene	3×10^9	1.5×10^9	3×10^9
Nitrosobenzene	4×10^{10}	—	2×10^{10}
Benzoate	3×10^9	10^9	4×10^9
p-Nitrobenzoate	—	10^9	2×10^9
Phenol	2×10^7	3×10^9	10^{10}
p-Nitrophenol	2.5×10^{10}	—	4×10^9
m-Nitrophenol	2.5×10^{10}	—	7×10^9
o-Nitrophenol	2×10^{10}	—	10^{10}

$$e_{aq}^- + C(NO_2)_4 \longrightarrow C(NO_2)_3^- + NO_2 \quad (58)$$

The radiolytic yield of $C(NO_2)_3^-$ is ~3.75, which is in accord with the total yield of radiolytic reducing species in irradiated water $G(\text{red.}) = G(H\cdot) + G(e_{aq}^-) \sim 3.5$. Oxygen will not increase the yield of $C(NO_2)_3^-$, since $O_2^{\cdot-}$ the product of the reaction of e_{aq}^- with O_2, is also readily oxidised by $C(NO_2)_4$ to form an equivalent yield of $C(NO_2)_3^-$.

Hydroxyl radicals do not react appreciably with TNM (Table 3), but they are capable of oxidizing the nitroform ion:

$$\cdot OH + C(NO_2)_3^- \longrightarrow \cdot C(NO_2)_3 + OH^- \quad (59)$$

The nitroform produced may react with NO_2 or NO_2^- to form TNM or nitroform ion respectively, therefore not contributing to any net destruction of TNM. In the presence of ·OH scavengers, increased destruction of TNM up to a yield $G \sim 5.8$ may result from the formation of ·OH-induced organic reducing agents:

$$\cdot OH + RH \longrightarrow \cdot RH(OH) \quad (60)$$

$$\cdot RH(OH) + C(NO_2)_4 \longrightarrow ROH + H^+ + C(NO_2)_3^- + NO_2 \quad (61)$$

B. Aromatic Nitro Compounds

As with aliphatic nitro compounds, nitroaromatic compounds readily accept electrons from e_{aq}^- (Table 3), $CO_2^{\cdot-}$, $(CH_3)_2\dot{C}OH$ and other radiolytic reducing species, to form an electron adduct with the electron localized on the electronegative nitro group:

$$HRNO_2 + e_{aq}^- \longrightarrow HRNO_2^{\cdot-} \quad (62)$$

TABLE 4. The pK_a values for protonation of electron adducts of aromatic compounds

Compound	pK_a	References
Nitrobenzene	3.2	79
4-Nitrobenzoate	2.8	79
3-Nitrobenzoate	3.0	79
2-Nitrobenzoate	2.6	79
4-Nitroacetophenone	2.6	107
1,4-Dinitrobenzene	2.1	79
1,3-Dinitrobenzene	2.4	79
1,2-Dinitrobenzene	2.2	79
2,4-Dinitrobenzoate	2.2	79
2,5-Dinitrobenzoate	2.1	79
3,4-Dinitrobenzoate	~2	79
3,5-Dinitrobenzoate	2.2	79
2,4,6-Trinitrobenzoate	2.0	79

The rate constant for the reaction of e^-_{aq} with nitrobenzene[6,55,56] (Table 3) is 3×10^{10} l mol^{-1} s^{-1}, which is diffusion-controlled. Nitro radical anions can undergo electron-transfer reactions, the rate constants for such reactions depending upon the difference between the one-electron reduction potentials of the donor–acceptor couple[70,79,101]. In acidic solutions, the nitro radical anions are protonated[79,107], with pK_a values generally in the range 2–4 (Table 4).

Hydroxyl radicals react predominantly with the aromatic moiety of organic nitro compounds to form an ·OH adduct[13]:

$$HRNO_2 + \cdot OH \longrightarrow H\dot{R}(OH)NO_2 \qquad (63)$$

In nitrobenzene, ·OH addition occurs principally at the *ortho*, *meta* and *para* positions. The resulting hydroxynitrocyclohexadienyl radicals decay by second-order disproportionation, leading to the formation of nitrophenols and nitrobenzenes[17]:

$$2\,H\dot{R}(OH)NO_2 \longrightarrow HRNO_2 + R(OH)NO_2 \qquad (64)$$

In the presence of strong electron acceptors such as $Cr_2O_7^{2-}$ or electron donors such as ferrocyanide, these radicals can undergo radical redox reactions to form diols or nitrobenzenes, respectively[17,31]. The nitrophenol yields are essentially unchanged in the presence of oxygen, due to the relative unreactivity of $O_2^{\cdot-}$, but some indirect evidence for phenol formation has been deduced from results of nitrite production, arising possibly from nitrite elimination from a peroxy radical[17]:

$$H\dot{R}(OH)NO_2 + O_2 \longrightarrow HR(OH)(O_2\cdot)NO_2 \qquad (65)$$

$$HR(OH)(O_2\cdot)NO_2 \longrightarrow \cdot ROH + O_2 + NO_2^- + H^+ \qquad (66)$$

An important consequence of ·OH addition to nitro compounds at the carbon atom adjacent to the NO_2 group is elimination of nitrous acid via oxidative denitration[37,48,77,109], the resulting radicals decaying by second-order radical–radical reactions:

$$H\dot{R}(OH)NO_2 \longrightarrow HNO_2 + H\dot{R}O \qquad (67)$$

C. Nitroso Compounds

The rate constant for the reaction of e_{aq}^- with nitrosobenzene[12] (Table 3) is 4×10^{10} l mol^{-1} s^{-1}. As in the case of nitrobenzene, the electron adds to the NO substituent to form a nitroso radical anion:

$$e_{aq}^- + RNO \longrightarrow RNO^{\cdot -} \quad (68)$$

This species can be protonated and the pK_a value is 11.7. The decay of the nitroso radical anion or its protonated derivative is believed to form nitrosobenzene and phenylhydroxylamine:

$$2\,RNOH \longrightarrow RNO + RNHOH \quad (69)$$

Hydroxyl radicals attack nitrosobenzene in a diffusion-controlled reaction (Table 3) to form in neutral solution, the nitrobenzene radical anion[11] (reaction 70), which disproportionates by

$$RNO + \cdot OH \longrightarrow RNO_2^{\cdot -} + H^+ \quad (70)$$

slow second-order reaction, forming nitrobenzene and nitrosobenzene.

VI. REDOX REACTIONS

A. Electron Transfer

From electrochemical studies, it is clear that nitro, nitroso and amino compounds are component parts of the complex series of possible oxidation–reduction products of organic nitrogen-containing compounds[9,58]:

$$RNO_2 \xrightarrow{2e^-} RNO \xrightarrow{2e^-} RNHOH \xrightarrow{2e^-} RNH_2 \quad (71)$$

Most, if not all, of the unstable intermediates in these redox reactions can be produced and studied radiation chemically[108]. The conditions within an irradiated aqueous solution can be manipulated, by the judicious use of selective free-radical scavengers, to create, simply and kinetically, either an essentially oxidizing or purely reducing environment. It will be seen in Section VIII how these redox reactions have a bearing on the biological toxicity of amines, nitro and nitroso compounds[58]. Analogous enzyme-catalysed redox processes[18] are involved in the metabolism of drugs and toxic chemicals[44] and in their cytotoxic side-effects[64].

Many radiation-induced redox reactions involving nitrobenzene, phenylhydroxylamine and aniline have been demonstrated and reported in detail[38,102]:

$$RNO_2 + e_{aq}^- \longrightarrow RNO_2^{\cdot -} \quad (72)$$

$$2\,RNO_2^{\cdot -} \xrightarrow{2H^+} RNO + RNO_2 + H_2O \quad (73)$$

$$RNO + e_{aq}^- \longrightarrow RNO^{\cdot -} \quad (74)$$

$$2\,RNO^{\cdot -} \xrightarrow{2H^+} RNO + RNHOH \quad (75)$$

$$RNHOH + e_{aq}^- \longrightarrow RNHOH^{\cdot -} \longrightarrow R\dot{N}H + OH^- \quad (76)$$

$$2\,R\dot{N}H \xrightarrow{H_2O} RNH_2 + RNHOH \quad (77)$$

TABLE 5. Rate constants for the self-reactions of nitroaromatic radical anions and their protonated forms, in the absence of oxygen

Compound	Rate constants ($l\ mol^{-1}\ s^{-1}$)		References
	k (·NBH + ·NBH)	k ($NB^{\cdot-}$ + $NB^{\cdot-}$)	
4-Nitroacetophenone	—	1.1×10^7	101
4-Nitrobenzoate	4.6×10^8	2.5×10^5	79
3-Nitrobenzoate	6.4×10^8	1.5×10^5	79
2-Nitrobenzoate	1.4×10^8	$<10^5$	79
1,4-Dinitrobenzene	2.9×10^8	3.3×10^8	79
1,3-Dinitrobenzene	2.4×10^8	8×10^6	79
1,2-Dinitrobenzene	7.2×10^8	2.4×10^8	79
2,4-Dinitrobenzoate	6.4×10^8	10^7	79
2,5-Dinitrobenzoate	3.4×10^8	1.5×10^7	79
3,4-Dinitrobenzoate	6.8×10^8	5.6×10^5	79
3,5-Dinitrobenzoate	2.8×10^8	6.4×10^5	79

Nitrobenzene is reduced by the strong nuleophile e^-_{aq}, at a diffusion-controlled rate of 3×10^{10} l mol^{-1} s^{-1} (Table 3), to yield the nitrobenzene radical anion $RNO_2^{\cdot-}$. This species is also produced by electron-transfer reactions involving $CO_2^{\cdot-}$ and α-hydroxyalkyl radicals such as $(CH_3)_2\dot{C}HOH$. In alkali, $RNO_2^{\cdot-}$ is relatively stable, lasting even for seconds. Nitro radical anions are protonated in acidic solution, and the pK_a values for protonation (Table 4) have been measured spectroscopically and kinetically, using pulse radiolysis[79,107]. For nitrobenzene, the pK_a value is 3.2. In the absence of oxygen, $RNO_2^{\cdot-}$ decays slowly be second-order kinetics, leading to nitroso formation (reaction 73), and the rate constant for this reaction at neutral pH is $< 10^6$ l mol^{-1} s^{-1}. Table 5 lists the rate constants for the self-reactions of various aromatic nitro radical anions and their protonated forms ($R\dot{N}O_2H$). The uncharged protonated radical anions, formed in acidic solution, decay much more rapidly than the negatively charged $RNO_2^{\cdot-}$ species. However, nitrosobenzene is believed to be formed, following disproportionation of $R\dot{N}O_2H$ and the elimination of water from $RN(OH)_2$. In the presence of oxygen, $RNO_2^{\cdot-}$ undergoes an electron-transfer reaction[101], reconstituting RNO_2 and forming $O_2^{\cdot-}$

TABLE 6. One-electron reduction potentials of nitroaromatic compounds

Compound	E^1_7 (mV)	References
1,4-Dinitrobenzene	−257	79
3,4-Dinitrobenzoate	−271	79
2,5-Dinitrobenzoate	−272	79
1,2-Dinitrobenzene	−287	79
3,5-Dinitrobenzoate	−344	79
1,3-Dinitrobenzene	−345	79
2,4-Dinitrobenzoate	−345	79
4-Nitroacetophenone	−355	70
4-Nitrobenzoate	−396	79
2-Nitrobenzoate	−412	79
3-Nitrobenzoate	−433	79
3-Nitroacetophenone	−437	70
Nitrobenzene	−486	70

(reaction 78). Rate constants for this reaction of oxygen with different nitro radical anions are given in Table 6; its biological implications will be dealt with in Section VIII.

$$RNO_2^{\cdot-} + O_2 \rightleftharpoons RNO_2 + O_2^{\cdot-} \quad (78)$$

Further reduction of nitrosobenzene by e_{aq}^- attack (reaction 74) or by an electron-transfer reaction involving RNO_2^- or other electron donors, produces the nitroso radical anion $RNO^{\cdot-}$. The fate of the nitroso radical anion is thought to involve phenylhydroxylamine formation (reaction 75), which following a further two-electron reduction process may lead to amine production.

The reverse process involving amine oxidation, through subsequent steps leading ultimately to nitrobenzene production, can be deduced from radiation chemical studies with the nucleophilic species ·OH as oxidant[38]:

$$RNH_2 + OH \longrightarrow \dot{R}NH + H_2O \quad (79)$$

$$2\,\dot{R}NH \xrightarrow{H_2O} RNHOH + RNH_2 \quad (80)$$

$$RNHOH + \cdot OH \longrightarrow \dot{R}NOH + H_2O \quad (81)$$

$$2\,\dot{R}NOH \longrightarrow RNO + RNHOH \quad (82)$$

$$RNO + OH \longrightarrow \dot{R}NO_2H$$

$$2\,\dot{R}NO_2H \longrightarrow RNO_2 + RNO + H_2O \quad (84)$$

In addition to being an oxidizing free radical, ·OH also undergoes addition reactions, particularly with aromatic compounds. Nevertheless, ·OH may oxidize amines to a small extent, by abstracting a hydrogen from $-NH_2$. Base-catalysed disproportionation of the resulting anilino radical leads to phenylhydroxylamine formation. Phenylhydroxylamine reacts rapidly with ·OH to form a species, believed to be $\dot{R}NH(OH)_2$, which undergoes water elimination to form $\dot{R}NOH$ (reaction 81). Disproportionation of $\dot{R}NOH$ leads to the formation of nitrosobenzene as an oxidation product. Hydroxyl radicals react rapidly with nitrosobenzene to form $RN\dot{O}_2H$, which dissociates at neutral pH to $RNO_2^{\cdot-}$. The second-order decay of $RNO_2^{\cdot-}$ leads to the production of RNO_2, thus completing the radiation-induced six-electron redox cycle of $RNH_2 \rightleftharpoons RNO_2$.

B. One-electron Redox Potentials

Nitro radical anions ($R^1NO_2^{\cdot-}$) can undergo one-electron transfer reactions, transferring electrons reversibly to other nitro compounds (R^2NO_2) or compounds such as quinones or oxygen as electron acceptors of higher electron affinity[70]:

$$R^1NO_2^{\cdot-} + R^2NO_2 \rightleftharpoons R^1NO_2 + R^2NO_2^{\cdot-} \quad (85)$$

One-electron reduction potentials of nitro compounds relative to a standard electron donor, can be determined kinetically by pulse radiolysis, from the forward and back reactions using the expression:

$$E\tfrac{1}{7}(R^2NO_2^{\cdot-}) = E\tfrac{1}{7}(R^1NO_2^{\cdot-}) + 0.059 \log k_{85}/k_{85} \quad (86)$$

Table 7 lists one-electron reduction potentials ($E\frac{1}{7}$, measured at pH 7, against NHE) of nitroaromatic compounds determined by pulse radiolysis techniques.

TABLE 7. Rate constants for the reactions of nitroaromatic radical anions with oxygen

Compound	Rate constant (l mol^{-1} s^{-1}) k ($NB^{\cdot-} + O_2$)	Reference
Nitrobenzene	7.7×10^6	101
4-Nitroacetophenone	1.4×10^6	101
4-Nitrobenzoate	2.9×10^6	101

C. Protonation of Nitro Radical Anions

Aromatic nitro radical anions are protonated in acidic solution[79,107], with pK_a values generally $\lesssim 3$ (Table 4):

$$RNO_2^{\cdot-} + H^+ \rightleftharpoons R\dot{N}O_2H \qquad (87)$$

The degree of dissociation of these electron adducts influences their subsequent reactivity. This is shown in Table 5 which lists rate constants for the disproportionation of nitro radical anions and their protonated forms. The protonated species are generally more reactive, presumably because of their free-radical nature, and the absence of any electrostatic repulsion.

Electron adducts of nitro compounds are also capable of reacting with oxygen[16,50,101], although rate constants for the transfer of electrons from $RNO_2^{\cdot-}$ to O_2 are, as expected, proportional to the difference in reduction potentials of oxygen and the nitroaromatic compound under investigation.

VII. MISCELLANEOUS

A. Radiation-induced Hydroxylation

Phenols are a common radiation product in irradiated organic nitro, nitroso and amino compounds. However, the G value for total phenol production is considerably less than $G(\cdot OH)$, and also the phenol yield shows a strong oxygen effect, indicating the possible involvement of $O_2^{\cdot-}$. Possible mechanisms to explain these results have been proposed[17,30,31,37]. The first step involves the addition of $\cdot OH$ to the aromatic ring, the rate of which is diffusion-controlled, to produce a substituted hydroxycyclohexadienyl radical adduct. The yields of phenols are dose-rate dependent, being maximum at low dose-rates[26,66], indicating a probable competition between first- and second-order reactions.

In the absence of oxygen, phenol production arises from the second-order disproportionation of hydroxycyclohexadienyl radicals (reaction 64). The radiation yield of phenols, $G = 0.65$, in nitrous oxide saturated aqueous solutions of nitrobenzene[37] indicates that simple disproportionation of hydroxycyclohexadienyl radicals is only one of several reaction pathways.

In aerated solutions, oxygen adds to hydroxycyclohexadienyl radicals to form peroxy radicals, which subsequently decay slowly yielding some phenol[26]. At low dose-rates, first-order decay processes (reaction 66), which more efficiently produce phenols, will predominate. At higher dose-rates, competing second-order disproportionation reactions between peroxy radicals, leading predominantly to peroxide and hydroperoxide formation, are favoured, thus effecting a reduction in the G value for phenol formation with increasing dose-rate.

B. Radiation-induced Carboxylation

The radiation-induced carboxylation of aliphatic amines[42], in aqueous solution containing carbon dioxide, has been reported. The mechanism proposed involves the reaction of the ·OH-induced α-amino radical (reaction 44) with $CO_2^{\cdot-}$ formed by e_{aq}^- and H· attack on CO_2:

$$\cdot RNH_2 + CO_2^{\cdot-} \longrightarrow NH_2RCOO^- \quad (88)$$

Although the α-amino radical is not the only radical produced by ·OH attack on amines, it is an interesting one in the above reaction, since it leads to the radiation-induced synthesis of amino acids.

C. Radiation-induced Deamination and Denitration

The radiolytic deamination of the α-amino acids glycine and alanine in deoxygenated solution was first observed by Stein and Weiss[96] and by Dale and coworkers[23]. That this process is efficient is indicated by the high yields of ammonia which approach $G(NH_3) \sim 5$. Evidence from steady-state radiolysis studies using selective free-radical scavengers[91,105] indicates that deamination is primarily a result of the reductive attack of e_{aq}^- on the amino group (reaction 42). Little or no reductive deamination is observed from β-amino acids[106], alkylammonium ions[85] or simple amines[43]. Consequently, Garrison[39,40] has proposed that e_{aq}^- adds initially to the carbonyl group of α-amino acids, producing an unstable adduct which breaks down with subsequent release of NH_3 and there is ESR evidence to support this[90].

Oxidative deamination of α-amino acids is also reported for aerated solutions[39,104]. This is believed to arise from the reaction of the ·OH-induced α-carbon radical with oxygen:

$$NH_3^+\dot{C}HCOO^- + O_2 + H_2O \longrightarrow NH_4^+ + CHOCOO^- + HO_2\cdot \quad (89)$$

The yield of ammonia in oxygenated solutions of glycine (Table 3) under conditions where e_{aq}^- is converted to the relatively unreactive $O_2^{\cdot-}$ species, emphasizes the importance of ·OH attack in radiation-induced deamination.

Hydroxyl radicals also have important consequences for nitro compounds. Oxidative denitration by ·OH has been reported for nitroaliphatic[33], nitroaromatic[37] and nitroheterocyclic[48,77,109] compounds. The mechanism is believed to involve the addition of ·OH to the α-C position resulting in an unstable intermediate which subsequently breaks down, eliminating the nitro group as nitrous acid:

$$RNO_2 + \cdot OH \longrightarrow \dot{R}(OH)NO_2 \longrightarrow \dot{R}O + HNO_2 \quad (90)$$

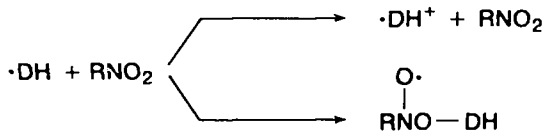
The efficiency of oxidative denitration is proportional to the fraction of OH which attacks the carbon atom to which the nitro group is attached. The low yields of nitrous acid released in irradiated nitroaromatic compounds is a result of the decreased probability of ·OH attack at the α-carbon atom.

D. Radical Oxidation versus Adduct Formation for Nitro Compounds

Nitro compounds, because of their high electron affinity, readily accept electrons from radiation-induced electron-donor species including e_{aq}^-, $CO_2^{\cdot-}$ and certain organic free radicals or radical anions, to form a nitro radical anion species. Electron donors which undergo fast and efficient electron transfer to nitroaromatic

compounds include the acetone electron adduct and its protonated form, the isopropyl radical[3] $(CH_3)_2\dot{C}OH$, electron adducts of nucleic acid bases[2,46], $CO_2^{\cdot-}$ and the radical NAD· produced by its reaction with the pyridine nucleotide NAD^+ [15].

In addition to a rapid one-electron reduction, nitro compounds may also form adducts to organic donor free radicals (·DH)[3,53,54,69], and for such reactions, a competition exists between free-radical oxidation and adduct formation[47]:



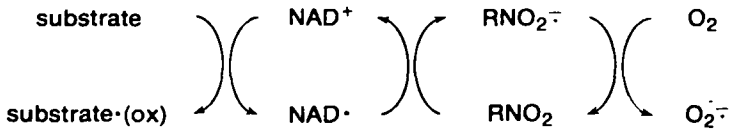
(91)

This competition is important in the mechanistic studies of the action of nitro compounds as chemical radiosensitizers[49,108].

In the case of α-hydroxyalkyl radicals formed by the preferential ·OH-induced abstraction of a hydrogen atom from the α-carbon position of alcohols, one-electron oxidation by nitro compounds predominates, whereas for oxygen-centred radicals, including those formed by ·OH attack on ethers, adduct formation is favoured. Although α- and β-hydroxy radicals have similar reactivities[49], α-hydroxyalkyl radicals are preferentially oxidized, whereas β-hydroxy radicals predominantly form adducts. In acidic solutions of α-hydroxy radicals, radical addition is favoured[69].

VIII. BIOLOGICAL APPLICATIONS

The majority of biological applications of the radiation chemistry of amines, nitro and nitroso compounds stem from the fact that the radiolysis products arise from redox intermediates which are formed as a result of radiation-induced oxidation/reduction reactions involving the primary water radiolysis species e_{aq}^-, H· and ·OH. These redox reactions resemble those occurring in living cells for the purpose of maintaining life processes, including electron transport, oxidative phosphorylation, digestion, respiration and metabolism, and any perturbation may have serious biological consequences. Consequently, radiation chemistry can be used as a tool, not only to generate and characterize important stable or transient metabolites, under carefully controlled physicochemical conditions, but also to monitor the kinetics of these intermediates and their reactions with biological chemicals.



(92)

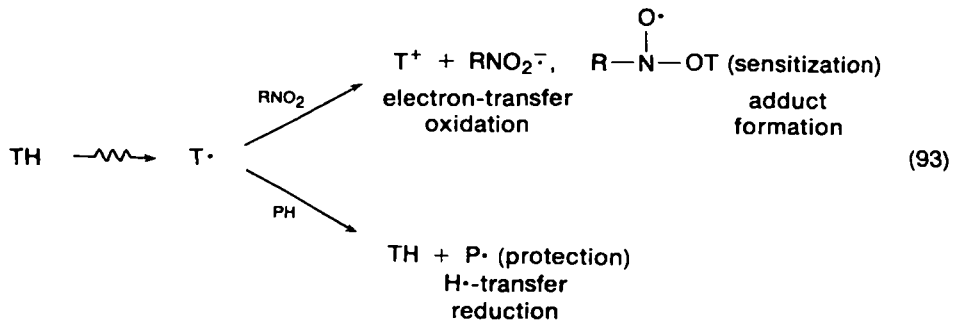
In this way, radiation chemistry provides a means of simulating biochemical pathways involved in normal and pathological processes, in order to study the action of radiosensitizers, antibiotics and carcinogens, to simulate drug metabolism and *in vitro* cytotoxicity, and to examine the usefulness of radiolytic detoxification of harmful drugs and chemicals.

A. Radiosensitizers

A direct clinical application of the radiation chemistry of nitroaromatic and nitroheterocyclic compounds is in the recent development of radiosensitizers for tumour cells used in radiotherapy. The success of many radiotherapy regimes in the

treatment of human cancers is believed to be limited by the presence of hypoxic, and therefore radioresistant cells in many tumours[20]. It has been found, as predicted by Adams and Cooke[1], that many electron-affinic nitro compounds mimic oxygen in their ability to differentially sensitize the killing of hypoxic cells[83] or the destruction of cellular components in deoxygenated aqueous solution[48] by ionizing radiation. The radiosensitizing efficacy of such compounds is directly correlated with their reduction potentials[4,87].

Detailed study of the free-radical reactions involving such nitro compounds, in the presence of biochemicals as important cellular radiation targets (TH), has led to a proposed redox model, based on reaction kinetics[49,108], to explain the molecular mechanism of chemical radiosensitization:



(93)

Oxidative radiation damage to DNA and other critical cell targets, produced by ·OH attack, leads, initially, to a potentially damaged reactive target radical T·. In the absence of oxygen, the intermediate T· disproportionates, leading to partial restoration of the target, and incomplete production of oxidative radiation damage to the target. Nitro compounds act like oxygen to sensitize the target to the effects of radiation, by efficiently intercepting target radicals in competition with the restorative back-reactions, to completely fix all the potential oxidative target radical damage. Extrapolation from chemical systems suggests that optimum sensitization *in vivo* can be achieved with oral or intravenous drug doses ~10–100 g, distributed uniformly throughout the blood of the patient. Such doses may be toxic, and this toxicity may be mediated by free-radical redox reactions.

B. Drug Toxicity and Metabolism

When foreign chemicals, especially aromatic nitro, nitroso and amino compounds are ingested, they are rapidly metabolized by inducible redox enzymes, particularly in the microsomes of the liver and kidneys[88]. The oxidoreductases in microsomes and mitochondria, including mixed function oxidases, 'nitroreductases' and cytochrome P-450, are able to reduce nitro or nitroso compounds and to oxidise amines, producing various stable and unstable redox intermediates[64] some of which (hydroxylamines, nitroxides, nitroso compounds) are toxic, mutagenic or carcinogenic[58].

The biochemical pathways (Figure 7) whereby nitrogen containing compounds are metabolized, generating intermediates of varying toxicity, are controlled by redox reactions involving sequential electron-transfer oxidation–reduction steps which produce unstable free-radical intermediates (reactions 72–84). Radiation chemistry is useful in the study of drug metabolism and toxicity, in that it provides a clean, direct method for initiating redox reactions and for producing and observing the reactive intermediates under controlled *in vitro* conditions, in the

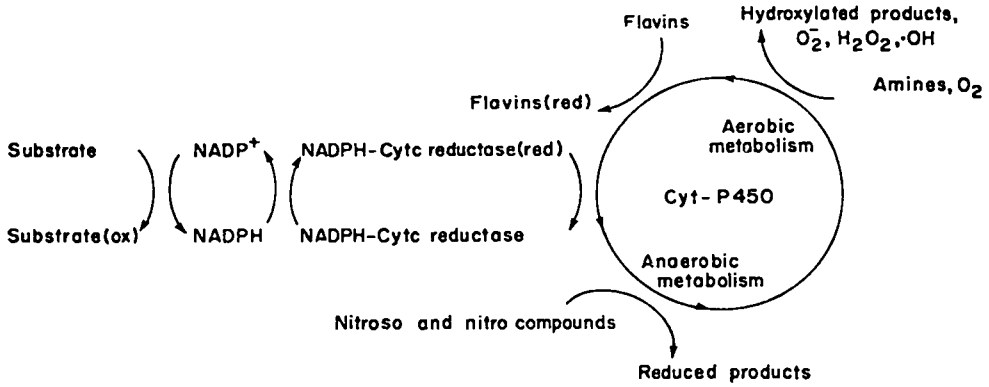


FIGURE 7. The sequence of redox equilibria involved in the liver microsomal metabolism of nitro, nitroso and amino compounds. Toxicity arises directly by the production of reactive metabolites, and indirectly through side-effects of aberrant metabolic pathways.

simulation of normal and pathological biochemical redox pathways. Such studies enable the sequence and kinetics of electron-transfer reactions to be determined, allow selective intermediates or interfering species to be produced and tested with respect to their toxicity, mutagenicity or carcinogenicity, and help to define more precisely the nature of the interference by foreign chemicals in normal metabolic processes[51].

C. Antibiotics

The role of the nitro group in determining antibiotic activity has been reviewed in a previous volume in this series[100]. Important nitro-containing antibiotics include the naturally occuring chloramphenicol and azomycin (2-nitroimidazole). In addition, there is now available a wide spectrum of synthetic drugs, including parathion (insecticide), nitro- and dinitro-phenol derivatives (fungicides and herbicides), nitrofurans and nitroimidazoles (antibacterial and antiprotozoal agents). In all cases, the biological action of these antibiotics arises from free-radical mediated metabolic pathways, leading to the production of selective toxins. These processes can be simulated radiation chemically in order to study the kinetics and molecular aspects of their antibiotic action.

The value of antibiotics stems from their ability to selectively effect foreign or invading microorganisms. Their therapeutic utility in the treatment of infectious diseases is not due to their action on the host, but rather to the selective deleterious effect on the offending microorganism. As is implied in their name, antibiotics affect all living organisms, and selective toxicity is relative, not only to the biochemical properties of the nitro group, but also to the physiological factors which determine drug delivery, permeability, biological retention and targetting, etc.

D. Chemical Carcinogens

Many aromatic amines, nitroso and nitro compounds are carcinogenic. Generally, these chemical carcinogens are relatively stable and nontoxic, and require metabolic activation before they become hazardous[71]. Activation by biological systems occurs

in the microsomes, and involves a series of enzyme-catalysed oxidation–reduction reactions. The 'activated' carcinogens result from Nature's unsuccessful attempt to metabolize foreign compounds. The activated carcinogenic intermediates formed in the aerobic metabolism of aromatic amines, nitroso and nitro compounds, including nitroxides, hydroxylamines, imines and nitroso derivatives, are produced in biochemical redox reactions, which, like the effects of ionizing radiation, are mediated by free-radical redox species, particularly ·OH and O_2^{-} [50]:

$$RNH_2, RNO, RNO_2 \xrightarrow[\text{reduction } (e_{aq}^{-}, H\cdot, O_2^{\cdot-})]{\text{oxidation } (\cdot OH,\ O_2^{\cdot-},\ H_2O_2)} RNO_2^{\cdot-}\ RN(H)O\cdot,\ R\dot{N}H, RNHOH \quad (94)$$

carcinogenic species

Radiation chemical studies of amino, nitroso and nitro compounds, under defined physicochemical conditions, can be used to probe the kinetics and mechanism of the redox activation of chemical carcinogens, to explore the possible additive or synergistic effects of radiation and chemical carcinogens, and to mimic the metabolic activation of chemical carcinogens[50].

Since both metabolic activation of chemical carcinogens, and the combined effects of radiation and toxic chemicals, involve free-radical processes, the possibility exists of chemical protection against carcinogenesis, using chemicals capable of scavenging or inactivating the free-radical intermediates involved[41,52,86,94].

E. Radiolytic Detoxification of Hazardous Chemicals

Many carcinogenic aromatic nitro (5-nitroquinoline-*N*-oxide), nitroso (dialkylnitrosamines) and amino (β-naphthylamine) compounds are being introduced into our environment in ever-increasing quantities, as by-products of industrial processes. In addition, many nitrogen-containing compounds, including dyes, drugs, food additives, preservatives and fertilizers find their way into waterways as pollutants. Radiation treatment of waste water is presently being evaluated in several centres[22,25,97,98].

In studying the basic mechanism of radiation damage to nitrogen-containing compounds in aqueous solution, it is clear that radiation-induced oxidation and hydroxylation, by ·OH attack and to a lesser extent by reactions of $O_2^{\cdot-}$, H_2O_2 and other oxidants formed during irradiation, provide an effective way to break down and deactivate toxic amines, nitroso and nitro compounds (NX):

$$NX \xrightarrow[\text{oxidation, hydroxylation}]{\text{radiolytic reduction}} \text{Less toxic products (phenols, aldehydes, carboxylic acids, nitrate, nitrite)} \quad (95)$$

The radiolytic approach to the treatment of liquid wastes is simple and efficient and lends itself to the development of automated systems with recycling in a closed loop, or flow-through systems. Studies in the literature[22,98] indicate that milligram quantities of highly toxic or carcinogenic materials in aqueous solution can be destroyed with Mrad doses of ionizing radiation, which is well within the capability of existing steady-state gamma irradiators and high-energy pulsed radiation sources. The development of full-scale radiolytic waste treatment facilities may prove uneconomic, but such an approach may have practical application in research institutes for the treatment of small amounts of hazardous chemicals which are difficult to handle or dispose of by other means.

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **8**

Electrochemistry of nitro compounds

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I. INTRODUCTION

There are available a number of reviews of various aspects of the electrochemistry of nitro compounds[1–3], and it would be no useful service to simply repeat or paraphrase them here. However, as it happens, there are a number of aspects of the subject which either have been investigated more recently or received little or no attention in previous reviews. These matters are the subject of the present review, together with sufficient overview of the general features of the electrochemical behaviour of nitro compounds to place these discussions in their proper context. The previous literature on this subject[1–3] should be consulted by those interested in other aspects of the problem. A monograph by the present author may be consulted for an extended discussion of the various techniques employed in synthetic and mechanistic electrochemistry[4].

Nitrogen in the nitro group is already at a very high oxidation level. It is therefore extremely difficult to remove an electron, and consequently anodic chemistry of the nitro group is essentially unknown; in fact, nitro compounds can be used as solvents for anodic oxidation of other substances[5]. On the other hand, the high oxidation state of nitrogen in the nitro group endows this functional group with a rich and

complex cathodic electrochemistry. By proper control of conditions, it is possible to convert a single nitro compound into a variety of products; nitrobenzene, for example, may be converted to phenylhydroxylamine, *p*-aminophenol, aniline, azoxybenzene, azobenzene or hydrazobenzene, depending upon conditions. For reasons which will become clear in later sections, not all nitro compounds can be led to produce all of these products, and sometimes other types of products are obtained. To understand the reasons for this, and because the wealth of possible products makes choice of experimental conditions critical, we shall first examine in detail the electrochemical behaviour of the most thoroughly studied substance, nitrobenzene, before proceeding to more complex substances in subsequent sections.

It should be noted that the scope of this review includes only electron-transfer processes involving the nitro group itself. It is possible to effect anodic coupling of carbanions stabilized by nitro groups[6] (equations 1 and 2), but these reactions only

$$R_2\bar{C}NO_2 \xrightarrow{-e^-} R_2\dot{C}NO_2 \longrightarrow R_2C(NO_2)CR_2(NO_2) \quad (1)$$

$$R_2\bar{C}NO_2 + NO_2^- \xrightarrow{-2e^-} R_2C(NO_2)_2 \quad (2)$$

involve the nitro group in a peripheral way – indeed it comes out of such reactions unchanged – and so such processes are not relevant here.

II. GENERAL CONSIDERATIONS

A. Mechanism of Reduction of Nitrobenzene

The general features of the electrochemical behaviour of nitrobenzene, in preparative terms at least, have been known for many years, since Haber's classic researches on the subject[7]. His work (which also represents the first application of controlled-potential electrolysis in organic electrochemistry) showed that by proper choice of electrode potential, pH, and temperature it is possible to obtain any of the products mentioned in the Introduction. Subsequent insights into the mechanisms of the various processes involved have come from application of a variety of electrochemical techniques, including polarography, cyclic voltammetry, electron spin resonance (ESR) and the use of aprotic solvents. The last of these applications will be taken up first, since under aprotic conditions anionic intermediates are often much longer lived than in protic solvents and follow-up chemical reactions are often suppressed, so that one can more readily identify the initial steps in the electrode reaction.

1. Aprotic media

Nitrobenzene (**1**) exhibits two polarographic waves in solvents such as dimethylformamide (DMF) or dimethyl sulphoxide (DMSO). The two waves correspond to reversible transfer of a single electron to nitrobenzene at the potential of the first wave, followed by an overall three-electron reduction at the second wave. Controlled-potential reduction at the first wave also consumes one electron, and affords the nitrobenzene radical anion (**2**) (equation 3). The identity of this species is readily confirmed by ESR spectroscopy[8]. The second polarographic wave is associated with a complex series of reactions initiated by reduction of **2** to the

$$\underset{(1)}{C_6H_5NO_2} \xrightarrow{e^-} \underset{(2)}{C_6H_5NO_2^{-\bullet}} \qquad (3)$$

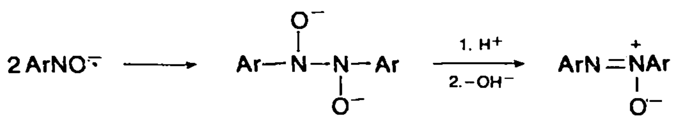
corresponding dianion (**3**). This strongly basic intermediate rapidly abstracts a proton from its surroundings to afford a species **4**, which then rapidly ejects hydroxide to afford nitrosobenzene (**5**) (equation 4). Finally, **5** is rapidly reduced to phenylhydroxylamine (**9**) (equation 5). Support for the sequence of steps

$$\mathbf{2} \xrightarrow{e^-} \underset{(3)}{C_6H_5NO_2^{2-}} \xrightarrow{H^+} \underset{(4)}{C_6H_5\bar{N}O_2H} \xrightarrow{-OH^-} \underset{(5)}{C_6H_5NO} \qquad (4)$$

$$\mathbf{5} \xrightarrow{e^-} \underset{(6)}{C_6H_5NO^{-\bullet}} \xrightarrow{H^+} \underset{(7)}{C_6H_5\dot{N}OH} \xrightarrow{e^-} \underset{(8)}{C_6H_5\bar{N}OH} \xrightarrow{H^+} \underset{(9)}{C_6H_5NHOH} \qquad (5)$$

summarized in equations (4) and (5) comes from a study of the electrochemical behaviour of nitrobenzene and nitrosobenzene in liquid ammonia[9]. Dianion **3** was observed as a long-lived species in this solvent, where proton transfers are slow, but when isopropyl alcohol was added as proton donor the one-electron second wave in cyclic voltammetry increased to a height corresponding to three-electron uptake as the reaction cascade shown in equations (4) and (5) was initiated by protonation of **3** by isopropanol.

The isomeric trifluoromethylnitrobenzenes exhibit somewhat anomalous behaviour in aprotic media[10]. The usual one-electron first wave is observed, but the second wave corresponds to uptake of only two electrons, and controlled-potential electrolysis results in formation of a mixture of azoxy (**11**) and azo compounds. It appears that protonation of the nitroso compound radical anion (**10**) is slow compared to **6** and that therefore dimerization of this species ultimately yielding the azoxy compound (equation 6) is competitive with protonation. Probably the

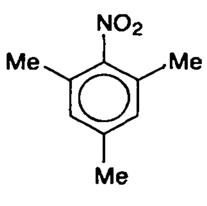


(6)

(**10**) (**11**)

powerful electron-withdrawing trifluoromethyl group inductively decreases the basicity of **10**. The azo compound formed in these reactions presumably arises by further reduction of the azoxy compound.

A number of investigators have observed steric effects upon the conversion of nitroarenes to the corresponding radical anions in aprotic media. For example, 2,4,6-trimethylnitrobenzene (**12**) is 0.25 V harder to reduce than nitrobenzene itself,



(**12**)

presumably because the nitro group in **12** is twisted out of the plane of the benzene ring, resulting in decreased delocalization of the unshared electron over the ring[11]. Similar effects have been observed by Geske and coworkers[12], who were able to demonstrate conclusively that the unshared electron is indeed localized to a greater degree on the nitro group in the presence of bulky *ortho* substituents by examining ESR hyperfine structure. As the nitro group is twisted out of planarity, the nitrogen hyperfine coupling constant increases and coupling to the ring carbon atoms diminishes[11]. Peover and Powell observed a kinetic effect upon the rate of electron transfer[13]: as the nitrogen hyperfine coupling constant and localization of charge on nitrogen in the radical anion increase with increasing deviation from planarity, the rate of heterogeneous electron-transfer to the nitro compound decreases. While the reasons for this correlation are not clear, it suggests that electron transfer to an isolated (unconjugated) nitro group should be rather slow. It is gratifying to learn from a recent study of the electrochemical behaviour of *t*-nitrobutane that this actually turns out to be the case[14].

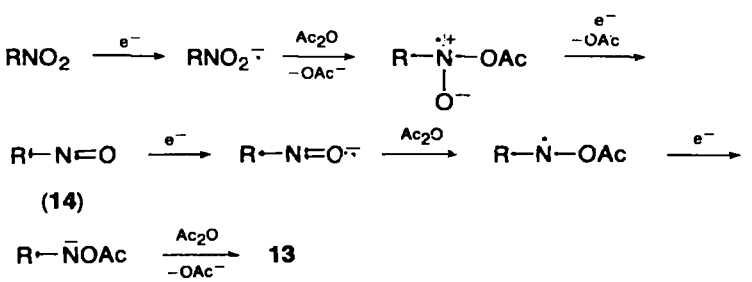
Ion pairing is not negligible even in the very polar solvents (DMF, DMSO, acetonitrile) commonly used in organic polarography, and indeed a large number of reports have appeared concerning ion pairing between hydrocarbon radical anions and the counterion of the polarographic supporting electrolyte[15,16]. Since charge is very substantially localized on the nitro group in a nitroarene radical anion[11], ion-pairing effects should be readily observable, and are so: Holleck and Becker have observed, for example, that substituted nitro compounds become noticeably easier to reduce as the size of the counterion decreases[17]. (This is the customary and expected effect in such cases – small ions ion pair more strongly for both steric reasons and because their charge/size ratio is greater; the ion-paired species is stabilized relative to the free anion, and hence is formed more readily from the neutral nitroarene.)

2. *Trapping agents*

The nucleophilicity of oxygen in the nitrobenzene radical anion **2** is sufficiently high to permit ready reaction with electrophiles added to the electrolysis medium. Electrolysis of nitro compounds in an aprotic solvent containing added acetic anhydride results in the formation of *O,N*-diacetylhydroxylamines (**13**) (equation 7) in moderate (50–85%) yield, together with small amounts of side-products[18].

$$RNO_2 \xrightarrow[Ac_2O]{e^-} \underset{\displaystyle Ac}{\overset{\displaystyle |}{RNOAc}} \qquad (7)$$

(13)



SCHEME 1

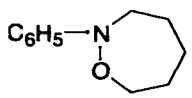
Compounds **13** are presumably formed by the sequence of reactions shown in Scheme 1. Nitrosobenzene (**14**), postulated as an intermediate (where R = C_6H_5) in this sequence, should and does afford **13** upon reduction in the presence of acetic anhydride.

Wagenknecht has shown[19] that the nitrobenzene radical anion may be trapped in similar fashion by alkyl halides to afford *N,O*-dialkylhydroxylamines (**15**) in up to 90% yield (equation 8).

$$C_6H_5NO_2 \xrightarrow[RX]{e^-} C_6H_5NOR \quad (8)$$

(**15**)

A very similar mechanism to that of Scheme 1 is suggested. Heterocycle **16** can be obtained by use of 1,5-dibromopentane in the reduction.



(**16**)

3. Protic media

Nitrobenzene exhibits a four-electron polarographic wave over the pH range 2 to 12; below pH 5 a second wave, corresponding to uptake of two electrons, is observed at more negative potentials[1–3]. Controlled potential electrolysis at the first wave affords phenylhydroxylamine (**9**) (equation 9); aniline (**17**) is formed from **9** by reduction at the second wave (equation 10). Equation (9), involving as it does four

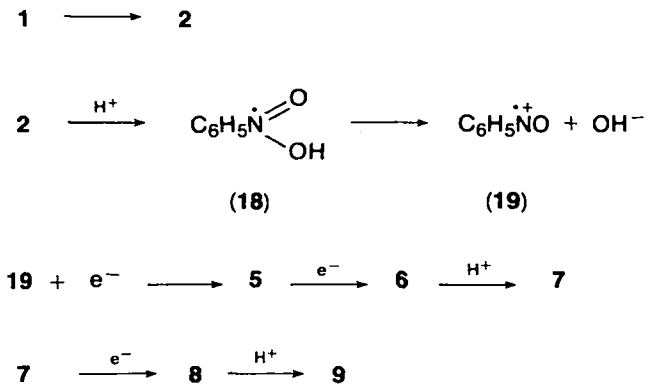
$$C_6H_5NO_2 + 4e^- + H^+ \longrightarrow C_6H_5NHOH + H_2O \quad (9)$$

(**9**)

$$\mathbf{9} + 2H^+ + 2e^- \longrightarrow C_6H_5NH_2 + H_2O \quad (10)$$

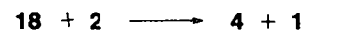
(**17**)

electrons and four protons, clearly must be a composite of several steps, proceeding through intermediates of increasingly lower oxidation state. The conversion of **1** to **9** must occur by a series of electron and proton transfers, and one aspect of the mechanistic challenge is to deduce the order in which these transfers occur. Another complication is introduced by the fact that certain intermediates may themselves serve as reducing agents toward the nitro compound or even other intermediates of higher oxidation state, thus competing with the electrode as electron sources. Although the mechanism of Scheme 2 serves as an adequate description of the overall reduction process, a number of variants are possible. For example, the sequence **18** → **19** → **5** could be replaced by a homogeneous electron exchange (equation 11), thus by-passing the formation of **19**. Alternate mechanisms involving the nitro compound dianion **3**, formed by disproportionation of **2**, may also be written. Sophisticated experiments involving flow cells and monitoring of the rates of disappearance of intermediates by cyclic voltammetry and optical and ESR spectroscopy[20–23] have permitted verification of certain of these steps and measurement of their rates. In this work it has proved possible, using such techniques, to measure the rather large bimolecular rate constants (10^2–10^5 mol^{-1}

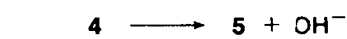


SCHEME 2

s^{-1}) for reaction of **2** with a number of inorganic ions (IO_4^-, $S_2O_8^{2-}$ and several Cu^{2+} complexes)[20].

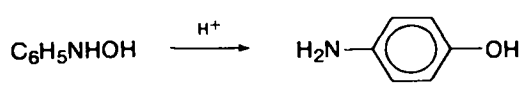


(11)



A polarographic study[24] has established that the rate-determining step in nitrobenzene (**1**) reduction over the pH range 2–5 is reduction of **1**; between pH 6 and 9 protonation of **2** becomes rate-limiting, while reduction of **2** to **3** is rate-determining above pH 11; the last two steps are both rate-controlling between pH 9 and 11. This is consistent of course with diminishing proton availability as pH increases.

Preparative-scale reduction of nitrobenzenes in strong acid[25] often affords *p*-aminophenols by acid-promoted rearrangement of the initial arylhydroxylamine (Gatterman rearrangement) (equation 12), especially when electrolysis is conducted at elevated temperature (see Section III).



(12)

It will be noted that the cascade of reactions in Scheme 2 which ultimately affords phenylhydroxylamine (**9**) is initiated by protonation of radical anion **2**; it is therefore this particular protonation step which constitutes the essential difference between the behaviour of nitrobenzene in aprotic and protic media. Holleck and Exner have illustrated this point nicely by their observation that addition of substances such as camphor, agar, gelatin, or tylose to protic media converts the single four-electron wave to two waves, the first a one-electron and the second a three-electron wave, as in aprotic solvents[26]. These substances are all strongly adsorbed on mercury from protic solvents, forming an adsorbed film which renders the electrode surface effectively aprotic, blocking protonation of **2** on the polarographic time-scale.

Electrochemical reduction of nitro compounds in base affords azoxy compounds, which may or may not be reduced further, depending upon the experimental conditions employed. As indicated previously (equation 6), the azoxy compounds presumably arise by dimerization of nitrosoarene radical anions. In this process the nitroarene consumes a total of three electrons; the discrepancy from the four

electrons consumed under polarographic conditions may well arise because dimerization of **10** is favoured relative to protonation (and further reduction) in the more concentrated solutions normally employed in preparative work. This is not the only aspect of the electrochemistry of nitroaromatics in alkaline media which could benefit from further investigation. The azoxy compound can be reduced further to an azo compound (**20**) and ultimately to a hydrazo compound (**21**) (equation 13). It appears that one can control the reduction so as to obtain **11**,

$$\underset{\text{(11)}}{ArN{=}\overset{+}{N}Ar\ (O^-)} \xrightarrow[H^+ \ -OH^-]{2e^-} \underset{\text{(20)}}{ArN{=}NAr} \xrightarrow[2H^+]{2e^-} \underset{\text{(21)}}{ArNHNHAr} \qquad (13)$$

20 or **21** by judicious use of conditions[2]. Most of the work in this area has involved empirical establishment of the proper conditions for obtaining a given type product by constant current electrolysis. Very little work has been done to establish the behaviour of azoxy and azo intermediates using the various electroanalytical techniques in media similar to those chosen for electrolysis, and therefore the reasons for the following facts are not always clear. Reduction of the nitro compound in concentrated solution or suspension in hot alkali affords the azoxy compound in 85–95% yield, apparently because under these conditions the azoxy compound precipitates from solution and is thus protected against further reduction. If the electrolysis is carried out under conditions where the azoxy compound remains in solution, e.g., sodium acetate in hot 95% ethanol, the azo compound can be obtained in 90–95% yield if electrolysis is terminated when hydrogen evolution begins; if the electrolysis is allowed to proceed past this point the hydrazo compound can be isolated in 90–95% yield. It is surprising that the azo compound should be isolable, in view of the fact that azobenzene is reported to be easier to reduce than azoxybenzene over the pH range 2–12[27]. I have suggested elsewhere that this apparent anomaly may be due to the fact that at the elevated temperatures used for the preparative work azoxybenzene becomes *easier* to reduce than azobenzene[2].

B. Choice of Experimental Conditions

In the most favourable cases, it is possible to convert a single nitro compound into a variety of products, depending upon the conditions chosen. Nitrobenzene itself is the substance which has been most frequently investigated. The available data as discussed in preceding sections are summarized in Table 1. A number of points should be made concerning this table. For example, constant-current electrolysis is mentioned for several conversions. There is no intrinsic advantage in constant-current electrolysis over controlled-potential electrolysis (indeed, quite the contrary), but much of the existing older work was done by constant-current electrolysis because until the commercial availability of potentiostats in the late 1960s controlled-potential electrolysis required tedious manual operation and was rarely used. Secondly, as indicated in a footnote to the table, the exact conditions of pH and temperature should rest upon polarographic measurements, since substituents may have a considerable effect upon the reduction (Section III). Thirdly, recall that stable aromatic radical anions may also be prepared (electrolysis in aprotic solvents), and that even dianions may be prepared by electrolysis in liquid ammonia at a potential corresponding to the second voltammetric wave. Finally, note that the combination of an initial electrolysis and a subsequent chemical reaction, or two successive electrolyses under different conditions can constitute routes to additional

TABLE 1. Electrolysis products of aromatic nitro compounds as a function of experimental conditions[a].

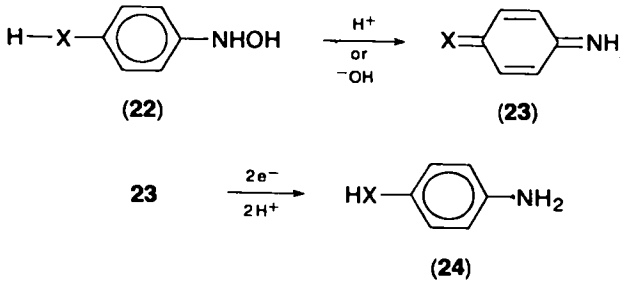
	Experimental conditions[b]		
Desired product	Electrolysis	Temperature (°C)	pH
Amine	Controlled-potential, at second polarographic wave	25	4
	or		
	Controlled-potential reduction of hydrazo or azo compounds (see below) in acid	25	2
Hydroxylamine	Controlled-potential, at first polarographic wave	25	6
p-Aminophenol	Controlled-potential at first polarographic wave	80	0–2
	or		
	Constant current, platinum cathode	25	ca. −1[c]
Azoxy compound	Controlled-potential, at first polarographic wave	25	8
	or		
	Constant-current, water as solvent	80	8
Azo compound	Constant-current, alcohol as solvent, limited time	80	8
Hydrazo compound	Constant-current, alcohol as solvent, prolonged electrolysis	80	8
Benzidine	Reduction to hydrazo compounds (see above), followed by rearrangement of the latter	80	0–2

[a]Taken from A. J. Fry, *Synthetic Organic Electrochemistry*, 1972, p. 233 and reproduced by permission of Harper and Row, Publishers Inc., New York.
[b]Approximate conditions; to be modified by voltammetric data in specific cases.
[c]Concentrated sulphuric acid.

products. Thus, reduction of a nitro compound to the hydrazo compound may first be carried out in base, and then the solution made strongly acidic to rearrange the hydrazo compound to the corresponding benzidine, or, alternately, the azo compound may be produced first, then reduced in acid to afford the benzidine. Also, one may electrochemically oxidize the *p*-aminophenol to a quinone[28], this sequence of reduction and oxidation constituting a one-pot conversion of a nitro compound to the corresponding quinone. In Section IV there is described an especially elegant route to an otherwise difficultly available fused-ring heterocyclic system by a sequence of three consecutive electrolyses (reduction, oxidation, then reduction again).

III. SUBSTITUTED NITROAROMATICS

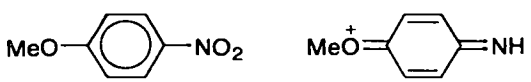
The electrochemical behaviour of a substituted nitrobenzene can differ in a number of ways from nitrobenzene itself. The substitutent(s) may merely shift the reduction potential, or may actually induce new chemistry. The first of these effects is fairly



SCHEME 3

straightforward: since the nitro group develops a negative charge upon conversion to the radical anion, electron-supplying groups retard, and electron-withdrawing groups facilitate, reduction, and there is a good linear correlation between the polarographic half-wave potential and the inductive effect of the substitutent[29,30].

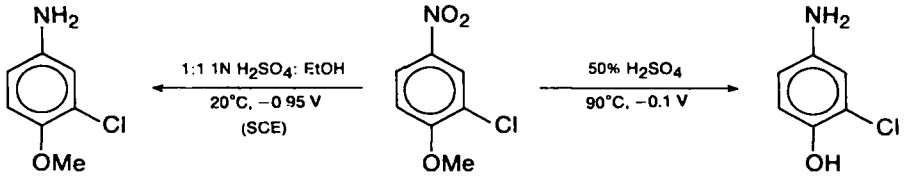
Substituents at the *ortho* or *para* position bearing unshared electrons can give rise to interesting consequences. For example, *p*-nitrophenol and *p*-nitroaniline undergo *six*-electron reduction under conditions where nitrobenzene undergoes four-electron reduction to the hydroxylamine[31]. This behaviour arises from the fact that the initial arylhydroxylamine (**22**) undergoes rapid dehydration to a quinoid species (**23**), which is then immediately reduced to the amine (Scheme 3). The presence of a proton on X in **22** is not absolutely necessary, though it does facilitate dehydration. Thus, *p*-nitroanisole (**25**) is reported to consume only four electrons upon controlled-potential coulometric reduction, while *p*-nitrophenol consumes six electrons under the same conditions[31]. Possibly dehydration of the hydroxylamine from the phenol (**22**, X = O) is faster than that from **25** because in the former case solvent can participate in cleavage of the O—H bond of the hydroxyl more or lesss concertedly with cleavage of the N—O bond, whereas **25** must first be converted to charged species **26**. Actually, dehydration of **22** must be fairly fast in order that



(**25**) (**26**)

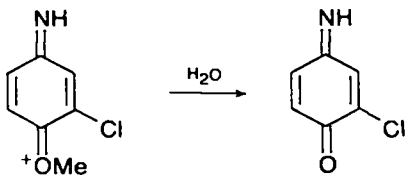
six-electron reduction be observable on the time-scale (seconds) of polarography. The rate constants for a few dehydration processes of type **22** → **23** have been measured by electrochemical relaxation techniques. Alberts and Shain obtained a value of $1.3\ s^{-1}$ for the pseudo-first-order dehydration rate constant for *p*-hydroxylaminophenol in 20% ethanol at pH 4.8[32], while Testa and Reinmuth measured a value of $0.2\ s^{-1}$ for the *ortho* isomer in 50% ethanol at pH 6.2[33]. It should be noted that these rates are approximately the same as the polarographic time-scale. Small changes in the dehydration rate constant between two similar compounds, or even the same compound under fairly similar conditions, could easily tip the balance from four- to six-electron uptake, explaining why compounds such as *p*-nitroanisole and *p*-dimethylaminonitrobenzene have been found to undergo four-electron reduction by some workers[31], and six-electron reduction by others[34,35]. *o*-Nitrophenol is itself borderline: polarography shows uptake of six electrons in acid or base, and four electrons under neutral conditions[36].

Alkoxynitroarenes (*ortho* or *para*) can undergo cleavage of the alkoxy group, especially when reduction is carried out under vigorous conditions (strong acid, elevated temperatures) (equation 14)[34,35,37,38]. It appears that under the more vigorous conditions intermediate **30** undergoes hydrolytic cleavage to **31** faster than it can be reduced to **28** (equation 15). This ether cleavage, where it occurs, can be



(14)

(28) **(27)** **(29)**

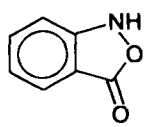


29 (15)

(30) **(31)**

suppressed by carrying out the electrolysis at room temperature and a more negative potential[34,35,37,38]. Under these conditions, apparently either the hydroxylamine is reduced as quickly as it is formed, or the charged quinoid intermediate is reduced before it can undergo hydrolysis.

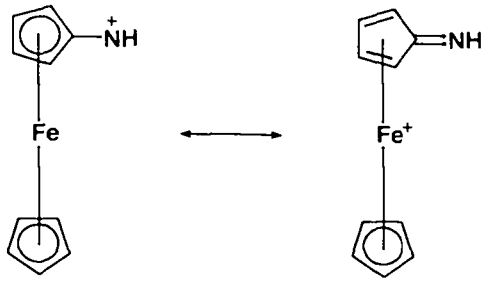
It should also be pointed out that *ortho*-substituted nitro compounds can afford cyclized products in certain cases. While, unsurprisingly, *o*-nitrobenzoic acid can be reduced to the hydroxylamine, amine or *p*-aminophenol by systematic variation in conditions in ways already discussed, it is also possible to convert it to heterocycle **32**[39].



(32)

In view of both the relatively facile conversion of *o*- and *p*-alkoxynitro compounds to amines, which is initiated by ionization to produce an intermediate of type **26**, and the powerful stabilizing effect of a ferrocene nucleus on a positive charge at the α-position, it is unsurprising that nitroferrocene undergoes six-electron reduction over a wide range of pH[40]. The intermediate hydroxylamine must undergo rapid conversion to intermediate (**33**), followed by reduction of **33** to aminoferrocene.

One feature of nitroarene electroreduction which has not received the attention it deserves is its potential for selectivity. The nitro group is fairly easy to reduce compared to most other functional groups, and therefore it is possible to reduce selectively the nitro group in a polyfunctional molecule, employing controlled-potential electrolysis, while leaving other functional groups untouched. Some examples of this general principle have been cited previously[2], and others have been found recently in this laboratory[41a]. For example, *m*-nitrophenylacetylene can

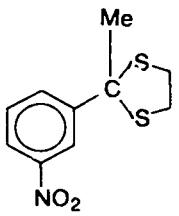


(33)

be reduced to *m*-aminophenylacetylene, a useful end-capping agent in polymer synthesis, in 80% yield (equation 16). Previously, no chemical reductant had been

$$m\text{-}O_2NC_6H_4C{\equiv}CH \xrightarrow[1:1\ EtOH:\ 1N\ H_2SO_4]{-1.3\ V\ (SCE)} m\text{-}H_2NC_6H_4C{\equiv}CH \qquad (16)$$

found to effect this selective reduction because of the similar reactivities of the nitro and ethynyl groups[41b]. It is also of interest that reduction of the nitro group in thioketal **34** can readily be carried out electrochemically[41a]; the sulphur atoms in **34**



(34)

might well be expected to poison a hydrogenation catalyst, preventing that route to the amine.

Nitrobenzene, as mentioned previously, exhibits two polarographic waves in the ratio of 1:3 in aprotic media, though addition of proton donors results in collapse to the single four-electron wave observed in protic media (Section II). Substituted nitroarenes exhibit similar behaviour, but special mention must be made of nitro compounds bearing acidic substituents. While *m*-nitroanisole exhibits the usual two waves in 1:3 ratio in DMSO solution, *m*-nitrophenol (**35**) exhibits more complex behaviour due to a series of self-protonation steps[42,43]. In controlled-potential coulometry at the first wave, **35** consumes almost the same amount of current as does *m*-nitroanisole (n = 0.8 and 1.0, respectively), but the value of product analysis is seen here when it is discovered that the products are actually starting material (80%), as the anion (**36**), and the hydroxylamine (20%). The stoichiometry is therefore as shown in equation (17); *m*-nitroanisole is simply converted to a stable radical anion

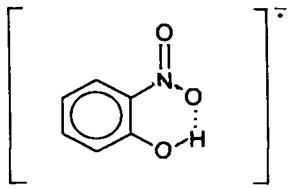
$$5m\text{-}HOC_6H_4NO_2 + 4e^- \longrightarrow m\text{-}HOC_6H_4NHOH + 4m\text{-}\bar{O}C_6H_4NO_2 + H_2O \qquad (17)$$

(35) (36)

under these conditions. A third wave in the polarogram of **35** arises from reduction of **36** to the radical dianion. *p*-Nitrophenol exhibits similar behaviour, but only one-seventh of the starting material is consumed, and the products and stoichiometry are shown in equation (18)[44].

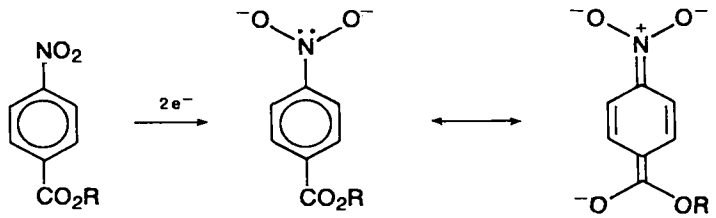
$$7p\text{-}HOC_6H_4NO_2 + 6e^- \longrightarrow p\text{-}HOC_6H_4NH_2 + 6p\text{-}\bar{O}C_6H_4NO_2 + 2H_2O \quad (18)$$

The *ortho* isomer displays yet a third type of behaviour, reduction to a fairly stable radical anion (**37**), whose stability compared to the *para* isomer was ascribed to hydrogen bonding (**37**)[44].



(**37**)

Another type of anomalous behaviour is exhibited in aprotic media by substituents in the *ortho* or *para* position which are capable of stabilization of a negative charge by resonance (CN, CO_2R, CHO, NO_2, etc.). In such cases, the second wave corresponds to a one-electron uptake rather than the usual three-electron process[17,45,46]. It appears that in such cases the dianion is especially stable, presumably because of contributions of quinoid structures to the resonance hybrid (see equation 19 for R = CO_2R). There may be some synthetic value for this



(19)

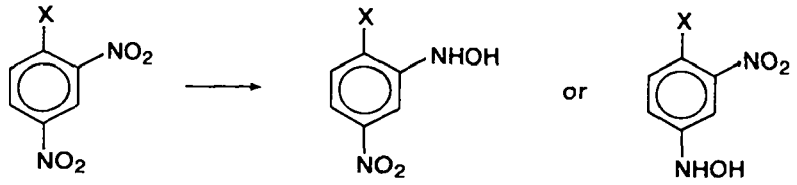
feature of such systems in facilitating the conversion $ArNO_2 \rightarrow ArOH$. Chambers and Adams have observed[45] that reduction of *o*- or *p*-dinitrobenzene at potentials corresponding to the second wave results in conversion to the corresponding nitrophenol. They have ascribed this to hydrolysis of the starting material by hydroxide, but other mechanisms are possible, such as reaction of the dianion itself with water or base, or reaction of the dianion with adventitious oxygen.

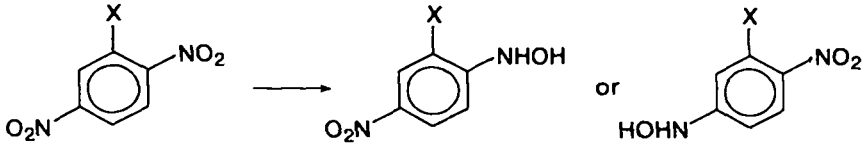
IV. AROMATIC DINITRO COMPOUNDS

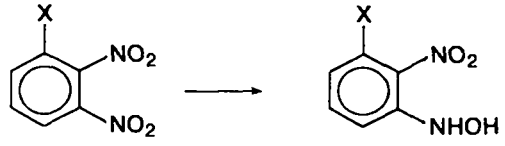
The polarographic behaviour of dinitro compounds is unexceptional in the light of the preceding discussions. Thus, the first wave of *m*-dinitrobenzene in DMF is positive (−0.86 V) compared to that of nitrobenzene (−1.115) due to the electronegative effect of one nitro group upon the reduction of the other, whereas the second group is harder to reduce (−1.192) than nitrobenzene because now the first nitro group (as the radical anion) bears a negative charge and is electropositive[29]. I have already alluded in the preceding section to the anomalous one-electron second polarographic wave of *o*- and *p*-dinitrobenzene[45].

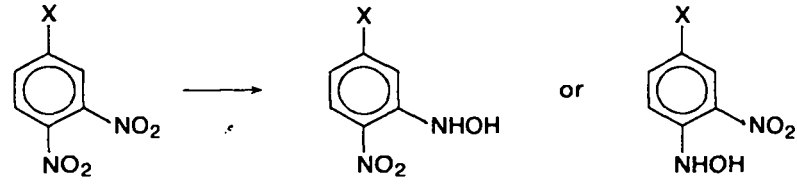
Tallec has carried out an extended survey of the cathodic behaviour of substituted dinitrobenzenes, employing mainly controlled-potential electrolysis[38,47–53]. His work contains the most extensive examination of the effects of variations in electrolysis conditions (potential, pH, temperature) ever carried out in this area, and confirms the major role such variations can play in determining which of the possible products is actually formed from a given nitro compound. A principal question in his work is

related to the question of which of the two nitro groups of a dinitro compound is reduced more easily. Tallec has found that reduction of dinitro-*X*-substituted benzenes usually results in selective reduction of one of the two nitro groups. His observations are summarized in equations (20)–(23). Which group is reduced first



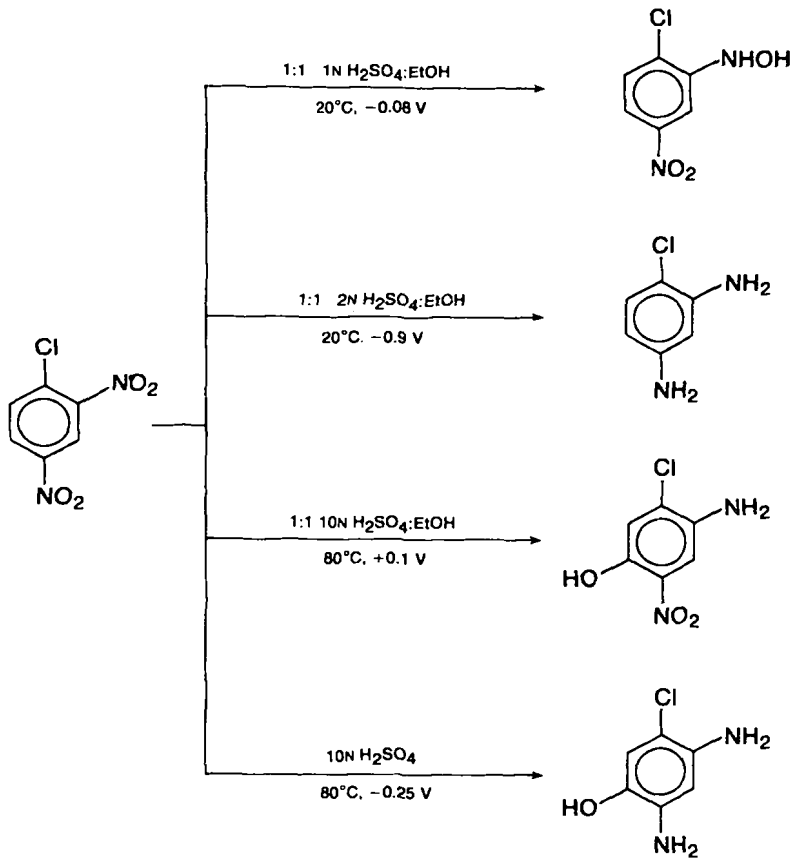






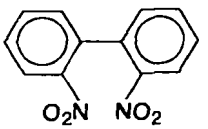
appears to be governed by a complex mix of electronic and steric factors, which are not completely predictable. This work probably represents the most extensive study to date of reduction of dinitro compounds by any method, electrochemical or otherwise, and demonstrates the value of controlled-potential electrolysis for such reductions. Of course, the reactions listed here represent only the initial reduction product under mild conditions; the products can be considerably different if electrolysis is conducted under more vigorous conditions, i.e., more acidic solution, more negative potential, and/or higher temperature. The reduction of 2,4-dinitrochlorobenzene is representative (Scheme 4)[49,53].

It is possible to effect intramolecular cyclization of a dinitro compound by electrolysis under conditions favouring azoxy compound formation. Thus, 2,2′-dinitrobiphenyl (**38**) can be converted to either benzocinnoline oxide (**39**) or the

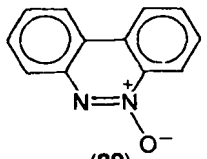


SCHEME 4

corresponding azo or hydrazo compounds, according to the experimental conditions chosen[54]. While **39** was produced in that study by a purely electrochemical process

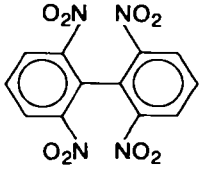


(38)

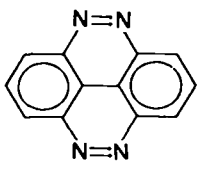


(39)

(probably coupling of two nitroso radical anions), cyclization may also be effected in alternate fashion by complete reduction to a *bis*-hydroxylamine followed by *in situ* electrochemical or air oxidation of the latter to the azoxy compound. When 2,2′,6,6′-tetranitrobiphenyl (**40**) was subjected to this reduction–oxidation sequence, a mixture of mono-, di-, tri- and tetra-*N*-oxides of the tetraazapyrene system (**41**) could be isolated in 7, 75, 8, and 0% yield, respectively, by air, and 11, 48, 32, and 1% yield by anodic, oxidation[55]. Final electrochemical reduction of the mixture of oxides afforded the pure monooxide (65%) or the *bis*-azo compound (**41**) (72%) itself, again depending upon experimental conditions. The higher proportion of



(40)

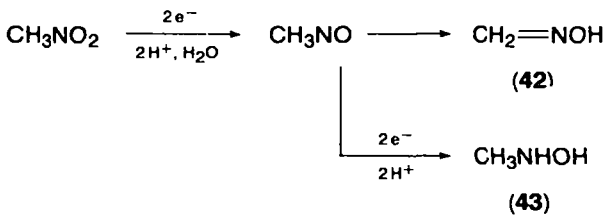


(41)

products in a higher oxidation state in the electrochemical oxidation (compared to air oxidation) is general and was observed also with **38**, 1,8-dinitronaphthalene, and 2,2'-dinitro-6,6'-diaminobiphenyl[55].

V. ALIPHATIC NITRO COMPOUNDS

Aliphatic nitro compounds undergo four-electron reduction to the hydroxylamine in protic media[2,3]. It is not possible to effect further reduction to the amine under more vigorous conditions, as one can with nitroarenes. The mechanism of hydroxylamine formation is undoubtedly the same as for nitroaromatics. Specifically, it is clear that nitroso compounds are intermediates. In the aliphatic case isomerization of these species to the corresponding oxime can compete, and indeed reduction of nitromethane affords formaldehyde oxime (**42**) as well as methylhydroxylamine (**43**) (equation 24)[56]. Hydroxylamine **43** arises by reduction of the nitroso compound, not



(42)

(43)

(24)

42, since it is known that **42** like other oximes, would suffer complete reduction to the amine. Reduction of ω-nitrostyrenes can in fact be carried out all the way to the β-phenethylamine in one step under vigorous electrolysis conditions (equation 25)[57–59].

$$ArCH{=}CHNO_2 \longrightarrow ArCH_2CH{=}NOH \longrightarrow ArCH_2CH_2NH_2 \qquad (25)$$

The radical anions from aliphatic nitro compounds are rather short-lived even in aprotic media, apparently because they eject nitrite ion (equation 26)[60–62]. The rate

$$RNO_2 \xrightarrow{e^-} RNO_2^{\cdot-} \xrightarrow{k_d} R^{\cdot} + NO_2^- \qquad (26)$$

constant, k_d, for this decomposition is quite insensitive to the structure of R[62]; it appears that the degree of steric hindrance in R has much more to do with determining k_d. Together these observations suggest that the transition state for fragmentation resembles the radical anion more than it does the fragments. Preparative electrolysis of nitro-*t*-butane (**44**) affords di-*t*-butyl nitroxide (**47**)[60,61], probably by the route shown in Scheme 5. Formation of **47** requires a rather close balance between the rates of cleavage of radical anion **45** and its combination with **46**, in order that **45** and **46** both be present simultaneously in significant concentration. Therefore it is not surprising that nitroxide formation is not general even with nitro compounds structurally quite similar to **44**[60,61].

$$t\text{-BuNO}_2 \xrightarrow{e^-} t\text{-BuNO}_2^{-\bullet}$$

(44) (45)

$$45 \longrightarrow t\text{-Bu}^{\bullet} + NO_2^-$$

(46)

$$45 + 16 \longrightarrow (t\text{-Bu})_2NO$$

(47)

SCHEME 5

VI. RELATED PROCESSES

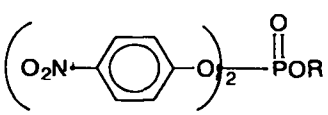
A. Fragmentation of Nitroarene Radical Anions

Nitroarene radical anions bearing leaving groups can decompose by ejection of the leaving group. The *p*-halonitrobenzenes (**48**) are representative: *p*-chloro-, bromo- and iodo-nitrobenzene are all reduced at the same potential as nitrobenzene, i.e., considerably easier than the corresponding halobenzenes lacking the nitro group[63]. Reduction involves injection of an electron into the π-system of the nitroarene to afford a short-lived radical anion (**49**), which then dissociates to halide ion and a *p*-nitrophenyl radical (**50**) (equation 27). Cyclic voltammetry both demonstrates the

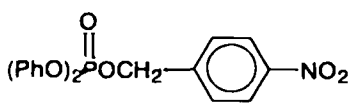
$$p\text{-}O_2NC_6H_4X \underset{}{\overset{e^-}{\rightleftharpoons}} p\text{-}O_2NC_6H_4X^{-\bullet} \overset{-X^-}{\rightleftharpoons} p\text{-}O_2NC_6H_4^{\bullet} \longrightarrow \text{products} \qquad (27)$$

(48) (49) (50)

existence of **49** and permits measurement of the rate of its dissociation to **50**. This type of behaviour, in which the π-electron system of a substituted arene accepts an electron and a σ-bond to the substituent is later broken, is quite common[63]. and has been well-characterized with nitrobenzyl halides[64–66]. Similar behaviour is exhibited by the *p*-nitro-phenyl and -benzyl phosphates **51** and **52**[67–70]. The



(51)



(52)

(**a**) R = H
(**b**) R = *p*-$NO_2C_6H_4$

nitrophenyl phosphates **51** accept an electron to form a species which then ejects the radical **50**. The latter then dimerizes to 4,4′-dinitrobiphenyl. Similarly, reduction of **52** leads to a *p*-nitrobenzyl radical, which then affords 4,4′-dinitrobibenzyl (major) and 4-nitrotoluene (minor).

B. Indirect Reduction

All of the electrochemistry mentioned thus far has had as its first step electron transfer from the electrode to the nitro compound (or a protonated form thereof). It

is also possible to effect indirect reduction of nitro compounds by electrochemically generating a species capable of reducing the nitro compound in a subsequent chemical step. For example, nitroarenes have been reduced by electrogenerated Cr(II) in 1.5M HCl, in coulometric studies primarily directed toward analytical determination of nitro compounds[71,72]. Christofis and coworkers have described the reduction of nitrobenzene by titanium(III) generated *in situ* by anodic oxidation of titanium metal[73]. This application is an example of the rare and novel process known as 'anodic reduction', in which anodic dissolution of a metal electrode generates an unstable low-valence metal ion capable of *reducing* a second component of the medium[74,75]. The various indirect methods do not appear to have any advantage over direct electrolytic reduction for synthetic purposes.

C. Reaction of Nitroarenes with Base

Until relatively recently organic chemists tended to assume that strong bases such as alkoxides or alkali metal amides generally react by one of two modes, i.e. proton abstraction or nucleophilic attack. It is now recognized that to these two must be added a third major class of behaviour, homogeneous solution electron transfer (SET) from the base to a reducible species in the solution. Since nitro compounds are relatively easily reduced, they are prime candidates for reaction by the SET route, and indeed there are numerous examples[76] of this process, dating in fact from the observation by Zinin in 1845 that nitrobenzene can be reduced by sodium ethoxide[77]. However, many times the reactions have been incorrectly interpreted in terms of mechanisms not involving electron transfer. For example, Sayigh[78], and Ogata and Mibae[79], have both written mechanisms for formation of reduction products by the reaction of bases with nitrobenzene which do not involve SET. The observations of these workers that, for example, electron-withdrawing groups favour reaction and electron-supplying groups retard the reaction, and that oxygen quenches the reactions, do however clearly point to electron transfer from the base to the nitro compound as the initial step. Recent workers now correctly recognize SET as important in such reactions[80].

It should be noted that acidity functions in strong base are commonly determined through measurement of the pK_as of a series of aromatic hydrocarbons. For a nitroarene, e.g. *p*-nitrotoluene (**53**), this would correspond to measurement of the equilibrium constant K_a for proton abstraction (equation 28). The equilibria are

$$p\text{-}CH_3C_6H_4NO_2 + :B^- \overset{K_a}{\rightleftharpoons} BH + p\text{-}CH_2C_6H_4NO_2 \qquad (28)$$

(**53**) (**54**)

usually measured spectrophotometrically, since anions such as **54** are usually intensely coloured. However, Fyfe and coworkers have recently pointed out the fact that electron transfer from the basic medium to **53** can seriously affect the measured pK_as, since the reduction products, e.g. the nitroarene radical anion, are usually intensely coloured themselves[81].

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **9**

Electrochemistry of amines

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I. INTRODUCTION

Interest in the electrochemical oxidation of amines dates back to the mid-1800s, when the oxidation of aniline was studied[1]. Fichter[2] has discussed much of the earlier work, and a number of reviews have been written recently on the subject of amine electrochemistry[3–12]. The present article focuses mainly on general problems, but also discusses some controversial aspects of the oxidation electrochemistry of amines; it is not intended as a literature review. Selected papers which illustrate the general nature of the chemistry are discussed. Amides, hydrazines, amino acids, enamines, phenylenediamines and aromatic *N*-heterocycles are not discussed. Many of the reviews mentioned above deal with these structures.

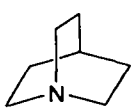
II. GENERAL CONSIDERATIONS

Normally, electrochemical oxidation of amines can be considered as involving the removal of an electron from the 'lone pair' on nitrogen. Since the nonbonded electrons interact with σ-bonds or π-systems this may be an oversimplification. The species formed will be referred to as a nitrogen cation radical or aminium radical even though the charge and unpaired electron may not be completely localized on nitrogen. The dominance of the aminium radical character in many reactions is partial justification for doing this.

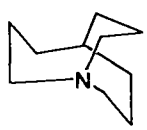
In aprotic organic media, protonation of the amine renders it unreactive electrochemically[5], while in aqueous systems proton transfers are so fast that a steady supply of free amine is assured. Clearly the availability of the lone-pair electrons on nitrogen is a requirement for oxidation at normal potentials.

It would seem reasonable that structural features which affect the availability of electrons on nitrogen would also influence their oxidation potentials. Indeed, many successful correlations between various free energy functions[13–18] or ionization potentials[19] and amine oxidation potentials have been published. A word of caution is in order concerning these correlations. Under many circumstances the electrochemical oxidation potentials of amines used are obtained under irreversible conditions. The measured potential is thus shifted from E^0 due to some kinetic feature of the reaction[20,21], usually either slow electron transfer, or a rapid chemical reaction following electron transfer. One of the probable reasons that the correlations work as well as they do is that the follow-up kinetic complications are similar for a series of similar compounds, and would be likely to have similar rates. The potentials would therefore be shifted uniformly from E^0.

The geometry about the nitrogen atom or the aminium radical can also influence the oxidation potential. Quinuclidine (**1**), which is pyramidal about nitrogen, is oxidized at E peak = 0.96 V versus SCE[15], while compound **2**, which is essentially planar about nitrogen, oxidizes at E peak = 0.38 V versus SCE[15]. The ease of oxidation of **2** reflects, at least in part, the facility of the compound to achieve the desired planarity about nitrogen for the aminium radical[22], while **1**‡ cannot be planar.



(1)



(2)

Amines have been shown to absorb on positively polarized electrodes[23–27]. This effect is more important in aqueous than nonaqueous solvents[28], and there seems to be little doubt about the existence of this phenomenon. Convincing evidence for adsorptive interactions between molecule and electrode influencing the stereochemistry of reactions has been discussed[29]. Adsorption arguments should be used with discretion when amines are involved, because upon oxidation, the nitrogen atom assumes the same charge as the electrode, and would most likely be rapidly desorbed. Following chemical reactions would have to be very rapid to be influenced by adsorption.

III. AMINIUM RADICALS

The aminium radical is the first intermediate in the electrochemical oxidation of

amines. An excellent review on the properties of nonaromatic aminium radicals has appeared recently[22].

Electron spin resonance data indicate that the aminium radical prefers to be planar[30] and is more rigid than the isoelectronic carbon free radical[22]. It undergoes substitution reactions at olefins and aromatic compounds[31]. Aromatic substitution proceeds with considerable electrophilic character, which has been suggested to arise from polar interactions in the transition state[31], while aminium radical additions to styrene show polar effects consistent with a ground-state electronic interaction between the cation radical and the π-electrons[39].

Secondary and primary aminium radicals can lose a proton from nitrogen forming an amine free radical[34,36,40,57,66]. Their pK_a values are typically about three units lower than the corresponding ammonium ion[34–36] due to the greater s-character in the N—H bond of the aminium radical[22]. An exception occurs with aromatic amines where the non-bonding nitrogen electrons are partly delocalized. This lowers the pK_a of anilinium ion to 4.6, while the pK_a of the corresponding aminium radical is 7.0[36]. The rates of deprotonation of aminium radicals in aqueous solution would be expected to be very fast, while the steady-state concentration would be pH-dependent.

The reactions of photochemically generated aminium radicals have been studied by Malatesta and Ingold[37] and Chow[38]. Second-order rate constants[37] for dimethylaminium radical decay are about 10^5–10^6 mol^{-1} s^{-1} in 1–5M H_2SO_4/CH_3CO_2H (or CF_3CO_2H), while the aminium radical derived from 2,2,6,6-tetramethyl-*N*-chloropiperidine in similar solvents gives second-order decay rates of about 10^2–10^4 mol^{-1} s^{-1}. The reaction rates appear to be independent of acid (except for solvent effects on the activity of ions) ruling out involvement of amino radicals. The favoured reaction mechanism for dimethylaminium radical is disproportionation to give the corresponding immonium and ammonium ions. 2,2,6,6-Tetramethylpiperidinium ion cannot follow the same route, and several other reaction paths have been compared, including hydrogen atom transfer to give ammonium and nitrenium ions. The products have not been determined.

Flash kinetic spectroscopy upon nitrosopiperidine[38] in aqueous acid indicates that the aminium radical intermediate decays with first-order kinetics with a rate constant of 1.85×10^4 s^{-1}, apparently involving reaction with liberated NO. In aqueous methanol at pH 2, the second-order decay rate of the aminium radical is 4.8×10^3 mol^{-1} s^{-1}, involving hydrogen atom abstraction from methanol. The addition of the aminium radical to cyclohexene is found to be 5000 times faster. It does not appear that the amine radical is an important intermediate in acid solution.

Cauquis and Genies[40] have observed, however, that amine radicals are produced when the solution contains an excess of added base. The electrochemical oxidation of 2,4,6-tri-*t*-butylaniline yields ESR spectra of both the aminium and amine radicals, apparently the latter being produced by deprotonation of the aminium radical.

Deprotonation of aminium radicals can also occur on the α-carbon[41,42]. Interaction between the carbon–hydrogen bond and the aminium radical orbital appears to be an important requirement for this reaction[22,41]. In photochemical studies involving charge-transfer complexes between aromatic ketones and amines, Cohen and Stein[43] have found that the intermediate aminium radical is deprotonated at the least hindered carbon. When benzoylbenzoic acid is photolysed in the presence of 2-butyldimethylamine, 83% formaldehyde and 6% 2-butanone form, indicating that methyl is more reactive than butyl. Methyl is also found to be more reactive than benzyl. Chlorine dioxide oxidations of amines, which involve

aminium radicals, also react at the least hindered carbon[44]. These observations parallel those under electrochemical conditions (see below).

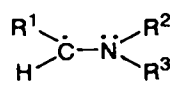
IV. MECHANISTIC CONSIDERATIONS

A. Deprotonation of Aminium Radicals

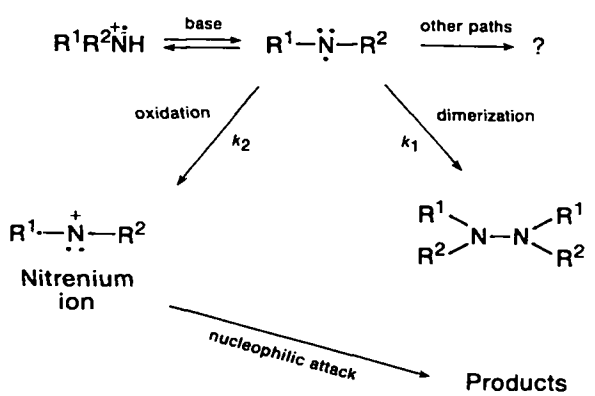
Loss of a proton from electrochemically generated aminium radicals to give the nitrogen radical has been suggested by several workers[33,40,45]. When the reaction is carried out in aprotic solvents such as acetonitrile, an added base, in addition to the parent amine, is usually required. The radical produced can decompose by numerous pathways, but two important reactions in electrochemical systems include oxidation and dimerization (see Scheme 1). The rate, k_2, of the oxidation path depends upon the electron-transfer rate, and has been proposed by Cauquis and coworkers[46–48] in cases where R^1 or R^2 is aromatic. Nucleophilic attack is found to occur on the aromatic ring, see below. Gassman[49] has suggested chemical tests for the intermediacy of nitrenium ions, which might be applied in electrochemical systems. The pathway which corresponds to k_1 (amine radical dimerization) has been proposed in several cases[33,40,45]. This route is base-dependent also, but would require significant steady-state radical concentration. The latter would be favoured at high current densities and base (amine) concentrations. These conditions might also favour other paths.

B. Deprotonation at Carbon

Loss of a proton from a carbon atom α to the aminium radical appears to be a major decomposition route for alkylamines. The intermediate produced is an α-amino radical (**3**), dubbed as a 'three-electron bond'[22,50]. The oxidation potential

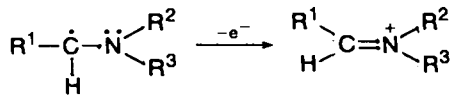


(**3**)

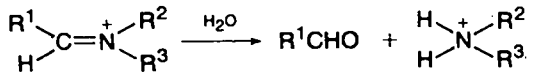


SCHEME 1

of this radical would normally be much less than the parent amine[51] and could therefore oxidize instantaneously at the electrode to afford the immonium ion (reaction 1), which would usually be followed by hydrolysis giving an aldehyde and ammonium ion (reaction 2).



(3) (1)



(2)

Disproportionation has also been suggest for the radical[52,53], but this pathway has been questioned on kinetic grounds[22], and has apparently lost favour[84]. Clearly disproportionation would depend upon radical concentration, while the electrochemical oxidation path is unbeatable if the radical is formed close to the electrode, assuming E^0 for the radical is considerably negative of the electrode potential.

C. Hydrogen Atom Abstraction by Aminium Radicals

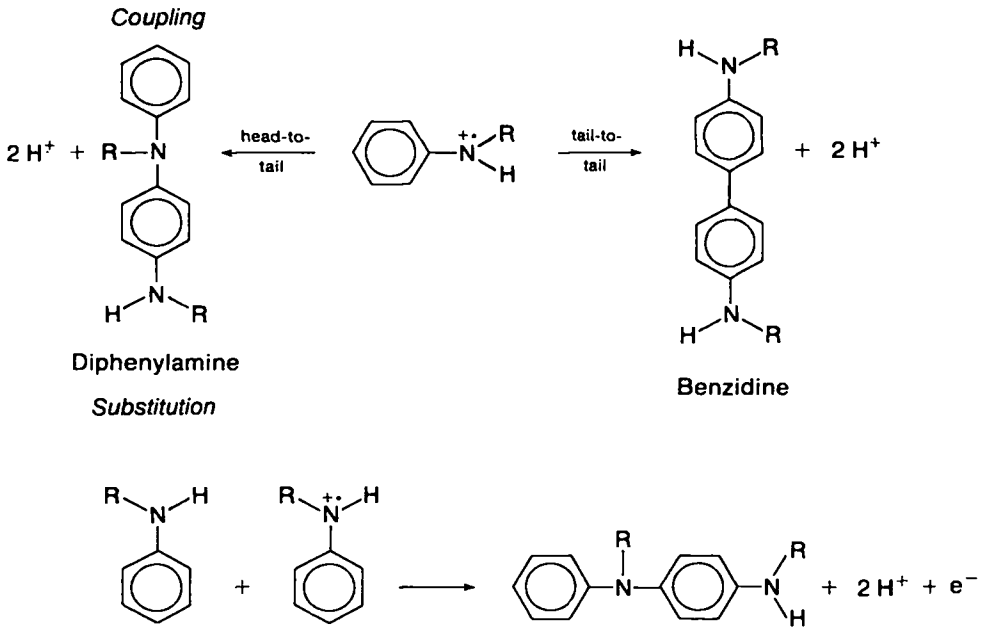
Aminium radicals can abstract hydrogen atoms from suitable donors, and this is an important process in the Hofmann–Lofler reaction[54]. The Hofmann–Lofler reaction involves production of an aminium radical which intramolecularly abstracts a hydrogen atom (usually from a δ-carbon) to give, initially, a δ-ammonium radical. Hydrogen atom abstraction was suggested in early electrochemical studies[55,56], but there is little evidence to suggest this as an important course in electrochemical oxidations. It is significant that the Hofmann–Lofler reaction is a chain process, which is not the case for electrochemical oxidations. Amine oxidations with a suitable hydrogen atom donor present could be used to evaluate this process. Hydrogen atom abstraction apparently does not occur in ether solvents[53].

D. Coupling Reactions

Aminium radicals generated chemically and photochemically undergo aromatic substitution with electrophilic character[3,31,39,44]. The rate and position of substitution is strongly dependent upon substituent[31] with *para* attack favoured, but normally also giving significant *ortho* and *meta* substitution. Methoxyl, hydroxyl, amino and alkyl substituents increase the reactivity compared with benzene, and chloro deactivates. Nitro, cyano and ammonium apparently inhibit the reaction[22,31]. It has also been noted that the rate of amination is inversely related to the bulkiness of the aminium radical[31].

Electrochemical reactions which could be interpreted in terms of homolytic substitution have usually been suggested to occur via the coupling of two aminium radicals[33], and in one case, by homolytic attack of an amine free radical on the aromatic substrate[58]. The first two possibilities are illustrated in Scheme 2.

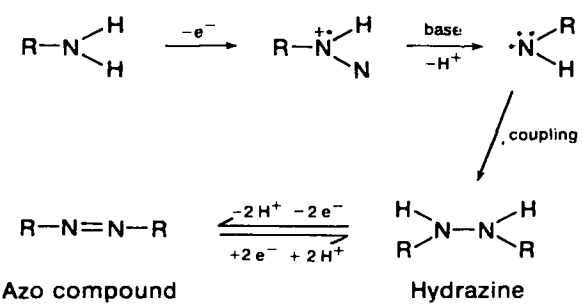
While the tail-to-tail coupling is clearly not a homolytic substition, several observations are consistent with homolytic substitution in the head-to-tail route. Bulky groups on nitrogen cause the product distribution to change from



SCHEME 2

p-aminodiphenylamine to benzidine[58]. This is to be expected for substitution, and may also be true for radical ion coupling. Head-to-tail coupling is also favoured at higher pH[58] in the region of the pK_a of the amine, which is also consistent with homolytic amination (the protonated amine is deactivating, see above). A clear distinction between homolytic attack versus radical cation coupling is complicated by the competing tail-to-tail coupling. If one assumes that the rate-determining step in both cases is the combination reaction, radical coupling involves two electrons in the rate-determining step, while substitution requires one electron. This might be a way to distinguish between these two possibilities.

Head-to-head coupling of nitrogen free radicals has been suggested to account for the formation of azo compounds[33,45,47,59]. In nonaqueous solvents, a base must be added in order for azo compounds to form. Reactions in which azo compounds have been detected either involved high concentration of substrate and high current densities or the presence of added base. These data are consistent with the formation of high concentrations of radicals (reaction 3).



(3)

When R = 2,4,6-tri-*t*-butylaniline, the ESR spectrum of the amine radical can be observed[40].

V. ELECTROCHEMICAL OXIDATION OF AROMATIC AMINES

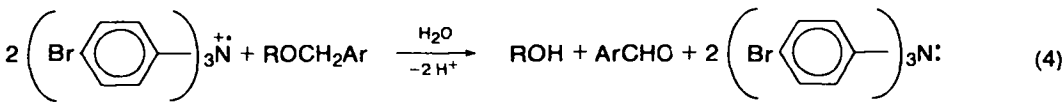
A. General

To explain the various reaction modes of aromatic amines, three categories of reactions can arise due to the type of amine involved. The reactions may depend upon (1) the hydrogen attached to α-carbon, (2) the hydrogen attached to nitrogen and (3) the nuclear substitution pattern on the aromatic ring.

B. Triarylamines

The simplest case involves the oxidation of triarylamines which are substituted in the *para* position. *Para* substituents can stabilize the cation radicals and inhibit dimerization at the *para* position.

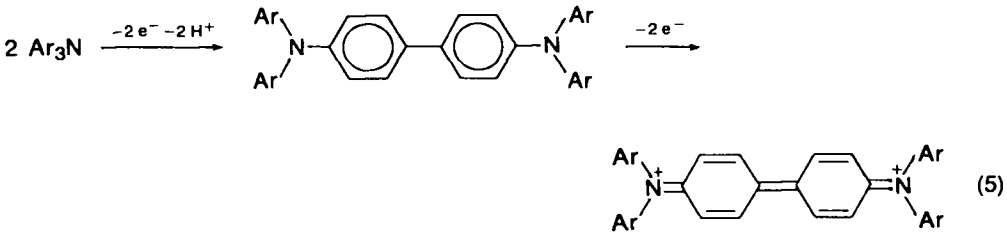
Schmidt and Steckham[60] have discovered an interesting application for the aminium radical of tris(*p*-bromophenyl)amine, which is readily prepared by electrochemical oxidation. They find this to be an effective reagent for removal of benzyl ether protecting groups by homogeneous electron transfer, which in the process regenerates the parent amine. A catalytic amount of amine is all that is necessary (reaction 4). The reaction is very clean compared with other deprotection



(4)

methods, and the selectivity for different benzyl ethers can be varied by changing the *para* substituent on the amine.

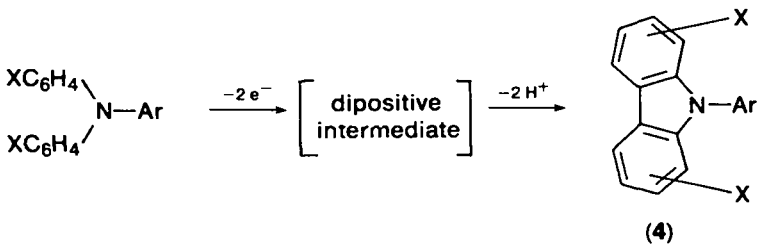
In the absence of just one *para* substituent, triarylaminium radicals can couple to produce benzidines, and finally benzidine salts (reaction 5).



(5)

The rates of the coupling reactions have been measured using several electrochemical methods[61–63]. Electron-withdrawing substituents (Cl, CN, NO_2) substituted in one or two rings increase the coupling rate, while methoxy stabilizes the cation radical. Mechanistic possibilities such as disproportionation of the cation radicals to give a reactive dication have been considered, but rejected on the basis of kinetic data[62].

When the oxidation potential of the electrode is increased, a two-electron (or two successive one-electron) transfer can occur. Carbazoles (**4**) have been identified under these conditions[64] (reaction 6).



(4) (6)

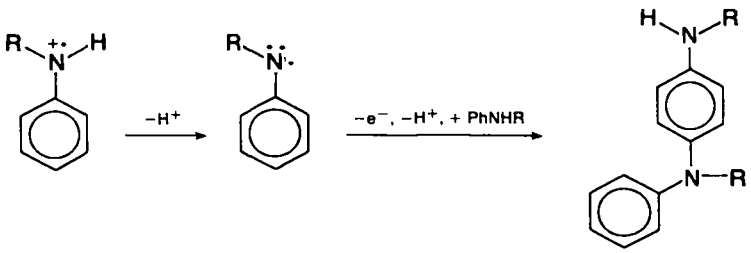
C. *N*-Alkylanilines

Electrochemical oxidation of several *N*-alkylanilines has been reported to form benzidines and diphenylamines[58], or substitution products when certain nucleophiles are added. The latter topic will be taken up in Section VII.

1. Benzidines versus diphenylamines

Nelson and Hand have studied the electrochemical oxidation of several *N*-alkylanilines in acetonitrile, 3M H_2SO_4 and buffered solutions[58]. The major products were similar in these solvents, affording *N*-alkylbenzidines and *N*-alkyl-*p*-aminodiphenylamines, the latter being converted to *p*-benzoquinone, *in situ*.

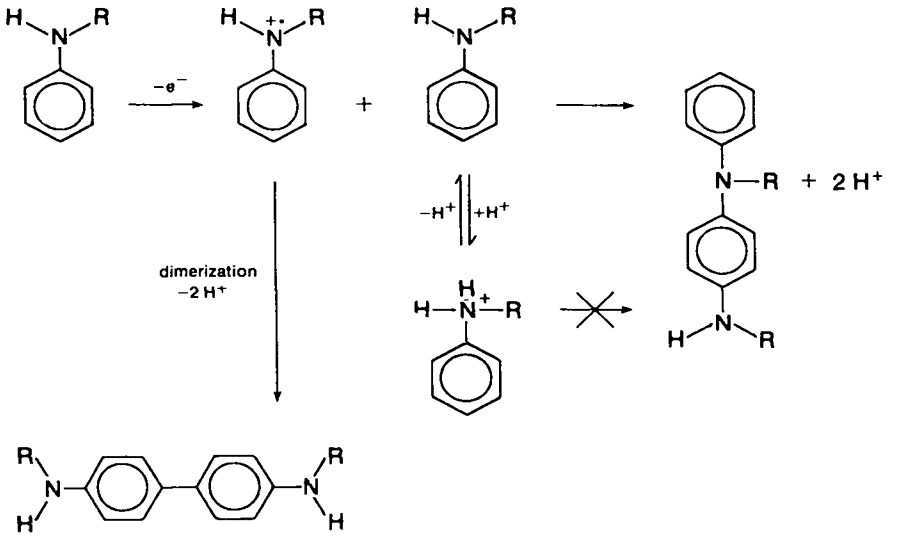
Using cyclic voltammetry and preparative electrolysis with product analysis in some cases, the following observations were made concerning the product distribution: (a) formation of benzidine is favoured by electrolysis at low concentration of the parent amine, large alkyl groups on nitrogen, low pH, and high current density, (b) formation of diphenylamines is favoured at high pH, high concentration of parent amine, low current density and small alkyl groups on nitrogen. It was concluded that large alkyl groups on nitrogen sterically hinder production of *p*-aminodiphenylamines. Benzidines were thought to form by coupling of two cation radicals, while diphenylamines were produced via loss of a proton from the parent cation radical forming an amino radical which then attacked the parent amine (reaction 7). The partitioning between the two pathways was



(7)

thought to depend upon the variation of radical/parent ratio near the electrode – when high, homolytic attack by an amine radical gives diphenylamine, when low, benzidine results.

It is surprising however, that in the acidic solutions studied, the amine radical has kinetic significance, since the protonated form (aminium radical) should overwhelmingly predominate (pK_a of $PhNH_2^{\cdot}$ is 7.0[36]). It has also been observed that in acetonitrile, an added base is necessary to produce the amine radical[40]. Yet, in sulphuric acid or acetonitrile, a significant amount of diphenylamine is produced.



SCHEME 3

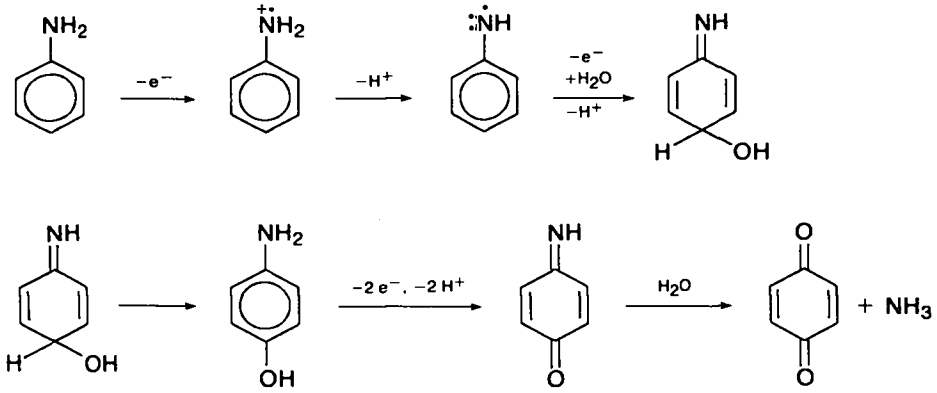
The formation of diphenylamine may instead result from homolytic attack of aminium radical upon the parent amine (Scheme 3). This would be consistent with the steric hindrance effect observed, and would not require the amine free radical under these low pH conditions. The pH effect can also be rationalized on the basis of the reactivity of the alkylaniline toward aminium radical substitution. At low pH, more of the alkylaniline would be protonated (pK_a of anilinium = 4.6), inhibiting the amination; see below. At high pH more free aniline is present which activates the amination. Thus at low pH the aminium radicals dimerize tail-to-tail giving benzidine, before encountering unprotonated aniline. The eventual products are *p*-benzoquinone and benzidine salts after further reaction.

D. Aniline Oxidations

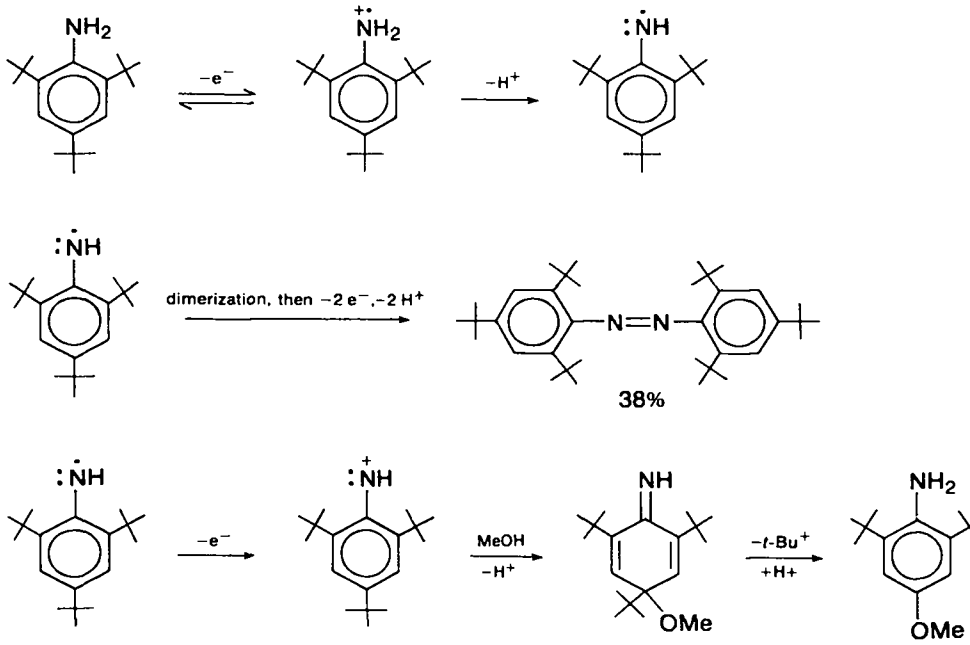
Early work on the oxidation of unsubstituted anilines is confusing. This is partly due to the random experimental conditions chosen, and the lack of modern instruments for carrying out the reactions and identifying the products. The unifying thread in these early studies is the isolation of insoluble, highly coloured products, called 'aniline black', 'emaraldine' or 'nigraniline'. Nelson[5] has treated this topic in some detail, and no further discussion will be given here. More recent work has led to the suggestion that these presumed oligomeric products may consist mainly of benzidine salts and quinhydrone[58].

In contrast to the coupling reactions which predominate at low pH, oxidation of aniline at pH 7.4 affords *p*-aminophenol and *p*-benzoquinone, plus some unidentified, possibly coupled products[65]. Radical intermediates have been suggested. A reaction pathway consistent with these products is shown in Scheme 4.

Cauquis and coworkers[32,40,46–48] have systematically examined the electrochemical oxidation of 2,4,6-tri-*t*-butylaniline in acetonitrile and methanol. In methanol containing sodium carbonate two major products were obtained, as shown in Scheme 5. Examination of this reaction in anhydrous acetonitrile produced mainly



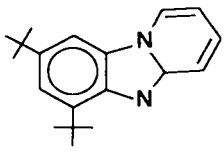
SCHEME 4



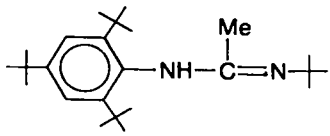
SCHEME 5

resinous products[32]; however, addition of pyridine produced two major products, **5** and **6**[48].

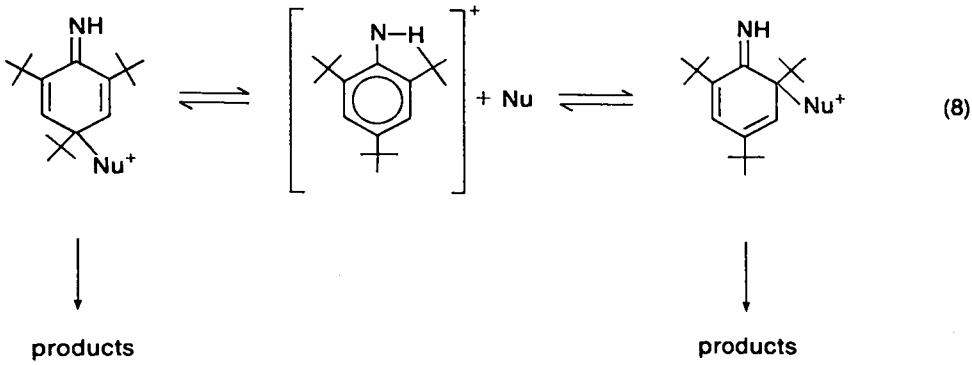
A stepwise two-electron oxidation was proposed, involving an intermediate amine radical, which was observed by ESR[40,48]. Since the position of attack on the aromatic ring was dependent upon the nucleophile, e.g. *ortho* with pyridine and *para* with water or methanol[47], it was suggested that product stability controlled the position of substitution, requiring reversibility of the addition of the nucleophile (reaction 8).



(5) 60%



(6) 25%

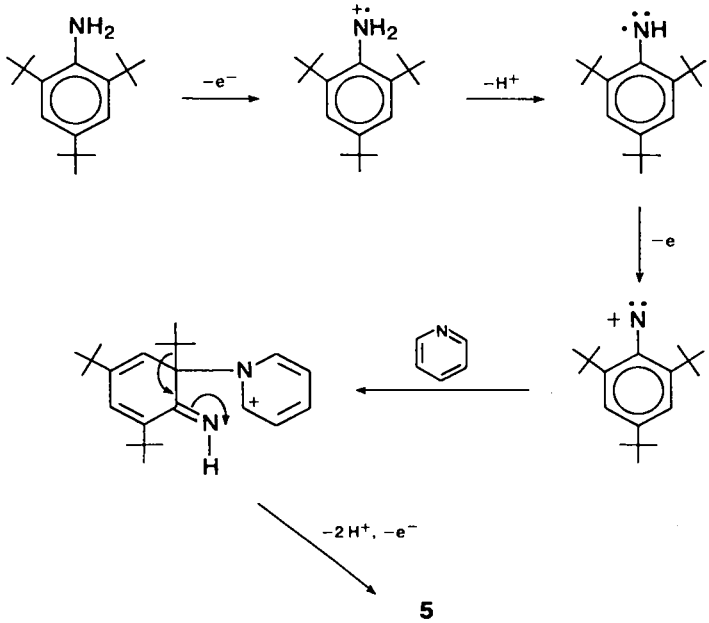


(8)

products products

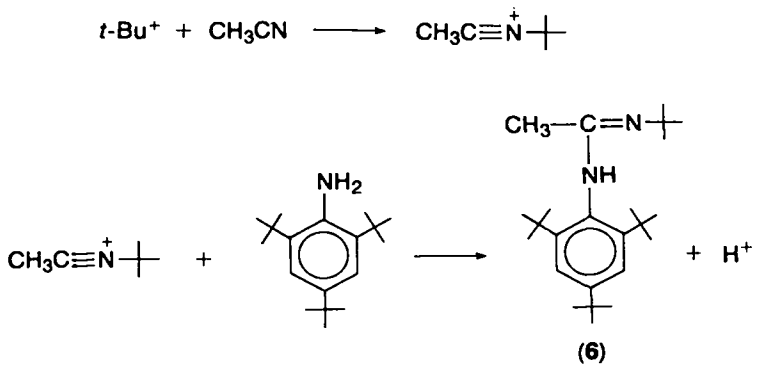
Nu = H_2O, MeOH, pyridine

The mechanism proposed[48] for the formation of **5** is shown in Scheme 6. Compound **6** would be formed by a Ritter reaction[67] (Scheme 7).



5

SCHEME 6



SCHEME 7

VI. ELECTROCHEMICAL OXIDATION OF ALIPHATIC AMINES

A. General

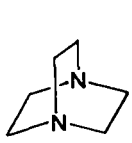
In rigorously dry aprotic solvents, the oxidation of aliphatic amines yields polymers[32,33,46,53]. The presence of water[53,68] leads to deprotonation at the α-carbon, followed by oxidation and hydrolysis and ultimately cleavage of the alkyl side-chain. It has also been suggested that the α-amino carbon radicals disproportionate to the enamine, but this pathway has been questioned[22,80] and has apparently lost favour[84]. Generally, primary, secondary and tertiary amines react similarly, although differences exist which will be pointed out.

The dealkylation reaction of tertiary amines containing different alkyl groups has been actively investigated in attempts to rationalize why primary alkyl group loss is generally favoured over secondary and benzyl[69–75]. In this connection, the factors which control the site of attack by nucleophiles upon the different alkyl side-chains of amines during electrochemical oxidation have been examined by several workers, some suggesting that adsorption controls the reactivity[70–75]. This topic will be examined in more detail in Section VII.

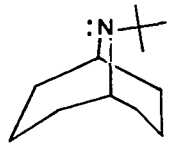
B. Tertiary Amines

With two exceptions, saturated aliphatic amines are electrochemically oxidized irreversibly. This usually means that the aminium radical undergoes rapid chemical reaction. Dabco, **7**, is one interesting exception[9,22,76,77]. The marked stability of dabco cation radical arises via stabilizing interactions between the two nitrogens through the bridging σ-bonds[78].

The second exception was reported by Nelsen and Kessel[41]. Compound $\mathbf{8}^{\ddagger}$ is the first case of a stable aliphatic monoamine cation radical. The stability of the aminium radical in methylene chloride or acetone sheds considerable light on the nature of the reactivity of aliphatic aminium radicals generated electrochemically. When the *t*-butyl group is replaced by *i*-propyl, the lifetime of the cation radical is decreased by over six orders of magnitude. The stability of $\mathbf{8}^{\ddagger}$ can be attributed in part to the lack of a C_α—H bond which can overlap with the spin-bearing orbital on the planar aminium radical. This factor could be partly responsible for the reactivities of different alkyl groups in dealkylations; see below.



(7)



(8)

Mann and coworkers have made extensive investigations on the oxidation of aliphatic amines. Triethylamine, upon oxidation, is reported to abstract a hydrogen atom from DMSO[55]. This early suggestion does not appear to be an important pathway, especially in view of the fact that the reaction apparently does not occur in either glyme or THF[53], which are superior hydrogen-atom-donating solvents. In subsequent work[53], the oxidation of tri-*n*-propylamine was studied in several solvent systems. In acetonitrile containing a small amount of water, the main reaction leads to dealkylation forming propionaldehyde and di-*n*-propylamine. The reaction produces hydrogen ions which protonate the remaining amines terminating the reaction after less than one Faraday of charge is passed. Because of this fact, the coulometric *n* values are a function of the extent of proton-producing reactions. Approximately 68–77% of tri-*n*-propylammonium ion, 20–26% di-*n*-propylammonium ion and 15–27% of propionaldehyde are produced, consuming around 0.97 Faradays of charge per mole of starting amine. The general mechanism suggested is shown in Scheme 8. As indicated, the aminium radical is the first intermediate which decomposes by loss of a proton giving the α-amino radical, **10**. This can either disproportionate giving the enamine (**12**, and parent, or undergo electrochemical oxidation to produce the immonium ion, **11**. The oxidation of *N*,*N*-dimethylbenzylamine (**13**) which cannot form an enamine, affords 51% of **13**—H^+, a 22% mixture of secondary amines and 16% benzaldehyde and formaldehyde. Trimethylamine which cannot give an enamine either, was reported

$$Pr_3N \xrightarrow{-e} Pr_3N^{\ddagger}$$
(9)

$$\mathbf{9} \longrightarrow Pr_2N\dot{C}HCH_2CH_3 + H^+$$
(10)

$$\mathbf{10} \xrightarrow{-e^-} Pr_2\overset{+}{N}{=}CHCH_2CH_3$$
(11)

and/or

$$2\ \mathbf{10} \longrightarrow Pr_3N + Pr_2NCH{=}CHCH_3$$
(12)

$$\mathbf{11} + H_2O \longrightarrow Pr_2NH + CH_3CH_2CHO + H^+$$

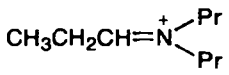
and/or

$$\mathbf{12} + H_2O \longrightarrow Pr_2NH + CH_3CH_2CHO$$

SCHEME 8

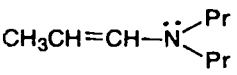
not to fragment, which was taken as support for the enamine mechanism. It was shown later however, that trimethylamine does indeed react[84,85].

In an effort to distinguish between disproportionation of the amino radical **10**, followed by hydrolysis to the aldehyde, versus immonium ion hydrolysis reaction, Portis, Bhat and Mann[52] examined the oxidation in dry acetonitrile with a small amount of D_2O added. They reasoned that the immonium ion would hydrolyse to propionaldehyde containing only protons (reaction 9), while enamine hydrolysis would afford deuterated aldehyde (reaction 10). The monodeuterated aldehyde was



$$CH_3CH_2CH{=}\overset{+}{N}(Pr)(Pr) \xrightarrow{D_2O} CH_3CH_2CHO + Pr_2ND + D^+ \qquad (9)$$

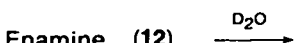
(11)



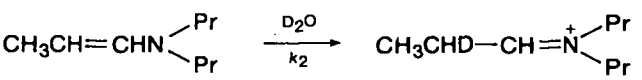
$$CH_3CH{=}CH{-}\ddot{N}(Pr)(Pr) \xrightarrow{D_2O} CH_3CHDCHO + Pr_2ND \qquad (10)$$

(12)

produced according to their NMR, mass spectral, and IR analysis. Since the enamine (**12**) and immonium ion (**11**) would normally be in equilibrium producing mixed deuteration products by either mechanism, it was concluded that hydrolysis of enamine (reaction 11) is faster than protonation (reaction 12) ($k_1 > k_2$). Unfortunately, this conclusion cannot be correct since the hydrolysis of enamines occurs through the immonium ion[79].



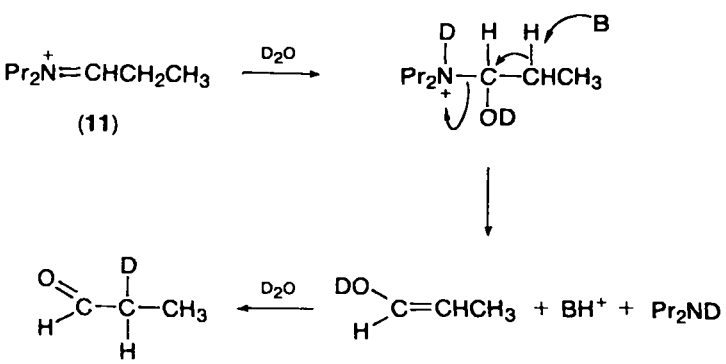
$$\text{Enamine (12)} \xrightarrow[k_1]{D_2O} \text{Aldehyde} \qquad (11)$$



$$CH_3CH{=}CHN(Pr)(Pr) \xrightarrow[k_2]{D_2O} CH_3CHD{-}CH{=}\overset{+}{N}(Pr)(Pr) \qquad (12)$$

(12) (11)

Ross[80] has suggested that monodeuteration occurs through a base-catalysed hydrolysis of immonium ion (either concerted or stepwise) giving an enol. The stepwise path seems more likely. Tautomerism of the enol in D_2O would account for the monodeuteration of the aldehyde (reaction 13).



$$Pr_2\overset{+}{N}{=}CHCH_2CH_3 \xrightarrow{D_2O} Pr_2\overset{+}{N}(D)-C(H)(OD)-CH(B)CH_3 \qquad (13)$$

(11)

$$\downarrow$$

$$\begin{matrix} O \\ \| \\ H-C-C(D)(H)-CH_3 \end{matrix} \xleftarrow{D_2O} DO-C(H)=CHCH_3 + BH^+ + Pr_2ND$$

Andrieux and Saveant[51] have succeeded in measuring the oxidation potential of an α-amino radical, and their work indicates that it is very unlikely that the radical

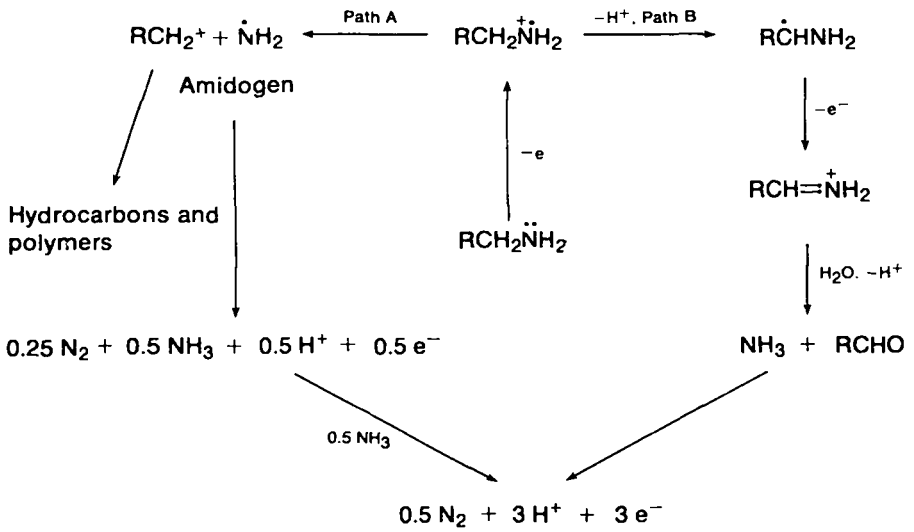
would have a lifetime long enough to disproportionate and form an enamine; rather oxidation to give an immonium ion would be preferred. Furthermore, Cohen and Chao[86] have shown that the aminium radicals produced by photooxidation do not disproportionate.

In the light of these observations, the immonium ion, **11** (Scheme 8), is the more likely source of aldehyde.

C. Primary Amines

Barnes and Mann[81] have studied the electrochemical oxidation of a series of primary amines in acetonitrile, including *n*-butyl-, *i*-butyl-, benzyl-, cyclohexyl-, methyl-, *t*-butyl-, ammonia and others. All were oxidized irreversibly, and at potentials more positive than the corresponding secondary or tertiary amines. They were observed to exhibit broad, rather drawn-out cyclic voltammetric waves, which was attributed to a slow chemical reaction interposed between two electron transfers (ECE mechanism). Other schemes could also account for these observations. Controlled potential coulometry produced current–time plots with a maximum about an hour after the beginning of a typical electrolysis, rather than the 'normal' exponential current–time decay. This behaviour would also be indicative of an intermediate, but with a much longer lifetime than the one proposed in the cyclic voltammetry experiments. Furthermore, when the electrolysis potential was increased from 1.2 V to 1.9 V, the current–time decay became exponential. *t*-Butylamine was an exception, giving normal electrolysis behaviour at either potential. On the basis of these and other data, Barnes and Mann proposed two parallel reaction pathways, one which was potential-dependent. These are illustrated in Scheme 9.

Note that the two parallel paths, A and B, partition from the aminium radical. Path B was thought to be a high-potential path owing to the assumed high oxidation potential of the α-amino radical. The slow build-up of current at low potential was ascribed to a slow reaction of the aminium radical to give the



SCHEME 9

carbonium ion and amidogen radical (path A), the latter oxidizing rapidly to form nitrogen and causing the current peak.

Path B was not competitive at low potential. At high potential, however, path B was thought to be followed, and all chemical and electrochemical steps were assumed to be fast, thus exhibiting normal current–time behaviour. Furthermore, continuous purging of ammonia from the system during electrolysis at low potential eliminated the peak of the current–time curve. The fact that *t*-butylamine behaved normally was ascribed to the facile formation of the tertiary carbonium ion, there therefore being no delay in amidogen production.

These proposals, for the most part, cannot be correct. The aminium radical lifetime is so short, as shown by cyclic voltammetry, that it cannot be responsible for a slow production of current via pathway A. Nor does it seem reasonable that the oxidation of the amino radical in path B should be potential-dependent. This follows from the fact that secondary and tertiary amines, which oxidize at much less positive potentials, follow path B and not A[53]. In addition, the work of Andrieux and Saveant[51] discussed earlier indicates that the radicals would be readily oxidized. It does appear, however, that the slow production of ammonia is partly responsible for the anomolous coulometric behaviour. It would be difficult to draw any sound conclusions on the mechanism with the data that are available.

While *t*-butylamine follows a carbonium path in acetonitrile, as observed by Barnes and Mann[81], controlled-current electrolysis in water with very high concentration of amine gives azo-*t*-butane (**14**) in 41% yield based upon charge[82] (reaction 14). Unlike the nonaqueous system, the dissociation equilibrium giving

$$2\ t\text{-BuNH}_2 \xrightarrow[-4\,H^+]{-4\,e^-} t\text{-BuN=NBu-}t \qquad (14)$$

(14)

the amine free radical should be more favourable. The radicals could then couple and oxidize to produce the final product, similar to the mechanism proposed by Cauquis, Cros and Genies[47] (reaction 15). The absence of hydrazine was used to

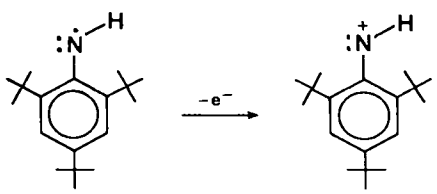
$$2\ t\text{-BuNH} \longrightarrow \xrightarrow[-2\,H^+]{-2\,e^-} t\text{-BuN=NBu-}t \qquad (15)$$

(14)

argue against the radical pathway, but if hydrazine had formed, it would have readily oxidized. The authors considered a nitrene path more likely. The likelihood of the nitrene would appear to depend upon the oxidation potential of the amine free radical which seems likely to lie on the reaction pathway (reaction 16). The

$$t\text{-BuNH}_2 \xrightarrow{-e^-} t\text{-BuNH}_2^{+\cdot} \xrightarrow{-H} t\text{-BuNH} \longrightarrow t\text{-BuN:} + H^+ \qquad (16)$$

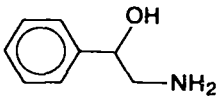
resonance-stabilized tri-*t*-butylaniline radical is oxidized, but the cation suffers nucleophilic attack, rather than lose a proton[46] to afford a nitrene (reaction 17).



(17)

In a study of the electrochemical oxidation of a series of phenethylamines, several products have been identified which do not seem to fit the patterns of

primary amine oxidation illustrated thus far[83]. For example, α-(aminomethyl)benzyl alcohol (**15**) produced methylamine, ammonia, nitrogen, benzaldehyde, protonated



(15)

starting amine, carbon dioxide and carbon monoxide. The possible route to methylamine under these oxidizing conditions is an interesting question, since it seems more likely to be found in a higher oxidation state. Several other interesting compounds have been studied, some giving surprising products, but unfortunately the yields have not been reported in many cases.

VII. REACTIONS WITH NUCLEOPHILES

Upon oxidation in the presence of certain nucleophiles, tertiary amines undergo substitution reactions, both at aromatic positions (when aromatic amines are involved), and in alkyl side-chains. Substitution on the alkyl side-chain occurs on the carbon α to the amine. Amines with different hydrocarbons attached to nitrogen are usually substituted at all possible positions, but nonstatistically. There is some variation from system to system, but generally in electrochemical systems, primary carbon attack is favoured over secondary and benzyl.

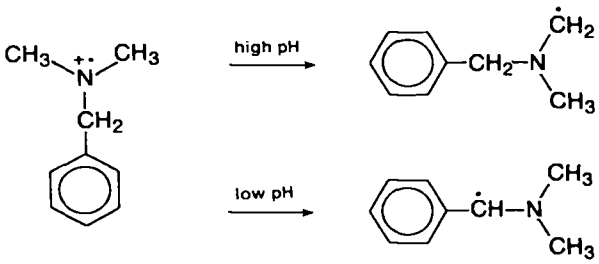
Weinberg and coworkers[72,73,75] have examined this general reaction in some detail. They found that oxidation of *N,N*-dimethylbenzylamine in methanol containing potassium hydroxide afforded *N*-methoxymethyl-*N*-methylbenzylamine and α-methoxy-*N,N*-dimethylbenzylamine in a ratio of 1:4 respectively. A statistically random process involving loss of hydrogens on α-carbon would give a ratio of 1:3. It was argued that hydrogens on methyl were more reactive than those on benzyl because the aromatic ring and the nitrogen atom were adsorbed onto the electrode surface, and the loss of a benzyl proton followed by oxidation giving a positive ion at a positive electrode would be disfavoured electrostatically. Therefore it was concluded that unabsorbed methyl was more reactive toward proton loss and further oxidation. This argument assumes that either proton loss from aminium radical is reversible under the electrolysis conditions, or proton loss and oxidation are concerted. If neither is the case, the formation of the intermediate radical would be product-determining, and the radical would not be subject to the electrostatic inhibition arguments cited above.

A similar adsorption argument[72] was put forth to account for the fact that oxidation of *N,N*-dimethylaniline gave *N,N*-bis (methoxymethyl)aniline, but not *N*-dimethoxymethyl-*N*-methylaniline.

The proposed adsorption mechanism was questioned[69] but reaffirmed by Weinberg with more detailed studies[75]. Several experiments were carried out which demonstrated that *N,N*-dimethylaniline was adsorbed. It is not clear, however, that the product-determining intermediate was adsorbed. A surface active agent added to the solution could change the stereochemistry and evaluate the adsorption process.

It is very interesting that photochemical[43] and chemical[44] production of aminium radicals of the type mentioned above, give similar product distributions, when adsorption cannot be operative. Chlorine dioxide oxidation[44] of *N,N*-dimethylbenzylamine involving the aminium radical intermediate was found to give products that depended upon pH. At pH 7.9–9.0 mostly alkyl reaction took place,

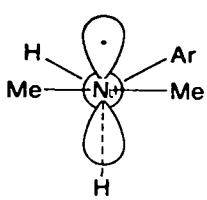
while at pH 6.4–6.6, benzyl reaction was favoured. Steric hindrance was thought to attenuate the reactivity of the benzyl position. Apparently at low pH the base which removes the proton from the aminium radical is more discriminate, choosing the more reactive, but more hindered benzyl hydrogen (reaction 18).



(18)

Chiba and Takata[74] have examined the cyanation of 15 different tertiary aliphatic amines in aqueous methanol containing sodium cyanide. The reaction sequence presumably involves (1) electrochemical oxidation to give the aminium radical, (2) loss of an α-proton and oxidation to form the immonium ion and (3) attack by cyanide on the immonium ion to give the monocyanide adduct. In all cases the mono-α-cyanoamine product was obtained, as this product is more difficult to oxidize than the parent. The tertiary amines examined included most permutations of methyl, ethyl, *n*-propyl, *i*-propyl, pyrrolidine and piperidine (e.g. all the *N*-alkyl-piperidines and -pyrrolidines were compared). The order of reactivity of the alkyl groups toward cyanation was determined by measuring the extent of attack on the different R groups of the tertiary amines, when oxidized separately. The order of reactivity was observed to be pyrrolidine > piperidine > methyl > ethyl >*n*-propyl > *i*-propyl (= 0). Here is an apparent exception to other observations that primary carbon is more reactive than secondary, but in this case the secondary positions are in piperidine or pyrrolidine rings. It was concluded that the reactivity was related to steric hindrance indirectly. Adsorption was suggested to be responsible for the reactivity, but that steric hindrance influenced the strength of adsorption. Large bulky groups were thought to be less strongly adsorbed, and therefore less reactive.

In the light of the recent work of Nelsen and Kessel[41] it would appear that the reactivity of hydrogen on carbon α to aminium radicals is very dependent upon the geometry of the system. Hydrogen is most reactive when the C—H bond can interact with the orbital on the aminium radical, as discussed earlier. It is suggested that this factor may be responsible for the substitution patterns observed during amine oxidations, rather than adsorption. Consider the Newman projection **16** for



(16)

the dimethylbenzylamine cation radical. When the benzyl C—H bond is coplanar with the aminium radical orbital, the methyl and phenyl groups are nearly eclipsed,

resulting in an unfavourable steric interaction. This would raise the energy necessary to remove the hydrogen from the benzyl position, by statistically favouring reaction from a less suitable conformation.

Additional support for this proposal is gained by examination of a molecular model of the *N*-methylpiperidine cation radical. Assuming a chair conformation with planar nitrogen, the axial hydrogens in the ring are coplanar with aminium radical orbital, and would therefore be expected to be very reactive. This is borne out by the preferred reaction in the ring, rather than of the methyl attached to nitrogen.

VIII. ACKNOWLEDGEMENTS

The generous financial support of the Robert A. Welch Foundation is gratefully acknowledged. Helpful discussions with Albert Fry, Edward Biehl and Perry Reeves are also acknowledged.

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CHAPTER **10**

Radical anion reactions of nitro compounds

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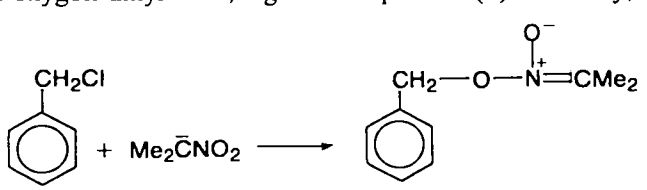
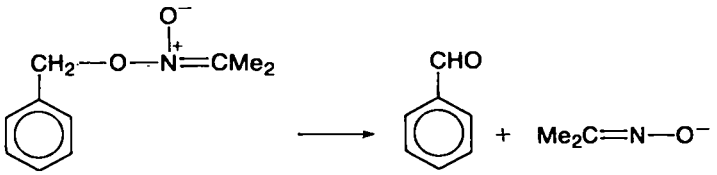
I. INTRODUCTION

Treatment of the salt of an aliphatic nitro compound with an alkyl halide generally results in oxygen alkylation, e.g. as in equation (1). Actually, the oxygen alkylate is



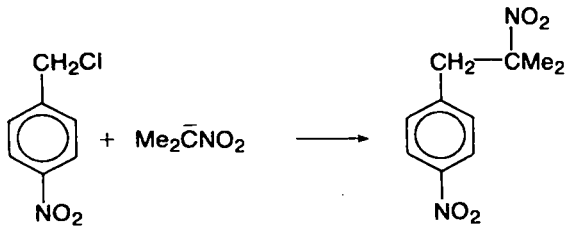
(1)

not isolated for it breaks down under the reaction conditions in the manner described by equation (2)[1]. Indeed, an excellent method for converting allylic and benzylic halides to the corresponding aldehydes is based on this sequence of reactions[2].



(2)

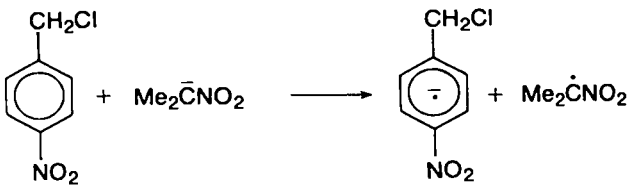
The behaviour of *p*-nitrobenzyl chloride on treatment with a nitroparaffin salt is in sharp contrast to the foregoing generalization: here carbon alkylation is predominant (equation 3).



(3)

92%

A detailed study of the alkylation of nitroparaffin salts led to the realization in 1961 that oxygen alkylation is the consequence of a simple S_N2 displacement by the nitroparaffin anion on the alkyl halide[3], and in 1964 it was shown that carbon alkylation derives from an electron-transfer process in which radical anions and free radicals are intermediates[4]. Additional evidence for the view that carbon alkylation is an electron-transfer process was presented in 1966, but by this time it had become clear that carbon alkylation of nitroparaffin salts is a chain-reaction. Hence, the original nonchain mechanism was amended[5]; the resulting chain sequence is given by equations (4)–(7). The widespread acceptance of this mechanism is based on a large and impressive body of evidence which will not be described here inasmuch as it was summarized in 1975[1]. It should be emphasized that in this chapter the electron-transfer chain mechanism is not ascribed to any reaction unless there is a clear experimental basis for such an assignment.



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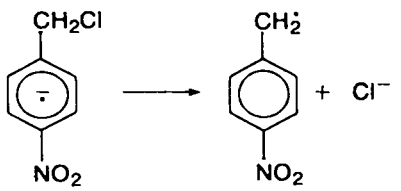

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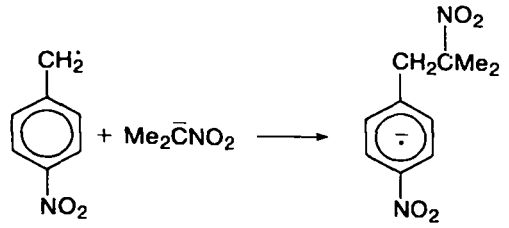
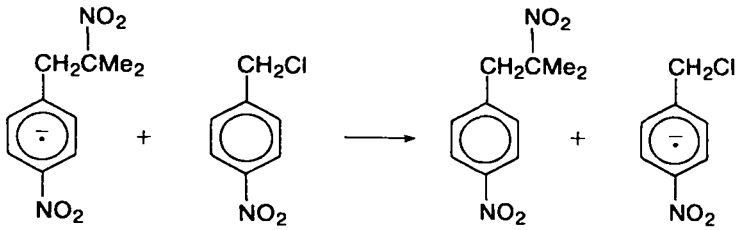


(6)



(7)

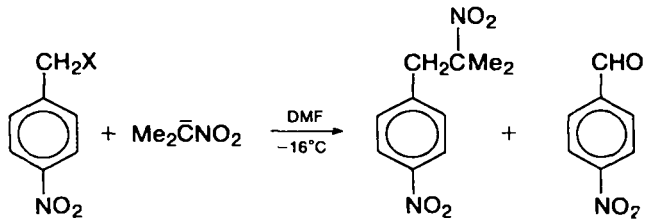
This novel type of substitution at a standard carbon atom would constitute an interesting but somewhat parochial phenomenon if it were restricted to the alkylation of nitroparaffin salts. But, in actuality, electron-transfer chain substitution turns out to be much more general than originally envisaged; new examples are constantly being discovered and it is likely that the surface has only been scratched. A most attractive feature of these reactions is that they proceed under very mild conditions and produce excellent yields of pure products. Also, in contrast to S_N2 displacements these radical anion substitution reactions are rather insensitive to steric hindrance. As a consequence, they are especially valuable for the synthesis of highly branched compounds[6].

II. THE *p*-NITROBENZYL SYSTEM

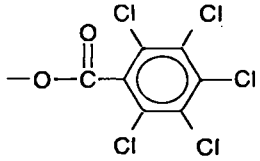
One wonders then with what types of compounds will radical anion substitution be observed, and under what circumstances? It is apparent from the mechanism of equations (4)–(7) that the ability to accept one electron favours the radical anion chain process. Since nitro groups are especially prone to one-electron reduction, it is not surprising that in most of the known examples of radical anion substitution a nitro group is present in the compound undergoing substitution, or in the attacking nucleophile. In the following sections the role of the nitro group as a facilitator of radical anion substitution will be demonstrated repeatedly. But parenthetically it must be emphasized that while the nitro group is very effective in facilitating electron-transfer chain substitution it is not unique. The cyano group, for example, is also able to foster electron-transfer chain substitution[7].

A second factor of great importance is the leaving group; that this is so is apparent from the data of equation (8)[3]. We see that with *p*-nitrobenzyl iodide oxygen alkylation is far and away the major process, i.e. the S_N2 displacement is so fast that the electron-transfer chain process does not compete effectively. As we move up the table the S_N2 displacement becomes less and less facile until with *p*-nitrobenzyl chloride electron transfer preponderates. With the top two entries, the pentachlorobenzoate ester and the quaternary ammonium salt, the difficulty of achieving an S_N2 displacement at $-16°C$ is so great that only electron-transfer substitution is observed.

It is noteworthy that in the unsubstituted benzyl system there is no leaving-group

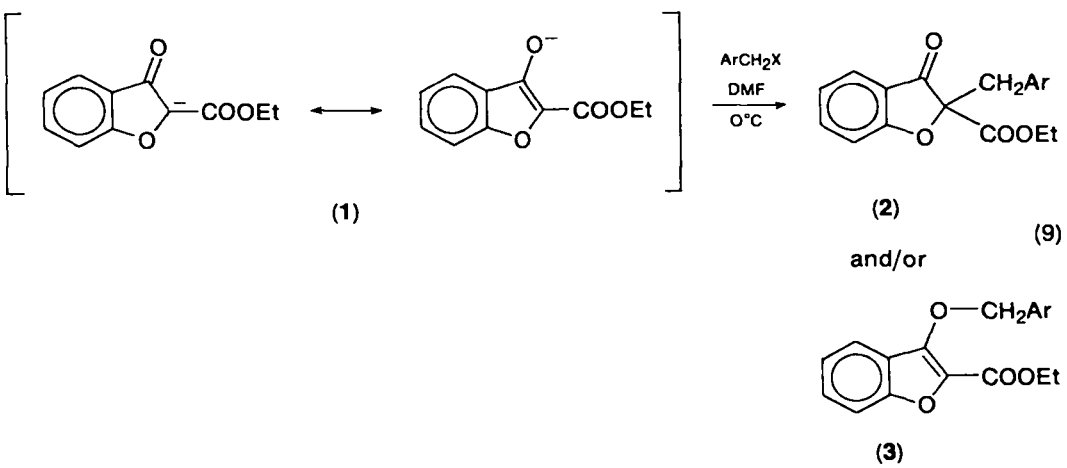


(8)

X	Yield (%)	Yield (%)
	93	0
	93	0
Cl	92	6
OTos	40	32
Br	20	65
I	7	81

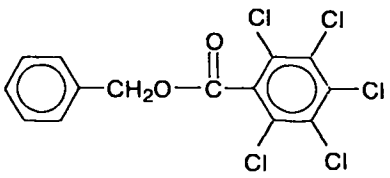
effect. With benzyl iodide, bromide, chloride and tosylate the yields of benzaldehyde are in the range 82–84% and little, if any, carbon alkylate is formed. Manifestly, in the absence of a *p*-nitro group the requisite one-electron transfer is so unimportant that even in the case of benzyl chloride the radical anion process cannot compete with the S_N2 displacement[4].

Precisely the same leaving-group effect is observed when the β-keto ester anion (**1**) is employed as the nucleophile[5a]. Benzyl iodide and *p*-nitrobenzyl iodide give identical yields of products (73% *C* and 18% *O*). Treatment with benzyl bromide and *p*-nitrobenzyl bromide results in the same yields of the isomeric alkylates (65% *C* and 27% *O*); but, whereas benzyl chloride gives 40% *C* and 51% *O*, *p*-nitrobenzyl chloride gives 90% *C* and 2% *O*[8]. Here, just as in the alkylation of nitroparaffin salts, the conjunction of a *p*-nitro group and a difficulty displaced

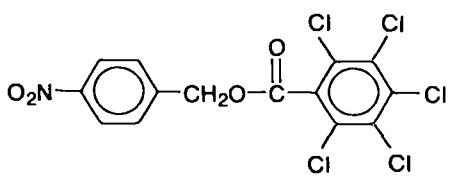


(9)

leaving group (chloride) produces a dramatic increase in the amount of carbon alkylation. This is so because the alkylation of **1** is an S_N2 process until one comes to *p*-nitrobenzyl chloride whereupon the reaction path involving radical anions becomes dominant[5a]. In conformity with this view the difference in behaviour of the benzyl and *p*-nitrobenzyl systems is especially striking when a leaving group even more difficult to displace than chloride, the pentachlorobenzoate, is involved. Whereas benzyl pentachlorobenzoate (**4**) is recovered quantitatively after exposure to the β-keto ester anion (**1**) for 960 h, with *p*-nitrobenzyl pentachlorobenzoate (**5**) a 72% yield of the *C*-alkylate is obtained after 112 h along with a 13% recovery of the ester; little, if any, *O*-alkylate is formed.



(4)

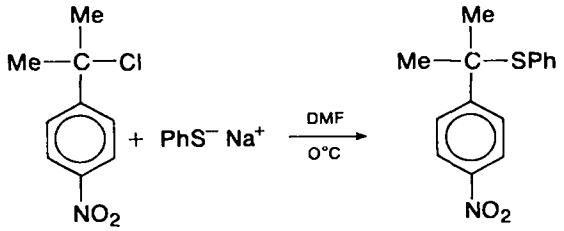


(5)

III. THE *p*-NITROCUMYL SYSTEM

With primary and secondary halides the radical anion pathway is in competition with the S_N2 displacement and it takes a difficultly displaced leaving group to provide an opportunity for the electron-transfer mechanism to predominate. The use of tertiary halides provides another device for removing competition by the S_N2 process.

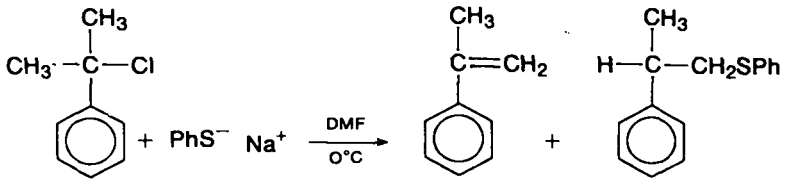
p-Nitrocumyl chloride (**6**) was the first tertiary halide studied[9]. At 0°C its reaction with sodium thiophenoxide is complete in 2 h and a 95% yield of the pure tertiary sulphide (**7**) is obtained. In contrast, cumyl chloride (**8**) reacts but slowly with



(6) (7) 95% (10)

sodium thiophenoxide. Ten days are required for complete reaction and a different path is followed. None of the tertiary sulfide $PhCMe_2SPh$ can be detected and, instead, the olefin **9** and the primary sulphide derived from it are produced (equation 11).

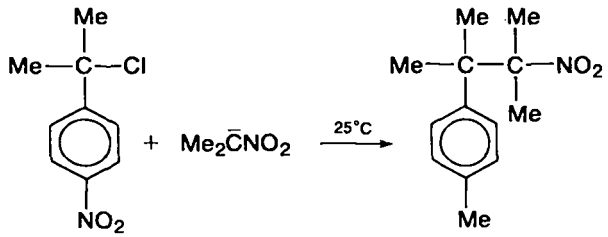
In the same way, the reaction of *p*-nitrocumyl chloride (**6**) with the lithium salt of 2-nitropropane at 25°C in DMF or DMSO produces the highly branched carbon alkylate **11** in 60–65% yield (equation 12)[9]; in HMPA the yield of **11** rises to 90%[10]. It is noteworthy that covalency formation occurs at the more hindered of the two available positions of this ambident anion despite the steric hindrance at the tertiary carbon atom of **6**.



(11)

(8) (9) (10)

6% 56%

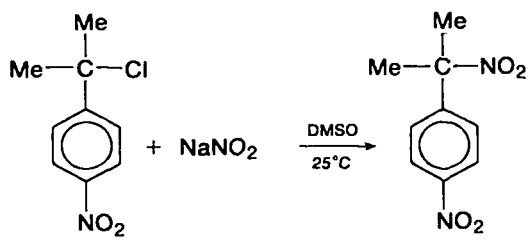


(12)

(6) (11)

60–90%

The reaction of *p*-nitrocumyl chloride (**6**) with sodium nitrite in DMSO at 25°C gives 92–95% yields of the dinitro compound **12**, a result again illustrative of the insensitivity of radical anion reactions to steric hindrance[9].



(13)

(6) (12)

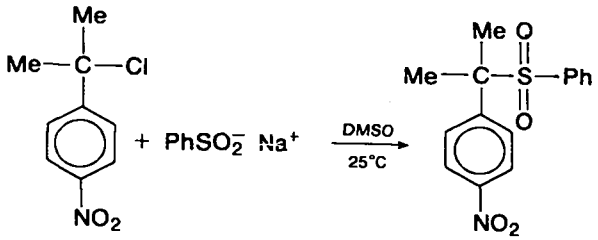
92–95%

Treatment of *p*-nitrocumyl chloride (**6**) with sodium benzenesulphinate in DMSO at room temperature results in a rapid reaction and the sulphone (**13**) is isolated in 95% yield (equation 14)[11]. If steric hindrance were important the sulphinate ester, rather than the sulphone, would have been produced.

Malonic ester anions also react with *p*-nitrocumyl chloride via the radical anion pathway[9]; a typical example is given by equation (15).

The foregoing by no means exhausts the list of anions which replace the chlorine of *p*-nitrocumyl chloride (**6**) in the manner shown by the general equation (16). Furthermore, it must be emphasized that substitution reactions corresponding to those of equation (16) are not observed when cumyl chloride (**14**) is employed. Clearly, the nitro group greatly facilitates radical anion substitution.

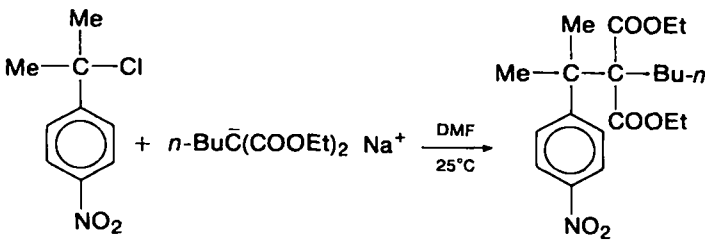
Electron-transfer substitution at the tertiary carbon atom of **6** also occurs with amines. For example, when **6** is treated with quinuclidine the pure quaternary



(14)

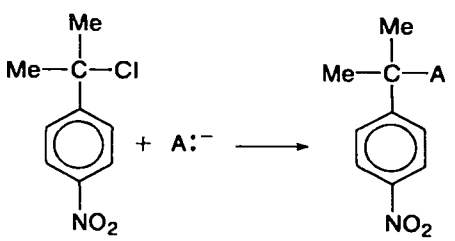
(13)

95%

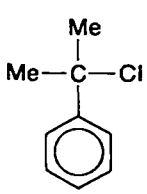


(15)

81%



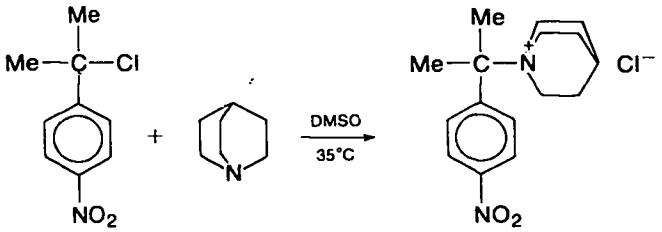
(16)



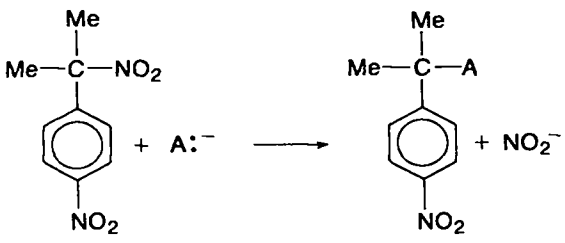
(14)

ammonium chloride (**15**) is isolated in 90% yield[12]. Here again, substitution at the tertiary carbon atom is not observed with cumyl chloride (**14**).

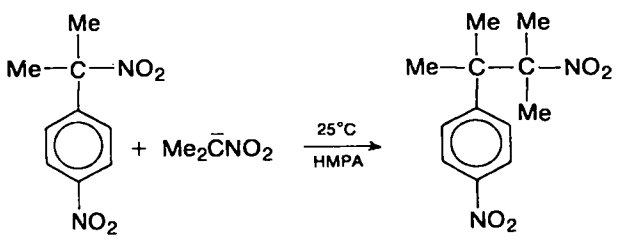
It is a striking attribute of radical anion processes that many groups which are not subject to S_N2 displacement behave as leaving groups in radical anion reactions. Thus, the displacement of a nitro group from a saturated carbon atom was unknown prior to 1967 when the electron-transfer substitution reactions summarized by equation (18) were reported[13]. Despite the fact that these reactions result in substitution at a tertiary carbon atom they proceed smoothly at room temperature. Furthermore, the yields of pure products are essentially the same as with *p*-nitrocumyl chloride (**6**). Equations (19)[10], (20)[14] and (21)[13] are illustrative.



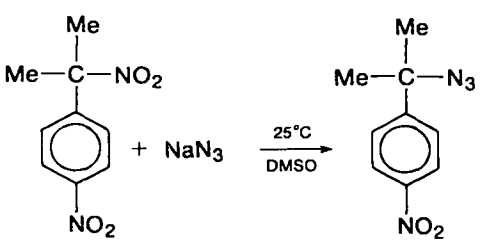
(6) (15) 90% (17)



(12) (18)



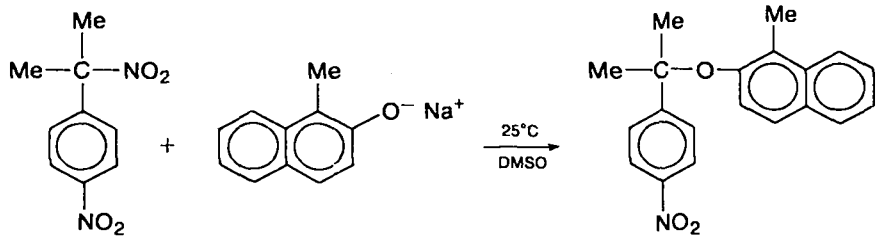
(12) (11) 90% (19)



(12) (16) 94% (20)

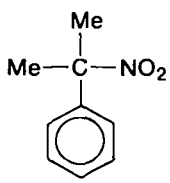
With phenolic salts elimination competes with substitution, as it does also in the case of *p*-nitrocumyl chloride (**6**); But, as can be seen from equation (22), substitution remains the major process[13,15].

(12) (17) 95% (21)



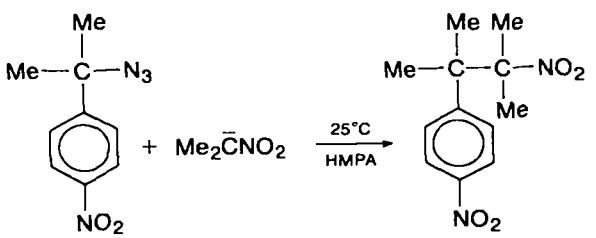
(12) (18) 72% (22)

In no instance does α-nitrocumene (**19**) undergo any significant amount of reaction when exposed to the various anions under conditions which result in complete reaction with α-*p*-dinitrocumene (**12**). Manifestly, the *p*-nitro group of α, *p*-dinitrocumene (**12**) is an important facilitator of these electron-transfer substitution processes.

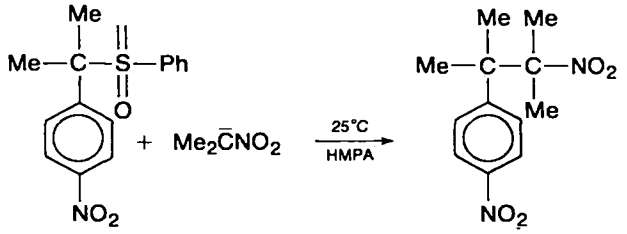


(19)

Some of the examples of this extraordinary type of substitution are shown in equation (23)–(25). The facility with which they occur is noteworthy; at room temperature the reaction of equation (23) requires 5 h, that of equation (24) takes

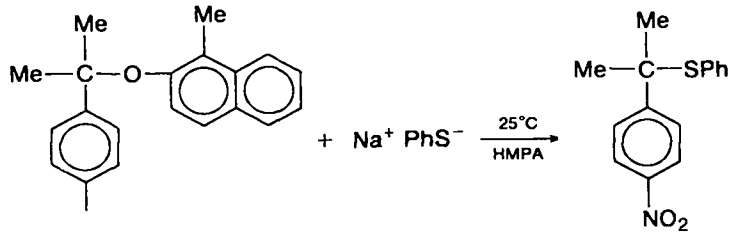


(16) 90% (23)



93%

(24)

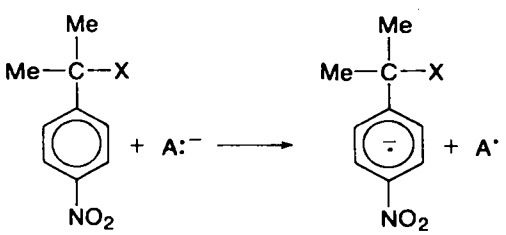


91%

(25)

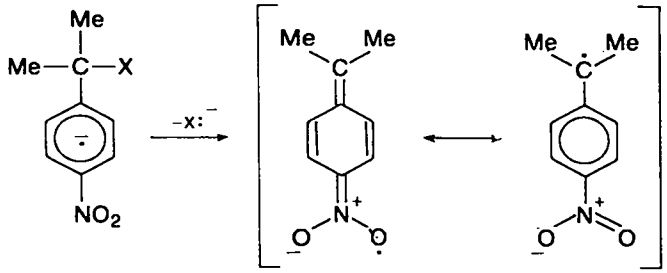
8 h, and that of equation (25) is complete in 30 min[11,16]. Furthermore with cumyl azide, or cumyl phenyl sulphone, or cumyl 1-methyl-2-naphthyl ether there is no reaction. Clearly, the *p*-nitro group plays an important role in the displacement processes of equations (23)–(25).

From the foregoing it is apparent that in contrast to S_N2 displacements, radical anion substitution reactions are rather insensitive to steric hindrance. The facility with which substitution at the tertiary carbon of the *p*-nitrocumyl system occurs, and the fact that with ambident anions steric effects do not influence the reaction course, leave little room for debate on this matter. (It goes without saying that even for a radical anion process a point will eventually be reached where steric effects become overriding.)[17] This indifference to steric hindrance is a consequence of minimal sensitivity to steric effects at each step of the chain sequence. The first step (equation 26) occurs at the unhindered nitroaromatic face of the *p*-nitrocumyl system. The second (equation 27) is an internal elimination and, as such, is not subject to steric hindrance; indeed, if anything, it should be subject to steric acceleration. The third step (equation 28) invokes addition to the planar system of a free radical; the sp^2 carbon atom of this radical is readily accessible to the attacking nucleophile. The last step of this chain sequence (equation 29) is a one-electron transfer from a nitroaromatic radical anion to a nitroaromatic

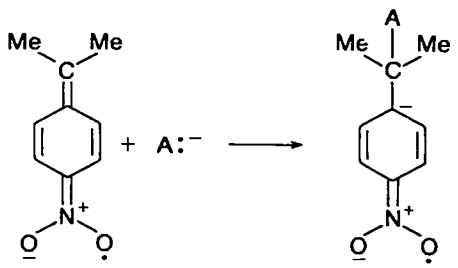


(26)

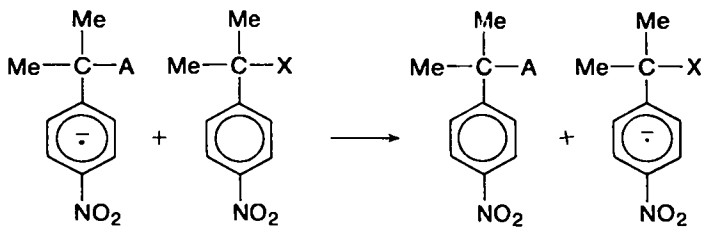
X = Cl, NO_2, N_3, $PhSO_2$, OAr



(27)



(28)

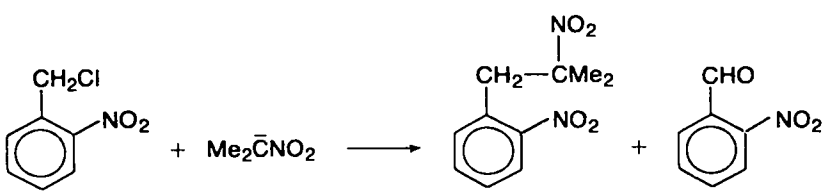


(29)

compound; such transfers are known to be very rapid[18] and steric effects again would be minimal. The upshot is that substitution at a highly hindered carbon atom is brought about by a series of steps in which steric effects are minimal at each step.

IV. THE *o*-NITROBENZYL SYSTEM

All the examples of radical anion substitution described thus far involve compounds in which a nitro group is *para* to the side-chain at which substitution occurs. An *o*-nitro group is also able to facilitate radical anion substitution but, apparently, it is less effective than a *p*-nitro group. Thus, as shown in equation (30), *o*-nitrobenzyl



(30)

(20) (21) (22)

31–46% 52%

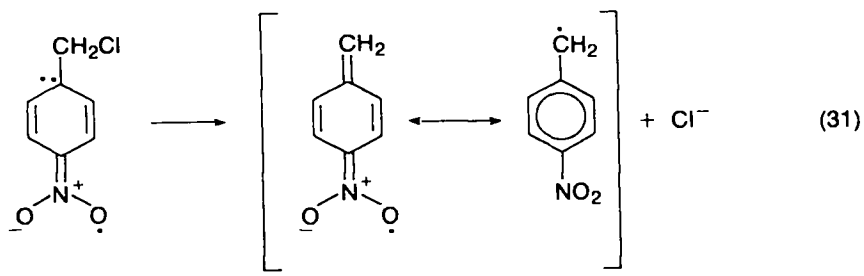
chloride gives much less carbon alkylate than *p*-nitrobenzyl chloride (equation 3)[4,19]. Also with *o*-nitrobenzyl bromide the yield of carbon alkylate (**21**) is ca. 1% whereas *p*-nitrobenzyl bromide gives a 20% yield (equation 8)[4]. Presumably carbon alkylation would be the major or exclusive result if, for example, *o*-nitrobenzyl azide or *o*-nitrobenzyl pentachlorobenzoate, were employed (cf. equation 8).

The diminished effectiveness of an *o*-nitro group in facilitating electron-transfer substitution is apparently due to steric hindrance to coplanarity in the *ortho* isomer. This, by tending to isolate the nitro group electronically from the ring, makes one-electron reduction more difficult and, so, slows down the chain sequence of equations (4)–(7). As a consequence the S_N2 displacement becomes the principal process.

The *o*-nitrocumyl system has not yet been studied. With *o*-nitrocumyl compounds competition from the S_N2 displacement would cease to be a problem; but, on the other hand, steric inhibition to resonance would be greater than in the *o*-nitrobenzyl system. It seems likely that *o*-nitrocumyl compounds will prove to be less reactive than the corresponding *p*-nitrocumyl compounds and that they will react via the radical anion pathway.

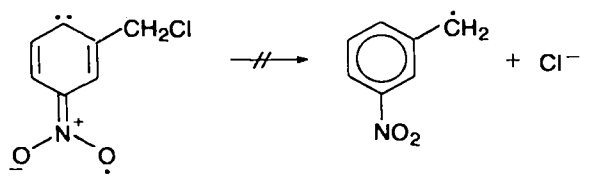
V. THE *m*-NITROBENZYL SYSTEM

There are no examples of radical anion reactions involving *m*-nitrobenzyl compounds. Treatment of *m*-nitrobenzyl chloride with the salt of 2-nitropropane results exclusively in oxygen alkylation[19], and the reaction of *m*-nitrobenzyl chloride with the β-keto ester anion (**1**) is a purely S_N2 process[5a]. This may well reflect the inability of *m*-nitrobenzyl chloride radical anion to lose chloride ion (equation 32) by an internal elimination analogous to that available to *p*-nitrobenzyl chloride radical anion[4] (equation 31). With this facile elimination pathway not available electron-transfer substitution is not able to compete with the S_N2 displacement. However, recent experience with the *p*-cyanobenzyl system[7] suggests that the use of *m*-nitrobenzyl compounds possessing leaving groups which are very difficult to displace in an S_N2 process (*m*-nitrobenzyl pentachlorobenzoate, for example) may enable the *m*-nitrobenzyl system to exhibit radical anion reactions.



(31)

(23) (24)

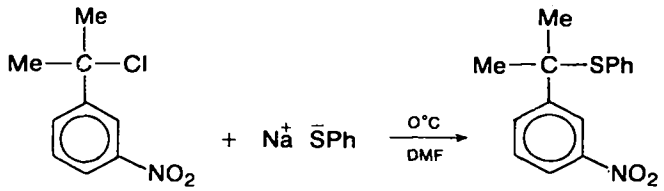


(32)

(25) (26)

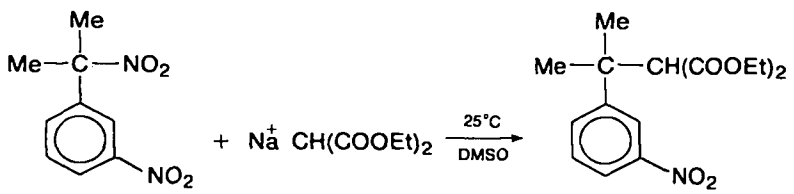
VI. OTHER CUMYLIC SYSTEMS

m-Nitrocumyl chloride (**27**), being a tertiary chloride, would not be expected to undergo S_N2 displacements and, since its radical anion is analogous to (25), elimination of chloride ion should be relatively difficult. Nonetheless, *m*-nitrocumyl chloride (**27**) undergoes substitution at the tertiary carbon atom when treated with nucleophiles. The reaction of equation (33) is illustrative[20]. The aliphatic nitro



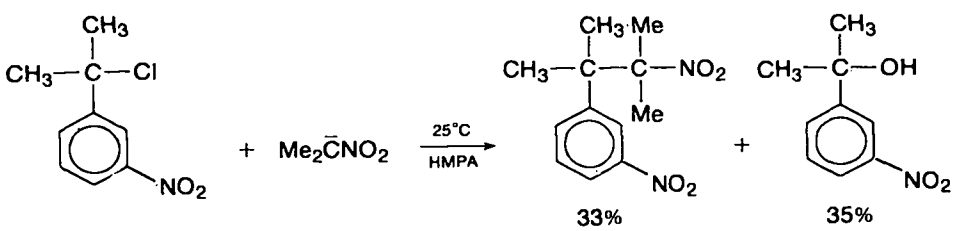
(27) 96% (33)

group of α,*m*-dinitrocumene (**28**) is also displaced by anions at easily measurable rates. For example, α,*m*-dinitrocumene reacts with sodiomalonic ester according to equation (34). With ambident anions, however, the very high yields of pure

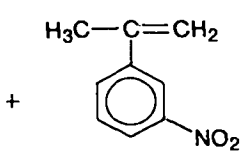


(28) 91% (34)

products which are almost effortlessly obtained in the *p*-nitrocumyl series are not obtainable from *m*-nitrocumyl compounds. Thus, whereas *p*-nitrocumyl chlorides and the lithium salt of 2-nitropropane, in HMPA, give a 90% yield of the carbon alkylate (equation 12), the corresponding reaction using *m*-nitrocumyl chloride gives but a 33% yield of the carbon alkylate (equation 35). This and other



(35)

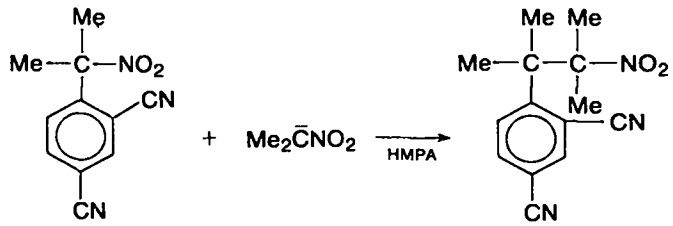


15%

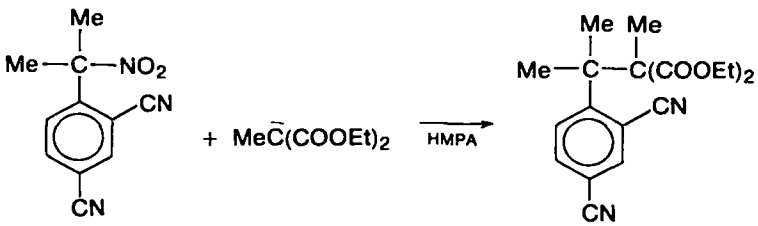
differences have led to the proposal that in the *m*-nitrocumyl series radical anions are intermediates, but that in contrast to the *p*-nitrocumyl system, a nonchain

process is the important pathway; in other words cage-collapse of radicals is the major process[20]. There is, however, no firm positive evidence for this mechanistic assignment and, indeed, a purely ionic mechanism cannot be excluded[21]. The only thing which is really clear is that the *m*-nitrocumyl system requires further study.

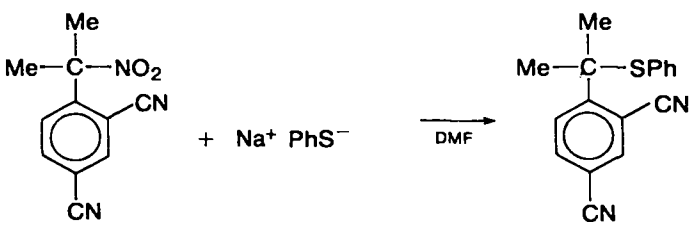
o,p-Dicyano-α-nitrocumene (**29**) readily undergoes electron-transfer chain substitution at the tertiary carbon atom; the reactions of equations (36)–(38) all take place at room temperature[22].



(29) 85% (36)

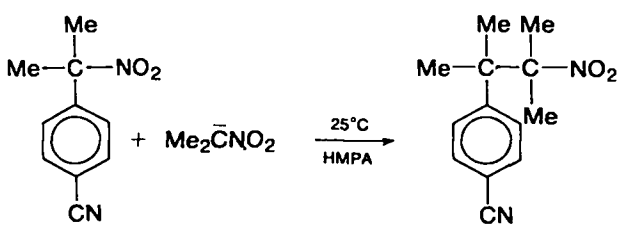


(29) 69% (37)



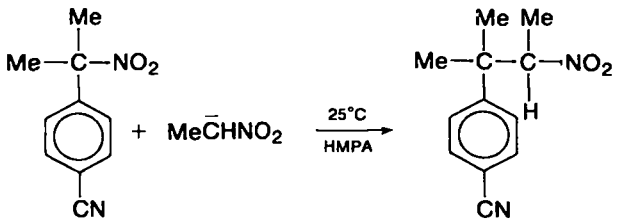
(29) 88% (38)

Radical anion chain substitution is also observed with *p*-cyano-α-nitrocumene (**30**). The reaction with the lithium salt of 2-nitropropane is relatively slow but, after 36 h, a 66% yield of the carbon alkylate (**31**) is isolated. On the other hand,



(30) (31) 66% (39)

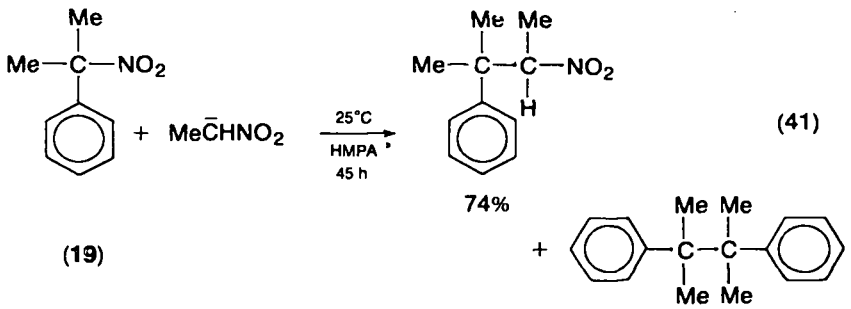
the reaction of the lithium salt of nitroethane requires only 7 h and gives a 94% yield of the pure carbon alkylate (equation 40)[22].



(40)

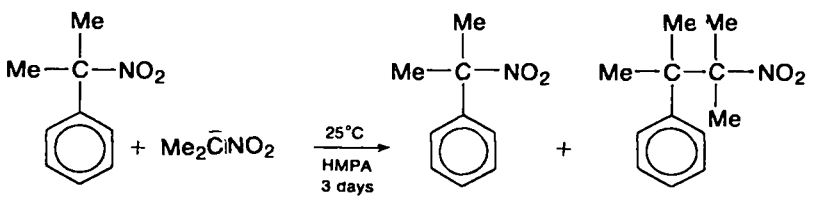
(30) 94%

Earlier in this chapter it was stated that α-nitrocumene (**19**) does not react to any significant extent with various anions under conditions which result in complete reaction with α,*p*-dinitrocumene (**12**). Recently, however, it has been found that α-nitrocumene will react with nitroparaffin salts if HMPA is the solvent and if relatively long reaction times are employed. Furthermore, it has been established that these are radical anion chain processes. The reaction with the lithium salt of nitroethane requires 45 h and is described by equation (41)[22]. The lithium salt of 2-nitropropane reacts even more slowly – after three days the reaction proceeds only two-thirds to completion – and now the principal product is bicumyl (equation 42)[22]. Finally, it is noteworthy that α-nitrocumene reacts relatively rapidly with the

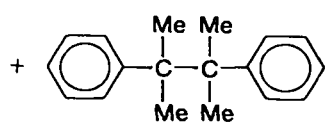


(41)

(19)

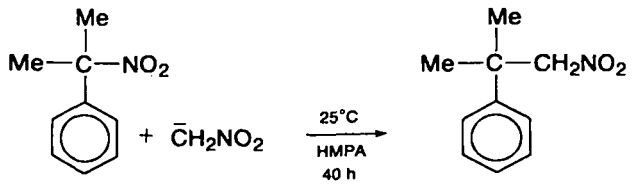


(19) 33% 21% (42)



45%

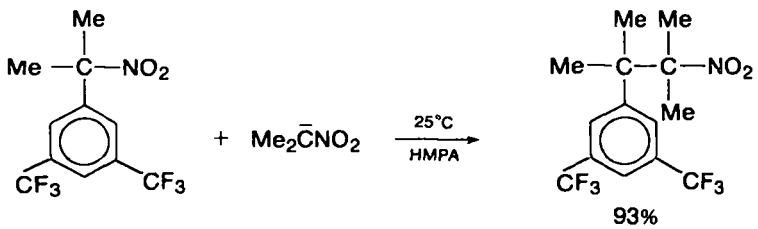
lithium salt of nitromethane and gives little, if any, bicumyl; instead, clean substitution occurs[23] (equation 43). It appears, then, that the reaction of a cumyl



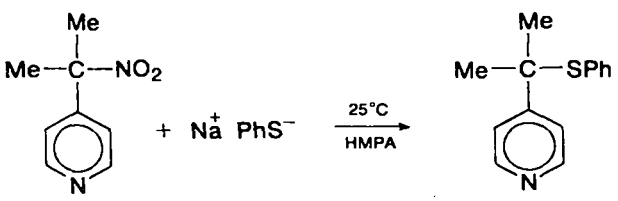
(19) 96% (43)

radical with a nitroparaffin anion suffers significantly in competition with dimerization as the steric requirement of the nitroparaffin anion is increased.

Numerous examples of electron-transfer chain substitution of the nitro group of tertiary nitro compounds are now known. The reaction of equations (44)–(47) involve systems which are relevant to the present discussion[24–26].

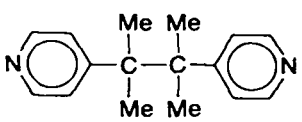


93% (44)

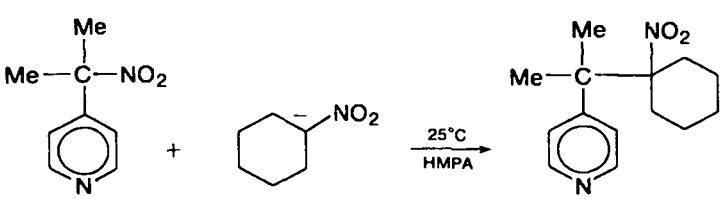


73% (45)

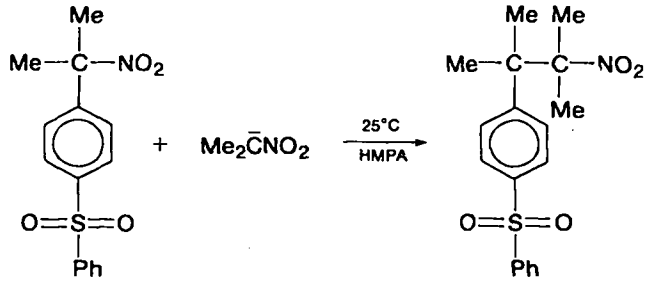
+



15%



89% (46)

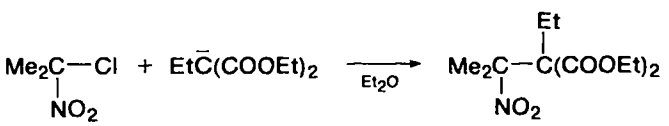


(47)

VII. PURELY ALIPHATIC AND ALICYCLIC SYSTEMS

There now exists a substantial literature concerned with radical anion substitution reactions of purely aliphatic and alicyclic nitro compounds. We shall discuss these processes under two headings – reactions in which the nitro group remains intact and reactions in which the nitro group is displaced.

The halogen atom of α-chloronitroalkanes, α-bromonitroalkanes and α-iodonitroalkanes can be displaced by a variety of nucleophiles. An early example is shown in equation (48)[27]. It will be noted that ethyl ether was employed as the solvent; this is not a commonplace. Instead, as shown by equations (49)–(51),



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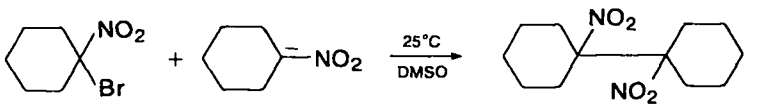
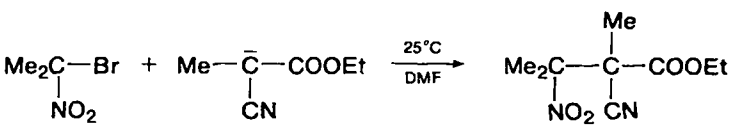
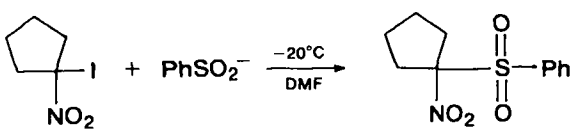


(49)



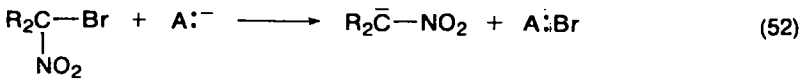
(50)



(51)

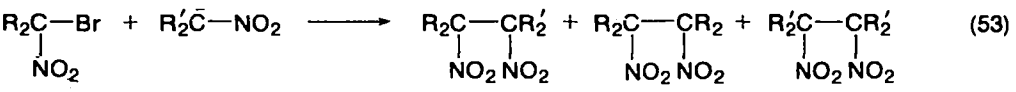
dipolar aprotic solvents are generally employed. The transformations of equations (49)–(51) take place rapidly and cleanly under mild conditions[28–30]. That of equation (51) routinely gives very high yields and is noteworthy because it is the only general method for preparing tertiary α-nitrosulphones[30].

With α-bromonitroalkanes bromine atom transfer between the nucleophile and the α-bromonitroalkane may intrude (equation 52) and when it does, symmetrical



(52)

coupling products may be produced along with the desired cross-coupled product[27–29]. For example, the preparation of unsymmetrical vicinal dinitro compounds by the reaction of equation (49) is unsatisfactory because substantial amounts of the two symmetrical compounds are also obtained (equation 53)[28]. (The

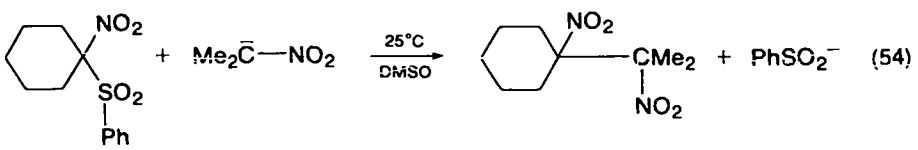


(53)

same problem is likely to be encountered when α-iodonitroalkanes are employed.) However, as will become apparent from what follows, this complication can be avoided by the simple device of using an α,α-dinitro compound, $R_2C(NO_2)_2$, or an α-nitrosulphone, in place of the α-bromonitroalkane.

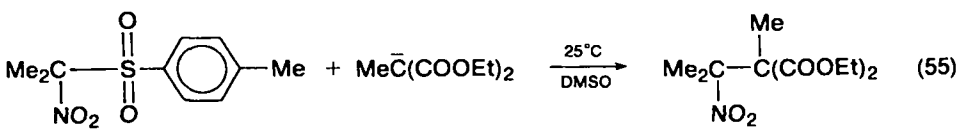
At room temperature α-nitrosulphones react rapidly with a variety of nucleophiles and, just as with the α-halonitroparaffins, these are radical anion chain reactions[31]. Some typical examples are given in equations (54)–(57).

There is good evidence for the view that these reactions of α-halonitro compounds, and of α-nitrosulphones, proceed via the electron-transfer chain mechanism of equation (58)–(61)[1a,31].



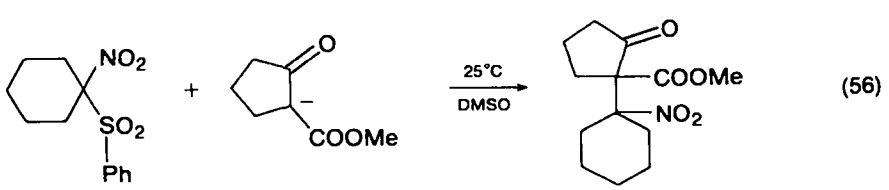
(54)

85%



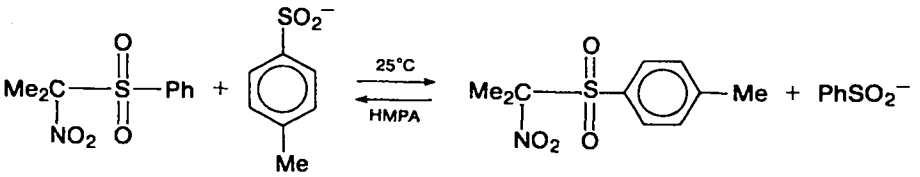
(55)

82%



(56)

77%



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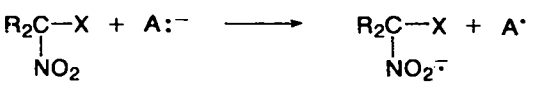
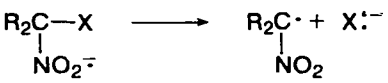


(58)

X = Cl, Br, I, $ArSO_2$



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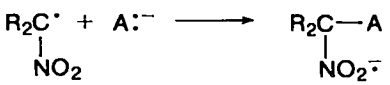
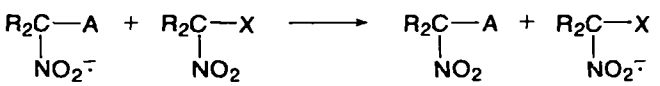
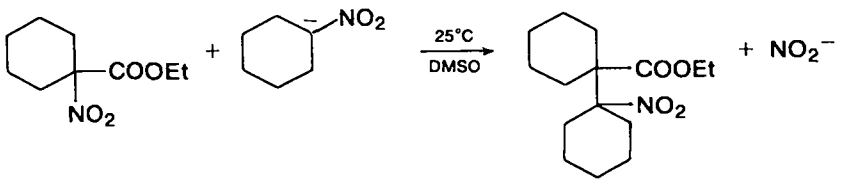


(60)



(61)

In 1970 a new reaction, the displacement of a nitro group from a variety of α-nitro esters, α-nitroketones, α-nitronitriles and α,α-dinitro compounds by nitroparaffin salts was described[32]. The reactions of equations (62)–(65) are illustrative.



(62)

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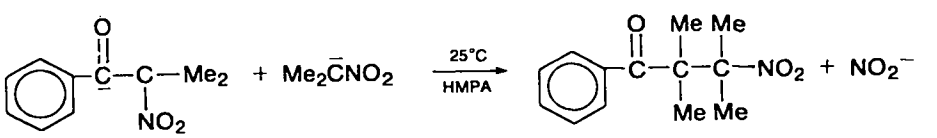
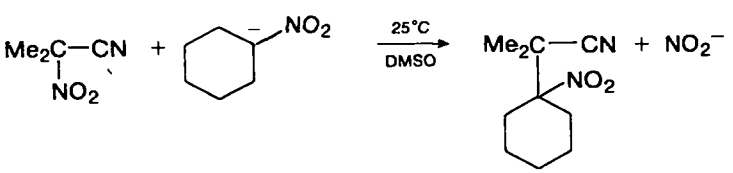


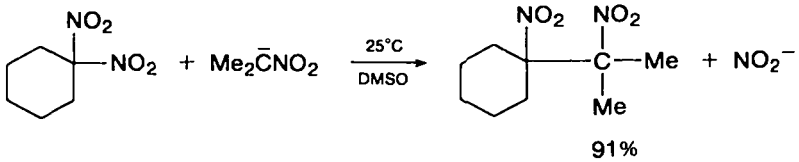
(63)

82%

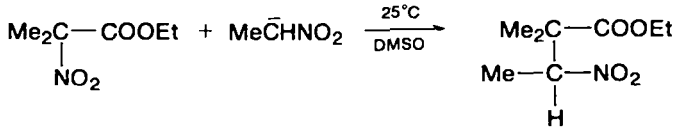


(64)

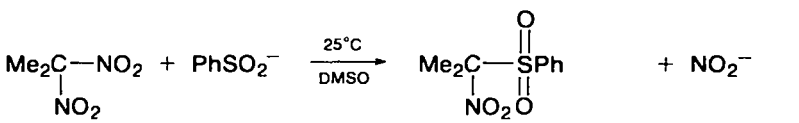
92%

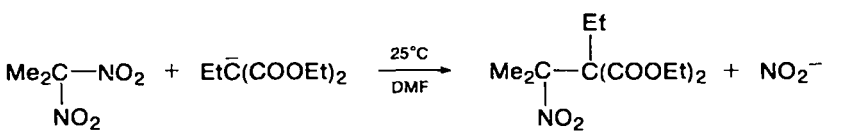


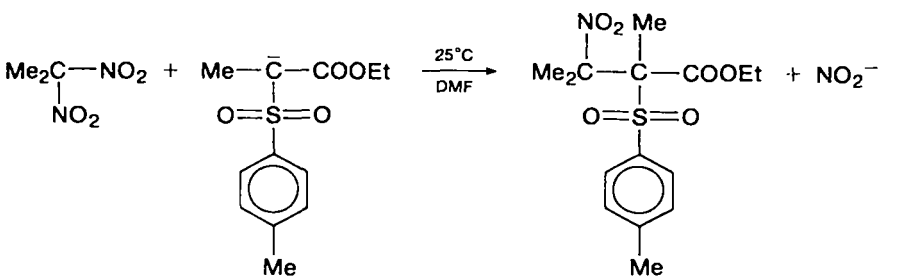
While most of the studies in this area have involved the salts of secondary nitro compounds it is clear that the salts of primary nitro compounds may also be employed. Thus, the transformation of equation (66) occurs readily and furnishes an excellent yield of the β-nitro ester.



The reactions of α,α-dinitro compounds are of considerable interest. To begin with, they are facile – the transformation of equation (65), for example, is complete in 15 minutes. But in contrast to what is observed with α-nitro esters, nitroparaffin anions are not the only nucleophiles which possess the capability of displacing a nitro group from α,α-dinitro compounds. Thus, although the reaction of equation (67) is relatively slow, it gives an 81% yield of the pure α-nitrosulphone[30]. Malonic ester anions, the anions of β-diketones and the anions of β-keto esters are also effective[29]; equation (68) is illustrative. Another interesting reaction of α,α-dinitro compounds is shown in equation (69)[33]. It should be noted that α,α-dinitro







compounds are readily obtained in yields of the order of 90% by the excellent synthesis due to Kaplan and Shechter[34].

$$R_2\bar{C}{-}NO_2 + 2\,AgNO_3 + NaNO_2 \xrightarrow[H_2O]{10^\circ C} \underset{\underset{NO_2}{|}}{R_2C{-}NO_2} + 2\,\dot{A}g \qquad (70)$$

90%

VIII. WHY NITRO COMPOUNDS DIFFER IN THEIR CAPABILITY FOR UNDERGOING RADICAL ANION SUBSTITUTION

Unlike α,α-dinitro compounds it appears, from admittedly incomplete studies[35], that α-nitro esters undergo substitution of the nitro group only when treated with nitroparaffin anions, e.g. as in equation (62) and (66). Since good grounds exist for regarding all the reactions of equations (62)–(69) as proceeding via a radical anion – free-radical chain sequence[1,32], it is necessary to enquire why α,α-dinitro compounds and α-nitro esters differ in their capability for reacting with nucleophiles.

The answer to this question and a number of related ones arises from the following consideration: a chain reaction involving radical anions is most likely to be observed when minimal energy is needed for the formation of the radical anions. It is known that the one-electron reduction of a nitro group is brought about relatively easily[36] – in other words, nitro radical anions are comparatively easy to produce. It is therefore not surprising that the chain sequences of equations (4)–(7), (26)–(29) and (58)–(61), which only invoke nitro radical anion formation, are feasible processes. The reason α,α-dinitro compounds are able to react with a variety of nucleophiles (equations 65 and 67–69) is that these transformations also invoke only nitro radical anion formation and they are, therefore, also feasible (equations 71–74).

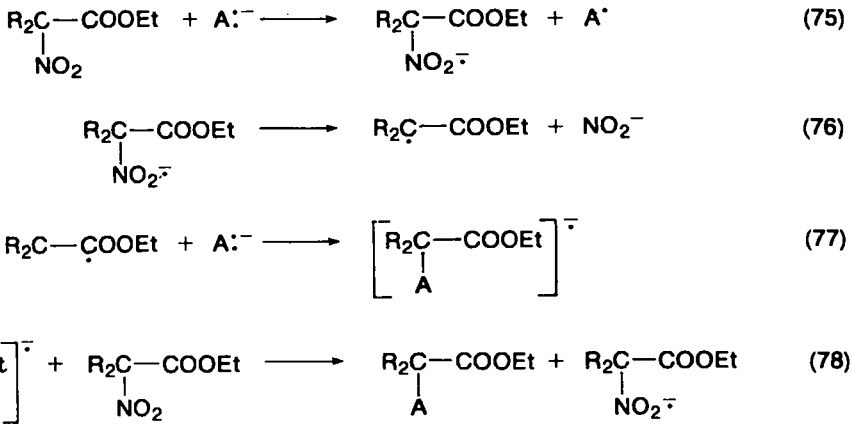
$$\underset{\underset{NO_2}{|}}{R_2C{-}NO_2} + A{:}^- \longrightarrow \underset{\underset{NO_2}{|}}{R_2C{-}NO_2^{\cdot-}} + A^{\cdot} \qquad (71)$$

$$\underset{\underset{NO_2}{|}}{R_2C{-}NO_2^{\cdot-}} \longrightarrow \underset{\underset{NO_2}{|}}{R_2C^{\cdot}} + NO_2^- \qquad (72)$$

$$\underset{\underset{NO_2}{|}}{R_2C^{\cdot}} + A{:}^- \longrightarrow \underset{\underset{NO_2^{\cdot-}}{|}}{R_2C{-}A} \qquad (73)$$

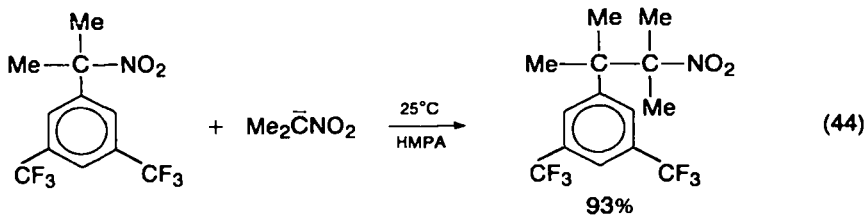
$$\underset{\underset{NO_2^{\cdot-}}{|}}{R_2C{-}A} + \underset{\underset{NO_2}{|}}{R_2C{-}NO_2} \longrightarrow \underset{\underset{NO_2}{|}}{R_2C{-}A} + \underset{\underset{NO_2}{|}}{R_2C{-}NO_2^{\cdot-}} \qquad (74)$$

With α-nitro esters the reaction with a nucleophile involves the sequence of equations (75)–(78). It will be seen that when $A{:}^-$ is a nitroparaffin anion, nitro radical anions will be involved and this apparently is the reason that substitution by nitroparaffin salts occurs. However, with sodium azide, sodium benzene sulphinate and sodiomalonic ester, where preliminary studies reveal that there is little or no reaction with an α-nitro ester[35], the presumption is that the radical anion of



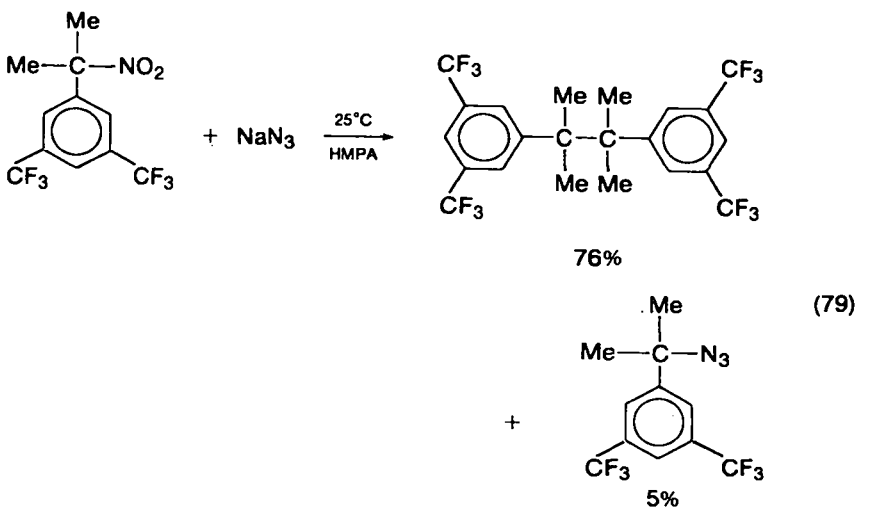
equation (77) is of relatively high energy and, therefore, the chain process is rendered essentially inoperative.

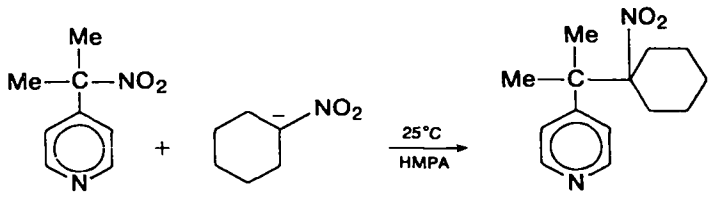
Analogous results are obtained with aromatic and heterocyclic systems. Thus, the reaction of equation (44) proceeds rapidly and gives a 93% yield of the pure



product. In contrast, when sodium azide is employed, a very slow reaction occurs and, as shown in equation (79), the principal product derives from the collapse of two cumylic radicals[24].

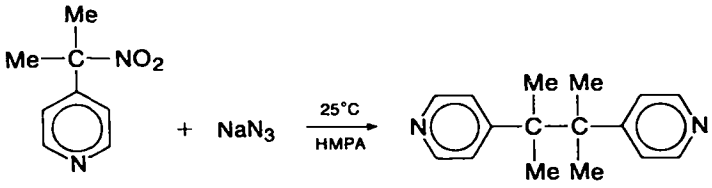
In the same way, the heterocycle of equation (46) gives an excellent yield of the substitution product on treatment with a nitroparaffin salt but with azide ion only dimerization is observed (equation 80)[25].





(46)

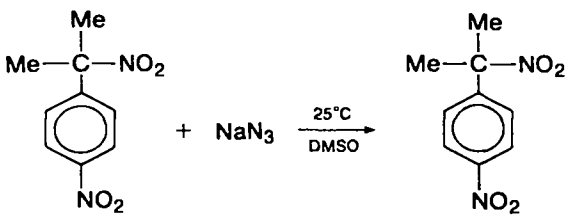
89%



(80)

93%

On the other hand, as can be seen from equation (20), substitution of a nitro group by azide ion occurs quantitatively when α,*p*-dinitrocumene is treated with sodium azide[14]. This is readily intelligible; the transformation of equation (20) proceeds via the chain sequence of equations (26)–(29) and, here again, only nitro radical anions are involved.



(20)

94%

To summarize: when a radical and an anion combine two possibilities for delocalization of the odd electron exist:

$$R^{\bullet} + A{:}^{-} \longrightarrow R{-}A^{\bullet -} \qquad (81)$$

and/or

$$R^{\bullet} + A{:}^{-} \longrightarrow {}^{\bullet -}R{-}A \qquad (82)$$

Thus, the reaction of equation (6) produces a radical anion of the type shown by equations (81) and (82); the presumption is that delocalization into the nitrophenyl moiety (equation 82) is more important. And clearly the radical anions of equations (60) and (73) correspond to that of equation (82).

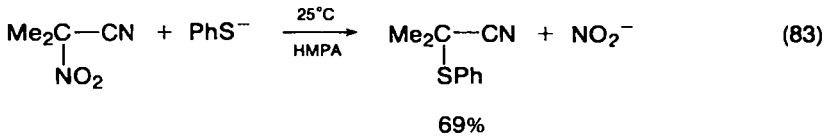
On the other hand, in reactions of α-nitro esters with nitroparaffin salts the radical anion of equation (77) corresponds to that of equation (81). In the same way, the substitution reactions of equations (44) and (46) follow the pattern of equation (81).

Finally, the lack of substitution noted in equations (79) and (80) must mean that radical anion formation according to equation (81) or (82) does not occur with the facility needed to propagate a chain-reaction. As a consequence, dimerization of

the cumylic radicals is observed. Clearly the azido group is a poor place to delocalize the odd electron and, equally clearly, neither the 3,5-*bis*-trifluoromethylphenyl nor the pyridyl system is able to delocalize an odd electron with anything approaching the effectiveness of the *p*-nitrophenyl group.

Displacement of the nitro group of α-nitronitriles by nitroparaffin anions occurs rapidly and cleanly, e.g. as in the example of equation (64). As pointed out earlier, these are radical-anion-free radical chain processes.

The fact that the reaction of equation (83) takes place readily at room temperature[10] suggests that α-nitronitriles may possess the capability of reacting in



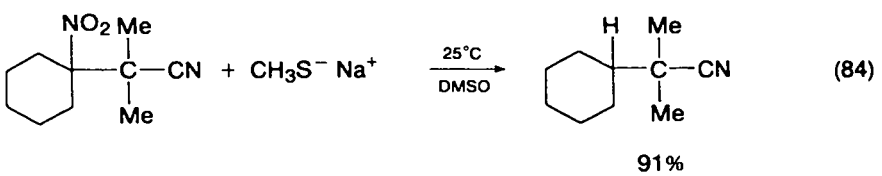
(83)

a synthetically useful manner with a variety of nucleophiles. While the mechanism of the reaction of equation (83) has not been established it is a reasonable assumption that it, too, is an electron-transfer chain process*.

IX. FURTHER NEW SUBSTITUTION REACTIONS OF TERTIARY ALIPHATIC AND ALICYCLIC NITRO COMPOUNDS

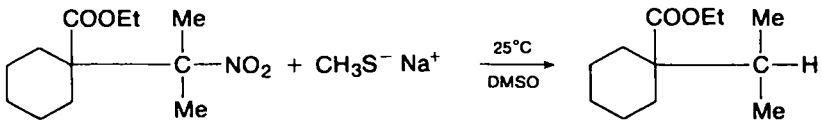
A number of reactions are now known which give excellent yields of pure aliphatic and alicyclic tertiary nitro compounds[37]. All of these reactions employ mild conditions and most of them are carbon–carbon bond-forming processes. It is of especial interest that they give rise to highly branched compounds, many of them all but unobtainable by other means. Still another important feature of these reactions is that they are capable of providing tertiary nitro compounds in which other functional groups are present, e.g. cyano, keto and ester. With such a wide variety of unusual structures readily available it is apparent that any process which results in the replacement of a nitro group by other atoms or groups of atoms has considerable value.

In 1978 a new reaction, the replacement of a nitro group by hydrogen, was reported[37]. It occurs at room temperature when the nitro compound is treated with the sodium salt of methyl mercaptan. Equations (84)–(86) are illustrative.

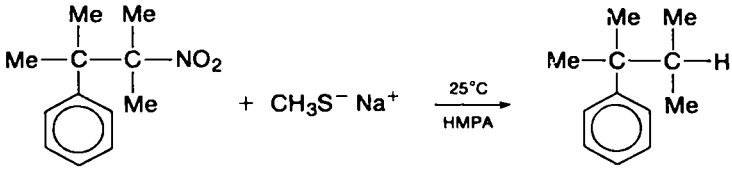


(84)

*In a brief communication entitled 'Nucleophilic displacement of the nitro group from nitroalkanes' Benn and Meesters[49] report that nitromethane reacts with *p*-$MeC_6H_4S^-$ K^+ in DMF at 85°C to give an 80% yield of *p*-MeC_6H_4SMe after an unspecified time. Under similar conditions nitroethane is said to give a 3% yield of *p*-MeC_6H_4SEt and with 2-nitropropane a 0.5% yield of *p*-$MeC_6H_4SCHMe_2$ is claimed; with tertiary nitrobutane *p*-$MeC_6H_4SCMe_3$ could not be detected. In view of all this it is unclear how the title was arrived at. Unfortunately, in a less than critical review of the Benn–Meesters communication, Ward[50] makes the following report which is quoted in its entirety. 'The powerful nucleophilic toluene-*p*-thiolate anion can displace a nitro group from simple unactivated primary and secondary nitroalkanes yielding alkyl *p*-tolyl sulphides, apparently by a conventional S_N2 displacement process.'



83% (85)



94% (86)

These transformations exhibit the characteristics of electron-transfer chain substitution reactions; a mechanism which is fully consonant with all the known facts is given by equations (87)–(90)[37,38].

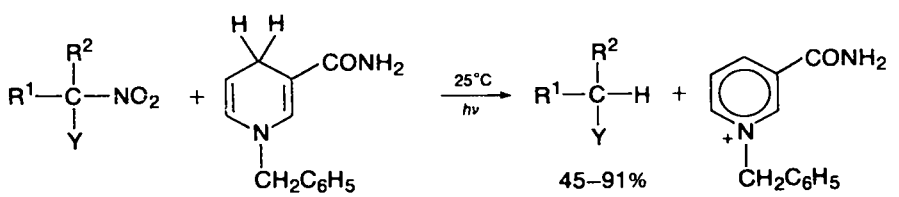
$$R_3C{-}NO_2 + CH_3S^- \longrightarrow R_3C{-}NO_2^{\cdot-} + CH_3S^{\cdot} \quad (87)$$

$$R_3C{-}NO_2^{\cdot-} \longrightarrow R_3C^{\cdot} + NO_2^- \quad (88)$$

$$R_3C^{\cdot} + H_3C{-}S^- \longrightarrow R_3C{-}H + H_2\dot{C}{-}S^- \quad (89)$$

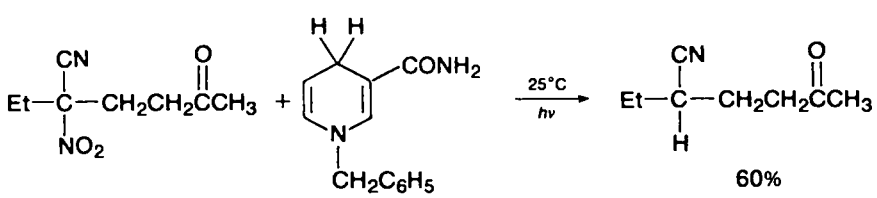
$$H_2\dot{C}{-}S^- + R_3C{-}NO_2 \longrightarrow H_2C{=}S + R_3C{-}NO_2^{\cdot-} \quad (90)$$

In 1980 it was reported that 1-benzyl-1,4-dihydronicotinamide is able to replace an aliphatic nitro group by hydrogen when the carbon undergoing substitution also is bonded to a cyano, an ester, or a keto group (equation 91)[39]. Despite this requirement it appears that in some cases the transformation of equation (91) may prove to be of special value, e.g. the reaction of equation (92).



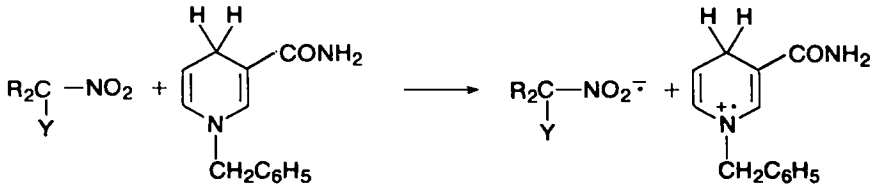
45–91% (91)

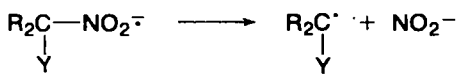
Y = CN, COOR, COAr

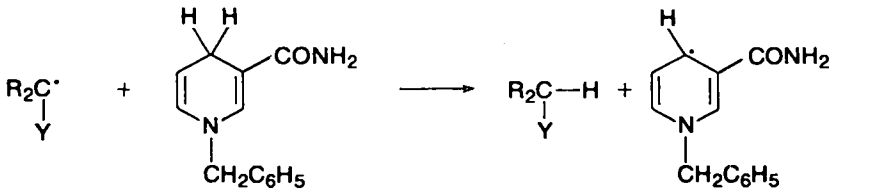


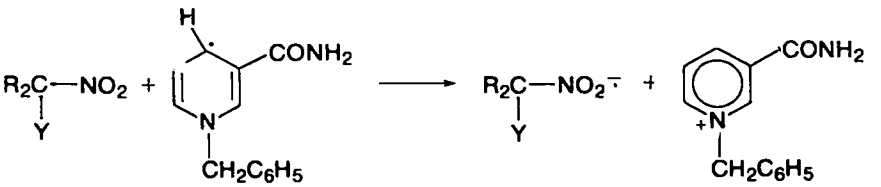
60% (92)

The proposal that replacement of the nitro group by hydrogen occurs via the electron-transfer chain mechanism of equations (93)–(96) is supported by a significant body of evidence[39].

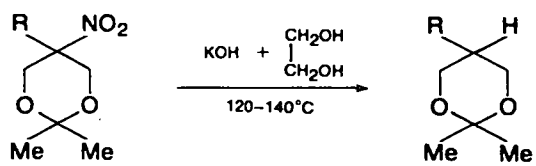






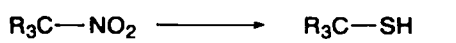


A rather more drastic method of replacing an aliphatic nitro group by hydrogen was described in 1979[40]. When 5-nitro-1,3-dioxanes are treated with potassium hydroxide in ethylene glycol at 120–140°C, the reaction of equation (97) is observed. The authors rationalize this transformation as a radical anion chain-reaction on much the same lines as the mechanism of equations (87)–(90).



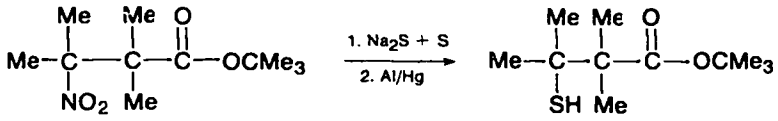
R = Me, Et, *n*-Pr, *n*-Bu 50–55%

Another recently discovered transformation of tertiary nitro compounds is the replacement of a nitro group by the mercapto group (equation 98)[41]. When a

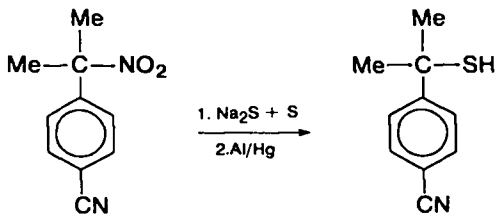


tertiary nitro compound is treated with a solution of sodium sulphide and sulphur in DMSO at 25°C smooth conversion to a mixture of the corresponding thiol and dialkyl polysulphides occurs; on subjecting this mixture to the action of amalgamated aluminium at 0°C the polysulphides are converted to the thiol. Equations (99)–(101) present some examples.

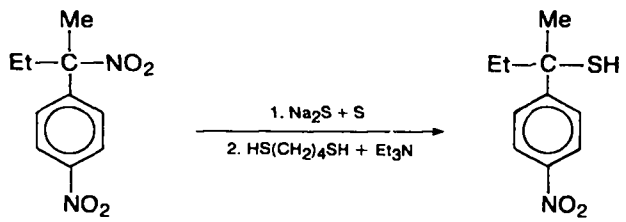
The reaction of equation (101) serves to remind one that whereas nitroaliphatic radical anions readily fragment into nitrite ions and free radicals, e.g. as in equation



85% (99)



93% (100)



73% (101)

(88), nitroaromatic radical anions do not. The speed with which the first step of the transformation of equation (101) occurs is striking: at 25°C it is complete in 45 seconds! Finally, it should be noted that when a nitro group is present, a different procedure for cleaving polysulphides is employed since the use of aluminium amalgam would hazard reduction of the nitro group.

Although the uncertainties and complexities associated with polysulphide solutions preclude a detailed mechanistic discussion, enough is known about electron-transfer substitution reactions of aliphatic nitro compounds to enable one to put forth the broad outlines of a mechanism. A number of closely related variants can readily be envisioned[41]:

$$R_3C{-}NO_2 + {}^{-}S{-}S_x^{-} \longrightarrow R_3C{-}NO_2^{\cdot-} + {}^{\cdot}S{-}S_x^{-}$$

$$R_3C{-}NO_2^{\cdot-} \longrightarrow R_3C^{\cdot} + NO_2^{-}$$

$$R_3C^{\cdot} + {}^{-}S{-}S_x^{-} \longrightarrow R_3C{-}S^{\cdot-}{-}S_x^{-}$$

$$R_3C{-}S^{\cdot-}{-}S_x^{-} + R_3C{-}NO_2 \longrightarrow R_3C{-}NO_2^{\cdot-} + R_3C{-}S{-}S_x^{-}$$

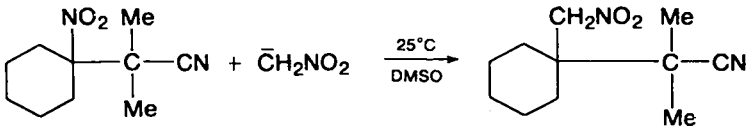
$$R_3C{-}S{-}S_x^{-} \longrightarrow R_3C{-}S^{-} + S_x$$

$$R_3C{-}S^{-} + R_3C{-}S{-}S_x^{-} \longrightarrow R_3C{-}S{-}SCR_3 + S_x^{2-}$$

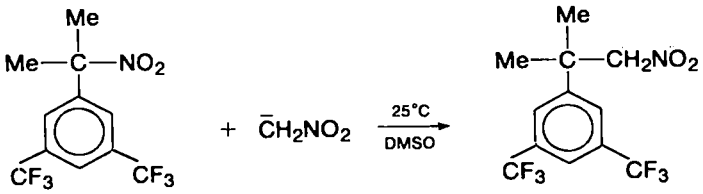
$x = 1, 2, 3, 4,$ etc.

It has now been found that tertiary nitro compounds readily undergo the general reaction of equation (102)[23,42]. Here again cyano groups and ester groups are not attacked; equations (103)–(105) are illustrative. Since there are well established

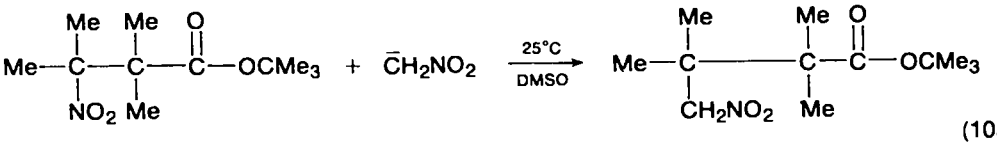
$$R_3C{-}NO_2 + \bar{C}H_2NO_2 \xrightarrow[DMSO]{25°C} R_3C{-}CH_2NO_2 + NO_2^- \qquad (102)$$



89% (103)

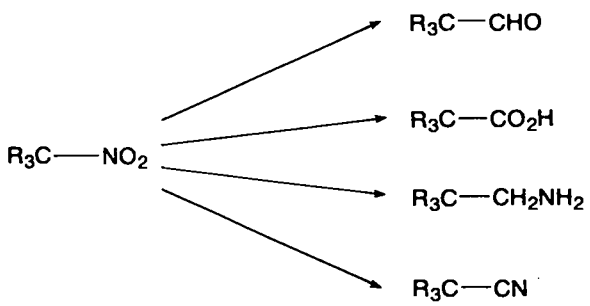


93% (104)



95% (105)

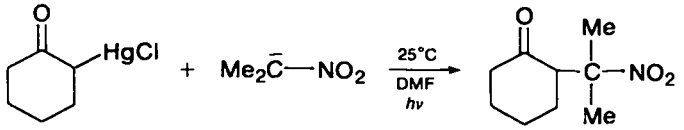
methods for converting $-CH_2NO_2$ into $-CHO$[23], $-CO_2H$, $-CH_2NH_2$ or $-CN$, the ability to replace $-NO_2$ by $-CH_2NO_2$ is tantamount to replacing a tertiary nitro group by these functions:



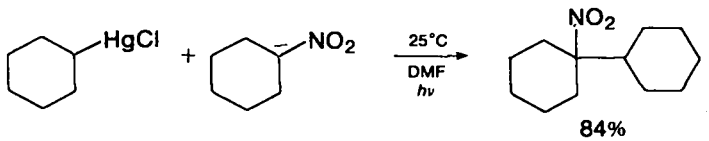
These transformations, it should be noted, generate a quaternary carbon atom and this significantly enhances their synthetic value.

X. MISCELLANEOUS RADICAL ANION REACTIONS

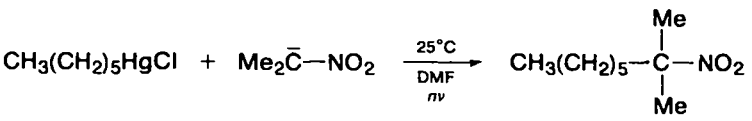
The reaction of nitroparaffin anions with alkylmercury chlorides provides a new and useful means of obtaining tertiary nitro compounds[43]; some specific examples are given by equations (106)–(108).



60–70% (106)

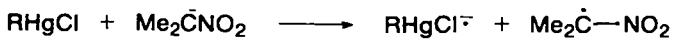


84% (107)



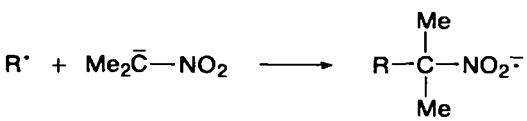
90% (108)

These reactions exhibit the characteristics of a free-radical chain process and the mechanistic sequence of equations (109)–(112) has been proposed.

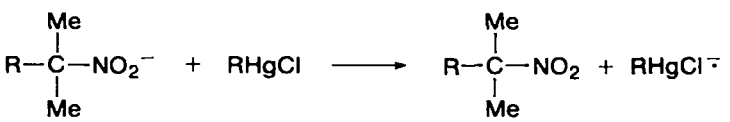


(109)

(110)



(111)

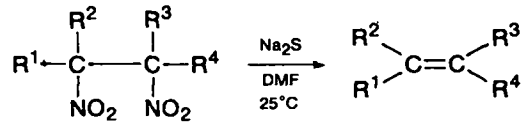


(112)

Apparently a nitroparaffin anion is required for these reactions (cf. equation 81); coupling is not observed when organomercury halides are irradiated in the presence of diethyl methylmalonate anions[43]. Thus it appears that we have here another example of the feasibility which attaches to chain processes that invoke nitro radical anions (see above).

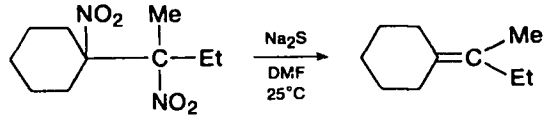
Attempts to bring about the coupling of phenyl- or vinyl-mercury halides with nitroparaffin anions have failed. This presumably reflects the difficulty of fragmentation along the lines of equation (110) and is reminiscent of the reluctance of nitroaromatic radical anions to fragment into a free radical and a nitrite ion, as noted in an earlier section of this chapter (cf. equation 101).

A new and general synthesis of tetrasubstituted olefins noteworthy for its simplicity and for producing pure products in high yields invokes the elimination reaction of equation (113)[44]. (The requisite vicinal dinitro compounds are readily prepared by radical anion reactions such as those of equations 49, 54 and 65.) Both



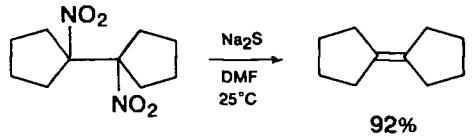
(113)

symmetrical and unsymmetrical olefins are readily obtained. Equations (114) and (115) provide some typical examples.



91%

(114)



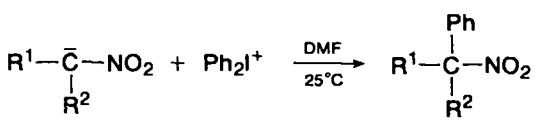
92%

(115)

It is clear that olefin formation is a chain process; there are reasons for thinking that radical anions and free radicals are intermediates even though the detailed mechanism has not as yet been elucidated[44*].

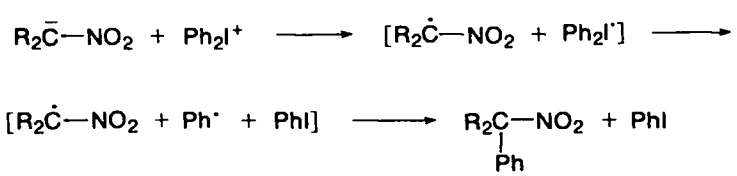
In closing two further points should be made. The first is that although we have primarily been concerned with electron-transfer chain substitution processes it is important to recognize that, in principle, electron-transfer *nonchain* substitution may also occur. The difficulty of demonstrating a nonchain process is considerable and few, if any, unequivocal examples involving nitro compounds are known. Nonetheless it seems likely that such nonchain processes exist.

For example, the phenylation of nitroparaffin salts (equation 117) may well be an electron-transfer cage-collapse process[46]. A nonchain mechanism along the lines



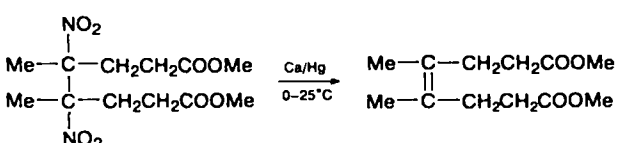
54–69%

(117)



(118)

*Calcium amalgam may also be used for these elimination reactions, for example equation (116)[45].



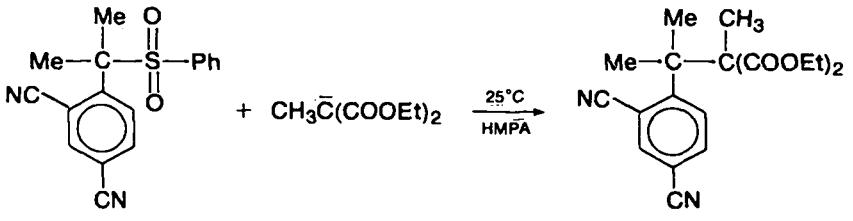
84% (*cis* plus *trans*)

(116)

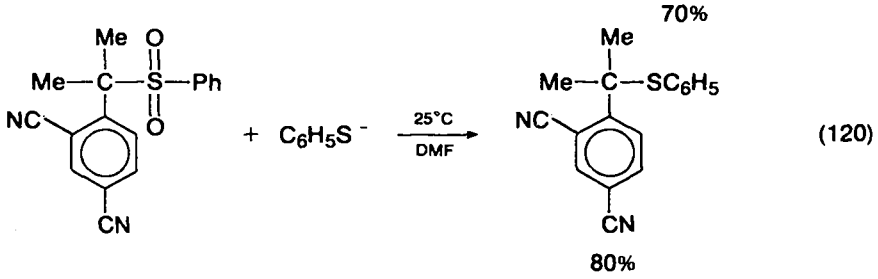
proposed by Beringer, Galton and Huang[47] for the phenylation of carbanions is a rather plausible possibility (equation 118).

XI. RADICAL ANION CHAIN SUBSTITUTION IN COMPOUNDS DEVOID OF NITRO GROUPS

Finally, it should be emphasized that electron-transfer substitution reactions are not restricted to nitro compounds. Recently a demonstration was provided that the cyano group also facilitates electron-transfer chain substitution, e.g. as in equations (119) and (120)[7].



(119)



(120)

As noted earlier, the ability of a function to accept one electron is a critical factor in facilitating electron-transfer substitution. Electrochemical data are available[48] which suggest that a variety of functions other than nitro and cyano may accept one electron readily enough to support radical anion substitution. In this connection the work of Bunnett and his students on radical anion substitution processes involving aromatic systems is especially noteworthy[6]. Also of interest are the studies by Wolfe, and Zoltewicz, of radical anion substitution reactions of heterocyclic halides[6]

XII. ACKNOWLEDGEMENT

This work has been facilitated by a grant from the National Science Foundation.

XIII. REFERENCES

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   (b) G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, **88**, 5663 (1966).

6. Although we are here concerned with electron-transfer substitution at a saturated carbon atom it should be noted that since 1970 J. F. Bunnett and his coworkers have found a number of examples of electron-transfer substitution at an aromatic carbon atom: *Acc. Chem. Res.*, **11**, 413 (1978). Furthermore, Wolfe, and Zoltewicz, have described electron-transfer substitution reactions in the quinoline and isoquinoline series: J. F. Wolfe, J. C. Greene and T. Hudlicky, *J. Org. Chem.*, **37**, 3199 (1972); *J. Am. Chem. Soc.*, **97**, 374 (1975); J. A. Zoltewicz and T. M. Oestreich, *J. Amer. Chem. Soc.*, **95**, 6863 (1973).
7. N. Kornblum and M. J. Fifolt, *J. Org. Chem.*, **45**, 360 (1980).
8. This is especially impressive when it is recognized that a well-defined leaving-group effect is operative in the alkylation of the acetoacetic ester anion by purely aliphatic halides – iodides give the most *C*-alkylate and chlorides the least: G. Brieger and W. M. Pelletier, *Tetrahedron Letters.*, 3555 (1965); W. J. le Noble and J. E. Puerta, *Tetrahedron Letters.*, 1086 (1966). Whatever its origin, it is important to note that this leaving-group effect is completely reversed in the reaction employing *p*-nitrobenzyl chloride.
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CHAPTER **11**

Direct aminations

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I. INTRODUCTION

The replacement of hydrogen by an amino group is generally considered as a multistep process[1]. It requires the introduction of an intermediary functional group (e.g. halogeno, azido and many others) and subsequent transformation (e.g. exchange or reduction) to the required amine. This chapter, however, is concerned

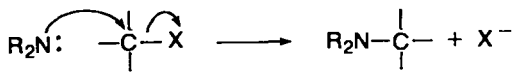
with reactions and reagents which enable direct displacement. Numerous such methods have been developed recently, a large proportion of them disregarding the concept that nitrogen atoms have to react through their lone-pair electrons.

The term amino has been broadened here to include also substituted and protected amines. The arrangement of the chapter is mechanistic. Reagents which are not definitely electrophilic, nucleophilic or radicals are classified as 'miscellaneous'.

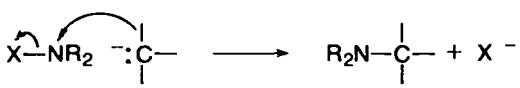
II. ELECTROPHILIC AMINATION

A. General

The underlying principle of electrophilic amination is the reversal of the usual role (equation 1) of the carbon and the nitrogen in the formation of the *C*-amino bond (equation 2).



(1)



(2)

X = leaving group

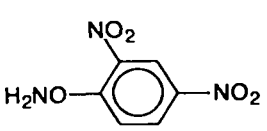
The nitrogen acts as an electrophile, the carbon as a nucleophile, and the reaction can be regarded as a nucleophilic displacement on nitrogen. This approach has been extensively used for the synthesis of hydrazines from amines or amide anions and of sulphinylimines from sulphides and sulphoxides. The results are summarized in two recent reviews[2,3]. Reports on carbon aminations are still rather sparse, but their number is constantly increasing, due to the obvious advantage of the method.

B. Amination Reagents

The required structural feature for electrophilic amination reagents is the attachment of a leaving group to an amino group. The earliest known compound of this type is chloramine (**1**)[4], which is highly reactive but unstable and hazardous. Another inorganic reagent is hydroxylamine-*O*-sulphonic acid (HOS) (**2**) which is quite stable and commercially available. Its use is, however, limited, due to solubility problems. Recently a series of organic reagents have been developed which make the amination a convenient and easy operation. All these reagents are

(1)

(2)



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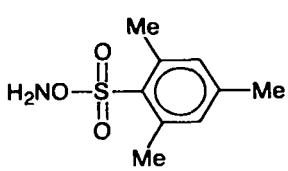
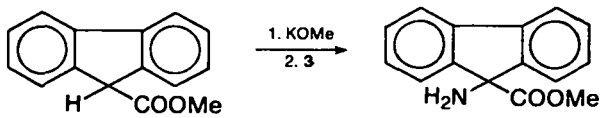


(4)

hydroxylamine derivatives and those in most ordinary use are *O*-2,4-dinitrophenylhydroxylamine (**3**)[5] *O*-mesitylenesulphonylhydroxylamine (**4**)[6]. A list of other potential reagents is given in Reference 3. Mechanistic studies on the reaction of **1**[7], **2**[8] and **3**[9] with various nucleophiles indicate that all the aminations proceed through S_N2-like displacement on nitrogen and exclude other possible interpretations.

C. α-Amination of Carboxylic Acids and Derivatives

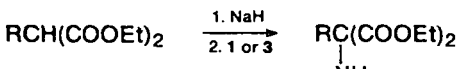
The direct transformation of carboxylic acids and their derivatives (esters, amides, etc.) to amino acids has attracted special attention. The first report[5,10] was on the amination of 9-carbomethoxyfluorene(**5**) with reagent **3**, which afforded **6** in 53% yield (equation 3).



(3)

(**5**) (**6**)

A series of diethyl malonates (**7**) was transformed to diethyl aminomalonates (**8**) using either chloramine (**1**[11] or reagent **3**[12] (equation 4 and Table 1). The products **8** could be directly saponified and decarboxylated to the corresponding α-amino acid.



(4)

(**7**) (**8**)

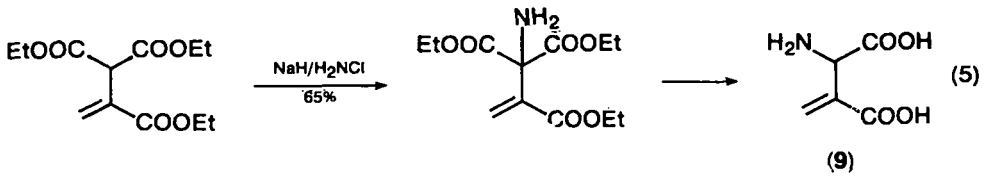
Noteworthy is the preparation of methyleneaspartic acid (**9**) (equation 5)[13]. Synthesis of this acid has failed with all the conventional methods.

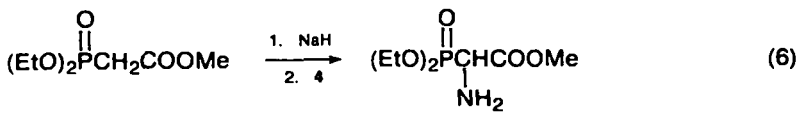
Methyl amino(diethylphosphono)acetate (**11**), a key intermediate for cepham synthesis, is obtained by the amination of **10** with reagent **4** in 47% yield (equation 6).[14]

TABLE 1. Amination of diethyl malonates (**7** → **8**)

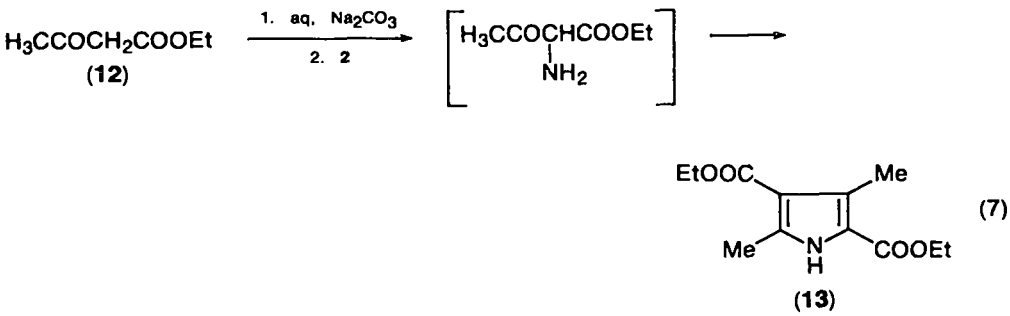
	Yield (%)	
	With **1**	With **3**
H	92	55
Me	85	78, 84[a]
Et	89	74[a]
i-Pr	70	—
n-Bu	—	46–57[a]
s-Bu	83	—
Ph	70	65
$PhCH_2$	72	73[a]
$EtOOCCH_2$	—	61[a]

[a]Converted directly to α-amino acids.

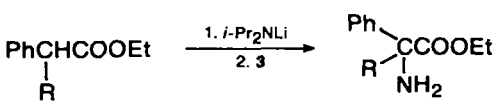




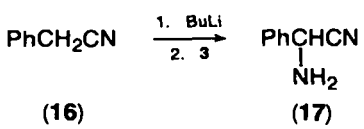
β-Keto esters (and β-diketones) have been aminated with HOS(**2**)[15]. The amino derivatives react further, thus ethyl acetoacetate (**12**) gives directly 2,4-dicarboethoxy-3,5-dimethylpyrrole (**13**) in a one-step Knorr pyrrole synthesis (equation 7). Upon decrease of the acidity of the aminated carbon, the yields drop



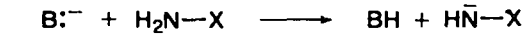
off considerably[12]. Thus the esters **14a** and **14b** give, on reaction with **3**, the amino esters **15a** and **15b** in 31% and 12% yields respectively (equation 8). Phenylacetonitrile (**16**) gives the amine **17** in 7% yield only (equation 9).



(**a**) R = H
(**b**) R = Me



It appears that highly basic salts abstract a proton from the amination reagent, resulting in its amination and decomposition (equations 10–12). A successful



$$HN^{-}{-}X + H_2N{-}X \longrightarrow H_2NNH{-}X + X^{-} \quad (11)$$

$$B:^{-} + H_2N{-}NHX \longrightarrow HN{=}NH + BH + X^{-} \quad (12)$$

amination would always require the use of reagents which are less acidic than the substrate. Some failures have been reported. For example the β-ketosulphonamide 18 does not afford **19** (equation 13), although its acidity is close to that of the malonates. A possible reason in this case is the decomposition of the product under the basic reaction conditions.[16].

$$PhCOCH_2SO_2NMe_2 \not\longrightarrow PhCOCHSO_2NMe_2 \quad (13)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

(18) **(19)**

According to these findings, dilithiated carboxylic acids can hardly be expected to undergo amination with reagents **3** or **4**. Indeed isovaleric acid (**20**) gives only traces of valine (with chloramine the yield was 7%). Replacement of the leaving group by a much weaker one, such as an alkoxy group, offers some improvement, but the yields are still low as the decrease in acidity results also in decrease in the electrophilicity of the nitrogen. With *O*-methylhydroxylamine the yield of valine (**21**) is 34% (equation 14) and of phenylglycine 55%. Leucine (11%), methionine (9%) and phenylalanine (7%) are also obtained by this method[17].

$$(CH_3)_2CHCH_2COOH \xrightarrow{i\text{-}Pr_2NLi} (CH_3)_2CHCHCOOLi \xrightarrow{H_2NOMe} (CH_3)_2CHCHCOOH \quad (14)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Li \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

(20) **(21)**

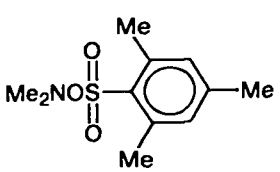
Attempts to aminate primary amides have also failed. However, the secondary amide **22**, gives with *O*-methylhydroxylamine the amino amide **23** in 30% yield[18] (equation 15).

$$PhCH_2CONHBu \xrightarrow[2.\ H_2NOMe]{1.\ i\text{-}Pr_2NLi} PhCHCONHBu \quad (15)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NH_2$$

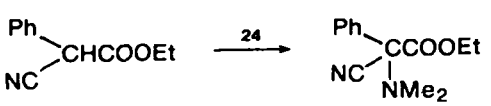
(22) **(23)**

D. Dialkylamination

Dialkylated amination reagents such as *N*,*N*-dimethyl-*O*-mesitylenesulphonyl-hydroxylamine (**24**) are nonacidic and therefore the competing pathway discussed



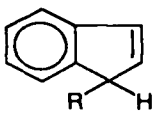
(24)



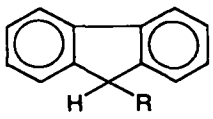
(16)

(25) **(26)**

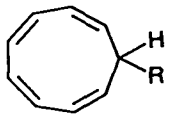
above cannot operate. Compound **24** has been used for the direct introduction of the dimethylamino group onto a series of organometallics and carbanions[19]. The ester **25** gives **26** in 95% yield (equation 16) (with **3** it is aminated in 54% yield only[12]). Examples of direct amination of hydrocarbons, which do not undergo unsubstituted amination at all, are those of indene (**27**), fluorene (**28**) and cyclononatetraene (**29**).



(**27**)



(**28**)



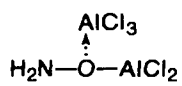
(**29**)

Yield(**a** → **b**) 57% 61% 69%

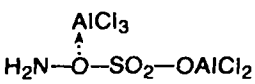
(**a**) R = H
(**b**) R = NMe_2

E. Aromatic Amination

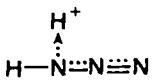
The direct electrophilic amination of benzene and substituted benzenes was systematically investigated by Kovacic and coworkers in the early sixties. It can be effected by reagents such as hydroxylamine and its salts[20], alkylhydroxylamines[21], hydroxylamine-*O*-sulphonic acid (**2**)[22] and hydrazoic acid[23]. Enhancement of the electrophilic reactivity by Friedel–Crafts catalysts (at least 2 moles) is always necessary. The coordination with the Lewis acid increases the polarization of the nitrogen–oxygen bond and thus increases the cationic character of the nitrogen. Examples of likely reacting species are **30**, **31** and **32**, derived from hydroxylamine, hydroxylamino-*O*-sulphonic acid and hydrazoic acid, respectively.



(**30**)

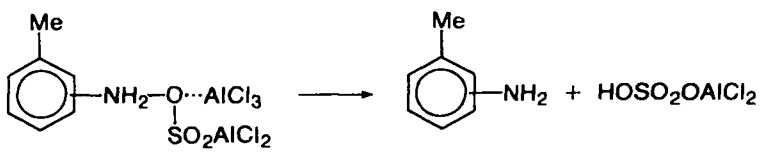


(**31**)



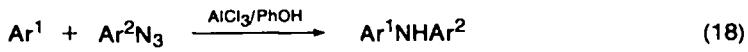
(**32**)

Comparison of isomer distribution (selectivity factors) on amination with those obtained in other electrophilic substitution reactions confirms the electrophilic nature of the reactions and indicates a concerted process, rather than involvement of NH_2^+. Consideration of steric factors supports this mechanism. The amination of toluene by **31** is presented in equation (17). Yields in these reactions are low to moderate (Table 2).



(17)

The reaction of aryl azides with aromatic substrates in the presence of aluminium chloride and a proton source (usually phenol) gives diarylamines in high yields[24] (equation 18). The mechanism of the aryl amination is probably similar to that of hydrozoic acid action. Benzene gives with phenyl azide 89% yield of diphenylamine. Toluene yields 91% of phenyltolylamines (ratio *o*:*m*:*p* = 13.3 : 0.1 : 86.6). Naphthalene gives 75% of 1-naphthylphenylamine.



(18)

TABLE 2. Direct amination of toluene

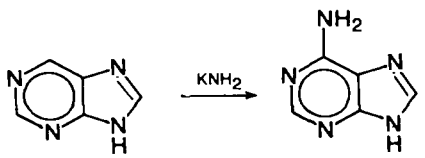
Reagent[a]	Total yield of toluidines (%)	Composition (%)			Reference
		o	*m*	*p*	
H_2NOSO_3H	50	51	13	36	22
H_2NOH	37	31	14	55	20
$H_2NOH{\cdot}HCl$	36	30	18	52	20
$(H_2NOH)_2{\cdot}H_2SO_4$	65	37	23	40	20
H_2NOCH_3	42	34	16	50	21
NaN_3	65	49	14	37	23

[a]With $AlCl_3$.

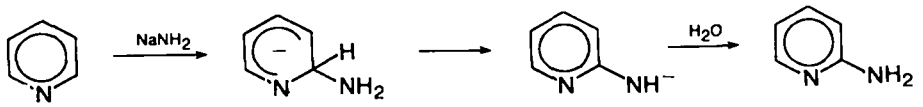
III. NUCLEOPHILIC AMINATION

A. Aromatic Amination by Alkali Amides (The Chichibabin Reaction)

The direct 2-amination of pyridine and related heterocycles by sodamide or potassium amide is the best known case of aromatic nucleophilic displacement of hydride ions. Early reviews[25,26] give long lists of aminations performed on various substrates including substituted pyridines, quinolines, isoquinolines and some diazines and diazols and their benzo derivatives. More recent additions are the aminations of naphthyridines[27,28], triazines[29,30] and of purine (**33**) which gives adenine (**34**) directly (equation 19). The reaction is an addition–elimination process which proceeds through an anionic σ-complex. The partial localization of the negative charge at the electronegative nitrogen atom, results in a pronounced activity of the α- and γ-positions. Pyridine (equation 20) is thus aminated at positions 2 and 6, and when those are occupied, at position 4.



(33) (34) (19)

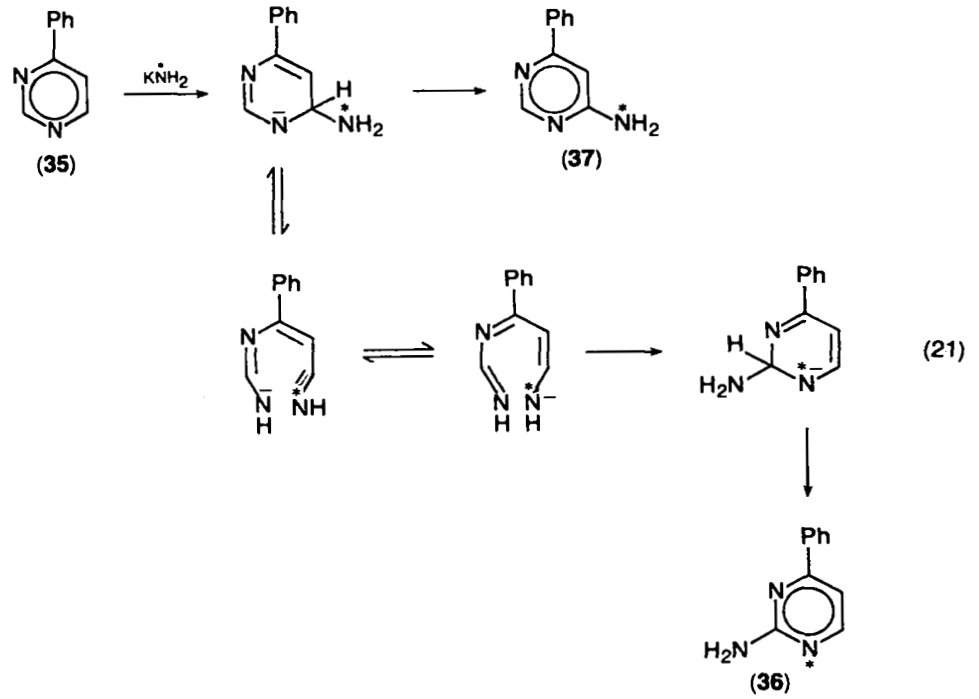


(20)

An elimination–addition mechanism which involves pyridines as intermediates has also been suggested[32]. It can however be ruled out since 3-alkylpyridines are aminated at position 2. Furthermore, no kinetic isotope effect has been detected on amination of deuterated pyridines[33].

Recently it has been found that like other nucleophilic substitutions by strong bases the Chichibabin reaction sometimes proceeds by the S_N(ANRORC) mechanism(Addition Nucleophilic Ring Opening Ring Closing)[34]. The detection of the occurrence of this mechanism is made by using ^{15}N-labelled potassium amide. An ANRORC process would lead to incorporation of ^{15}N in the ring, while according to other substitution mechanisms it would be present in the exocyclic

amino group. The amination of 4-phenylpyrimidine (**35**) gives both 2-amino-4-phenylpyrimidine (**36**, 60%) and 4-amino-6-phenylpyrimidine (**37**, 15%). The formation of **36** occurs almost exclusively via ring-opening while **37** is formed via the usual addition–elimination route[35] (equation 21).

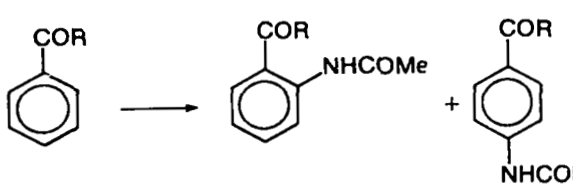


(21)

B. Amination by Nitriles

1. *In acidic media (The Ritter reaction)*

The use of the C—H linkage as carbonium ion source for the Ritter reaction[36] has been reported by Haaf[37]. Treatment of methylcyclohexane (**38**) with sulphuric acid, *t*-butanol (which serves as hydride acceptor) and HCN yields directly 23% 1-amino-1-methylcyclohexane (**39**) with some (3%) 2-methylcyclohexylamine

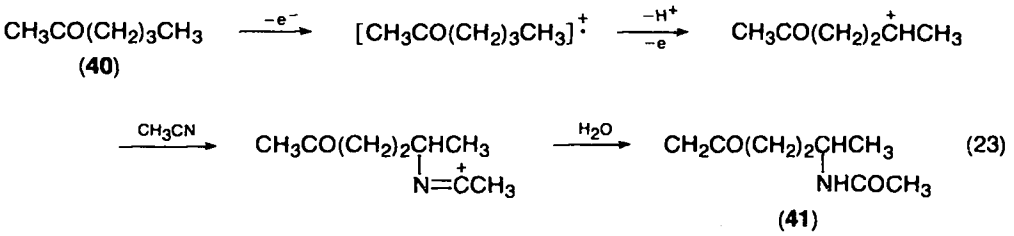


(equation 22). Several other tertiary hydrocarbons have been aminated in low yields. Good results have been achieved with adamantane, which affords 1-formylaminoadamantane in 78% yield.

2. Anodic acetamidation

Anodic oxidation of aromatic compounds to cations or cation radicals in acetonitrile makes them susceptible to nucleophilic attack by the solvent. Toluene is thus aminated at its methyl group[38] and anthracene at position 9 (82% yield)[39]. Benzenes carrying carbonyl substituents are aminated at the *ortho* and *para* positions (Table 3)[40]. This reaction is particularly useful since these substituents are usually *meta*-directing.

The anodic oxidation of aliphatic unbranched ketones in acetonitrile results in acetamidation at remote (γ,δ,ε) positions[41]. 2-Hexanone (**40**) yields 40% of 5-acetamido-2-hexanone (**41**), probably through the mechanism shown (equation 23). 2-Octanone gives a mixture of 5-acetamido (7%), 6-acetamido (30%) and



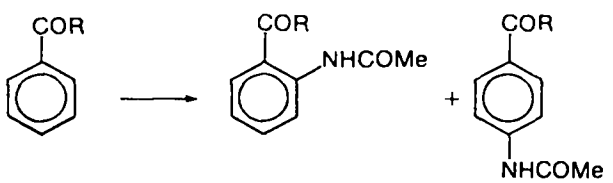
7-acetamido (21%) derivatives. Amination of α-branched ketones occurs with α-cleavage[49] and of β-branched with rearrangement.

C. Amination by Trichloramine

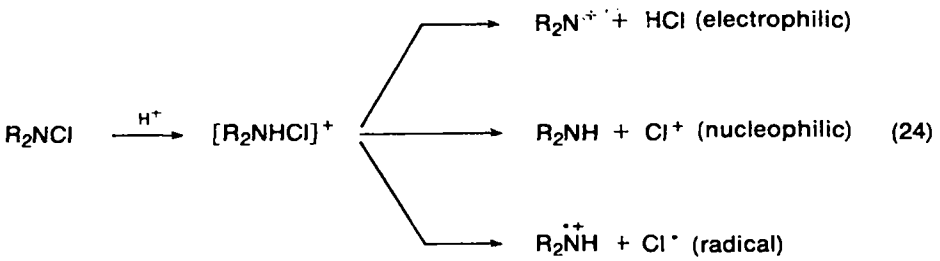
1. General

The direct amination by chloramine derivatives in acidic media can occur by three different aminating species via different mechanistic pathways (equation 24). The trichloramine–aluminium chloride system, extensively studied by Kovacic and his group[4], belongs to the nucleophilic category. This apparently unlikely interaction of

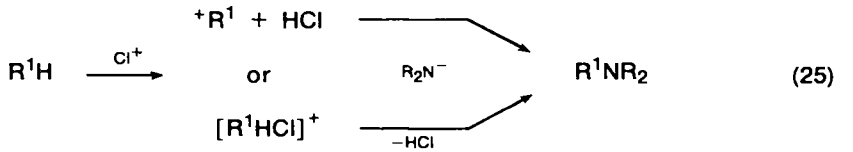
TABLE 3. Anodic acetamidation of monosubstituted benzenes



R	% *ortho*	% *para*
Me	70	24
i-Pr	52	23
OEt	18	14
OH	54	11

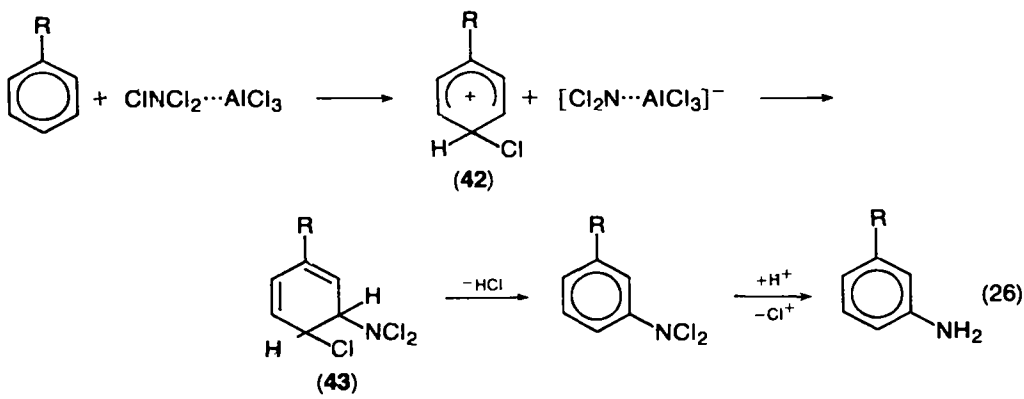


very weak electrophiles (hydrocarbons) and weak nucleophiles (chloramines) takes place in two stages, namely by an initial attack by Cl^+ and subsequent interaction of the highly reactive charged species formed (equation 25).



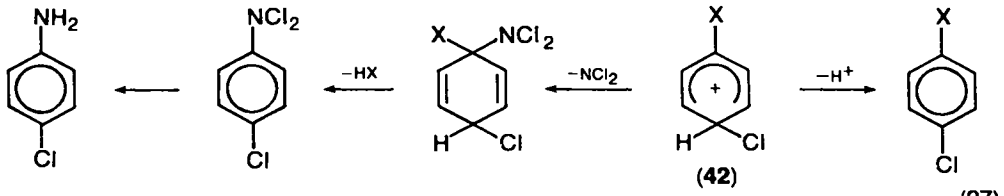
2. *Aromatic amination*

The significant feature of the aromatic amination by the NCl_3–$AlCl_3$ system is the unusual orientation. Toluene is directly converted, almost exclusively, to *m*-toluidine[43], *m*-xylene gives 3,5-dimethylaniline and *o*-xylene gives 2,3- and 3,4-dimethylanilines[44]. These results are well accommodated by an addition–elimination mechanism (σ-substitution) which involves the intermediacy of the chloroarenoium cation **42** and the dihydrobenzene **43** (equation 26).



A kinetic study of the amination of a series of alkylbenzenes and xylenes has confirmed this mechanism[45]. Additional evidence is the formation of products of competing processes which also involve the cation **42**. These include electrophilic substitution by Cl^+ which gives chloroarenes and nucleophilic σ-substitution (observed mainly on amination of halobenzenes) which gives chloroanilines[46] (equation 27). The amination by trichloramine provides a useful preparative method for 3-alkyl-[45] and 3,5-dialkyl-anilines[47], otherwise available by indirect multistep routes. The yields, however, are 30% or less.

Similar reactions have been carried out, less successfully, with related reagents. The amination of toluene with chloramine–aluminium chloride gives *m*-toluidine in

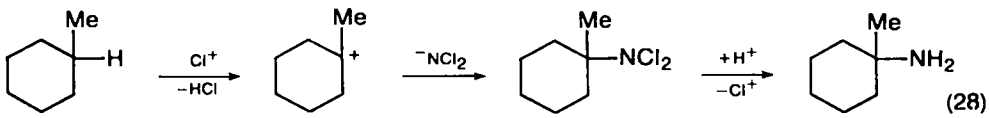


(27)

13% yield[48]; with *N,N*-dichloroalkylamines and *N*-chlorodialkylamines the yields of *m*-*N*-alkyl- and dialkyl-toluidine are even lower (< 5%). However, these reagents work very well through the radical pathway (see Section IV).

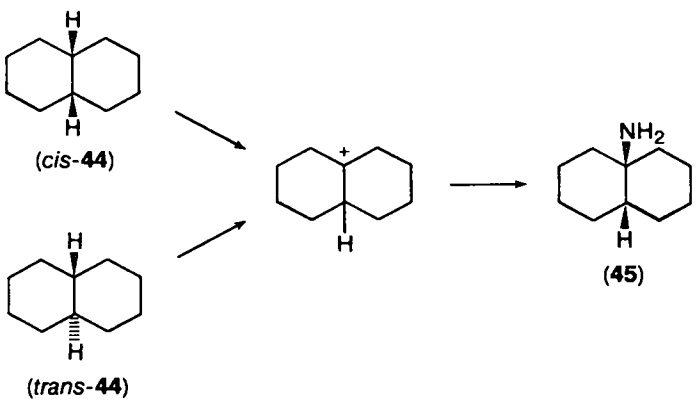
3. *Aliphatic amination*

The system trichloramine–aluminium chloride can also be used for the direct amination of tertiary alkanes. All the available evidence indicates that the reaction proceeds via initial hydride abstraction by the chloronium ion, to form a carbonium ion which subsequently couples with the nitrogenous anionic nucleophile. The first substrate studied was methylcyclohexane which afforded 1-amino-1-methylcyclohexane in 82% yield[50] (equation 28). The method has been extended



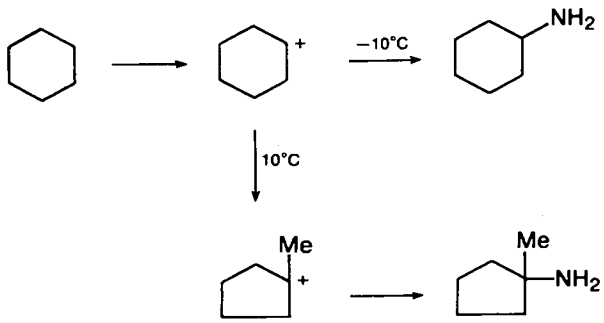
(28)

to include aminations of various cyclic hydrocarbons. Decalin (**44**) (either one stereoisomer or a mixture) gives stereospecifically *cis*-9-aminodecalin (**45**) (50%)[51] (equation 29) and norbornane gives *exo*-2-aminonorbornane (39%)[52]. The highest yields are obtained on the amination of adamantane and some derivatives[53].



(29)

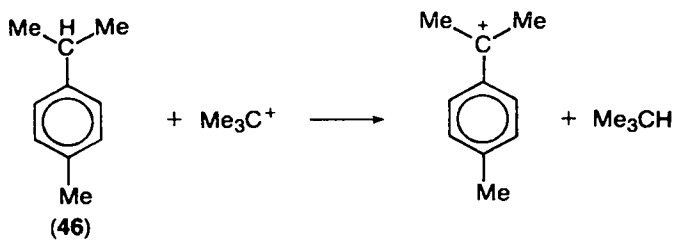
In many cases the aminations are accompanied by skeletal rearrangements or cleavages normally associated with carbonium ion reactions. Isobutane affords 82% yield of *t*-butylamine, which is also the major product from the reactions of higher acyclic alkanes[54]. With cycloalkanes ring-contractions are encountered, thus cycloheptane gives 1-amino-1-methylcyclohexane. Cyclohexane gives, in a temperature-dependent reaction, either cyclohexylamine or 1-amino-1-methylcyclopentane (equation 30)[51]. Tricyclic hydrocarbons, which are precursors of adamantane, give high yields of aminoadamantane[52].



(30)

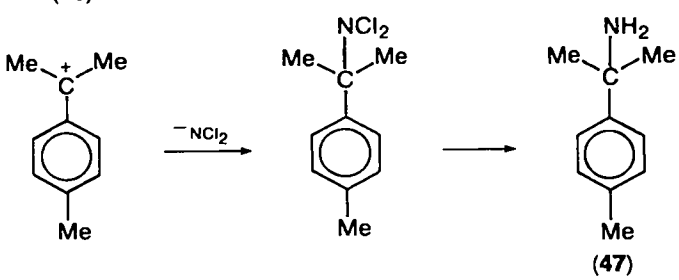
The amination of *p*-cymene (**46**) under the usual conditions gives a complex product mixture, resulting from attack on both the ring and the side-chain[55]. If however *t*-butyl bromide is added to act as hydride-transfer agent, carbonium ion formation is promoted and side-chain amination predominates. *p*-Cymene thus gives 80% yield of its 8-amino derivative (**47**)[56] (equations 31–33) and the method is used for the successful amination of a series of aryldialkylmethanes[57].

$$Me_3CBr + AlCl_3 \longrightarrow Me_3C^+ + [AlCl_3Br]^- \qquad (31)$$



(32)

(46)



(33)

(47)

IV. FREE-RADICAL AMINATION

A. With Alkylchloramine and Related Reagents

The homolytic cleavage of alkyl- and dialkyl-chloramine in acid media (equation 24) affords amino cation radicals (aminium radicals) which attack benzene rings to give directly the corresponding *N*-alkylated anilines.

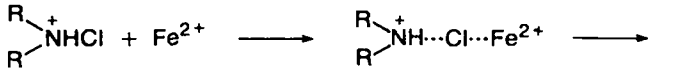
The radicals can be generated by photolysis[58], thermolysis[58] or a redox process (with reducing metal salts)[59] and aminations which utilize these three techniques have been described. The redox process seems to be the most practical, as it requires much shorter reaction times and milder conditions, thus side-reactions are minimal. Table 4 presents reaction conditions for reaction (34).

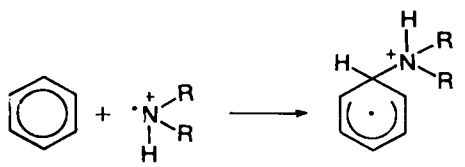
TABLE 4. Reaction conditions for reaction (34)

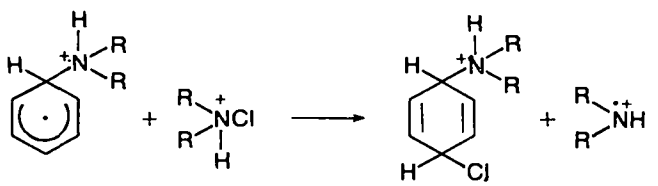
Technique	Time	Medium	Additive	Yield (%)	Reference
$h\nu$	15 h	conc. H_2SO_4	—	78	58
Δ(80°C)	8 h	conc. H_2SO_4	Na_2SO_4	56	58
Redox	20 min	H_2SO_4/CH_3COOH (3:1)	$FeSO_4$	76	60

$$C_6H_6 + ClNMe_2 \longrightarrow C_6H_5NMe_2 \quad (34)$$

A very extensive study of the redox amination has been carried out by Minisci and coworkers[61]. The mechanism suggested[62] involves the following steps: radical formation (equation 35), addition of the amino radical to the aromatic ring (equation 36), a chain-propagating step involving the addition of *N*-chloroamine to the aromatic radical (equation 37) and finally aromatization by elimination of HCl (equation 38). Termination of the chain-reaction most probably occurs by the reduction of the amino cation radicals by a metal salt (equation 39). The main


(35)


(36)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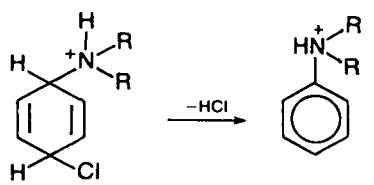
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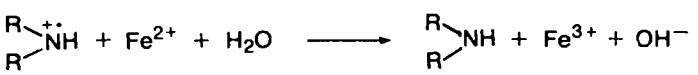

(39)

factors which influence the reaction are the following. An increase in the steric requirements of the reagent causes a decrease in the yields[63], thus the yield of *N*-phenylpiperidine (from benzene) is 51%, of diethylaniline 31% and of *N*-*n*-butyl-*N*-methylaniline 15%. Monoalkylanilines are consistently obtained in relatively low yields due to the instability of the reagents[64] (*N*-methylaniline, 60%). The activation and orientation effects of ring-substituents are the same as those well known for electrophilic attacks. Hydroxy, alkoxy and acylamino groups

TABLE 5. Direct dimethylamination of monosubstituted benzenes

Substituent	Technique	Yield (%)	Isomer distribution (%)		
			o	*m*	*p*
OMe	Redox	54	37	—	63
NHCOMe	Redox	93	Traces	—	~100
Br	Redox	45	21	4	75
Me	Redox	82	10	54	36
Me	*hν*	65	9	53	38
Me	Δ	83	9	53	38

activate the ring and orient to *ortho* and *para* positions. Halogens deactivate and cause the same orientation, while substituents such as $-NO_2$, —CN or —COR do not allow the reaction to occur. Alkyl substituents are an exception as they give a high proportion of *meta* substitution. The suggested interpretation is that radical substitution is sensitive to the inductive effects of the substituents, but not to the hyperconjugative effects. Side-reactions caused by substituents are electrophilic ring-chlorination and -sulphonation (in phenol and derivatives) and benzylic chlorination (in alkylbenzenes). Selected examples are given in Table 5. A full discussion and complete lists of reactions performed (up to 1973) can be found in Reference 61.

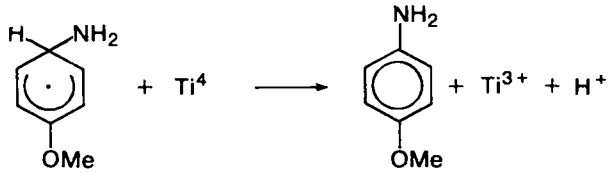
B. With Hydroxylamine and Derivatives

Hydroxylamine and hydroxylamino-*O*-sulphonic acid (HOS) can be reduced by metal salts to amino radicals which aminate benzene rings[59,65] (equations 40 and 41). The aminations with hydroxylamine proceed in very low yields (aniline from

$$NH_2OH + Ti^{3+} \longrightarrow H_2N^{\cdot} + Ti^{4+} + OH^- \quad (40)$$

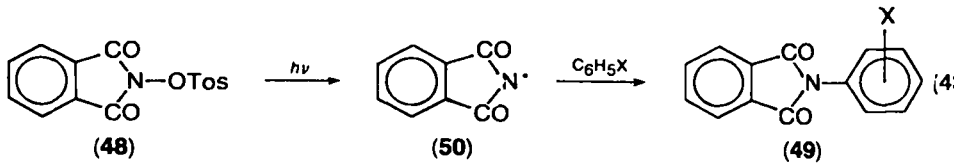
$$H_3\overset{+}{N}OSO_3^- + Fe^{2+} \longrightarrow H_3\overset{+}{N}^{\cdot} + Fe^{3+} + SO_4^{2-} \quad (41)$$

benzene ~5%). Electron-releasing substituents offer some improvement (anisole gives 19% *o*- and *p*-anisidines in a ratio of 37:63) probably due to the easier oxidative rearomatization of the cyclohexadienyl radical in these cases[61] (equation 42). With hydroxylamine-O-sulphonic acid amination yields are 10–40%.



(42)

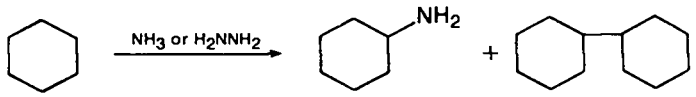
The photolysis of *N*-tosyloxyphthalimide (**48**) in solutions of aromatic substrates gives direct amination of the solvent[66]. In the case of anisole the pthaloylanisidine mixture (**49**, X = OMe) is obtained in quantitative yield, with a product ratio of *o:m:p* = 55:3:42. Other substituted benzenes are aminated in lower yields. The mechanism is an ordinary homolytic aromatic substitution by the radical **50** (equation 43).



(48) (50) (49) (43)

C. Photolytic Amination with Ammonia or Hydrazine

The photolyses of either ammonia[67] or hydrazine[68,69] in cyclohexane give cyclohexylamine and bicyclohexyl (equation 44). Both reactions proceed through initial formation of the amino radical (equations 45 and 46), subsequent generation of the cyclohexyl radical (equations 47 and 48) and radical couplings (equations 49 and 50). Yields up to 45% have been reported for the hydrazine reaction[68].



(44)

$$NH_3 \xrightarrow{h\nu} {}^{*}NH_3 \longrightarrow H_2N^{\cdot} + H^{\cdot} \quad (45)$$

$$H_2NNH_2 \xrightarrow{h\nu} H_2NNH_2^{*} \longrightarrow 2\ H_2N^{\cdot} \quad (46)$$

$$C_6H_{12} + H_2N^{\cdot} \longrightarrow C_6H_{11}^{\cdot} + NH_3 \quad (47)$$

$$C_6H_{12} + H^{\cdot} \longrightarrow C_6H_{11}^{\cdot} + H_2 \quad (48)$$

$$C_6H_{11}^{\cdot} + H_2N^{\cdot} \longrightarrow C_6H_{11}NH_2 \quad (49)$$

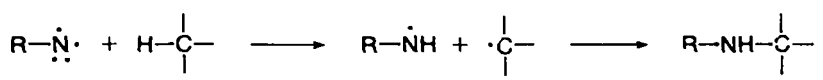
$$2\ C_6H_{11}^{\cdot} \longrightarrow C_6H_{11}{-}C_6H_{11} \quad (50)$$

V. MISCELLANEOUS AMINATIONS

A. Nitrene Insertion into C—H Bonds

1. *Aliphatic insertion*

The insertion of nitrenes into a C—H bond to form substituted or protected amines is one of the most characteristic nitrene reactions and has been comprehensively described and discussed in reviews on nitrene chemistry[70]. Mechanisms which involve triplet nitrenes (through hydrogen abstraction and radical coupling, equation 51) and singlet nitrenes (through one-step insertion, equation 52) have been suggested. The yields of cyclohexylamine derivatives



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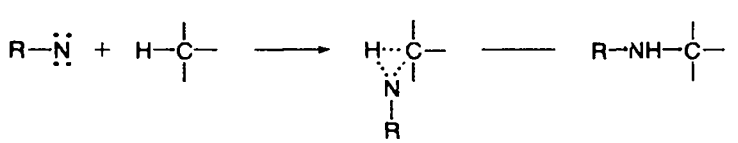
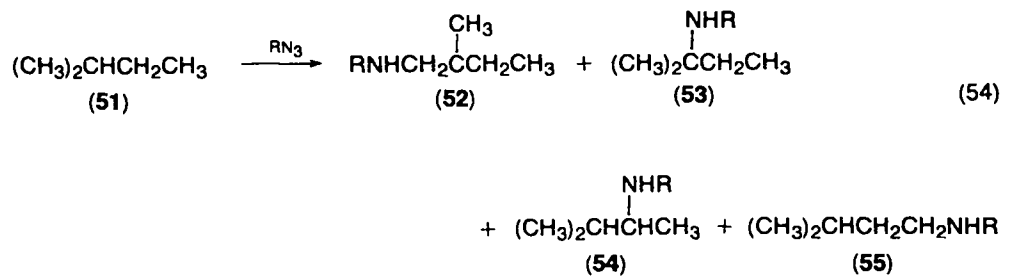


(52)

(53)

obtained from various azides (via nitrenes) and cyclohexane (equation 53) are compared in Table 6. Other nitrene reactions which compete and lower the intermolecular insertion yields are rearrangements, hydrogen abstraction and internal insertions. The synthetic usefulness of the reaction is also limited by the low selectivity. For example the reaction of 2-methylbutane (**51**) affords a mixture of the four possible products (**52–55**). The order of reactivity of C—H bonds is



(54)

always tertiary > secondary > primary. The selectivity is decreased on increase in the nitrene reactivity and is also influenced by steric effects in the substrate (Table 7).

The most studied nitrene source is ethyl azidoformate which furnishes the ethoxycarbonyl nitrene. Its insertion was shown to be a reaction of the singlet state, since amination of an optically active tertiary carbon (in 3-methylhexane) proceeds with complete retention of configuration[80]. Solvents which stabilize the singlet state, such as methylene chloride[83,84] or hexafluorobenzene[76] improve the yields.

Selective insertion can also be caused by functional groups present in the substrate. For example, it has been found that cyclic[85] and acyclic[86] ethers are aminated almost exclusively at their α-position. A mechanism which involves initial electrophilic attack of singlet nitrene on the oxygen (equation 55) has been proposed. Tetrahydrofuran is thus converted to **56** (25%) and diethyl ether to **57** (31%) by photolysis of ethyl azidoformate.

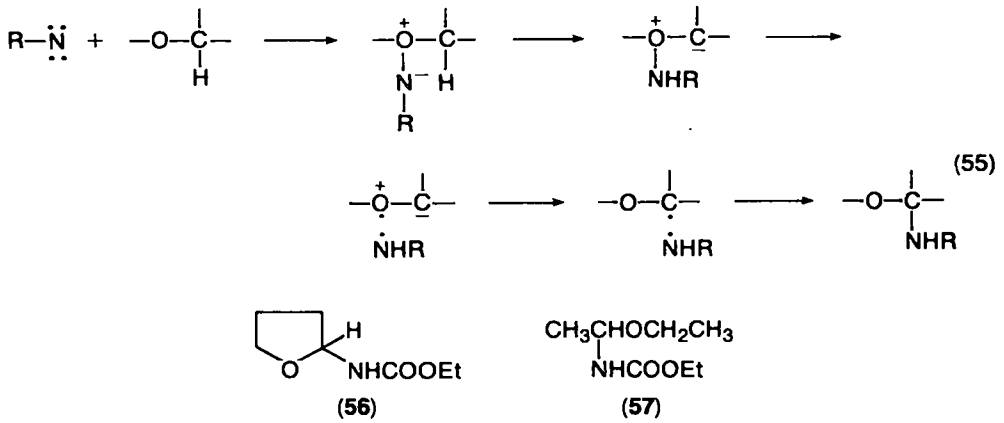
TABLE 6. Examples of reaction (53)

R	Mode of decomposition	Yield (%)	Reference
Me	Thermal	0.4	71
Ph	Thermal	8	72
EtOOC—	Photochemical	51	73
		78	74
EtOOC—	Thermal	52	75
EtOOC—	Thermal + C_6F_6[a]	76	76
p-$MeC_6H_4S(O_2)$—	Thermal	58	77
		17	71
$(EtO)_2P(O)$—	Photochemical	88	78

[a]Singlet stabilizer, see text.

TABLE 7. Relative reactivities of C—H bonds (after statistical correction) in nitrene insertion

Nitrene	Substrate	Type of C— H bond			Reference
		Tertiary	Secondary	Primary	
PhN	2-Methylbutane	140–280	7	1	72
EtOCN	2-Methylbutane	34	9	1	79
EtOCN	3-Methylhexane	17.6	6.2	1	80
EtOCN	2,4-Dimethylpentane	12	4.7	1	81
CH_3SO_2N	2-Methylbutane	9.6	4.2	1	82
CH_3SO_2N	2,4-Dimethylpentane	5.8	2.2	1	81
$(EtO)_2PN$	2-Methylbutane	6	4.3	1	78

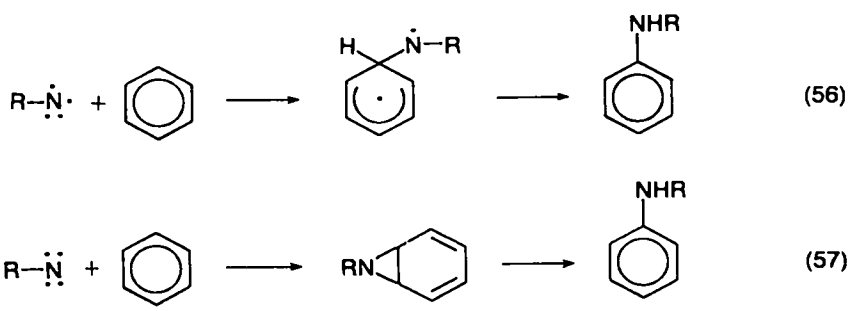


(55)

(56) (57)

2. *Aromatic insertion*

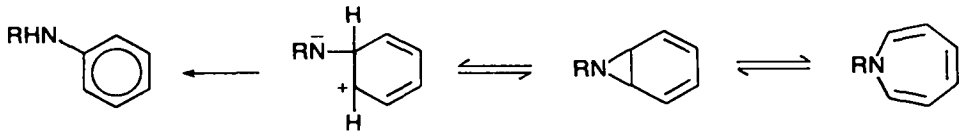
Aromatic amination by nitrenes can result from homolytic substitution by triplet nitrenes (equation 56) or addition by singlet nitrenes (equation 57).



(56)

(57)

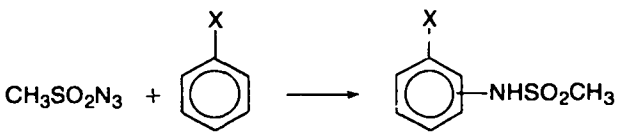
The decompositions of azidoformates and of sulphonyl azides in aromatic solvents are singlet reactions[87]. The aziridine **58** can undergo either valence-bond isomerization to the azepine **59** or ring-opening to the dipolar intermediate **60** (equation 58). In practice ethoxycarbonylnitrene gives mainly azepines[88]



(60) (58) (59)

(58)

while sulphonylnitrenes give sulphonylanilines. However, the formation of sulphonylazepine, a product of kinetic control, has been detected by trapping[89]. The utilization of sulphonyl azides for the direct sulphonylamination of benzene rings was first studied by Curtius and coworkers. *N*-Tosylaniline was obtained from benzene in 85% yield[90]. A table and references are given in Reference 97. More recent work deals mainly with mechanistic aspects. It has been established that the addition is slightly accelerated by electron-releasing substituents and that the ring substituents determine the product distribution by controlling the direction of ring-opening of the aziridine[87]. Rings carrying electron-withdrawing substituents are aminated in low yields, probably by triplet action[91] (equation 56). Results of the thermal decomposition of methanesulphonyl azide in monosubstituted benzenes (equation 59) are given in Table 8.



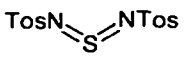
(59)

B. Allylic Amination by Imido-sulphur and -selenium Compounds

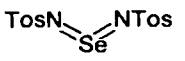
The direct introduction of amino groups (protected as the *N*-tosyl derivatives) into allylic positions of olefins and acetylenes is completely analogous to the allylic oxidation by selenium dioxide. It can be effected by reagents such as bis(*N*-tosyl)sulphodiimide (**61**)[92,93] and bis(*N*-tosyl)selenodiimide (**62**)[94], and very likely occurs via the same sequence of 2,3-sigmatropic and ene reactions which was

TABLE 8. Products of reaction (59)[91]

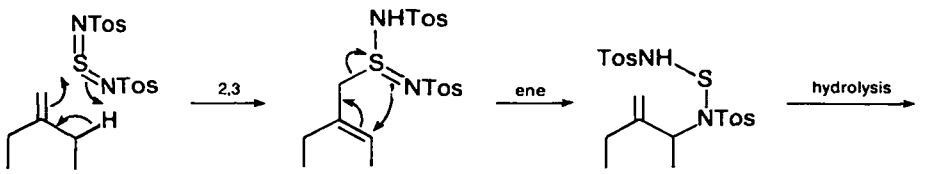
X	Yield (%)	Total rate ratio	Isomer distribution (%)		
			o	*m*	*p*
H	55	1			
Me	77	1.86	65.4	2.4	32.2
OMe	70	2.54	55.5	1.2	43.3
Cl	65	0.44	57.4	0.9	41.7
COOMe	21	0.30	64.3	34.4	1.3
NO_2	5	—	55.4	13.4	31.2
CN	5	—	68.9	31.1	—
CF_3	25	0.07	53.0	46.1	0.9



(61)



(62)

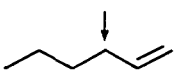
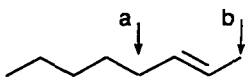
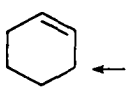
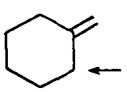
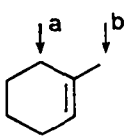
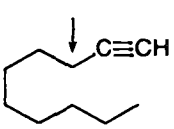


(60)

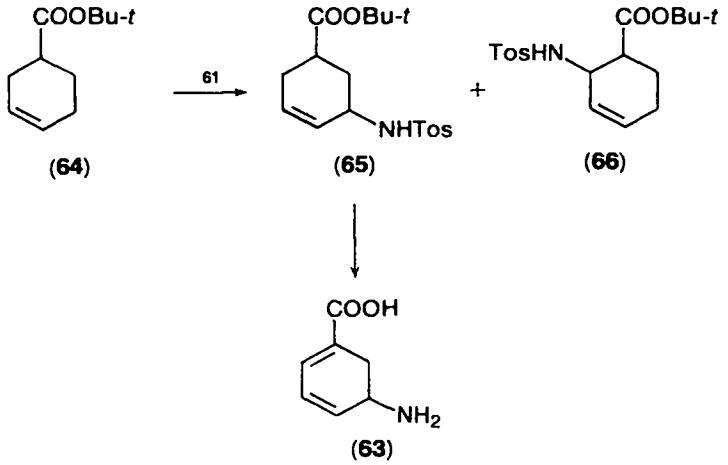
established previously for the oxidation (equation 60). A few examples are given in Table 9.

The potential synthetic utility of this amination method has been demonstrated by Sharpless in a synthesis of gabaculine (**63**)[95]. Amination of cyclohexene-3-carboxylic acid (**64**) is the key step and yields (70%) both **65** and **66** in a ratio of 3:1, the positional selectivity being caused by the steric effects of the

TABLE 9. Allylic aminations

Substrate and position aminated	Yield (%)	
	With **61**[92]	With **62**[94]
	45	54
	a:56, b:3	a:51, b:11
	70	45
	84	74
	a:38, b:33	a:35, b:20
	37	23

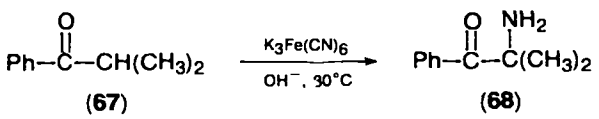
t-butyl group. Electrochemical removal of the tosyl group, introduction of the second double bond and hydrolysis of the ester complete the synthesis (23% overall yield) (equation 61).



(61)

C. Oxidative Amination of Ketones

Treatment of certain ketones with alkaline ferricyanide gives moderate yields of α-aminoketones[96]. The reaction is specific, occurring only at enolizable tertiary α-positions. Isopropyl phenyl ketone (**67**) for example, yields 51% of **68** (equation 62). The mechanism and the actual nitrogen source remain obscure, however the precursor of the source must by the cyanide, since it is the only nitrogenous entity in the reaction.



(67) (68) (62)

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **12**

Pyrolysis of nitrites, nitrates, nitro compounds, nitroso compounds and amines

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I. INTRODUCTION

Because these compounds were reviewed last in 1972[11], the detailed literature survey for this review was confined to the period from 1970 up to the present. However, other references are included either out of interest, or because they had been omitted earlier, or because the interpretation was either unknown or incorrect at the time of writing.

The compounds are dealt with in the order nitrites, nitrates, nitro compounds, nitroso compounds and amines. The decomposition reactions of nitrites, nitrates, nitro compounds and nitroso compounds are closely linked, with the mechanism for the decomposition of nitrites being superimposed upon both that for nitrates and nitro compounds, and that for nitrates upon nitro compounds. The reactions of nitroso compounds are also important in these systems. The chemistry of both nitric oxide and nitrogen dioxide is important in kinetic studies because the first is used as an inhibitor and the second is a powerful sensitizer. Both nitrites and *C*-nitroso compound dimers can exist in *cis* and *trans* forms. Nitrates and nitro compounds have important explosive properties. Although not very much work has been

carried out on amines, they are of potential importance since they may play a critical role in the chemistry of biological systems especially after the interaction of radiation. Also, compounds such as nitrosamines have known carcinogenic properties.

When considering the pyrolysis of these compounds two modes of reaction are possible: a free-radical split or a molecular elimination process. In terms of a thermochemical formulation of the transition state theory, the preexponential factor (A) for a unimolecular process is given by $A = (ekT_m/h)e^{\Delta S^{\neq}/R}$ where T_m is the mean temperature and $\Delta S^{\neq}$ is the entropy of activation. If A is $10^{15-17}\ s^{-1}$, $\Delta S^{\neq}$ is both large and positive, indicating a radical split. If A is $10^{11-13}\ s^{-1}$, $\Delta S^{\neq}$ is small or negative, indicating a cyclic transition state and therefore a molecular elimination process. Alternatively a low A factor might indicate the presence of a heterogeneous or chain process. For the free-radical split the activation energy (E) is related to the bond dissociation energy D by the relationship $D = E + RT_m = \Delta H^{\ominus}_{T_m}$.

II. ALKYL NITRITES

Subsequent to the development of the Lindemann theory for unimolecular reactions[1], molecules such as ethers and alkyl nitrites (RONO) were used as examples to test the theory. However, Rice and Herzfeld suggested that many of the supposed unimolecular reactions were in fact free-radical chain process[2]. (It took until 1956 for Benson to show that the decomposition of dimethyl ether was a free-radical chain process[3].) Alkyl nitrites are very suitable compounds for such tests because they are easily prepared and handled. (There is one drawback in that inhalation of their vapours causes headaches so that manipulation in a fume-cupboard is obligatory.) In addition, their pyrolysis leads to the production of nitric oxide, a powerful radical trap, so that sensitized decomposition of the alkyl nitrite is limited, but this leads to a disadvantage which will be referred to later. Current interest is in terms of their being clean sources of alkoxy radicals (thermal and photochemical) and alkyl radicals (thermal). Most of the work described here is confined to the gas phase. Relatively little work has been carried out in the liquid phase presumably because the RO—NO bond strength is only 41 ± 1 kcal/mole (171 ± 4 kJ/mole)[4,5]. This normally confines studies to temperatures above the boiling points of both the nitrites and typical solvents.

Early work has been reviewed by Szwarc[6], Steacie[7], Gray and Williams[8], Benson[9], Gray, Shaw, and Thynne[10] and Strausz, Lown and Gunning[11]. The consensus of opinion is that the thermal decomposition is initiated by the breaking of the RO—NO bond[64]:

$$RONO \longrightarrow R\dot{O} + NO \qquad (1)$$

For tertiary alkyl nitrites such as t-butyl nitrite[12], this step is followed by the decomposition of the alkoxy radical and combination reactions of the alkyl radical produced in reaction (3) and nitric oxide:

$$t\text{-BuONO} \longrightarrow t\text{-Bu}\dot{O} + NO \qquad (1a)$$

$$t\text{-Bu}\dot{O} + NO \longrightarrow t\text{-BuONO} \qquad (2)$$

$$t\text{-Bu}\dot{O} \longrightarrow \dot{M}e + Me_2CO \qquad (3)$$

$$\dot{M}e + \dot{M}e \longrightarrow C_2H_6 \qquad (4)$$

$$\dot{Me} + NO \longrightarrow MeNO \quad (5)$$

Clear evidence for the inhibiting step (2) has been given by Levy[13]. Conversely, no evidence is available for hydrogen atom abstraction from *t*-butyl nitrite by either of the radicals (R) produced in steps (1) and (3) although the product acetone probably is involved in such processes[13]:

$$\dot{R} + Me_2CO \longrightarrow RH + MeCO\dot{C}H_2$$

For primary and secondary alkyl nitrites, the alkoxy radicals that are produced have α-hydrogen atoms adjacent to the oxygen atom. This allows the extra step, disproportionation, to take place between the alkoxy radical and nitric oxide:

$$R\dot{O} + NO \longrightarrow RO_{-H} + HNO \quad (6)$$

One of the fates of the nitroxyl molecule (HNO) is bimolecular interaction via an unknown mechanism to form both water and nitrous oxide:

$$2\,HNO \longrightarrow H_2O + N_2O \quad (27)$$

As the H—NO bond strength is only 50 kcal/mol (209 kJ/mol)[14] nitroxyl may also take part in abstraction reactions such as[16]:

$$R\dot{O} + HNO \longrightarrow ROH + NO \quad (7)$$

For nitrites such as *i*-propyl nitrite, it is likely that the similar abstraction reaction (8)[15] will take place, although it is difficult to come to unequivocal conclusions since the same products arise from different reactions:

$$i\text{-}Pr\dot{O} + i\text{-}PrONO \dashrightarrow i\text{-}PrOH + Me_2\dot{C}ONO \quad (8)$$

$$Me_2\dot{C}ONO \longrightarrow Me_2CO + NO$$

Clearly the decomposition mechanisms can become complex at large extents of reaction and with high pressures of nitrites. The abstraction reaction (8) has been shown to be important in the liquid phase[17–19]. In suitable solvents (R′H), hydrogen atom abstraction is a dominant process[18,20–22]:

$$R\dot{O} + R'H \longrightarrow ROH + \dot{R}' \quad (9)$$

This also demonstrates quite clearly the production of alkoxy radicals.

Clear evidence for the production of nitric oxide, reaction (1), and nitrous oxide, reactions (6) and (27), has also been obtained. It has also been shown that nitrogen is produced in both decomposition phases. The origin of this product is not so clear. Christie and coworkers have shown that multiple addition of nitric oxide to methyl radicals can lead to the production of both nitrogen and nitrogen dioxide[23]:

$$\dot{Me} + NO \longrightarrow MeNO \quad (5)$$

$$MeNO + NO \longrightarrow Me\overset{NO}{\underset{|}{N}}\dot{O} \quad (10)$$

$$Me\overset{NO}{\underset{|}{N}}\dot{O} + NO \longrightarrow MeN(NO)_2 \quad (11)$$

$$\mathrm{MeN(NO)ONO} \longrightarrow \mathrm{N_2} + \dot{\mathrm{N}}\mathrm{O_3} + \dot{\mathrm{M}}\mathrm{e} \qquad (12)$$

$$\dot{\mathrm{N}}\mathrm{O_3} + \mathrm{NO} \longrightarrow 2\,\mathrm{NO_2} \qquad (13)$$

A similar mechanism has been invoked for nitrogen and nitrogen dioxide production involving the nitroxyl molecule (HNO)[46–48].

Gray, Rathbone and Williams have suggested that in the pyrolysis of benzyl nitrite[22], the following reaction is responsible for the production of nitrogen:

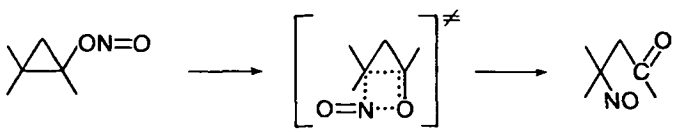
$$\mathrm{Ph\dot{C}O} + \mathrm{N_2O} \longrightarrow \mathrm{Ph\dot{C}O_2} + \mathrm{N_2} \qquad (14)$$

One other reaction is thought to be important in the pyrolysis of nitrites. This involves a displacement process with methyl radicals such as:

$$\dot{\mathrm{M}}\mathrm{e} + t\text{-BuONO} \rightleftharpoons t\text{-BuO}\overset{\mathrm{Me}}{\underset{|}{\mathrm{N}}}\dot{\mathrm{O}} \longrightarrow t\text{-Bu}\dot{\mathrm{O}} + \mathrm{MeNO} \qquad (15)$$

Reaction (15) is essentially thermoneutral. Kharasch, Metzer and Nudenberg explained the production of nitrosomethane from the pyrolysis of diacetyl peroxide in 2-butyl nitrite and 3-amyl nitrite in this way[24], and Gray[25], Gray and Rathbone[26] and Jest and Phillips[27] subsequently invoked this mechanism in the pyrolysis of alkyl nitrites.

Cyclopropoxynitrites decompose at very low temperatures (−80 to +20°C) compared to normal aliphatic nitrites[28]. It appears that pyrolysis involves ring-opening and isomerization of the nitrite to a nitroso compound via a four-centre transition state:



(16)

This reaction probably involves the *cis* form of the nitrite. One other conclusion is that cyclopropoxy radicals are not formed from these nitrites, contrary to the title of the paper[28].

Kuhn and DeAngelis pyrolysed four vicinal dinitrites[29]. In the vapour phase propane-1,2-dinitrite produced formaldehyde, acetaldehyde and nitric oxide in 87% yield, butane-2,3-dinitrite produced acetaldehyde (88%) and nitric oxide (98%), and *cis*- and *trans*-cyclohexane-1,2-dinitrite produced adipic aldehyde and nitric oxide (>70%). The following stoichiometric equation accounts for the major products:

$$\mathrm{RCH(ONO)CH(ONO)R} \longrightarrow 2\,\mathrm{NO} + 2\,\mathrm{RCHO} \qquad (17)$$

The mechanism is probably:

$$\mathrm{RCH(ONO)CH(ONO)R} \longrightarrow \mathrm{RCH(ONO)CH(\dot{O})R} + \mathrm{NO} \qquad (18)$$

$$\mathrm{RCH(ONO)CH(\dot{O})R} \longrightarrow \mathrm{R\dot{C}HONO} + \mathrm{RCHO} \qquad (19)$$

$$\mathrm{R\dot{C}HONO} \longrightarrow \mathrm{RCHO} + \mathrm{NO} \qquad (20)$$

These look like clean reactions. The liquid-phase decomposition of butane-2,3-dinitrite is more complex. This is because reaction (21) is involved:

$$RCH(ONO)CH(\dot{O})R + (RCHONO)_2 \longrightarrow RCH(ONO)CH(OH)R + R\dot{C}(ONO)CH(ONO)R \quad (21)$$

$$RCH(ONO)CH(OH)R \longrightarrow RCH(\dot{O})CH(OH)R + NO \quad (22)$$

$$RCH(\dot{O})CH(OH)R + (RCHONO)_2 \longrightarrow (RCHOH)_2 + R\dot{C}(ONO)CH(ONO)R \quad (23)$$

The fate of the fragment $R\dot{C}(ONO)CH(ONO)R$ is unknown but it appears that the final product is $(RCO)_2$. The following mechanism is speculative:

$$R\dot{C}(ONO)CH(ONO)R \longrightarrow RC(O)CH(ONO)R + NO \quad (24)$$

$$RC(O)CH(ONO)R \longrightarrow RC(O)CH(\dot{O})R + NO \quad (25)$$

$$RC(O)CH(\dot{O})R + NO \longrightarrow (RCO)_2 + HNO \quad (26)$$

$$2\,HNO \longrightarrow H_2O + N_2O \quad (27)$$

Nonvicinal dinitrites follow different modes of decomposition[30]. In the gas phase for propane-1,3-, butane-1,3- and pentane-2,4-dinitrites, the steps are:

$$RCH(ONO)CH_2CH(ONO)R \longrightarrow RCH(\dot{O})CH_2CH(ONO)R + NO \quad (28)$$

$$RCH(\dot{O})CH_2CH(ONO)R \longrightarrow RCHO + \dot{C}H_2CH(ONO)R \quad (29)$$

$$\dot{C}H_2CH(ONO)R \longrightarrow CH_2CHR + NO_2 \quad (30)$$

The second nitrite group thus breaks at the O—C bond instead of the O—N bond. Butane-1,3-dinitrite can decompose by two different routes. If the primary O—NO bond breaks first the products are:

$$MeCH(ONO)CH_2CH_2\dot{O} \longrightarrow CH_2O + NO_2 + MeCH{=}CH_2 \quad (31)$$

If the secondary O—NO bond breaks first the products are:

$$MeCH(\dot{O})CH_2CH_2ONO \longrightarrow MeCHO + NO_2 + CH_2CH_2 \quad (32)$$

The relative rates of reactions (31) and (32) are given by $R_{31}/R_{32} \sim 14$, indicating that the secondary O—NO is weaker than the primary by ~3 kcal/mol (12 kJ/mol). This is quite contrary to the situation found for mononitrites. In mineral oil solution, the decomposition of propane-1,3-dinitrite differs from the gas phase in that the breaking of the O—NO bonds is followed by hydrogen atom abstraction from the solvent to form the diol:

$$CH_2(ONO)CH_2CH_2\dot{O} + RH \longrightarrow CH_2(ONO)CH_2CH_2OH + \dot{R} \quad (33)$$

$$CH_2(\dot{O})CH_2CH_2OH + RH \longrightarrow CH_2(OH)CH_2CH_2OH + \dot{R} \quad (34)$$

Butane-1,4- and hexane-2,5-dinitrites involve isomerization of the alkoxy radical. For example, the former yields γ-hydroxybutyraldehyde. This product may be formed via a six-membered ring transition state:

$$\dot{O}(CH_2)_4ONO \longrightarrow \left[\begin{array}{l} H_2C\overset{O\cdots H}{\diagup\quad\diagdown}CHONO \\ H_2C\diagdown\ \diagup C \\ \qquH_2 \end{array}\right]^{\neq} \longrightarrow NO + HO(CH_2)_3CHO \quad (35)$$

The fact that neither diol nor dialdehyde is formed provides strong evidence for *intra*molecular hydrogen atom transfer. This provides rather more tangible evidence for isomerization of alkoxy radicals via six-membered ring transition states. The latter have been suggested to be important in photochemical smog chemistry under some conditions[31,32]. Interestingly, when no α-hydrogen atom is available on the alkoxy-radical-containing carbon atom, i.e. for tertiary alkoxy radicals, hydrogen atom transfer or isomerization does not take place. Thus for 2,5-dimethylhexane-2,5-dinitrite, the products are acetone and ethene:

$$Me_2C(ONO)(CH_2)_2C(ONO)Me_2 \longrightarrow Me_2CO + Me_2C(ONO)(CH_2)_2^{\cdot} + NO \quad (36)$$

$$Me_2C(ONO)(CH_2)_2^{\cdot} \longrightarrow Me_2\dot{C}ONO + C_2H_4 \quad (37)$$

$$Me_2\dot{C}ONO \longrightarrow Me_2CO + NO \quad (38)$$

Decomposition of the alkoxy radical produced from pentane-1,5-dinitrite also involves a six-membered ring transition state:

$$ONO(CH_2)_5\dot{O} \longrightarrow \left[\begin{array}{c} C \\ C \quad C \\ O \cdots H \cdots C \cdots O \cdots NO \end{array}\right]^{\neq} \quad (39)$$

$$\downarrow$$

$$NO_2 + CH_2{=}CH(CH_2)_3OH$$

The product pentenol demands a six-membered ring precursor rather than the seven-membered ring involving an α-hydrogen atom transfer. The six-membered ring is presumably favoured on energetic grounds. The decomposition of hexane-1,6-dinitrite yields nitric oxide and 6-hydroxyhexene. If this product involved isomerization of the alkoxy radical, the transition state would involve an eight-membered ring which seems unlikely.

The bond-breaking process, reaction (1), has been associated with the rate-determining step. Sometimes a factor of two is introduced depending upon whether it is thought that step (1) is followed by (8)[15] or (7)[16] or (3) and combination reactions of the alkyl radicals and nitric oxide. The early work, based almost entirely on pressure measurements, showed that the processes were first-order processes with only minor heterogeneous contributions. The results are shown in Table 1. The mean values for the Arrhenius parameters are $E_1 = 36.1 \pm 1.4$ kcal/mol (151 ± 6 kJ/mol) and $\log(A_1/s^{-1}) = 13.5 \pm 0.8$. There are two objections to these values. First, on the assumption that process (2a) has zero activation energy:

$$RONO \longrightarrow R\dot{O} + NO \quad (1)$$

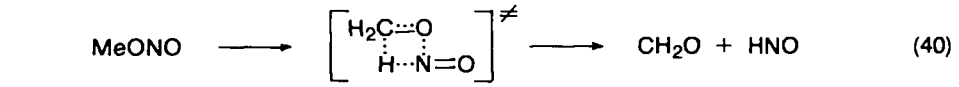
$$R\dot{O} + NO \longrightarrow RONO \quad (2a)$$

E_1 is associated with the RO—NO bond dissociation energy[6,8]. Recent thermochemical measurements have shown that D(RO—NO) = 41 ± 1 kcal/mol (171 ± 4 kJ/mol)[4,5], incompatible with the above. Second, in terms of the transition-state theory and a thermochemical formulation $A_1 = (ekT_m/he_1^{\Delta S^{\neq}/R})$. Since

TABLE 1. Arrhenius parameters for the pyrolysis of nitrites (RONO)

R	E (kcal/mol)	E (kJ/mol)	$\log(A/s^{-1})$	Reference
Me	36.4	152	13.3	33
	36.4	152	—	34
	37.0	155	13.6	35
	34.3	144	12.2	16
	34.0	142	12.9	36
Et	37.7	158	14.1	37
	34.3 ± 3	144 ± 13	—	38
	37.5	157	13.8	39
	37.0	155	14.7	40
n-Pr	37.7	158	14.4	41
	34.7	145	13.0	42
i-Pr	37.0	155	14.1	43
n-Bu	36.0	151	13.0	44
	37.0	155	14.5	45
$PhCH_2$	34.0 ± 2	142 ± 8	12.4 ± 2	22

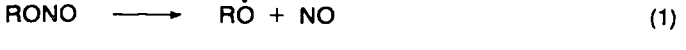
at the mean temperature (T_m) of the kinetic studies (450 K) ekT_m/h is $10^{13.8}$ s^{-1}, this implies that $\Delta S_f^{\neq} \sim 0$, or, worse, negative. This is completely untenable for such a bond-breaking process[49], and leads to the suggestion that there is a participation from an elimination process involving a cyclic transition state[16,50]:



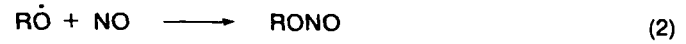
(40)

The participation of such a reaction would reduce both the observed preexponential factor and activation energy as opposed to that expected for a bond-stretching and breaking process[50].

Batt and coworkers have studied the decomposition of a number of alkyl nitrites under conditions where the initial step (1) could be isolated[11,51–58]. This was achieved by using small concentrations of nitrite (~10^{-4} M) and low extents of reaction (~1%). Under these conditions and in the presence of high concentrations of inert gas (carbon tetrafluoride, ~1 atm), $k_3 \gg k_2[NO]$ and the carbonyl compound produced in reaction (3) was a direct measure of the rate of process (1):



(1)



(2)

(3a)

In the presence of large amounts of nitric oxide (1 atm) the products in reaction (3a) were almost completely suppressed thus verifying the mechanism. For methyl nitrite, the methoxy radical produced in step (1) could not be persuaded to decompose because the activation energy was too high[60]. Here a C—H bond would have to be broken, as opposed to a C—C bond in the other alkoxy radicals. In this case the inert gas carbon tetrafluoride was replaced by isobutane (*t*-BuH) and virtually every methoxy radical produced in reaction (1) was converted to methanol (9a):

TABLE 2. Kinetic and thermodynamic data for the pyrolysis of alkyl nitrites (RONO)

$$RONO \longrightarrow R\dot{O} + NO \quad (1)$$

R	$\log(A_1/s^{-1})$	E_1 (kcal/mol)	E_1 (kJ/mol)	$\Delta H_1^{\ominus}$ (kcal/mol)	$\Delta H_1^{\ominus}$ (kJ/mol)	Reference
Me	15.9 ± 0.4	41.3 ± 0.8	173 ± 3	41.4 ± 0.5	173 ± 2	52
Et	16.0 ± 0.4	41.8 ± 0.9	175 ± 4	41.6 ± 1.3	174 ± 5	53
i-Pr	16.2 ± 0.4	41.0 ± 0.8	172 ± 3	41.6 ± 0.8	174 ± 3	54
n-Bu	16.5	41.0	172	—	—	57
s-Bu	16.2 ± 0.4	40.9 ± 0.8	171 ± 3	40.8 ± 1	171 ± 4	56
t-Bu	16.3 ± 0.4	40.3 ± 0.8	167 ± 3	41.0 ± 0.9	172 ± 4	12
	15.8	39.3	164	—	—	58
	16.4 ± 0.5	42.8 ± 1	179 ± 4	—	—	59
t-Am	16.3 ± 0.1	40.3 ± 0.1	167 ± 0.4	40.8 ± 1.3	171 ± 5	56
CF_3CO	14.3 ± 0.2	33.8 ± 0.4	141 ± 2	—	—	63

$$Me\dot{O} + t\text{-}BuH \longrightarrow MeOH + t\text{-}B\dot{u} \quad (9a)$$

Thus the yield of methanol was a direct measure of reaction (1). In all cases the rate of reaction was both homogeneous and first order. Thermochemical and kinetic data for the alkyl nitrites are given in Table 2. The values for $(E_1 + RT)$ and $\Delta H_1^{\ominus}$ are identical, within experimental error, and both may be identified with the RO—NO bond dissociation energy. This means that the value of E_2 is 0 ± 1 kcal/mol (0 ± 4 kJ/mol). Another feature of this study is that the values for the preexponential factors, $A_1 = 10^{16.1\pm0.3}$ s^{-1}, are acceptably much higher than those previously quoted. (For methyl nitrite, at least, clear evidence was provided for the pressure dependence of k^1. This was why 1 atmosphere of inert gas or isobutane was added.) These results were confirmed when similar values were determined from shock-wave techniques[59] and very low pressure pyrolysis (VLPP)[58] (Table 2). From $\Delta S_1^{\ominus}$ (Table 3), values for

TABLE 3. Rate constants for the reaction:

$$R\dot{O} + NO \longrightarrow RONO \quad (2)$$

R	$\Delta S_1^{\ominus}$ (cal deg^{-1} mol^{-1}) (± 1)	$\Delta S_1^{\ominus}$ (J deg^{-1} mol^{-1}) (± 4)	$\log(k_2/M^{-1}\ s^{-1})^a$
Me	34.8	146	10.1 ± 0.4
Et	35.1	147	10.3 ± 0.4
i-Pr	34.9	146	10.5 ± 0.4
s-Bu	35.8	150	10.4 ± 0.4
t-Bu	35.6	149	10.4 ± 0.4
t-Am	35.6	149	10.5 ± 0.2

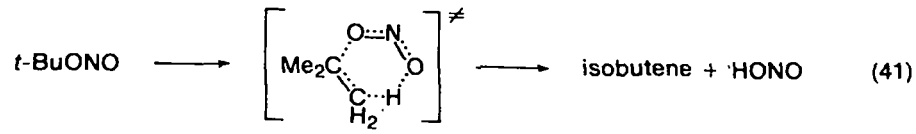
[a]Calculated from the relationship:

$$\log(A_1/A_2) = \Delta S_1^{\ominus}/R - (1 + \ln R'T)$$

where R' = 0.082 litre-atm
R = 1.987 cal deg^{-1} mol^{-1} or 8.314 J deg^{-1} mol^{-1}.

A_+^2, and hence k_2 since $E_2 = 0$, have been calculated to be $10^{10.3\pm0.2}$ M^{-1} s^{-1}. These values for k_2 are three powers of ten higher than those previously quoted.

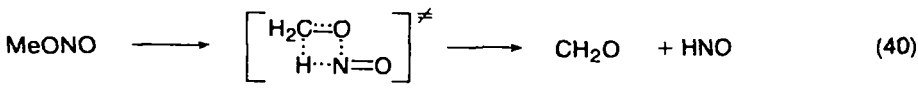
For *t*-butyl nitrite an additional product was isobutene, the production of which was unaffected by the addition of nitric oxide. It was concluded that isobutene arose via a molecular elimination of nitrous acid. This involved a six-membered cyclic transition state:



(41)

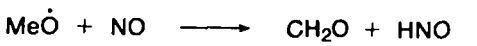
The Arrhenius parameters are given in Table 4. The preexponential factor A_{41} was in agreement with a value calculated in terms of a six-membered cyclic transition state[12]. The global rate constant was given by $(k_1 + k_{41}) = 10^{14.7}\ 10^{-36.2/\theta}\ s^{-1}$ ($\theta = 2.303\ RT$ kcal/mol). This value is similar to earlier values for k_1 (Table 1) so that the apparent disagreement between kinetic and thermochemical data was resolved in terms of the two parallel reactions (1) and (41).

The pyrolysis of *t*-amyl nitrite also leads to products that are accounted for by the elimination of nitrous acid[56]. However, contrary to the case for *t*-butyl nitrite, they are of minor importance. The reason for this is not clear. For primary and secondary nitrites the elimination process (41) is also much less important and an elimination reaction involving nitroxyl formation was contemplated (40)[51]:



(40)

However this was later rejected[61]. The discrepancy here was attributed to errors associated with the disproportionation reaction (6a):



(6a)

It was concluded that under these conditions at least the displacement process (15) was unimportant although it may play a role at higher radical and nitrite concentrations.

Many determinations have been made of the ratio $k_6/k_2 = \Delta$. This ratio is important in relation to the value of the observed rate constant for the decomposition of the nitrites. There is a considerable variation in the value of Δ for R = Me (Table 5). It was later shown that this variation was due to the pressure dependence of reaction (1) for methyl nitrite[63]. At high pressures the value of Δ reduced to ~0.01. For primary and secondary nitrites, reaction (6) becomes a significant step in the pyrolysis of the nitrites. For small extents of reaction the

TABLE 4. Arrhenius parameters for *t*-butyl nitrite

Process	$\log(A/s^{-1})$ ($\pm$ 0.4)	*E* (kcal/mol) ($\pm$ 0.8)	*E* (kJ/mol) ($\pm$ 3)
(1)	16.3	40.3	169
(41)	12.9	33.6	141
(1) + (41)	14.7	36.2	152

TABLE 5. Values for the ratio $k_{6a}/k_{2b} = \Delta$

$$MeO\cdot + NO \longrightarrow CH_2O + HNO \quad (6a)$$

$$MeO\cdot + NO \longrightarrow MeONO \quad (2b)$$

Δ	Temperature (°C)	System[a]	Reference
0	113–145	$(MeO)_2$(Py)	205
0	25	Hg^* + MeOH[b]	206
0.042	180	$(MeO)_2$(Py)	207
0	25	MeI(P)	208
0.5	174	$(MeO)_2$(Py)	209
0	90	MeCHO + NO_2(Py)	210
0.125	25	MeONO(P)	211
<0.5	130	$(MeO)_2$(Py)	212
0.5	727	MeONO + shock waves	36
0.17	25–150	MeONO(P)	213
0.01	110–150	$(MeO)_2$(Py)	63

[a]Py = pyrolysis, P = photolysis.
[b]Mercury ($^3P_1$)-sensitized decomposition.

mechanism is:

$$RONO \longrightarrow R\dot{O} + NO \quad (1)$$

$$R\dot{O} + NO \longrightarrow RONO \quad (2a)$$

$$R\dot{O} + NO \longrightarrow RO_{-H} + HNO \quad (6)$$

$$2\,HNO \longrightarrow H_2O + N_2O \quad (27)$$

A steady-state analysis of this scheme leads to the result that the rate of decomposition of the nitrite is first order, as observed experimentally, with $k_{exp} = k_1k_6/(k_2 + k_6)$. Since it has been shown that Δ is independent of temperature, the observed experimental activation energy may be identified with E_1 and the observed preexponential factor may be identified with $A_{exp} = A_1\Delta/(1 + \Delta)$. This analysis fits nicely with the experimental results (Table 6). In particular the value of A_{exp} for R = Me of 10^{14} s^{-1}, previously accepted as a normal value for a unimolecular process such as reaction (1), is readily interpreted on the basis of this mechanism. Since the Arrhenius parameters for trifluoroacetyl nitrite are very close to these values[62] (Table 2), it is tempting to invoke a similar mechanism which involves inhibition by the product nitric oxide. However, it has been clearly shown that added nitric oxide has no effect on the homogeneous rate of decomposition of the nitrite, and therefore reaction (42) is the rate-determining step:

$$CF_3COONO \longrightarrow CF_3CO_2^{\cdot} + NO \quad (42)$$

$$CF_3CO_2^{\cdot} \longrightarrow \dot{C}F_3 + CO_2 \quad (43)$$

$$\dot{C}F_3 + NO \longrightarrow CF_3NO \quad (44)$$

The lower preexponential factor A_{42} must either reflect the standard entropy change $\Delta S^{\ominus}_{42}$ or an unusually low value for the rate constant k_{45}:

TABLE 6. Values of $\Delta = k_6/k_{2a}$ and $k_{exp} = k_1k_6/k_{2a}$ for several nitrites

$$RONO \longrightarrow R\dot{O} + NO \quad (1)$$

$$R\dot{O} + NO \longrightarrow RONO \quad (2a)$$

$$R\dot{O} + NO \longrightarrow RO_{-H} + HNO \quad (6)$$

R	Δ	$\log(A_{exp}/s^{-1})$	E_{exp} (kcal/mol)	E_{exp} (kJ/mol)	Reference
Me	0.04	14.5	40.6	170	63
Et	0.08	14.9	39.9	167	61
i-Pr	0.01	14.3	38.9	163	61
s-Bu	0.16	15.4	40.8	171	55

$$CF_3CO_2^{\cdot} + NO \longrightarrow CF_3CO_2NO \quad (45)$$

Similarly the lower activation energy E_{42} must also reflect a lower RO—NO bond dissociation energy.

III. ALKYL NITRATES

Alkyl nitrates have a number of interesting properties. They have been used as 'antiknocks' in diesel fuel, in upgrading coal-derived fuel oils and as a fuel in starter motors of large jet engines. They are also used as pressurizers, monopropellants and explosives.

The mechanism for the decomposition of alkyl nitrates ($RONO_2$) has always been considered to be more complex than that for alkyl nitrites[9]. This is because the nitrogen dioxide molecule is produced in the initial step:

$$RONO_2 \longrightarrow R\dot{O} + NO_2 \quad (1')$$

Nitrogen dioxide is a powerful sensitizer for several reasons.

(*i*) The H—ONO bond strength is not much less than the aldehydic C—H bond strength. Thus for the process:

$$CH_2O + NO_2 \longrightarrow \dot{C}HO + HONO \quad (46)$$

$\Delta H^{\ominus} = +8.8$ kcal/mol (+36.8 kJ/mol). Carbonyl compounds are produced in the pyrolysis of alkyl nitrates via the reaction:

$$R\dot{O} + NO_2 \longrightarrow RO_{-H} + HNO_2 \quad (6')$$

Under the conditions of these pyrolyses, the interaction of nitrogen dioxide and aldehydes is considerable[65–67]. It is not possible to differentiate between reaction (46) as the first step and one that involves complex formation followed by the elimination of HONO via a six-membered ring transition state:

$$CH_2O + NO_2 \rightleftharpoons \dot{C}H_2ONO_2 \quad (47)$$

$$\dot{C}H_2ONO_2 \longrightarrow \left[\begin{array}{c} H \\ C{:::}O \\ H \quad\quad O \\ O{-}N \end{array}\right]^{\neq} \longrightarrow \dot{C}HO + HONO$$

The first step is simpler and therefore seems the more likely process[69]. This reaction is probably followed by reactions between the formyl radical and nitrogen dioxide to produce the observed products:

$$\dot{C}HO + NO_2 \begin{cases} \longrightarrow CO + HONO \\ \longrightarrow H\dot{C}O_2 + NO \end{cases} \quad (48)$$

$$H\dot{C}O_2\ (+ M) \longrightarrow CO_2 + \dot{H}\ (+ M) \quad (49a)$$

$$\dot{H} + NO_2\ (+ M) \longrightarrow HONO\ (+ M)$$

$$H\dot{C}O_2 + NO_2 \longrightarrow HONO + CO_2 \quad (49b)$$

$$2\,HONO \longrightarrow H_2O + NO + NO_2\ (wall)$$

(*ii*) In the pyrolysis of alkyl nitrates, alkyl radicals are produced via the decomposition (e.g. reaction 3) of the alkoxy radical produced in the first step:

$$t\text{-}Bu\dot{O} \longrightarrow Me_2CO + \dot{M}e \quad (3)$$

The methyl radical can react with nitrogen dioxide in two ways:

$$\dot{M}e + NO_2 \begin{cases} \xrightarrow{M} MeONO + M \\ \longrightarrow MeONO^* \longrightarrow Me\dot{O} + NO \end{cases} \quad (50)$$

$$\dot{M}e + NO_2 \longrightarrow MeNO_2 \quad (51)$$

Nitromethane is stable under the pyrolytic conditions but methyl nitrite is not by virtue of the fact that it is vibrationally excited. The result is that the methyl radical is replaced by the much more reactive methoxy radical. It is commonly believed that the reason for the increase in reactivity is due to differences in $\Delta H_r^{\ominus}$ – in favour of the methoxy radical – for hydrogen atom abstraction reactions. In fact the difference is slightly in favour of the methyl radical reaction:

$$Me\dot{O} + t\text{-}BuH \longrightarrow t\text{-}\dot{B}u + MeOH \quad (9a)$$

$$\dot{M}e + t\text{-}BuH \longrightarrow t\text{-}\dot{B}u + CH_4 \quad (52)$$

Here $\Delta H_{52}^{\ominus} - \Delta H_{9a}^{\ominus} = -1.5$ kcal/mol (-6.3 kJ/mol), so that the increase in reactivity must therefore be attributed to the polarity of the alkoxy radicals[68]. For

the higher alkyl radicals in the homologous series there is also the possibility of disproportionation

$$\dot{E}t + NO_2 \longrightarrow C_2H_4 + HONO \quad (53)$$

(*iii*) Nitrates have a reputation for their explosive properties. This point will be returned to later.

A number of reviews have been written on the pyrolysis of alkyl nitrates[6–10,50,78] of which the most recent is that by Strausz, Lown and Gunning[11], and the most useful for the preparation of alkyl nitrates is by Boschan, Merrow and van Dolah[79].

As already indicated, the mechanism for the decomposition of alkyl nitrates closely parallels that for alkyl nitrites:

$$RONO_2 \longrightarrow R\dot{O} + NO_2 \quad (1')$$

$$R\dot{O} + NO_2 \longrightarrow RONO_2 \quad (2')$$

$$R\dot{O} + NO_2 \longrightarrow RO_{-H} + HONO_2$$

These processes are then followed by reactions between the carbonyl compound and nitrogen dioxide as already indicated. This mechanism adequately accounts for the products obtained from the decomposition of methyl nitrate[70,71]. For ethyl nitrate, for which most experimental work has been carried out[72–78], a number of specific tests for the mechanism have been made. Addition of nitrogen dioxide lowers the rate of decomposition[75,76]. This is in accord with the participation of reaction (2′). Conversely the addition of nitric oxide increases the rate of production of nitrogen dioxide and therefore also the extent of reaction[75,76] via preferential reaction with alkoxy radicals to form ethyl nitrite:

$$Et\dot{O} + NO \longrightarrow EtONO \quad (2c)$$

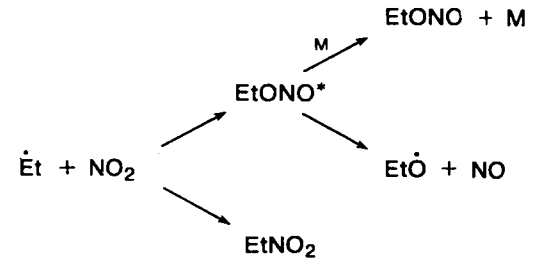
Similarly addition of acetaldehyde also increases the observed rate of decomposition via preferential reaction with ethoxy radicals[75]:

$$Et\dot{O} + MeCHO \longrightarrow EtOH + Me\dot{C}O \quad (54)$$

Levy has also observed that oxygen inhibits the rate of decomposition[75]. He attributes this to the reconversion of nitric oxide to nitrogen dioxide. This increases the importance of reaction (2′) while decreasing that of reaction (2). Houser and Lee have studied the reaction in a stirred-flow reactor at higher temperatures (242–260°C) and found that the reaction is one-half order with respect to ethyl nitrate[78]. They have interpreted these results in terms of a chain mechanism. Apart from the results in this work, the mechanism for the decomposition of ethyl nitrate is identical to that of methyl nitrate. For *n*-propyl nitrate the results indicate that reaction (1′) is followed by either reaction (2) with formation of nitrite or by decomposition of the *n*-propoxy radical[80]:

$$n\text{-}Pr\dot{O} \longrightarrow CH_2O + \dot{E}t \quad (3b)$$

The activation energy for the decomposition of the *n*-propoxy radical is less than that for either methoxy or ethoxy[60]. Evidence for reaction (3b) comes both from the production of formaldehyde and nitroethane[79]. No evidence for reaction (6′) is reported. Surprisingly in the interaction of ethyl radicals and nitrogen dioxide, only nitroethane is formed with no evidence for ethyl nitrite formation:



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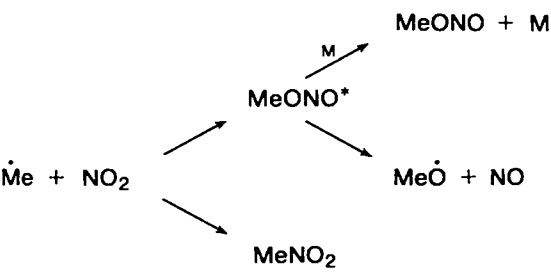
(56)

This means that nitric oxide is formed only from the interaction of nitrogen dioxide and the formaldehyde formed in reaction (3). The mechanism for the decomposition of *i*-propyl nitrate[81] incorporates the features of the methyl, ethyl and *n*-propyl nitrates. This involves both decomposition of the *i*-propoxy radical and disproportionation with either nitric oxide or nitrogen dioxide. In the decomposition of *n*-butyl nitrate, the yield of alkyl nitrite is much less than for the alkyl nitrates discussed so far[81,82]. There are two reasons for this. (*i*) The *t*-butoxy radical decomposes very readily under the experimental conditions[60]. (*ii*) The only carbonyl product is acetone which is incapable of converting nitrogen dioxide to nitric oxide at these temperatures[81]. The latter can only be formed from the interaction of methyl radicals and nitrogen dioxide. The mechanism for the decomposition is:

$$t\text{-BuONO}_2 \longrightarrow t\text{-BuO} + NO_2 \qquad (1'')$$

$$t\text{-BuO} + NO_2 \longrightarrow t\text{-BuONO}_2 \qquad (2'')$$

$$t\text{-BuO} \ (+ M) \longrightarrow Me + Me_2CO \ (+ M) \qquad (3)$$



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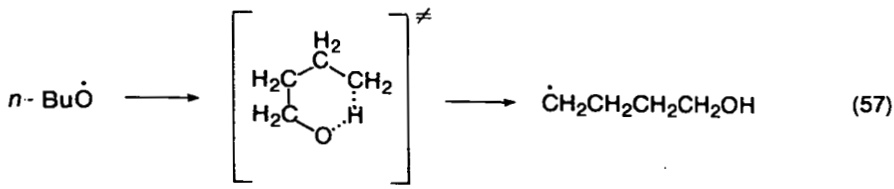
$$t\text{-BuO} + NO \longrightarrow t\text{-BuONO} \qquad (2)$$

Some decomposition of the more thermally stable methyl nitrite[52] and *t*-butyl nitrite[12,58] would be expected to take place together with combination reactions of the methyl radical and nitric oxide. The decomposition of *n*-butyl nitrate has been studied in the liquid phase at 120°C[83]. The mechanism for the reaction appears to be similar to that of the other nitrates but differs in two respects. *n*-Butanol and *n*-butyl butyrate are major products. It was suggested that the *n*-butoxy radical could isomerize to the hydroxy radical:



(57)

followed by hydrogen atom abstraction to form the alcohol. Baldwin and Golden subsequently showed that this isomerization was important in the pyrolysis of *n*-butyl nitrite[57]. The importance of this reaction in connection with smog chemistry has already been mentioned.

Kinetic studies of the decomposition of these nitrates in the gas phase show that they are first-order processes with no traces of any heterogeneous effects. The results for early work are given in Table 7. By analogy with the mechanism for the decomposition of alkyl nitrites, for primary and secondary nitrates the rate-determining steps would be expected to be:

$$RONO_2 \longrightarrow R\dot{O} + NO_2 \qquad (1')$$

$$R\dot{O} + NO_2 \longrightarrow RONO_2 \qquad (2')$$

$$R\dot{O} + NO_2 \longrightarrow RO_{-H} + HNO_2 \qquad (6')$$

A steady-state analysis of this scheme gives the result $k_{exp} = k_{1'}k_{6'}/(k_{2'} + k_{6'}) = k_{1'}/(1 + \Delta')$, where $\Delta' = k_{6'}/k_{2'}$. This also predicts a first-order process in agreement with the experimental results. This fits very well for the results of the decomposition of methyl nitrate[70]. The results for other nitrates are spurious like those early values reported for nitrites (Table 1), although in some cases the activation energies obtained are close to that expected from $\Delta H_1^{\ominus}$. Other workers have isolated the first step. This involves adding nitric oxide[74,85], shock-wave techniques[59] or very low pressure pyrolysis[58]. Values for $k_{1'}$ are given in Table 8. The results lead to acceptable values for both $\Delta H_{1'}^{\ominus} = D(RO—NO_2) = E_1 + RT$ and the preexponential factor $A_{1'}$.

As mentioned earlier alkyl nitrates also decompose explosively. Gray and Rogers have shown that under these conditions the decomposition of methyl nitrate can be expressed by the stoichiometric equation[71]:

$$MeONO_2 \longrightarrow NO + \tfrac{3}{4}CO + \tfrac{1}{4}CO_2 + \tfrac{3}{4}H_2O + \tfrac{3}{4}H_2$$

TABLE 7. Arrhenius parameters for the pyrolysis of alkyl nitrates

R	$E_{1'}$ (kcal/mol)	$E_{1'}$ (kJ/mol)	$\log(A/s^{-1})$	Reference
Me	39.5	165	14.4	70
Et	39.9	167	15.8	73
	36.0	151	13.9	84
	39.3	164	15.1	75
	38.0 ± 0.4	159 ± 2	14.7	76
n-Pr	36.0	151	14.7	84

TABLE 8. Arrhenius parameters for reaction (1′)

$$RONO_2 \longrightarrow R\dot{O} + NO_2 \qquad (1')$$

R	$E_{1'}$ (kcal/mol)	$E_{1'}$ (kJ/mol)	$\log(A_{1'}/s^{-1})$	Reference
Me	40.0 ± 0.9	167 ± 4	16.6 ± 0.5	85
Et	41.2 ± 0.5	172 ± 2	16.9	74
n-Pr	40.0	167	16.5	58
	40.2 ± 1	168 ± 4	16.4 ± 0.5	59
i-Pr	38.1 ± 1.3	159 ± 5	15.7 ± 0.7	84

This process is exothermic to the extent of 36.5 kcal/mol (153 kJ/mol). However, Gray and Yoffe ascribe the explosion to both thermal and chain effects[86]. Polynitrates have been used extensively as explosives. Studies of their decomposition have shown that the rate-controlling step is the same as the mononitrates, that is, the breaking of an O—NO_2 bond (Table 9)[87–89]. However, particularly in the liquid and solid phases, the Arrhenius parameters are spuriously high. The reason for this is not clear but may be connected with the exothermicity of the process or a chain-sensitized decomposition[90,91].

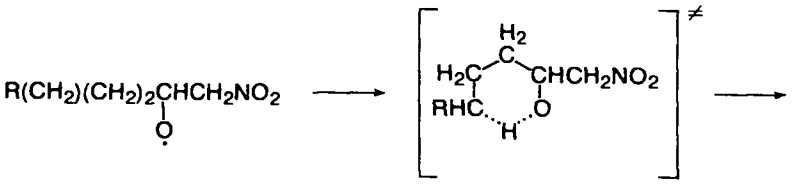
Kreuz and Larkin have shown that β-nitroalkyl nitrates thermally rearrange to produce dinitro alcohols in paraffinic and aromatic solvents[92]. The mechanism involves an intramolecular hydrogen atom abstraction via a six-membered cyclic transition state as noted previously:

$$R(CH_2)(CH_2)_2\underset{\displaystyle ONO_2}{\underset{|}{C}}HCH_2NO_2 \longrightarrow R(CH_2)(CH_2)_2\underset{\displaystyle O\cdot}{\underset{|}{C}}HCH_2NO_2 + NO_2 \qquad (58)$$

TABLE 9. Arrhenius parameters for polynitrates

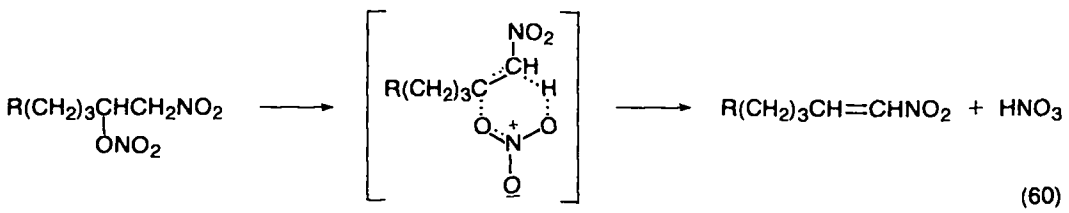
Nitrate	Temp. range (°C)	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
Ethyleneglycol dinitrate	85–105	15.9	39	163	87
Trimethyleneglycol dinitrate	85–110	15.2	38.1	159	87
Propyleneglycol dinitrate	80–100	15.2	37.4	157	87
Nitroglycerine[a]	75–105	17.1	40.3	169	87
Trimethylolnitromethane trinitrate	75–95	15.3	36.4	152	87
Nitrocellulose	142–190	16.5	40.1 ± 1.7	168 ± 7	89
Nitroglycerine	115–160	15.5	36	151	88
Nitroglycerine[a]	115–160	20.2	46.9	196	88
	90–125	18.0	42.6	178	88
Pentaerythritol tetranitrate[a]	161–233	19.8	47	197	88
Pentaerythritol tetranitrate[b]	171–238	16.1	39.5	165	88

[a]Liquid.
[b]5% Solution.



$$R\dot{C}H(CH_2)_2CH(OH)CH_2NO_2 + NO_2 \longrightarrow \underset{NO_2}{\overset{|}{R}}CH(CH_2)_2\underset{OH}{\overset{|}{C}}HCH_2NO_2 \quad (59)$$

The activation energy for the first-order process is 40 kcal/mol (167 kJ/mol) indicating once again that the rate-determining step is the breaking of the O—NO_2 bond. Compared to simple nitrates, the rate is much faster, this being reflected by a high preexponential factor of $10^{18.5}\,s^{-1}$. Again the reason for this is not clear. When olefinic solvents are used nitro olefins are produced[93]. Although the authors did not come to this conclusion, it appears likely that the mechanism involves the elimination of nitric acid via a six-membered transition state at the other end of the molecule:



(60)

There is no evidence for such an elimination taking place with simple alkyl nitrates in the gas phase[58].

There is considerable interest in the properties of peroxynitrates because of their possible importance in stratospheric chemistry and a number of compounds have been prepared[94]. The results of studies of their decomposition are given in Table 10. The O—NO_2 bond is certainly much weaker than the three types of nitrates already considered. Finally, mention is made of acyl nitrates[102]. One important property is that they are dangerously explosive compounds. When decomposed in

TABLE 10. Arrhenius parameters for peroxynitrates

Compound	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
$MeCO_3NO_2$	14.9	24.9	104	95
	16.3	26.9	112.6	96
	15.4	25.7	107.3	97
$EtCO_3NO_2$	18.0	29.2	122.1	97
$ClCO_3NO_2$	16.8	27.7	155.9	98
$HOONO_2$	16.4	23.0	96.2	99
$CCl_3O_2NO_2$	15.6 ± 1	21.9	210.5	100
$CCl_2FO_2NO_2$	16.6 ± 1	24.4	235.6	101

dilute solution they produce nitroalkanes. The mechanism for the reaction is:

$$RCO_2NO_2 \longrightarrow R\dot{C}O_2 + NO_2 \quad (61)$$

$$R\dot{C}O_2 \longrightarrow \dot{R} + CO_2 \quad (62)$$

$$\dot{R} + NO_2 \longrightarrow RNO_2 \quad (63)$$

$$\dot{R} + NO_2 \longrightarrow [RONO] \longrightarrow R\dot{O} + NO \quad (64)$$

Since the alkyl radical and nitrogen dioxide are involved, alkyl nitrites are also formed, but since they are unstable under the experimental conditions decomposition occurs. It is claimed that this method is superior to conventional methods for the preparation of a number of nitroalkanes[102].

IV. NITROALKANES AND NITROARENES

The mechanism for the decomposition of nitro compounds incorporates features of the mechanisms involved in both nitrite and nitrate pyrolyses. For example, the fragments produced from the initial step may recombine in two ways:

$$RNO_2 \longrightarrow \dot{R} + NO_2 \quad (65)$$

$$\dot{R} + NO_2 \begin{cases} \nearrow RONO \longrightarrow R\dot{O} + NO \\ \searrow RNO_2 \end{cases} \quad (66)$$

Under the conditions where nitro compounds will decompose, any nitrite that is formed will be unstable so that products from its decomposition and those of nitrates are superimposed upon those from the nitro compound. This occurs both in the formation and the decomposition of nitrates and in the nitrogen dioxide-sensitized decomposition of aldehydic products:

$$R\dot{O} + NO_2 \begin{cases} \nearrow RONO_2 \longrightarrow R\dot{O} + NO_2 & (2') \\ \searrow RO_{-H} + HONO & (6') \end{cases}$$

$$RO_{-H} + NO_2 \longrightarrow \text{products} \quad (67)$$

Based upon the studies of several workers[103–114] a complete mechanism may be given for the decomposition of nitromethane:

$$MeNO_2 \longrightarrow \dot{M}e + NO_2 \quad (68)$$

$$Me + CH_3NO_2 \longrightarrow CH_4 + \dot{C}H_2NO_2 \quad (69)$$

The fragment $\dot{C}H_2NO_2$ has the choice of reacting with nitrogen dioxide in two ways:

$$NO_2CH_2NO_2 \longrightarrow NO_2 + \dot{C}H_2NO_2 \quad (70)$$

$$\dot{C}H_2NO_2 + NO_2 \longrightarrow ONOCH_2NO_2 \longrightarrow NO + CH_2O + NO_2 \quad (71)$$

Since the C—NO_2 bond strength is weaker in polynitrates (see later), the dinitromethane formed by combination of the $\dot{C}H_2NO_2$ fragment with nitrogen dioxide decomposes very rapidly, which leads to no net reaction. When combination leads to the formation of unstable nitromethyl nitrite, the result is the production of formaldehyde. This reaction is also a major source of nitric oxide. In a static system over the temperature range 305–440°C, the order for the rate of removal of nitromethane is 1.4 below 100 Torr[110]. Also below 380°C there is an induction period perhaps suggesting a chain-reaction:

$$NO_2 + MeNO_2 \longrightarrow HONO + \dot{C}H_2NO_2 \quad (72)$$

$$NO_2 + \dot{C}H_2NO_2 \longrightarrow ONOCH_2NO_2 \longrightarrow NO + CH_2O + NO_2 \quad (73)$$

Alternatively this might indicate the pressure dependence of the Me—NO_2 bond-breaking step. This is supported by the fact that above 100 Torr of nitromethane, both the rate of disappearance of nitromethane and rate of formation of methane are first-order processes. Thus most of the methyl radicals react with nitromethane. At lower pressures interaction with nitrogen dioxide accounts for the observed products such as methyl nitrite and methanol:

$$\dot{M}e + NO_2 \longrightarrow MeNO_2 \quad (74)$$

$$\dot{M}e + NO_2 \longrightarrow MeONO \longrightarrow M\dot{e}O + NO \quad (75)$$

$$M\dot{e}O + MeNO_2 \text{ or } CH_2O \longrightarrow MeOH + \dot{C}H_2NO_2 \text{ or } \dot{C}HO \quad (76)$$

The initiation step[106]:

$$MeNO_2 \longrightarrow MeNO + O \quad (77)$$

is excluded on thermochemical grounds. Also the production of formaldehyde directly from CH_2NO_2:

$$CH_2NO_2 \longrightarrow \left[H_2C\cdots N{=}O \right]^{\neq} \longrightarrow CH_2O + NO \quad (78)$$

is excluded on thermochemical grounds, considering the strain energy involved in forming a three-centre transition state and the low preexponential factor thereby ensuing. At very high pressures an important product is hydrogen cyanide[106]. This is almost certainly formed from the interaction of methyl radicals and nitric oxide:

$$\dot{M}e + NO \rightleftharpoons MeNO \longrightarrow CH_2NOH \longrightarrow HCN + H_2O$$

The initial product formaldehyde is converted to carbon monoxide/carbon dioxide as described before. Kinetic results are given in Table 11.

TABLE 11. Arrhenius parameters for the first-order decomposition of nitromethane

	E_{68}			
$\log(A/s^{-1})$	(kcal/mol)	(kJ/mol)	Pressure	Reference
11.4	42.8	179	10 Torr	104
14.6	53.6	224	200–400 Torr	105
13.4	50	209	1 atm (N_2)	107
14.1	55.2	231	>150 Torr	109
12.8	48.1	201	1–2.8 atm	112[a]
16.2	58.5	245	∞	111

[a]Pressure dependence noted.

For higher homologues like nitroethane[104,105,114–117], 1- and 2-nitropropane[104,114–117], there is evidence that the major process is molecular elimination to form an olefin and nitrous acid, e.g.:

$$EtNO_2 \longrightarrow C_2H_4 + HONO \qquad (79)$$

In principle it is also possible for the same products to be formed via a free-radical mechanism:

$$EtNO_2 \longrightarrow \dot{E}t + NO_2 \qquad (80)$$

$$\dot{E}t + NO_2 \xrightarrow{EtNO_2} C_2H_4 + HONO \qquad (56), (81)$$

$$\dot{E}t + NO_2 \longrightarrow EtONO \longrightarrow Et\dot{O} + NO \qquad (55)$$

There are several but not conclusive objections to this mechanism. There is no evidence for the participation of reaction (81). The rate constant k_{55} is 1.3×10^{10} M^{-1} s^{-1} [111]. This route accounts for at best 10% of the products, so that k_{81} like k_{56}[68] is 10^{11} M^{-1} s^{-1}, a not impossible value. However, under these conditions the rate of ethene formation is given by $R_{C_2M_4} = k_{80}/2.[EtNO_2]$. In fact the Arrhenius parameters (Table 12) are much lower than expected for a bond-breaking process and are more in line with an elimination process. Also there is no evidence for the product ethane which would be expected if ethyl radicals are produced. By using very low pressures, Benson and Spokes were able to isolate the elimination process[116]. On the basis of these results Shaw was able to predict values for several nitro- and dinitro-alkanes[119]. However, Benson and Spokes did consider that the value of the A factor[116] for reaction (79) should be about thirty times higher than that found. This implies the participation of heterogeneous components. Using shock-wave techniques, it is possible to isolate the bond-breaking step[110–112]. Values for k_{80} are given in Table 13. At these temperatures the elimination process should be a minor process. Using the recommended value of Benson and Spokes for k_{79} and Glänzer and Troe's value for k_{80} the relative rates at 1000 K are given by $k_{80}/k_{79} = 6$. This result means

TABLE 12. Arrhenius parameters for the elimination of HONO from RNO_2

Compound	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
$EtNO_2$	11.5	41.5	174	104
	13.0	47 ± 2	197 ± 8	105
	13.0 ± 0.9	46.8 ± 3	196 ± 13	115
	11.8 ± 0.6	43 ± 2	180 ± 8	116
n-$PrNO_2$	11.7	41.5	174	104
	—	~50	~209	105
	13.4	47.7	200	115
	11.5 ± 0.6	42 ± 2	176 ± 8	116
i-$PrNO_2$	11.3	39	163	104
	11.0[a]	39	163	115
	11.1	39.3	164	118
	11.3 ± 0.2	40 ± 0.5	167 ± 2	116
1,1-Dinitroethane	11.5	43	180	119
1,1-Dinitropropane	11.5	47	197	119
1,2-Dinitroethane	11.5	43	180	119
1,2-Dinitropropane	11.5	46	193	119
2,2-Dinitropropane	11.5	39	163	119
$CH_2{=}CHNO_2$	12.1	45.8	192	132
$MeCH{=}CHNO_2$	11.8	42.2	177	132
$EtCH{=}CHNO_2$	11.9	42.0	176	132
$PhCH{=}CHNO_2$	12.0	41.0	172	132
$EtC(NO_2){=}CH_2$	12.2	44.7	187	132
$MeCHFNO_2$	12.6	44.0	184	132
$MeCH_2CHCl(NO_2)$	12.6	39.6	166	132
$EtCHBr(NO_2)$	12.5	41.5	174	132
$MeCCl(NO_2)Et$	13.4	41.0	172	132
$MeCBr(NO_2)Me$	13.4	42.2	177	132
$MeCCl(NO_2)CHMe_2$	13.2	40.0	167	132
$MeCBr(NO_2)CHMe_2$	13.2	39.6	166	132

[a]Corrected by Smith and Calvert[118].

that the mechanism for the decomposition of the mononitroalkanes other than nitromethane remains uncertain[108].

Substitution of other groups into the nitroalkanes lowers the R—NO_2 bond dissociation energy. Smith and Steacie have studied the decomposition of trichloronitromethane (chloropicrin)[20]. The decomposition is a first-order process producing nitrosyl chloride, nitric oxide and chlorine. Based on the results discussed for nitroalkanes so far, the mechanism would be:

$$CCl_3NO_2 \longrightarrow \dot{C}Cl_3 + NO_2 \qquad (82)$$

$$\dot{C}Cl_3 + NO_2 \begin{cases} \nearrow CCl_3NO_2 \\ \searrow CCl_3ONO \longrightarrow CCl_3\dot{O} + NO \end{cases} \qquad (83)$$

TABLE 13. Arrhenius parameters for the breaking of the R—NO_2 bond

Compound	$\log(A/s^{-1})$	E_{80} (kcal/mol)	E_{80} (kJ/mol)	Reference
$EtNO_2$	15.9	57	239	111
n-$PrNO_2$	15.5	55	230	111
i-$PrNO_2$	15.5	54	226	111
$Me_2C{=}CHNO_2$	11.8	36.2	152	131
$C(NO_2)_4$	17.5	40.9	171	123
	16.3	38.2	160	127, 128
$(NO_2)_3CC(NO_2)_3$	18.6	38.9	163	124
	17.3	35.8	150	128
CCl_3NO_2	15.7	37.7	158	120
	15	37.6	157	127
$ClC(NO_2)_3$	15.8	36.4	152	128
$Cl_2C(NO_2)_2$	15.3	34.3	143	128
$BrC(NO_2)_3$	16.1	36.2	152	128
$IC(NO_2)_3$	15.3	34.4	144	128
$MeC(NO_2)_2Me$	18.5	50.5	211	122
$MeC(NO_2)_3$	17.2	43.2	181	127
$EtC(NO_2)_3$	16.9	42.3	177	127
n-$PrC(NO_2)_3$	17.7	43.6	182	127
Me_2NNO_2	20	53	222	129
	15.8	46.2	193	125
	14.1	40.8	171	130
HMX[a]	16.4	46.2	193	125

[a]1,3,5,7-Tetranitro-1,3,5,7-tetraazacyclooctane.

$$CCl_3\dot{O}\ (+\ M) \longrightarrow CCl_2O + Cl(+M) \quad (84)$$

$$Cl + NO\ (+M) \longrightarrow NOCl\ (+M) \quad (85)$$

or

$$CCl_3ONO \longrightarrow CCl_2O + NOCl \quad (86)$$

This is in agreement with Gray's conslusions[121]. The rate constant is given by $k_{82} = 10^{15.7-37.7/\theta}\ s^{-1}$, such that process (82) is the rate-determining step. The results imply a considerably weakened C—NO_2 bond. Polynitro compounds involve similar mechanisms for their decomposition[122–128]. Once again the results (Table 13) show that the C—NO_2 bond is weakened by the presence of NO_2 and other groups. The preexponential factors are very high and may reflect the restricted rotation of the NO_2 groups in the ground state compared to completely free rotation in the transition state. There is no evidence, when the possibility exists, for any elimination of HONO or HNO_2. The pyrolysis of dimethylnitramine also[129,130] appears to follow the same mechanism (Table 13), the final products being mainly nitric oxide and dimethyl nitrosamine (8.8%).

$$Me_2N{-}NO_2 \longrightarrow Me_2\dot{N} + NO_2 \quad (87)$$

$$Me_2\dot{N} + NO \longrightarrow Me_2NNO \quad (88)$$

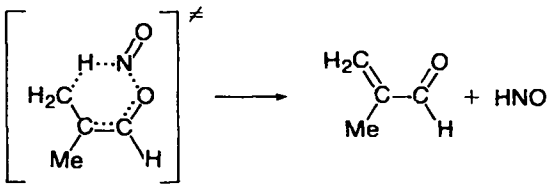
How the nitrogen dioxide is reduced to nitric oxide remains unclear but may involve the elimination process:

$$Me_2N{-}NO_2 \longrightarrow MeN{=}CH_2 + HONO$$

and attack by nitrogen dioxide on *N*-methylmethylimine. The principal product in the decomposition of 2-methyl-1-nitropropene is methacrolein[131]. A plausible mechanism involves nitrite formation followed by elimination of nitroxyl rather than disproportionation of the alkoxy radical and nitric oxide produced from the nitrite:

$$Me_2C{=}CHNO_2 \rightleftharpoons Me_2C{=}\dot{C}H + NO_2 \quad (90)$$

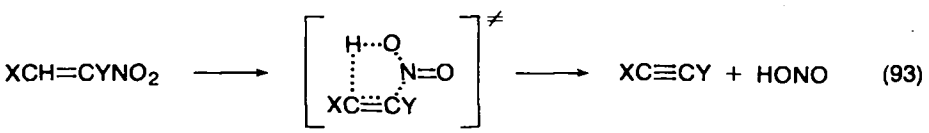
$$Me_2C{=}\dot{C}H + NO_2 \longrightarrow Me_2C{=}CHONO \quad (91)$$



(92)

However, the Arrhenius parameters (Table 13) are not in accord with the C—NO_2 bond-breaking process being the rate-determining step unless pressure dependence is involved.

When an α-hydrogen atom is available the dominant reaction is the elimination of nitrous acid[132]:



(93)

The Arrhenius parameters (Table 12) are in keeping with a five-centre transition state.

Nitrobenzene would be expected to decompose to phenyl radicals and nitrogen dioxide[133]:

$$PhNO_2 \longrightarrow \dot{P}h + NO_2 \quad (94)$$

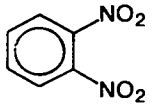
This has been disputed but the gas-phase initial step[134]:

$$PhNO_2 \longrightarrow PhNO + O \quad (95)$$

has to be discounted on thermochemical grounds. However, there is considerable evidence for heterogenous effects. What is undisputed is the production of nitric oxide. This is easily accounted for by the production and subsequent decomposition of nitrite from the fragments produced from breaking the C—NO_2 bond[138]:

$$\dot{P}h + NO_2 \longrightarrow PhONO \longrightarrow Ph\dot{O} + NO \quad (96)$$

The pyrolysis of dinitrobenzenes in benzene mixtures (ratio 1:10) indicates the breaking of the C—NO_2 bonds followed by hydrogen atom abstraction and addition processes[135]:



$$\longrightarrow C_6H_4NO_2^{\cdot} + NO_2 \quad (97)$$

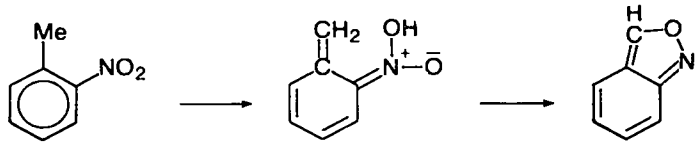
$$C_6H_4NO_2^{\cdot} + C_6H_6 \longrightarrow C_6H_5NO_2 + C_6H_5^{\cdot} \quad (98)$$

$$C_6H_4NO_2 + \dot{P}h \longrightarrow NO_2C_6H_4Ph \quad (99)$$

$$C_6H_5NO_2 \longrightarrow \dot{P}h + NO_2 \quad (100)$$

$$\dot{P}h + \dot{P}h \longrightarrow Ph_2 \quad (101)$$

Kinetic results for dinitrobenzenes are given by Maksimov[136]. Nazin and coworkers[131] have investigated the decomposition of the three nitrotoluene isomers. The results are given in Table 14. These first-order processes – in the presence of inhibitors – indicate in the case of the *meta* and *para* isomers that the initial step is the breaking of the C—NO_2 bonds. If this is the case, the C—NO_2 bond dissociation energy is greater by ~8 kcal/mol than those for the aliphatic compounds. The *ortho* isomer appears to involve a cyclic intermediate[136]:



$$+ H_2O \quad (102)$$

A kinetic isotope effect of $k_H/k_D = 1.54$ is found. No deuterium isotope effect is found for the other two isomers. The cyclic intermediate is also important for 2,4,6-trinitrotoluene homologues except the *t*-butyl derivative. Here no hydrogen atom is available to form the cyclic complex[137,139,140]. Ring formation also appears to be important in the pyrolysis of nitrostyrenes[141]:

$$\longrightarrow PhCHCO + MeNCO \quad (103)$$

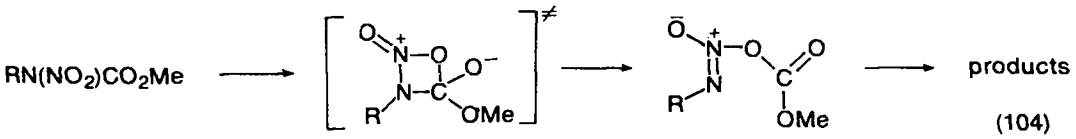
TABLE 14. Arrhenius parameters for aromatic nitro compounds

Compound	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
Nitrobenzene	17.3 ± 0.4	69.7 ± 1.4	292 ± 6	133
p-Nitrotoluene	16.6 ± 0.4	65.9 ± 1.1	276 ± 5	131
m-Nitrotoluene	17.0 ± 0.4	68.0 ± 1.3	285 ± 5	131
o-Nitrotoluene	12.4 ± 0.5	49.5 ± 1.3	207 ± 5	136
1,2-Dinitrobenzene	16.7	61.5	257	136
1,3-Dinitrobenzene	13.0	52.9	221	136
1,4-Dinitrobenzene	13.5	53.7	225	136
2,4-Dinitrotoluene	13.4	49.1	205	136
3,5-Dinitrotoluene	12.4	48.2	202	136
1,2,3-Trinitrobenzene	4.8!	23.4	98	136
1,2,4-Trinitrobenzene	12.3	46.2	193	136
1,3,5-Trinitrobenzene	13.6	51.9	217	136

TABLE 15. Arrhenius parameters of *N*-nitrocarbanates[142]

Compound	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)
n-$BuN(NO_2)CO_2Me$	12.8	34.3 ± 0.5	144 ± 2
s-$BuN(NO_2)CO_2Me$	12.3	30.8 ± 0.2	129 ± 1
t-$BuN(NO_2)CO_2Me$	12.8	28.8 ± 1.2	120 ± 5

A similar four-centre transition state is involved in the first-order decomposition of *N*-nitrocarbamates[142]:



The Arrhenius parameters are given in Table 15.

V. NITROSO COMPOUNDS

The chemistry of *C*-nitroso compounds differs from that of nitro compounds in one important aspect: the ability of nitroso compounds to dimerize via the formation of an N—N bond:

$$2\ RNO \longrightarrow (RNO)_2 \qquad (105)$$

Both *cis* and *trans* structures are possible. Gowenlock and Lüttke reviewed these compounds in 1958[143]. The equilibrium of dimer and monomer in solution (Table 16) has been dealt with by Boyer[144] and Smith[145] and so will only be covered briefly here. The equilibrium is displaced to the right in nonhydroxylic solvents for aliphatic compounds[149]. Hydroxylic solvents facilitate isomerization to oximes although *cis*- and *trans*-nitrosomethane are very stable in aqueous solutions. Electron-withdrawing groups stabilize the monomers. The *trans* dimers are more stable than the *cis* dimers. The *cis–trans* isomerization has been studied in absolute ethanol[146]. Two mechanisms have been suggested, either direct isomerization or intermediate monomer formation. The Arrhenius parameters are shown in Table

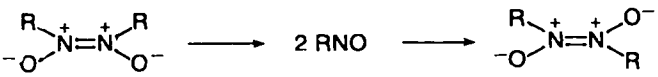
TABLE 16. Heats of dimerization for *C*-nitroso compounds (RNO_2[103]

R	$\Delta H^{\ominus}$ (kcal/mol)	$\Delta H^{\ominus}$ (kJ/mol)
Ph	<1	<4
p-BrC_6H_4	<1	<4
p-$NMe_2C_6H_4$	<1	<4
c-C_6H_{11}	20.5 ± 0.2	86 ± 0.8
$PhCH_2$	20.6 ± 0.2	86 ± 0.8
Me_2CCOMe	25.6 ± 0.2	167 ± 0.8
2,4,6-$Me_3C_6H_2$	12.1 ± 0.2	51 ± 0.8

TABLE 17. Arrhenius parameters for the conversion of *cis* to *trans* dimers[146]

R	log(A/s^{-1})	E (kcal/mol)	E (kJ/mol)	$\Delta H^{\ominus}$ (kcal/mol)	$\Delta H^{\ominus}$ (kJ/mol)
Me	11.6 ± 0.3	19.1 ± 0.4	80 ± 2	−8.5	−36
i-Bu	13.9 ± 0.5	22.1 ± 0.7	93 ± 3	−3.5	−15

17. These values imply intermediate monomer formation because they are so similar to those for the decomposition of the *trans* dimers in ethanol (Table 18):



(106)

However, this conflicts with the concept of rapid isomerization of monomer in ethanol. Notice that the difference in activation energies give the correct order of stability, i.e. ΔH° (*cis–trans*) is exothermic. The correct assignment of *trans* dimer has been made by comparing spectra with those of cyclic internal dimers – 1,4-dichloro-1,4-dinitrosocyclohexane and 2,2′-dinitrosobiphenyl – whose structures enforce a *cis* configuration[147]. These dimers are extraordinarily stable[148]. In contrast to aliphatic nitroso compounds, nitrosobenzene derivatives are more stable as monomers in solution. This is because delocalization of the benzene ring with the N—O group dominates compared to delocalization of the ONNO dimer framework. Electron-donating groups in the *para* position enhance the stability of the monomers. Conversely, *ortho*-substituted groups enhance the stability of the dimers by twisting the benzene ring out of the N—O plane, thus weakening delocalization there. This also explains the stability of the crystalline *cis*-nitrosobenzene dimer. Rotation about the Ar—N bond has also been observed in *o*-nitrosotoluene[150]. The rate of dissociation of *trans* dimers has been followed in both the gas phase and solution (Table 18). Good agreement was obtained with results in the gas phase and ethanol but spurious effects were observed in carbon tetrachloride and cyclohexane[151]. For tertiary compounds a linear relationship was observed between E_a and $\Delta S^{\neq}$ in different solvents[152].

The decomposition of monomeric *C*-nitroso compounds is important because of the use of nitric oxide in classical studies of the inhibition of gas-phase free-radical reactions[153,154]. The most important compound is nitrosomethane. It is pertinent to point out here that Leathard and Purnell concluded that the use of nitric oxide in

TABLE 18. Arrhenius parameters for the dissociation of *trans* dimers[151]

R	Solvent or phase	log(A/s^{-1})	E (kcal/mol)	E (kJ/mol)
Me	EtOH	12.9	27.4	115
i-Bu	EtOH	13.9	25.6	107
s-Am	EtOH	13.6	26.6	111
c-C_6H_{11}	EtOH	11.4	22.9	96
$PhCH_2$	EtOH	12.3	23.4	98
$PhCH_2CH_2$	EtOH	13.2	25.5	107
Me	Gas	11.8	22.0	92
i-Bu	Gas	14.4	25.6	107

inhibition experiments totally confuses the issues in the pyrolyses of paraffins[155]. One reason for this is that at the high temperatures involved the alkyl radical + nitric oxide adduct is extremely unstable. It has already been mentioned that hydroxylic solvents cause the very rapid isomerization of nitroso compounds, in particular nitrosomethane:

$$CH_3NO \ (+ \text{ solvent}) \longrightarrow CH_2NOH \ (+ \text{ solvent}) \qquad (107)$$

In the gas phase, isomerization of nitrosomethane has a marked heterogeneous character[156]. Christie and Mathews showed that the rate constant for the heterogeneous isomerization was 10^{-5} s^{-1} at 25°C[157], the value being reduced when the pressure increased, indicative of surface-sensitive reaction. They also found that the rate of isomerization was independent of nitric oxide concentration. Even at 300°C there is a considerable heterogeneous contribution to the rate of isomerization[156]. At higher temperatures the heterogeneous contribution should become less important. There are two other factors that should be considered in relation to the decomposition of nitrosomethane: (*a*) the relative rates of isomerization versus C—NO bond breaking:

$$MeNO \longrightarrow CH_2NOH \qquad (108)$$

$$MeNO \longrightarrow \dot{M}e + NO \qquad (109)$$

(*b*) the pressure dependence of both these reactions. In relation to (*a*) it is important to obtain a reliable value for D(R—NO)[5]. Probably the most reliable value for nitrosomethane is that based on the heat of formation of nitrosomethane: D(Me—NO) is 40.0 ± 0.8 kcal/mol (25°C), 167 ± 3 kJ/mol[158]. This value has been updated to correspond with the most recent value for ΔH_f°(Me) of 35.1 ± 0.15 kcal/mol (147 ± 0.6 kJ/mol)[159]. The value for D(Me—NO) is in good agreement with that for D(CF_3—NO) of 42 ± 2 kcal/mol (176 ± 8 kJ/mol) determined from the kinetics of decomposition of trifluoronitrosomethane by shock-wave techniques, and D(*t*-Bu—NO) of 39.5 ± 1.5 kcal/mol (165 ± 6 kJ/mol) determined by the kinetics of decomposition of 2-methyl-2-nitrosopropane by very low pressure pyrolysis[161] * but not in such good agreement with the values of Van den Bergh and Callear[163] and Carmichael, Gowenlock and Johnson[164] (see Table 19 and Reference 5). The more recent data indicate that D(R—NO) is 40 ± 2 kcal/mol (167 ± 8 kJ/mol) independent of the nature of R just like D(R—NO_2) for nitro compounds[5]. This is confirmed for aromatic compounds where almost identical values for D(C_6H_5—NO) and D(C_6F_5—NO) of 51 ± 1.5 kcal/mol (213 ± 6 kJ/mol) were obtained[165] (Table 19). However, more values are needed. The pressure dependence of the combination of methyl radicals with nitric oxide has been demonstrated by several workers[163,166,167]

$$\dot{M}e + NO \longrightarrow MeNO \qquad (5)$$

The rate constant is close to its limiting high-pressure value at 1000 Torr of propane[163]. Milne and Batt used this value for k_5 of 10^{10} M^{-1} s^{-1} to calculate a value from the standard entropy change for the preexponential factor

*The pyrolysis of 2-methyl-2-nitrosopropane by a conventional static system led to a very complex mechamism[162].

TABLE 19. Bond dissociation energies for *C*-nitroso compounds (RNO)

R	*D*(R—NO) (kcal/mol)	*D*(R—NO) (kJ/mol)	Reference
Me	40.0 ± 0.8	167 ± 3	158
CCl_3	32.0 ± 3	134 ± 13	164
CF_3	42.0 ± 2	176 ± 8	160
	31.0 ± 3	130 ± 13	164
i-Pr	36.5 ± 3	153 ± 13	164
t-Bu	34.0 ± 3	142 ± 13	164
	39.5 ± 1.5	165 ± 6	161
t-Am	36.0 ± 3	151 ± 13	164
Ph	41.0 ± 3	172 ± 13	164
	51.5 ± 1	216 ± 4	165
C_6F_5	50.5 ± 1	211 ± 4	165

$A_{109} = 10^{15.3}\ s^{-1}$ [158]:

$$MeNO \longrightarrow \dot{M}e + NO \qquad (109)$$

Using the most recent value for $\Delta H^{\ominus}_{109}$ this makes $k_{109} = 10^{15.3-39.4/\theta}\ s^{-1}$. Considerations of pressure dependence also apply to reaction (102). There are no reliable experimental values for k_{108}, but Benson and O'Neal estimated k_{108} to be $10^{12.9-39.3/\theta}\ s^{-1}$ [50]. It was assumed that the isomerization involved a four-centre transition state:

$$MeNO \longrightarrow \left[\begin{array}{l} H_2C\cdots N \\ \quad\vdots\ \ \vdots \\ \quad H\cdots O \end{array}\right]^{\neq} \longrightarrow CH_2{=}NOH \qquad (108)$$

From the point of view of inhibition experiments involving nitric oxide, it is necessary to assume, firstly, that formaldoxime is inert and stable or leads to molecular products. Thus hydrogen cyanide and water are produced via another four-centre transition state:

$$CH_2NOH \longrightarrow \left[\begin{array}{l} HC{\equiv}N \\ \quad\vdots\ \ \vdots \\ \quad H\cdots O{-}H \end{array}\right]^{\neq} \longrightarrow HCN + H_2O \qquad (110)$$

This reaction is catalysed by high concentrations of nitric oxide, sometimes explosively[167]. Secondly, the three reactions (5), (108) and (109) have to be considered together:

$$\dot{M}e + NO \rightleftharpoons MeNO \longrightarrow CH_2NOH$$

The near coincidence of activation energies for reactions (5) and (109) means that at any temperature the relative rates are determined by the ratio of their preexponential factors, at least for homogeneous processes. Hence $k_{109}/k_{108} = 10^{2.4}$ which emphasizes the reversibility of reaction (5), and nitrosomethane only 'leaks' away to stable products via reaction (108)[168]. One might wonder how nitric oxide achieved the reputation of being an efficient radical trap! However, the situation may be brought into perspective by considering the decomposition of a typical compound that decomposes via a free-radical chain mechanism, that of dimethyl

ether at 800 K. In the initial stages, the decomposition can be accounted for by the following mechanism:

$$MeOMe \longrightarrow MeO^{\cdot} + Me^{\cdot} \quad (111)$$

$$Me^{\cdot} + Me_2O \longrightarrow CH_4 + {}^{\cdot}CH_2OMe \quad (112)$$

$$CH_2OMe + M \longrightarrow CH_2O + Me^{\cdot} + M \quad (113)$$

$$MeO^{\cdot} + M \longrightarrow CH_2O + H + M \quad (114)$$

$$H + Me_2O \longrightarrow H_2 + {}^{\cdot}CH_2OMe \quad (115)$$

$$Me^{\cdot} + Me^{\cdot} \longrightarrow C_2H_6 \quad (4)$$

Assuming a steady-state concentration for the intermediates involved, one may easily show that $[Me^{\cdot}] = (k_{111}/k_4)^{1/2}[Me_2O]^{1/2}$. Taking a value for $[Me_2O]$ of 10^{-2} M, i.e. 500 Torr, Batt and Alvarado-Salinas' value for k_{111} of $10^{16.5-82/\theta}$ s^{-1} [85] and $k_4 = 10^{10.5}$ M^{-1} s^{-1} [169], we find $[Me^{\cdot}] = 10^{-9.2}$ M. When one Torr (2×10^{-5} M) of nitric oxide is added, there is a dramatic drop in the rate (Figure 1). Batt and Robinson have shown that k_{114} is $10^{4.4}$ s^{-1} under similar conditions to these[170]. It has already been stated that k_{ba} is $10^{8.2}$ M^{-1} s^{-1} [63].

$$MeO^{\cdot} + NO \longrightarrow CH_2O + HNO \quad (6a)$$

so most of the methoxy radicals react as before. The termination step is replaced by:

$$Me^{\cdot} + NO \underset{(109)}{\overset{(5)}{\rightleftharpoons}} MeNO \xrightarrow{(108)} CH_2NOH \quad (116)$$

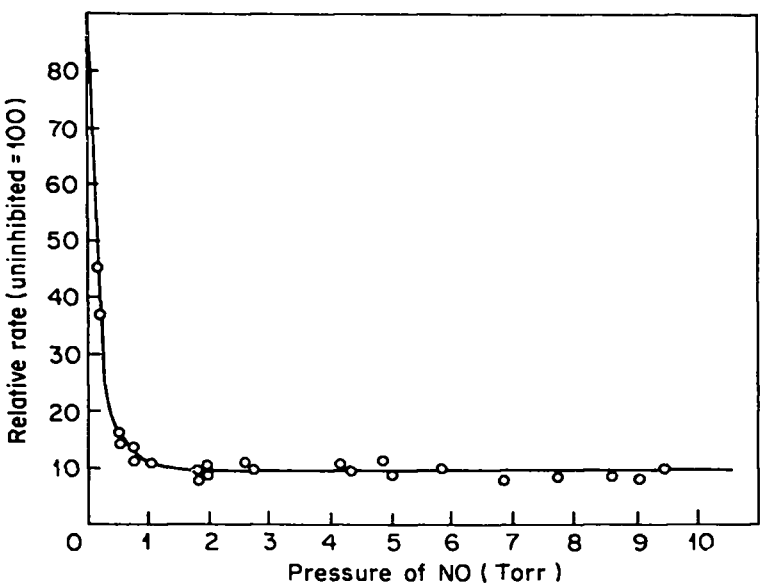


FIGURE 1. Decomposition of dimethyl ether in the presence of nitric oxide at 800 K. Reproduced from D. J. McKenny, B. W. Wojciechowski and K. J. Laidler in *Can. J. Chem.* **41**, 1993 (1963), by courtesy of the Canadian Journal of Chemistry and N.R.C.

k_{116} is given by:

$$k_{116} = k_{108}k_5/k_{109} = 10^{7.6}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$$

This value, incidentally, is very close to that originally assigned to the rate of combination of methyl radicals and nitric oxide[7]. Under these conditions, the steady-state concentration of the methyl radical is given by:

$$[\dot{\mathrm{M}}\mathrm{e}] = 2k_{111}[\mathrm{Me_2O}]/k_{116}[\mathrm{NO}] = 10^{-10.3}\mathrm{M}$$

This has decreased its steady-state concentration by about a factor of 10 in agreement with the results (Figure 1). While there is clear evidence for inhibition by nitric oxide in the pyrolyses of ethers and hydrocarbons, for compounds which have weaker C—H bonds such as aldehydes, catalysed decomposition takes place. Clearly the radical-trapping reactions still occur:

$$\mathrm{MeCHO} \longrightarrow \dot{\mathrm{M}}\mathrm{e} + \mathrm{CHO} \qquad (117)$$

$$\dot{\mathrm{M}}\mathrm{e} + \mathrm{NO} \rightleftharpoons \mathrm{MeNO} \longrightarrow \mathrm{CH_2NOH} \qquad (116)$$

$$\dot{\mathrm{C}}\mathrm{HO} + \mathrm{NO} \longrightarrow \mathrm{HNO} + \mathrm{CO} \qquad (118)$$

In addition nitric oxide sensitizes the decomposition via:

$$\mathrm{NO} + \mathrm{MeCHO} \longrightarrow \mathrm{HNO} + \mathrm{Me}\dot{\mathrm{C}}\mathrm{O} \qquad (119)$$

Conversely, despite observed inhibition, this reaction undoubtedly takes place with the other compounds mentioned especially at higher concentrations of nitric oxide. Higher concentrations of nitric oxide may also lead to multiple addition of nitric oxide to radicals as observed earlier. In this context it should be noted that multiple addition of methyl radicals to methyl radicals may also take place[171]. This makes the inhibiting effect of nitric oxide a very complex process as observed by several reviewers[154,155,172,173].

At the temperatures employed ($\geq$600 K) nitric oxide becomes a diagnostic test rather than a quantitative tool in the study of free-radical reactions, because of the instability of the initial adduct both to decomposition and other reactions. At much lower temperatures and in particular with reactions involving alkoxy radicals the use of nitric oxide as a radical trap is both specific and quantitative[174]. Here the adduct (alkyl nitrite) is both stable and not susceptible to further reactions with either nitric oxide or free radicals. However, even at these temperatures, alkyl radical–nitric oxide reactions are still complex as evidenced by studies of the decomposition of nitrosoethane[175] and 2-methyl-2-nitrosopropane[162], nitroxide formation[145] and disproportionation reactions which are typical of nitroso-benzenes[176]:

$$3\,\mathrm{ArNO} \longrightarrow \mathrm{Ar{-}\overset{+}{N}{=}N{-}Ar} + \mathrm{ArNO_2} \qquad (120)$$

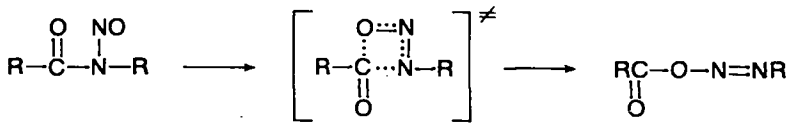
$$\qquad\qquad\qquad\qquad\qquad\quad \mathrm{O^-}$$

Few studies have been carried out on *N*-nitroso compounds. Pyrolysis at 335°C gives the disproportionation products expected from dialkylamino radicals[177]:

$$\mathrm{R_2N{-}NO} \longrightarrow \mathrm{R_2}\dot{\mathrm{N}} + \mathrm{NO} \qquad (121)$$

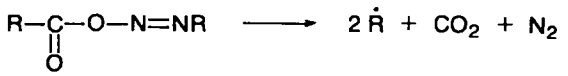
$$2\,\mathrm{R_2}\dot{\mathrm{N}} \longrightarrow \mathrm{RN{=}CHR'} + \mathrm{R_2NH} \qquad (122)$$

N-nitrosoamides decompose readily in solution. The rate-determining step appears to be rearrangement to a diazo ester via a four-centre transition state[78,179]:



(123)

The ester, not isolated, breaks down to give two radicals Ṙ:



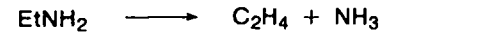
(124)

The half-life for its first-order decomposition depends upon the solvent used (Table 20). Activation energies for a series of *N*-nitrosamides have also been determined (Table 21)[180].

VI. AMINES

In 1972 Strausz, Lown and Gunning reported that very little data was available on the pyrolysis of amines[11]. The same conclusion may be made now although some progress has been made since then. Apart from methylamine, since the C—N and C—C bonds are of comparable strength [D(Me—NH_2) = 86.6 kcal/mol (362 kJ/mol) D(Et—NH_2) = 83.5 kcal/mol (349 kJ/mol) D(Me—CH_2NH_2) = 89.6 kcal/mol (375 kJ/mol)], three possible unimolecular reactions have to be considered:

(i) elimination of ammonia

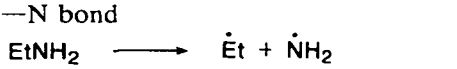


(125)

(ii) the splitting of the C—C bond

(126)

(iii) the splitting of the C—N bond



(127)

TABLE 20. Half-lives for the first-order decomposition of *N*-nitrosoacetanilide in different solvents

Solvent	Half-life (min)
MeCOOH	930
1-$BrC_{10}H_7$	134
PhCl	84
PhH	78
c-C_6H_{12}	70
$PhNO_2$	70
Me_2CO	67
Pyridine	57.5

TABLE 21. Activation energies for the decomposition of *N*-nitrosoamides

	E	
$R(CH_2)_nNNOCOCH_3$	(kcal/mol)	(kJ/mol)
R = Et, n = 1	29.1	122
R = Ph, n = 0	22.3	93
R = Ph, n = 1	28.0	117
R = Ph, n = 2	26.5	111
R = Ph, n = 3	28.6	120

Tsang found very little evidence for the elimination of ammonia in the case of *t*-amylamine[181]. This would rule out the two unimolecular elimination processes proposed for the decomposition of *t*-butylamine[182].

$$t\text{-BuNH}_2 \longrightarrow \begin{cases} \text{isobutene} + \text{NH}_3 \\ \text{C}_3\text{H}_7\text{N} + \text{CH}_4 \end{cases} \tag{128}$$

Benson and O-Neal have suggested that the mechanism probably involves methyl and amino radicals[50]. Based on this evidence it is tentatively suggested here that the elimination of ammonia is unimportant in the decomposition of amines.

Emeléus and Jolley have studied the decomposition of methylamine over the temperature range 550–670°C[183]. The products are methane, ammonia, hydrogen and hydrogen cyanide. The rate of reaction is accelerated in a packed reaction vessel, but in a spherical vessel is first order with respect to methylamine. The rate of reaction is given by $k_{exp} = 10^{13.3-58/\theta}\ s^{-1}$. Since the activation energy is much less than the C—N bond strength and the preexponential factor is much less than that expected for a bond-stretching process, this rate constant rules out the following reaction as the rate-determining step:

$$\text{MeNH}_2 \longrightarrow \dot{\text{M}}\text{e} + \dot{\text{N}}\text{H}_2 \tag{129}$$

As Emeléus and Jolley have suggested, the products methane and ammonia are accounted for by abstraction reactions:

$$\begin{matrix} \dot{\text{M}}\text{e} \\ \text{or} \\ \dot{\text{N}}\text{H}_2 \end{matrix} + \text{MeNH}_2 \longrightarrow \begin{matrix} \text{CH}_4 \\ \text{or} \\ \text{NH}_3 \end{matrix} + \begin{matrix} \dot{\text{C}}\text{H}_2\text{NH}_2 \\ \text{or} \\ \text{MeN}\dot{\text{H}} \end{matrix} \tag{130}$$

The paucity of data does not allow a decision to be made about the fate of the CNH_4 radicals, but they presumably decompose to form hydrogen cyanide and both a hydrogen molecule and atom (in two steps):

$$\text{CNH}_4^{\bullet} \longrightarrow \text{HCN} + \text{H}_2 + \text{H} \tag{131}$$

The hydrogen atom then either abstracts a hydrogen atom from methylamine or terminates:

$$\text{H} + \text{MeNH}_2 \longrightarrow \text{H}_2 + \text{CNH}_4 \tag{132}$$

$$\text{H} + \text{H} + \text{MeNH}_2 \longrightarrow \text{H}_2 + \text{MeN}\dot{\text{H}}_2 \tag{133}$$

A steady-state analysis of mechanism, assuming long chains, leads to the result:

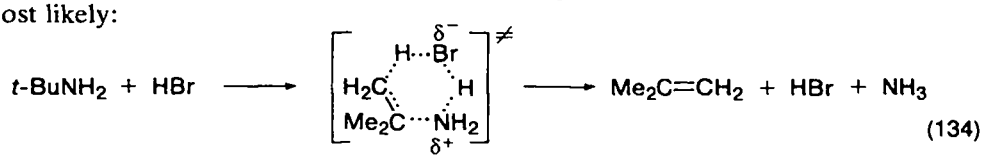
$$-R_{\text{MeNH}_2} = k_{132}\left(\frac{k_{129}}{k_{133}}\right)^{1/2}[\text{MeNH}_2]$$

This is in agreement with a first-order dependence observed experimentally. Making reasonable assumptions for the preexponential factors[9,181]:

$$k_{exp} = 10^{10.5}\left(\frac{10^{16}}{10^{10}}\right)^{1/2} 10^{-(E_{129}/2 + E_{132})/\theta}\ s^{-1}$$

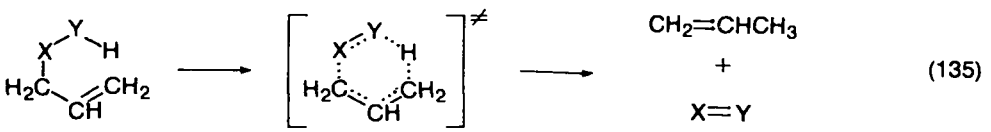
On the assumption that $\Delta H^{\circ}_{129}(T) = E_{129} + RT$ we have E_{129} = 86.0 kcal/mol (360 kJ/mol) and therefore the result is in good agreement with the experimental results if E_{132} = 15 kcal/mol (64 kJ/mol).

Ethylamine[184], *n*-propylamine[185], *i*-propylamine[186] and dimethylamine[187] also decompose via first-order processes, but in these cases, tests for heterogeneity have proved negative. The main products appear to be the corresponding olefin and ammonia. These results lead to the conclusion that the mechanism involves the molecular elimination of ammonia. In agreement with this the activation energies (~40 kcal/mol, 167 kJ/mol) are much lower than that for methylamine. However, the preexponential factors are far too low (~10^9 s^{-1}, Table 22) for a four-centre transition state. This suggests that, as mentioned earlier, more than one process may be involved in the initial step which may make the mechanism very complex. These very early studies involved essentially only pressure measurements. Clearly more work is required. Estimates for the rate of their bond-breaking processes have been made by Tsang (Table 23)[181]. Benson and coworkers[188–190] have used the VLPP technique to study the decomposition of a number of aromatic amines and substituted hydrazines. The amines all decompose via a radical split process (Table 23) which involve either a C—C or a C—N bond-breaking. The hydrazines (Table 24) either involve four-centre elimination of hydrogen or ammonia or a radical split process. The conclusions arrived at in these studies are different from those arrived at earlier[191–195], some of which involve the use of the toluene and aniline carrier gas techniques. Maccoll and Nagra have studied the hydrogen-bromide-catalysed decomposition of ethylamine, *i*-propylamine and *t*-butylamine[196]. The products are identical to the uncatalysed reaction, i.e. olefin and ammonia. The reaction is first order with respect to both amine and hydrogen bromide, and homogeneous. Three mechanisms have been considered of which a polar six-centred transition state is most likely:



(134)

Egger and coworkers[197,198] have studied the decomposition of a number of allylamines. These first-order, essentially homogeneous, processes involve a six-centre transition state with the production of propene:



(135)

TABLE 22. Arrhenius parameters for the first-order decomposition of amines (RNH_2)

Amine	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
$MeNH_2$	13.3	58	243	183
$EtNH_2$	9.3	43	180	184
n-$PrNH_2$	9.9	45.8	192	185
i-$PrNH_2$	8.8	40	167	186
t-$BuNH_2$	14.8	67.1	281	182
Me_2NH	10.5	46.6	195	187

TABLE 23. Arrhenius parameters for the reactions:

$$RCH_2NH_2 \longrightarrow R\dot{C}H_2 + \dot{N}H_2 \quad (127a)$$

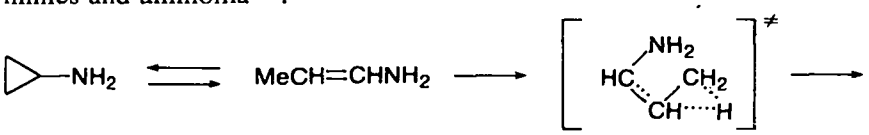
$$RCH_2NH_2 \longrightarrow \dot{R} + \dot{C}H_2NH_2 \quad (126a)$$

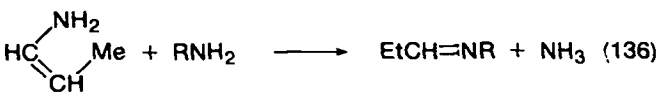
Reaction	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
$MeNH_2 \longrightarrow \dot{M}e + \dot{N}H_2$	16.0	83.9	351	181
$EtNH_2 \longrightarrow \dot{E}t + \dot{N}H_2$	16.3	80.7	338	181
$EtNH_2 \longrightarrow \dot{M}e + \dot{C}H_2NH_2$	16.7	82.3	344	181
$Me_2CHNH_2 \longrightarrow Me_2\dot{C}H + \dot{N}H_2$	16.4	80.7	338	181
$Me_2CHNH_2 \longrightarrow \dot{M}e + MeCHNH_2$	16.8	83.5	349	181
$t\text{-}BuNH_2 \longrightarrow t\text{-}\dot{B}u + \dot{N}H_2$	15.7	80.1	335	181
$t\text{-}BuNH_2 \longrightarrow \dot{M}e + Me_2\dot{C}NH_2$	16.5	80.5	337	181
$t\text{-}AmNH_2 \longrightarrow t\text{-}\dot{A}m + \dot{N}H_2$	15.9	78.9	330	181
$t\text{-}AmNH_2 \longrightarrow \dot{E}t + Me_2\dot{C}NH_2$	16.5	76.5	320	181
$PhCH_2NH_2 \longrightarrow Ph\dot{C}H_2 + \dot{N}H_2$	15.1	70.5	295	181
$PhCH_2NH_2 \longrightarrow Ph\dot{C}H_2 + \dot{N}H_2$	15.2	71.9	301	188
$PhCH_2NHMe \longrightarrow Ph\dot{C}H_2 + \dot{N}HMe$	15.1	68.7	287	188
$PhCH_2NMe_2 \longrightarrow Ph\dot{C}H_2 + \dot{N}Me_2$	15.2	60.9	255	188
$PhCH_2CH_2NH_2 \longrightarrow Ph\dot{C}H_2 + \dot{C}H_2NH_2$	14.7	63.9	267	189
$PhN(H)Me \longrightarrow Ph\dot{N}H + \dot{M}e$	15.1	66.7	279	189
$PhNMe_2 \longrightarrow Ph\dot{N}Me + \dot{M}e$	15.1	64.7	271	189

TABLE 24. Arrhenius parameters for the decomposition of some hydrazines[190]

Reaction		log(A/s^{-1})	E (kcal/mol)	E (kJ/mol)
$MeNHNH_2$	$CH_2NH + NH_3$	13.2	54	226
	$MeN{=}NH + H_2$	13.5	57	239
	$Me_2\dot{N} + \dot{N}H_2$	17.6	63	264
Me_2NNH_2	$CH_2{=}NMe + NH_3$	13.2	51	213
	$2\ Me_2\dot{N}$	17.7	54	226
Me_2NNMe_2	$CH_2{=}NMe + Me_2NH$	13.5	43	180

The results are given in Table 25. The activation energies are strongly sensitive to substitution at X and Y. Cyclopropylamine has been shown to isomerize to give propenylamine followed by reaction with another alkylamine molecule to give imines and ammonia[199]:



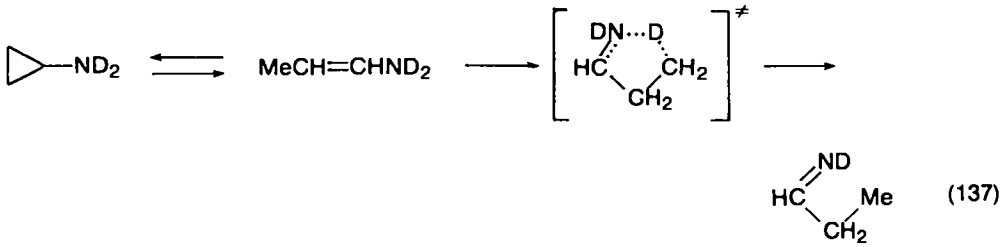


R=c-Pr, Et, *n*-Pr, *i*-Pr, allyl

TABLE 25. Arrhenius parameters for the decomposition of some alkylamines (reaction 135)

Compound	log(A_{135}/s^{-1})	E_{135} (kcal/mol)	E_{135} (kJ/mol)	Reference
Diallylamine	11.04 ± 0.13	37.11 ± 0.33	155 ± 1	198
Triallylamine	11.74 ± 0.07	38.27 ± 0.19	160 ± 0.8	198
N-Allylcyclohexylamine	11.44 ± 0.21	42.18 ± 0.57	177 ± 2	197
N-Allyl-*N*-methylamine	11.37 ± 0.56	43.4 ± 1.6	182 ± 7	198
N-Allyl-*N*-methylaniline	13.75 ± 0.43	48.5 ± 1.2	203 ± 5	198

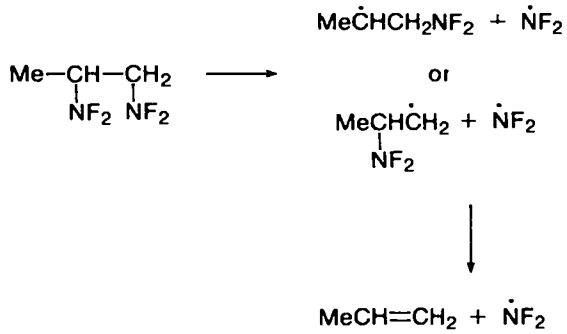
Pyrolysis of cyclopropylamine-*N*-d_2 shows no significant kinetic isotope effect[200], thus ruling out propylideneamine as an intermediate:



(137)

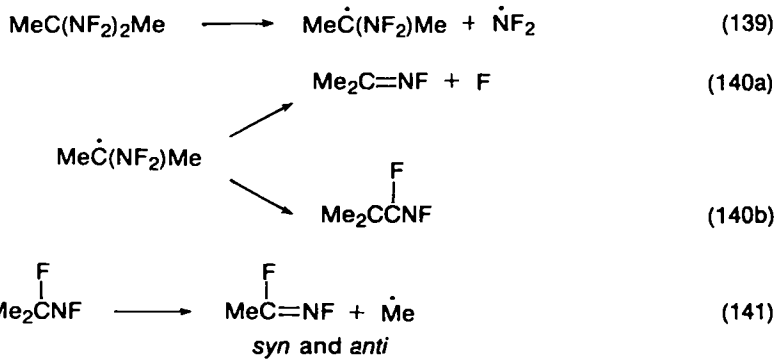
The preexponential factor of $10^{15.06}\ s^{-1}$ was more consistent with the transition state suggested in reaction (136) rather than reaction (137).

Ross, Mill and Hill have studied the decomposition of difluoroaminopropanes in a flow system using pressures of 10^{-3}–10^{-2} Torr[201]. Both the use of low pressures and high temperatures minimize surface catalysis and chain-reactions. For the 1,2-compound, stepwise elimination of the difluoroamino radical takes place with the production of olefin (650–750°C):



(138)

An estimate of 55 kcal/mol (230 kJ/mol) was made for the C—N bond dissociation energy which was in good agreement with a value of 56 kcal/mol (234 kJ/mol) obtained for the reverse process[202]. The 2,2-isomer decomposes at lower temperatures (450–550°C) first by C—N fission followed by both migration of fluorine from nitrogen to carbon and loss of a fluorine atom:



(139)

(140a)

(140b)

(141)

syn and *anti*

The ratio R_{140a}/R_{140b} is 1:3, and the C—N bond energy some 10 kcal/mol (42 kJ/mol) weaker than in the 1,2-compound. A more detailed study of

TABLE 26. Arrhenius parameters for fluoroamino compounds

Compound	$\log(A/s^{-1})$	E (kcal/mol)	E (kJ/mol)	Reference
$C(NF_2)_4$	16.14	40.4	169	203
$FC(NF_2)_3$	16.45	48.3	202	203
$F_2C(NF_2)_2$	15.75	53.6	224	203
$ClC(NF_2)_3$	13.2 ± 3.5	36 ± 3.2	151 ± 13	204
$NH_2C(NF_2)_3$	11.7 ± 0.4	29.6 ± 0.9	124 ± 4	204
$CH_3COC(NF_2)_3$	13.3 ± 0.8	36.1 ± 1.8	151 ± 8	204

difluoroaminomethanes has shown quite clearly that the rate-determining step is the breaking of the C—NF_2 bond[203]. The reaction is homogeneous and first order with respect to reactant and the preexponential factor is typical of a bond-breaking process (Table 26). The mechanism is e.g. for $C(NF_2)_4$:

$$C(NF_2)_4 \longrightarrow \dot{C}(NF_2)_3 + \dot{N}F_2 \quad (142)$$

$$\dot{C}(NF_2)_3 \longrightarrow (NF_2)_2C{=}NF + F \quad (143)$$

$$\dot{N}F_2 + F + M \longrightarrow NF_3 + M \quad (144)$$

The observed activation energies are also a measure of the C—NF_2 bond dissociation energies. Rauch and Fanelli have come to the same conclusions for the very explosive substituted (X = NH_2, Cl and MeO) tris(difluoroamino)methanes [$XC(NF_2)_3$][204]. They have also found that the decompositions are first-order processes, but there is evidence for a heterogeneous reaction. The preexponential factors (Table 26) are much lower ($\sim 10^{13}\ s^{-1}$) which suggest either elimination processes or, more likely, a chain mechanism. This is supported by the observation of induction periods in some runs.

VII. CONCLUSIONS

It is concluded that the mechanisms for the decompositions of alkyl *mono*nitrites and alkyl nitrates are now well understood. This is particularly true for the nitrates, which had previously been considered to be complex[9]. However, the mechanism for the decomposition of nitrites is superimposed upon that for the nitrates because they are formed during the pyrolysis of the nitrates. In one respect the mechanism for the nitrates is simpler than that of the nitrites because there is no indication of heterogeneous components. Only in the case of *t*-butyl nitrite does an elimination process make an important contribution to the mechanism. There is no evidence whatsoever for molecular elimination reactions from the nitrates. Apart from nitromethane, it appears that for the simple nitroalkanes the dominant reaction is the molecular elimination of nitrous acid via a four- or five-centred transition state. A radical split also makes a contribution but the evidence is not absolutely clear-cut. Conversely for nitroso compounds the dominant process is the radical split. At large extents of reaction the mechanism becomes complex.

The bond dissociation energies D(RO—NO), D(RO—NO_2), D(R—NO_2) and D(R—NO) are independent of the nature of the alkyl group R. For the last two compounds this may reflect a compensating activation energy for the combination process, $\dot{R}$ + NO_2 or NO for secondary or tertiary $\dot{R}$.

Very little quantitative information is available for the mechanism of the decomposition of amines. The most recent evidence suggests that for simple amines the most important route for decomposition involves a radical split. Complexities appear because the C—C and C—N bond dissociation energies are comparable in value. Much more work is required in order to understand the mechanism for the decomposition of these compounds.

VIII. ACKNOWLEDGEMENTS

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **13**

Nitrones and nitronic acid derivatives: their structure and their roles in synthesis

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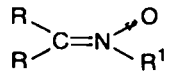
I. INTRODUCTION

The nitrone function is represented by formula **1** (R = H, alkyl or aryl). If R^1 = OH, the compound is a nitronic acid. The present review is divided into two parts: the first dealing with nitrones, the second with nitronic acids.



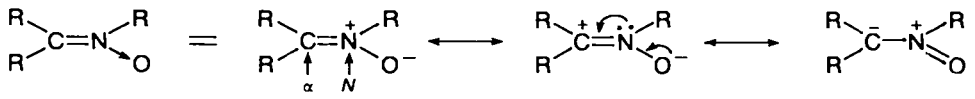
(1)

II. NITRONES

The subject of nitrones has been reviewed several times in the past[1–10]. The most recent general reviews concerning nitrones were published in the mid-sixties[2–4]. Specific aspects of the chemistry of nitrones, namely their rearrangements[5] and their participation in 1,3-dipolar cycloaddition reactions[6] were reviewed later. In view of the considerable expansion in the knowledge and understanding regarding the chemistry of nitrones during the past decade, the preparation of a new and up-to-date review seemed appropriate. The present review will not be concerned with the preparation of nitrones[7–9], and their uses in medicinal chemistry[10]. These subjects have been reviewed recently and adequately.

A. Structure of Nitrones

Nitrones are usually represented by formulae such as **2** or **3**, which imply that there is a positive charge on the nitrogen. However it has to be made clear that this positive charge is delocalized between the nitrogen and the α-carbon as represented by **3** ↔ **4**, resulting in a 1,3-dipolar structure.



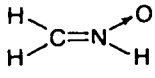
(2) (3) (4) (5)

The extent of this delocalization will naturally be influenced by the substituents in the α-position as well as on the nitrogen, which therefore will also have a marked influence upon the reactivity of the nitrone function. Another electronic structure that has to be considered is **5**. There is evidence that it contributes little in the ground state but certain phenomena can be best explained by invoking it (see below).

It is necessary to make a general remark regarding the various nomenclatures used in nitrones. There are two positions in the parent nitrone molecule: the α-position and the *N*-position (see formula **3**), the α-position is often referred to as the *C*-position. In addition nitrones are often called Schiff base *N*-oxides (e.g. *N*-benzylidene-*N*-methylamine *N*-oxide) or aldehyde *N*-alkyloximes or aldehyde *N*-alkyl nitrones. In the older literature nitrones were often called oxime *N*-alkyl ethers. The names of cyclic nitrones are usually derived from the name of the parent heterocycle.

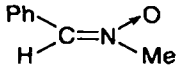
1. Theoretical calculations

Ab initio molecular orbital calculations have been carried out for the parent molecule **6** and its eight isomers, showing that formamide is far more stable than the other isomers[11]. However, the calculated dipole moment of 4.99 D was quite far



(6)

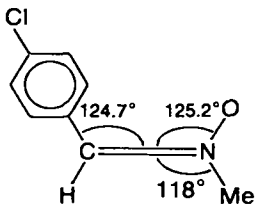
from the experimental value of 3.37–3.47 D (see Section II.A.2.c). Subsequent CNDO/2 and INDO calculations gave results closer to the experimental values[22]. CNDO/2 was also used to calculate the σ- and π-electron density of α-phenyl *N*-methyl nitrone (**7**)[12].



(**7**)

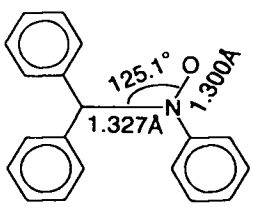
2. *Nonspectral physical methods*

a. X-ray studies. The structures of two nitrones have been determined by this method. Lipscomb and coworkers have determined the structures of *C-p*-chlorophenyl *N*-methyl nitrone (**8**) and compared its bond lengths to those of the isomeric *O*-methyloximes of *p*-chlorobenzaldehyde[13]. The bond angles of **8** are indicated in the formula. The N—O bond length in **8** was found to be 1.284 Å, considerably shorter than the N—O distance in the isomeric *syn* oxime(1.408 Å),



(**8**)

indicating the partial double-bond character of this bond in the nitrone. Moreover the C=N distance of 1.309 Å in the nitrone is longer than the corresponding bond in the *O*-methyloxime (1.260 Å). The data found for α,α,*N*-triphenyl nitrone (**9**) are



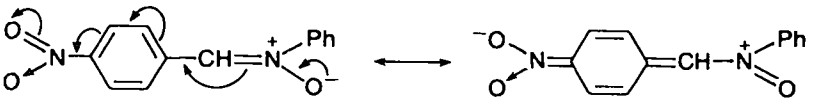
(**9**)

indicated in the formula[14]. These data lend support to the ideas regarding the structure of nitrones that were expressed in Section II.A.

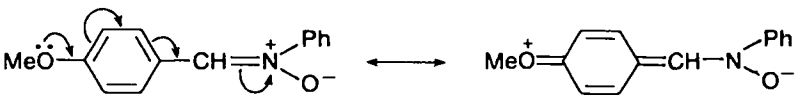
b. Mesomorphism. Some nitrones are found to exhibit mesomorphism. This property can be exploited for the formation of liquid crystals[15–17].

c. Dipole moment and acid–base properties. Dipole moments have been determined for several series of nitrones and found to be 3.37–3.47 D; this confirms the dipolar structure indicated previously[12,18–21].

In a study of a series of *N*-phenyl nitrones having variously substituted aryl or heteroaryl groups in the α-position it was found that the *N*-oxide group is capable of acting either as an electron acceptor or as an electron donor[19], contributing to the effects of electron-donating and electron-withdrawing substituents. This can be illustrated for α-(*p*-nitrophenyl) (**10**) and α-(*p*-anisyl) (**11**) nitrones. Similar results have been found in a series of *N*-methyl nitrones[12].

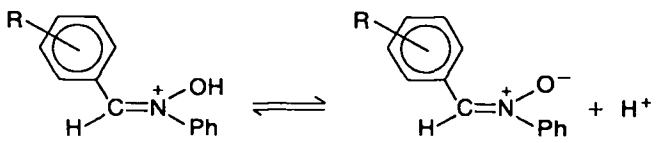


(10)



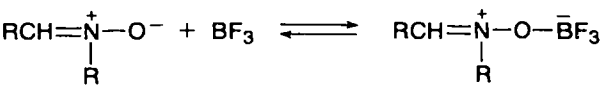
(11)

The ionization constants of a series of conjugate acids of substituted phenyl nitrones (e.g. **12**) and other aryl nitrones have been determined by potentiometric



(12)

titration[23,24]. The values obtained could best be correlated with the σ^+ values of the substituent R. The basicity of nitrones towards a Lewis acid (BF_3) has also been studied. Complexation with boron trifluoride (equation 1) increased the dipole



(1)

moment by approximately 5 D[25]. Calculations indicated that approximately 0.43 e was transferred from the oxygen to the boron.

The rate constants of the exchange of α-hydrogens in α,*N*-diaryl nitrones and the α and methyl hydrogens of α-aryl *N*-methyl nitrones with deuterium have also been correlated with the substituent constants of the groups in the aryl rings[26]. The electron-withdrawing effect of the *N*-oxide group has been found to have strong influence on the sensitivity of the methine hydrogen exchange to substituent effects[26].

The capability of nitrones to serve as electron donors is also manifested by their tendency to serve as ligands in nickel complexes[27,28] (see Section II.B.9.e).

3. Spectra of nitrones

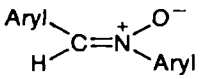
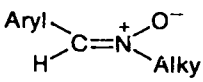
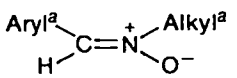
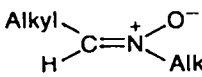
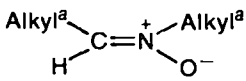
a. Photoelectron spectra. The photoelectron spectra of a number of nitrones have been measured and various ionization potentials have been assigned[29–32]. The correlation of these with the mode of 1,3-cycloadditions of nitrones has also been discussed[30].

b. Ultraviolet spectra. A large number of papers report on the ultraviolet spectra of nitrones. Most of these are reported in the previous reviews[2,3]. More recent reports[33–37] deal with special aspects such as the influence of steric effects[33–35,37] and of solvent effects[34–36] upon the ultraviolet spectra of nitrones.

Spectral data of various types of nitrones are summarized in Table 1.

c. Infrared spectra. This subject has also been discussed in the previous reviews[2,3] and since then no papers have been especially devoted to this subject. It

TABLE 1. Ultraviolet spectral data of various types of nitrones in alcohol solvents

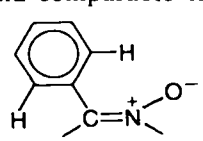
Type	λ_{max} (nm)	$\varepsilon_{max} \times 10^{-3}$	References
	227–240 247–280 310–372	7–17 6–12 8–20	2, 36
	205 221 290	8 7 14–17	2
	211 228 304	6 12 16	2
	244	6	35
	230–235	8–9	2

[a]The two groups are connected to form a ring.

is generally accepted now that nitrones exhibit two characteristic bands resulting from N → O and C=N bond stretching vibrations. The N → O band appears in aromatic ketonitrones in the region of 1200–1300 cm^{-1}, while in aldonitrones it is seen between 1050–1170 cm^{-1}. The C=N stretching vibration appears in aromatic nitrones at 1550–1600 cm^{-1} and in aliphatic and alicyclic nitrones at 1570–1620 cm^{-1} [38,39]. In the related 4-substituted 3-imidazoline-3-oxides frequencies up to 1340 and 1630 cm^{-1} have been observed[40].

d. Nuclear magnetic resonance spectra. Only proton chemical shifts are available. Some typical chemical shifts of protons adjacent to the nitrone function are listed in Table 2.

In addition to these general data there are some additional features of interest in the NMR spectra of nitrones. The spectra of α-aryl aldonitrones and α,α-diaryl nitrones show signals corresponding to two hydrogens at a field lower than the rest of the aromatic hydrogens[35,36,43,44]. These low field signals have been assigned to the two *ortho* hydrogens of the phenyl group situated *syn* to the nitrone oxygen (see **13**) and apparently arise from its deshielding influence. The magnitude of this deshielding influence has been found comparable to that of the nitro group[35,36]. In



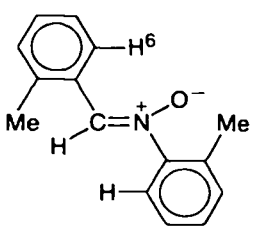
(13)

contrast, the deshielding effect of the nitrone group upon the *meta* protons of aryl groups attached to it is very weak[35,36]. From a study of a series of substituted

TABLE 2. Approximate chemical shifts of protons in the vicinity of the nitrone function[35,36,38,41,42]

Position	Chemical shift, δ (ppm)
Alkyl CH=N(+)(O(−))R	6.4–6.7
Aryl CH=N(+)(O(−))R	7–8
CH_3—CH=N(+)(O(−))R	2
RCH=N(+)(O(−))CH_3	3.4–4
RCH=N(+)(O(−))CH_2Aryl	5

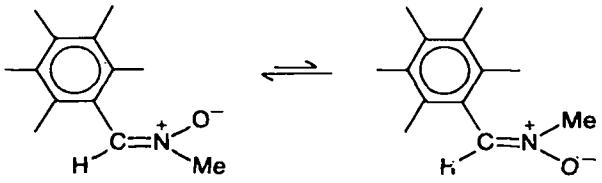
α,*N*-diaryl nitrones it appears that there are nonbonded interactions between the *ortho* substituent of the α-phenyl group and the *N*-oxygen, as there are between the *ortho* substituent of the *N*-phenyl group and the α-hydrogen. As a consequence of this the stable conformation of 2,2′-dimethyl-α-*N*-diphenyl nitrone would be as indicated by formula **14**, and the hydrogen at position 6 appears at the unusually low field of 9.5 ppm due to the deshielding effect of the oxygen[36]. In



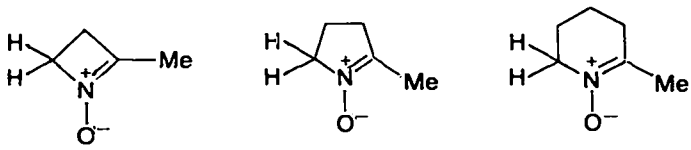
(14)

2,6-unsubstituted α-phenyl nitrones the phenyl group rotates freely and the two *ortho* hydrogens become magnetically equivalent. With more hindered 2,6-disubstituted aryl groups in the α-position of a nitrone it has been possible to obtain and isolate stable (*E*)-aldonitrones in addition to the predominant (*Z*) isomers (e.g. **15**)[45] (see Section II.A.4). The NMR spectra show the *N*-methyl of (*E*)-**15** at higher field (3.4 ppm) than that of the (*Z*) isomer (3.90 ppm), while the opposite trend is observed for the vinyl proton [(*Z*)-**15**: 7.6 ppm; (*E*)-**15**: 7.9 ppm][45].

In cyclic nitrones of various ring-size it has been found that there is a homoallylic coupling between two groups that lie in a transoid fashion across the nitrone function. The magnitude of the coupling constant varies somewhat with the ring-size (**16–18**)[46].



(*Z*-15) (*E*-15)

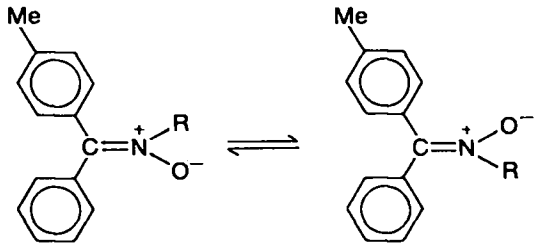


b a b a b

J_{ab} = 1.95 Hz J_{ab} = 1.84 Hz J_{ab} = 1.50 Hz

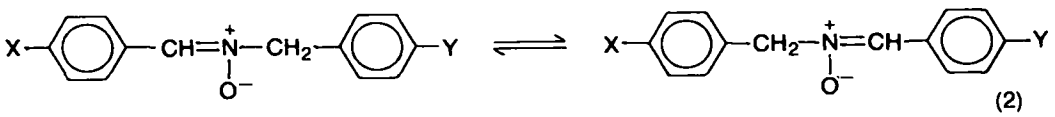
(16) (17) (18)

NMR spectroscopy has also become a convenient tool to study geometrical and other isomerizations of nitrones since the spectra of the pairs of compounds involved are often found sufficiently different. For example the interconversion between the (*Z*) and (*E*) isomers of **19** has been followed by examining the



(*E*-19) (*Z*-19)

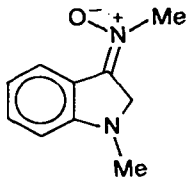
aromatic methyl signal[47], while the equilibrium composition of a series of α-aryl *N*-benzyl nitrones has been examined by integrating the *N*-benzyl CH_2 signal (equation 2)[39].



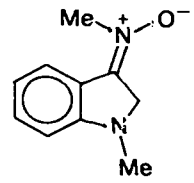
(2)

Specialized techniques such as the aromatic solvent-induced shift (ASIS) and shift reagents have also been used in connection with NMR spectra measurement of nitrones. The stereochemistry of the two geometric isomers of **20** has been assigned on the basis of ASIS[48]. The use of shift reagents has proved valuable in assigning the structures of the geometrically isomeric steroidal nitrones **21**[49,50], as well as the (*E*) configuration to α-phenyl-α,*N*-dimethyl nitrone (**22**)[51].

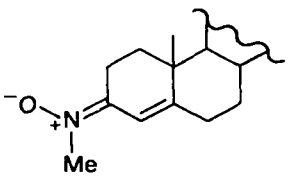
e. Mass spectra. The mass spectra of variously substituted and deuterated α,*N*-diaryl nitrones have been studied by several groups[52–54]. In all spectra appears



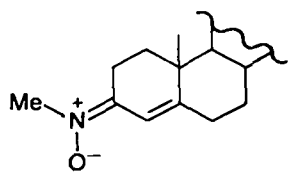
(*E*-**20**)



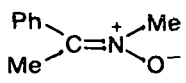
(*Z*-**20**)



(*E*-**21**)

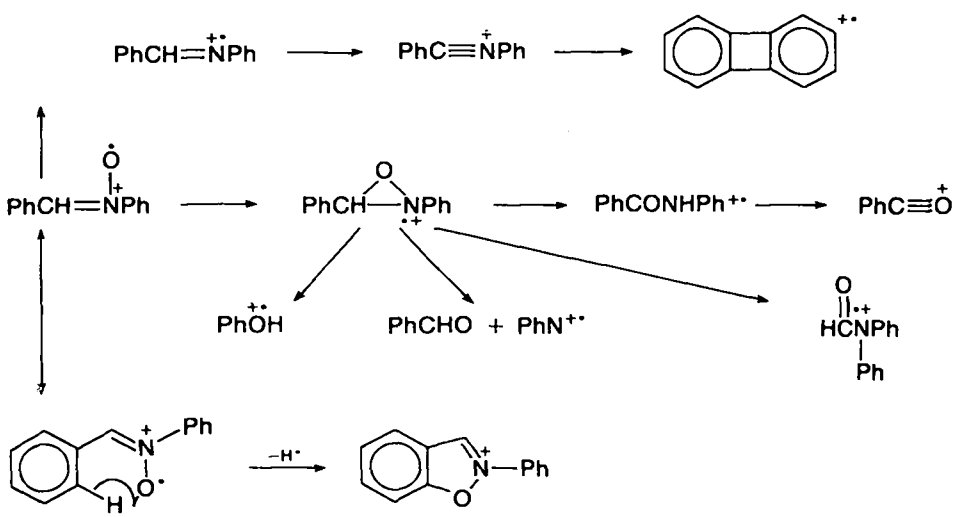


(*Z*-**21**)



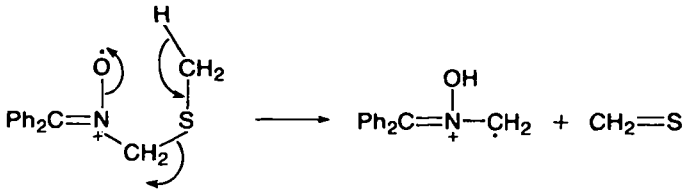
(*E*-**22**)

the M − 16 peak, which results from the loss of oxygen. This is a peak of some diagnostic value for *N*-oxides[55]. A summary of the mass spectral processes which α,*N*-diaryl nitrones undergo is presented in Scheme 1. The presence of the benzoyl cation requires oxygen migration from nitrogen to carbon and presumably the intermediacy of an oxaziridine, which may rearrange to an amide, which in turn may provide the fragment $PhC{\equiv}O^+$. In addition to this in all spectra the biphenylene radical cation and the 2-substituted benzisoxazolium cation are produced.



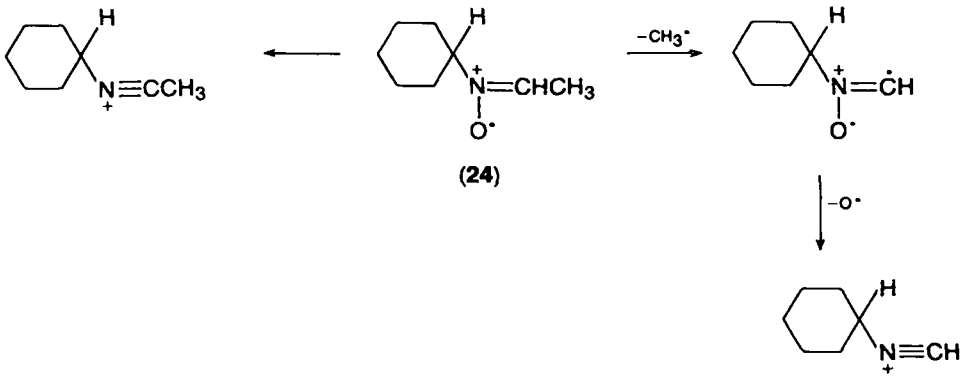
SCHEME 1

N-methyl α-aryl[56] and α,α-diaryl[57] nitrones show analogous fragmentation patterns, as does α,α-diaryl *N*-methylthiomethyl nitrone (**23**) which undergoes a McLafferty-type rearrangement in addition to the normal fragmentation pattern[57].



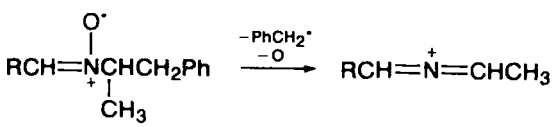
(**23**)

The mass spectrum of *N*-ethylidenecyclohexylamine *N*-oxide (**24**) is a representative of that of an aliphatic nitrone[58]. The peak M − 16 is not seen in this case. A peak M − 15 results from the loss of the methyl group by α-cleavage.



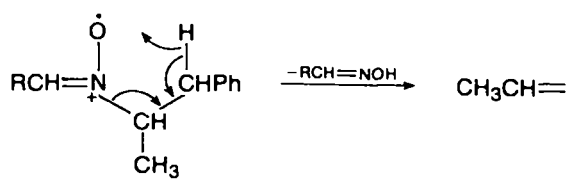
(**24**)

The mass spectrum of the isomeric oxaziridine shows a similar pattern so interconversion with the nitrone cannot be ruled out. The mass spectra of *N*-alkylidene *N*-(1-cyanoalkyl) *N*-oxides have also been examined, showing similar patterns[58]. *N*-alkyl-*N*-arylalkylidene nitrones (**25**) undergo different kind of fragmentations indicated by equations (3), (4) and (5)[59]. The mass spectra of some α-aminonitrones have also been determined[60].



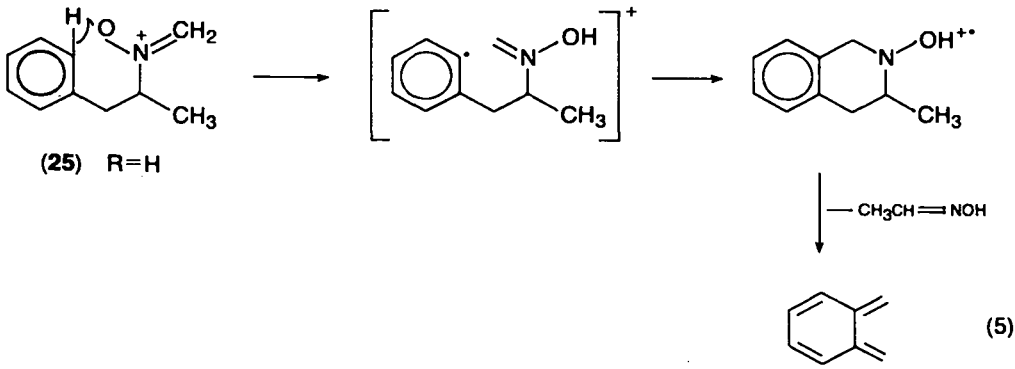
(3)

(**25**) R≠H



(4)

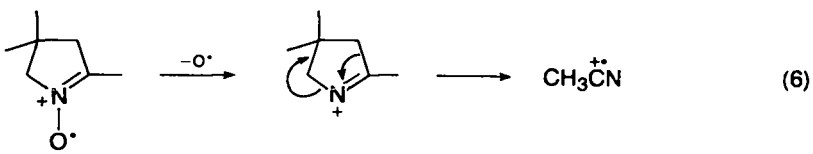
(**25**) R ≠ H



(25) R=H

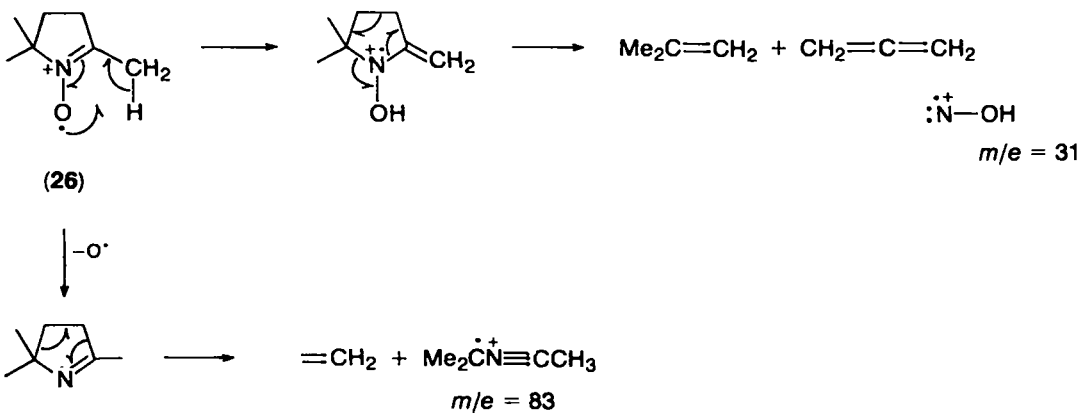
(5)

Alicyclic nitrones are somewhat different. 2,4,4-Trimethylpyrroline *N*-oxide gives a base peak of $m/e = 41$ which was assigned as $CH_3\overset{+\cdot}{C}N$[61], (equation 6), although



(6)

the fragment $m/e = 41$ was observed in pyrroline *N*-oxides that have no methyl substituent at the 2-position, and therefore was assigned by others as $C_3H_5^+$[55]. The isomeric 2,5,5-trimethylpyrroline *N*-oxide (**26**) shows a base peak believed to correspond to $[NOH]^{\cdot +}$, along with other peaks e.g. $m/e = 83$.



(26)

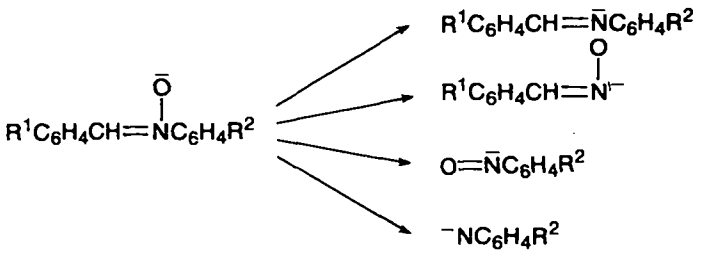
$m/e = 31$

$m/e = 83$

The negative-ion mass spectra of some α,*N*-diaryl nitrones have also been measured[62]. These spectra are found to be much simpler than the positive-ion spectra and the fragmentations are indicated in Scheme 2.

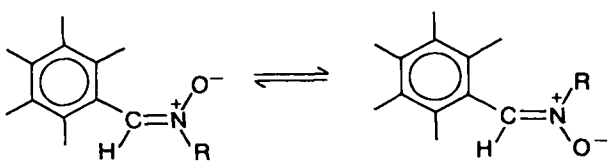
4. Geometrical isomerism of nitrones

The phenomenon of geometrical isomerism in nitrones has long been recognized and in many instances pairs (*E*) and (*Z*) isomers have been separated and configurations assigned[2,3,49,50]. However it is only recently that such pairs of isomers have been successfully isolated in acyclic aldonitrones, which usually exist entirely as the (*Z*) isomers (**27**). It has been found that in derivatives of **27** with highly



SCHEME 2

substituted aryl groups it is possible to isolate the stable (*E*) isomers (**28**)[45]. Apparently in these cases the increased steric requirements of the α-aryl group cause it to twist out of its normal coplanar conformation (**27**) and assume an orthogonal orientation (**29**).



(**27**) (**28**)

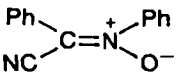
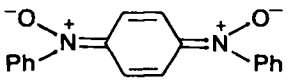
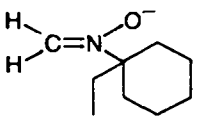
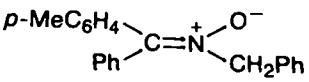
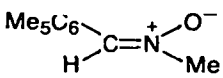
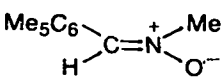
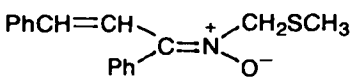
(**29**) (**30**)

In this conformation there is increased repulsion between the negative oxygen and the electron-rich aromatic ring, resulting in an increase in the ground-state energy of the (*Z*) isomer and greater ease of formation of the (*E*) isomer (**28**). This effect can be counteracted by the size of the *N*-substituent. Indeed only one isomer (*Z*) is observed with nitrones (**27**) containing bulky R groups such as *t*-butyl, neopentyl or adamantyl[45].

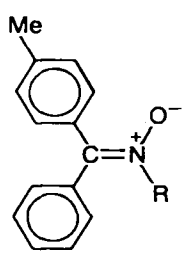
There have been a number of investigations regarding (*E*) $\rightleftharpoons$ (*Z*) isomerizations. The activation energies of such isomerizations have been determined in a number of cases and some representative data are listed in Table 3.

The influence of the *N*-substituent upon the rate of isomerization has been studied in the α,α-diphenyl nitrone series (**31**)[63]. The approximately twofold rate of isomerization of **31b** as compared to **31a** is considered to be due to increased ground-state energies of the former caused by the stronger nonbounded interactions between the benzyl and the α-phenyl groups. However the fact that the benzhydryl derivative **31c** isomerizes 10 times faster than **31a** is taken as an indication that a new mechanism is operating in this case. It has been suggested that the

TABLE 3. Energy of activation of $(E) \rightleftharpoons (Z)$ isomerization of representative nitrones

Nitrone	E_A (kcal/mol)	References
	24.6	64
	12	65
	23.2	66
	33.6	63
	33.1	45, 67
	34.6	45, 67
	28.2	68

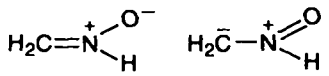
isomerization of *N*-benzhydryl nitrones proceeds, at least in part, via dissociation to iminoxy radicals followed by fast isomerization of the radical and recombination.



(a) R = Me
(b) R = CH_2Ph
(c) R = $CHPh_2$

(31)

The question of the mechanism of $(E) \rightleftharpoons (Z)$ isomerization has been approached theoretically. CNDO/2 and INDO calculations on the parent nitrone, **6**, indicate a high charge density on the oxygen and are consistent with a major contribution of structure **6a** in the ground state[22]. The twisted conformation, which is proposed to be the transition state for the rotation around the C=N bond, appears, however, to be well represented by **6b** since there is a high electron density on the carbon. However the calculated rotational barriers of 60 and 80 kcal/mol by these methods

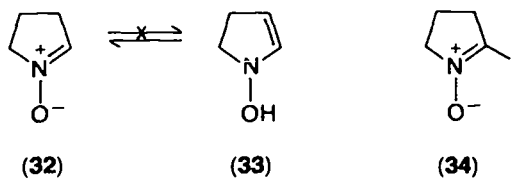


(6a) (6b)

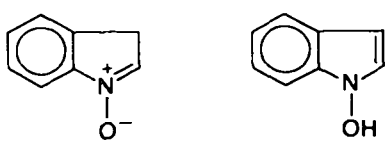
are much higher than those observed experimentally[22]. Results from a more recent MINDO/3 study are consistent with a concerted rotation–pyramidalization pathway for the $(E) \rightleftharpoons (Z)$ isomerization[69]. According to this as the dihedral angle between the CH and the NH bonds increases the CH_2 undergoes deformation from its initial planar trigonal geometry and the carbon becomes pyramidal along the rotation coordinate. The driving force for this presumably arises from the negative charge density at the carbon ($\phi\upsilon$) and the known preference of carbanions to be pyramidal. The MINDO/3 rotational barrier of 40.2 kcal/mol is closer to the experimental values (Table 3) than those obtained in the previous calculations.

5. *Tautomerism of nitrones*

a. Nitrone–hydroxyenamine tautomerism. This type of tautomerism is analogous to the keto–enol tautomerism of carbonyl compounds. The question of such tautomerism has been the subject of a number of papers. *N*-Hydroxy-Δ^2-pyrrolines (**33**) are not detectable by NMR in Δ^1-pyrroline *N*-oxides (**32**)[70]. Similar conclusions have been reached on the basis of deuterium exchange studies showing that only the hydrogens of the 2-methyl group undergo exchange in substituted Δ^1-pyrroline *N*-oxide derivatives (e.g. **34**)[61]. However in the case of indolenine *N*-oxides (e.g. **35**) the *N*-hydroxyindole tautomers (**36**) do exist, and their proportion can be increased using polar solvents[71,72].

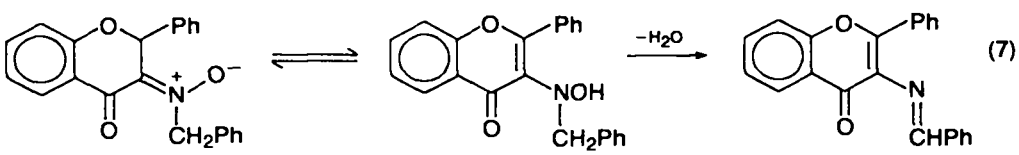


(32) (33) (34)



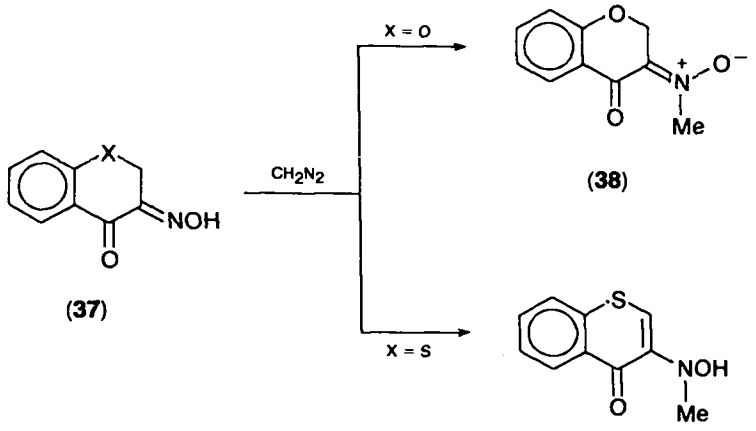
(35) (36)

This type of tautomerization is assumed to be involved also in the base-catalysed reaction of the flavanononitrone, which leads to the Schiff base as one of the products (equation 7)[73]. Interestingly the nitrone–hydroxyenamine equilibrium is found to be influenced by the heteroatom in the chromane system. Thus reaction of



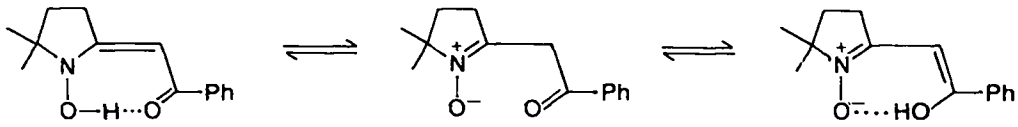
(7)

the oxime **37** (X = O) with diazomethane leads to nitrone **38**, whereas the thio analogue **37** (X = S) with the same reagent affords the hydroxylaminothiochromane **39**[74].



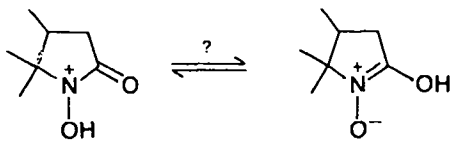
(37) **(38)** **(39)**

A keto group appropriately situated relative to the nitrone function will enhance tautomerism similarly to β-dicarbonyl compounds. Indeed the infrared spectrum of phenacylpyrroline *N*-oxide (**40**) shows bonds attributable to an intramolecular hydrogen bond which could result from either or both structures **40a** or **40b**[75].



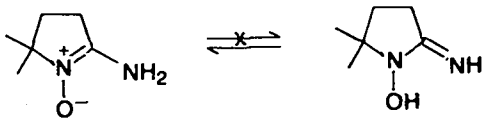
(40b) **(40)** **(40a)**

A band at 1700 cm^{-1} in the infrared spectrum of the cyclic hydroxamic acid **41** was interpreted as indicating the presence of the α-hydroxynitrone tautomer **41a**[76]. The

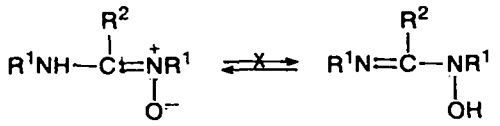


(41) **(41a)**

related question of α-aminonitrone/*N*-hydroxy-*N*,*N*′-disubstituted amidine tautomerism also should be considered in this section. A number of cases belonging to different categories have been examined by spectral methods and have been assigned the α-aminonitrone structure (see **42**, **44** and **45**) although acylation reactions of **42** afford acylation products derived from **43**[77].



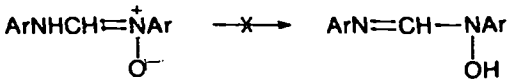
(42) **(43)** (Ref. 77)



(Ref. 78)

(44)

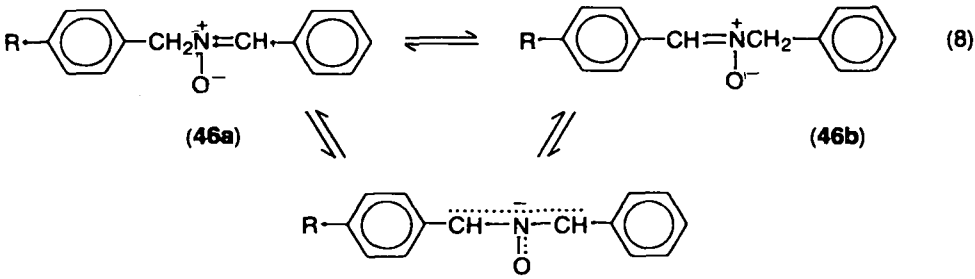
R^1 = aryl or alkyl
R^2 = alkyl or H



(Ref. 79)

(45)

b. Behrend rearrangement. Since this type of tautomerism was first reported by Behrend in 1891[80] it is often referred to by this name. It is represented by equation (8). The history of this tautomerism has been reviewed[2,3,5]. The reaction clearly involves base-catalysed proton abstraction leading to a delocalized carbanion (e.g. **47**), which can be converted by protonation to either of the two nitrones. However this has never been demonstrated by experimental means such as by deuterium incorporation. The influence of substituents in the aromatic ring upon the equilibrium in a series of α-aryl *N*-benzyl nitrones (**46**) has been studied by NMR[39].

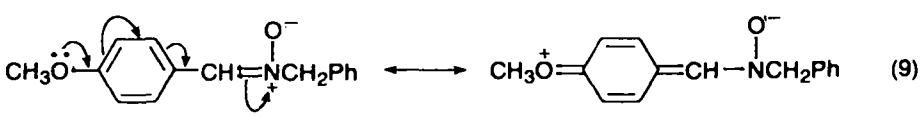


(8)

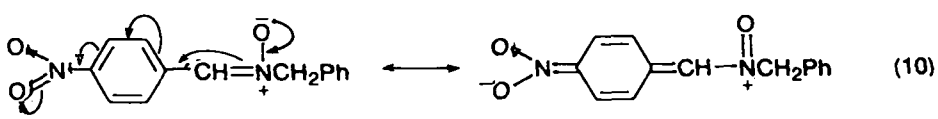
(46a) (46b)

(47)

It has been found that all *para* substituents (NO_2, Cl, Me, OMe) favour nitrone type **46b** over **46a** although in the *p*-NO_2 case the equilibrium constant is not far from 1. This reasserts the previously mentioned assumption (Section II.A.2.c) that the nitrone function is electronically amphoteric and can interact both with electron-releasing and electron-withdrawing groups (see equations 9 and 10). This



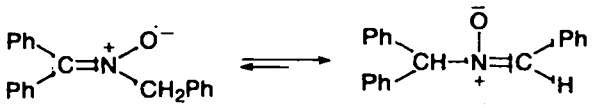
(9)



(10)

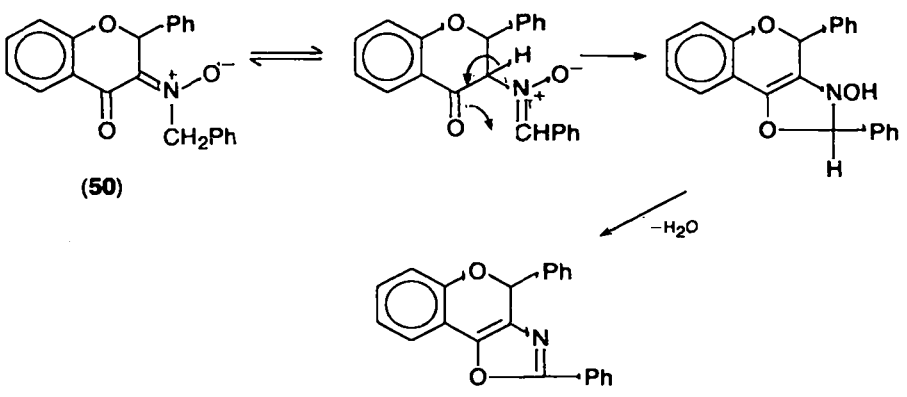
conclusion is supported by the fact that *meta* substituents disfavour the substituted benzylidene isomers. In the *ortho*-substituted nitrones the substituted benzylidene is also disfavoured. This latter result can be rationalized in terms of steric interference

of the substituent with conjugation. The question of the equilibrium in α,α-diphenyl *N*-benzyl nitrone (**48**), which was one of Behrend's first examples has also been reexamined[39]. It has been found that **49** predominates approximately by a factor of 2 over **48** presumably due to steric hindrance in the latter.



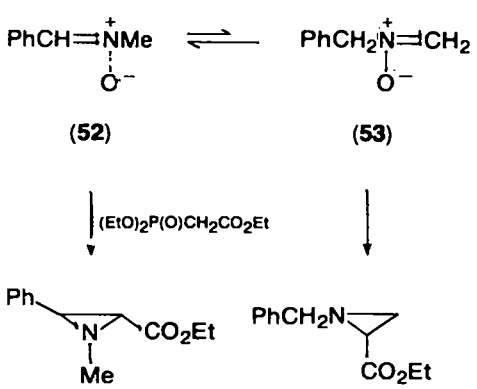
(**48**) (**49**)

In certain instances Behrend rearrangement is indicated by the structure of the end-product obtained. Thus the base-catalysed conversion of the flavanononitrone **50** to the oxazole **51** can be rationalized by assuming Behrend rearrangement followed



(**50**) (**51**)

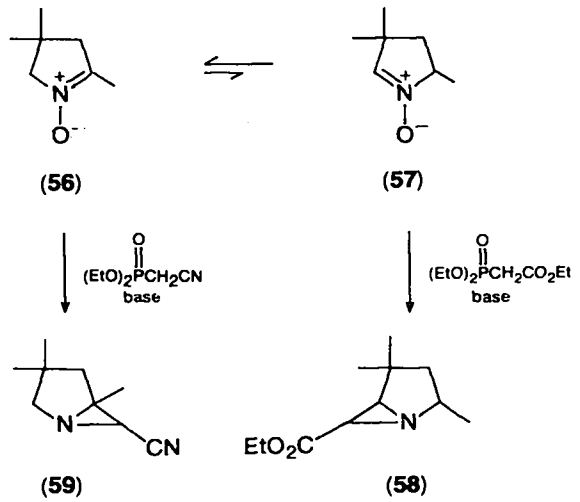
by cyclization and loss of a water molecule[73]. The base-catalysed reaction of α-phenyl *N*-methyl nitrone (**52**) with triethyl phosphonoacetate leads predominantly to 1-benzylaziridine-2-carboxylate (**55**) and less to its isomer **54** indicating the involvement of the unstable but reactive *N*-benzyl nitrone (**53**) in the reaction[81].



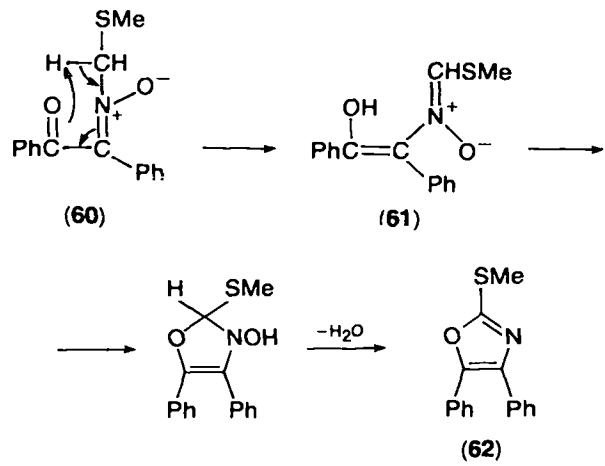
(**52**) (**53**) (**54**) (**55**)

Similarly the reaction of 2,4,4-trimethylpyrroline *N*-oxide (**56**) with triethyl phosphonoacetate gives only product **58** resulting from the less stable but more reactive aldonitrone (**57**), whereas the more reactive diethyl

cyanomethylphosphonate is capable of reacting with the ketonitrone **56** to give product **59**[82].

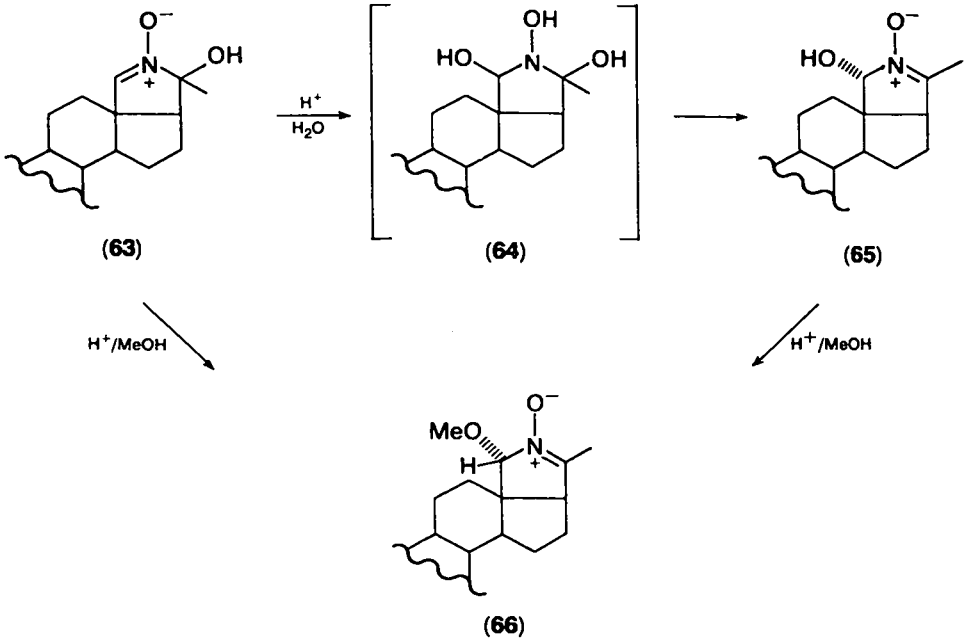


An unusual thermal transformation occurs in (*E*)-α-benzoyl-α-phenyl *N*-methylthiomethyl nitrone (**60**). The formation of the oxazole (**62**) is rationalized by assuming the conversion of the α-benzoyl nitrone to the *N*-(2-hydroxyvinyl) nitrone **61** by a [1,5] proton shift, which then undergoes cyclization (see Section II.A.5.c) followed by loss of water to **62**[68]. The (*Z*) isomer of 60 does not undergo this reaction[68].

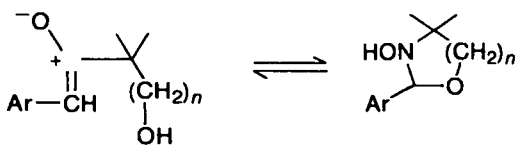


An isomerization which can be viewed as formally if not mechanistically related to the Behrend rearrangement is observed in steroidal nitrones. It is found that hydroxynitrone **63** is converted by acid to its isomer **65**, presumably through intermediate **64**[83]. Both **63** and **65** furnish the same methoxynitrone **66** upon treatment with methanolic acid[83].

c. Ring–chain tautomerism. Early examples of this type of tautomerism have been reviewed[2]. More recently the preparations of a large series of α-aryl *N*-(2-hydroxyalkyl) nitrones (**67**)[84,85] and one example of α-aryl *N*-(3-hydroxyalkyl)



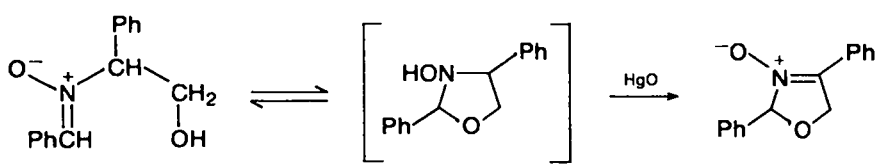
(63) (64) (65) (66)



(67) n = 1
(68) n = 2
(69) n = 3

(68) and of α-aryl *N*-(4-hydroxyalkyl) (69) nitrone[85] have been reported. There is no spectral evidence found to indicate the presence of any cyclic tautomer in any of these cases. Acetylation of 67 gives, however, mixtures of the open-chain and cyclic acetates[84].

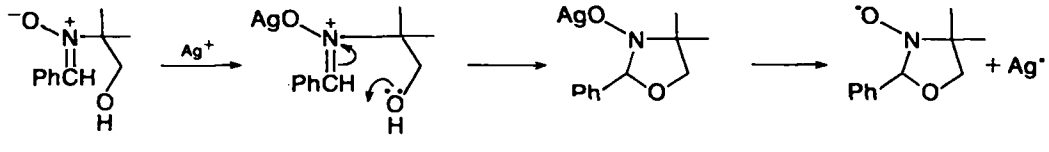
Oxidation of an *N*-(2-hydroxyalkyl) nitrone of type 67 with mercuric oxide leads to an oxazoline *N*-oxide indicating involvement of the cyclic tautomer in the reaction (equation 11)[84]. The *gem*-dimethyl nitrone 67 is oxidized by silver ion to the cyclic



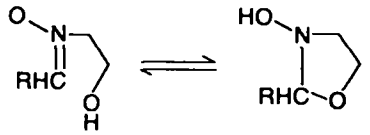
(11)

nitroxide radical 70[85]. It has been suggested that in this case the cyclization is facilitated by the silver ion acting as a Lewis acid[85].

In contrast to the α-aryl nitrones mentioned, examination of a series of aliphatic aldonitrones by spectroscopic methods has revealed the presence of the cyclic

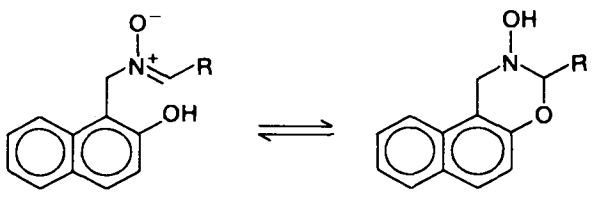


(67) (70)

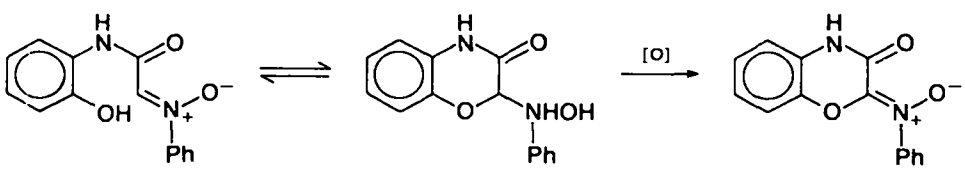


(12)

tautomers in the equilibrium mixture (equation 12). Acylation gives derivatives of the cyclic tautomer[86]. Ring–chain tautomerism has also been studied in 2-hydroxynaphthalene derivatives, **71**[87,88]. The equilibrium composition is influenced by R as well as by the medium. Acetylation gives derivatives of the cyclic tautomer **72**[89]. The *o*-hydroxyphenylaminoacyl nitrone **73** could be converted to the cyclic tautomer **74**, which could be oxidized to the new nitrone **75**[90,91]. Acetylation of both

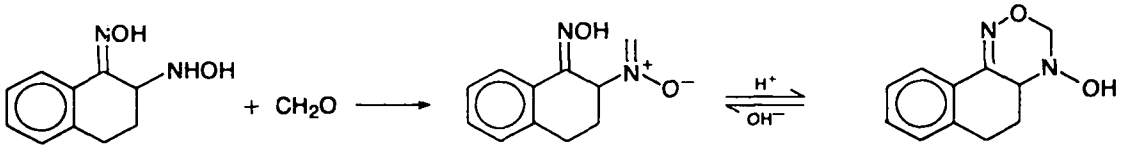


(71) (72)



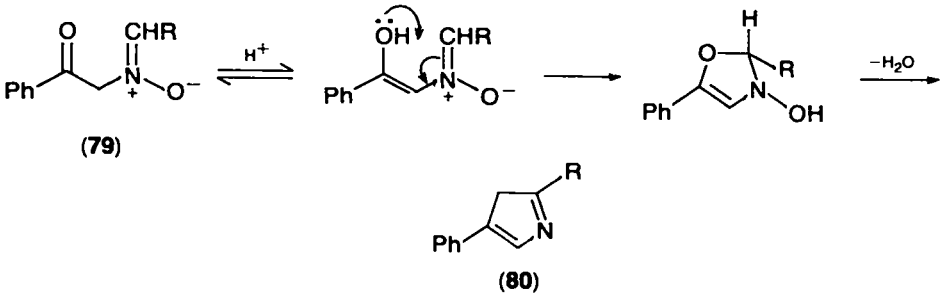
(73) (74) (75)

tautomers is reported to lead to the derivative of the open-chain tautomer, **74**. The condensation products of α-hydroxyaminooximes (e.g. **76**) with aliphatic aldehydes exhibit pH-dependent ring–chain tautomerism (**77** ⇌ **78**)[92]. Acylation in these cases

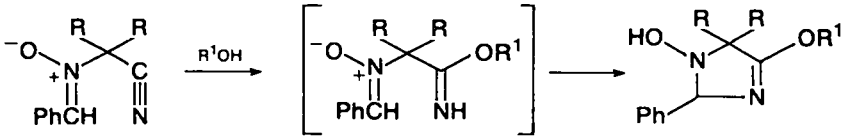


(77) (78)

leads to derivatives of the cyclic tautomers[92]. The related *N*-(2-ketoalkyl) nitrones (**79**) undergo acid-catalysed cyclization–dehydration to oxazoles (**80**) through their enol tautomers[93]. Attempts to convert *N*-(2-cyanoalkyl) nitrone **81** to the corresponding imino ether, **82**, have resulted in the formation of the imidazoline derivative **83**[94].



(79) (80)



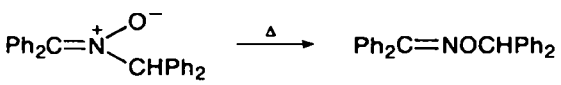
(81) (82) (83)

B. Reactions of Nitrones

1. Rearrangements of nitrones

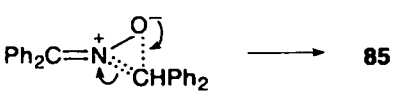
Nitrone rearrangements have been reviewed extensively by Lamchen in 1968[5]; also some photochemical processes of nitrones can be found in a more general review concerning *N*-oxides[95]. Consequently this chapter will not be concerned with the historical background.

a. Formation of oxime O-ethers – the Martynoff rearrangement. This rearrangement, which is represented by the thermal conversion of α,α-diphenyl *N*-benzhydryl nitrone (**84**) to benzophenone oxime *O*-benzhydryl ether (**85**) is far



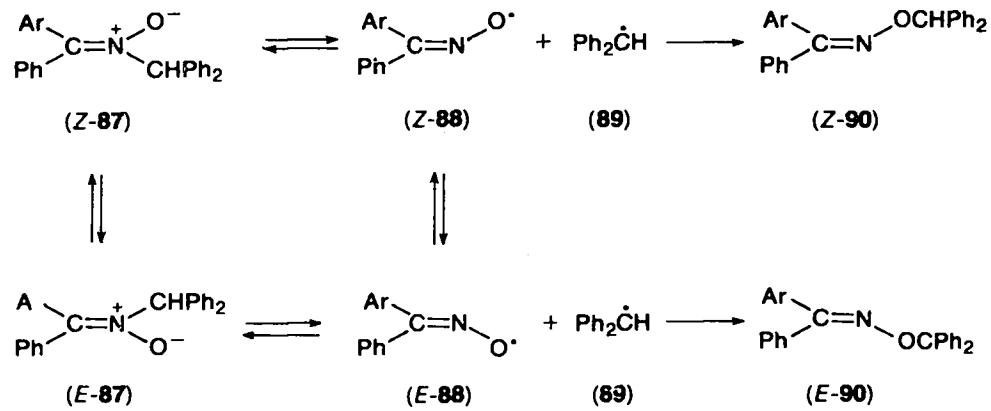
(84) (85)

from being a general reaction. For example *N*-alkyl, *N*-aryl or *N*-benzyl nitrones do not undergo this reaction. In spite of its limited synthetic importance the mechanism of this reaction has been thoroughly studied by a variety of experimental techniques. The initially proposed concerted mechanism[96] involving a three-membered cyclic transition state (**86**) has been disproven. The mechanism which is supported by all



(86)

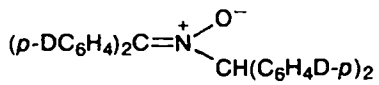
experimental results involves dissociation to iminoxy radicals (e.g. **88**) and benzhydryl radicals (**89**) which then recombine to form the oxime benzhydryl ether. ESR spectra indicate the presence of iminoxy radicals[97], while the presence of benzhydryl radicals has been shown by chemically induced nuclear polarization[98] and also be the isolation of tetraphenylethylene. By careful study of the steric course of



(*Z*-87) (*Z*-88) (89) (*Z*-90)

(*E*-87) (*E*-88) (89) (*E*-90)

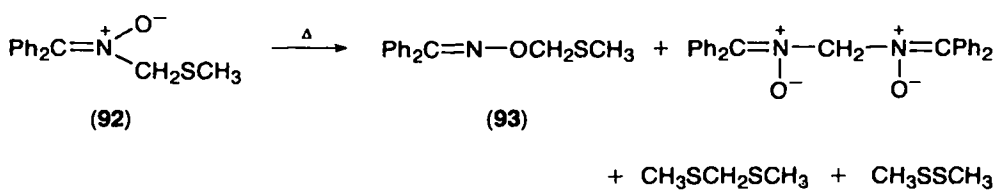
the rearrangement of (*E*)- and (*Z*)-nitrones **87**, it was found that the formation of ethers is not stereoselective due to (*E*) ⇌ (*Z*) isomerization of the iminoxy radicals which is faster by several orders of magnitude than the isomerization of nitrones and of oximate anions under the reaction condition[99]. Other studies include a kinetic investigation of the effect of substituents in the aromatic ring. The lack of significant substituent effect upon the rate of the rearrangement argues against an ionic mechanism[100]. This rearrangement has also been studied using mixtures of α,α-diphenyl *N*-benzhydryl nitrone (**84**) and its tetradeuterio derivative **91**. On the



(**91**)

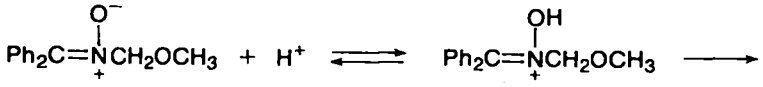
basis of the crossover products that were observed, the extent of the intermolecularity of the reaction has been determined[101]. It was found that the intermolecular process is solvent-dependent. The thermal rearrangement of *N*-(diphenylmethylene)methylthiomethylamine *N*-oxide (**92**) yields, beside the oxime *O*-alkyl ether **93**, several products (see Scheme 3)[102]. The formation of these products is rationalized by assuming that several competing free-radical reactions take place simultaneously. Some free radicals are observed by ESR.

N-Methylthiomethyl nitrone **92** also undergoes rearrangement with acid catalysis to the same products. These results are rationalized by mechanisms that involve protonation of the nitrone oxygen followed by reaction with a nucleophile present[103]. The related methoxymethyl nitrone **94** rapidly isomerizes under the influence of acid catalysis to the corresponding oxime ether, which, however, decomposes slowly under the reaction conditions[104]. The mechanism suggested for this reaction consists of a protonation step, followed by dissociation to the oxime and methoxymethyl carbonium ion which recombine to yield the protonated oxime ether (**95**).

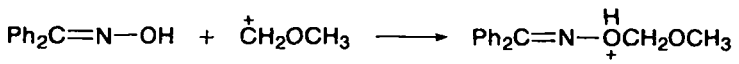


(**92**) (**93**)

SCHEME 3

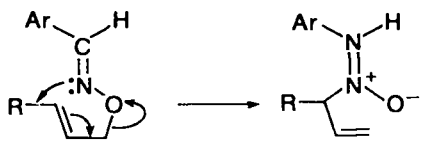


(94)



(95)

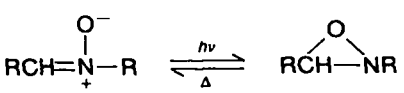
The reverse reaction, namely the rearrangement of oxime *O*-ethers to nitrones has also been observed in the case of *O*-allyl ethers[105–107]. This reaction has been considered initially as a [2,3] sigmatropic rearrangement (**96–97**)[105]. Subsequently it



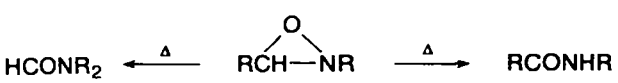
(96) (97)

has been suggested on the basis of ESR spectra[106] that, at least in part, it proceeds by a radical dissociation–recombination mechanism.

b. Formation of oxaziridines. This rearrangement is represented by equation (13). The stability of the three-membered ring products is varied, some are quite stable and others are formed as transient intermediates which undergo transformation to other products, mainly to one or both of the two possible amides (equation 14). Oxaziridines can sometimes undergo thermal rearrangement back to nitrones[2].

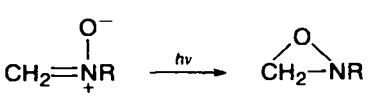


(13)



(14)

The earlier studies regarding this rearrangement can be found in the reviews[2–5]. Recent additions to the existing reports on stable oxaziridines are the *N*-monosubstituted compounds **99** that can be formed by irradiation of methylene nitrones, **98**[108]. These oxaziridines can be further rearranged to the corresponding formamides.

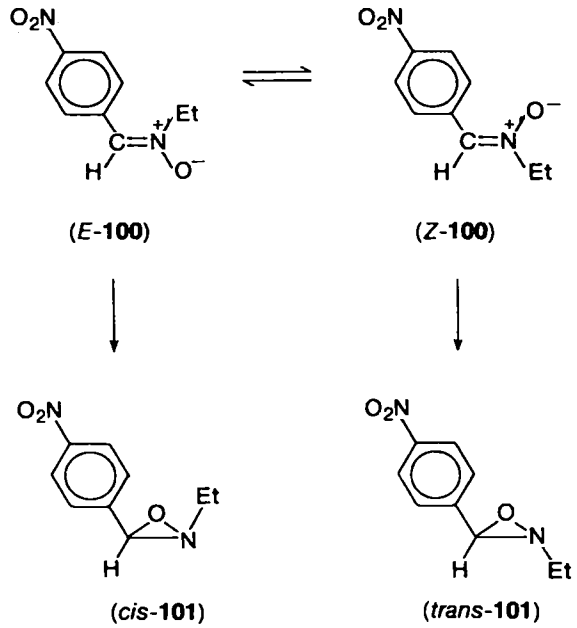


(98) (99)

R = adamantyl, *t*-butyl

Studying the mechanism and stereochemistry of this rearrangement, Boyd and coworkers reported that irradiation of α-(*p*-nitrophenyl) *N*-alkyl nitrones (e.g. **100**) at room temperature gives rise to mixtures of *cis*- and *trans*-oxaziridines, with the latter predominating, but the composition of which depends upon the solvent[109]. These findings were disputed by Splitter and coworkers, who observed at −60°C the

exclusive formation of *trans*-oxaziridines (**101**)[110]. They also found that under the conditions of partial irradiation a photostationary state consisting of the two



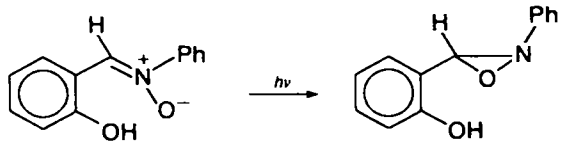
(*E*-**100**) (*Z*-**100**)

(*cis*-**101**) (*trans*-**101**)

geometrical isomers of nitrone **100** in the ratio 37% *E*/63% *Z* is attained. Comparing the ratio of products calculated from the quantum yields of the reaction of each nitrone isomer with the the experimental results it was found that the reaction of conversion of nitrones to oxaziridines is stereospecific[110].

In attempts to achieve asymmetric syntheses of oxaziridines nitrones were irradiated in a chiral solvent[111] as well as in an asymmetric liquid crystalline cholesteric medium[112]. While in the asymmetric solvent oxaziridines were obtained in optical yields of about 30%, the products from the experiments in cholesteric media showed negligible optical rotation.

The effect of intramolecular hydrogen bonding on the nitrone photoisomerization has also been studied[113]. The effect of different solvents upon the quantum yield of oxaziridine formation from *N*-phenyl salicylaldonitrone (**102**) with intramolecular

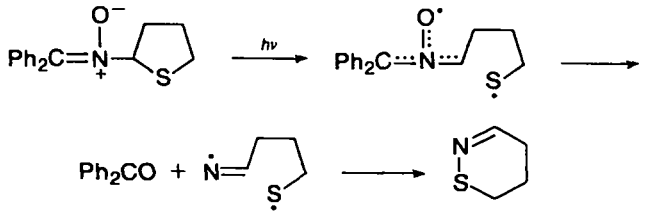


(**102**)

hydrogen bonds have been correlated. The quantum yields in the reaction of **102** increase with decreasing temperature. In contrast the quantum yield in the reaction of α,*N*-diphenyl nitrone is not temperature-dependent[113].

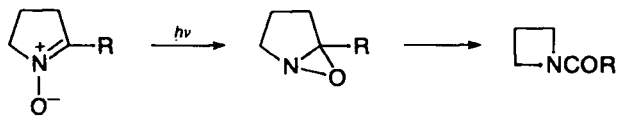
The photolysis of some interesting sulphur-containing nitrones has been shown to lead to methyleneoxaziridine radicals and via these to benzophenone and to sulphur–nitrogen heterocycles[114,115] (e.g. Scheme 4).

Oxaziridines derived from cyclic nitrones such as pyrroline *N*-oxides often undergo



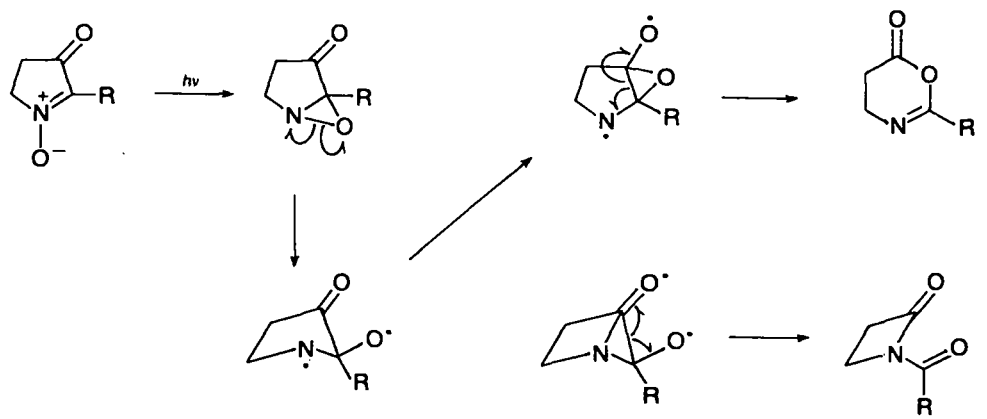
SCHEME 4

ring-contraction reactions that lead to 1-acylazetidines[5] (see equation 15). Some new examples of this reaction have been reported[116,117a,b]. Similarly to acyclic

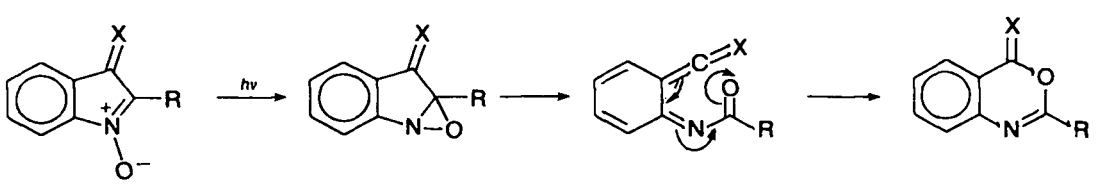


(15)

ketonitrones that upon irradiation yield imides[118,119] as a consequence of acyl migration in the intermediate oxaziridines, the irradiation of 3-oxo-Δ^1-pyrroline *N*-oxides yield β-lactams accompanied by 1,3-oxazine-6-one derivatives[120] (see Scheme 5). When the five-membered ring is condensed to a benzene ring only the ring-expansion reaction leading to benzoxazines is observed as has been demonstrated in several cases (equation 16)[121–123]. The first example of this series



SCHEME 5

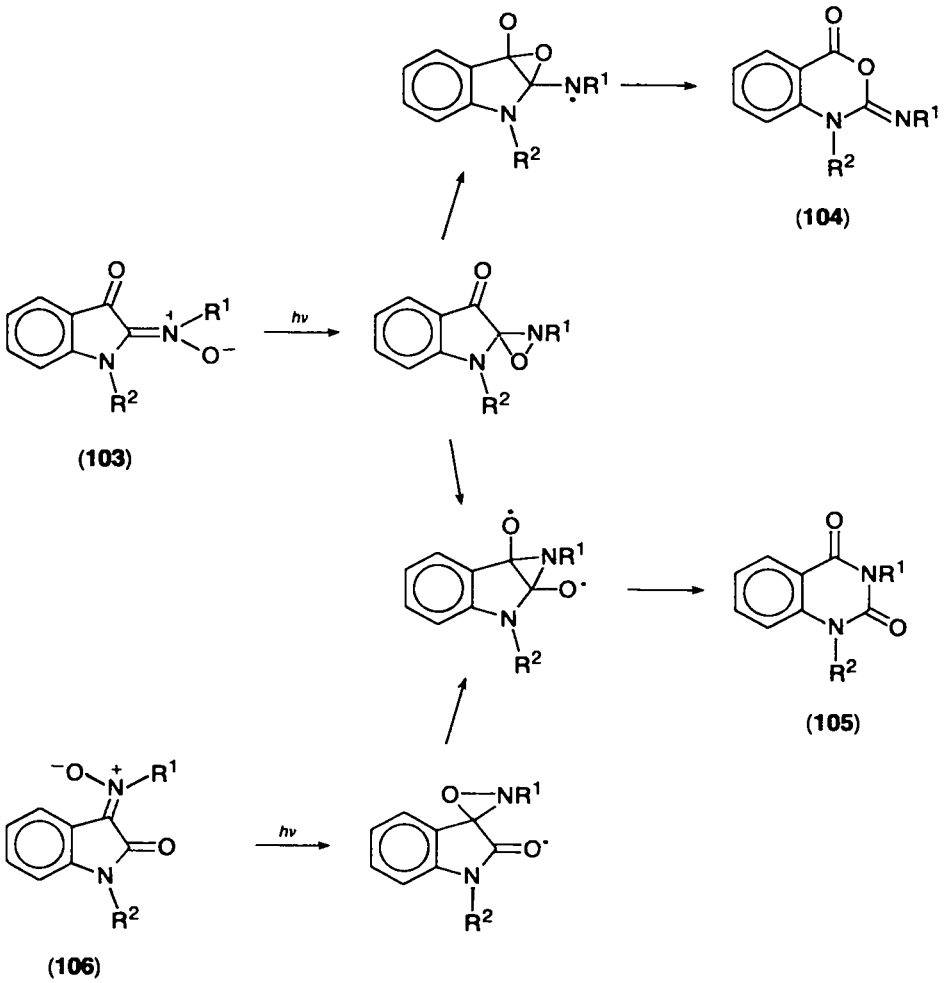


X = Me_2 (Ref. 121)
X = O (Ref. 122)
X = NPh (Ref. 123)

(16)

(X = Me_2) cannot accommodate a free-radical-type mechanism because of the presence of the two *gem*-dimethyl groups. However the 3-keto and the 3-phenylimino derivatives may react through a biradical pathway similar to that in Scheme 5.

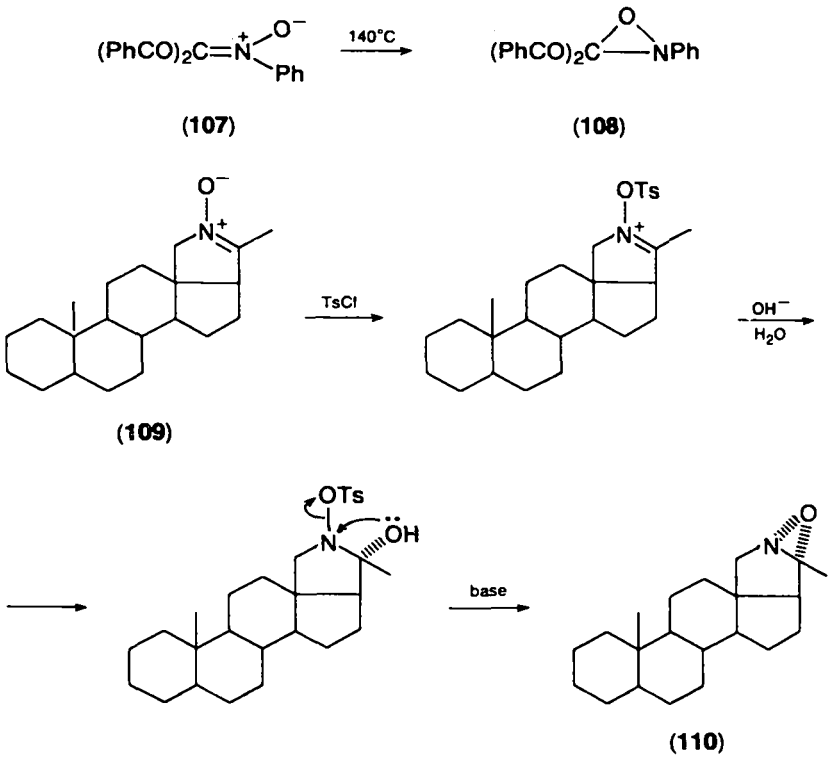
The photorearrangement of related indolinylidene *N*-oxides also results in ring-enlargements via oxaziridines. Thus amidine *N*-oxides (**103**) yield mixtures of benzoxazines (**104**) and benzopyrimidines (**105**) in addition to products resulting from deoxygenation[124]. The isomeric *N*-oxide derivatives (**106**) also yield **105** in



addition to products of hydrolysis and of geometrical isomerization. In addition to the photochemical processes there are other reports concerning the isomerizations of nitrones to oxaziridines. One paper reports the thermal conversion of α,α-dibenzoyl *N*-phenyl nitrone (**107**) to the oxaziridine **108**[125].

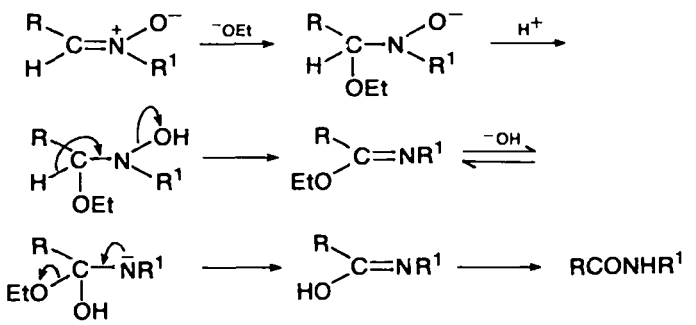
In another paper[126] it has been reported that the steroidal nitrone **109** is converted to the isomeric oxaziridine **110** by *p*-toluenesulphonyl chloride followed by base.

c. Formation of amides. The rearrangement of nitrones to amides has already been mentioned in the previous section, as amides are often the end-products of the

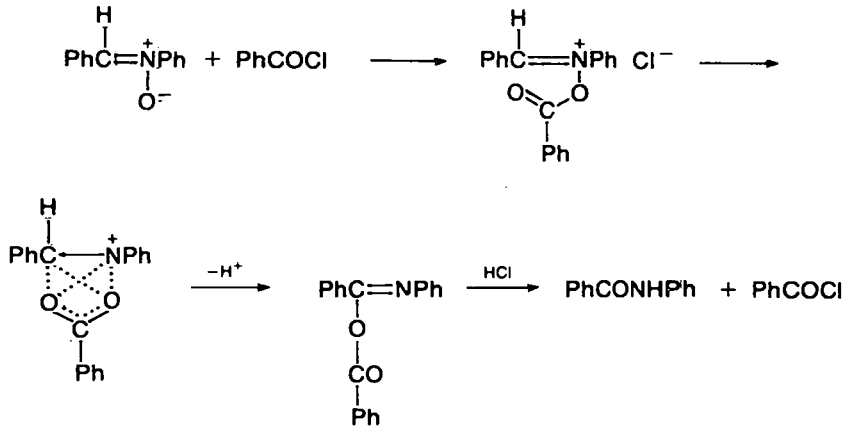


nitrone–oxaziridine rearrangement[25]. However in addition to this mode of amide formation there are several ways to effect the nitrone–amide rearrangement under conditions that clearly do not involve oxaziridines as intermediates. These include reactions which proceed under the catalytic effect of sodium alkoxides as well as acid anhydrides and acyl halides, catalysts normally used in the Beckmann rearrangement. Most of these examples can be found in the reviews[2–5,127]. Therefore it will suffice here to limit the discussion to the mechanism and to some recent new examples.

It seems reasonable to represent the mechanism of the base-catalysed rearrangement of nitrones to amides by the sequence of additions and eliminations depicted in Scheme 6.



SCHEME 6



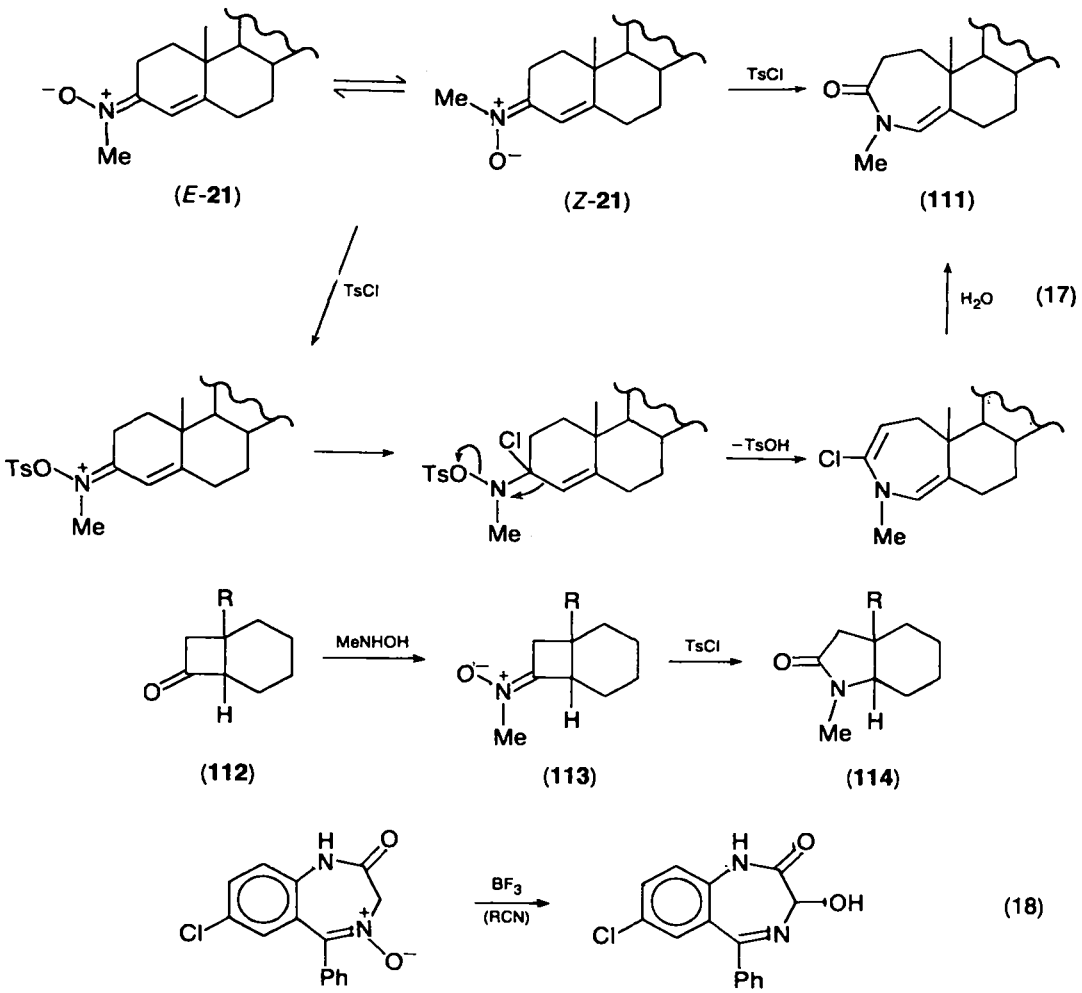
SCHEME 7

The other types of catalysts that can effect the nitrone–amide rearrangement include acetic anhydride, acetyl chloride, benzoyl chloride, phosphorus pentachloride and *p*-toluenesulphonyl chloride. By the use of ^{18}O-labelled acetic anhydride[128] and benzoyl chloride[129] it has been shown that the rearrangement reaction of α,*N*-diphenyl nitrone to benzanilide under the influence of these reagents proceeds with the partial incorporation of ^{18}O into the amide. It has been suggested that these results are consistent with the initial formation of acyloxyimine which rearranges in part by a cyclic and in part by a 'sliding' mechanism as depicted in Scheme 7. A simple scrambling which would result from the dissociation–recombination of an acyloxyimino compound is ruled out on the basis of the ^{18}O incorporation data[129]. There is no incorporation of ^{18}O into the amide when *p*-toluenesulphonyl chloride-^{18}O or phosphorus oxychloride are used for the rearrangement. This is taken as an indication that in these cases the reaction proceeds entirely by the 'sliding' mechanism[129].

This rearrangement, which was initially only known for aldonitrones was more recently extended to ketonitrones and represents an analogy to the Beckmann rearrangement. In contrast to the latter, however, its outcome does not depend on the stereochemistry of the starting material since (*Z*)- and (*E*)-nitrones (**21**) were found to interconvert rapidly under the reaction conditions and they both give the same lactame **111**[50].

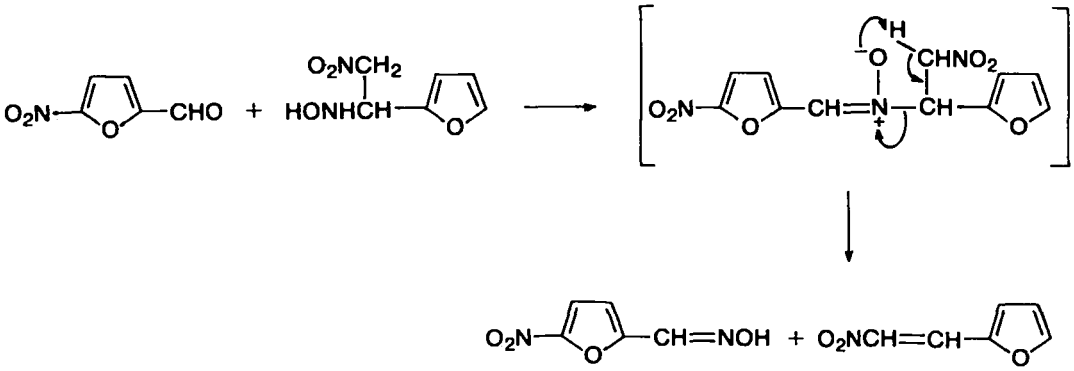
A mechanism which is consistent with the experimental results and which resembles that of the Beckmann rearrangement is presented in equation (17)[50]. This rearrangement has recently been applied to a series of bicyclo[4.2.0]octanones (**112**), which rearrange via the corresponding nitrones **113** to perhydroindolone, **114**. The conventional Beckmann rearrangement leads to the isoindole skeleton[130]. Other reactions of nitrones with acid anhydrides and acyl halides, that do not result in Beckmann type rearrangement are reviewed in Section II.B.7.a.

d. Oxygen migration. This is a rather unusual reaction somewhat reminiscent of the acetic-anhydride-induced reaction of aromatic *N*-oxides. It was found[131] that the oxygen of the *N*-oxide in a benzodiazepine derivative migrates to the position α to the nitrogen under the influence of a Lewis acid in a nitrile solvent (equation 18). The presence of nitrile was claimed essential to the success of the rearrangement, however, it was not specified in what solvents the experiments failed.

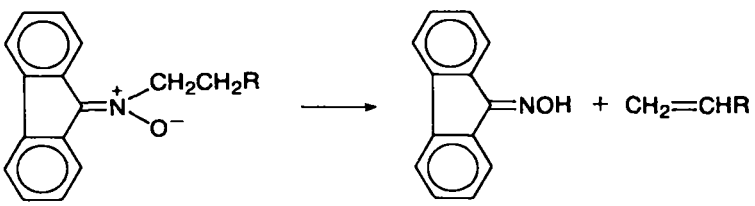


2. *Formation of olefins by elimination of nitrones*

The possibility of this reaction, which resembles the Cope elimination, was first pointed out by Kim and Weintraub in order to explain the formation of oxime and nitroolefin products in an attempted preparation of nitrones[132] (see Scheme 8). It was suggested that the nitrone is an intermediate in the reaction. This behaviour was found to be general for aldehydes possessing electron-withdrawing groups. The first examples of authentic elimination reactions of nitrones were reported by Boyd[133,134]. It was shown that *N*-alkyl-*N*-fluorenylidene *N*-oxides undergo elimination to olefins under mild conditions (equation 19). The proportion of 1-butene (58%) and 2-butene from the *N*-2-butyl-*N*-fluorenylidene nitrone and other results indicate that the direction of elimination is influenced by statistical and steric factors. There have been kinetic studies of eliminations from *N*-fluorenylidene-*N*-alkyl *N*-oxides[135] as well as from various α,α-diaryl *N*-alkyl nitrones[135–137]. It was concluded on the basis of activation entropy values that were found to be close to zero, that the reaction is concerted and proceeds through a cyclic transition state[135–137]. Examination of the

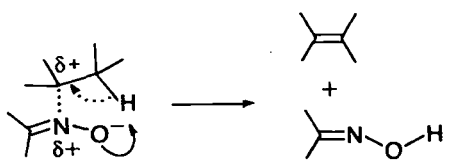


SCHEME 8



(19)

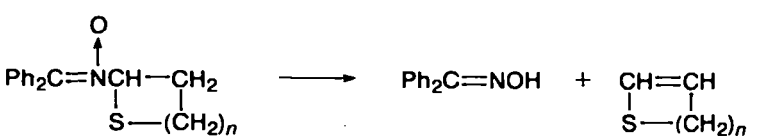
effect of substituents in substituted benzophenones upon the rate gives further evidence that the reaction is not synchronous, but that the N—C bond breakage precedes considerably the formation of the O—H[135] (equation 20). Radicals that



(20)

have been observed in pyrolytic elimination of α-aryl *N-t*-butyl nitrones[138] have been suggested to arise from minor side-reactions[135].

In a series of α,α-diphenyl *N*-alkylthioalkyl nitrones olefin-forming eliminations were sometimes accompanied by N to O migration. However the reaction could be used for thiacycloalkene formation (equation 21)[137].



(21)

$n = 2,3$

In conclusion this elimination reaction seems to be fairly general and might find uses for special cases of olefin synthesis.

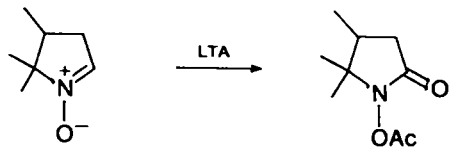
3. *Oxidation of nitrones*

The influence of a variety of oxidizing agents upon nitrones has been examined.

a. Lead tetraacetate (LTA). This reagent reacts with several types of nitrones.

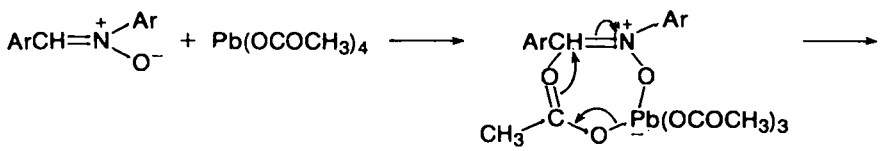
Similarly to its reaction with aromatic *N*-oxides, arylaldonitrones yield *N*-acetoxy-*N*-acylamines, that can also be viewed as *(N)O*-acylhydroxamic acids (**115**)[139–142]. A similar result has been reported for the cyclic aldonitrone (**116**) which gives *N*-acetoxy-2-pyrrolidone (**117**) in good yield[76].

(**115**)

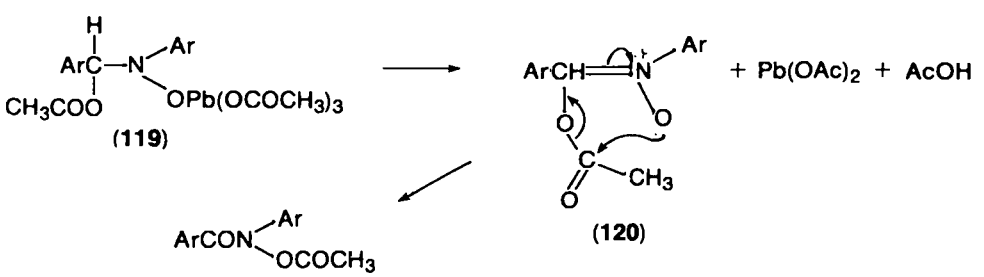


(**116**) (**117**)

Various mechanisms can be considered for this reaction; however, it seems reasonable to assume that the reaction leads in the first step to a pentocoordinated lead derivative (**118**) which subsequently rearranges to **119**. The latter collapses to the α-acetoxynitrone (**120**) with the loss of acetic acid and lead (II) acetate. Intramolecular transfer of the acetyl group in **120** leads to the end-product (**115**). In



(**118**)

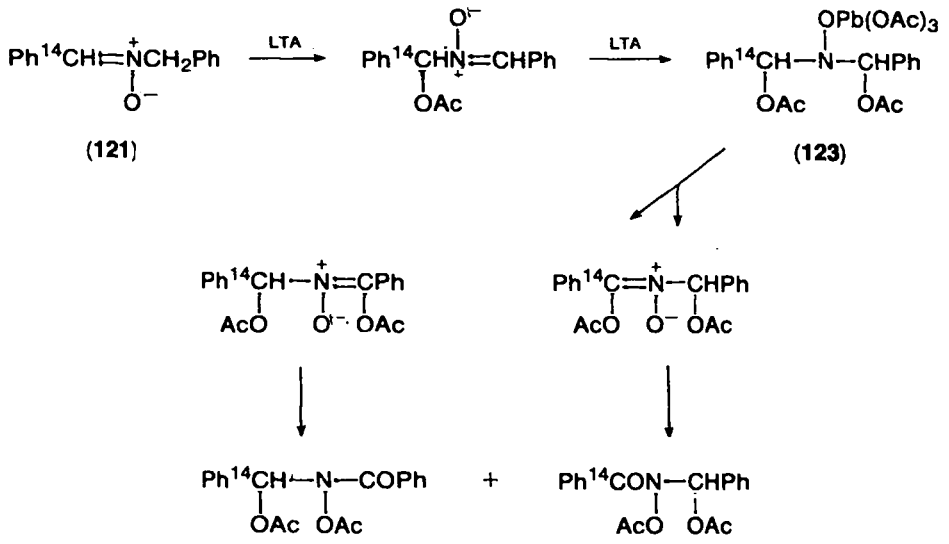


(**119**) (**120**) (**115**)

the reaction of α-phenyl *N*-*t*-butyl nitrone with LTA free radicals are observed; however, it has not been shown that hydroxamic acetates are formed therefore there is no conclusive evidence for a free-radical mechanism in this reaction.

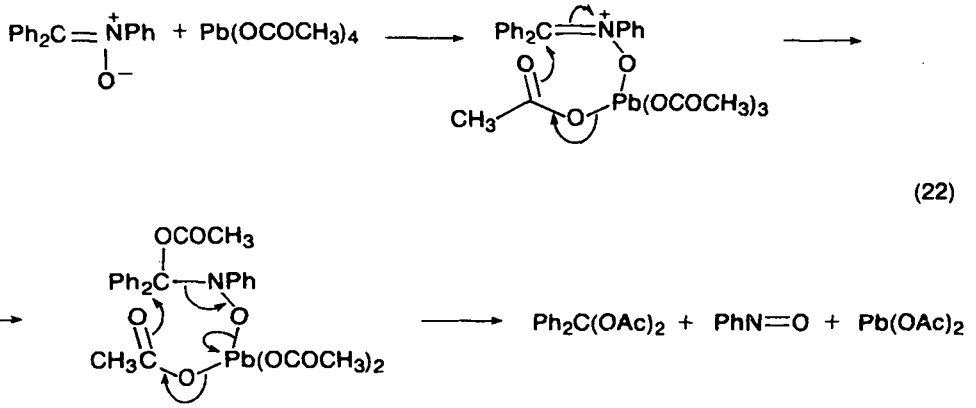
In a study using labelled starting material it has been shown that the reaction of α-phenyl *N*-benzyl nitrone (**121**) with LTA gives a scrambled product (**122**)[143]. Consequently it has been assumed that a symmetrical intermediate (**123**) is involved in the reaction.

Ketonitrones react with LTA giving a different product since there is no possibility



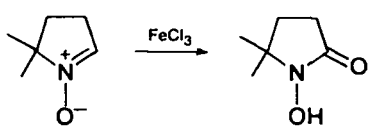
(121) (123) (122)

of eliminating acetic acid from the intermediate. α,α,*N*-triphenyl nitrone gives with LTA benzophenone diacylal and nitrosobenzene[144] presumably via the sequence shown in equation (22).



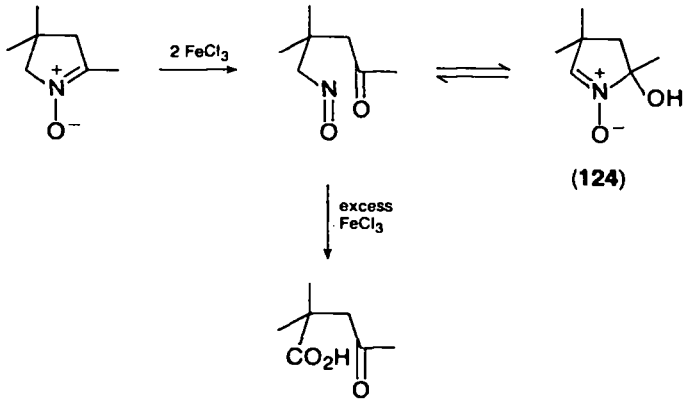
(22)

b. Iron (III) salts. Ferric chloride has been shown to oxidize aldonitrones of the pyrroline *N*-oxide series to hydroxamic acids (e.g. equation 23)[145]. The kinetics and



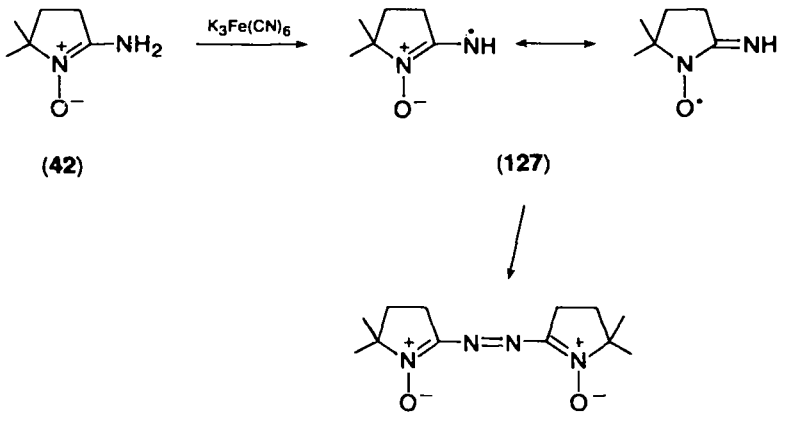
(23)

the mechanism of this reaction have been studied[146,147]. In contrast to this, ketonitrones can be oxidized either to nitrosoketones or to products devoid of nitrogen, depending upon the amount of oxidizing agent used. For example using two moles of ferric chloride the hydroxynitrone **124** may be isolated; however, excess reagent leads to the keto acid (**125**).



(125)

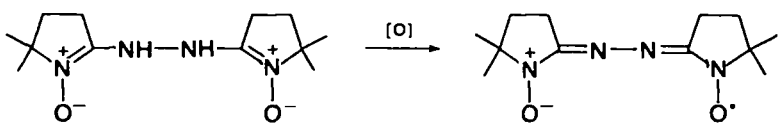
The oxidation of some 2-amino-Δ^1-pyrroline *N*-oxides with potassium ferricyanide has also been studied[77]. It has been shown that aminonitrone **42** yields upon treatment with alkaline ferricyanide (or neutral permanganate) the dimeric azopyrroline *N*-oxide (**126**) presumably via the radical intermediate **127**.



(42) (127)

(126)

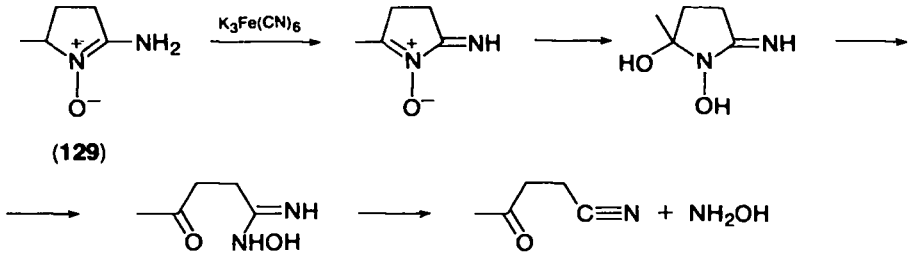
Oxidation of the related hydrazonitrone **126a** (which is obtained by hydrogenation of **126**) can be effected by air, giving the blue radical anion **128** which can be kept indefinitely in the absence of air[77] (see also Section II.B.4a).



(126a) (128)

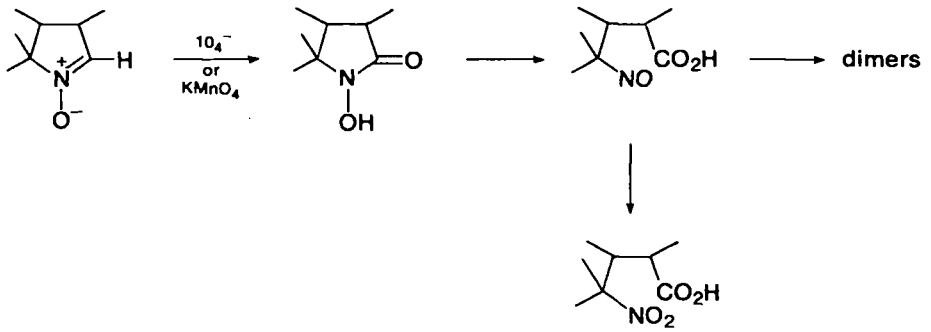
In contrast to this, ferricyanide oxidation of the monomethyl nitrone **129** leads to laevulinonitrile presumably via the sequence shown in equation (24)[77].

c. Periodate. Sodium and tetraethylammonium periodate have been used for the oxidation of pyrroline *N*-oxides[148,149]. It has been shown that variously substituted



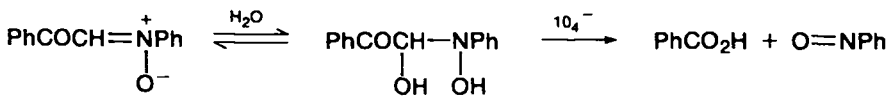
(129) (24)

pyrroline *N*-oxide aldonitrones can be oxidized by periodate to give nitrosopentanoic acids, isolated as the dimers (equation 25).



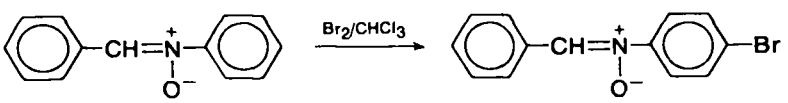
(25)

In contrast a 2-substituted pyrroline *N*-oxide was found to be stable under the reaction conditions[149]. α-Benzoyl *N*-phenyl nitrone (**130**) reacted slowly with periodate; however, its hydrate (**131**) underwent a facile oxidation to benzoic acid and nitrosobenzene[149].



(**130**) (**131**)

d. Halogenation. An attempted preparation of an α-bromonitrone by direct bromination of α,N-diphenyl nitrone with bromine resulted in bromination of the *N*-phenyl ring[150] (equation 26).

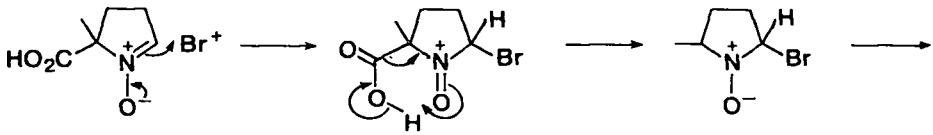


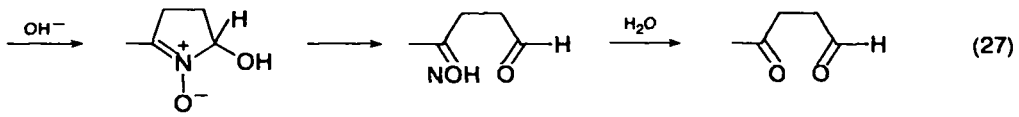
(26)

Hypobromite presumably introduces the bromine atom into the α-position of variously substituted pyrroline *N*-oxide derivatives; however, the products hydrolyse rapidly in the reaction mixture (equations 27 and 28)[151]. The cyclic hydroxamic acid can be isolated from the oxidation of 5,5-dimethylpyrroline *N*-oxide-2-carboxylic acid if excess hypobromite is avoided[151] (equation 28).

Chlorination of some aliphatic open-chain nitrones was achieved by *N*-chlorosuccinimide. This reagent introduced the chlorine atom into the β-position[152] (e.g. equation 29).

2-Substituted 5,5-dimethylpyrroline *N*-oxides (**132**) undergo bromination at the 3-position by *N*-bromosuccinimide. In case of the 2-cyano derivative (**132**, R = CN)





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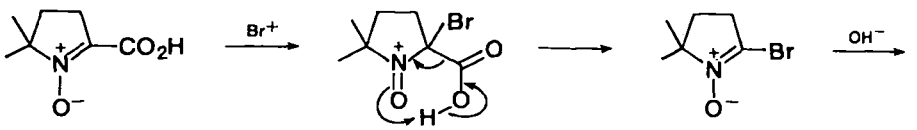
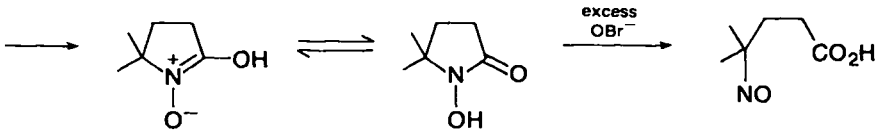
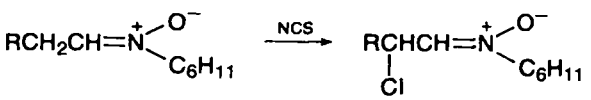


(28)

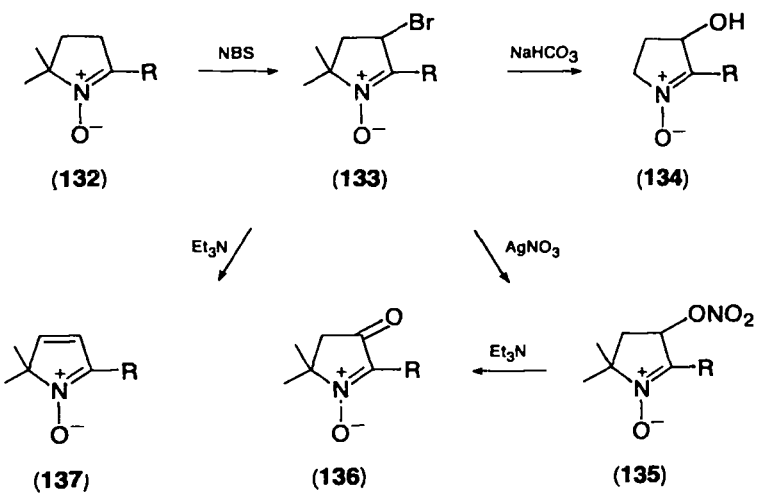




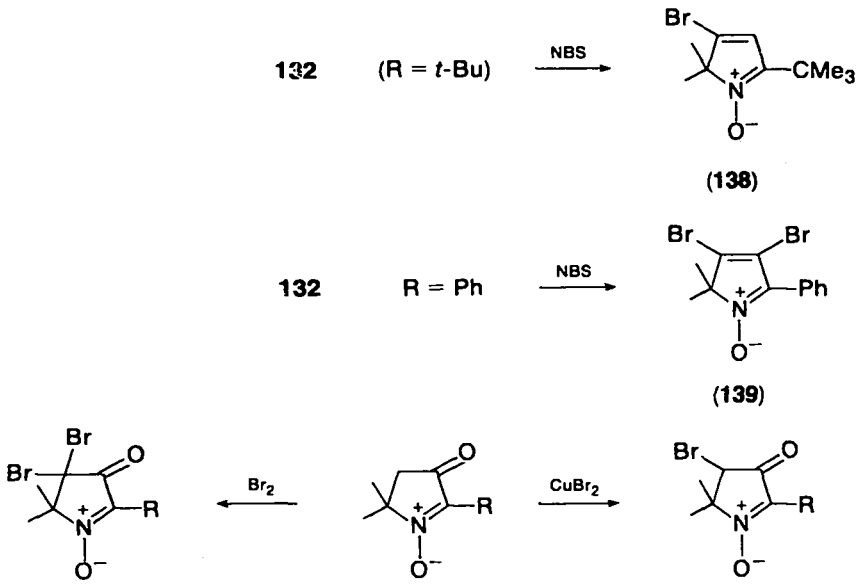
(29)

R = H, Me

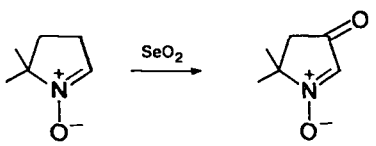
the 3-bromo compound (**133**) is obtained[153]. The latter can undergo various transformations indicated by the formulae. The reaction of the 2-*t*-butyl-5,5-dimethylpyrroline *N*-oxide (**132**, R = *t*-Bu) with NBS leads to the 4-bromo derivative (**138**) presumably through the intermediate **137**[154]. The same



reaction with the 2-phenyl derivative (**132**, R = Ph) gives the dibromopyrrolenine *N*-oxide derivative (**139**)[159]. Bromination of the related 3-oxonitrones (**140**) gives the 4-bromo or the 4,4-dibromo compounds[159].

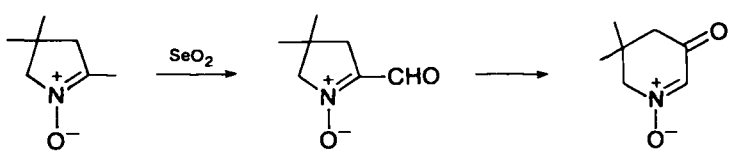


e. Selenium dioxide. This reagent is capable of oxidizing in variable yield a methyl or methylene group attached to the α-position of a nitrone function (e.g. equation 30)[155]. 2,4,4-Trimethylpyrroline *N*-oxide had previously been reported to yield upon

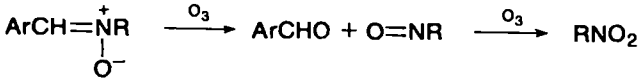


(30)

oxidation the six-membered ketonitrone (**142**) as a result of rearrangement of the initially formed aldehyde **141**[3]. More recently it has been reported that the aldehyde **141** can be obtained in satisfactory yield if the oxidation is conducted at room temperature[156].

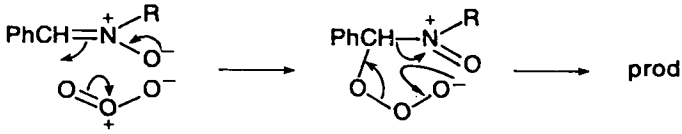


f. Ozone. Aldonitrones undergo ozonolysis rapidly at −78°C to yield aldehydes and nitro compounds. However, it has been shown that if the reaction is stopped after 1 mole of ozone is absorbed, nitroso compounds can be isolated (equation 31)[157]. The effect of substituents upon the rate ozonization has been studied, and on



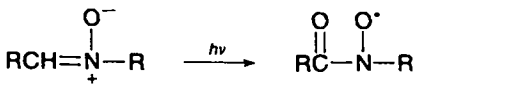
(31)

the basis of the results the conclusion has been reached that the reaction proceeds via an electrophilic attack of the ozone molecule upon the α-position of the nitrone (equation 32)[158].



(32)

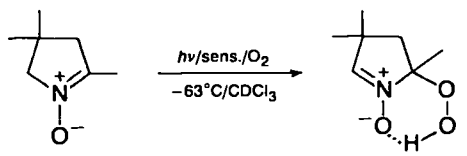
g. Photooxidation. Ultraviolet irradiation of some α,*N*-diaryl nitrones of α-phenyl *N*-*t*-butyl nitrone in solution was shown to produce aroyl nitroxide radicals (equation 33)[159].



(33)

Various mechanisms could be suggested to rationalize this observation. The source of oxygen was assumed to be either the nitrone or the isomeric oxaziridine that could be formed under the reaction conditions.

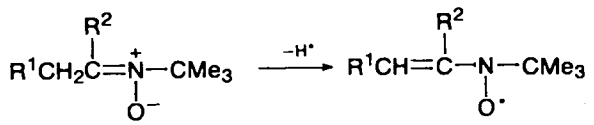
Singlet oxygen reacts with 2,4,4-trimethylpyrroline *N*-oxide to give the explosive hydroperoxide **143**[160]. The aldonitrone 4,5,5-trimethylpyrroline *N*-oxide is recovered unchanged from such a reaction.



(143)

h. Miscellaneous. Methylene groups attached to the α-position of the nitrone function that are adjacent to additional activating groups exhibit particular sensitivity to oxidation.

The activated nitrones (**144**) undergo easy oxidation by nickel peroxide or by lead dioxide to the stable radicals vinylaminyl oxides or vinyl nitroxides **145**[161]. The

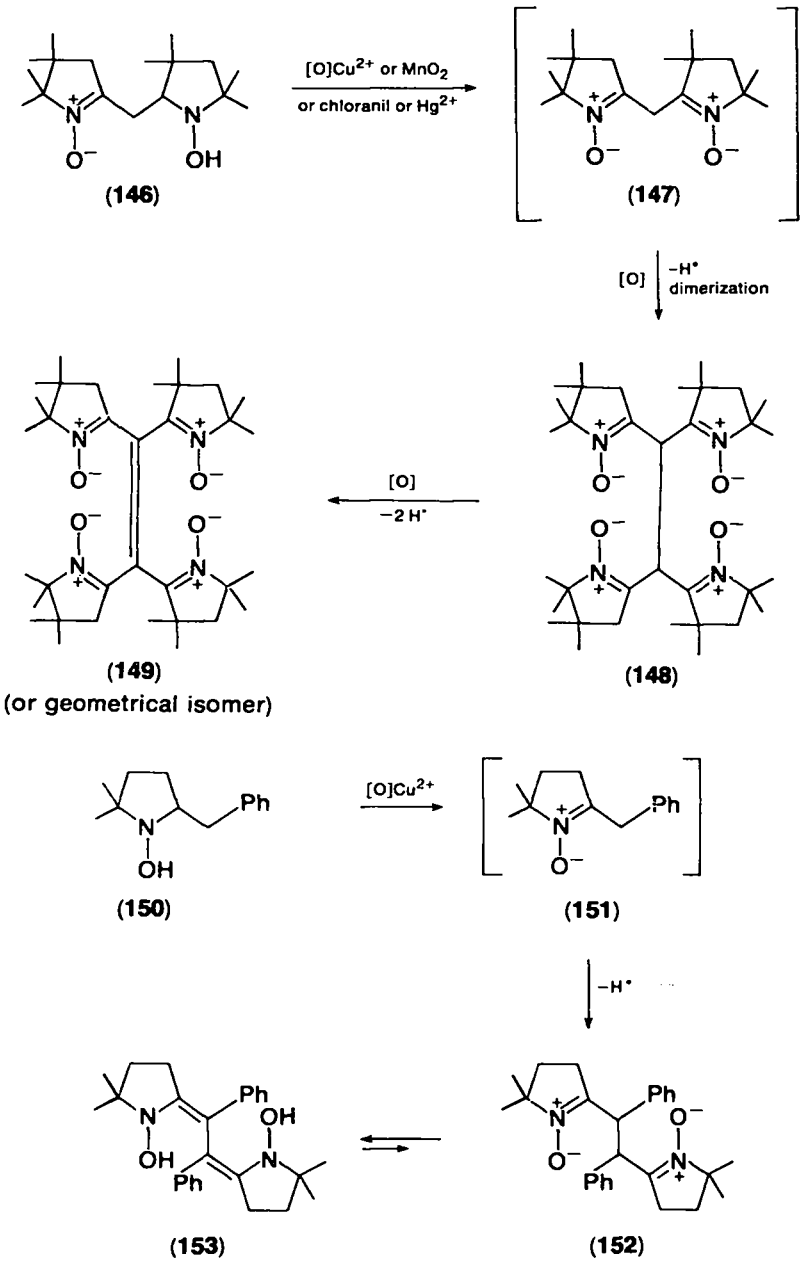


(144) **(145)**

R^1	R^2
$PhSO_2$	H
$PhSO_2$	Ph
MeOCO	MeOCO

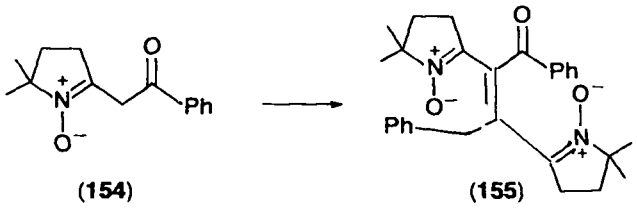
stability of the radicals is probably due to the presence of the electron-withdrawing groups R'[161]. Indeed, oxidation of nitrones containing active methylene groups that are not adjacent to electron-withdrawing groups results in the formation of dimers probably via the reactive free radicals. This is demonstrated by the reactions of various pyrroline *N*-oxide derivatives.

Attempts to prepare β-dinitrone **147** by the oxidation of the hydroxylaminonitrone **146** resulted in the formation of the dimeric products **148** and **149**[162,163]. Similarly the



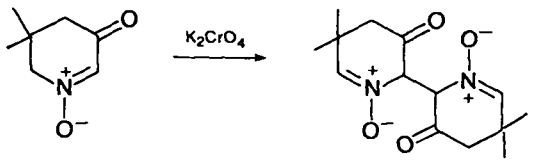
α-benzyl nitrone **151** could not be isolated. The oxidation of the hydroxylamine **150** led to the dimer **153** presumably via **151** and **152**[164].

The γ-ketonitrone **154** is a stable compound but it can also be easily oxidized to the dimer **155**[75].



(154) **(155)**

Chromate oxidation of the six-membered ketonitrone **156** also gives a dimeric product **157**[165].

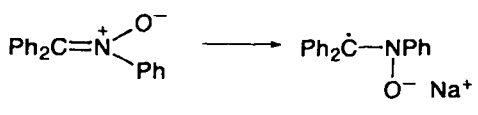


(156) **(157)**

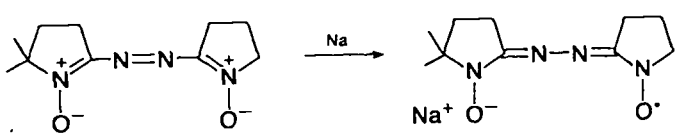
4. Reduction of nitrones

Nitrones can be reduced to the corresponding radical anions by the addition of one electron. They can be deoxygenated to imines as well as reduced to hydroxylamines or to amines by a variety of reducing agents. The earlier knowledge of these aspects is summarized in the previous reviews[2,3].

a. Reduction to radical anions. The addition of one electron to a nitrone converting it to a radical anion has been achieved using sodium metal as the reducing agent. α,α,*N*-Triphenyl nitrone has been converted to **158**[166] and **126** to **128**[77] by this method (see also Section II.B.3.b).



(158)



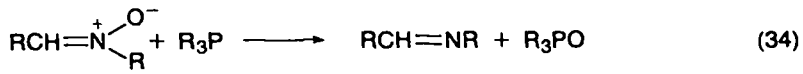
(126) **(128)**

b. Deoxygenation. A summary of typical deoxygenation procedures of aromatic *N*-oxides that are also applicable to nitrones is available in a recent book[166]. Only more recent methods will be discussed in this section.

Deoxygenation of a nitrone is reported to be induced by iron pentacarbonyl[167]. Some nitrones derived from cinnamaldehyde are successfully deoxygenated by treatment with sodium borohydride at room temperature[168]. At higher temperatures

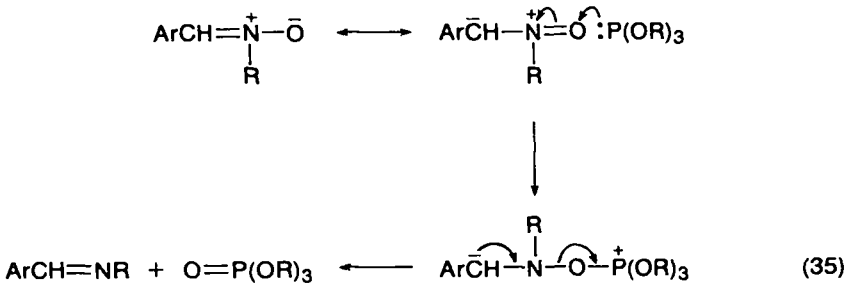
further reduction is observed. Hydrogenation over a freshly prepared W4 Raney nickel has been found a reliable method for the deoxygenation of Δ^1-pyrroline *N*-oxides[75]. Recently hexachlorodisilane has been shown to act as a mild reagent, capable of selective deoxygenation of nitrones and *N*-oxides in good yields at room temperature in chloroform[169].

One of the most common methods for the deoxygenation of nitrones and *N*-oxides is by the use of trivalent phosphorus compounds such as phosphorus trichloride, phosphines and phosphites (equation 34). The reaction of nitrones with phosphites

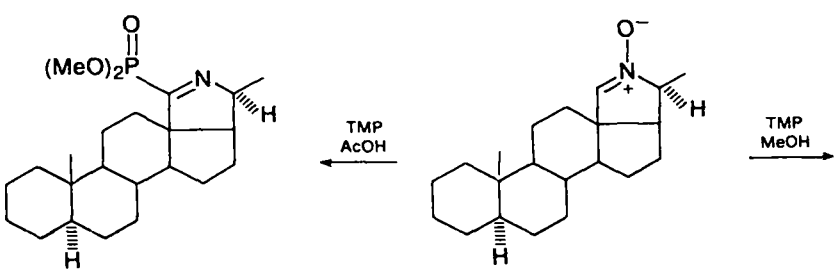


(34)

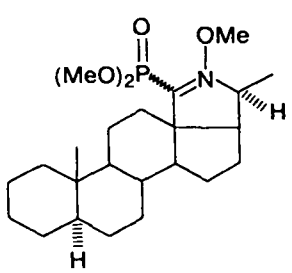
has been studied in some detail. Using α,N-diaryl nitrones substituted in both rings[170], as well as α-aryl *N*-alkyl nitrones substituted in the aromatic ring[171], it was found that the rate is enhanced by electron-withdrawing substituents, and retarded by electron-donating ones. It was suggested that the deoxygenation reaction proceeds by nucleophilic attack of the phosphorus upon the nitrogen[171]. However, a mechanism involving attack of the phosphorus upon the oxygen seems more reasonable and is in accordance with the substituent effects observed (equation 35).



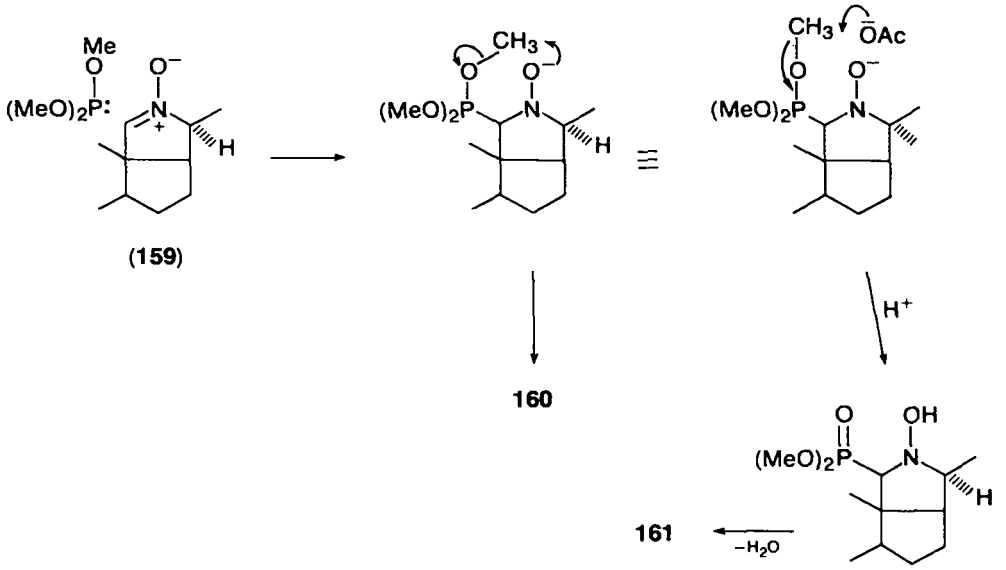
(35)



(161) (159)



(160)



SCHEME 9

Recently it has been reported that the reaction of a steroidal cyclic nitrone with trimethyl phosphite may take a variety of courses, but can be controlled to give, selectively, different products[172]. Thus, reaction of *N*-demethyl5α-Δ^{18}-conenine *N*-oxide (**159**) with trimethyl phosphite (TMP) in refluxing methanol leads to a 18-epimeric mixture of *N*-methoxyphosphonates **160**. On the other hand reaction of **159** with TMP in acetic acid gives iminophosphonate **161**[172]. The formation of these two products is rationalized by Scheme 9.

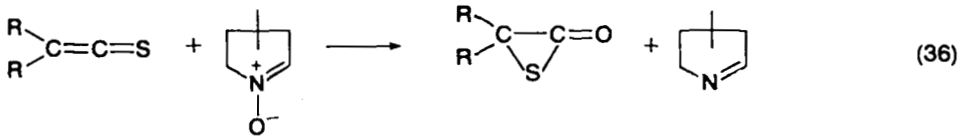
Finally simple deoxygenation of **159** can be achieved by using TMP in the presence of triethylamine.

c. Reduction to hydroxylamines and to amines. Complex metal hydrides have been reported to reduce nitrones to *N,N*-disubstituted hydroxylamines[2,3]. These include lithium aluminium hydride and sodium or potassium borohydride. Some recent examples of partial and total reduction of dinitrones by such reagents have been reported[165,173,174].

Trichlorosilane has been reported to effect reduction of *N*-aryl and *N*-alkylketo- and aldo-nitrones to the corresponding *N,N*-dialkylhydroxylamines at low temperatures and in high yields[169]. The polarographic reduction of nitrones to secondary amines via the corresponding imines has also been reported[175].

d. Nitrones as oxidizing agents. It is pertinent to this section to mention reports concerning the ability of nitrones to act as oxygen donors. There are numerous reactions of nitrones with ketenes and ketene imines in which the major product consists of the elements of the heterocumulene with the addition of the oxygen, which on mechanistic grounds can be assumed as originating from the nitrone. There is also the imine by-product isolated in these reactions. These reactions can be viewed as nitrone-induced oxidative rearrangements and are discussed in Sections II.B.6.a and b. A simple case of oxidation by a nitrone is supplied by the reaction of thioketenes with pyrroline *N*-oxides which yields α-thiollactones (equation 36)[176].

Recently it has been reported that flavin *N*(5)-oxide **162** oxidizes under illumination at ambient temperature a variety of substrates, such as phenols to

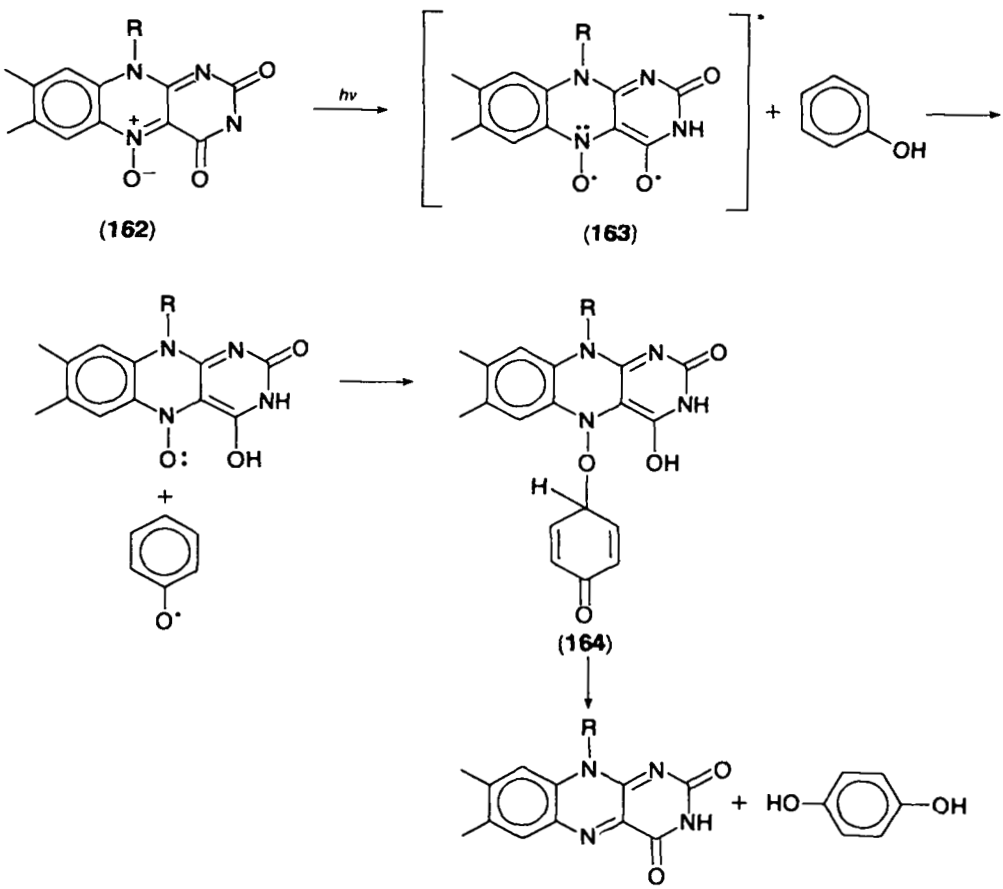


(36)

p-quinones, *N,N*-dialkylhydroxylamines to nitrones and *N,N*-dialkylbenzylamines to benzaldehyde. The reaction is assumed to proceed via the nitroxyl radical **163** as illustrated by the conversion of phenol to hydroquinone (Scheme 10)[177]. An attempt has been made to rationalize a number of flavin-dependent enzymatic oxidations in biological systems on the basis of this finding. It is proposed that nitroxyl radical **163** could also be formed from 4*a*-hydroperoxyflavin, which has previously been suggested to be the initial product of binding of molecular oxygen to flavin.

5. *Cycloaddition reactions of nitrones*

a. 1,3-Dipolar cycloadditions. This aspect of the chemistry of nitrones is clearly by far the most studied one. The mechanism of the reaction has been given a great



R = Tetraisobutyrylribityl

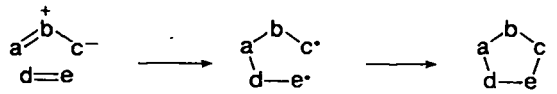
SCHEME 10

deal of attention within the context of the general 1,3-dipolar cycloaddition which encompasses reactions of a variety of 1,3-dipoles[178]. There also exist a number of recent reviews dealing with the synthetic aspects of this reaction[179–181]. The emphasis in this section will be placed on more recent papers not included in the previous reviews.

Huisgen, who was the first to formulate 1,3-dipolar cycloadditions in modern, generalized terms, advocates a concerted mechanism which assumes that the two sigma bonds are formed simultaneously[182] (equation 37a). The diradical mechanism of

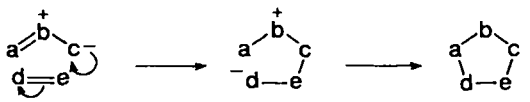
(37a)

Firestone depicts the formation of the ring in two steps, the first leading to a diradical, the second involving the cyclization (equation 37b)[183] An attempt to



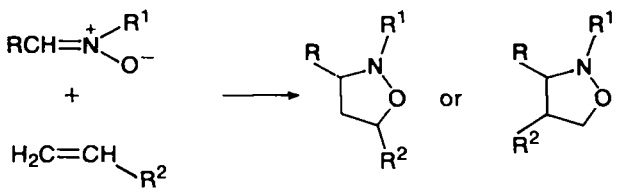
(37b)

reconcile the conflicting points between the two mechanisms has been made by Harcourt, who proposes a concerted diradical mechanism for these reactions[184]. The apparent lack of influence of solvent polarity in most 1,3-dipolar cycloadditons rules out mechanism involving ions or zwitterions[182,185], although this type of mechanism (equation 38) needs to be considered for reactions of highly polarized alkene dipolarophiles[186].



(38)

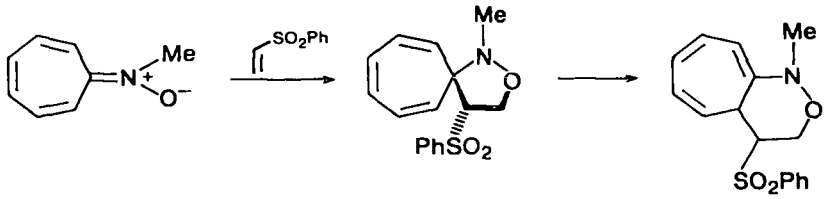
Most cycloaddition reactions between a nitrone and a monosubstituted ethylene lead to 5-substituted isoxazolidines **165** rather than the 4-substituted heterocycles **166**, regardless of whether the R^2 group is electron-withdrawing or



(165) **(166)**

electron-releasing. Only cycloadditions of nitrones with very electron-deficient alkenes lead predominantly to 4-substituted isoxazolidines. Initial attempts to explain this behaviour invoked both electronic and steric effects[187–189]; however, subsequently this aspect has been successfully treated by application of the perturbation theory. According to this the course of the reaction will be determined by the selection of the favoured frontier orbital interaction[190]. More recently it has also been shown that the amount of 4-substituted isoxazolidine also depends upon the nature of the nitrone[30]. The more electron-rich the nitrone the higher the relative proportion of the 4-substituted product. This can also be predicted by experiment, namely by determining the ionization potential of the nitrone by means of photoelectron spectroscopy. The lower the ionization potential of a nitrone the larger the tendency for a 4-substituted isoxazolidine formation, provided that the second

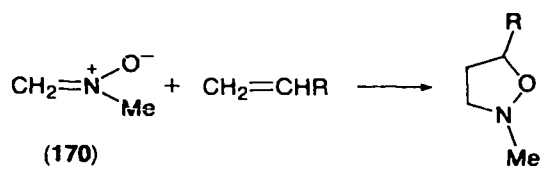
condition is fulfilled, namely that the dipolarophile is sufficiently electron-deficient. These results are rationalized in terms of frontier orbital interactions[30]. The unusual nitrone *N*-cycloheptatrienylidenemethylamine oxide (**167**), reacts with the strongly electron-deficient phenyl vinyl sulphone to give only the unstable 4-substituted isoxazolidine **168** which rapidly rearranges by a 1,7-sigmatropic shift to the final stable product **169**[191].



(**167**) (**168**) (**169**)

It is necessary to mention several recent papers with mechanistic or theoretical objectives. The kinetics of α,*N*-diaryl nitrones with *N*-phenylmaleimide[192] and dibenzoylethylene[193] have been studied. The stereochemistry of the reaction was studied using 3,4-dichlorocyclobutene[194], indene[195], 3,4-dihydronaphthalene[195], bicycloheptadiene[196] and 2-methylene[2,2,1']bicycloheptane[197] as dipolarophiles. The influence of secondary orbital interactions upon the mode of cycloadditions of nitrones with unsaturated esters has been studied by the group of Carrie and Hamelin[198]. These interactions are of two types, one between the nitrogen of the nitrone and the ester carbonyl group of the dipolarophile and the second type, between the α-phenyl group of the nitrone and the alkyl oxygen of the ester group.

Synthetic applications of the 1,3-dipolar cycloadditions of nitrones can be found in the previously mentioned reviews[179–181]; however, there are significant recent contributions that deserve mentioning. A convenient method for cycloaddition with *in situ* prepared *N*-methyl nitrone (**170**) has been published[199] (equation 39). **170** can



(**170**) (39)

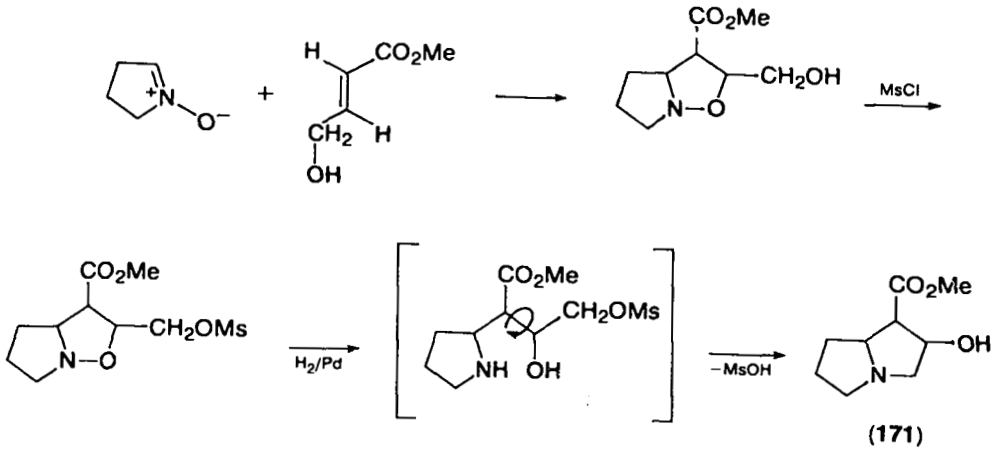
53%

be prepared by adding *N*-methylhydroxylamine to an aqueous solution of formaldehyde in the presence of a dipolarophile.

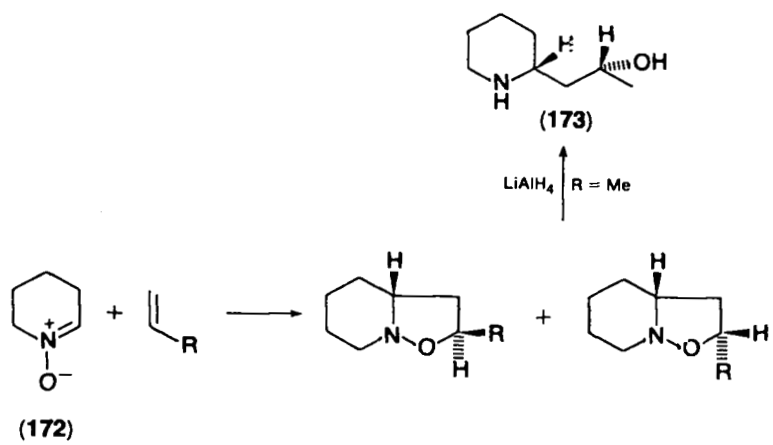
The 1,3-dipolar cycloaddition serves as a key step in a number of natural product syntheses. A simple entry to the pyrrolizidine alkaloid system is presented in Scheme 11[200].

Compound **171** is converted to alkaloids by standard methods. An analogous synthesis based on tetrahydropyridine *N*-oxide (**172**) provides entry to the quinolizidine group[201]. Compound **172** has also been reacted with styrene and with propene providing syntheses of sedridine (**173**), sedamine (**174**) and allosedamine (**175**) (Scheme 12)[202].

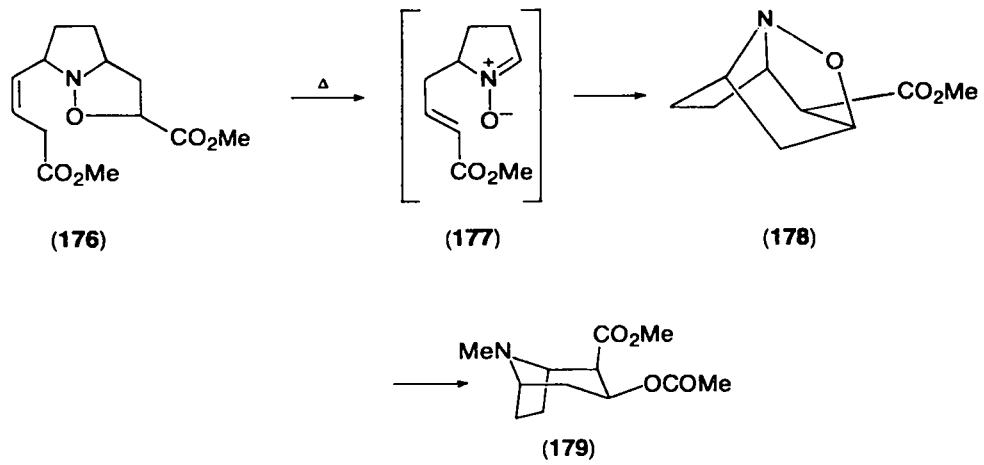
The synthesis of cocaine has also been reported recently by Tufariello and coworkers[203–205] (Scheme 13). The key intermediate in this synthesis is the unsaturated nitrone ester **177**, which was expected to cyclize intramolecularly as indicated. The efforts to synthesize **177** were initially met with severe difficulties[203].



SCHEME 11



SCHEME 12



(176) (177) (178)

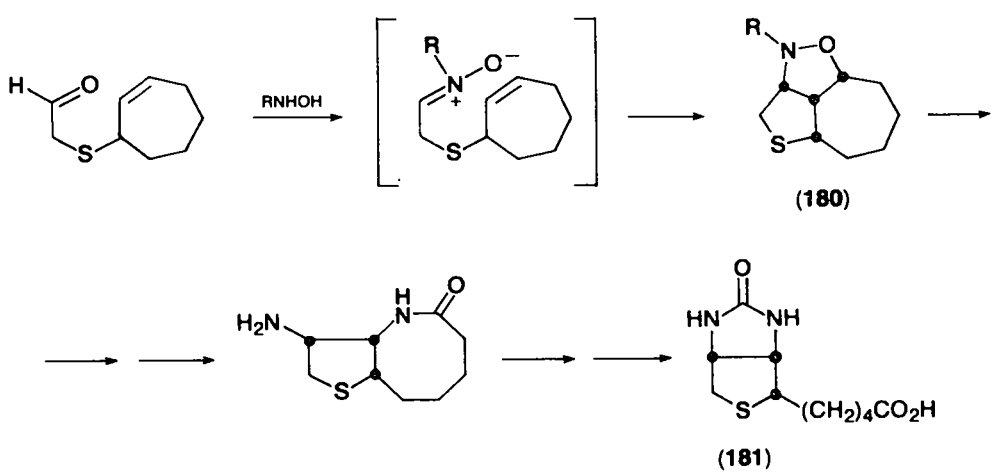
(179)

SCHEME 13

However, when the nitrone function was protected as the 1,3-cycloadduct (**176**) the side-chain could be elaborated in good yield. Finally heating **176** caused retrocycloaddition liberating the nitrone function which *in situ* cyclized to the bridged product **178**. Further elaboration gave *dl*-cocaine (**179**).

Another example of use of an intramolecular 1,3-dipolar cycloaddition reaction is a new synthesis of biotin (**181**)[206]. The key step again is the intramolecular cycloaddition leading to the tricyclic compound **180**. This can be carried out either by the use of nitrile oxide, or by the use of a nitrone 1,3-dipole. The latter is indicated in Scheme 14.

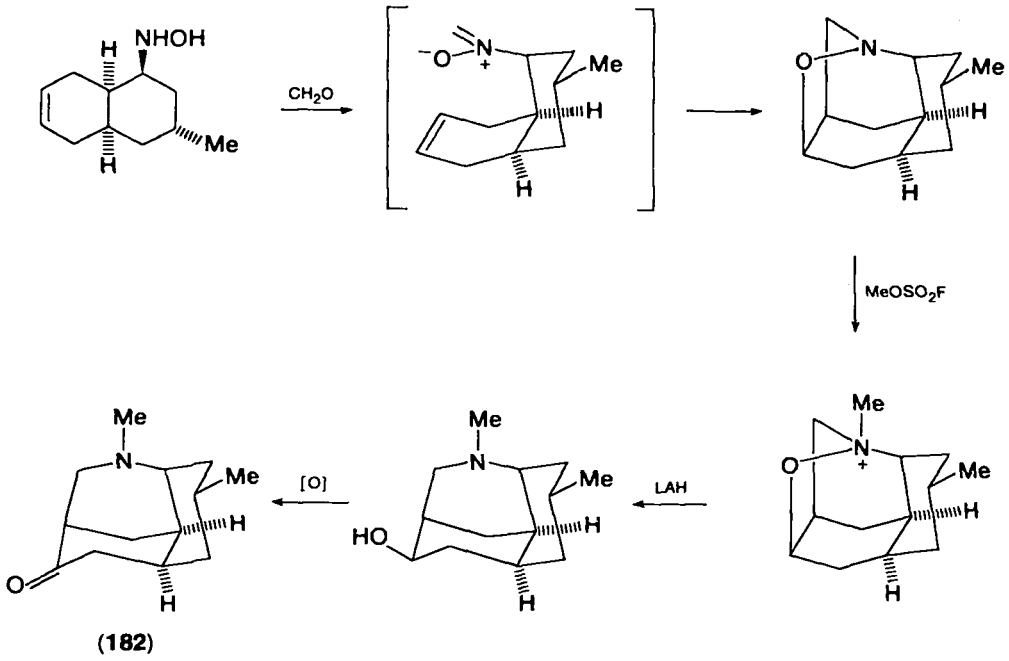
An enantioselective total synthesis of the alkaloid (+)-luciduline (**182**) has also been accomplished recently by intramolecular nitrone–olefin cycloaddition followed by methylation, reduction and oxidation[207]. Fortunately only the 'right' regioisomer was obtained in the cycloaddition step (see Scheme 15).



(180)

(181)

SCHEME 14

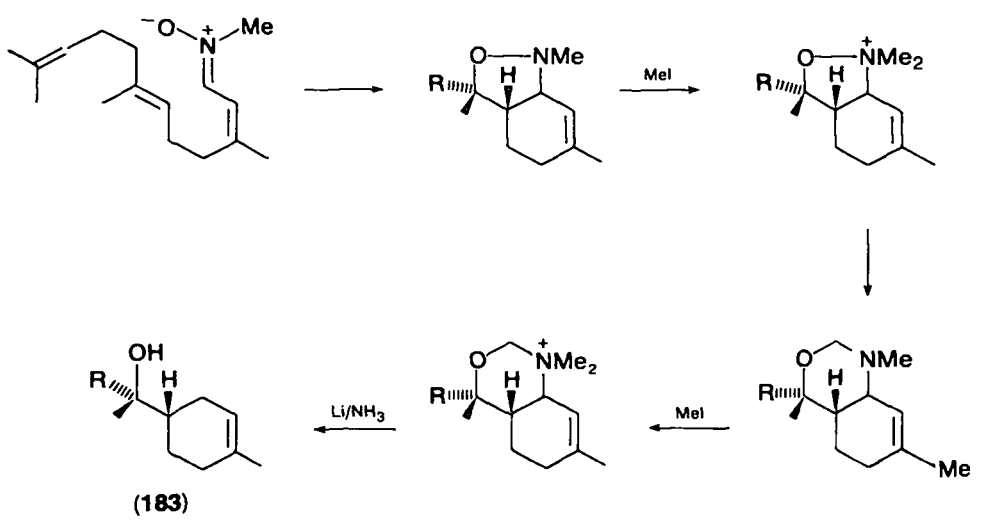


(182)

SCHEME 15

The stereospecificity of the intramolecular nitrone–olefin cycloaddition has recently been exploited for the synthesis of the sesquiterpene bisabalol (**183**)[208]. Intramolecular cycloaddition of the nitrone derived from farnesol is followed by several steps that have to be taken in order to remove the nitrogen from the molecule (Scheme 16).

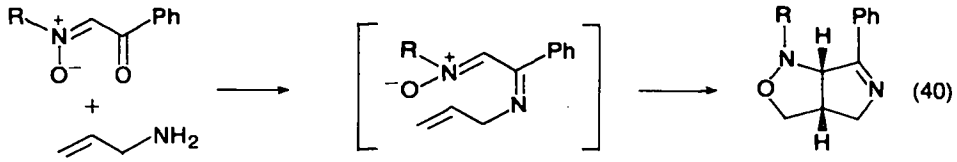
An elegant way to utilize intramolecular 1,3-dipolar cycloaddition for the



(183)

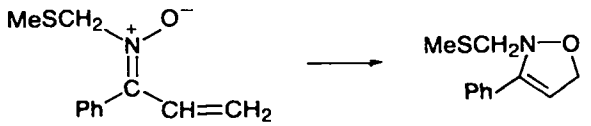
SCHEME 16

construction of two heterocyclic rings has been devised by Black and coworkers. They have shown that the reaction of *C*-acyl nitrones with allylamine results in the formation of tetrahydropyrroloisoxazoles (equation 40)[209].



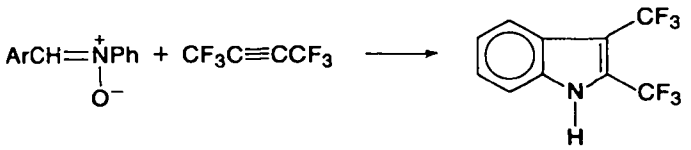
(40)

In a related intramolecular cycloaddition, vinyl nitrone **184** undergoes thermal cyclization to the isoxazoline **185**[68]. This reaction is the first reported case of a nitrone participating in a 1,5-dipolar cyclization[210].



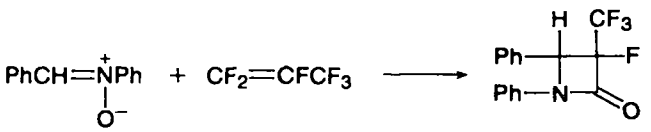
(184) **(185)**

Unusual products are obtained in the reactions of perfluoro-alkenes and -alkynes with diaryl nitrones. Although isoxazolines, which are the primary products of the cycloaddition of nitrones with alkynes, have been shown to undergo a variety of rearrangements[179], only recently has it been reported that the reaction of α-aryl *N*-phenyl nitrone with hexafluoro-2-butyne leads to indole **186**[211].



(186)

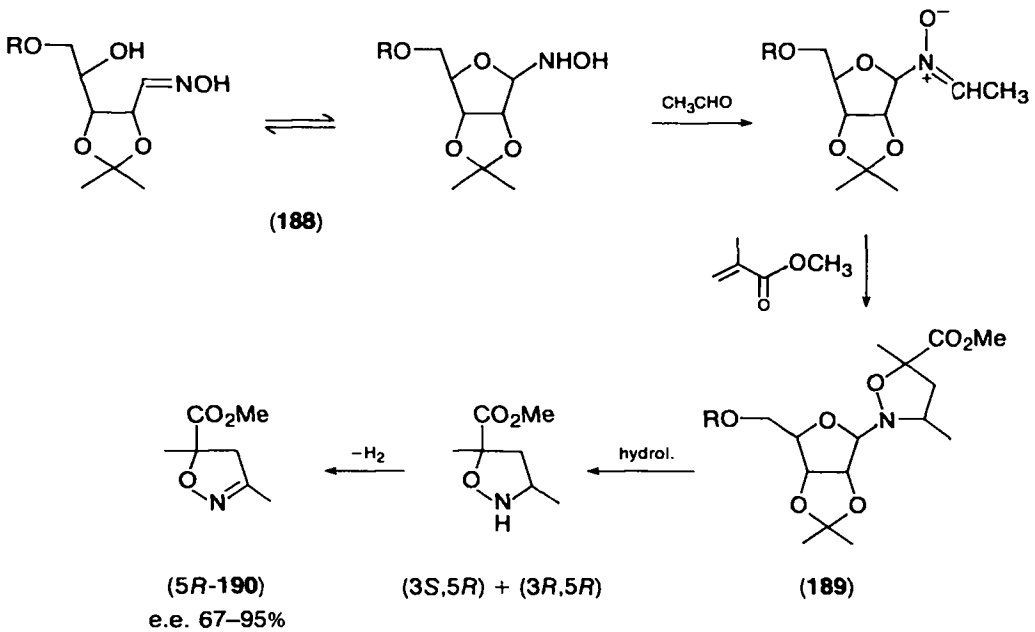
Another unusual observation is the formation of β-lactam **187** in the reaction of *C,N*-diphenyl nitrone with hexafluoropropene[212], in contrast to previous reports of normal reactions of nitrones with hexafluoropropene[213].



(187)

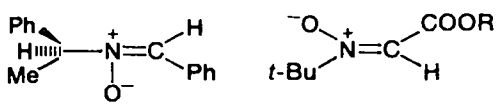
There are a number of reports concerning cycloadditions of chiral nitrones, Some nitrones derived from sugars have been reported to undergo such reactions with the formation of two epimers[214,215]. Some of the products are intermediates in the synthesis of nucleoside analogues.

The question of asymmetric induction has been studied by Vasella in nitrones derived from D-ribose[216]. Reactions of the protected ribose oxime **188** with aldehydes or acetone give nitrones that enter into cycloadditions with methyl methacrylate yielding adducts of type **189**. Cleavage of the glycoside bond and dehydrogenation give isoxazolines **190** in enantiomeric excess (e.e.) of 67–95%. An example using actaldehyde is depicted in Scheme 17.



SCHEME 17

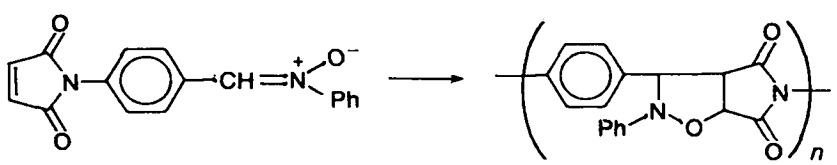
The presence of a chiral group linked to the nitrogen has been found to be very effective in inducing asymmetry. For example *C*-phenyl *N*-(*S*)-1-phenylethyl nitrone (**191** gives dipolar cycloaddition products in some cases in enantiomeric excess of 100%[217]. Unfortunately reactions of this nitrone with many dipolarophiles give mixtures of three or all four of the possible regio- and stereo-isomers. Another nitrone that gives products of high optical purity is a derivative of L(−)-menthyl glyoxalate, **192**[217].



(**191**) (**192**)

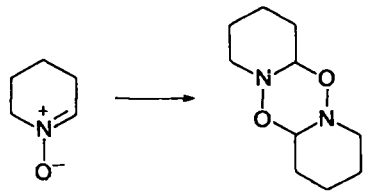
R = (−)-menthyl

A different use of the 1,3-dipolar cycloaddition is its application to the polymerization of appropriately designed olefinic nitrones. One such compound is α-(*p*-maleimidophenyl) *N*-phenyl nitrone (**193**) which polymerizes readily by intermolecular cycloaddition to give a polymer of the structure **194**[218].



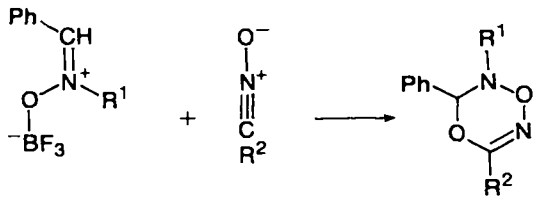
(**193**) (**194**)

b. Cycloaddition to other 1,3-dipoles. The six-membered cyclic nitrone, 3,4,5,6-tetrahydropyridine *N*-oxide (**195**) undergoes rapid dimerization to **196**[2] as a



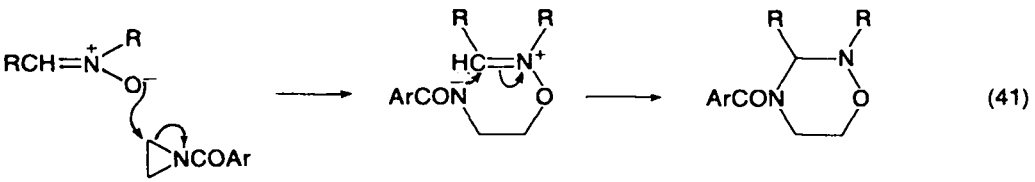
(**195**) (**196**)

consequence of dipole–dipole interaction. This type of interaction could conceivably involve two different 1,3-dipoles with the formation of unsymmetrical products. There are only a few examples of this principle in the literature. Dioxadiazine (**179**) have been obtained in the reactions of nitrile oxides with nitrone–boron trifluoride adducts in 20–45% yields[219].

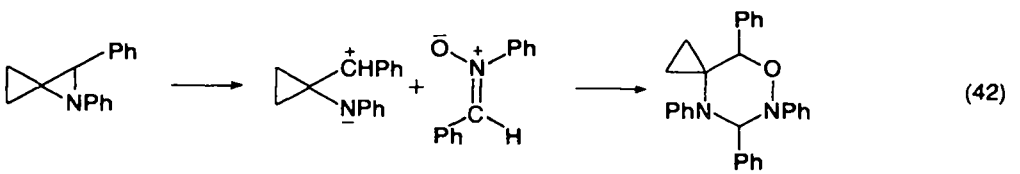


(**197**)

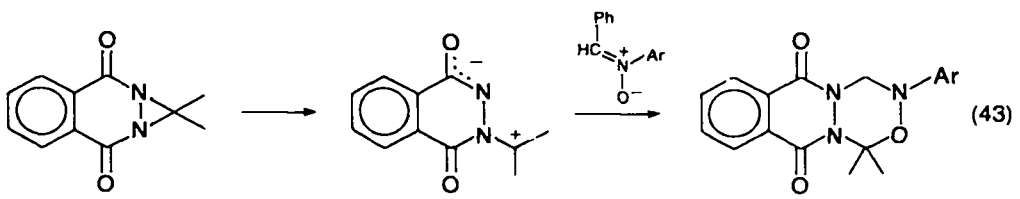
Some aziridines and diaziridines behave as masked 1,3-dipoles in reactions toward certain dipolarophiles. Such are 1-aroylaziridines, which undergo cycloaddition, when heated with nitrones, to oxadiazines (equation 41)[220]. Similar behaviour is shown by azaspiropentanes (equation 42)[221] and diaziridines (equation 43[222].



(41)

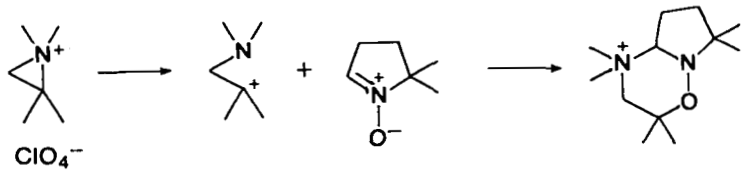


(42)



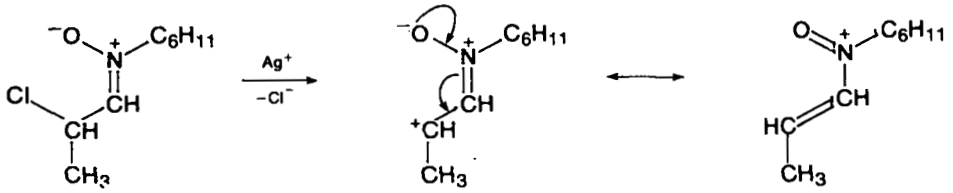
(43)

Related to this section is the reaction of nitrones with an aziridinium compound which is defined as a '1,3-polar' moiety since it behaves as a β-aminocarbonium ion. Its reaction with a nitrone is shown in equation (44)[223].



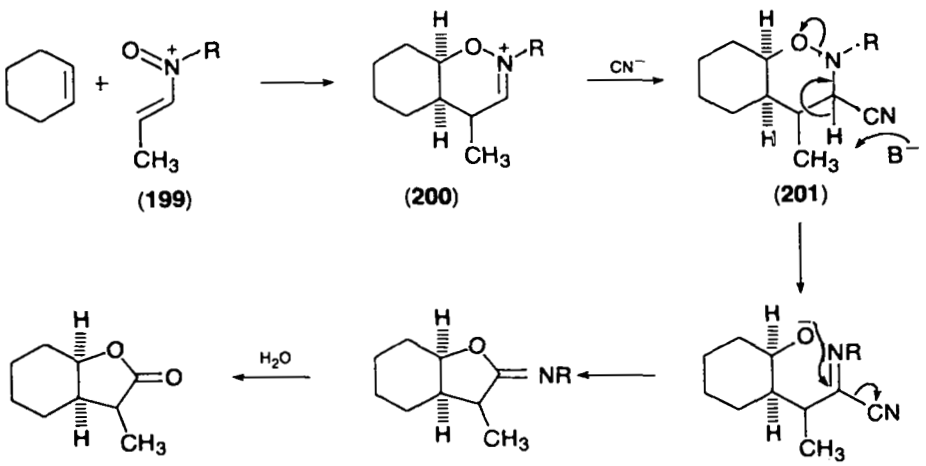
(44)

c. Reactions of C-(1-chloroalkyl)nitrones ('*α-chloronitrones*'). This class of compounds, represented by formula **198** was introduced by Eschenmoser and named by him 'α-chloronitrones'[152]. This name is incorrect and contrary to *Chemical Abstracts* nomenclature, since the clorine is not located at the α-position of the nitrone function. The name α-chloronitrone is also misleading in view of the existence of true α-chloronitrones[224,225]. The usefulness of this class of compounds



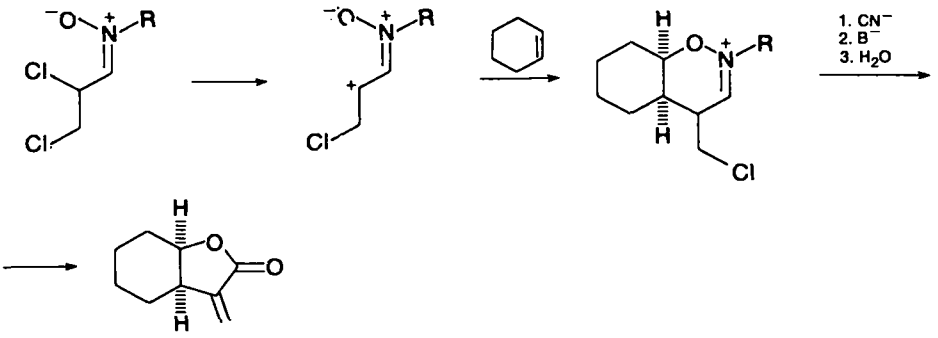
(198) **(199)**

stems from the fact that ionization of the chloride (brought about by silver ion) leads to the development of a positive charge in the α-position of the masked aldehyde function (*Umpolung*), which can be stabilized by the nitrone function to form the heterodienic *N*-alkyl-*N*-vinylnitrosonium cation (**199**). This is an electron-deficient diene and is capable of undergoing Diels–Alder-type cycloaddition to unactivated olefins[152] and acetylenes[226]. Double bonds that are capable of undergoing such cycloaddition may have up to four alkyl substituents or may be of enol ethers[227–229]. The adducts obtained from the cycloaddition of *N*-alkyl-*N*-vinylnitrosonium cations (e.g. **199** → **200**) can be used in a number of ways. For example stabilization of the

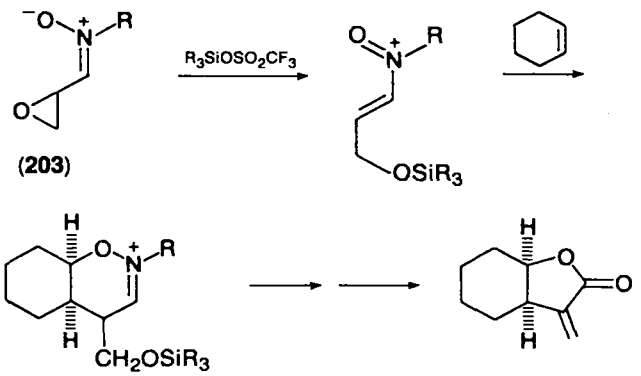


(199) **(200)** **(201)**

(202)



SCHEME 18a

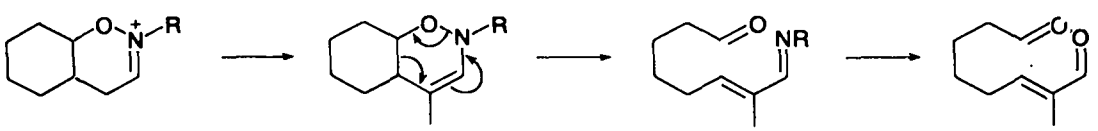


SCHEME 18b

oxazinium cation **200** by cyanide ion leads to a stable molecule **201** that can easily be converted to a γ-lactone (**202**)[230]. If *C*-(1,2-dichloroethyl) nitrones('α,β-dichloronitrones') are used as starting materials, the same sequence of reactions leads to α-chloromethyl-γ-lactones, which can easily be converted to α-methylene-γ-lactones (Scheme 18a)[231].

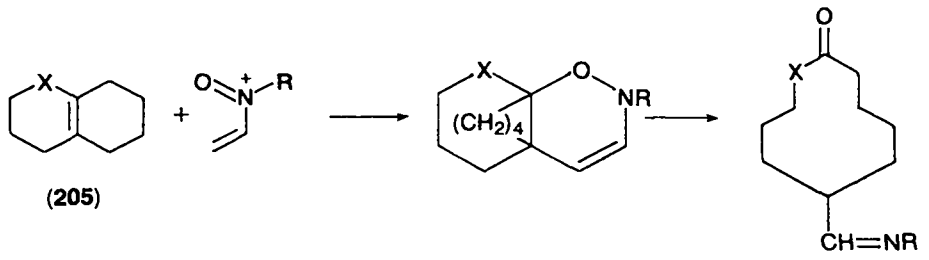
Recently is has been reported that epoxynitrones (**203**) are also useful for the synthesis of this group of compounds (Scheme 18b)[232].

Another possible way to utilize the oxazinium salts (**200**) synthetically is to convert them by base to the enamine-like derivatives **204** which undergo a thermal



(**200**) (**204**)

cycloreversion reaction with cleavage of the weak N—O bond to yield a monounsaturated dicarbonyl compound[233]. If this reaction is carried out using bicyclic olefins such as **205** large-ring ketones (**206**, X = CH_2) or lactones (**206**, X = O) may be obtained[234].



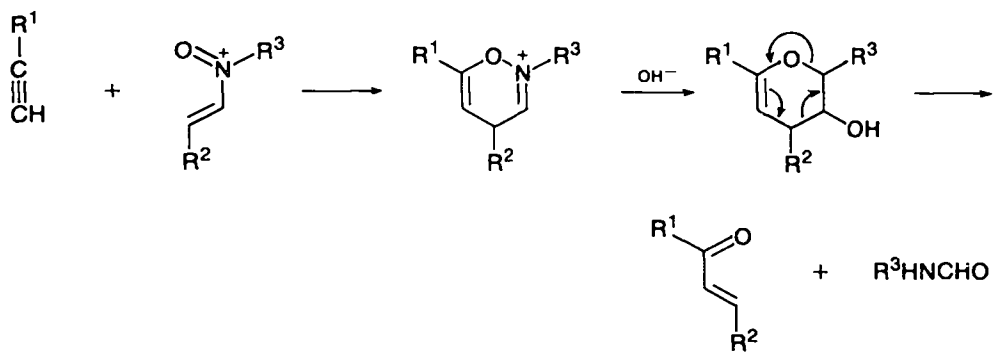
(205)

(206)

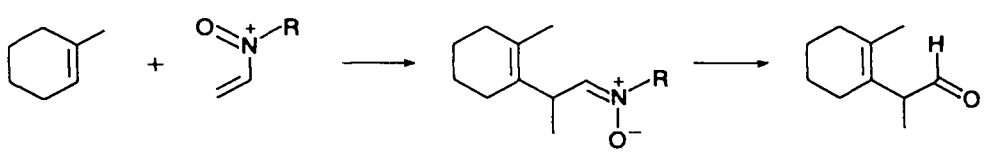
Cycloaddition of the chloronitrone-derived heterodienes with acetylenes provides a route to α,β-unsaturated ketones[226] (Scheme 19).

The cations obtained by the ionization of chloronitrones may also react as electrophiiic reagents in Friedel–Crafts-like substitution reactions toward olefins and activated aromatic compounds[235]. If the reactions of *N*-alkyl-*N*-vinylnitrosonium cations with olefins are carried out in polar solvents such as liquid sulphur dioxide the main products are β,γ-unsaturated aldehydes (Scheme 20)[235]. Similarly reactions with activated aromatic systems yield α-arylaldehydes (Scheme 21)[235]. In these reactions the *N*-alkyl-*N*-alkenylnitrosonium ions serve as masked α-acylcarbonium ions (*Umpolung*).

N-Alkyl-*N*-alkenylnitrosonium ions derived from chloronitrones have also been found to cleave ethers[229,234]. A particularly elegant application of such a nitrosonium ion was its use by Eschenmoser and coworkers for selective hydrolysis of the amide function in cobyrinic acid hexamethyl ester monoamide to the

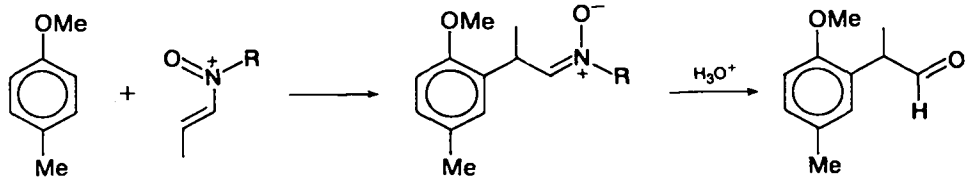


SCHEME 19

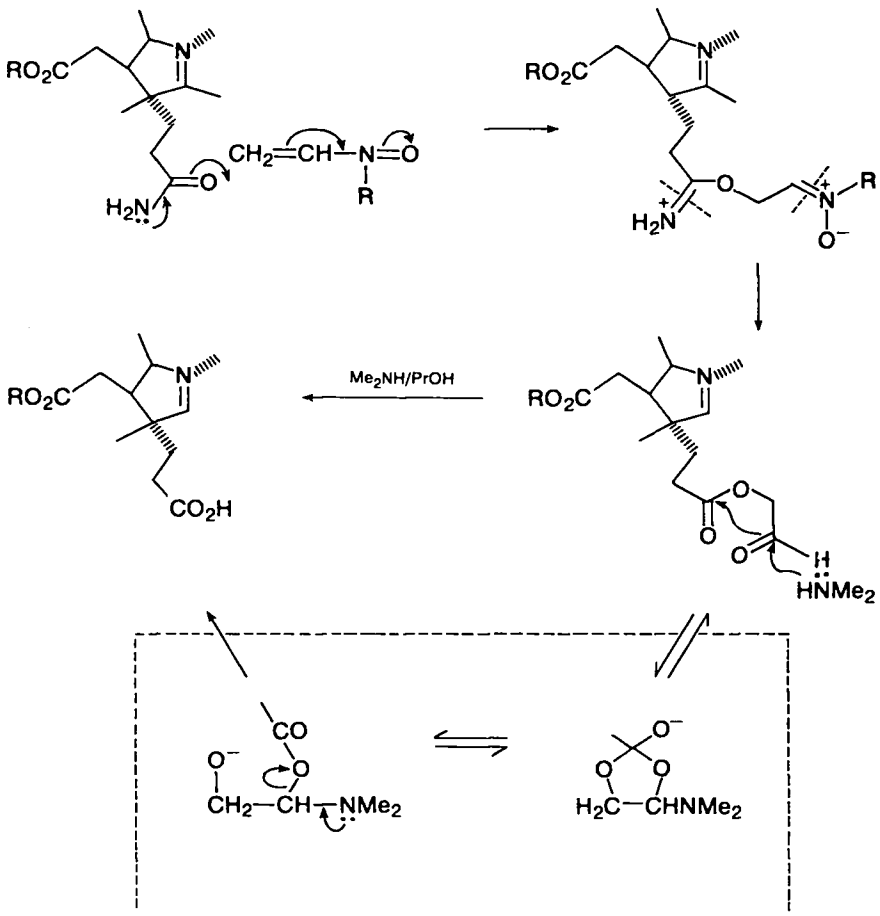


60%
+
30% cycloadduct

SCHEME 20



SCHEME 21

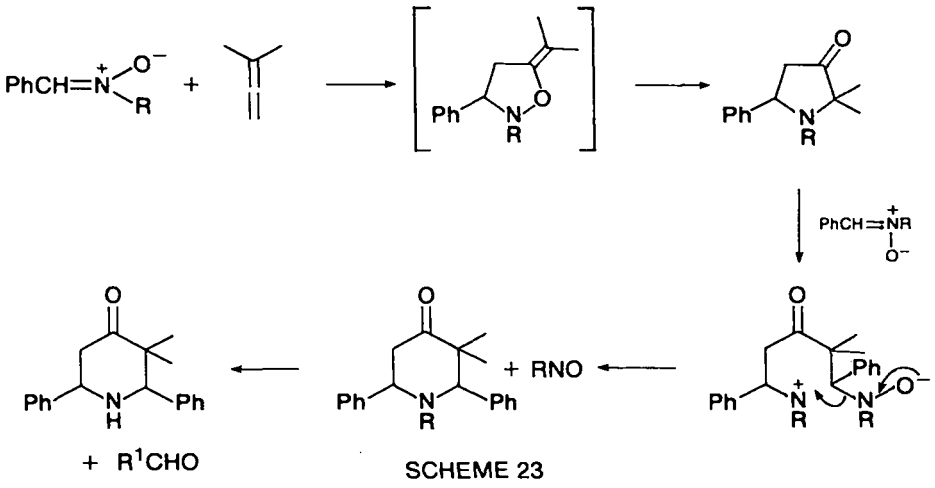


SCHEME 22

hexamethyl ester monoacid in the total synthesis of vitamin B_{12}[236]. This is illustrated in Scheme 22 using partial structures.

6. *Reactions of nitrones with heterocumulenes*

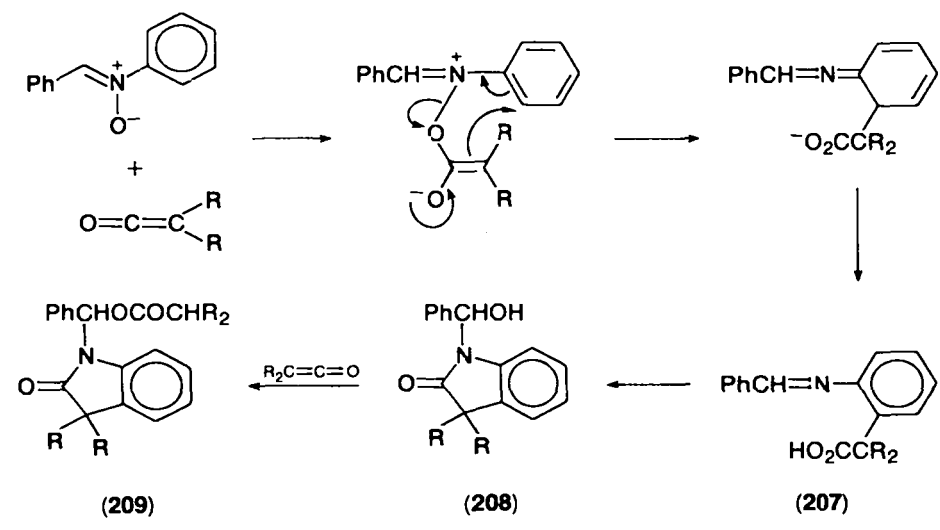
With the exception of a recent report describing an unusual mode of reaction of nitrones with allenes leading to a rearranged product depicted in Scheme 23[237], in



SCHEME 23

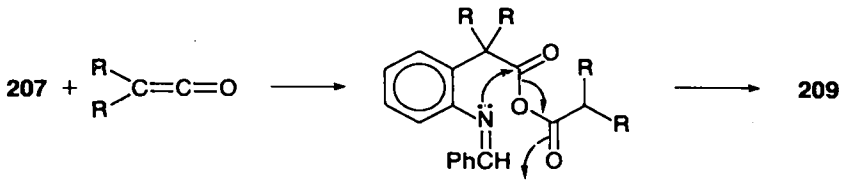
general the reactions of nitrones with allenes lead to cycloaddition products in analogy to simple olefins. In contrast, reactions of many heterocumulenes with nitrones take a course entirely different from that of 1,3-dipolar cycloaddition. This difference in behaviour can be attributed in part to the polar nature of the double bonds (or at least one double bond) in heterocumulenes. There are also similarities that can be noted between many of the reactions discussed in this section and the one dealing with electrophilic reagents (Section II.B.7.a) due to the same reasons.

a. Ketenes. The reaction of nitrones with ketenes was first studied by Staudinger and Miescher[238]. They, and later others[239,240], found that *N*-aryl nitrones react with ketenes to produce *o*-imino-α,α-disubstituted-arylacetic acids (**207**). The mechanism suggested differs from cycloaddition, and involves attack of the nitrone oxygen upon the carbonyl carbon of the ketene, followed by sigmatropic rearrangement and proton transfer (Scheme 24).



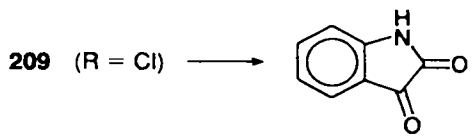
SCHEME 24

Other products that were also isolated from these reactions are the oxindoles **208** and **209**. The formation of **209** can be rationalized either by reaction of **208** with ketene or by the reaction of **207** with a second molecule of ketene leading to the mixed anhydride **210** that rearranges to **209**.



(210)

This reaction has been recently utilized for a new synthesis of isatins (**211**) by reacting *N*-aryl nitrones with dichloroketene[241]. Oxindole **209** (R = Cl), which was obtained initially, could be hydrolysed to isatins in good yields.

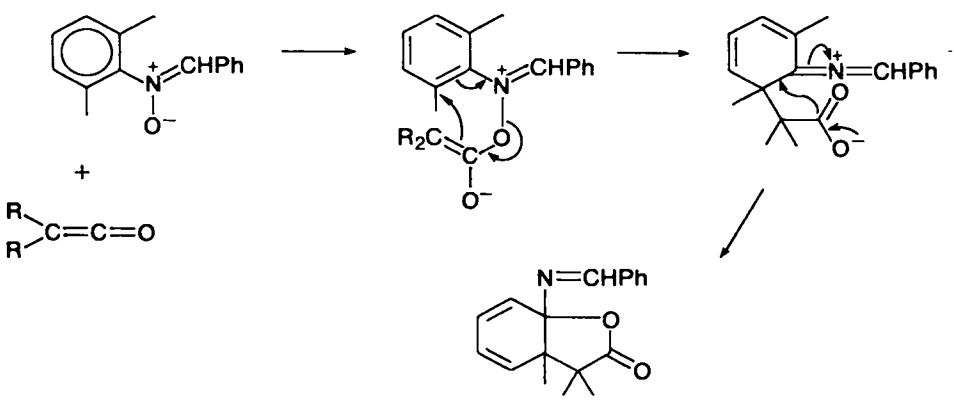


(211)

In contrast the reaction of the *N*-2,6-disubstituted-aryl nitrone gives lactone **212**, presumably through a mechanism which is similar to that described previously (Scheme 25)[242].

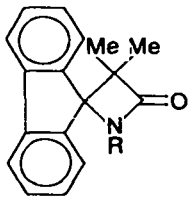
Further work by Taylor and coworkers has concerned reactions of nitrones derived from 9-fluorenone. *N*-Alkyl nitrones of this series have given with dimethylketene spiranic products **213** and **214**[243].

It was assumed that the β-lactam, **213**, resulted from deoxygenation of the nitrone followed by cycloaddition of the fluorenone imine to the ketene. The reaction of the same nitrones with diphenylketene give the analogous oxazolidinones (**214**, R^1 = Ph) but a different kind of β-lactam (**215**)[244]. The formation of these products is

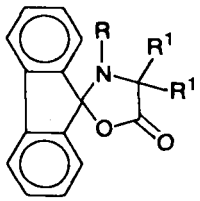


(212)

SCHEME 25



(213)

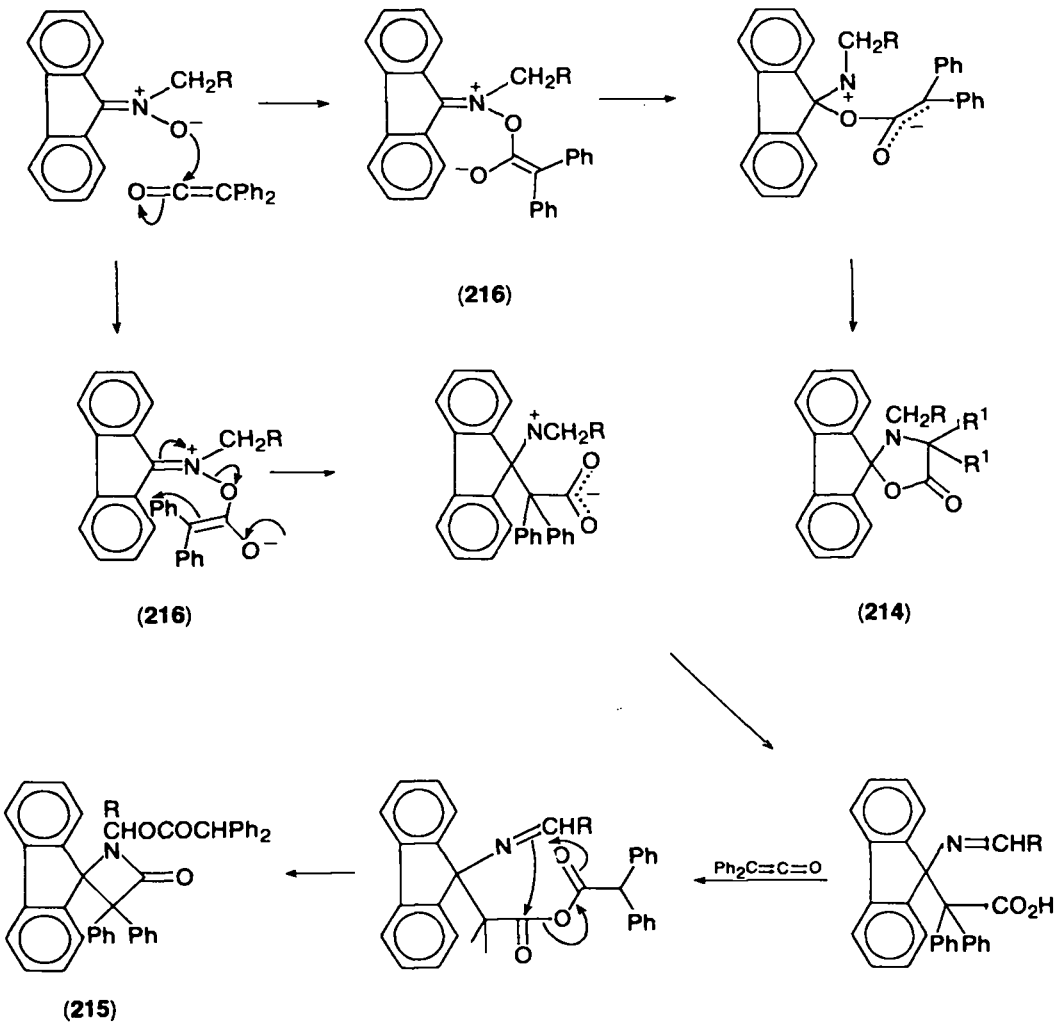


(214)

R^1 = Me

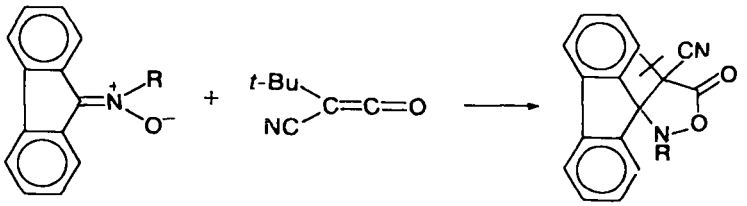
rationalized by assuming the formation of the zwitterionic intermediate **216**, which may undergo two types of sigmatropic shifts leading to the two products (Scheme 26).

The more electron-deficient α-cyano-*t*-butylketene reacts with *N*-alkyl-*N*-

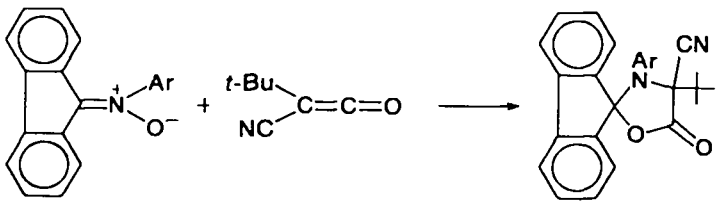


SCHEME 26

fluorenylidene *N*-oxides to afford the product of 1,3-cycloaddition, **217**[245]. The same ketene reacts with *N*-arylfluorenone nitrone to give oxazolidinones (equation 45)[245].



(217)



(45)

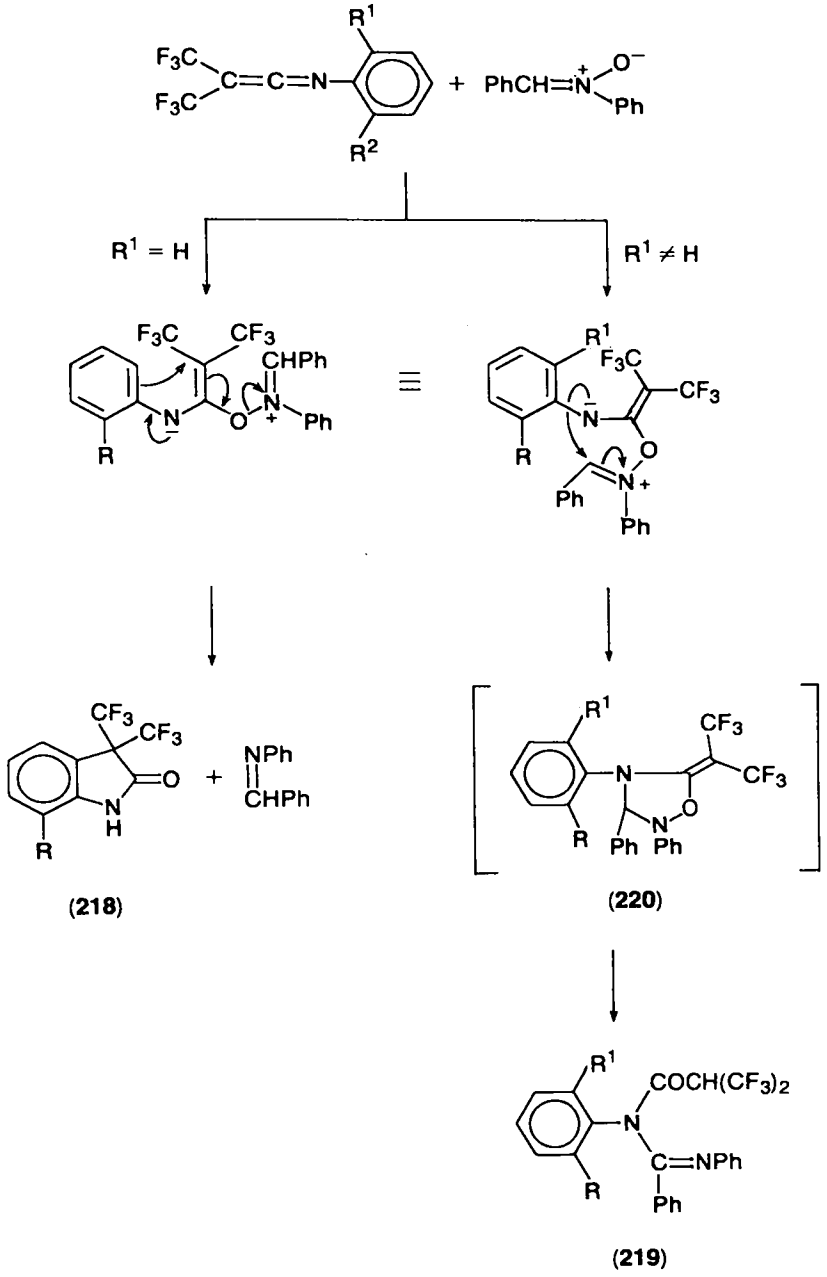
b. Ketene imines. The reactions of nitrones with ketene imines have been studied in a number of laboratories. Del'tsova and coworkers have reported that *N*-arylketene imines and nitrones may yield two types of products, namely oxindoles (**218**) and amidines (**219**)[246,247]. Reactions of *C,N*-diphenyl nitrones with *N*-arylketene imines with at least one *ortho* position of the *N*-aryl group unoccupied give oxindoles, while those with both *ortho* positions substituted are unable to follow this course and lead to an unstable cycloaddition product **220** which subsequently rearranges (Scheme 27). The oxindoles are formed with the elements of the ketene imines, with only the oxygen atom contributed by the nitrone. The latter is reduced in this reaction to the imine. Therefore these reactions can also be viewed as oxidative rearrangements in which the nitrones act as oxidizing agents.

In contrast to the above-mentioned results Barker and coworkers have reported the formation of iminoisoxazolidines (**221**) resulting from cycloaddition of the nitrone across the C=C bond[248,249]. This structure assignment has been disputed by Ohshiro and coworkers, who suggest the imidazolidinone structure **222** on the basis of the ^{13}C spectrum. They suggest that **222** is a product of rearrangement of **221**[250]. These workers have observed the formation of an imidazolidinone of type **222** in the reaction of *C*-phenyl *N-t*-butyl nitrone with *N*-aryldimethylketene imine. This nitrone, when reacted with diphenyl-*N*-arylketene imine gives the oxindoles **223** and **224** and the aldimine[250].

c. Isocyanates and isothiocyanates. The functional groups add the nitrone across the C=N bond. In the reactions of isocyanates the products are oxadiazolidinones (equation 46)[209].

The reactions of nitrones with phenyl isothiocyanate proceed in an analogous manner; however, other isothiocyanates, such as *p*-tolyl- or benzoyl-methyl isocyanates add nitrones across the C=S bond to yield unstable products which undergo fragmentation to thioamides and isocyanates (e.g. equation 47)[251].

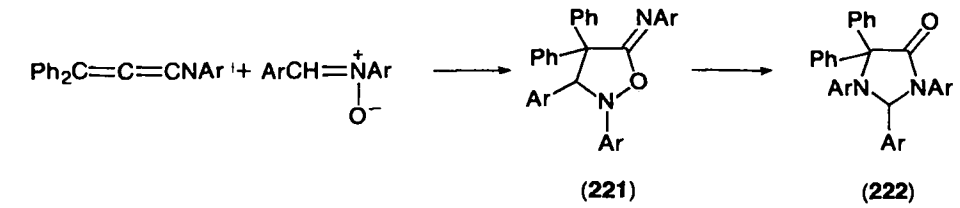
d. Carbodiimides. Reactions of alkyl nitrones with diphenylcarbodiimide yield the cycloaddition product **225**[252]. However, the analogous products from *N*-aryl nitrones are apparently not as stable and therefore only secondary products are isolated (Scheme 28)[253].



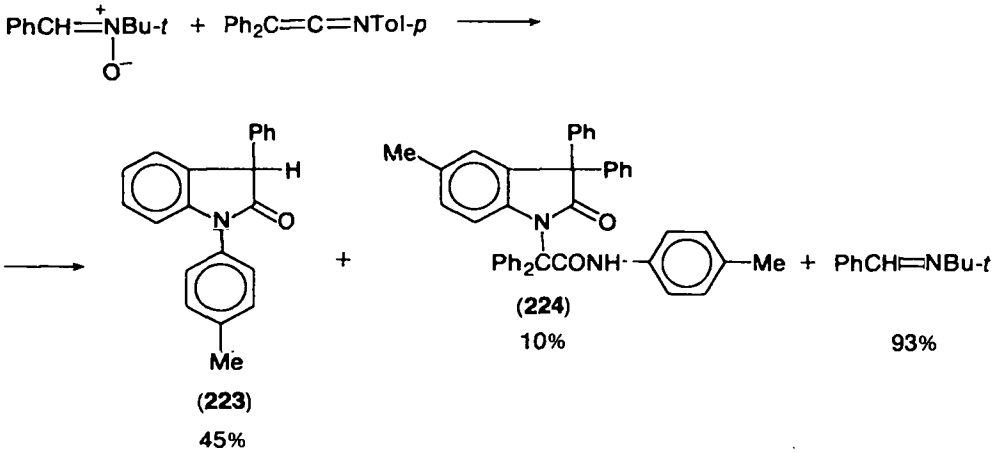
SCHEME 27

The fragmentation leading to amidine with loss of isocyanate is reminiscent of what was observed in the case of isothiocyanate. The amidine formation is sometimes accompanied by the migration of a group from the carbon to nitrogen[253].

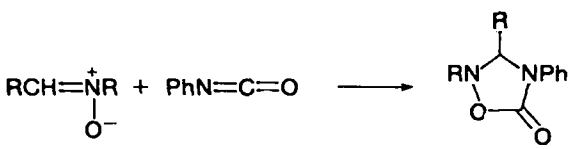
e. Sulphines. There is only one paper concerned with the reaction of this



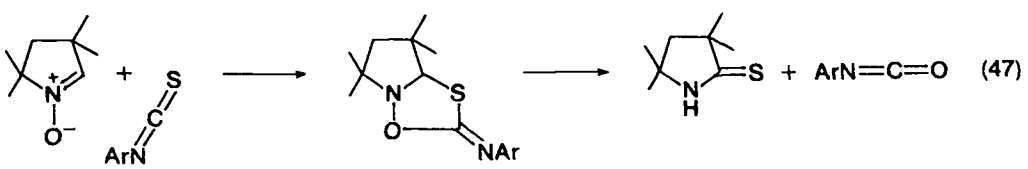
(221) (222)



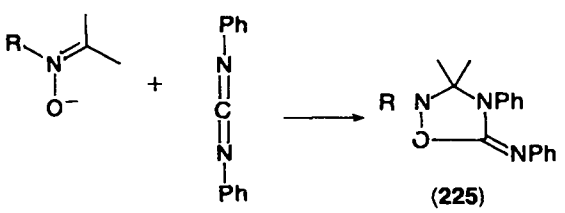
(223) 45% (224) 10% 93%



(46)

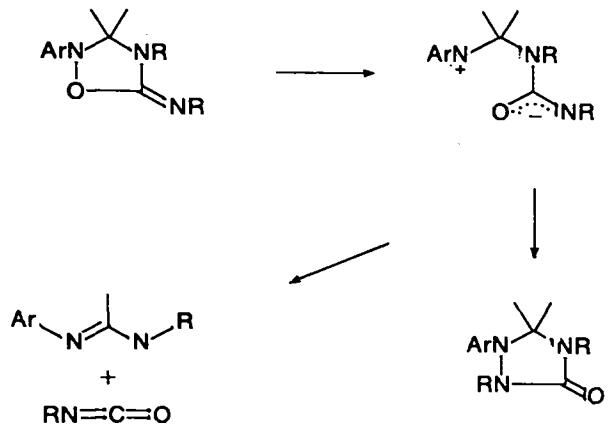


(47)



(225)

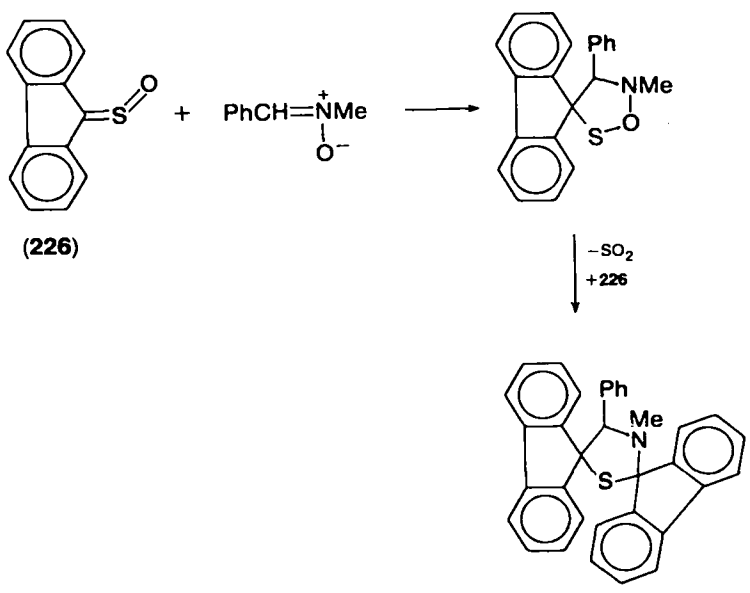
heterocumulene function with nitrones[254]. Reaction of 9-thiofluorenone *S*-oxide (**226**) with *C*-phenyl *N*-methyl nitrone gives in high yield product **227** formed from two moles of thiofluorenone and one mole of nitrone with the loss of sulphur dioxide (Scheme 29).



SCHEME 28

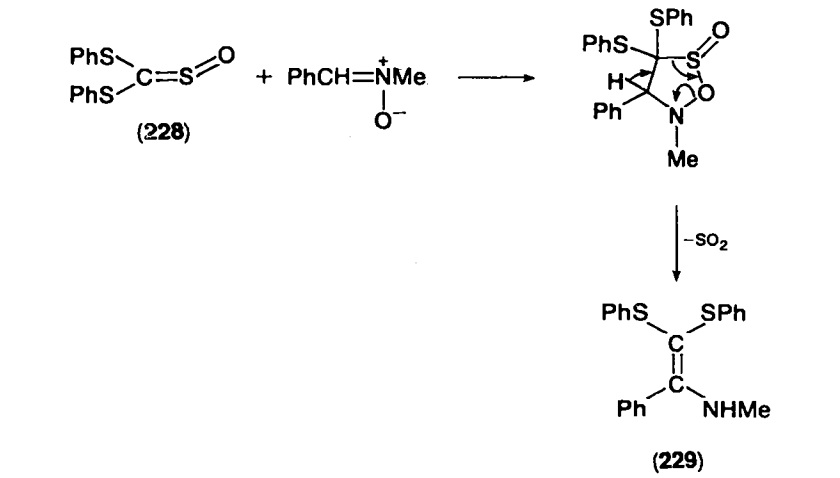
Sulphines derived from thiobenzophenone and its substituted derivatives were found to be not sufficiently reactive towards this nitrone. Bis(phenylthio)sulphine (**228**) was found to react slowly with *C*-phenyl *N*-methyl nitrone to give in high yield the enamine **229**[254].

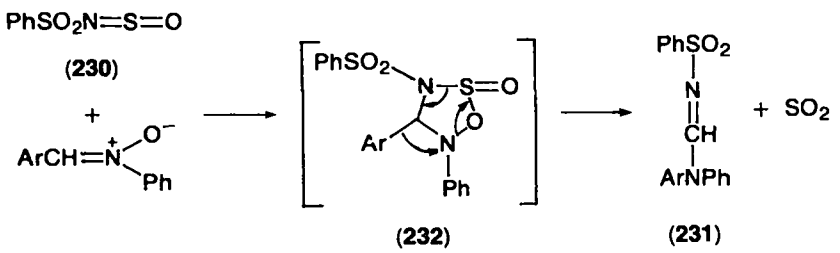
f. N-*Sulphinyl compounds.* The reaction of *N*-sulphinylbenzenesulphonamide (**230**) with two types of nitrones has been studied. The reaction between **230** and *C,N*-diaryl nitrones yields *N*-benzenesulphonyl-*N'*,*N'*-diarylformamidine (**231**) (Scheme 30). The formation of this product is postulated to proceed via the fragmentation of the cycloadduct **232** involving carbon to nitrogen migration of an aryl group similarly to what was observed with the products of carbodiimides[255]. The reaction of an *N*-alkyl nitrone also yields an amidine (**233**) which in this case is



(**226**) (**227**)

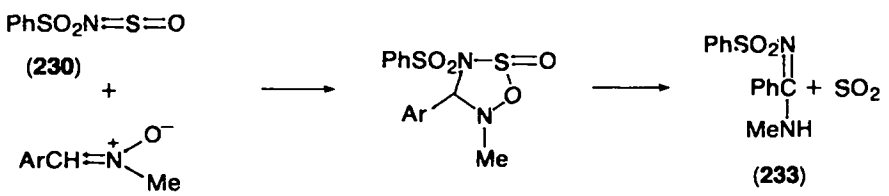
SCHEME 29



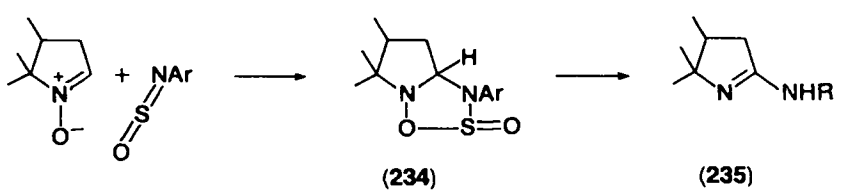


SCHEME 30

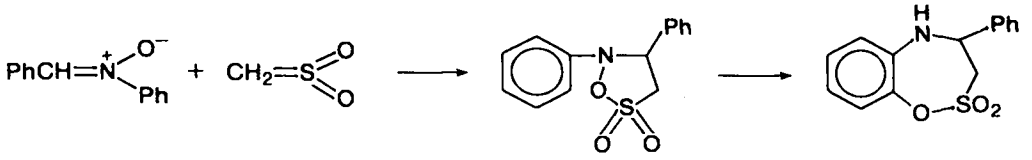
formed without skeletal rearrangement[255]. It seems that the higher electron density of N(2) in the precursor of **233** as compared to **232** makes the phenyl migration less favoured.



Reactions of *N*-sulphinylanilines with cyclic aliphatic nitrones have been shown to lead to amidines (**235**) through the cycloadduct **234** and the loss of sulphur dioxide[256].



g. Sulphenes. The reaction of *N*-aryl nitrones with sulphene has been shown by Truce and coworkers to lead to benzoxathiazepines **237** via rearrangement of the initial cycloadduct **236**[257–259]. The rearrangement is essentially a migration from



(236) **(237)**

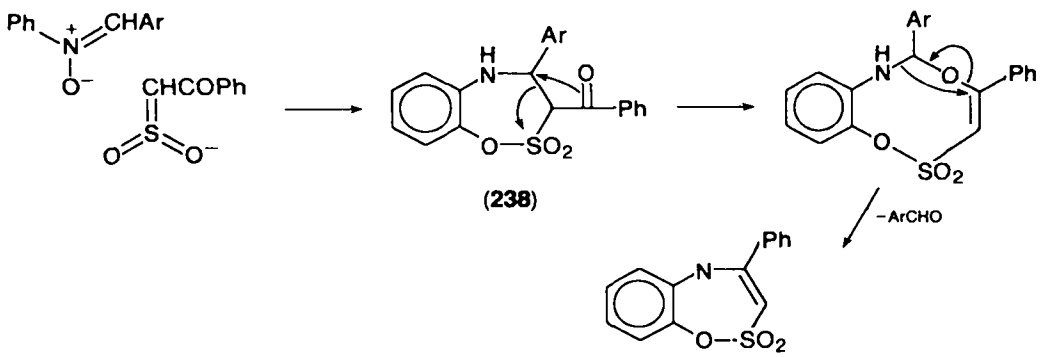
nitrogen to the *ortho* position of the aromatic ring, to which there are many precedents in the literature. Several mechanisms have been considered for this rearrangement[258].

α-Ketosulphenes have been reported to react with *N*-aryl nitrones similarly to sulphene[260]. Thus the reaction of benzoylsulphene with a *C,N*-diaryl nitrone yields two benzoxathiazepines **238** and **239**, the first of which has been shown to lose a benzaldehyde in a fragmentation involving an unusual rearrangement leading to **239**, for which the pathway depicted in Scheme 31 has been proposed[260].

Cyclic nitrones of the pyrroline *N*-oxide series react with sulphene or with phenylsulphene in benzene to yield the corresponding iminosulphonic acids[261,262] (equation 48).

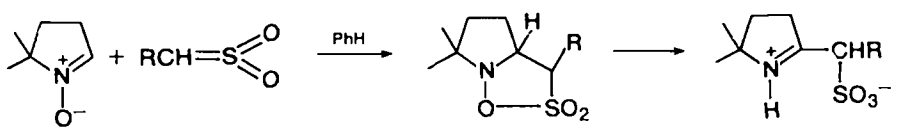
In contrast the reactions of α-ketosulphenes with these nitrones in dioxane lead to ketoenamines (**240**) which may react with a second mole of ketosulphene[262] (Scheme 32). Similar behaviour is shown by cyclic ketosulphenes derived from indane and tetralin.

The reaction of α-methyl nitrone (**241**) with a ketosulphene yields a product with a rearranged skeleton **242**, which may add a second mole of ketosulphene to yield **243**[262]. The reaction of ketosulphenes can be directed towards the formation of iminosulphonic acids by performing the reactions in methylene chloride or acetonitrile instead of dioxane[262].

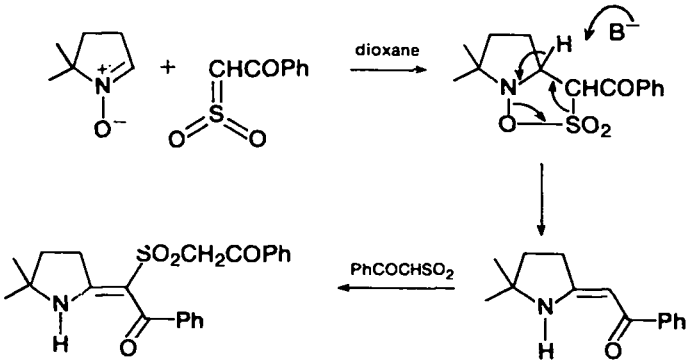


(238) **(239)**

SCHEME 31

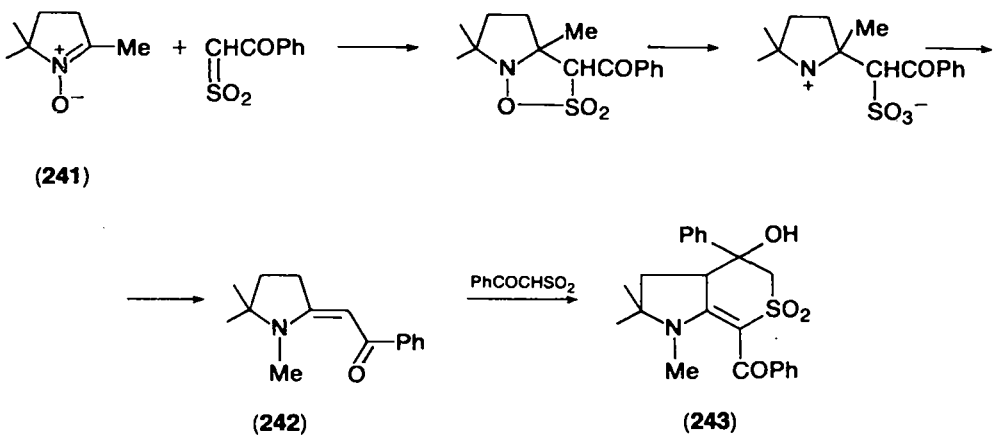


(48)



(240)

SCHEME 32

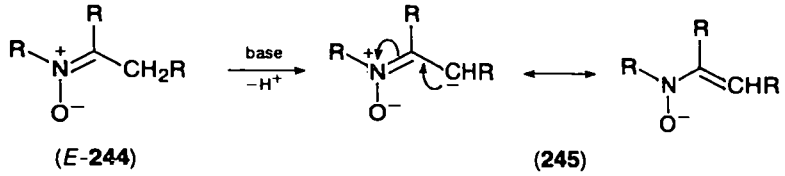


(241) (242) (243)

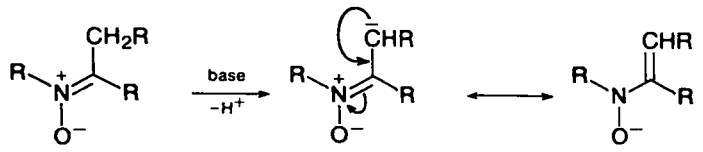
7. *Reactions of nitrones with electrophiles*

It is expected from the dipolar nature of nitrones that the oxygen of the nitrone function will behave as a nucleophile. On the other hand, the polarity of the nitrone function also increases the acidity of the protons in the β-position. The magnitude of this stabilizing effect probably depends on the stereochemistry of the nitrone, but so far there are no comparative data on the acidities of β-carbons in geometrical isomers such as (*E*)- and (*Z*)-**244**, or the relative stabilities of the two types of carbonions **245** and **246**.

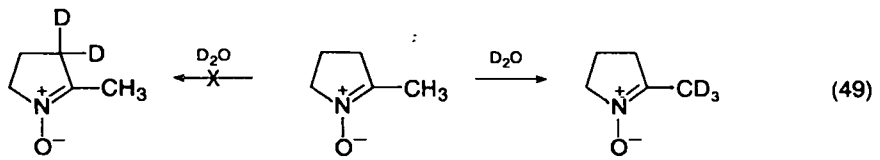
The tendency of 2-methylpyrroline *N*-oxide derivatives to undergo deuterium exchange[61] (equation 49) and aldol-type condensation[2,3] (equation 50) involving the methyl group rather than the 3-position seems to indicate the preference for **245** over **246**. However, the fact that the two groups being compared are unequal (i.e. one is a methyl group and the other is a methylene in a five-membered ring) might account for a considerable part of the difference and therefore one cannot draw a definite conclusion.



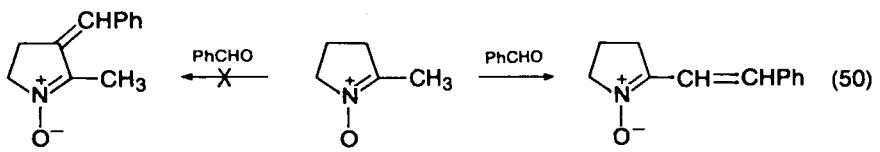
(*E*-**244**) (**245**)



(*Z*-**244**) (**246**)



(49)



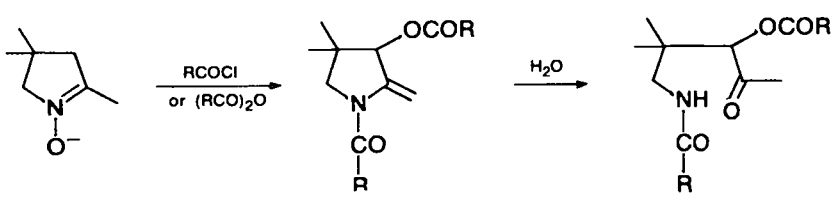
(50)

Another relevant aspect is the question of *O*- versus *C*-alkylation, which has received a great deal of attention in carbonyl compounds, but has not been studied systematically in nitrones.

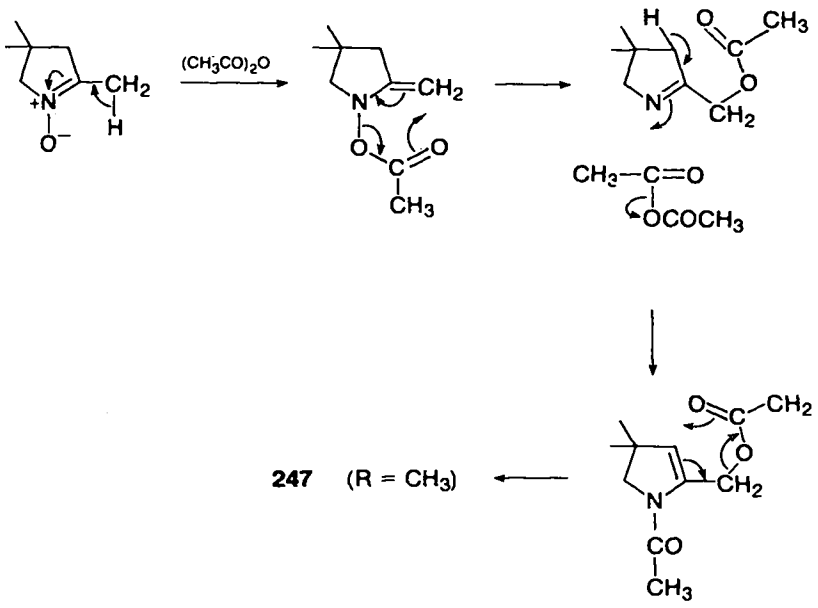
However, nitrones clearly are ambident nucleophiles and they may react with electrophilic reagents either as oxygen or as carbon nucleophiles and accordingly this section will be divided into two parts.

a. Nitrones as oxygen nucleophiles. In addition to the reactions that will be reviewed here it is appropriate to point out that the acid-catalysed Beckmann rearrangement of nitrones (Section II.B.1.c) as well as many of the reactions of nitrones with heterocumulenes (Section II.B.6) may be classified as belonging to this section, as their first step is a nucleophilic attack of the nitrone oxygen upon the electrophilic site of the reagent. The present discussion deals almost exclusively with reactions of nitrones with acid derivatives.

The reaction of 2,4,4-trimethylpyrroline *N*-oxide with acetic anhydride[156] or benzoyl chloride[263] yields the diacyl derivatives of type **247**. It is reasonable to assume the formation of **247** as taking place by the mechanism indicated by Scheme 33[61].

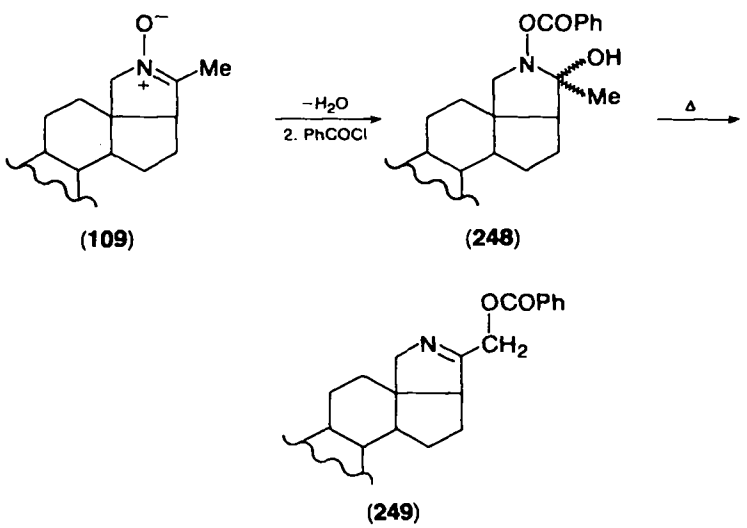


(**247**)



SCHEME 33

The steroidal nitrone **109** (cf. Section II.B.1.b) exhibits a different kind of behaviour. Its treatment with benzoyl chloride followed by water gives the α-hydroxy *N*-benzoyloxy compound (**248**) which can be rearranged thermally to the imine **249**[126].

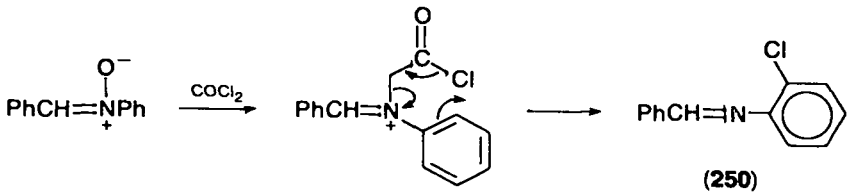


(109) (248)

(249)

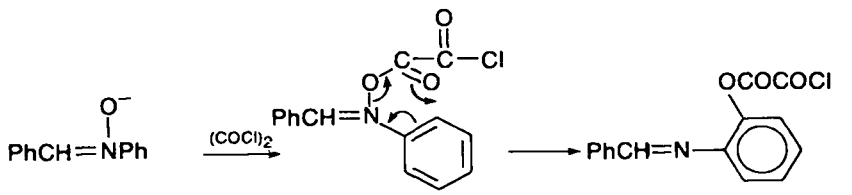
The reactions of *N*-aryl nitrones take a different course. Almost all reactions of *N*-aryl nitrones with acid derivatives lead to *ortho* substitution in the aromatic ring resembling the reactions of ketenes that lead to indoles (Section II.B.6.a). *C,N*-diaryl

nitrones react with phosgene or with thionyl chloride to give in high yield, and in most cases exclusively, the *ortho*-chlorinated imine **250**[264,265]. A cyclic mechanism has



(250)

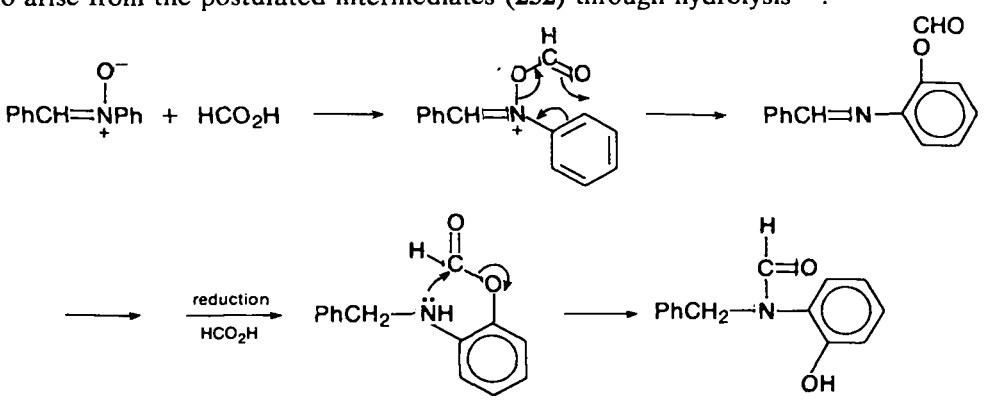
been suggested for the reaction. The related reaction of *N*-aryl nitrones with oxalyl chloride leads to the introduction of the chlorooxalyl group into the *ortho* position of the *N*-aryl group (equation 51)[266].



(51)

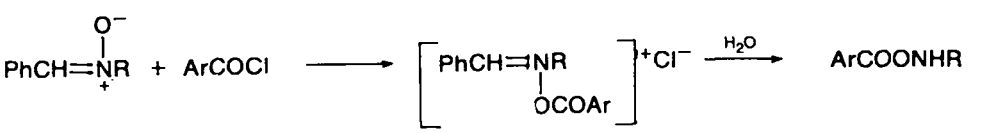
Reaction of *C,N*-diphenyl nitrone with formic acid results also in a product of *ortho* substitution and reduction, **251**[267]. Its formation is rationalized in Scheme 34.

Seeking evidence for the existence of *N*-aroyloxy-*N*-benzylideneammonium chloride (**252**), the assumed intermediate in the acyl-halide-catalysed Beckmann rearrangement of nitrones, Heine and coworkers treated α-phenyl *N*-alkyl nitrones with aroyl chlorides in wet solvents. The products, *N*-alkyl-*O*-aroyloxyhydroxylamines (**253**) which were isolated in good yields can be considered to arise from the postulated intermediates (**252**) through hydrolysis[268].

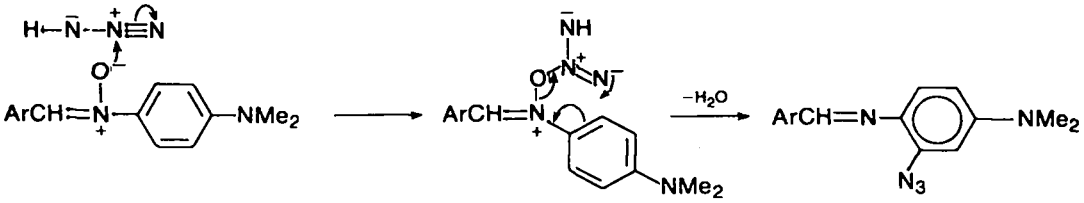


(251)

SCHEME 34



(252) **(253)**

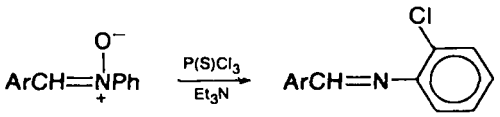


SCHEME 35

In contrast, treatment of *N*-aryl nitrones with aroyl chlorides resulted in *ortho* substitution and the *N,O*-diacyl derivative of the corresponding *o*-aminophenol was isolated[268].

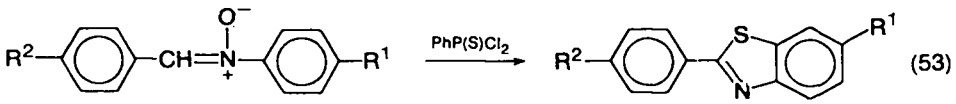
The reaction of α-phenyl *N*-*p*-dimethylaminophenyl nitrone that leads to the introduction of an azido group into the *ortho* position[269] may be represented by Scheme 35.

The reactions of some thiophosphoryl compounds with *C,N*-diaryl nitrones have been reported to give puzzling results. While thiophosphoryl trichloride gave *ortho* chlorination, similar to thionyl chloride and phosgene[270] (equation 52), the reaction

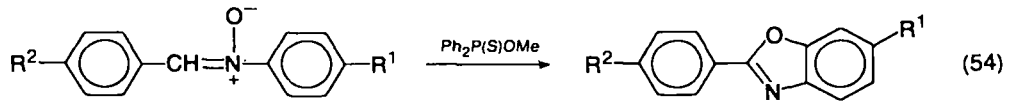


(52)

of phenylphosphonothioic dichloride with *C,N*-diaryl nitrones gave benzothiazoles[270] (equation 53). In contrast reactions of methyl diphenylphosphonothioate gave the corresponding benzoxazoles (equation 54)[270].

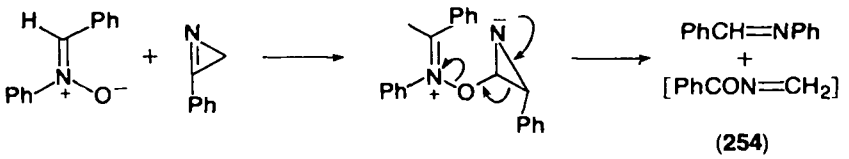


(53)



(54)

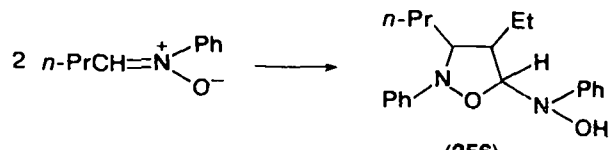
A different type of electrophilic centre is provided in the C=N bond of phenylazirines. It has been found by Padwa that nitrones react as oxygen nucleophiles with such compounds, transferring their oxygen, and causing an oxidative rearrangement to the unstable benzoylimine intermediate **254** which will further react with the medium[271].



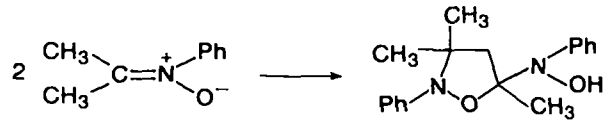
(254)

b. Nitrones as carbon nucleophiles. Earlier examples of aldol-type condensations of nitrones with carbonyl compounds (e.g. equation 50) can be found in the reviews[2,3]. There are also reports of aldol-type condensations involving nitrones both

as the nucleophile and the electrophile. However older structure assignments should be viewed with caution. Since the publication of the review of Hamer and Macaluso[2] the structures of the *N*-phenyl nitrones derived from acetone and from butyraldehyde have been reexamined by X-ray crystallography as well as by mass and NMR spectra, and have been revised. The dimers are isoxazolidines as shown by formulae **255**[272] and **256**[273,274].

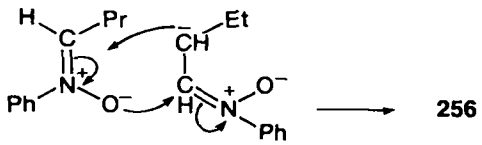


(256)



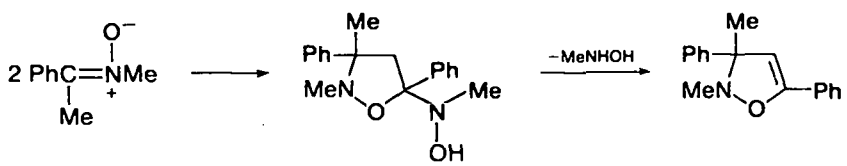
(255)

The formation of these dimers can be rationalized by assuming an aldol-type dimerization followed by intramolecular nucleophilic attack of the oxide anion on the α-position of the nitrone (Scheme 36). Recently it has been reported that such dimerization may be accompanied by the loss of hydroxylamine leading to an isoxazoline (equation 55)[275].



256

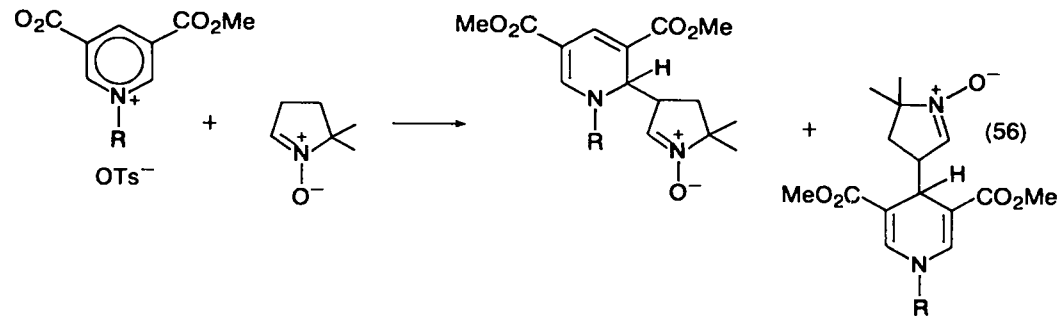
SCHEME 36



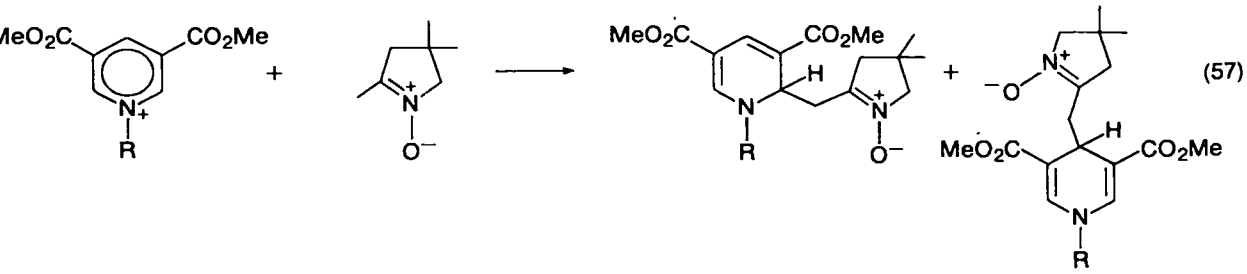
(55)

Derivatives of pyrroline *N*-oxide have been reported to undergo reactions with 3,5-dicarbomethoxypyridinium tosylate to yield 1,4- and 1,2-dihydropyridines[276]. An aldonitrone of this series reacted through the 3-carbanion (equation 56) while a 2-methylpyrroline *N*-oxide formed the anion on the methyl carbon affording products in which the two rings are connected by a methylene group (equation 57)[276]. Equation (56) represents a rare example indicating the formation of a carbanion of type **246**, *anti* to a nitrone oxygen (see introduction to Section II.B.7).

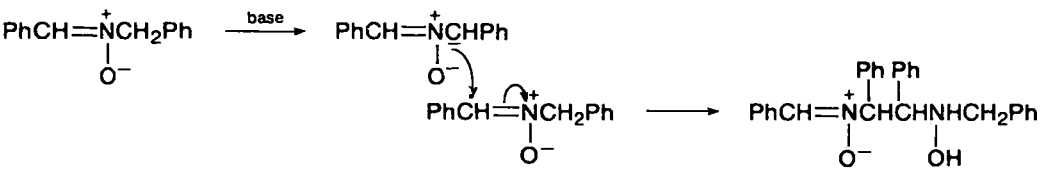
A different kind of aldol-like condensation, involving a carbanion obtained by deprotonation of the *N*-alkyl group was found in the process of elucidating the mode of base-induced formation of desoxybenzoin from *N*-benzyl α-phenyl nitrone[277]. It was found that under base catalysis this nitrone dimerizes to form the hydroxylaminonitrone **257** which subsequently undergoes a series of reactions that produce, among other products, desoxybenzoin[277].



(56)



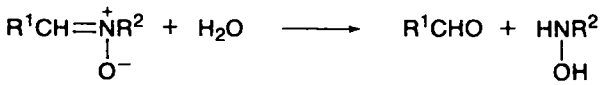
(57)



(257)

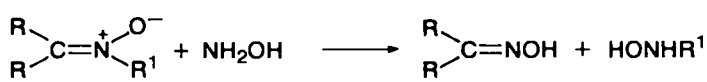
8. *Reactions of nitrones with nucleophiles*

The simplest reaction belonging to this class is the hydrolysis of a nitrone to an *N*-substituted hydroxylamine and the carbonyl compound (equation 58). This



(58)

reaction constitutes the final step of the Kröhnke aldehyde synthesis[278], and is usually carried out by acid catalysis. A number of more recent papers report acid-catalysed hydrolysis of nitrones[279–285] in addition to those cited earlier[2,3]. Nitrones also undergo cleavage by hydrazine or its derivatives[2,280,286] or by hydroxylamine[2,287,288] to furnish directly the hydrazone or oxime of the carbonyl compound and the *N*-substituted hydroxylamine (e.g. equation 59).

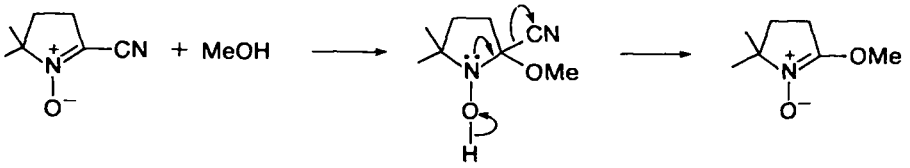


(59)

The reaction of aryl nitrones with arylnitroso compounds leading to azoxyarenes has been shown to involve hydrolysis to the *N*-arylhydroxylamine in the first step[289].

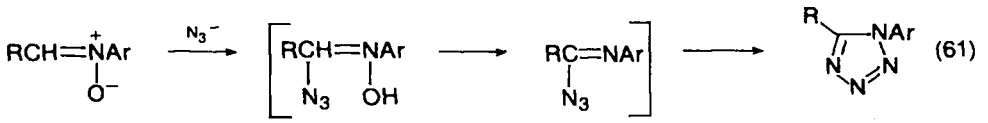
Methanol can add to suitably activated nitrones such as 2-cyanopyrroline *N*-oxides

with the formation of the corresponding hydroxylamine, which upon heating loses hydrogen cyanide to furnish the α-methoxynitrone (equation 60)[290]. This reaction



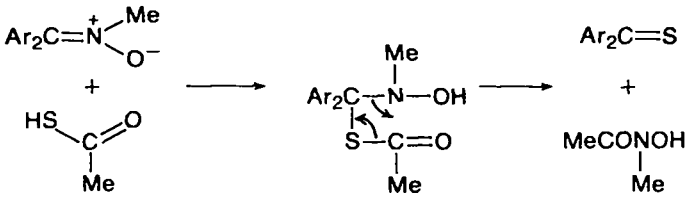
(60)

may serve as a general method to α-alkoxynitrones. Similarly suitably activated nitrones add azide ion to give tetrazoles, presumably via α-azidoimines[291] (equation 61) in addition to other competing reactions.



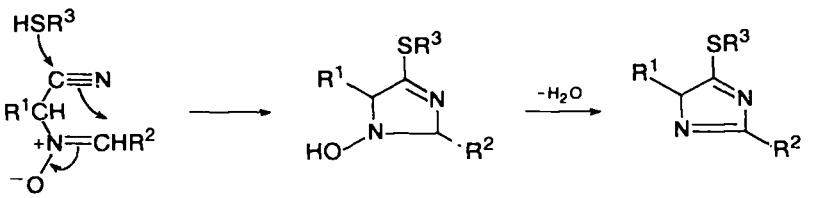
(61)

C,C-Diaryl nitrones may be converted to the corresponding thiobenzophenones and *N*-alkylhydroxamic acids in good yields by treatment with thio acids[292]. This reaction involves nucleophilic attack of the thiocarboxylate anion upon the nitrone, followed by decomposition for which a cyclic mechanism has been suggested (equation 62)[292]. In contrast reactions of *N*-(1)cyanoalkyl)-*N*-alkylideneamine



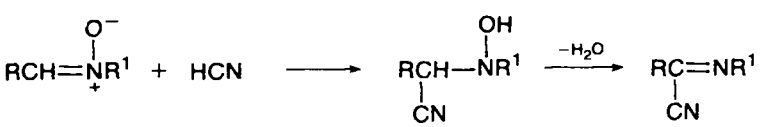
(62)

N-oxides with thiols yield imidazoles. Nucleophilic attack of the thiolate anion upon the cyano group initiates the reaction, followed by cyclization and loss of water (equation 63)[293].



(63)

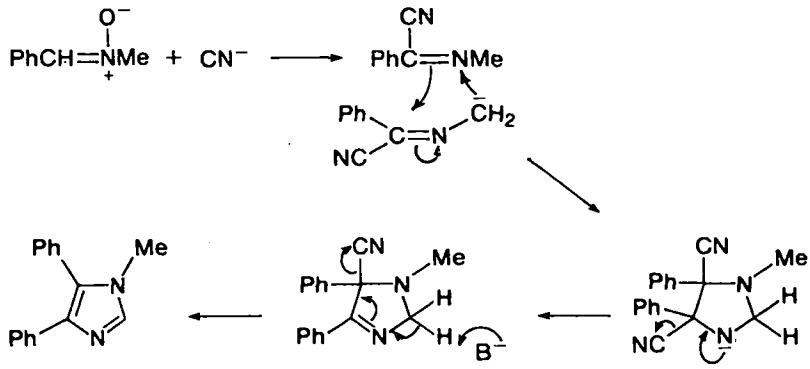
Cyanide has long been known to add to nitrones providing the corresponding cyanoimines (equation 64)[2,294,295]. Recently it has been shown that the reaction of



(64)

C-aryl *N*-alkyl nitrones with cyanide can form imidazoles directly via the corresponding cyanoimines[296]. The mechanism in Scheme 37 has been suggested for this process[296].

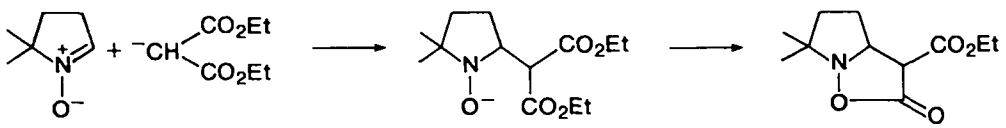
The ability of carbanions to add to the nitrone function has also been recognized.



SCHEME 37

Early examples that include nitromethane and 2-methylpyrroline *N*-oxide have been reviewed[2].

More recently reactions of active methylene compounds and of some ylids have been studied. The reactions of diethyl malonate with Δ^1-pyrroline *N*-oxides proceeds beyond the initially obtained product and with the loss of ethanol isoxazolidines are formed (equation 65)[297]. The reaction has been further studied by Stamm reacting a



(65)

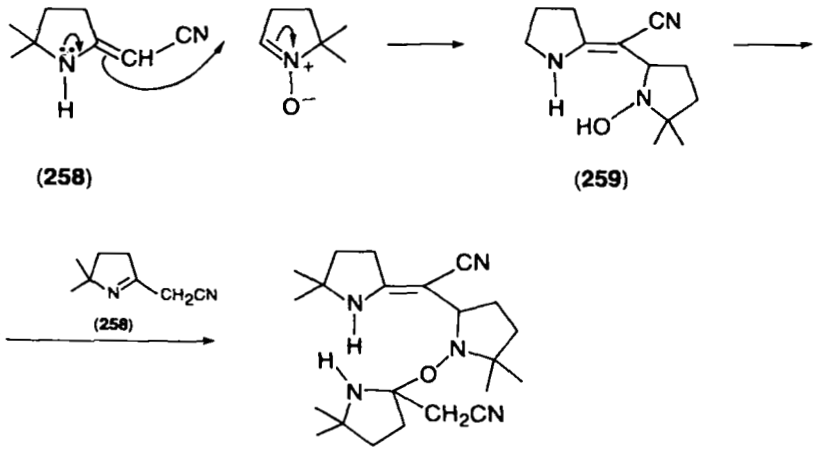
series of *C*-aryl *N*-alkyl nitrones with carbanions derived from diethyl malonate, malonamide, α-ethoxycarbonyl-γ-butyrolactone, ethyl phenylacetate and ethyl cyanoacetate to yield predominantly the 3,4-*trans*-isoxazolidinones[298–300] (e.g. equation 66). The yields have been found to vary with the steric requirements of the *N*-alkyl group of the nitrone and with the nature of the carbanion.

(66)

X = CO_2Et, CN, Ph, etc.

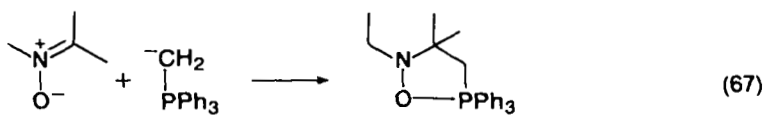
Although simple enamines add to nitrones in a 1,3-dipolar fashion[179] it was found recently by Zbaida and Breuer that the enaminonitrile **258** can add as a nucleophile to a nitrone function. The hydroxylamine product **259** is capable of adding to a second mole of enaminonitrile if an excess of the latter is present in the reaction mixture (Scheme 38)[301].

The reaction of nitrones with phosphorus ylids has been studied in some depth. Huisgen and Wulff have reported that the reaction of triphenylphosphonium ylids with nitrones leads to stable oxazaphospholidines (equation 67)[302]. Later it was shown by Black and Davis that reaction of ethoxycarbonylmethylenephosphorane with 5,5-dimethyl-Δ^1-pyrroline *N*-oxide leads, with the extrusion of triphenylphosphine oxide, to a mixture of aziridine (**260**) and the enamino ester **261** (equation 68)[303].

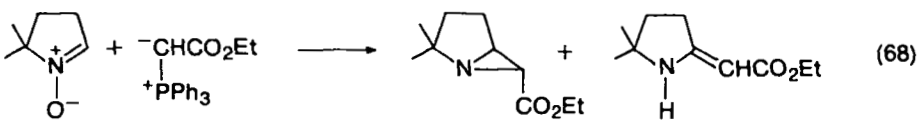


(258) (259)

SCHEME 38



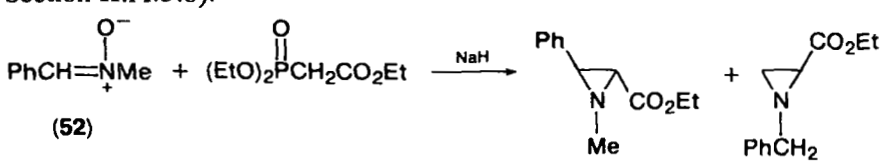
(67)



(68)

(260) (261)

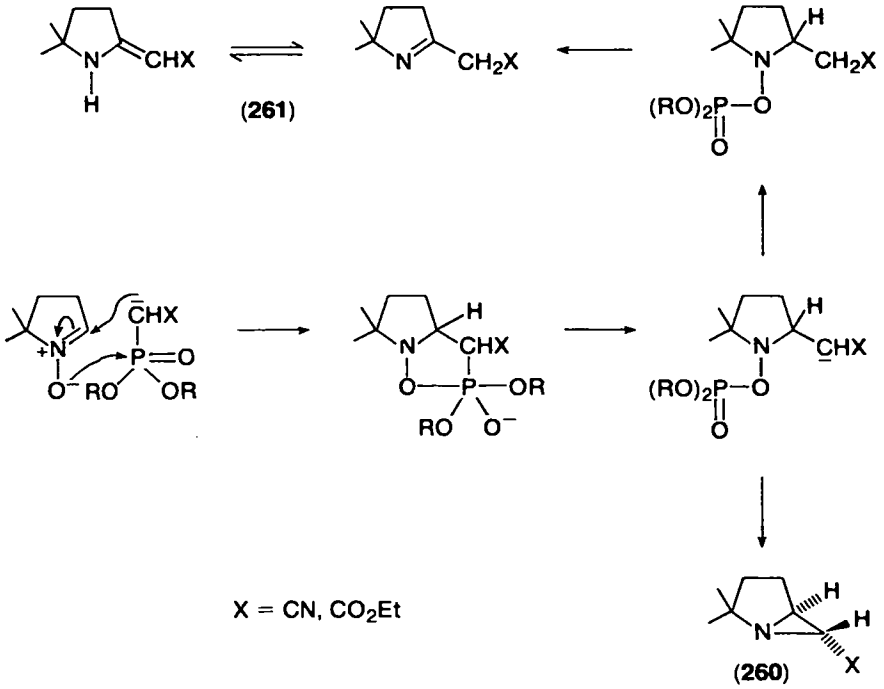
The formation of aziridines from nitrones by the action of phosphono ylids was first reported by Breuer and coworkers, who found that the reaction of triethyl phosphonoacetate and *C*-phenyl *N*-methyl nitrone (**52**) gives a mixture of two aziridines **54** and **55** due to tautomerism in nitrone **52** under the reaction conditions[81] (see Section II.A.5.b).



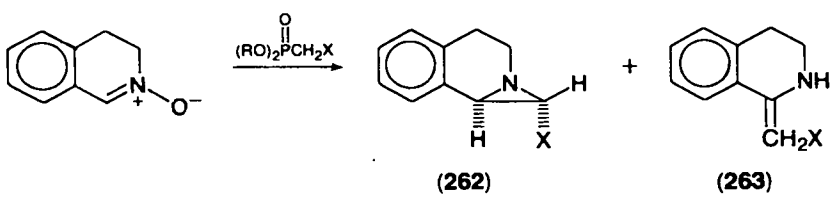
(52) (54) (55)

The reaction of phosphonates with nitrones of the pyrroline *N*-oxide series has been studied by Black and Davis[303] and by Breuer and coworkers[304,305]. It has been found that the reaction leads to *trans* aziridines (**260**) and enamines (**261**)[303–305], and that in certain cases it can be directed to lead predominantly, or even exclusively, to yield one of the products by appropriate choice of solvent and counterion[304,305]. Protonation inhibits aziridine formation and then base-catalysed elimination leads to enamine (Scheme 39).

Similarly the reactions of 3,4-dihydroisoquinoline *N*-oxide with phosphonates lead to the aziridine **262** (X = CO_2Et) or enamines **263** (where X may be either CN or CO_2Et)[306]. Subsequently it has been shown that the course of the reactions of



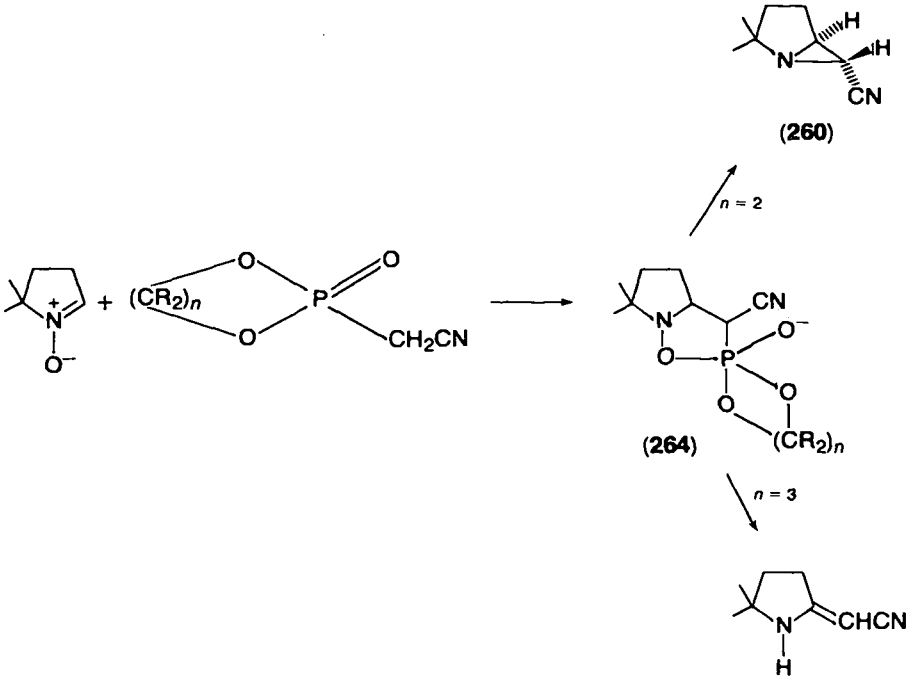
SCHEME 39



nitrones with phosphonates can also be controlled by using cyclic phosphonates of varying ring-size. The reactions of five-membered cyclic phosphonates give predominantly aziridines while those of the six-membered compounds yield enamines[307–309]. This is rationalized in terms of varying basicities of the intermediate **264** as a function of the size of the dioxaphosphacycloalkane ring and their differing tendencies to undergo protonation (Scheme 40). The existence of intermediate **264** (n = 2) has been established by means of ^{31}P-NMR spectroscopy[310]. The reactions of some nitrones with phosphinoxy ylids have also been shown to give aziridines and enamines[301].

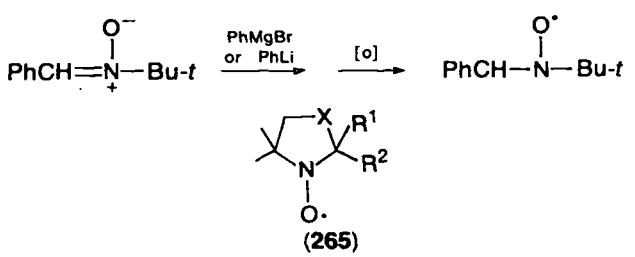
9. *Reactions of nitrones with organometallic compounds*

a. Organo-lithium and -magnesium compounds. The Grignard reaction of nitrones has been known for over 60 years[2,3]. It is one of the reactions upon which the recognition of the similarity between the carbonyl and nitrone functions was



SCHEME 40

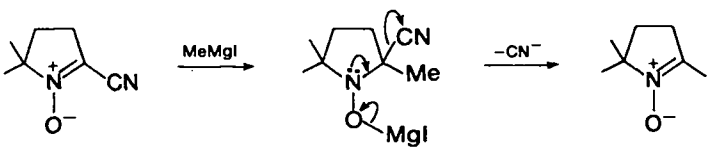
based. The increased interest in this subject in recent years is stimulated by the usefulness of the products, *N,N*-disubstituted hydroxylamines. Oxidation of compounds of this type yields stable nitroxide radicals used as spin labels. In some cases the tendency for oxidation of the *N,N*-dialkylhydroxylamines is so great that their isolation is difficult and the Grignard reactions yield the nitroxide radicals directly. Benzhydryl-*t*-butylnitroxide radicals have been synthesized through the addition of phenylmagnesium bromide or phenyllithium to α-phenyl *N*-*t*-butyl nitrone and oxidation of the hydroxylamine (equation 69)[311]. Radicals derived from pyrrolidine (**265**, X = CH_2)[312] or oxazolidine (**265**, X = 0)[313] have been prepared by a similar reaction sequence.



(69)

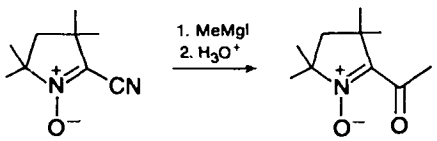
The α-cyanonitrone (**266**) reacts with a Grignard reagent with the loss of the cyanide (equation 70)[314]; however, the tetrasubstituted derivative **267** is too hindered to react on the nitrone function and the α-acetylnitrone **268** is obtained from the reaction of the cyanide group[314].

Reactions of β-ketonitrones with Grignard reagents have been studied in the



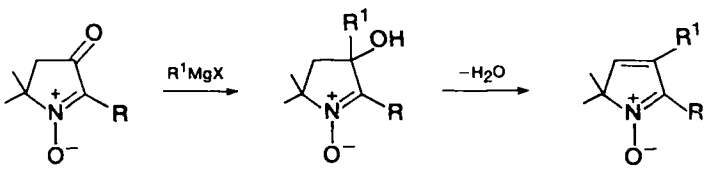
(70)

(266)



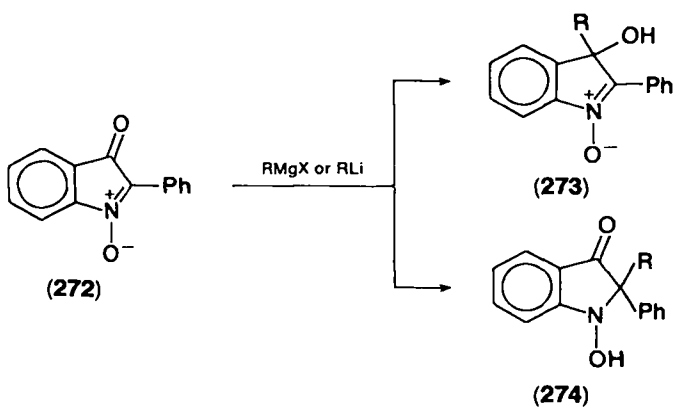
(267) (268)

pyrroline system and with isatogens. 3-Oxo-1-pyrroline *N*-oxides (**269**) react at the carbonyl group to afford alcohols **270** that easily undergo dehydration to 2*H*-pyrrole 1-oxides (**271**)[315]. The reaction of phenylisatogens (**272**) with Grignard or lithium reagents has been shown to yield two types of products, one (**273**) resulting from addition to the carbonyl group and a second (**274**) to the nitrone function[316].



(269) (270) (271)

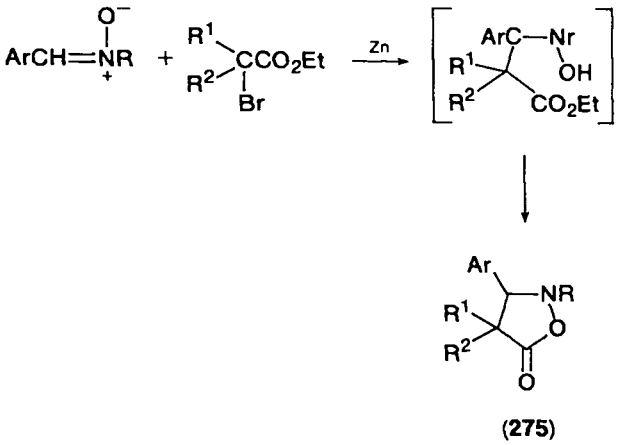
R = Ph, *t*-Bu



(272) (273) (274)

Oxidation of **274** leads to nitroxide radicals[316]. Related studies concerning Grignard reactions of 2-alkylquinoline *N*-oxides[317] and 2,3-disubstituted benzimidazole 1-oxide[318] have shown that these can also lead to nitroxide radicals.

b. Organo-zinc and -copper compounds. *C*-Aryl *N*-alkyl nitrones undergo the Reformatzky reaction with organozinc compounds derived from α-bromo esters, such as α-bromo-acetate, -propionate, -butyrate and -isobutyrate[319,320]. The reactions lead to the formation of isoxazolidinones, **275** (Scheme 41) resembling the reaction of nitrones with diethyl malonate (Section II.B.8).



(275)

SCHEME 41

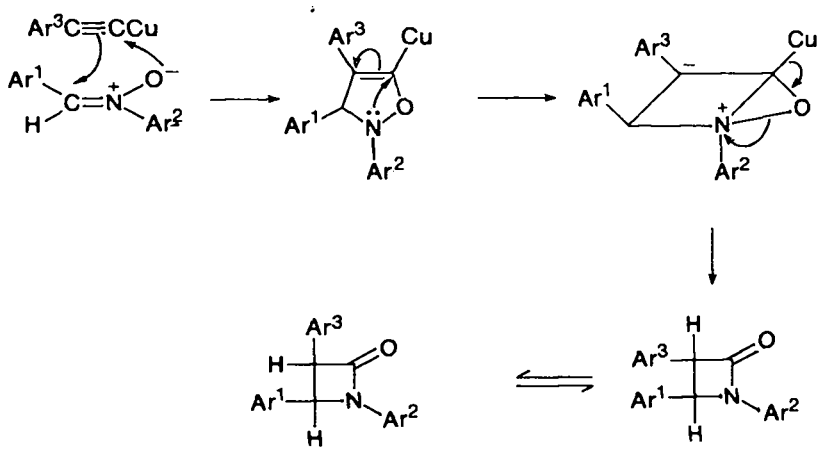
The reaction of a copper acetylide with nitrones was shown to give β-lactams[321,322]. Tracer studies indicate that the carbonyl oxygen originates from the nitrone, while the hydrogen in the 3-position originates from the solvent[322]. A mechanism which is consistent with these results is presented in Scheme 42.

Reactions of copper acetylides with 5- or 6-membered cyclic nitrones result in bicyclic β-lactams **276** and **277**[322].

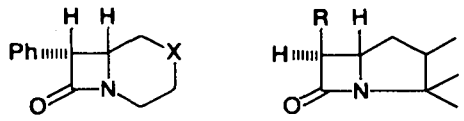
c. Organogermanium compounds. Germanium hydrides can react with nitrones via three different pathways: (*i*) polar addition of Ge—H to the nitrone to yield Ge—C-bonded products (**278**), (*ii*) a dark homolytic reaction to give a Ge—O-bonded product (**279**), and (*iii*) a photocatalysed homolytic reaction to give a Ge—C-bonded product[323–325].

d. Organo-lead, -tin and -mercury compounds. The photolysis of these organometallic compounds yields radicals (see Section II.B.10).

e. Transition metal derivatives. This aspect of the chemistry of nitrones is almost completely unexplored. Iron pentacarbonyl has been reported to cause

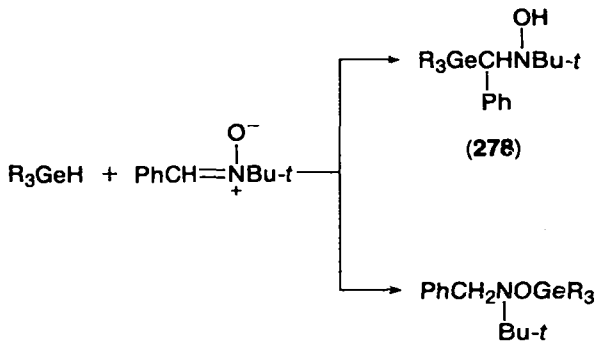


SCHEME 42



(276) (277)

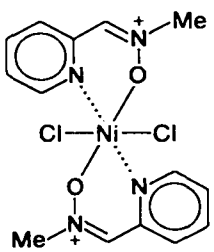
X = O, CH_2



(278)

(279)

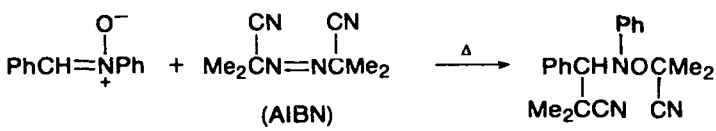
deoxygenation of a nitrone[167]. Nitrones can serve as ligands in nickel complexes[27,28]. For example, *N*-methyl *C*-(2)pyridyl) nitrone forms complex **280** with nickel.



(280)

10. Reactions of nitrones with free radicals

It has been shown that free radicals generated thermally from azobisisobutyronitrile (AIBN) add in the 1,3-manner to α,*N*-diphenyl nitrone (equation 71)[326]. Similar adducts have been obtained from related nitrones, and the reaction

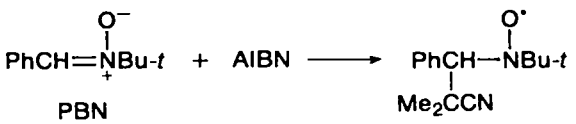


(71)

shown to involve free radicals by chemically induced nuclear polarization (CIDNP)[327]. Other workers have reported, in contrast, that α-,*N*-diphenyl nitrone reacts with radicals to give nitroxides[328].

The formation of nitroxide radicals is a general reaction with the more hindered

α-phenyl *N*-*t*-butyl nitrone (PBN). Reaction of this nitrone with free radicals generated from AIBN gives the crystalline stable free radical **281**[329].

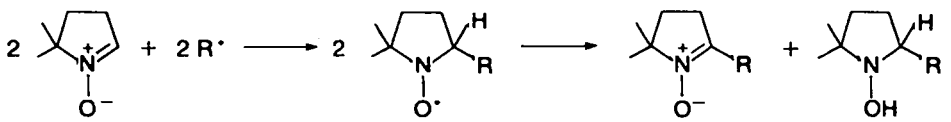


PBN

(**281**)

m.p. 121–122°C, red needles

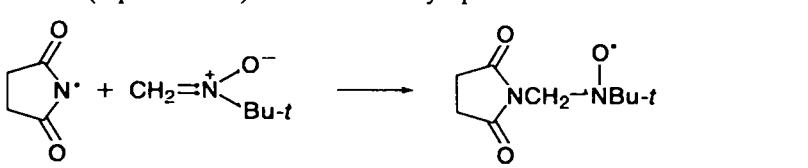
5,5-Dimethylpyrroline 1-oxide can also trap free radicals with the formation of nitroxides, but these products found to be relatively unstable and to disproportionate readily (equation 72)[329]. Earlier the arylation of pyrroline *N*-oxides by arenediazonium salts was postulated to proceed by a free-radical mechanism[165].



(72)

Subsequently it was rapidly recognized that nitrones can be useful traps for short-lived reactive free radicals, since their reactions can produce more stable radicals detectable by ESR and whose hyperfine coupling parameters permit identification of the initial radical trapped. This technique has been named spin trapping[330]. Radicals generated by the decomposition of organo-lead, -tin and -mercury compounds were thus trapped by PBN and the structures of the resulting radicals of type **281** were confirmed by alternate synthesis[142]. Later the complicating influence of the presence of traces of air in the reaction mixture was recognized, especially since the nitrones used were not selective and they reacted with alkyl, alkoxy and alkylmetaloxy radicals giving a variety of products[331]. PBN was reported to add alkoxy and alkylperoxy radicals obtained from photolysis of di-*t*-butyl ketone in $^{17}O_2$-saturated solvents[332] and also from alkyl halides by reaction with potassium superoxide[333]. The trapping of hydroxy and hydroperoxy radicals with PBN and 5,5-dimethyl pyrroline 1-oxide was also reported[334], but disputed recently[335].

Less reactive radicals such as succinimidyl (**282**) have been successfully trapped by *N*-*t*-butyl nitrone (equation 73)[336,337]. Recently special nitrones have been designed

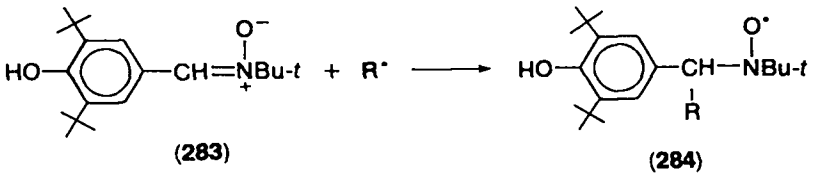


(**282**)

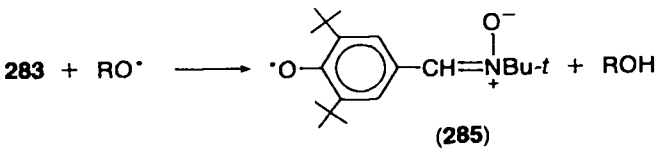
(73)

to serve as radical traps. An interesting bifunctional trap is α-(3,5-di-*t*-butyl-4-hydroxyphenyl) *N*-*t*-butyl nitrone (**283**)[338]. This nitrone differentiates between alkyl and alkoxy radicals. Alkyl radicals add to the nitrone function (equation 74) to give nitroxy radicals **284**, and alkoxy radicals abstract the phenol proton leading to the phenoxy radical **285** (equation 75). The ESR spectra of the two radicals are markedly different. α-(4-Pyridyl 1-oxide) *N*-*t*-butyl nitrone (**286**) is particularly suitable for trapping hydroxyl radicals in aqueous solutions[335].

The most recent additions to this arsenal of nitrones, with a nonpolar hydrocarbon

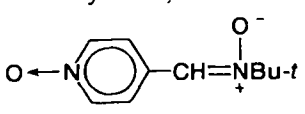


(283) (284) (74)

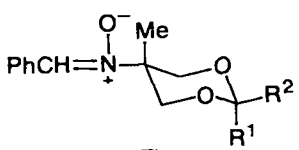


(285) (75)

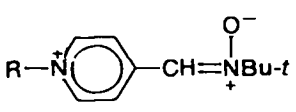
chain that are particularly suitable to serve as spin traps in complex biphasic systems containing regions of different viscosity and polarity, are the two general structures **287** and **288**[339]. The methods developed for these two nitrones permit the synthesis of nitrones with a variety of R, R^1 and R^2 side-chains.



(286)

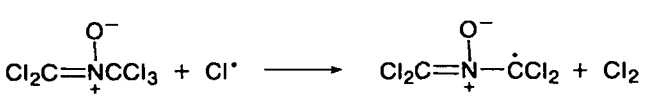


(287)



(288)

An unusual type of reaction of a nitrone with a free radical is shown by the perchloronitrone **289**, which loses a chlorine atom under the influence of radicals to yield a new species **290**[225].



(289) (290)

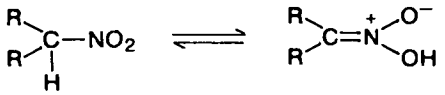
III. NITRONIC ACID DERIVATIVES

A. Nitroalkane–Nitronic Acid Tautomerism

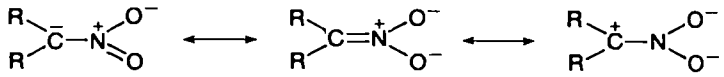
Nitronic acids (**292**) are tautomers of aliphatic nitro compounds (**291**)[340], sharing a common anion, the structure of which can be represented by formulae **293–295**.

The tautomeric equilbrium usually favours the nitro compounds **291** rather than the nitronic acids **292** since the former are normally weaker acids. The mechanism of the tautomerization **291** ⇌ **292** and data concerning the acidity constants of aliphatic nitro compounds and nitronic acids were presented by Nielsen[340].

In recent years the thermodynamic and kinetic acidities of nitroalkanes have been



(291) (292)



(293) (294) (295)

more intensively studied[341-350] and some anomalies have become apparent. In measuring rates of deprotonation and equilibrium acidity constants of nitroalkanes and nitrocycloalkanes it became apparent that an increase in equilibrium acidity is not necessarily paralleled by the same trend in rates of deprotonation. For example, 2-nitropropane is more acidic (by 2.5 pK_a units) than nitromethane, yet it undergoes deprotonation 89 times slower than the latter[347]. Also nitrocyclobutane is less acidic than nitrocyclopentane by nearly 2 pK units, but deprotonates at a four times faster rate. Two series of arylnitroalkanes, namely 1-aryl-2- nitropropanes[344] and 1-arylnitroethanes[343,344] bearing various substituents on the aromatic ring have also been studied. One surprising result was that the substituent effect in one series paralleled that in the other in spite of the difference in distance between the aromatic ring and the nitro group between the two series. This is explained by indirect resonance effects relayed by induction since in the 1-aryl-2-nitropropanes the transmission of direct resonance effects is not possible. It has also been found[344,346], that substituent effects are greater on the rate of deprotonation of the nitroalkane, than on the equilibrium acidities. All the results can be rationalized by visualizing the mode of deprotonation, which leads first to the pyramidal carbanion, **293**. The rate of formation of this species will be the kinetic acidity, and it is easy to see that in an arylnitroalkane substituents in the aromatic ring will influence it. This carbanion has to undergo reorganization to the planar nitronate, **294**, the stability of which will determine the equilibrium acidity of the nitro compound.

Consider the case of nitromethane and 2-nitropropane. The tertiary hydrogen of the latter would be expected to be less acidic than the hydrogens of nitromethane, and this is reflected by the lower ionization rate or kinetic acidity of 2-nitropropane. The higher equilibrium acidity of the latter clearly results from the increased stability of $Me_2C{=}NO_2^-$ (as compared to $CH_2{=}NO_2^-$) and its relatively low rate of protonation on carbon. The situation is analogous in arylnitroalkanes. For example, a substituent such as m-NO_2 increases the rate of deprotonation of $ArCHMeNO_2$, but it also increases the rate of protonation of $ArCMe{=}NO_2^-$[344].

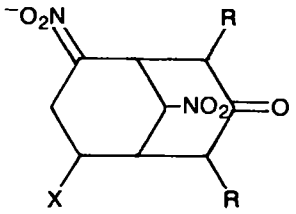
Recently it has been suggested[350], that since the nitroalkane anomalies are observed always in protic solvents, they can be explained by assuming that stabilization of the nitronate anion **294** by hydrogen bonding of the solvent is the major factor determining equilibrium acidity, while hydrogen bonding has little or no stabilizing influence upon the transition state leading to **293**. Therefore, substituents will affect more the stability of **293** than that of **294**. Indeed a linear Brønsted plot was found for a series of substituted arylnitromethanes, whose equilibrium acidities and rates of deprotonation were measured in dimethyl sulphoxide.

The stereochemistry of protonation of nitronates was also discussed previously[340]. Later papers conclude that this is a kinetically controlled process in which steric hindrance may control the direction of approach and give preponderantly one isomer[351-353].

B. Structure of Nitronic Acid Derivatives

1. Theoretical considerations

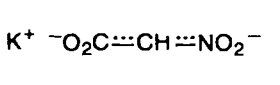
Hückel molecular orbital calculations have been carried out for a series of delocalized bicyclic anions (**296**)[354]. These calculations indicate that the negative charge resides on the oxygen atoms of the nitronate and that the carbon framework is slighly positive.



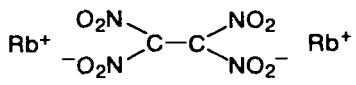
(**296**)
X = NO_2, CN

2. X-ray studies

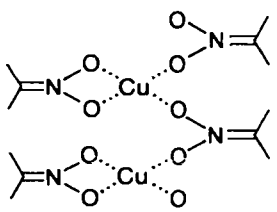
The molecular dimensions of the following nitronates have been determined by X-ray crystallography: dipotassium nitroacetate (**297**)[355], dirubidium tetranitroethanediide (**298**)[356], bis(propane-2-nitronato)copper (**299**)[357], and 2-nitro-1,3-indanedione hydrate (**300**)[358]. The results obtained in these works are consistent with



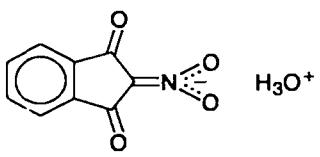
(**297**)



(**298**)



(**299**)

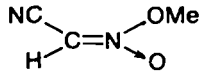


(**300**)

the ideas previously accepted for the structure of nitronate anions. It is found that the nitronate anion is planar. The C—N bond length is between 1.35–1.38 Å, which is shorter than a single (1.45 Å) and longer than a double (1.23Å) bond indicating partial double-bond character. The N—O bond lengths found (1.25–1.27 Å) are somewhat longer than those in nitro groups, indicating considerable contribution of resonance structures in which both oxygens are equally negatively charged.

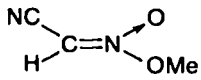
3. Dipole moments

This method is useful for the determination of the structures of geometrically isomeric nitronate esters. Grée and Carrié separated the isomeric pair **301**[359] and



(*Z*-**301**)

μ = 2.25 D



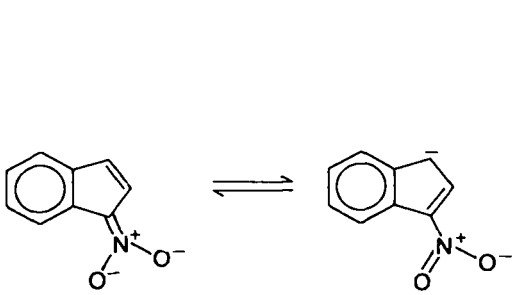
(*E*-**301**)

μ = 4.71 D

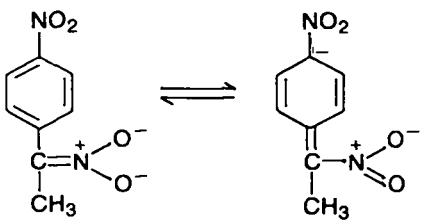
determined their dipole moments. The experimental values (indicated) corresponded well with those calculated by two different methods for various rotational conformers around the N—OMe bond.

4. Spectra

Fundamental spectral properties of nitronic acids, nitronates (salts and esters) are available in the previous review[340]. Apart from some additional ^{1}H-NMR data of (*E*) and (*Z*) nitronic esters[359], almost all recent work has been devoted to the study of the effect of solvent upon various spectral properties of nitronate salts. It is now apparent[343,360] that the ultraviolet absorption maximum can be shifted to higher wavelengths by as much as 150 nm upon changing from a hydroxylic solvent (e.g. MeOH) to a dipolar aprotic solvent such as hexamethylphosphoric triamide. This change in the spectrum reflects the transfer of the negative charge from the oxygens of the nitronate anion, where it can no longer be stabilized in the absence of a hydrogen-bonding solvent, to the carbon of the nitronate, resulting in lesser stabilization, and accordingly the $\pi \rightarrow \pi^*$ transition occurs at lower energy (higher wavelength). This phenomenon is illustrated by some examples. The potassium salt of 1-nitroindene (**302**) has an absorption maximum of 338 nm in ethanol and 418 nm in HMPA[360], whereas the sodium salt of 1-*p*-nitrophenylnitroethane (**303**) absorbs at 394 nm in methanol but at 557 nm in HMPA[343].



(**302a**) (**302b**)



(**303**)

Earlier infrared studies also indicate that the charge of nitronates is concentrated on the oxygen atoms[361,362], but investigation of the infrared spectra of a series of lithium, sodium, and potassium nitronates derived from 2-nitropropane has shown that the C=N stretching bond shifts from 1603 cm^{-1} (for the K^+ salt) to 1637 (for Li^+), showing that the latter has more C=N double-bond character due to tighter coordination between the lithium and the oxygen[343].

Similar conclusions can be reached from examining NMR spectra. Although the NMR data found for some sodium alkylnitronates in water are consistent with a structure in which the negative charge resides on the oxygens, studies of solvent effects upon the ^{1}H-NMR spectrum of 1-nitroindene indicate[360] that there is a downfield shift of H(2) and an upfield shift of H(3) upon passing from trifluoroethanol to HMPA. In addition, there is a change in the magnitude of the

coupling constant of the olefinic protons $J_{2,3}$. The latter has a value of 5.6 Hz (as in indene) in the hydroxylic solvents, but the value decreases to 5.0 Hz in HMPA. All these are consistent with the assumption that in the aprotic solvent there is increased electron density at C(3) and a lower π-bond order between C(2)–C(3) (see structure **302b**).

Some ^{13}C-NMR results confirm these conclusions, as it was found that the chemical shift of the nitronate carbon is also highly solvent-dependent[363]. In a series of sodium nitronates the nitronate carbon appears at a lower field by 10 ppm in methanol than in dimethyl sulphoxide.

C. Reactions of Nitronic Acid Derivatives

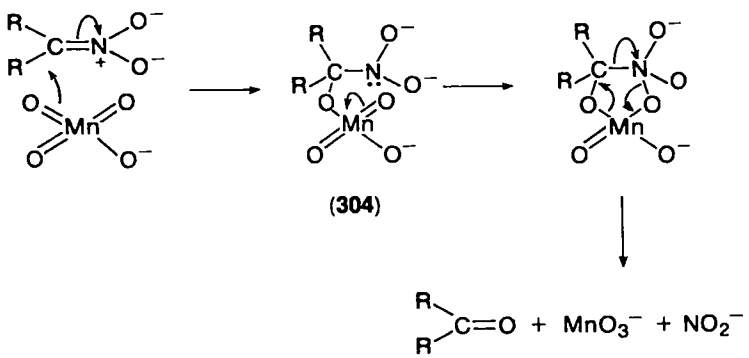
1. Oxidation of nitronates

Oxidation of nitronates is one of the most popular alternatives for the usual hydrolytic conditions of the Nef reaction (Section III.C.5). Permanganate oxidation has been shown previously to give carbonyl products[340]. More recently this reaction has been employed in prostaglandin synthesis[364,365]. Recent kinetic results from studies of this reaction are consistent with a mechanism which consists of rate-determining attack of permanganate upon the C=N double bond leading to species **304** which is transformed to products by the sequence shown in Scheme 43[366–369]. Other oxidizing agents that provide high-yield alternatives to the Nef reaction are ozone[370–371] and singlet oxygen[372].

Nitronate salts are also oxidized by persulphate. This reagent can also affect the conversion of nitronate salts to carbonyl compounds[373,374], but it can also be directed to yield vicinal dinitro compounds if carried out in the presence of an organic solvent which extracts the product formed (equation 76)[373,374]. In the absence of such a solvent, various other secondary oxidation products, such as nitro olefins (**305**) or 3,4,5-trisubstituted isoxazoles (**306**) can be formed[374,375]. This persulphate oxidation reaction is catalysed by silver ions[374].

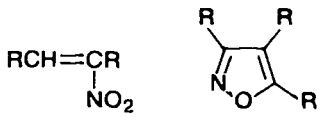
Recently, it has been shown that nitronates derived from arylnitromethanes can be converted to 3,4,5-triarylisoxazoles by silver ion in dimethyl sulphoxide (equation 77)[376]. *t*-Butyl hydroperoxide oxidation of nitronates catalysed by vanadium acetylacetonate has also been shown to give Nef products[377].

Many examples of direct halogenation of nitronates have been known for some time[378]. Recently, it has been shown that nitronates can also be fluorinated directly



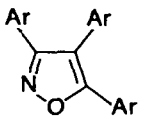
SCHEME 43

$$RCHNO_2^- + S_2O_8^{2-} \longrightarrow \underset{NO_2}{\overset{}{RCH}}-\underset{NO_2}{\overset{}{CHR}} + 2\,SO_4^{2-} \quad (76)$$



(305) (306)

$$3\,ArCHNO_2^- + Ag^+ \longrightarrow \quad (77)$$



by treatment with fluorine in aqueous solution to give α-fluoronitro compounds[379–382].

2. Reduction of nitronates

The treatment of nitronate salts with reducing agents under hydrolytic conditions provides an additional alternative to the Nef reaction. These reactions presumably proceed via the formation of the oxime, which undergoes hydrolysis to the carbonyl compound (equation 78). Reducing agents that have been employed include

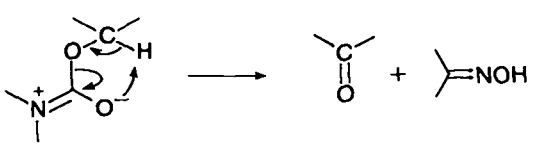
$$RCH{=}\overset{+}{N}\begin{matrix}O^- \\ O^-\end{matrix} \xrightarrow[H^+]{\text{red.}} RCH{=}NOH \xrightarrow{H_2O} RCHO \quad (78)$$

titanium trichloride[383,384] vanadium II chloride[385], chromium II chloride[386] and ascorbic acid[387].

Similarly to other *N*-oxide-type compounds, nitronates can also be deoxygenated by appropriate oxygen acceptors. Thus, silyl nitronates can be converted to *O*-silyloximes by trimethyl phosphite (equation 79)[388].

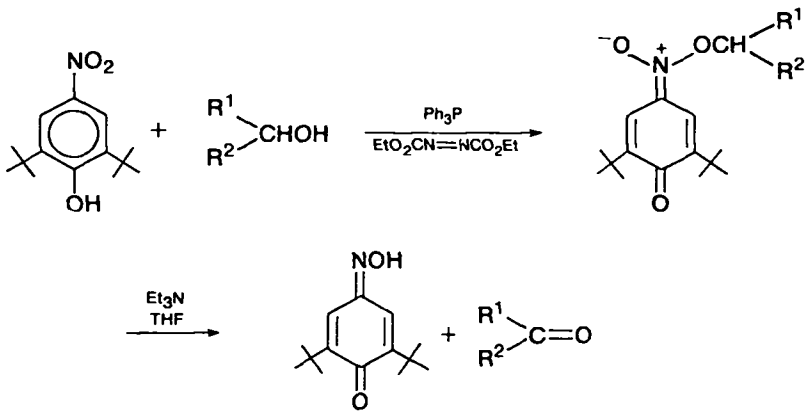
$$\begin{matrix}R \\ R\end{matrix}\!\!>\!C{=}\overset{+}{N}\!<\!\begin{matrix}O^- \\ OSiR_3\end{matrix} + (MeO)_3P \longrightarrow \begin{matrix}R \\ R\end{matrix}\!\!>\!C{=}N\!<\!OSiR_3 + (MeO)_3PO \quad (79)$$

A fragmentation of nitronate esters that results in the formation of carbonyl compounds from the alcohol moiety of the nitronate may be viewed as an intramolecular oxidation by a nitronate (equation 80)[340]. This fragmentation has



(80)

recently been developed into a method for the oxidation of alcohols via nitronates. These can be synthesized in good yield from the alcohol and 2,6-di-*t*-butyl-4-nitrophenol and subsequently decomposed to the carbonyl compounds (Scheme 44)[389].

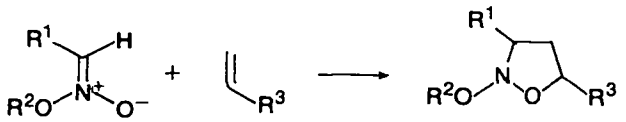


SCHEME 44

3. 1,3-Dipolar cycloaddition reactions of nitronates

1,3-Dipolar cycloadditions have been discussed in Section II.B.5.a and in reviews of this subject[178,182–184,340].

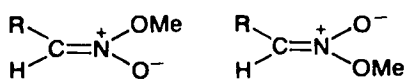
The regiospecificity of the nitronate cycloaddition has been reconfirmed. In all known cases cycloaddition of a nitronate to a monosubstituted olefin leads to a 5-substituted isoxazolidine (equation 81)[34,390–394]. In contrast to nitrones (Section



(81)

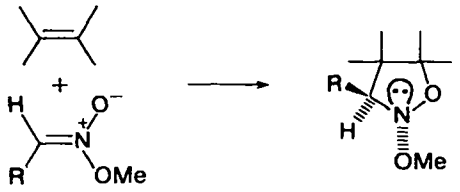
II.B.5.a) no variation in regioselectivity has been observed in reactions of nitronic esters. Disubstituted olefins such as methyl crotonate or crotononitrile give products with the electron-withdrawing group in position 5[393], and trisubstituted olefins react with formation of 5,5-disubstituted products[392b]; 1,3- and 1,4-dienes react with nitronic esters with the participation of each double bond separately[395]. Boron trifluoride has been shown to catalyse the 1,3-dipolar cycloaddition of a nitronic ester[400].

The influence of the structure of the nitronic ester upon its reactivity in 1,3-dipolar cycloaddition and the stereoselectivity of the reactions have been extensively studied by Carrié and his group[396–399]. They have found that (*Z*) nitronic esters (**307**) are more reactive in these reactions than their (*E*) isomers (**308**)[396]. (*Z*) Nitronic esters react with olefins with the exclusive formation of

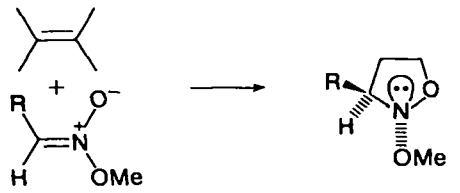


(*Z*-**307**) (*E*-**308**)

isoxazolidines with the OMe and R groups *cis*-related (equation 82), while the reaction of the (*E*) isomer (**308**) yields only the stable *trans* invertomer (equation 83)[396,397]. These results were discussed in terms of secondary orbital interactions of the two reactants. It was concluded that the governing factor is the interaction between the orbitals of the central atom of the 1,3-dipole and those of the



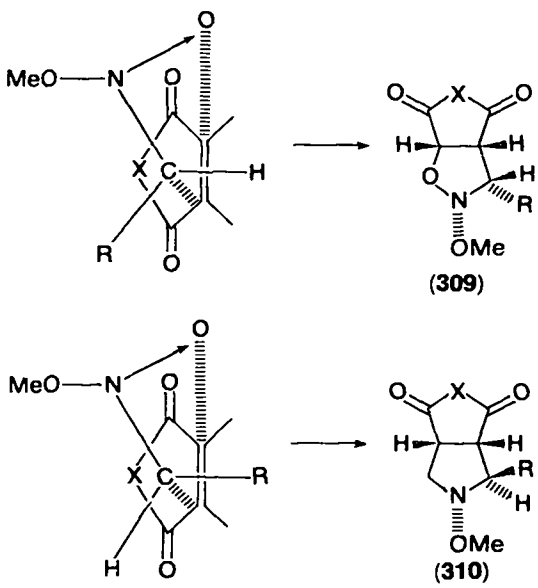
(307) (82)



(308) (83)

substituent on the dipolarophile[398]. The mode of approach of nitronic esters to dipolarophiles has also been determined. Using maleic anhydride and maleic imides as models for 1,2-disubstituted dipolarophiles, it was found that the reaction proceeds by the *endo* approach illustrated in Scheme 45[399], yielding, stereoselectively, the corresponding *N*-alkoxyisoxazolidines **309** and **310**, which exist as stable invertomers on the nitrogen. In contrast to this, the mode of approach in the cycloaddition reactions of nitronates with monosubstituted olefins varies with the substituent of the dipolarophile and with the reaction conditions; both *endo* and *exo* approaches have been observed[397].

The products of nitronate ester cycloadditions may undergo various further transformations. Acid catalysis may induce the elimination of alcohol with the

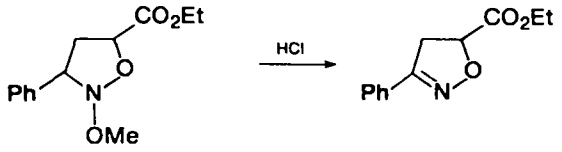


(309)

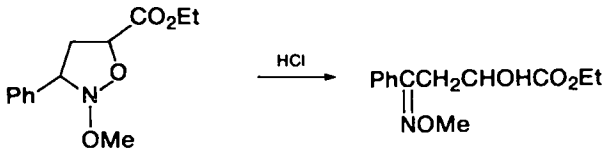
(310)

SCHEME 45

formation of an isoxazoline (equation 84)[391] or cleavage of the ring and the formation of an acyclic product (equation 85)[391]. This type of ring-opening can also



(84)



(85)

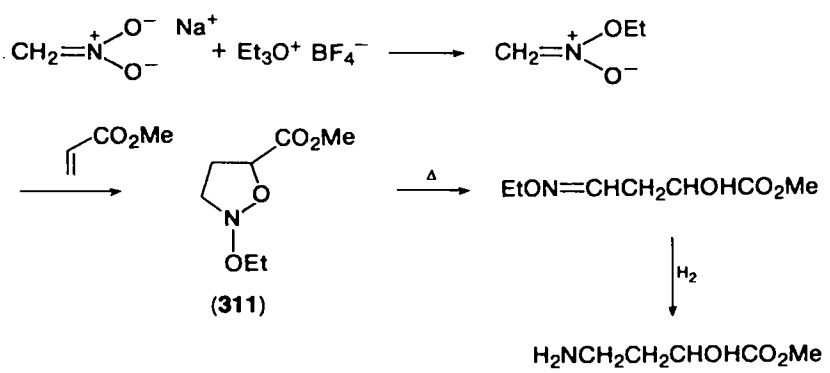
be caused thermally, as has been elegantly used for the synthesis of γ-amino-α-hydroxybutyric acid, which is a constituent of some aminoglycoside antibiotics (see Scheme 46)[392a]. Ethyl nitronate reacts with methyl acrylate to give the isoxazolidine **311**. Thermolysis of **311** gives the oxime ether, which can be reduced catalytically to the desired product in good yield[392a].

The cycloaddition of acetylenes to nitrones leads to 4-isoxazolines, which rearrange easily to acylaziridines[401]. In contrast nitronate esters with alkenes give directly *N*-alkoxy-2-acylaziridines also, presumably, through 4-isoxazolines[402]. Grée and Carrié have shown that the reaction is stereoselective and from each geometric isomer of the nitronic ester a different pair of products is formed[402]. Thus a (*Z*) nitronic ester gives two aziridines **312** and **313** with R and OMe *cis*-related, while the (*E*) isomer gives the two other stable invertomers **314** and **315**. Various mechanistic possibilities for the isoxazoline–acylaziridine rearrangement are discussed[402].

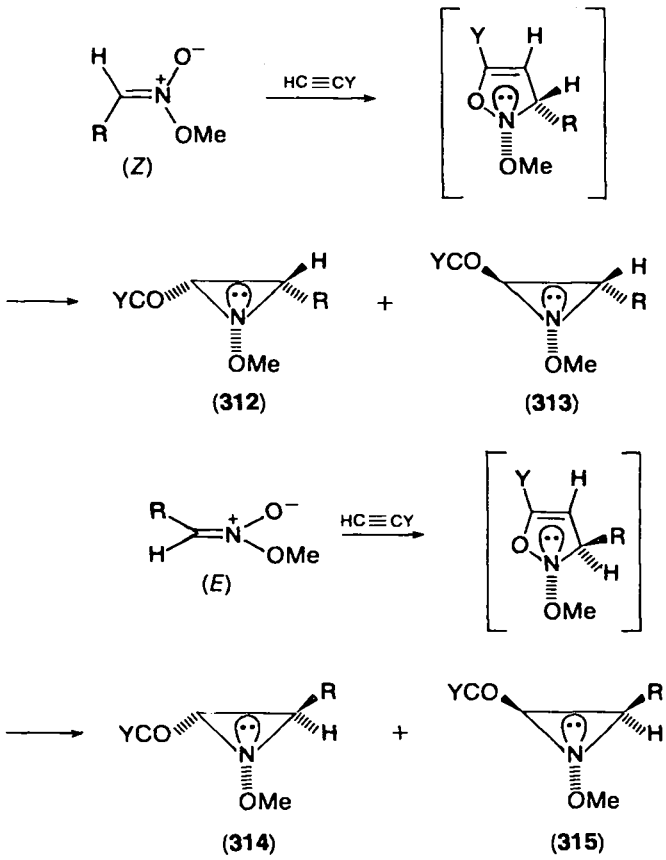
4. *Reactions of nitronates with electrophiles*

It follows from their structures (**293** and **294**) that nitronates may behave as ambident nucleophiles that can react with electrophiles either at the oxygen or at the carbon. Accordingly, this section is divided into two parts.

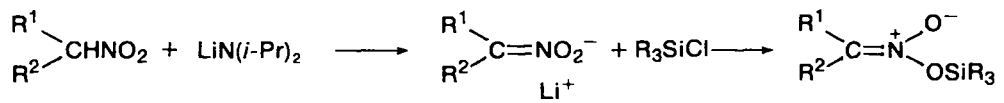
a. Nitronates as oxygen nucleophiles. In general, the carbon atom of a nitronate



SCHEME 46



anion is a poor nucleophile, therefore alkylation or acylation of the oxygen is the reaction that is most often observed[403]. Quenching of nitronate anions, generated from nitroalkanes with lithium diisopropylamide, with a trialkylsilyl chloride results in silyl nitronates that are useful synthetic intermediates[393,394,404,405] (equation 86).



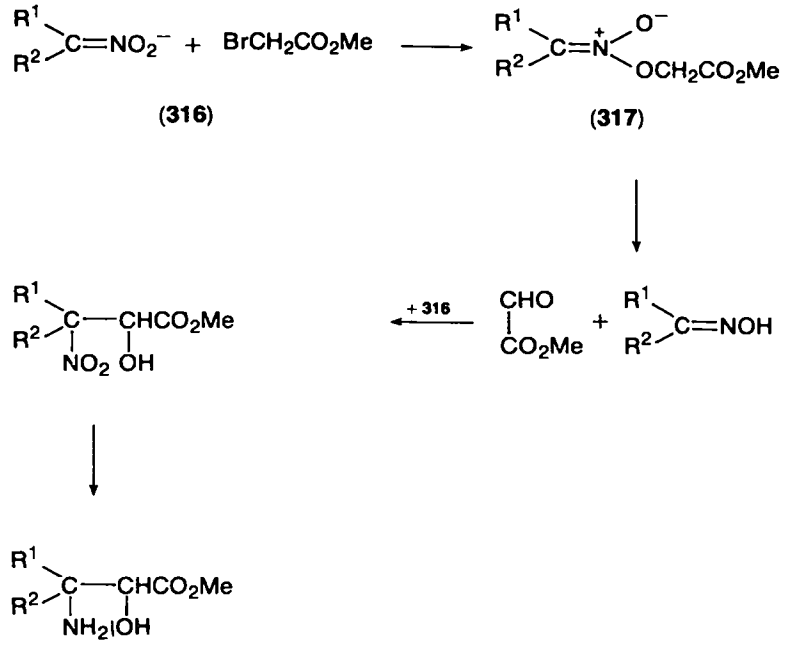
(86)

The *O*-alkylation of nitronates by methyl bromoacetate is the first step in a novel synthesis of β-amino-α-hydroxy acids of some importance in antibiotics (Scheme 47)[406]. The primary product of this reaction (**317**) undergoes fragmentation into an oxime and methyl glyoxylate (cf. Section III.C.2); the latter enters the Henry reaction (Section III.C.4.b) with a second mole of nitronate **316**, resulting in an α-hydroxy-β-nitro acid, which can further be reduced to the end-product[406].

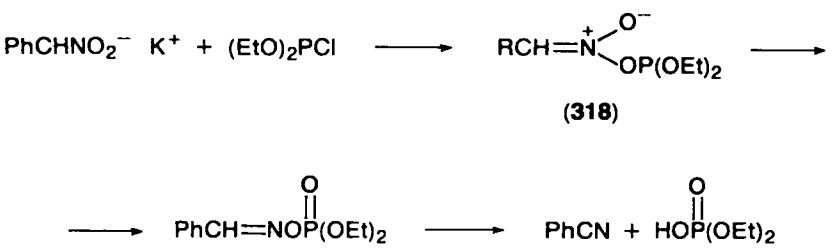
The reactions of nitronates with acylating agents result in end-products that are different from the *O*-acylnitronates that are the postulated primary products.

Nitronates derived from primary nitroparaffins are converted by chlorodiethoxyphosphine to nitriles via the *O*-acylated product **318** as illustrated in Scheme 48[407].

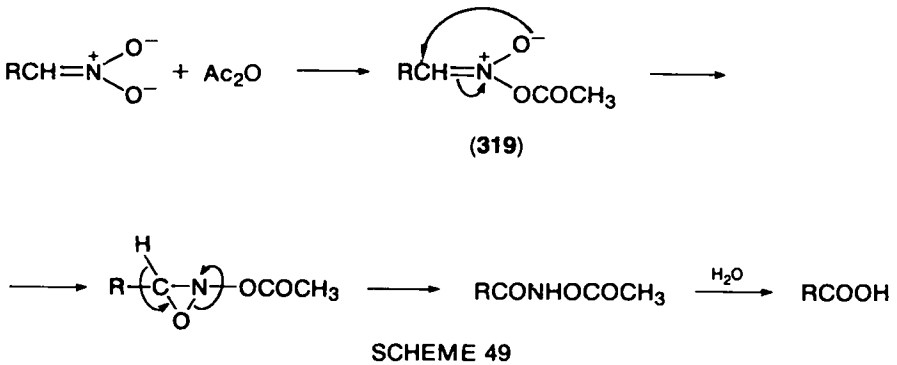
More recently it has been proposed that the conversion of primary nitroalkanes to carboxylic acids[408,409] by acetic anhydride–sodium acetate proceeds through the



SCHEME 47



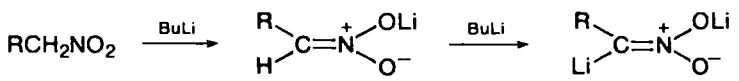
SCHEME 48



SCHEME 49

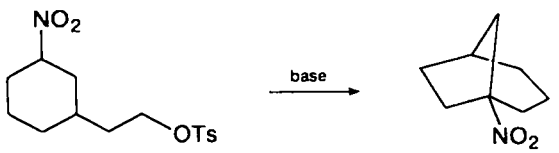
intermediacy of a mixed carboxylic nitronic anhydride (**319**) (Scheme 49)[410]. Mixed anhydrides of type **319** may also lose carboxylic acid to give nitrile oxides which can be trapped by dipolarophiles[410,411].

b. Nitronates as carbon nucleophiles. This aspect of the reactivity of nitronates is probably the most interesting one, since the importance and synthetic utility of any synthon will be related to its ability to serve as partner in carbon–carbon bond-formation reactions. Although nitronates are rather weak carbon nucleophiles, there are examples indicating that they can be alkylated and acylated on the carbon as well as they can add to a carbonyl group or to a polar carbon–carbon double bond (Michael reaction). Recently, it has been discovered that, by the addition of two equivalents or butyllithium to a nitroalkane, 'doubly deprotonated' species such as **320** can be produced (equation 87)[412].

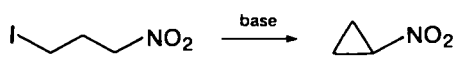


(87)

(i) C-Alkylation of nitronates. Alkylations of nitronates that proceed by radical chain mechanisms[413] are reviewed in a separate chapter in this volume[414]. The earlier literature contains only intramolecular *C*-alkylations of nitronates as indicated in equations (88)[415] and (89)[416].

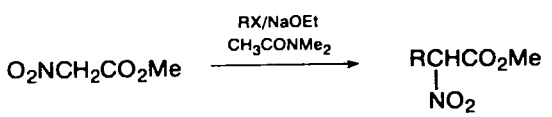


(88)



(89)

Since in dipolar aprotic solvents the negative charge resides upon the carbon of the nitronate anion (Section III.B.4) carbon alkylations are promoted by the use of solvents such as *N,N*-dimethylacetamide and yields up 88%, depending upon the alkyl halide, can be obtained (equation 90)[417–419]. This reaction has been developed into a synthesis of amino acids.



(90)

Katritzky and coworkers have reported recently that nitronate anions can be carbon-alkylated by 1-substituted 2,4,6-triphenylpyridinium cations, also in dipolar solvents[420]. However, the mechanism of this reaction has not yet been clarified.

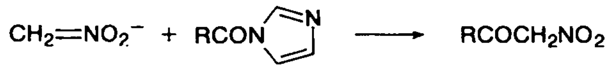
Nitroalkanes that cannot be alkylated by alkyl halides via nitronates have been shown to undergo smooth alkylation using the 'doubly deprotonated' (cf. **320**) derivatives[421].

(ii) C-Acylation of nitronates. Although most acylating agents attack nitronate anions on the oxygen, some give *C*-acyl products. Such reagents are methyl methoxymagnesium carbonate (equation 91)[422], aroyl cyanides (equation 92)[423–425] acylimidazoles (equation 93)[426] and isatoic anhydride (**321**) (equation 94)[427].

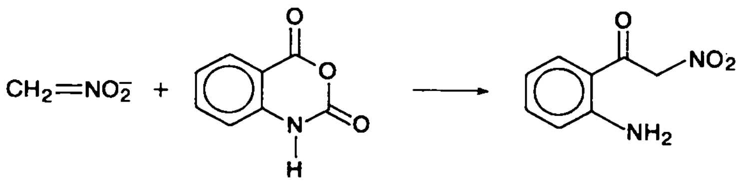
Dilithiated derivatives are considerably more reactive than nitronates toward

$$RCHNO_2^- + CH_3OCO_2MgOCH_3 \longrightarrow RCH(CO_2CH_3)NO_2 \qquad (91)$$

$$RCHNO_2^- + R^1COCN \longrightarrow R^1COCH(R)NO_2 \qquad (92)$$



(93)

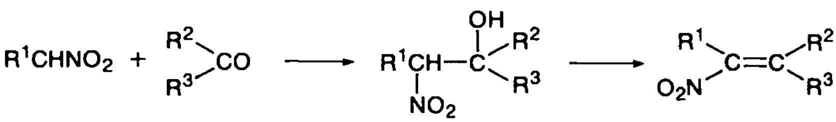


(321)

(94)

acylating agents as, in contrast to the monoanions, they can be acylated by anhydrides and esters to give cleanly *C*-acylnitro compounds[388,412].

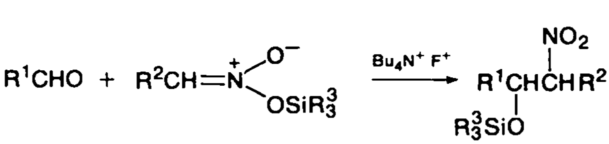
(iii) *C*-Hydroxylalkylation of nitronates. This reaction, the addition of nitronates to the carbonyl group of aldehydes and ketones, is known as the Henry or the nitroaldol reaction[403]. The formation of nitro alcohols is often accompanied by spontaneous loss of water with the formation of nitro olefins (equation 95). In this



(95)

case too, the use of dianions presents an improvement since the product formed from the dianion is stable and the reaction is not reversible[388,412].

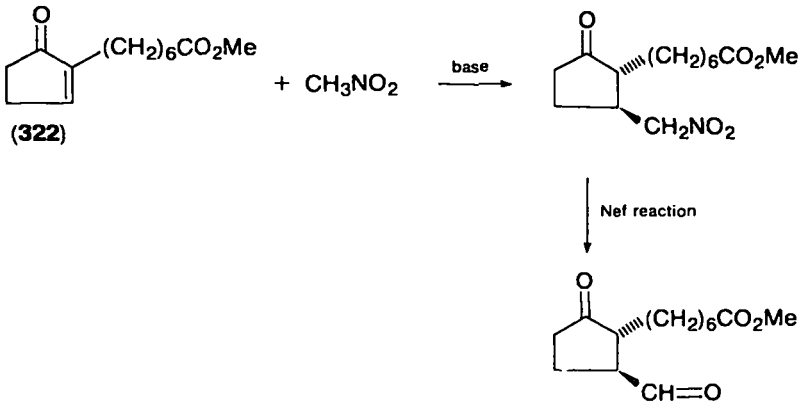
Another improvement in the nitroaldol condensation has been reported by Seebach. It was found that silyl nitronates derived from primary nitroalkanes add to the carbonyl group of aldehydes in the presence of a catalytic amount of tetrabutylammonium fluoride (equation 96)[405].



(96)

(iv) Addition of nitronates to polar C═C bonds. The Michael addition of nitroalkanes to α,β-unsaturated aldehydes, ketones, esters and nitriles, as well as to unsaturated sulphones and nitro olefins is a very efficient reaction. An extensive survey of it can be found in Houben–Weyl[403]. Some recent applications have been used in the synthesis of natural products. The Michael addition of nitromethane to the cyclopentenone **322** has been used by two groups to introduce carbon-13 of the prostaglandin molecule (Scheme 50)[364,428].

The Michael addition of a nitronate may sometimes be followed by the elimination of nitrite. In such cases the net result is the Michael addition of a vinyl



SCHEME 50

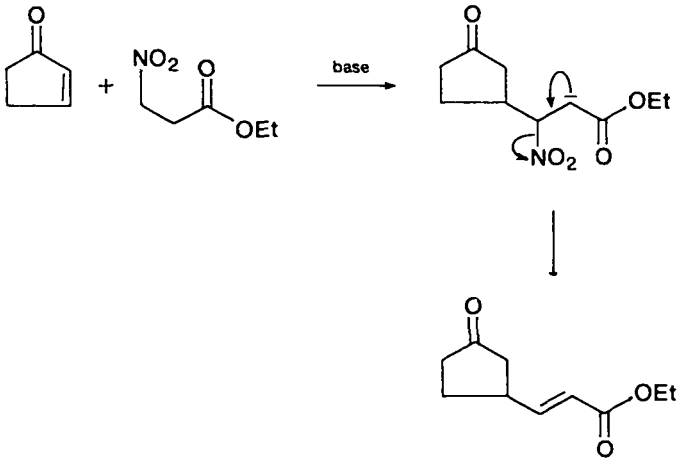
carbanion. This is illustrated in the reaction of β-nitropropionate with cyclopentenone (Scheme 51)[429].

Another application of the Michael reaction is the addition of nitronates derived from 2-nitro alcohols to acrolein. These reactions yield, nitropolydeoxy sugars, which can be converted to aminopolydeoxy sugars; some of these are components of antibiotics (e.g. Scheme 52)[430].

5. *Reactions of nitronates with nucleophiles*

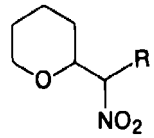
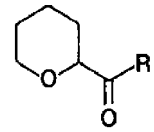
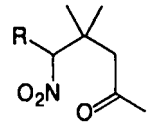
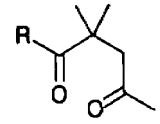
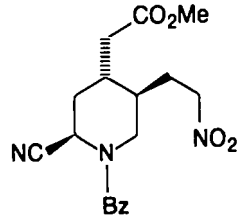
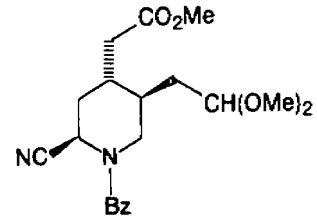
One of the most important reactions of nitroalkanes is the Nef reaction[431]. This reaction is the hydrolysis of a nitronic acid derived from a primary or secondary nitroalkane to yield an aldehyde or a ketone (equation 97).

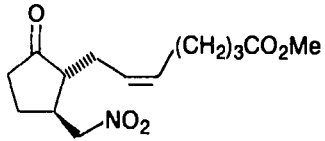
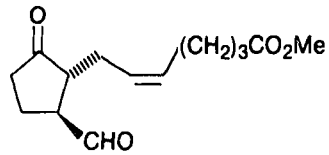
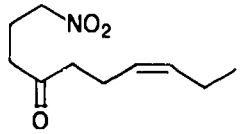
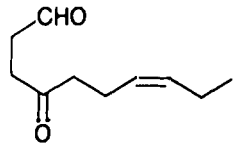
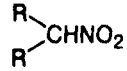
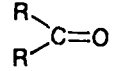
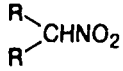
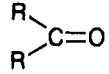
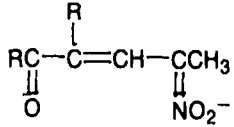
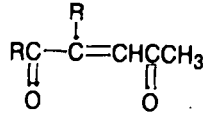
The yields in this reaction are not always high, and therefore, some effort has been directed towards improvements. Some variants, using oxidizing or reducing conditions, have already been presented in Sections III.C.1 and III.C.2, respectively. In addition to these, there exist several recent reports concerning the Nef reactions using solvolytic or neutral conditions or solid catalysts. These are presented in Table 4.

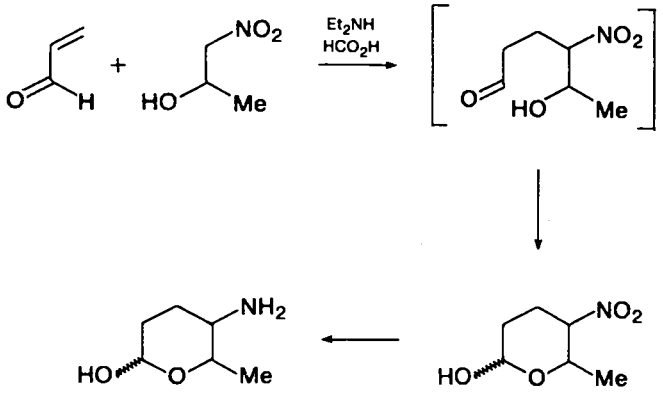


SCHEME 51

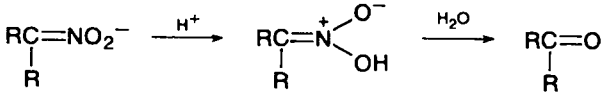
TABLE 4. Some recent examples of the Nef reaction

Reagent	Starting material	Product	Yield (%)	References
1. Me_2NH 2. HCl/H_2O			55–65	432
1. NaOH/EtOH 2. HCl/H_2O			70	433
1. NaOMe/MeOH 2. H_2SO_4/MeOH			78	434

1. NaOMe 2. H_2SO_4/H_2O			56	428
1. $NaOEt/H_2O/THF$ 2. H_2SO_4			45	435
$NaNO_2$/*n*-PrONO/DMSO			70–85	408, 409
$NaOMe/SiO_2$			80–95	436, 437
SiO_2			35–65	373, 438



SCHEME 52



(97)

Finally, attention is drawn to two recently published review articles concerning the synthetic utility of aliphatic nitro compounds[388,439].

IV. ACKNOWLEDGEMENTS

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Supplement F The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives
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CHAPTER **14**

Nitroxides*

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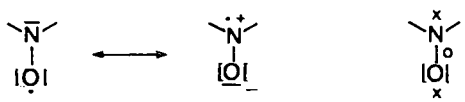
*Dedicated to Prof. Dr. K. Dimroth on the occasion of his 70th birthday.

I. GENERAL AND THEORETICAL ASPECTS

A. Stabilization of the Nitroxide Group

Nitroxides[1–4] are *N,N*-disubstituted NO radicals, the unpaired electron being delocalized between the nitrogen and oxygen atoms, as is indicated by the mesomeric formulae A and B. Following IUPAC rules these radicals should be named aminyl oxides, but aminoxyl would be more appropriate. In the Soviet literature the name nitroxyl or even iminoxyl is frequently used. Nevertheless, we prefer the term nitroxide in view of the vast amount of literature using that name.



The resonance hybrid formulation A ↔ B and the Linnett formulation[5] C indicate the unique stabilization of these radicals in which three π-electrons are distributed over two atomic centres. A simple MO picture shows the remarkable gain in energy resulting from delocalization of the three π-electrons within the two molecular π-orbitals, obtained by a linear combination of the two atomic p_z-orbitals (Figure 1). Since the nitrogen atom of the skeleton has formally two positive charges, one has to assume that its atomic p_z-orbital lies below the atomic p_z-orbital of the singly charged oxygen atom. Two of the π-electrons occupy the low-lying bonding π-orbital, the third one is in the antibonding π*-orbital, thus yielding a net π-bonding of one electron. That the NO bond of the nitroxide group is in fact a one-and-a-half bond (one σ-bond and a half π-bond) is indicated by the bond energy of approximately 100 kcal/mol[6]. This is compared to 53 kcal/mol for the N—O single bond and 145 kcal/mol for the N=O double bond[6]. Further evidence of the bond order is found in the position of the IR frequencies for the NO valence vibration. For 2,2,6,6-tetramethylpiperidine-*N*-oxyl and 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl, the delocalization energy is of the order of 30 kcal/mol[6], as shown by thermochemical studies. Thus, dimerization through formation of an O—O bond cannot occur (equation 1), because the gain of about 35 kcal/mol for

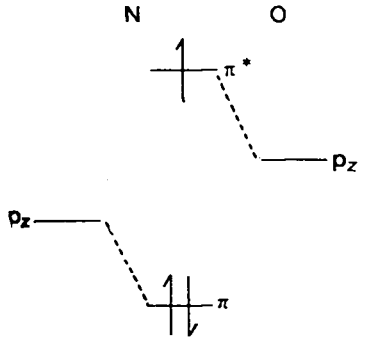
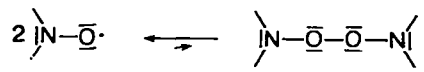


FIGURE 1. Molecular orbitals of nitroxides using linear combination of atomic orbitals.

the new bond cannot compensate for the loss of delocalization energy for the two nitroxide molecules. The gain in energy from delocalization compared to a hypothetical radical without delocalization, such as represented by formula A, is defined

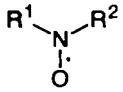


(1)

according to Ingold's proposal[7] as stabilization of the nitroxide group. This means that every nitroxide radical is considerably stabilized. On the other hand, the persistence of nitroxides may be very different. There are, for example, nitroxides which have life-times of several years in the solid state. On the other hand, in solution some nitroxides exist for only a split second and therefore can be detected only under special conditions.

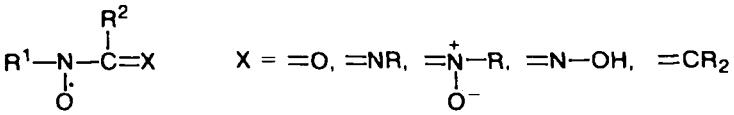
B. Types of Nitroxide Radicals

The variety of substituent groups which can be used in nitroxides is great[8]. Besides the parent compound, $R^1 = R^2 = H$, nitroxides with primary, secondary and tertiary alkyl groups, aryl, alkoxy and amino groups, and with substituents derived from other elements of the higher periods are known. Recently, nitroxides substituted by transition metal complexes have been described

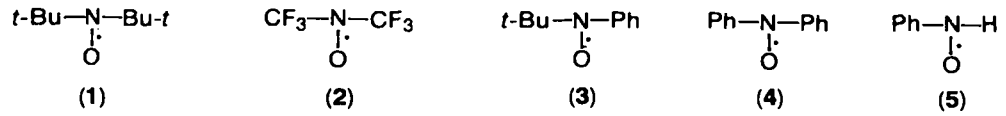


R^1 and/or R^2 = H, Me, *n*-, *s*- and *t*-alkyl, aryl, OR, SR, NR_2, PR_2, SiR_3, ML_n (M = transition metal, L = ligand)

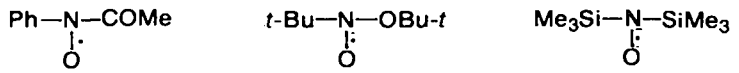
Whereas the delocalization of the unpaired electron in nitroxides with alkyl groups is restricted to the nitroxide group, in aryl nitroxides and nitroxides with conjugated double bonds or substituents with a free electron pair further delocalization can occur. These nitroxides can be characterized as nitroxides with extended delocalization. Nitroxides with acyl, imino, nitrone and vinyl groups, belong to this class of radicals:



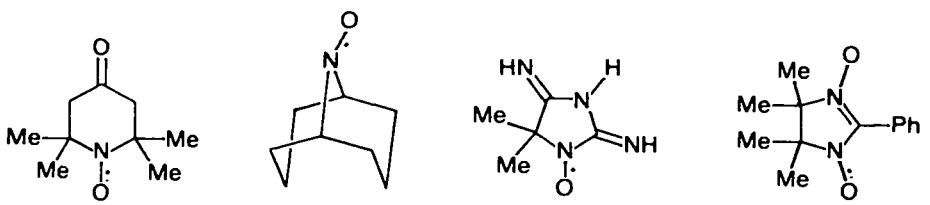
One such nitroxide with extended delocalization, the porphyrexide **11**, is the first known isolable organic radical[9]. Radicals **1–12** are some representative nitroxides. Finally, many diradicals and polyradicals with nitroxide groups are known. In these radicals two or more nitroxide moieties are connected by various bridges[10], as shown for instance in structure **13**.



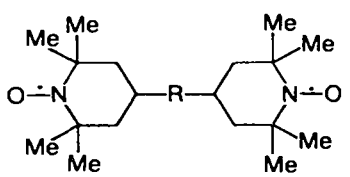
(1) (2) (3) (4) (5)



(6) (7) (8)



(9) (10) (11) (12)

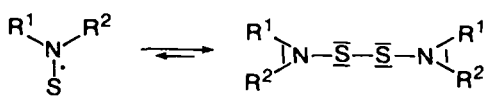


(13)

C. Related Radicals

1. *Thionitroxides*

Substitution of the oxygen in nitroxides by sulphur leads to thionitroxides. Since the electronegativity of sulphur is less than that of oxygen and the bond distance between nitrogen and sulphur is larger, the thionitroxides are less stabilized than nitroxides. Furthermore, dimerization is favoured in the case of thionitroxides due to the higher bond energy for formation of a S—S bond (equation 2). Therefore thionitroxides can be detected in only a few cases under favourable circumstances[11–13].



(2)

2. *Iminoxyls*

The oxidation products of oximes, the iminoxyls, are fundamentally different from nitroxides. Whereas nitroxides are π-radicals, in which the unpaired electron

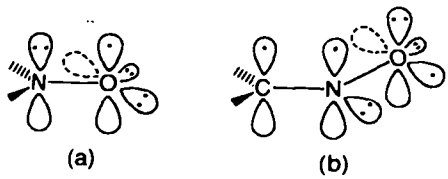


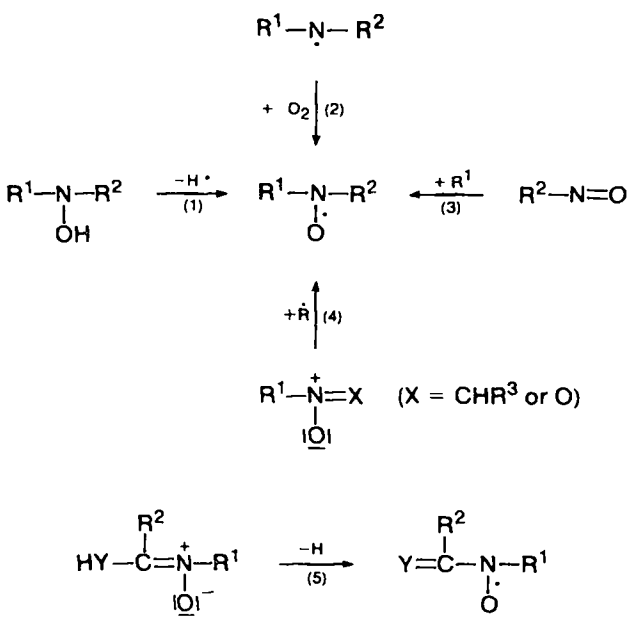
FIGURE 2. Electronic configuration of (a) nitroxides and (b) iminoxyls.

occupies the π^*-orbital in the z-plane, in iminoxyls the unpaired electron occupies a molecular orbital which results from a linear combination of the nitrogen sp^2-orbital and the oxygen p_y-orbital and is therefore orthogonal to the z-plane. Since this orbital has some s-character, iminoxyls are called σ-radicals. Obviously, an electron configuration joining four electrons in the three-centre molecular orbital system of the z-plane and three electrons in the two-centre molecular orbital system of the y-plane is more favourable than the alternative possibility with only three electrons in the three-centre molecular orbital system of the z-plane but four electrons in the two-centre molecular orbital system of the y-plane (see Figure 2).

II. FORMATION OF NITROXIDES

Because of their high stabilization nitroxides are easily formed. This is true for nitroxides which are persistent enough to be isolated as well as for those which are only intermediates in a reaction sequence. The most important methods of nitroxide formation are shown in Scheme 1:

(1) The oxidation of hydroxylamines or the corresponding anions, including cases where the hydroxylamino group is only an intermediate.



SCHEME 1

(2) Addition of an oxygen atom to an aminyl radical.
(3) Addition of a radical R$^{\bullet}$ to a nitroso group.
(4) Addition of a radical R$^{\bullet}$ to nitrones (X = CHR^3) or nitro compounds (X = O).
(5) Oxidation of nitrones with heteroatoms Y in the β-position (especially Y = N), yielding conjugated nitroxides.

Routes (3) and (4) are known as spin trapping.

A. Oxidation of the Hydroxylamino Group

In hydroxylamines such as *N*-hydroxy-2,2,6,6-tetramethylpiperidine and *N*-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine, the bond energies for the OH bond are relatively low, 69.6 and 71.8 kcal/mol, respectively, compared to 80–85 kcal/mol for the corresponding oximes[14]. Thus, oxidation of hydroxylamines occurs readily. This method of preparation is very important because hydroxylamines synthesized from amines or nitroso compounds, respectively, can be oxidized directly without isolation of the intermediate.

1. Formation from hydroxylamines

Oxidation of hydroxylamines occurs with a variety of reagents[15,16]. Potassium hexacyanoferrate (III), silver oxide, lead dioxide, lead tetraacetate, nickel peroxide and mercury oxide are frequently used. In some cases oxidation can occur using oxygen itself either with or without a catalyst. Organic compounds such as nitroso compounds can also oxidize hydroxylamines[17]. In this connection, the formation of monoaryl[18]- or monoalkyl nitroxides[19] from hydroxylamines and nitroso compounds should also be mentioned (equation 3).

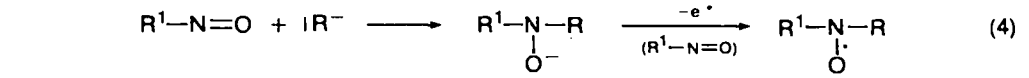
$$R^1{-}N(H){-}OH + R^2{-}N{=}O \rightleftharpoons R^1{-}N(\cdot){-}O + R^2{-}N(H){-}O(\cdot) \rightleftharpoons R^1{-}N{=}O + R^2{-}N(H){-}OH \quad (3)$$

2. Formation from amines

Oxidation of secondary amines is one of the most important methods of preparing disubstituted nitroxides. Hydrogen peroxide in the presence of tungstate, molybdate or vanadate, alkaline hydrogen peroxide, perbenzoic acid and substituted perbenzoic acids, hydroperoxides and lead dioxide are among the many oxidizing agents used[20]. The course of this reaction is not well known. In principle, oxidation of amines can occur through aminyl radicals as the direct precursors of the nitroxides, but in most cases it is assumed that hydroxylamines are the direct precursors of the nitroxides[21].

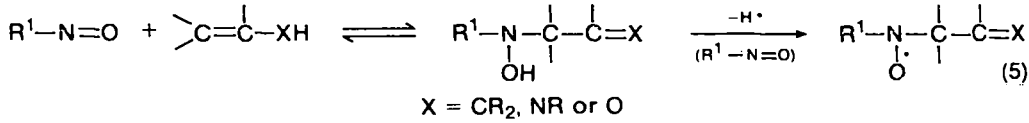
3. Formation from nitroso compounds

Addition of nucleophiles to nitroso compounds leads to hydroxylamines or the corresponding anions, which can be easily oxidized to nitroxides (equation 4)[22]. Frequently, the oxidation is performed by the nitroso compound itself which is partly reduced to azoxybenzene. In particular, Grignard compounds and organolithium compounds react according to equation (4)[23]. Sulphinic acids[24] and



(4)

the hydrogen sulphite ion[25,26] also yield adducts with nitroso compounds, which are oxidized directly to the nitroxides **14** and **15**, respectively. Alkenes bearing at least one hydrogen atom at the allylic position may easily add to aromatic nitroso compounds forming nitroxides by the subsequent oxidation reaction (5)[27]. For instance, 2,3-dimethyl-2-butene yields **16** in this manner[28]. Radicals **17** and **18** are formed from imines[29] and ketones[30], respectively, which react in their tautomeric enamine and enolic forms in an analogous manner. Finally, 4-morpholino-1-cyclohexene and aromatic nitroso compounds yield nitroxides **19**[31].



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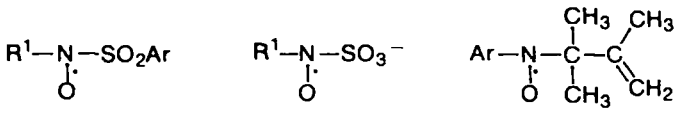
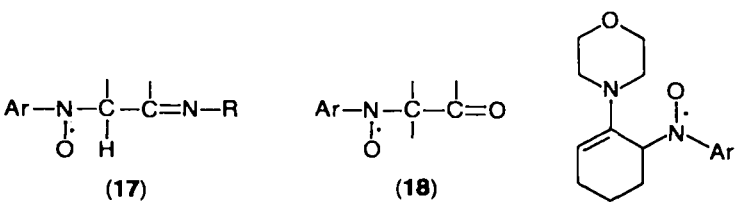


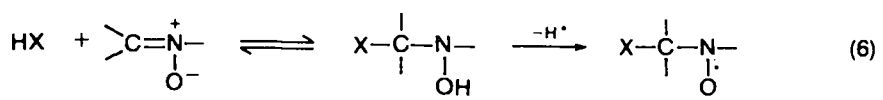
(14) **(15)** **(16)**



(17) **(18)** **(19)**

4. Formation from nitrones

In the same way, adducts from nucleophiles and nitrones may be converted to nitroxides (equation 6). Thus, Grignard compounds or organilithium compounds attack nitrones, the adducts **20** being subsequently oxidized to nitroxides **21**[32] (equation 7). The addition of amines to nitrones usually occurs to only a small extent giving an equilibrium mixture. Nevertheless, the adduct can be oxidized to nitroxides (equation 6, $X = R_2N$)[33,34]. The oxidation of nitrones **22**, yielding nitroxides **23** with extended delocalization[35,36] (see route 5 in Scheme 1), can formally be considered as a reaction of the tautomeric hydroxylamine (equation 8).



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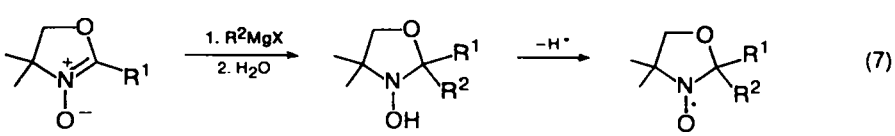
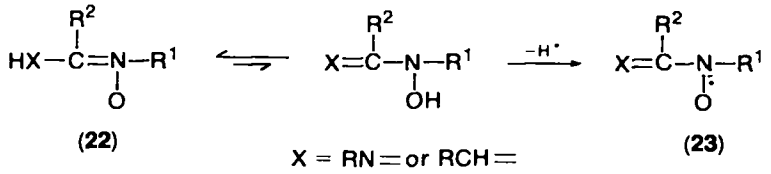


(20) **(21)**

(7)

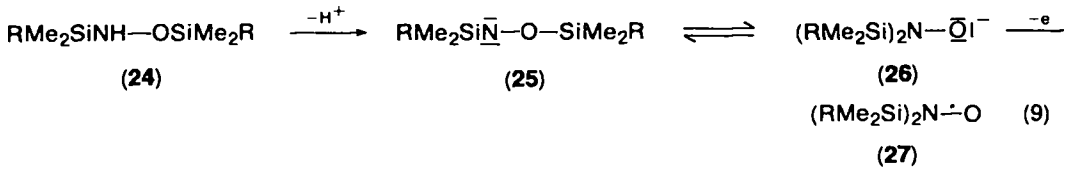


(22) (23) (8)

X = RN= or RCH=

5. Formation from O-substituted hydroxylamines

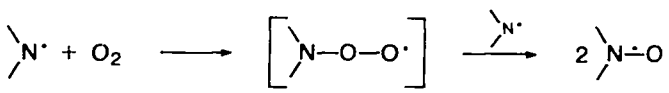
O,*N*-Disubstituted hydroxylamines can, in special cases, be converted to nitroxides. Thus, deprotonation of **24** gives the anion **25** which exists in equilibrium with the rearranged anion **26** (equation 9). Oxidation of the latter, either by oxygen or electrochemically, gives the nitroxide **27**[37].



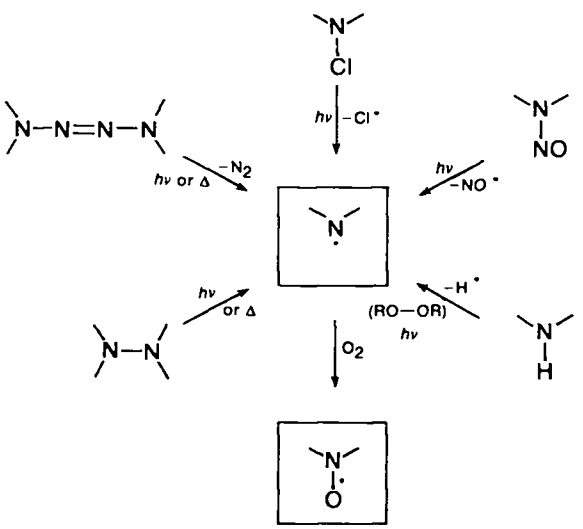
(24) (25) (26) (27) (9)

B. Nitroxides from Aminyl Radicals

Contrary to nitroxides, aminyl radicals which are substituted by two alkyl groups are not stabilized, and even when substituted by two aryl groups only to a small degree. Consequently, aminyl radicals are very reactive, forming in most cases nitroxides on reacting with oxygen (equation 10). Unambiguous evidence for the direct reaction of aminyl radicals and oxygen was obtained from the reaction of



(10)



SCHEME 2

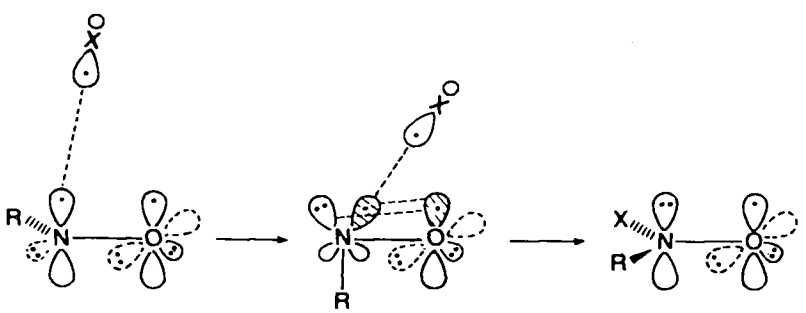
2,2,6,6-tetramethylpiperidyl radical and oxygen-17 at low temperatures[38]. The reaction rate is so fast that it cannot be measured. An adduct of the aminyl radical and an oxygen molecule is assumed to be an intermediate in the formation of the nitroxide. This method is extremely important in ESR spectroscopic investigations. It is especially suitable for the ^{17}O-labelling of nitroxides. The precursors of the nitroxides, the aminyl radicals, can be easily generated in the cavity of an ESR spectrometer by either photolysis or thermolysis of tetrazenes or hydrazines, by photolysis of *N*-chloroamines or *N*-nitrosoamines and by hydrogen abstraction from secondary amines[39] (see Scheme 2).

C. Spin Trapping

1. General remarks

The reaction of a short-lived radical with a nitroso compound, a nitrone or any other suitable compound, affording a new, persistent radical is called spin trapping because, in using this process the radical character, the spin, is retained[40,41]. This method has wide applications for two reasons. Firstly, it can be used to obtain nitroxides which are difficult to generate using other methods. Secondly, it can be used to study indirectly the mechanism of certain reactions, since it allows the detection of transient radicals. In the latter case, one must consider the possibility that the formation of a 'spin adduct' can also arise by the addition of a nonradical nucleophile to the spin trap, followed by oxidation of the adduct[42]. Furthermore, the high sensibility of the ESR method can easily lead to misinterpretations insofar as radicals arising from side-reactions are also trapped.

The exceptionally high reactivity of nitroso compounds in radical addition reactions was discovered many years ago. Szwarc found that nitrosobenzene reacts with methyl radicals about 10^5 times faster than benzene does[43]. This high reactivity can be understood if one assumes that the transition state itself is already stabilized by partial delocalization owing to the developing nitroxide moiety. Theoretical considerations suggest that the reaction begins with the transfer of electron density from the radical to the unoccupied antibonding π^*-orbital of the nitroso group. Consequently, the NO bond is stretched, reducing the bond energy and facilitating twisting of the NO group. During the progress of the reaction, one electron of the original NO double bond is used in the formation of the new bond with the attacking radical, the other one being localized at the oxygen. This decoupling of the electron pair is facilitated by the increasing twist of the stretched NO bond leading to an increase in overlap between the p_z-orbital of the oxygen with its single electron, and the original sp^2-orbital of the nitrogen with its electron pair. The latter gets more and more p-character which results in the final formation of the two molecular π-orbitals of the nitroxide group by linear combination with the single occupied orbital of oxygen:

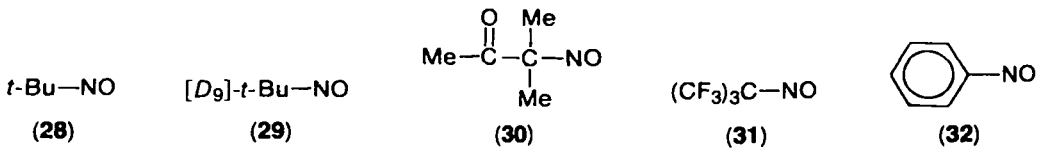


Similar arguments can be used to explain the high reactivity of nitrones in radical trapping reactions. In this case, the decoupling of the C=N double bond with the beginning of C—R bond formation is facilitated by the increasing gain in delocalization energy connected with the formation of the nitroxide moiety. Furthermore, it seems reasonable that the addition of radicals is rendered more difficult if the nitrone is stabilized by conjugation with other groups, such as the phenyl group.

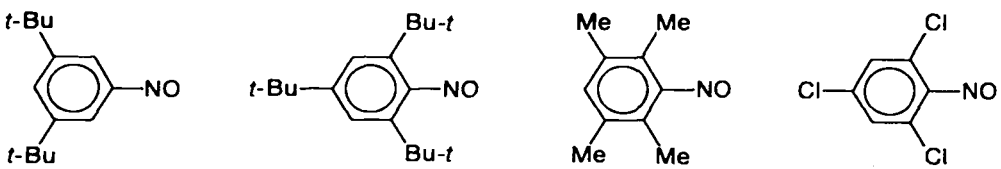
On the other hand, decoupling of an electron pair of the considerably stabilized nitro group is much more difficult. Thus, nitro compounds do not trap alkyl radicals, except when the nucleophilic character of the radical is enhanced by electron-donating groups[44].

2. *The properties of spin traps*

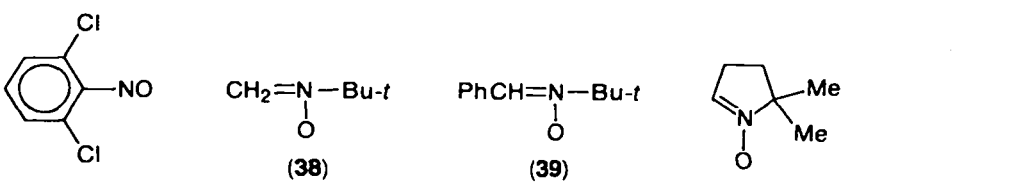
Formulae **28–43** show a selection of spin traps. The use of nitroso compounds has the advantage over nitrones that the radical being trapped is directly attached



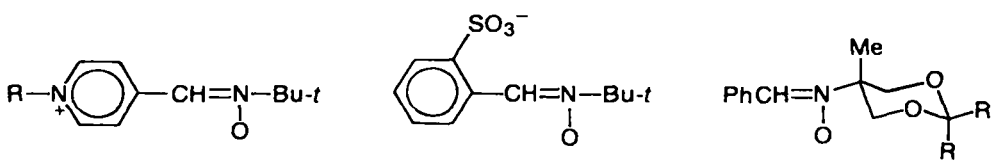
(28) **(29)** **(30)** **(31)** **(32)**



(33) **(34)** **(35)** **(36)**



(37) **(38)** **(39)** **(40)**



(41) **(42)** **(43)**

to the nitroxide group and thus makes a contribution to the splitting of the ESR spectrum, enabling, in most cases, unambiguous identification of the original radical. On the contrary, the ESR spectra of spin adducts with nitrones give less information. However, the ESR spectra arising from partial decomposition of the nitroso compounds are often superimposed on the spectra of spin adducts derived from nitroso compounds. Aliphatic (e.g. 2-methyl-2-nitrosopropane) as well as aromatic (e.g. nitrosobenzene) nitroso compounds may be cleaved to some extent thermally, even at room temperature, or photochemically, to nitrogen oxide and the corresponding alkyl or aryl radical which is trapped by intact nitroso compound, giving dialkyl or diaryl nitroxides, respectively[45]. This is not true for spin traps **34–37** which are finding increasing use. Nitrosodurene (**35**) easily gives spin adducts[46], though even in solution an equilibrium between dimeric and monomeric forms exists.[47,48]

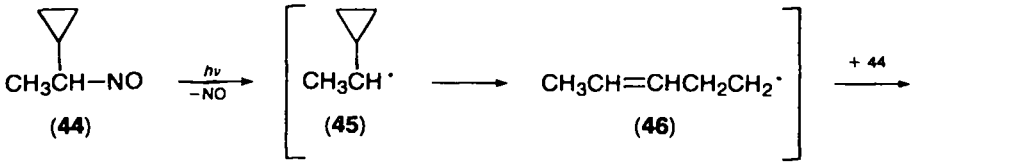
As was shown recently, 2,6-dichloronitrosobenzene (**37**) and similar compounds (2,6-dibromonitrosobenzene, 2,4,6-tribromonitrosobenzene) react with compounds like *o*-xylene at slightly elevated temperature by abstraction of hydrogen and trapping of the benzylic radical, thus acting as a spin trap as well as a radical-generating reagent[49].

For nitrone spin traps the possibility for variations at the side-groups is greater. The compounds **41–43**, which have been synthesized only recently[50,51], are of special interest. The water-soluble compound **42**[50] is the first anionic spin trap. In nitrones **41** and **43** long-chain alkyl groups may also be introduced[51]. These spin traps are of particular interest for application in complex biphasic systems; as such they may be of value for the study of reactions in biological systems. The lifetime of the cationic spin adducts derived from **41** is longer than those of corresponding neutral spin adducts, since disproportionation to the corresponding nitrone and hydroxylamine is retarded by the positive charge[51].

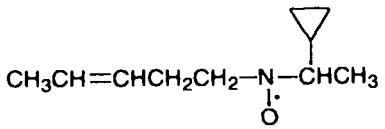
3. Examples of spin trap reactions

In addition to the many different types of carbon-, nitrogen, oxygen-, sulphur- and phosphorus-centred radicals[52], an increasing number of transition metal complexes has recently been trapped by nitroso compounds[53]. A great number of radicals has also been trapped by nitrones.

Free-radical formation by the photolysis of aliphatic nitroso compounds in solution has been unambiguously confirmed by de Boer[54]. From compound **44** he has obtained nitroxide **47** which can arise only via the intermediate free radical **45** and its rearrangement product **46**. An example of intramolecular spin trapping is



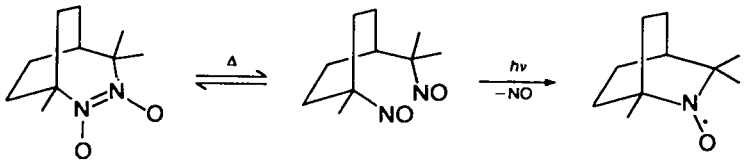
(**44**) (**45**) (**46**)



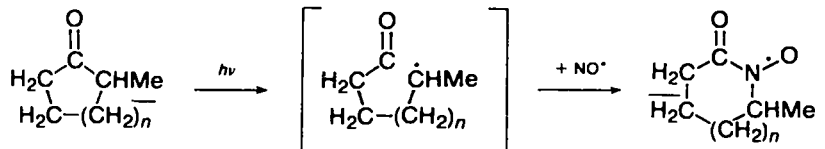
(11)

(**47**)

the photochemical conversion of **48** to the nitroxide **49**[55]. On the other hand, the acylnitroxides **52** may be obtained by a twofold spin trapping process between the intermediate diradicals **51**, generated by photolysis of cyclic ketones **50**, and nitrogen oxide[56].



(48) (49) (12)

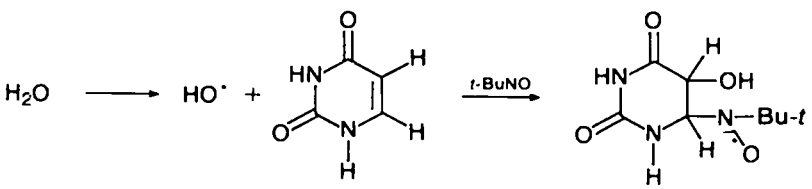


(50) (51) (52) (13)

n = 1 or 2

After many unsuccessful attempts, peroxy radicals have been recently trapped by *t*-butyl phenyl nitrone (**39**) at low temperature, the adduct being converted to the corresponding alkoxy adduct at 0°C[57]. Using 2-methyl-2-nitrosopropane, adducts of peroxy radicals have also been detected[57].

The following example shows that spin trapping can also be used in the investigation of biological processes. Radicals formed by γ-irradition of aqueous solutions of dipeptides or of bases such as uracil or thymine, may be trapped using 2-methyl-2-nitrosopropane (equation 14)[58].

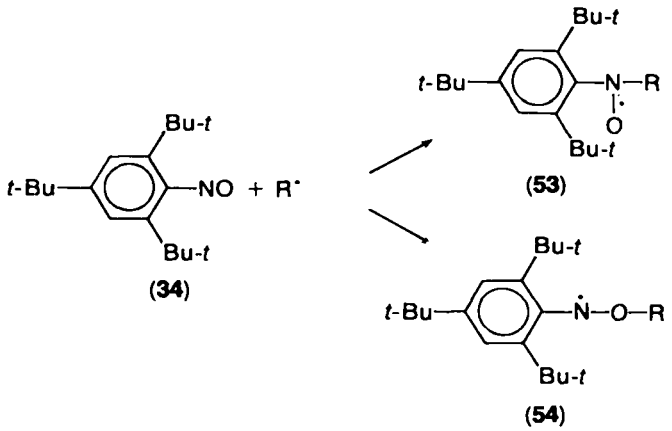


(14)

4. *Selectivity in spin trap reactions*

Some spin traps show a certain selectivity in their reaction with the attacking radicals. For instance, 2,4,6-tri-*t*-butylnitrosobenzene (**34**) yields the usual *N*-adducts **53** with primary alkyl radicals, whereas with tertiary alkyl radicals, only *O*-adducts **54** are formed. Secondary alkyl radicals give both adducts[59]. Nitrosoethylene (**55**) adds alkyl radicals that are formed from alkyl bromides and tri-*t*-butylstannyl hydride with the formation of nitroxides **56**[60]. On the other hand, *t*-butyl radicals generated by the irradiation of 2,2-azoisobutane surprisingly yield spin adduct **57**[61].

Nitrone **58** allows for the differentiation between carbon- and oxygen-centred radicals[62]. Alkyl and aryl radicals add to the nitrone group, whereas oxygen-centred radicals abstract hydrogen from the hydroxy group thus affording a radical **59** that may be considered as both phenoxyl and nitroxide.



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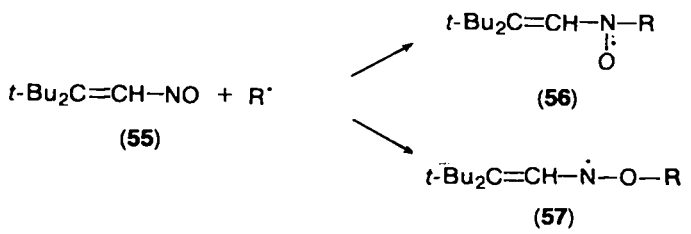

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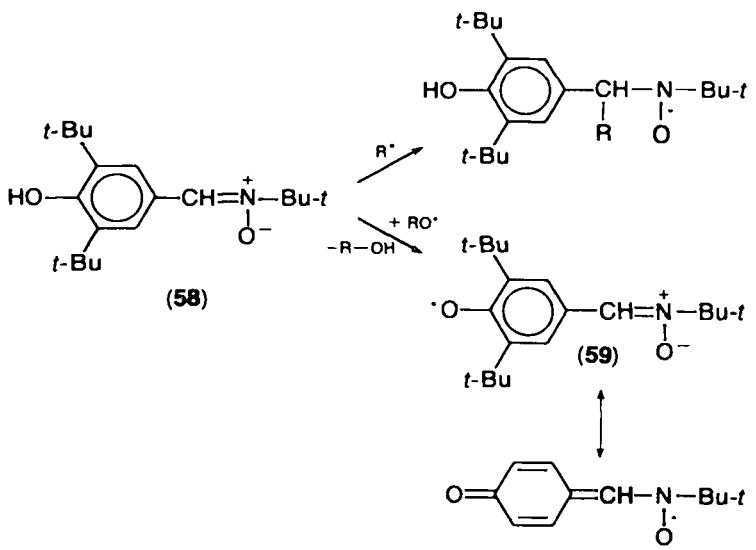
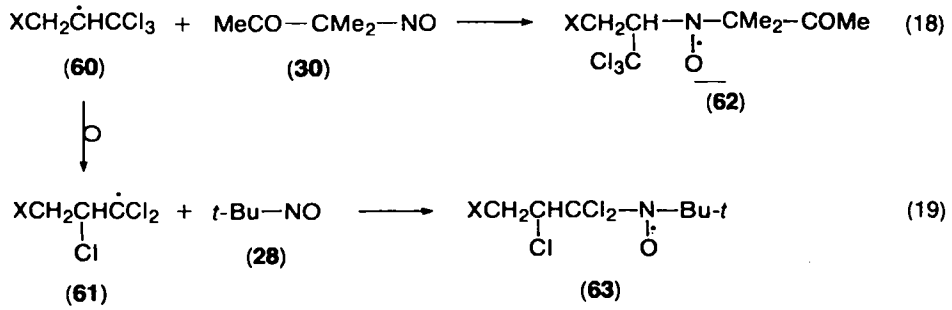
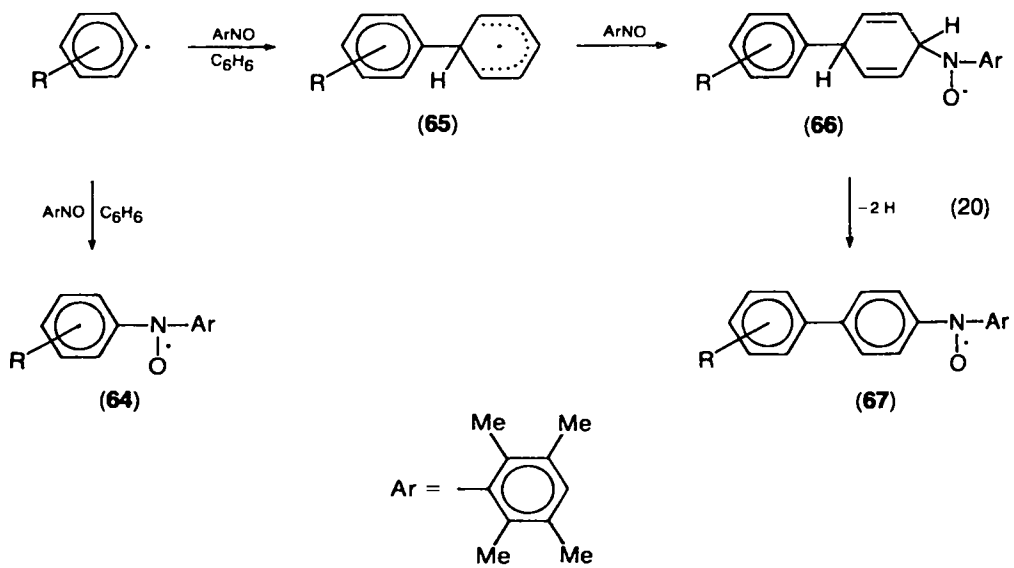


(17)

With the aid of selective spin traps **30** and **28**, the rearrangement of radical **60** has been demonstrated. Compound **30** having strong acceptor properties traps radical **60** in a fast reaction before rearranging, yielding adduct **62**. On the other hand, with compound **28** having weaker acceptor properties, rearrangement of the radical is faster and only the spin adduct **63** of the rearranged radical **61** is detected[63].



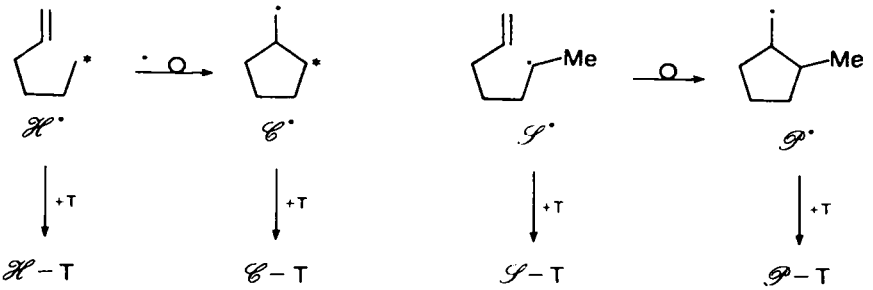
The example in equation (20) shows how the donor properties of the attacking radical influence the course of the reaction, indicating that a transfer of electron density is occurring from the radical to the spin trap before the new bond is formed. Aryl radicals substituted by an electron-donating group are sufficiently nucleophilic to attack nitrosodurene directly in benzene solution yielding radicals **64**. On the other hand, aryl radicals substituted by electron-accepting groups react primarily with the solvent benzene to form cyclohexadienyl radicals **65** which are then trapped by nitrosodurene, affording radicals **66**. These may be further oxidized to yield **67**[64]. Similar trends are observed using nitrones as the spin trap, but the effects are smaller[65].



64: R = 4-Me, 2-Me, 4-OMe, 2, 4, 6-Me_3
66/67: R = 4-Cl, 4-Br, 4-NO_2, 2, 4, 6-Cl_3, 2, 4, 6-Br_3

5. *Kinetic studies of spin trapping*

Ingold has determined the reaction rates for spin trapping for several spin traps. For this purpose, the competition between ring-closure of the ^{13}C-labelled 5-hexenyl radical $\mathscr{H}$·[66] or the 6-hepten-2-yl radical $\mathscr{G}$·[48] and the trap reaction was utilized.



From the rate of cyclization $\mathscr{H}^{\bullet} \rightarrow \mathscr{C}^{\bullet}$ or $\mathscr{S}^{\bullet} \rightarrow \mathscr{P}^{\bullet}$ and the proportion of spin adducts, $\mathscr{H}$–T/$\mathscr{C}$–T or $\mathscr{S}$–T/$\mathscr{P}$–T, absolute rate constants were calculated. The

TABLE 1. Relative rate constants for the spin trapping of alkyl radicals in benzene at 40°C[48]

Spin trap	Primary ($\mathscr{H}^{\bullet}$)	Secondary ($\mathscr{S}^{\bullet}$)
2-Methyl-2-nitrosopropane (**28**)	100[a]	68
Nitrosodurene (**35**)	450	450
Tri-*t*-butylnitrosobenzene (**34**)	5.2	0.2
5,5-Dimethylpyrroline-1-oxide (**40**)	29	4.7
N-Methylene-*t*-butylamine-*N*-oxide (**38**)	34	14.5
N-Benzylidene-*t*-butylamine-*N*-oxide (**39**)	1.4	0.75

[a]Assumed for standard.

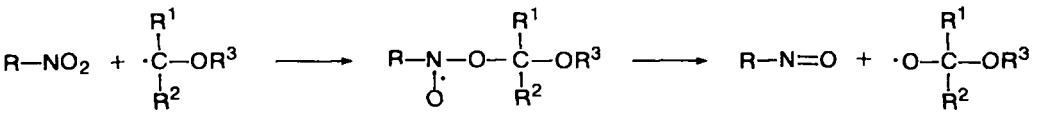
relative rate constants[48] are given in Table 1.

The relative values show that nitroso compounds, with the exception of the sterically hindered **34**, are superior to nitrones in reactions with alkyl radicals. Similar results have been obtained by Yoshida[47]. He has estimated the relative rates of spin trapping from competition experiments with 2-methyl-2-nitrosopropane and a second spin trap using *t*-butyl radicals.

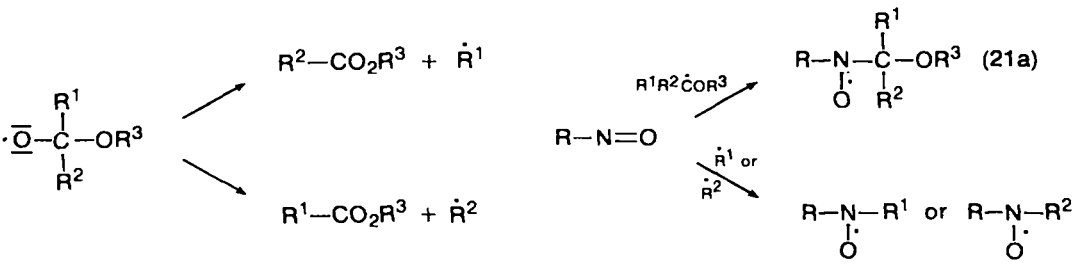
The activation energy for the addition of primary alkyl radicals to nitroso compounds is in the range of 1–2 kcal/mol; for addition to nitrones it is somewhat higher[66]. With the exception of nitrosodurene, the rate of the trap reaction is in the order primary > secondary > tertiary alkyl radicals[48]. Aliphatic nitrones (e.g. **38** and **40**) react faster than aromatic nitrones (e.g. **39**). The reason is that addition to aromatic nitrones like **39** is not only sterically more hindered, but also disfavoured because conjugation between the aromatic ring and the nitrone group must be disrupted. Finally, it should be mentioned that in reactions with the electrophilic *t*-butoxy radical, nitrones are the better spin traps compared to nitroso compounds[67].

6. *Spin trapping with nitro compounds*

The low reactivity of nitro compounds in spin trap reactions requires a high degree of electron transfer in the transition state. Thus, only carbon-centred radicals substituted by electron-donating groups are sufficiently nucleophilic to be trapped by nitro compounds[68]. Frequently the reactions are performed photochemically. The primarily formed spin adduct **68** can be easily split to afford a nitroso compound and an alkoxy radical. The nitroso compound can then add to the original carbon-centred radical (equation 21a), or to the alkyl radicals being formed by cleavage of the alkoxy radical (equation 21b).



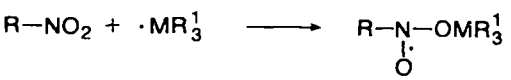
(68) (21)



(21a)

(21b)

Contrary to carbon-centred radicals, the highly nucleophilic silyl-, germanyl- and stannyl-centred radicals are easily trapped by nitro compounds[69,70] (equation 22), the reaction being further favoured by the gain of bond energy in the formation of the metal–oxygen bond.



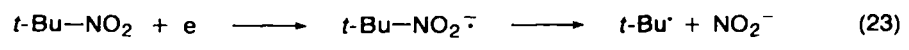
(22)

M = Si, Ge, Sn

D. Further Modes of Formation of Nitroxides

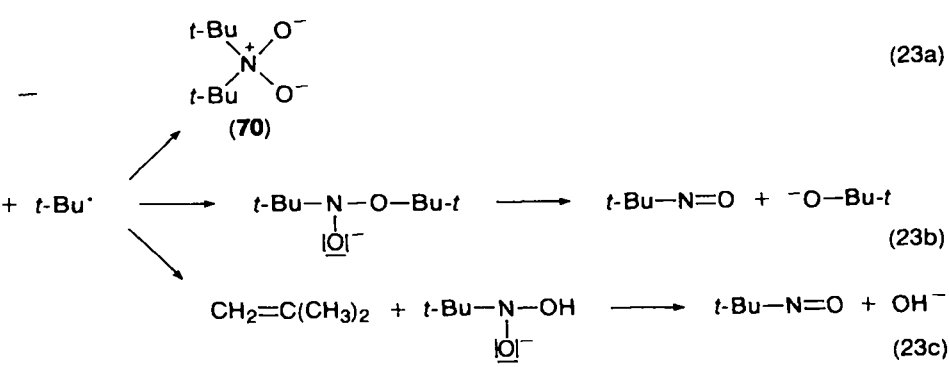
1. *From nitro compounds*

The reduction of 2-methyl-2-nitropropane either with sodium or electrochemically, yields as the final product di-*t*-butyl nitroxide[71,72]. At first, the anion radical of 2-methyl-2-nitropropane (**69**) is formed, this readily decomposes to nitrite ion and *t*-butyl radical. The latter reacts further with additional anion radicals as indicated (equations 23a–c). Di-*t*-butyl nitroxide can then arise directly



(23)

(69)



(23a)

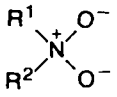
(70)

(23b)

(23c)

by the addition of *t*-butyl radicals to 2-methyl-2-nitrosopropane as well as by the hydrolysis of anion **70** during work-up. With the exclusion of water, the anion **70** can be isolated.

The reaction of phenylsodium with 2-methyl-2-nitropropane yields an analogous anion radical **71** (R^1 = Ph, R^2 = *t*-Bu), the hydrolysis of which gives *t*-butyl phenyl nitroxide[73]. A very important method for the preparation of nitroxides is the reaction of nitro-*t*-alkanes with aryl or *t*-alkyl Grignard compounds or of aromatic nitro compounds with *t*-alkyl Grignard compounds (equation 24). It is suggested that in these reactions also, the anion **71** is initially formed[74].

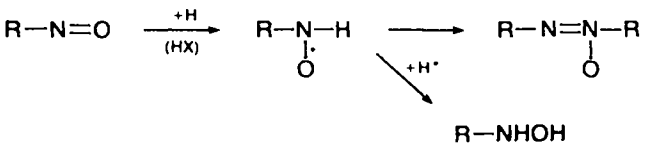


(71)

$$R^1NO_2 + R^2MgX \longrightarrow R^1{-}\underset{\underset{\cdot}{O}}{N}{-}R^2 \qquad (24)$$

2. *From nitroso compounds*

The high tendency for the formation of nitroxides due to their high stabilization implies that nitroso compounds may not only trap free radicals but are also capable of oxidizing other compounds. Thus, nitroso compounds are converted into monoaryl or monoalkyl nitroxides, which can dimerize to give azoxy compounds or may subsequently be reduced further to hydroxylamines (equation 25). In this way not only hydroxylamines (see Sections II.A.1) but also amines can be oxidized by nitroxo compounds[75].

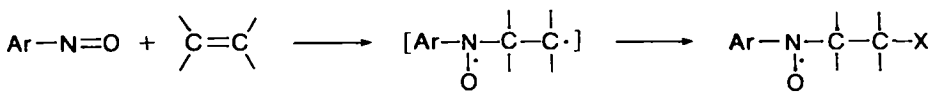


$$R{-}N{=}O \xrightarrow[(HX)]{+H} R{-}\underset{\underset{\cdot}{O}}{N}{-}H \longrightarrow R{-}\underset{\underset{\cdot}{O}}{N}{=}N{-}R \qquad (25)$$

$$R{-}\underset{\underset{\cdot}{O}}{N}{-}H \xrightarrow{+H^{\cdot}} R{-}NHOH$$

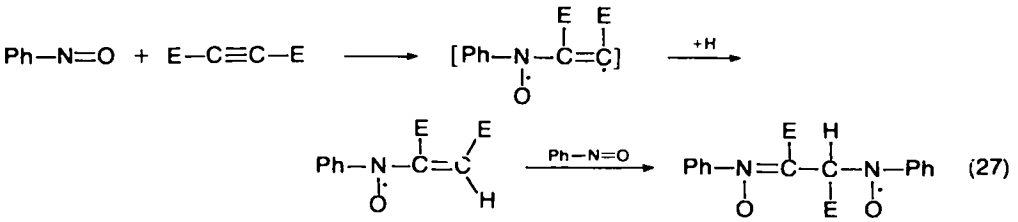
HX = RNHOH, R_2NH, RNH_2

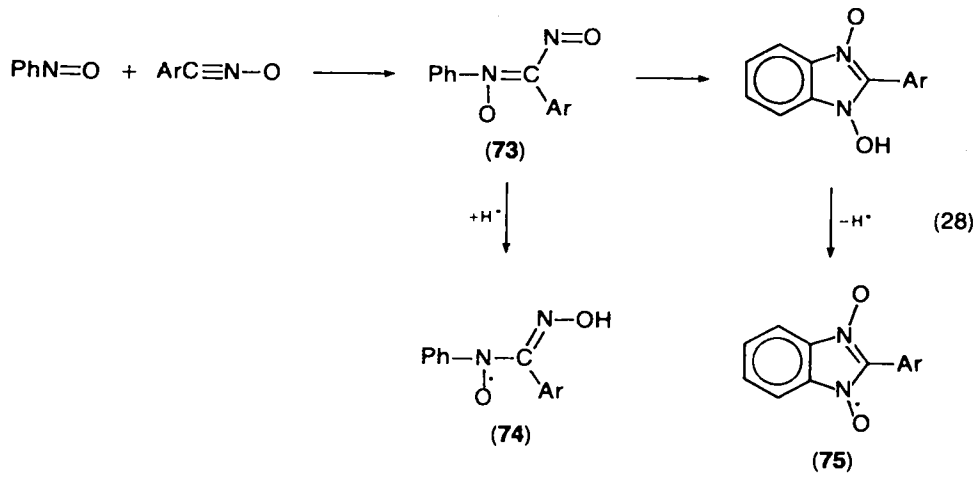
The formation of nitroxides in reactions of aromatic nitroso compounds and alkenes having no hydrogen atom in the allylic position has also been observed. It is assumed that diradicals are formed first and that these are converted to nitroxides of unknown structures in the course of the reaction (equation 26)[76].



$$Ar{-}N{=}O + \diagdown C{=}C \diagup \longrightarrow [Ar{-}\underset{\underset{\cdot}{O}}{N}{-}\overset{|}{C}{-}\overset{|}{C}{\cdot}] \longrightarrow Ar{-}\underset{\underset{\cdot}{O}}{N}{-}\overset{|}{C}{-}\overset{|}{C}{-}X \qquad (26)$$

Alkynes such as dimethylacetylenedicarboxylate react with nitrosobenzene in a similar manner affording nitroxides, for which a probable structure is **72** (equation 27)[77]. Reaction of aromatic nitroso compounds and nitrile oxides yielding *N*-hydroxybenzimidazole-*N*-oxides through the intermediates **73**[78] is accompanied by redox processes with the formation of nitroxide **74** or benzimidazole-3-oxyl-1-oxide **75** depending on the reaction conditions (equation 28)[79].



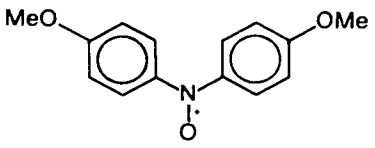


III. INVESTIGATION OF NITROXIDES BY PHYSICAL METHODS

A. X-ray Analysis and Electron Diffraction

Most physical methods of structure elucidation can be applied to nitroxides which are isolable in crystalline form. Obviously one of the most informative methods is X-ray analysis. X-ray analysis and electron diffraction data for some nitroxides are collected in Table 2. The electron diffraction results are congruent with the X-ray studies. For all nitroxides studied the NO bond lengths are in the range 1.23–1.29 Å, intermediate between the NO single bond (1.44 Å) and the NO double bond (1.20 Å). This confirms the existence of a two-centre-three-electron bond in nitroxides.

The other outstanding problem in discussing the structure of nitroxides is whether or not the nitroxide group is planar or pyramidal. As shown in Table 2, the out-of-plane angle α (dihedral angle between the NO bond and the C—N—C plane) is not uniform. The different values, such as for the similar piperidine-*N*-oxyls **9**, **79** and **80**, indicate that even small differences can cause a



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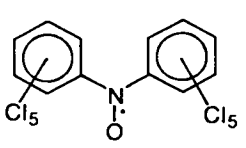

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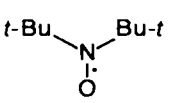

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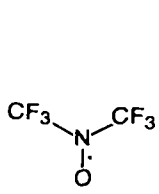
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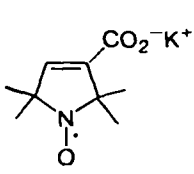
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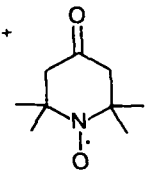
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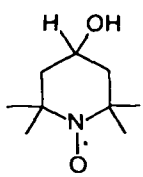
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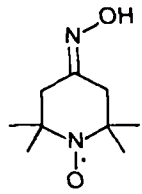
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TABLE 2. Bond lengths (Å) and bond angles (degrees) for some nitroxides

	r_{NO}	r_{NC}	C—N̂—C	O—N̂—C	α^a	Reference
76	1.23	1.44	124[b]	—	0	80
77	1.272	1.435	119.9[c]	120.0	0	81
1[d]	1.28	1.51	136	—	0	80
2[d]	1.26	1.441	120.9	117.2	21.9	80
78	1.27	1.50	114.5	122.5	0	82
9	1.276	1.483	123.5	118.3	0	80
79	1.291	1.499	125.4	116.2	15.8	80
80	1.27	1.49	125	115	25.8	83

[a]See text.
[b]The phenyl rings are twisted about 33°.
[c]The phenyl rings are twisted about 57°.
[d]Electron diffraction.

considerable change in the geometry of the nitroxide group. In fact, several calculations show very little difference in the energy of an optimized pyramidal configuration and a planar configuration[84–87]. Thus it seems reasonable that results from studies in the crystalline or gaseous state cannot be easily applied to the structure of nitroxides in solution. There does seem, however, to be general agreement that the nitroxide group of diaryl nitroxides is planar in solution also[85].

B. Dipole Moment Measurements

The delocalization of the unpaired electron as shown by the two mesomeric formulae, a neutral one and a charged dipolar one, shows the probable existence of a relatively high dipole moment. This is in fact true, as a comparison of the dipole moments of nitroxides and the corresponding hydroxylamines shows[88]. The absolute dipole moment of 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl is reduced, since the dipole moment of the carbonyl group is opposed to that of the nitroxide group (Table 3).

TABLE 3. Dipole moments of nitroxides and hydroxylamines[88]

Compound	μ (D)
2,2,6,6-Tetramethylpiperidine-*N*-oxyl	3.14
Diphenyl nitroxide	3.00
4-Oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl	1.36
N-Hydroxy-2,2,6,6-tetramethylpiperidine	1.76
N,*N*-Diphenylhydroxylamine	1.30

C. Electron Spin Resonance

The most important method in the investigation of nitroxides is Electron Spin Resonance (ESR), which is the preferred method for detection of free radicals. ESR spectroscopy makes it possible to get a more or less detailed picture of the structure of a vast number of persistent and transient nitroxides. Even radicals with a lifetime of only a split second can be studied when generated continuously in the cavity of the ESR spectrometer.

1. *Anisotropic ESR spectra*

Besides the ESR study of nitroxides in nonviscous solvents, nitroxides can be investigated under various special conditions. ESR spectra can be recorded from single crystals and from nitroxides included in host crystals, as well as in liquid crystals, from matrix-isolated radicals, and from nitroxides in the polycrystalline or powder state, in rigid glasses (frozen solutions) and in viscous solutions. The ESR spectra are characterized by three constants: the g-factor, the coupling constants of the nuclei with a nonzero nuclear spin, especially the nitrogen nucleus, and the line-width.

If a single crystal is orientated in the ESR spectrometer aligning the magnetic field with the principal axes of the nitroxide, three different spectra are obtained for the three principal axes (x-axis: parallel to NO bond, z-axis: parallel to the nitrogen p_z-orbital, y-axis: perpendicular to both the x- and z-axes).

For example the following are the values found for di-*t*-butyl nitroxide[90]:

$$g_{xx} = 2.00881 \quad g_{yy} = 2.00625 \quad g_z = 2.00271 \quad g_{iso} = 2.00592$$

$$a_{xx} = 7.59\ \text{G} \quad a_{yy} = 5.95\ \text{G} \quad a_{zz} = 31.78\ \text{G} \quad a_{iso} = 15.1\ \text{G}$$

In nonviscous solvents these anisotropic effects are nearly averaged to zero by the Brownian molecular motion, affording an isotropic spectrum with average values of g and a. However, small residual effects remain as time-dependent perturbations. Essential for the disappearance of anisotropy is a fast rotational motion. This rotational motion is dependent on several factors such as molecular size, temperature, viscosity of solvent and possible association with other molecules.

If the rotational motion of the nitroxides decreases, the spectra become increasingly asymmetric and change their line-shape[89]. Computer simulation of the line-form of the ESR spectra with the aid of known values of a_{xx}, a_{yy}, a_{zz} and the anisotropic g-factors, gives the rotational correlation time τ which is inversely related to the tumbling rate of the molecule. Thus, important information concerning the molecular environment of the molecules is obtained. This effect can therefore be used in the study of biological systems (see Section VI).

Anisotropic effects are also observed in ESR studies of nitroxide radicals and biradicals in nematic solvents[91]. In this case the solvent molecules first align themselves in the direction of the external magnetic field, then the radical molecules dissolved in the mesophase are forced to partially align with the field due to the solute–solvent interactions. This alignment causes anisotropy in the ESR spectrum. The observed anisotropic hyperfine splitting constants can be used to determine the orientation of the radicals in the liquid crystal. It has been found that the molecular shape of a molecule makes a major contribution to its ordering properties. Thus the degree of orientation increases with increasing molecular length and is more pronounced the narrower the molecular shape.

TABLE 4. Coupling constants a^N and a^{17O} for some nitroxides (in Gauss)

Compounds	a^N	a^{17O}
Dialkyl nitroxides	14 –16.5	18.5–19.5
Alkyl aryl nitroxides	10.5–13.5	≈18.3
Diaryl nitroxides	9 –11	≈17.3
Monoalkyl nitroxides	12.0–13.5	—
Monoaryl nitroxides	8.5– 9.5	—
Acyl nitroxides	6.5– 8.5	≈20.4
Imino nitroxides	7.5–10.0	18.0–19.5
Nitronyl nitroxides	6.5– 7.5	≈12.2 (Ref. 95)
Alkyl alkoxy nitroxides	24 –29	≈18.5
Alkoxy aryl nitroxides	13 –15.5	—

2. *Isotropic ESR spectra*

The g-values in the isotropic spectra are usually of the order 2.0055 to 2.0065[92]. Heteroatoms in the vicinity of the nitroxide group shift the g-factor (for instance bistrialkylsilyl nitroxide: $g \approx 2.0093$). Since the g-factor of aminyl radicals lies generally between 2.0030–2.0045[93], an unambiguous differentiation between nitroxides and aminyls is possible on examination of the g-factor.

The isotropic coupling constants of the different nuclei of a radical yield even more information. The spectra of nitroxide radicals are best characterized by the nitrogen coupling constant a^N, but the proton coupling constants of neighbouring alkyl groups or conjugated aryl groups, as well as the coupling constants of the nuclei of conjugated groups, can also give interesting information. Only recently, some ^{17}O-labelled nitroxides were prepared to determine the oxygen coupling in the nitroxide group[39,94] (see Table 4).

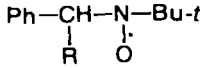
D. NMR Spectroscopy and ENDOR Spectroscopy

In general, radicals can be studied by NMR spectroscopy[96]; however, a disadvantage of this method is that concentrated solutions of radicals (>0.1 M) must be used. On the other hand, resolution is better by one to two orders of magnitude compared to ESR. Thus NMR is particularly used in the determination of small coupling constants. In this way, coupling through several bonds in mono- and bi-cyclic nitroxides can be detected[97]. Not only the magnitude of hyperfine coupling but also its sign can be determined by NMR. Contrary to ESR spectra, NMR spectra are relatively simple since for every group of equivalent nuclei only a single line is obtained. The coupling constant for these nuclei can be determined from the shift of the line relative to its position in the corresponding diamagnetic molecule according to equation (29):

$$\Delta H = -a(\gamma_e/\gamma_n)(g\beta H/4\,kT) \tag{29}$$

A shift to a lower field corresponds to a positive coupling and vice versa. In dilute solutions the lifetime of the electron-spin state is too large, hence NMR spectra of radicals are not observed. However, the lifetime can be reduced through intramolecular spin exchange thus giving sharp lines. This can be attained by very high concentrations of the radical (>0.5M) or by using a paramagnetic solvent such as di-*t*-butyl nitroxide.

Concerning NMR spectroscopy, a very high concentration of radical is necessary for the application of the ENDOR method (Electron Nuclear Double Resonance). Even very small coupling constants can be detected by this method. For instance, in nitroxides **81** the coupling constants of R have been detected[98]. These nitroxides are formally spin adducts of radicals R• and *N*-benzylidene-*t*-butylamine-*N*-oxide; they can, however, be prepared in sufficiently high concentration only by the addition of organometallic compounds to the nitrone and subsequent oxidation of the adduct.



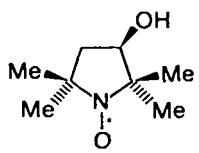
(81)

E. Other Spectroscopic Methods

In accordance with the proposed one-and-a-half bond of nitroxides, the characteristic IR absorptions for the NO bond lie in the range from 1340–1380 cm^{-1} (diphenyl nitroxide 1342[99], di-*t*-butyl nitroxide 1345[99], 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl 1380[100] and 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl 1371 cm^{-1})[100].

In the UV and visible spectra of dialkyl nitroxides, absorption maxima at 240 nm ($\varepsilon = 3000$) and 410–460 ($\varepsilon = 5$) were found[101]. Whereas the position of the first maximum is independent of the solvent, the second maximum is shifted to lower wavelengths with increasing polarity of solvent, according to a $n \rightarrow \pi^*$ absorption. The absorption is shifted to higher wavelengths by conjugation.

The absolute configuration of the chiral radical **82** has been determined using circular dichroism. The circular dichroism agrees with the octant rule if the molecule in solution adopts a half-chair conformation as it does in the crystalline state[105].



R (+) form

(82)

The photoelectron spectra of di-*t*-butyl nitroxide and 2,2,6,6-tetramethylpiperidine-*N*-oxyl have been studied[106]. The vertical first ionization potentials were found to be 7.20 and 7.31 eV, arising from the unpaired electron in the antibonding π^*-orbital.

The mass spectra of several persistent nitroxides have been recorded[107]. Ionization by electron bombardment gives rise to an even-electron molecular ion

TABLE 5. Absorption maxima of conjugated nitroxides

Nitroxide	Absorption maxima (nm)	Reference
Bis(4-methoxyphenyl) nitroxide	493, 407, 333, 323, 262	102
2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (**90**)	588, 360, 263, 238	103
N^2-Aryl-N^1-*t*-butylformamidine-N^1-oxyl	597, 542	104
N^1,N^2-Diarylformamidine-N^1-oxyl	607, 550	104

species. The fragmentation mode of the ions arising by this ionization is dependent on the structure of the different nitroxides in a specific manner.

IV. SPECIFIC PROPERTIES OF NITROXIDES AS STUDIED BY ESR

A. Spin Density Distribution

According to the polar character of the mesomeric formula B, the spin density distribution in nitroxides should be solvent-sensitive. In fact, an increasing spin density at nitrogen ρ^N and a decreasing spin density at oxygen ρ^O is observed with

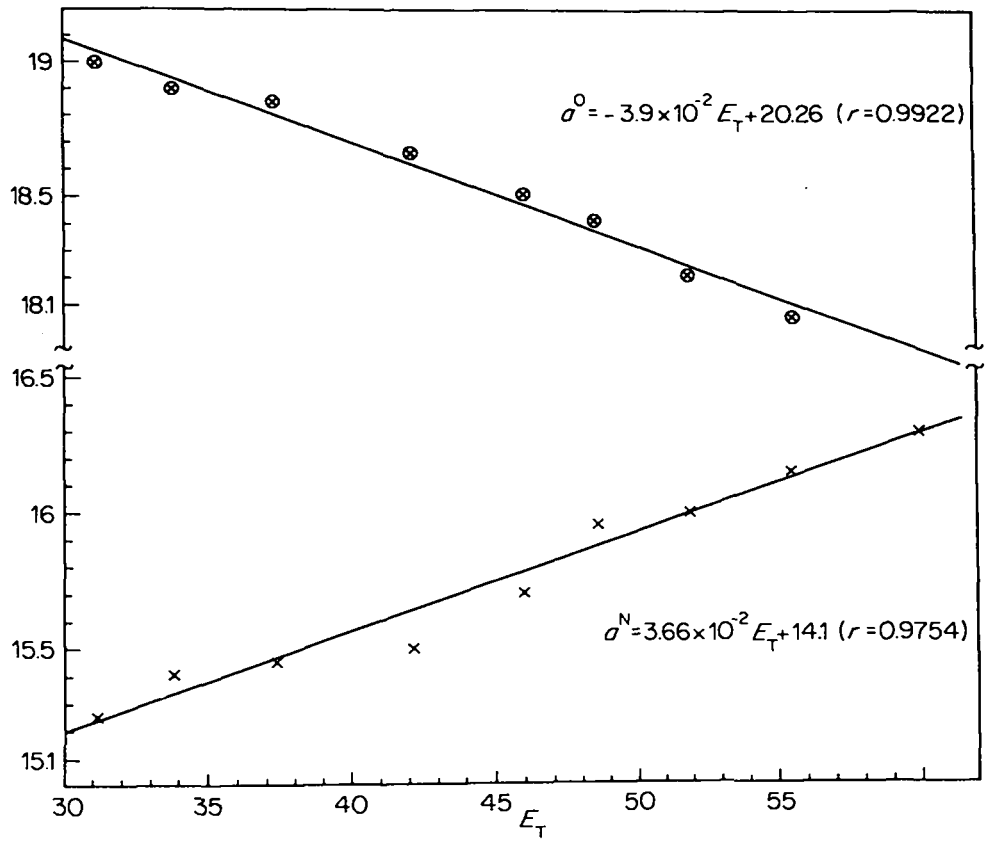


FIGURE 3. Values a^N and a^{17O} of tetramethylpiperidine-*N*-oxyl versus the solvent parameter E_T. Solvent (E_T): cyclohexane (31.2), toluene (33.9), tetrahydrofuran (37.4), acetone (42.2), acetonitrile (46.0), isopropyl alcohol (48.6), ethanol (51.9) and methanol (55.5). E_T is a solvent polarity paramter based on the transition energy (kcal/mol) for the largest wavelength solvatochromic absorption band of a pyridinum-*N*-phenol betaine[229]. Reproduced from H. G. Aurich, K. Hahn, K. Stork and W. Weiss, *Tetrahedron*, **33**, 971 (1977) by permission of Pergamon Press.

increasing polarity of the solvent as indicated by the increasing values of a^N and the decreasing values of a^O [94]. A linear correlation between a^N and the solvent polarity has been found by many workers[108]. The correlation between the E_T values of several solvents and the a^N and a^O values for tetramethylpiperidine-*N*-oxyl is shown in Figure 3.

Conversion of coupling constants to spin densities is performed with the aid of equations (30a) and (30b):

$$a^N = Q_N^N \cdot \rho^N + Q_{ON}^N \cdot \rho^O \tag{30a}$$

$$a^O = Q_O^O \cdot \rho^O + Q_{NO}^O \cdot \rho^N \tag{30b}$$

where Q_X^X or Q_{YX}^X is the contribution to the hyperfine splitting constant a^X expected for unit spin population at the atom X or Y, respectively. Since different Q values have been used by several authors, large discrepancies occur in the prediction of the spin densities. Thus for simple dialkyl nitroxides, spin densities from $\rho^N = 0.2$ to $\rho^N = 0.9$ have been discussed. More recently, it has been concluded from the determination of anisotropic coupling constants for nitrogen and oxygen that $\rho^N \approx \rho^O \approx 0.5$.

Using the dependence of a^N and a^O on solvent polarity, the simplified equations (31) and (32) were derived empirically[94]. Applications of these simplified equations to the determination of the approximate spin density distributions for different types of nitroxides gave good results.

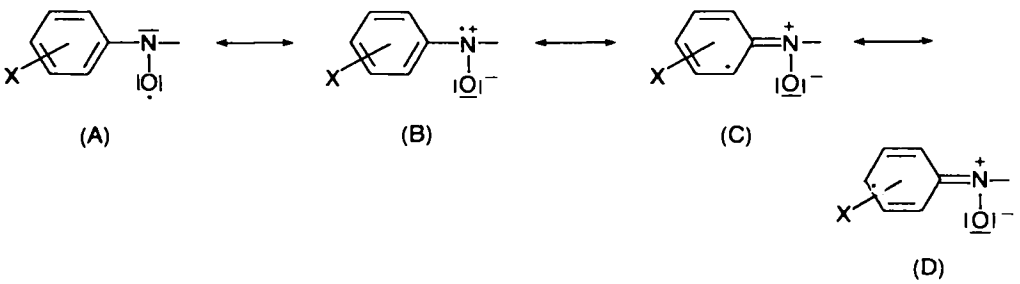
$$a^N = 33.1\ \rho^N\ \text{G} \tag{31}$$

$$a^O = 35.3\ \rho^O\ \text{G} \tag{32}$$

The spin density at the various positions of the phenyl rings in diaryl, monoaryl and alkyl aryl nitroxide radicals, for example, may be detected from the proton hyperfine coupling using the McConnell equation (33). The spin density at the *meta*-positions is generally negative.

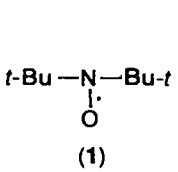
$$a^H = -27\ \rho^C\ \text{G} \tag{33}$$

Whereas electron-accepting substituents in the phenyl group shift the spin density distribution towards the mesomeric formula A, thus decreasing a^N, electron-donating substituents operate in the opposite direction, i.e. a^N increases.



(A) (B) (C) (D)

Hammett plots for a^N have been discussed together with other ESR-derived Hammett plots. In all cases the best agreement was obtained using σ^- values for *para* substituents[109,110]. The values in Table 6 indicate the increasing delocalization of the unpaired electron in the order **1** < **83** < **84** < **85**. The sum of the spin densities in the phenyl ring of **83** is 0.1 and in either of the phenyl groups of **84** is



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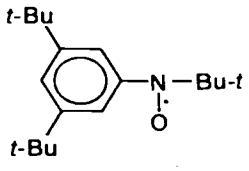

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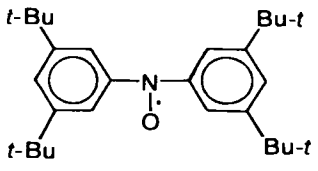

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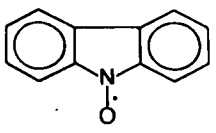

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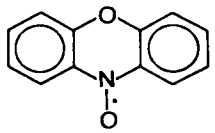


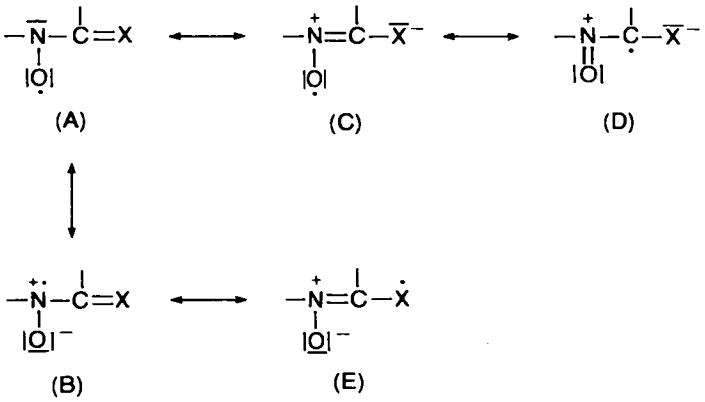
(86)

TABLE 6. Coupling constants a^N and a^{17O} (in Gauss) and spin densities ρ^N and ρ^O for some nitroxides[94]

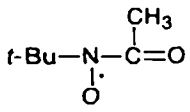
	a^N	a^{17O}	ρ^N	ρ^O
1	15.0	19.1	0.455	0.54
83	12.6	18.3	0.38	0.52
84	9.9	17.3	0.30	0.49
85	6.65	16.5	0.20	0.47
86	9.50	13.1	0.29	0.37

0.12. The delocalization of the spin density into the phenyl rings occurs mainly at the expense of ρ^N. Another situation arises with radical **86**. In this case the additional π-electron pair of the ring-oxygen causes the spin density within the nitroxide group to be shifted more towards the oxygen atom.

In nitroxides with conjugated groups C=X, increasing electronegativity of X should increase ρ^O and ρ^C and decrease ρ^N and ρ^X. Inspection of Table 7 shows that this is true[39]. As expected, the spin density distribution is strongly modified if the π-system is extended by an additional oxygen atom as in **90**[95].



The fact that the simplified equations (31) and (32) with unchanged values for Q may be applied to these different types of nitroxides is considered as evidence that



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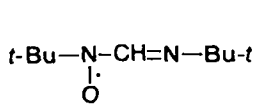

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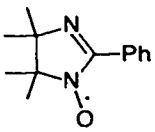

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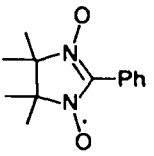
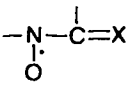


(90)

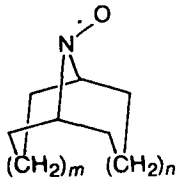
TABLE 7. Spin density distribution in nitroxides with conjugated groups[39,95]:



	ρ^{O}_{NO}	ρ^{N}_{NO}	ρ^{C}	ρ^{X}
87	0.58	0.23	0.07	0.12
88	0.55	0.28	−0.05	0.21
89	0.51	0.28	−0.06	0.28
90	0.34	0.22	−0.12	*a*

[a]See ρ^{O}_{NO} and ρ^{N}_{NO}.

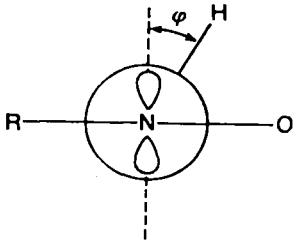
all these radicals, including the dialkyl nitroxides, have virtually the same geometry of the nitroxide group in solution[111] and therefore should be approximately planar[39]. Since any deviation from planarity should introduce some s-character in the singly occupied orbital, an increased value of a^N compared to the planar structure should result. Thus, a total spin density considerably greater than one should be obtained on the application of equations (31) and (32). However, this has only been found to be true for alkoxy alkyl nitroxides[39] and for the bicyclic nitroxides **91–93**[112] for which a planar nitroxide group seems unreasonable due to considerable ring-strain. Nevertheless, discussions on the structure of the nitroxide groups, especially in dialkyl nitroxides, is continuing[113–115].



(**91**) $m = n = 1$
(**92**) $m = 1, n = 0$
(**93**) $m = n = 0$

B. Conformation of Nitroxides

Conclusions concerning the conformation of nitroxides can be derived from the coupling constants of the β-protons[116,117], the coupling of which is caused by hyperconjugation. The magnitude of the coupling constants depends on the angle φ between the single occupied orbital and the CH σ-orbital according to equation (34)[116].

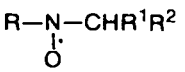


$$a_{CH\text{-}\beta} = \rho^N(B_0 + B_2\cos\varphi) \qquad B_0 \approx 0 \quad B_2 \approx 59\ G \tag{34}$$

Assuming that ρ^N is approximately 0.45, the following values of a^H for some values of φ are given:

φ(degrees)	0	30	45	60	90
a^H (Gauss)	26	19.5	13	6.5	0

TABLE 8. Coupling constants a_β^H and a^N for some nitroxides[116]:



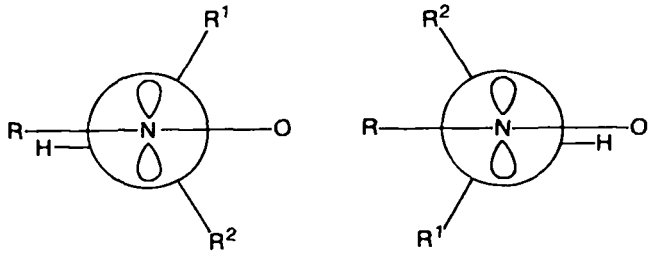
(94)–(99)

	R	R^1	R^2	a^N	a_β^H
94	*t*-Bu	H	H	16.4	12.7 (3H)
95	*t*-Bu	H	Me	15.7	10.7 (2H)
96	*t*-Bu	H	Ph	14.6	7.7 (2H)
97	*t*-Bu	Me	Me	16.8	1.8 (1H)
98	Et	Me	Me	16.0	4.8 (1H)
99	H	Me	Me	12.7	12.1 (1H)

In Table 8 some examples of β-proton couplings are given along with a^N values, which may be interpreted as follows. The methyl group in **94** rotates freely, thus for each individual proton a time-averaged angle of 45° may be assumed, according to a coupling constant of 13 G. In the case of methylene and methyne groups, rotation is restricted with the exception of **99**. Thus, molecules adopt preferred conformations, the energy of which is determined by the interactions of the various substituents. Steric effects have the largest influence, but hyperconjugation and the formation of hydrogen bridges can also contribute to these interactions. Therefore, quantitative conclusions are difficult and the discussion rests on a more qualitative basis.

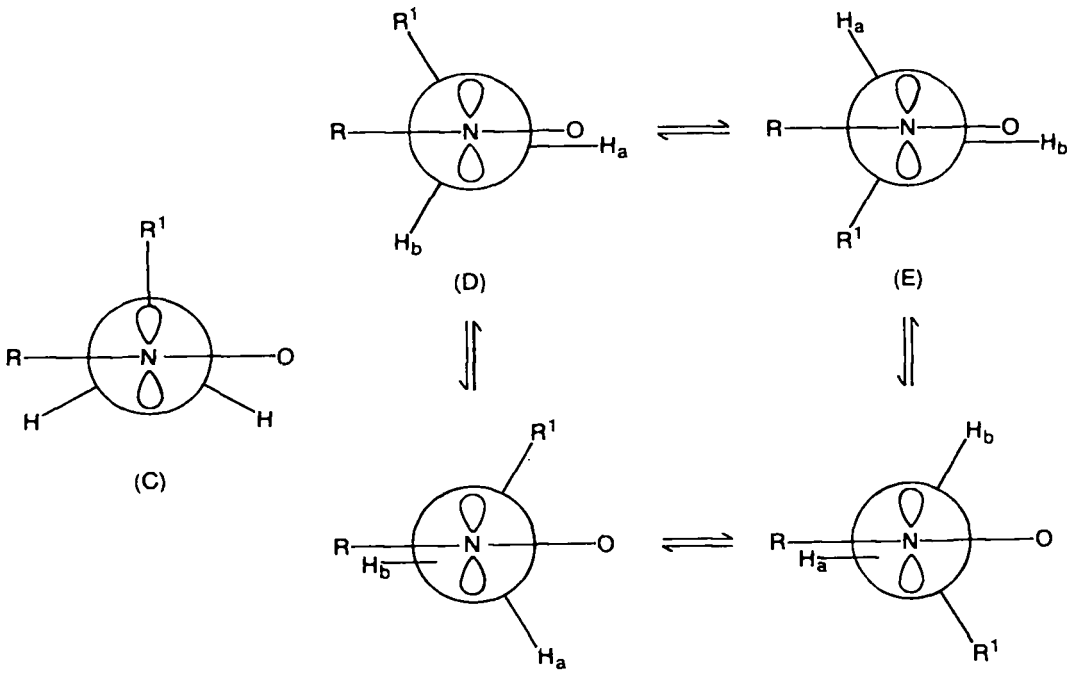
For methyne group conformations A and B have the lowest energy, A being somewhat more favourable in the case of R = *t*-Bu. For both conformations, it would be expected that $a_\beta^H \approx 0$. The larger the substituent R, the more frequently the molecule should adopt conformation A or B, averaged over the time and the less the value of a_β^H. This effect explains nicely the trend in a_β^H values for nitroxides **97–99**. For **99**, free rotation of the isopropyl group is assumed.

The situation for the methylene group is even more complicated. Besides conformation C, conformations D–G must also be considered. In conformation C, a_β^H is expected to be about 6.5 G for both hydrogens. Thus, this conformation



(A) (B)

seems to be important, as for example in **96**, for the benzyl group only. With other groups such as ethyl, *n*-propyl and *n*-butyl, the a_β^H values are larger for two equivalent protons. In conformations D–G, a_β^H values ≈19.5 G for one proton and $a_\beta^H \approx 0$ G for the other proton are expected. However, a fast exchange between the enantiomeric conformations D and E, or F and G, would make both hydrogens equivalent so that a value of about 9.75 G for both protons would be expected. This is in agreement with the observed value of 10.7 G. Thus it may be concluded that radical **95** as well as other similar radicals exist preferentially in rapidly interchanging conformations similar to D–G.



(C) (D) (E) (F) (G)

The results obtained for ethyl-*t*-octyl nitroxide[113] at various temperatures merit special comment. At room temperature, $a_\beta^H = 10.7$ G for two protons, as in the case of **95**, whereas at −100°C different coupling constants of 8.75 and 12.75 G are found for the two protons. This means that the rapid interconversion between the enantiomeric pairs D ⇌ E and F ⇌ G is frozen at lower temperatures and only

interconversion of the diastereomeric pairs D ⇌ F and E ⇌ G can occur. In this case, the two protons are no longer equivalent and therefore exhibit different coupling constants.

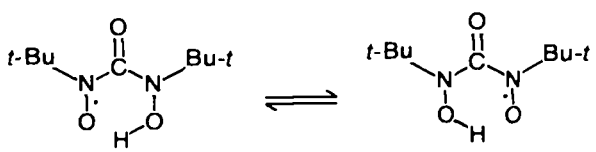
The equivalence of both protons is also lost by the introduction of a chiral group R^1, when D and E, or F and G, are no longer enantiomers but diastereomers instead. For nitroxides of this type, even at room temperature, two different values for a_β^H have been found[119].

The fast ring-inversion in piperidine-*N*-oxyl at +110°C causes the equivalence of the four β-protons. At −100°C, however, the rate of the ring-inversion is sufficiently slow on the ESR time-scale that the molecule appears frozen in one conformation. Thus two different coupling constants are detected (a^H_{axial} = 26.3 G, $a^H_{equatorial}$ = 3.78 G)[120].

Coupling constants of protons distant from the nitroxide group (γ- or δ-protons), are usually very much smaller; γ- or δ-coupling constants can also be used to study conformational problems especially in cyclic and bicyclic nitroxides[97]. Frequently very small coupling constants can be detected by NMR spectroscopy only.

C. Dynamic Processes in Mono- and Poly-radicals

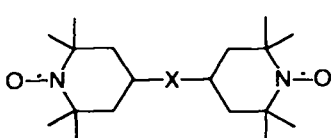
Dynamic processes in radicals can also be studied by ESR spectroscopy[121]. As already mentioned for nitroxides with a methylene group, the two β-protons are equivalent because of rapid interchange of the two enantiomeric conformations at room temperature, whereas at low temperature the conformational change is slow and two individual proton couplings are observed. In the intermediate temperature range, the change in position of the two protons causes broadening of the ESR lines. From the temperature dependence of the line-broadening, the activation energy for the conformational interchange can be determined. In this way, the activation energy for the rotation of the ethyl group in ethyl *t*-octyl nitroxide was estimated to be ≈7.5 kcal/mol[118]. Similar conformational changes in nitroxides have been studied by Janzen[122]. The study of ring inversion in piperidine-*N*-oxyl afforded an activation energy of 5–6 kcal/mol[123]. In radical **100**, a fast exchange of the hydrogen atom, as indicated, makes the two nitrogen atoms equivalent. For this process an activation energy of 4.5 kcal/mol was estimated from the temperature dependence of the line-widths[124].



(35)

(100)

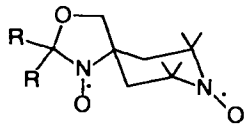
Similar dynamic processes are observed in di- and poly-radicals. As shown for diradicals of the type **101**, spin exchange between the two radical centres can occur[125]. In cases where spin exchange *J* is slow ($a \gg J$), the two halves of the



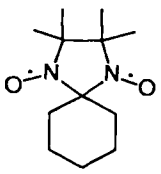
(101)

e.g. X = $-O-CO-(CH_2)_n-CO-O-$

diradical act as independent monoradicals and the hyperfine splitting is a triplet splitting, as has also been found for the analogous monoradical. When spin exchange is fast ($J \gg a$), each nitrogen nucleus interacts with both electrons and the hyperfine splitting drops to one half of the value of the coupling in the analogous monoradical, yielding a five-line spectrum with the intensity ratio 1:2:3:2:1. In the intermediate range, complicated spectra can result[126]. The magnitude of spin exchange J seems to be a complex function of the biradical structure being influenced by temperature and solvent as well as by the chemical nature of the connecting bridges[127]. Particularly rigid diradicals such as **102–105** have been proposed as structural probes in biological systems[128,129]. For polyradicals **106**, the



(102)



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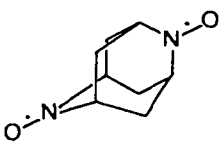
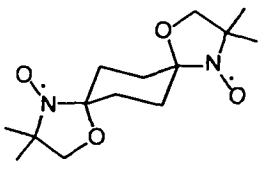


(104)



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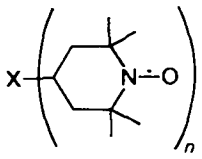


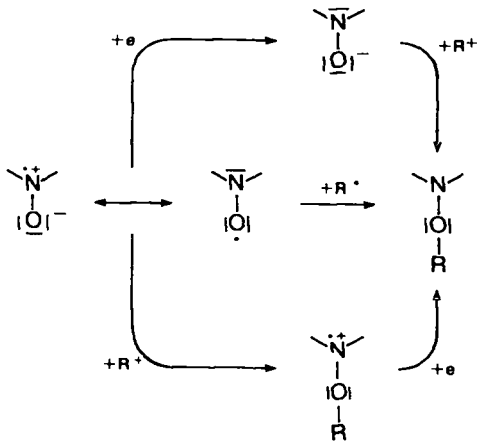
(106)

X = P, n = 3
X = Si, n = 4

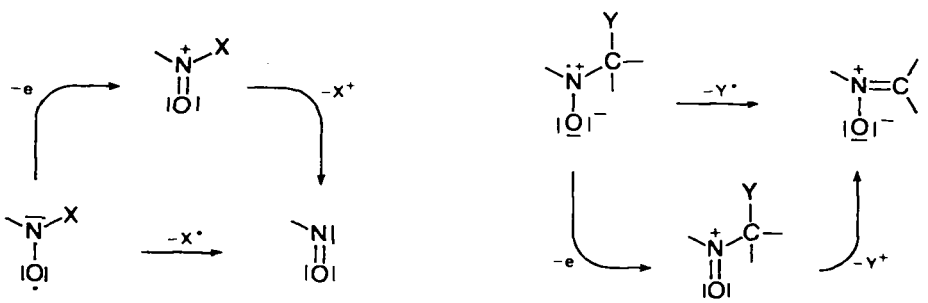
situation is analogous. For instance, the ESR spectra of triradicals, for which $J \gg a$ is valid, show hyperfine splitting into seven lines, a^N being one third of the usual value[130].

V. REACTIONS INVOLVING THE NITROXIDE GROUP

In general most nitroxide group reactions can be divided into reductive processes yielding hydroxylamines and oxidative processes yielding nitroso compounds or nitrones (see Schemes 3 and 4). For instance, radicals can add to the oxygen atom of the nitroxide group affording *O*-substituted hydroxylamines. A special case of this reaction is the addition of a hydrogen atom. On the other hand, an electron can be transferred to the nitroxide group giving at first an anion, which subsequently can accept a cationic species, especially a proton, to yield a hydroxylamine. Protonation or complexation of the nitroxide group does not



SCHEME 3



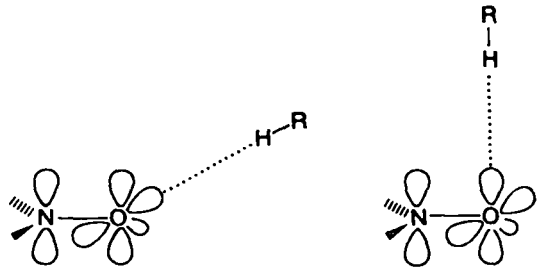
SCHEME 4

change the oxidation level, but stabilization due to delocalization of the unpaired electron is for the most part lost. Thus cationic species easily accept an electron, being reduced to hydroxylamines.

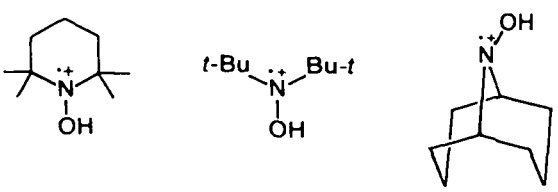
Removal of an electron leads to nitrosonium cations which are for the most part unstable. The nitrosonium cations can afford nitroso compounds or nitrones by splitting off the groups X^+ or Y^+, respectively. On the other hand, homolytic cleavage of the N—X bond (α-cleavage) or of the C—Y bond (β-cleavage) can give the nitroso or nitrone group directly.

A. Protonation and Complex Formation of Nitroxides

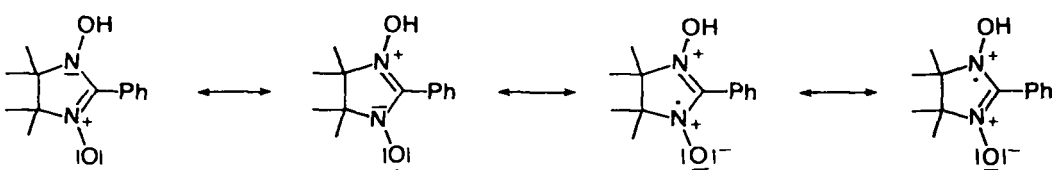
Nitroxides can interact with electrophiles via their free electron pair. The formation of hydrogen bridges in protic solvents such as alcohols, slightly increasing the spin density at nitrogen, is a weak interaction of this kind[131]. For hydrogen bridging, a σ-model and a π-model have been discussed, the former being favoured[132].



Protonation of nitroxides occurs only with strong acids. pK_A values of dialkyl nitroxides are in the range of −5.5. ESR spectra of protonated nitroxides, **107–109**, have been detected in concentrated sulphuric acid, in trifluoroacetic acid with added sulphuric acid[133], and in methylene chloride with added wet aluminium trichloride[134]. However, in dilute sulphuric acid (10%), the spectra of the unprotonated nitroxides are obtained. Increasing the acid concentration to 40% causes the lines to broaden, and at 55%, they disappear entirely, due to fast exchange of the protons between the nitroxide molecules. The fast exchange process stops only at very high acid concentration when the protonated species can be observed. Nevertheless, the yield of protonated nitroxide is surprisingly only about 0.3% in concentrated sulphuric acid[133]. Since the spin density at nitrogen is increased by protonation, the values of a^N increase. Protonation of carbazol-*N*-oxyl in a mixture of benzene and trifluoroacetic acid causes a^N to increase by approximately the same factor as for **107–109** to 8.8 G[135]. 2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (**12**) can also be protonated in benzene



	(107)	(108)	(109)
a^N(G)	21.6	20.7	24.5



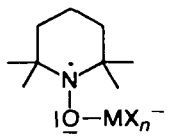
(110)

and trifluoroacetic acid[103] to give 110. However, in this case it is obvious that protonation leads to an increasing spin density at the oxygen atom of the unprotonated site of the molecule. Thus, the decrease in spin density at both the nitrogen atoms causes a^N to drop to 5.7 and 4.5 G, compared to a value of 7.5 G for both nitrogens in

the unprotonated radical. In aqueous hydrogen chloride (1N) only the spectrum of the unprotonated form is obtained.

No individual spectra corresponding to the unprotonated and protonated species are obtained in the pH range from 7 to −1 for 2-phenyl-4,4,5,5-tetramethyl imidazoline-1-oxyl[136,137]. With increasing acidity, a continuous decrease in $a^{N}_{nitroxide}$ and increase in a^{N}_{imino} is observed. In this case, a fast proton transfer causes an averaging of the spectra of the two species. The pK_A for this radical is estimated to be 1.9[136] and 1.6[137].

With Lewis acids such as BX_3[138], AlX_3[139], SiX_4[140], GeX_4[140] and SnX_4[140] and others[141] formation of complexes (**111**) is observed, resulting in a more or less strong increase in a^N.



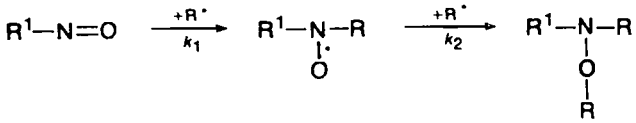
(**111**)

MX_n	BCl_3	$AlCl_3$	$SiCl_4$	$GeCl_4$	$SnCl_4$
a^N(G)	21.18	19.86	16.5	16.6	18.53

Nitroxides can act as electron donors and thus form electron donor–acceptor complexes (EDA) with various π-electron acceptors. For di-*t*-butyl nitroxide, complex formation with tetracyanoethylene, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and pyromellitic dianhydride has been confirmed[142]. The resulting complexes show charge-transfer absorption bands. From the effect of complex formation on the hyperfine splitting constant a^N, a contribution of electrostatic forces to complex formation has been demonstrated. However, in the case of complexes with strong acceptors such as tetracyanoethylene, the values of the hyperfine coupling constant have indicated a significant contribution of charge-transfer interaction to complex formation. Similarly, the formation of π-complexes from *t*-butyl mesityl nitroxide with various aromatic compounds and alkenes, substituted by electron-accepting groups, has been established[143]. The bond energy for the formation of these complexes is estimated to lie in the range 3–8 kcal/mol.

B. Addition of Radicals to the Nitroxide Group

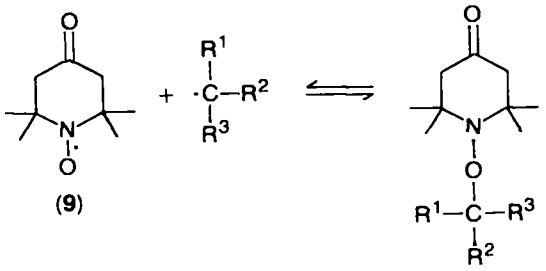
Addition of a radical R• to the nitroxide group (equation 36) occurs if the gain in energy for R—O bond formation overcomes the loss of delocalization energy which is of the order of 30 kcal/mol for the nitroxide group. This is true for most alkyl radicals. The kinetic studies of spin trapping have shown that the decay



(36)

reaction of the nitroxides, caused by the addition of alkyl radicals, is even faster than the formation of nitroxides ($k_1 < k_2$)[47,66].

Furthermore, 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl (**9**) readily adds 2-cyano-2-propyl radicals generated from the azoisobutyronitrile by thermal decomposition with formation of a stable adduct[144]. Even the stabilized 1,1-diphenylethyl radical is added to the nitroxide 9, but in solution this adduct is unstable. There exists an equilibrium with the precursor radicals (equation 37)



(37)

(**9**)

(**a**) $R^1 = R^2 = Me$, $R^3 = CN$
(**b**) $R^1 = R^2 = Me$, $R^3 = Ph$
(**c**) $R^1 = Me$, $R^2 = R^3 = Ph$

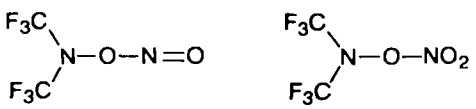
($\Delta H = -21.4$ kcal mol^{-1}, $\Delta S = -36$ cal deg^{-1} mol^{-1})[145] which obviously induces the decomposition to give 1-hydroxy-2,2,6,6-tetramethylpiperidine and 1,1-diphenylethylene. As expected, dissociation is far less in the case of the adduct of the cumyl radical, the adduct being much more stable. The high tendency for formation of such adducts is pertinent to the use of nitroxides in the inhibition of the autoxidation of hydrocarbons[146]. For the same reason, nitroxides can interrupt chain-reactions in polymerization and are thus frequently used as inhibitors[147].

Addition reactions of diaryl nitroxides have been known for a long time. Diphenyl nitroxide reacts with triphenylmethyl to give a 1:2 adduct, whereas from bis(4-nitrophenyl) nitroxide a 1:1 adduct has been obtained[148]. Furthermore, diphenyl nitroxide adds to the *para* position of tri-*t*-butylphenoxyl. Aminyl radicals can also add to the oxygen atom of nitroxides. For instance, diphenyl nitroxide and dianisylaminyl radicals react through an intermediate adduct with exchange of the oxygen atom, as indicated in equation (38)[148].

$$Ar_2N\cdot + O\dot{-}NPh_2 \longrightarrow Ar_2N{-}O{-}NPh_2 \longrightarrow Ar_2N\dot{-}O + Ph_2N\cdot \quad (38)$$

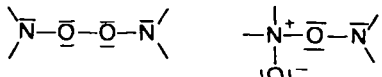
Ar = *p*-$MeOC_6H_4$

Bis(trifluoromethyl) nitroxide, the stabilization of which is reduced due to the electron-accepting properties of the trifluoromethyl groups, can even form stable adducts with nitrogen oxide or nitrogen dioxide[149]:



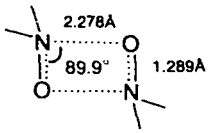
C. Dimerization of Nitroxides

Contrary to the addition of alkyl radicals to the nitroxide group, the dimerization of nitroxides to afford dimers **112** or **113** is improbable due to energy considerations (see Section I.A).



(112) (113)

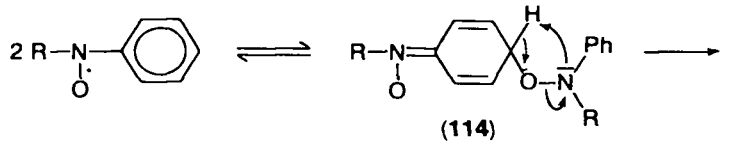
Nevertheless, some sterically unhindered nitroxides such as the Fremy salt[150], bis(trifluoromethyl) nitroxide[150], tetraphenylpyrrol-*N*-oxyl[150], 9-azabicyclo[3.3.1]-nonane-3-on-9-oxyl[150] and 8-azabicyclo[3.2.1]octane-8-oxyl[151], respectively, exist as dimers in the crystalline state. However, in the dimer of 9-azabicyclo[3.3.1]-nonane-3-on-9-oxyl, the distance between the nitroxide groups is estimated to be 2.278 Å by X-ray analysis, indicating that there is no genuine covalent bond between the groups[152]:



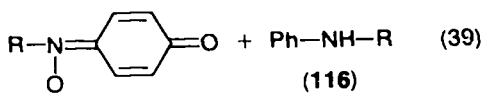
In the case of sterically hindered nitroxides formation of diamagnetic dimers could no longer be observed. Instead, formation of radical pairs of tetramethyl piperidine-*N*-oxyl in the plastic phase of carbon tetrachloride[153] and of di-*t*-butyl nitroxide in the plastic phase of camphene[154] have been recently detected. In these radical pairs, the two nitroxide groups are at a distance of about 7.0 Å, but are in a relatively rigid orientation[153].

In solution, reversible dimerization is detected for methyl (2,4,6-tri-*t*-butyl) phenyl nitroxide[155], 8-azabicyclo[3.2.1]octane-8-oxyl[151] and 9-azabicyclo[3.3.1]-nonane-9-oxyl[151] at low temperatures, affording diamagnetic species. By comparison with the situation in the solid state it seems probable that these dimers are not covalently bonded, but rather are molecular complexes for which the geometry of the nitroxide group is only changed slightly. The bonding situation can arise by combination of the two singly occupied molecular orbitals to afford a bonding and an antibonding molecular-complex orbital, the former being capable of taking up the two originally odd electrons with gain of energy, provided that their spin is opposite. Similar dimers of nitrogen oxide have been detected in the gas phase, for which the van der Waals' bonding forces have been found to be only about 1% of the energy of the usual covalent bonds[156]. For the nitroxide dimers, however, calculations show that dipolar attraction forces of about 5 kcal/mol are operative between the two nitroxide groups. In this work has Ingold stated that the dipolar attraction can provide a very significant fraction of the enthalpy for dimerization of unhindered nitroxides in solution[151].

For nitroxides with extended delocalization there is an alternative way of dimerization. Phenyl-substituted nitroxides can form dimers of the type **114** which are obviously energetically less favourable than their monomers but can decompose



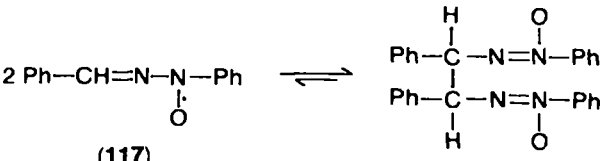
(114)



(115) (116) (39)

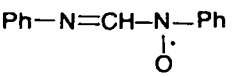
irreversibly with formation of the stable products **115** and **116**[157]. Curiously, since the nitroxide is additionally stabilized through delocalization of the unpaired electron into the phenyl group, it becomes even less persistent than di-*t*-alkyl nitroxides, Bulky substituents at the *para*, or even at the *meta*, positions prevent the radical from dimerization and consequently from decomposition.

Radical **117** can be detected at only slightly elevated temperatures by ESR spectroscopy. The gain of about 80 kcal/mol for formation of the carbon–carbon bond in the dimerization to yield **118** causes the equilibrium to lie far to the right at room temperature[158,159].



(117) (118) (40)

On the other hand, analogous dimerization of nitroxide **119** through formation of a nitrogen–nitrogen bond affords only about 40 kcal/mol and is therefore not sufficient to compensate the loss of delocalization energy for the two radicals. Thus, nitroxides like **119** are persistent for several hours or even days in solution,

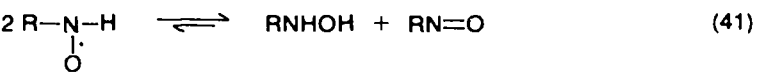


(119)

although they rapidly decompose when the solvent is removed[104]. In this way the persistence of acyl nitroxides can also be understood. One of the few known vinyl nitroxides dimerizes through formation of a C—C bond as does **117**, but in this case the dimer cannot dissociate reversibly to the monomeric radical but rather decomposes to afford other products[36].

D. Disproportionation of Nitroxides

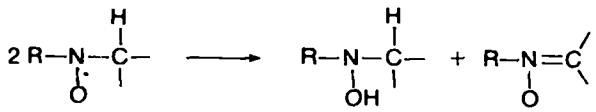
Disproportionation is an alternative pathway for radical decay. Aryl nitroxides as well as alkyl nitroxides can easily disproportionate to yield hydroxylamines and nitroso compounds, or the corresponding oximes. Formally the oxidation reaction is an



(41)

α-scission. As kinetic studies have shown, this is a fast bimolecular reaction whose rate is barely influenced by the nature of the group R[160]. The reaction is reversible in the case of phenyl nitroxide and *t*-butyl nitroxide. This means that a small concentration of nitroxide is formed by mixing of the corresponding hydroxylamine and nitroso compounds (R = *t*-Bu:$\Delta H = -10.4$ kcal mol^{-1}; $\Delta S = +8.2$ cal mol^{-1} deg^{-1}; R = Ph: $\Delta H = -7.2$ kcal mol^{-1}; $\Delta S = -2.9$ cal mol^{-1} deg^{-1}). Whereas, however, the concentration of phenyl nitroxide decreases continuously according to the formation of azoxybenzene, *t*-butyl nitroxide is persistent for several days, because *t*-butylhydroxylamine and 2-methyl-2-nitrosopropane form the corresponding azoxy compound only extremely slowly, if at all.

Dialkyl nitroxides can usually disproportionate only if there is a hydrogen atom in the β-position, when the oxidation process affords a nitrone (equation 42). This is

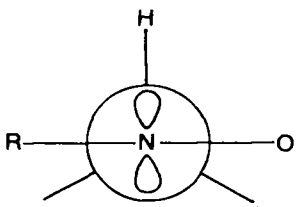


(42)

also a bimolecular reaction, the carbon–hydrogen bond being broken in the rate-determining step. Isotope effects k_H/k_D between 6 and 14 have been found[161]. The disproportionation of diethyl nitroxide is calculated to be exothermic by 28 kcal/mol. The rate of disproportionation is very different for different nitroxides as can be seen from the relative values in Table 9[161].

It has been shown that the formation of a dimer precedes the disproportionation in the last three cases of Table 9, but the nature of this dimer is not known. Although Ingold has formulated a structure with a covalent oxygen–oxygen bond for the dimer, he himself has expressed doubts for thermodynamic reasons about this structure[162]. On the other hand, no dimer formation is observed in the disproportionation of diisopropyl nitroxide[161] or *t*-butyl isopropyl nitroxide[163], the reaction of which is also very slow.

The different reaction rates can be understood if one realizes that hydrogen abstraction from a nitroxide molecule affording a nitrone can proceed with a relatively small activation energy only if the molecule adopts a conformation **120** in which the hydrogen atom to be abstracted and the single occupied orbital are in the same plane. Diisopropyl nitroxide, *t*-butyl isopropyl nitroxide and other



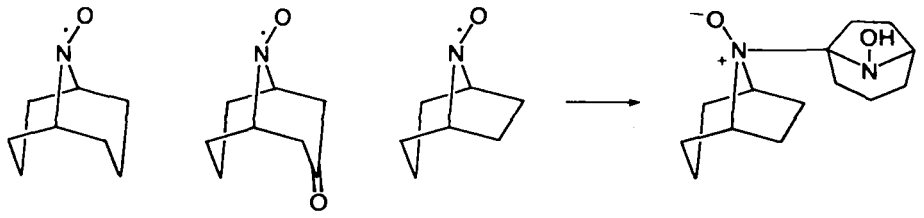
(120)

similar nitroxides, can adopt such a conformation only if supplied with an additional amount of energy, thus raising the activation energy for the reaction. The bicyclic nitroxides **10**, **121** and **92** can never adopt such a conformation. Thus **10** and **121** are very persistent radicals[151], whereas **92** surprisingly yields a dimer, **122**, which must have been formed from the corresponding nitrone[164]. Of course the formation of this dimer is very slow and the decay of **92** is about 10^9 times slower than that of diethyl nitroxide.

Isolation of the primary disproportionation products is often difficult, since secondary reactions can easily occur[165]. For example, the disproportionation of *t*-butyl isopropyl nitroxide affords products, the formation of which can be

TABLE 9. Relative rate of disproportionation of nitroxides[161]

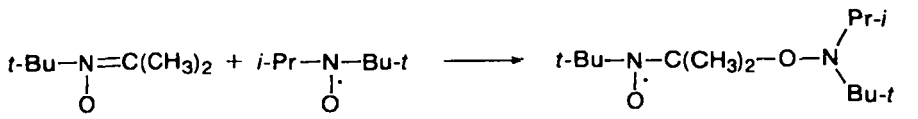
Nitroxide	k_{rel}
Diisopropyl nitroxide	1
Diethyl nitroxide	1.3×10^3
Dimethyl nitroxide	3.9×10^3
Piperidine-*N*-oxyl	31×10^3



(43)

(10) (121) (92) (122)

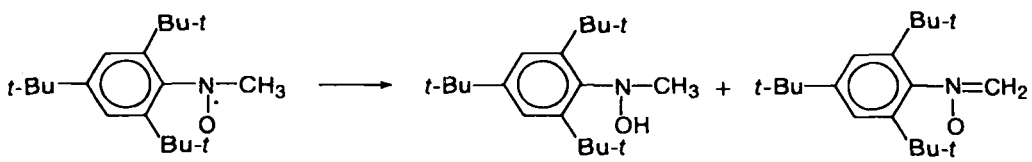
explained by the addition of unchanged nitroxide to the nitrone **123** formed in this reaction, to give adduct **124** (equation 44), followed by decomposition of this adduct to several fragments[163].



(44)

(123) (124)

Only the nitrone **127** formed by the disproportionation of *N*-methyl (2,4,6-tri-*t*-butyl)phenyl nitroxide (**125**) was isolated directly, but the simultaneously formed hydroxylamine **126** was also detected (equation 45)[155]. As

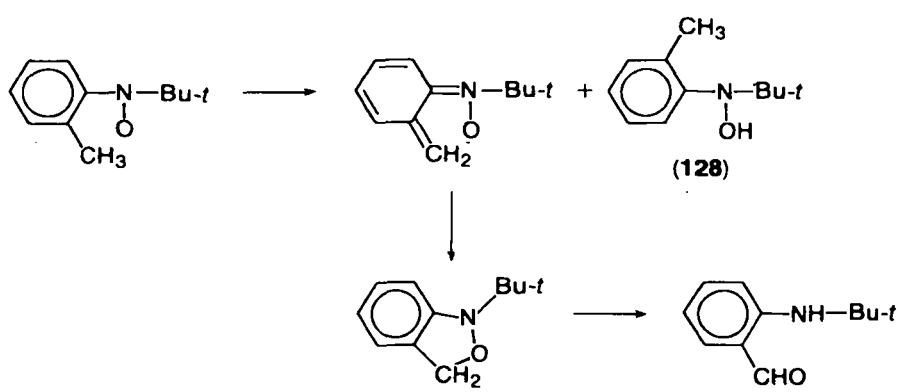


(125) (126) (127)

(45)

shown by the isolation of the products **128** and **129**, *ortho*-substituted aryl *t*-butyl nitroxides can disproportionate in an analogous manner (equation 46)[166].

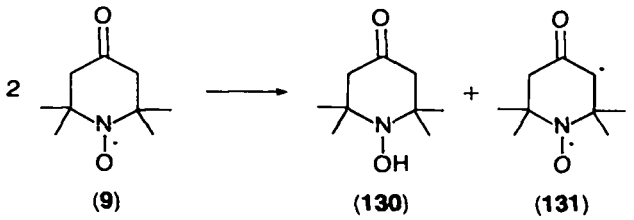
Contrary to nitroxides substituted by primary or secondary alkyl groups, di-*t*-alkyl nitroxides are usually very persistent. For instance, di-*t*-butyl nitroxide and 2,2,6,6-tetramethylpiperidine-*N*-oxyl remain unchanged over periods of several



(46)

(128) (129)

months or even years. On the other hand, 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl (**9**) decomposes after six months, a dimer of structure **132** being formed. The diradical **131** is formulated as an intermediate in this decomposition reaction. Nitroxide **9** also decomposes yielding hydroxylamine **130** (60%), a polymer of unknown structure and phoron **134** (trace) by heating to 100 °C or by refluxing in benzene for several hours. It is suggested that the diradical **131** is also an intermediate in this reaction[167].



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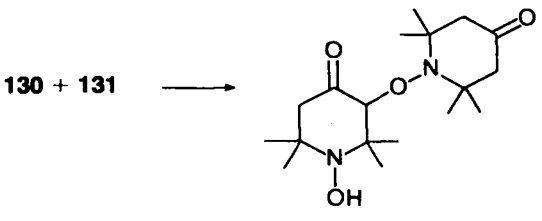
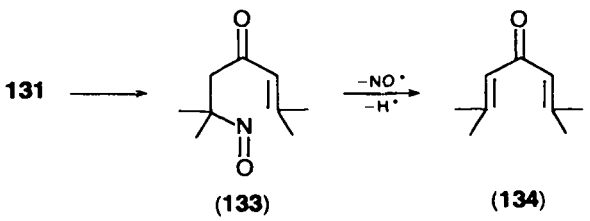
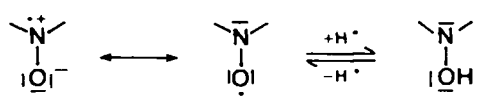




E. Reduction of the Nitroxide Group

An increasing spin density at oxygen (increasing weight of contribution structure A) should enhance the electrophilic character of the nitroxide, enhancing the tendency for hydrogen abstraction (equation 48). This should be reflected by the O—H bond dissociation energy of the corresponding hydroxylamines. A high bond dissociation energy is indicative of a strong tendency for hydrogen abstraction in the nitroxide.



(48)

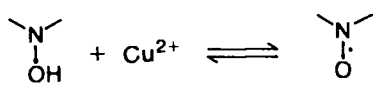
Inspection of Table 10 shows that bicyclic nitroxides and acyl nitroxides should be reduced more easily than normal nitroxides. This is in fact found to be true. But the bistrifluoromethyl nitroxide shows an even higher tendency to be reduced. On

TABLE 10. O—H bond dissociation energies (D_{OH}) of hydroxylamines

Hydroxylamine	D_{OH} (kcal/mol)	Reference
N-Hydroxy-2,2,6,6-tetramethypiperidine	69.6	14
N-Hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine	71.8	14
N-Hydroxy-8-azabicyclo[3.2.1]octane	77.0	14
N-Hydroxy-9-azabicyclo[3.3.1]nonane	76.2	14
N-*t*-Butylarylhydroxamic acids	76–80	168

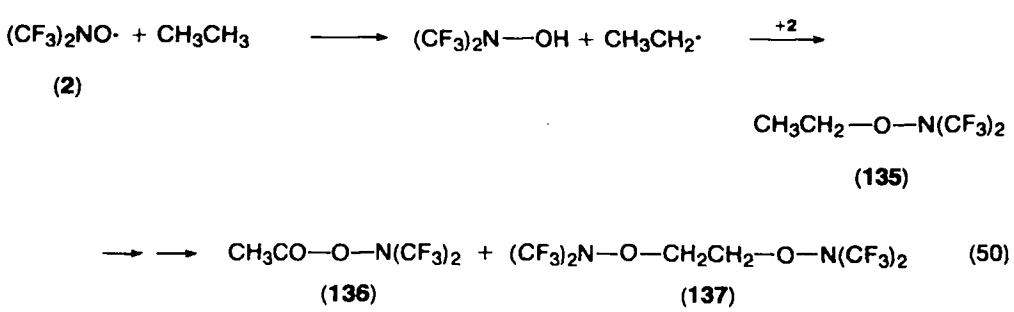
the other hand, the fact that di-*t*-butyl nitroxide can abstract a hydrogen atom from 1-hydroxy-2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide giving the corresponding nitronyl nitroxide[103] indicates that in the nitronyl nitroxides the tendency to be reduced is very small. This order of reactivity for the reduction of nitroxides agrees with the spin density at oxygen as determined by the ^{17}O-coupling constants*.

In general, the reduction of a nitroxide to yield the corresponding hydroxylamine is possible with mild reducing reagents such as hydrazine, phenylhydrazine, hydrazobenzene, ascorbic acid and thio alcohols[169,170]. Catalytic reduction using a platinum catalyst also gives hydroxylamines, whereas the use of Raney nickel yields amines[169,170]. On the other hand, in many cases nitroxides can also be used as oxidizing agents. For instance, they may oxidize substituted phenylenediamines to give the corresponding radical cations, and hydroxybenzoquinones or phenols, to give quinones[169]. Heterocyclic compounds such as 1,5-dihydroflavines and 1,5-dihydrolumiflavines can also be oxidized by nitroxides[171]. The reaction of a nitroxide and a hydroxylamine which leads to an equilibrium between the two nitroxides and their parent hydoxylamines is catalysed by cupric ions. The catalysis can be explained by the process shown in equation (49)[172].



(49)

The strong electrophilic character of bis(trifluoromethyl) nitroxide is indicated by the fact that this nitroxide can abstract a hydrogen atom from hydrocarbons with the exception of methane. Reaction with ethane proceeds slowly, and the ethyl radical formed reacts with a second nitroxide molecule to yield **135**. Further reaction affords **136** and **137** (equation 50)[173] On the other hand, reaction with



(50)

*^{17}O-labelling of bistrifluoromethyl nitroxide has not yet been performed but in *t*-butyl trifluoromethyl nitroxide $a^{17}O$ is larger than in the other nitroxides[39].

$(CH_3)_3C{-}O{-}N(CF_3)_2$ (138)

$(CH_3)_2C(CH_2{-}O{-}N(CF_3)_2){-}O{-}N(CF_3)_2$ (139)

methylpropane occurs easily, the products **138** and **139** being formed. Formation of **139** occurs via the intermediate methylpropene[173]. Reaction of bis(trifluoromethyl) nitroxide (**2**) and toluene in the ratio 2:1 affords mainly **140**, whereas a large excess of nitroxide yields products **141**, **142** and **143**. These products are formed by the reaction sequences shown in equation (51)[174]. It seems remarkable that even the aldehydic hydrogen atom can be abstracted by the radical.

$$PhCH_3 + 2\,(CF_3)_2NO^{\cdot} \longrightarrow PhCH_2{-}O{-}N(CF_3)_2 + (CF_3)_2NOH$$

(2) (140) (141)

$$\downarrow +2$$

$$PhC^{\cdot}H{-}O{-}N(CF_3)_2 + \mathbf{141} \qquad (51)$$

$$\downarrow$$

$$PhCOO{-}N(CF_3)_2 + \mathbf{141} \xleftarrow{+2\times2} PhCH{=}O + (CF_3)_2N^{\cdot} \xrightarrow{+2} (CF_3)_2N{-}O{-}N(CF_3)_2$$

(142) (143)

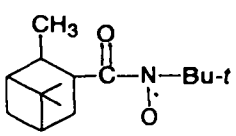
Acyl nitroxides are also good hydrogen acceptors. Although benzoyl *t*-butyl nitroxide **144a** reacts with ethylbenzene only at elevated temperatures to yield **145** (equation 52), this reaction is faster by a factor of 10^3 than with dialkyl nitroxides,

$$ArCO{-}N(\cdot O){-}Bu\text{-}t + H{-}R \longrightarrow ArCO{-}N(OR){-}Bu\text{-}t \qquad (52)$$

(144) (145)

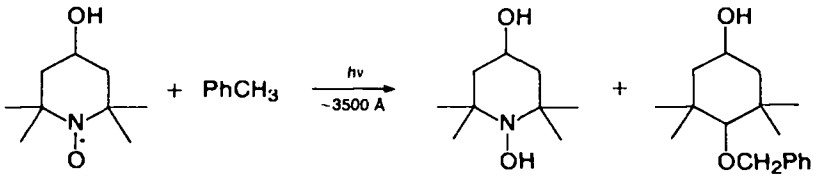
(**a**) Ar = C_6H_5,
(**b**) Ar = 3, 5-$(NO_2)_2C_6H_3$, R = $C_6H_5CHCH_3$ or *c*-C_6H_{11}

The more reactive 3,5-dinitrobenzoyl *t*-butyl nitroxide **144b** can even attack cyclohexane[175]. **144b** can also oxidize alcohols, for instance, cyclohexanone is formed from cyclohexanol[175]. An aspect of special interest is the application of the chiral acyl nitroxide **146**, which can, for instance, oxidize benzoin in an enantioselective manner[176].



(146)

Whereas dialkyl nitroxides in the ground state do not usually react with hydrocarbons or the reaction is extremely slow, photochemical reaction with hydrocarbons occurs very readily. Thus, 4-hydroxy-2,2,6,6-tetramethyl piperidine-*N*-oxyl (**79**) is converted to hydroxylamine **147** and *O*-benzylhydroxylamine **148** in a 1:1 ratio when irradiated in toluene (equation 53)[177]. **148** is the addition product of nitroxide **79** and the benzyl radical. Hydrogen abstraction from alkanes

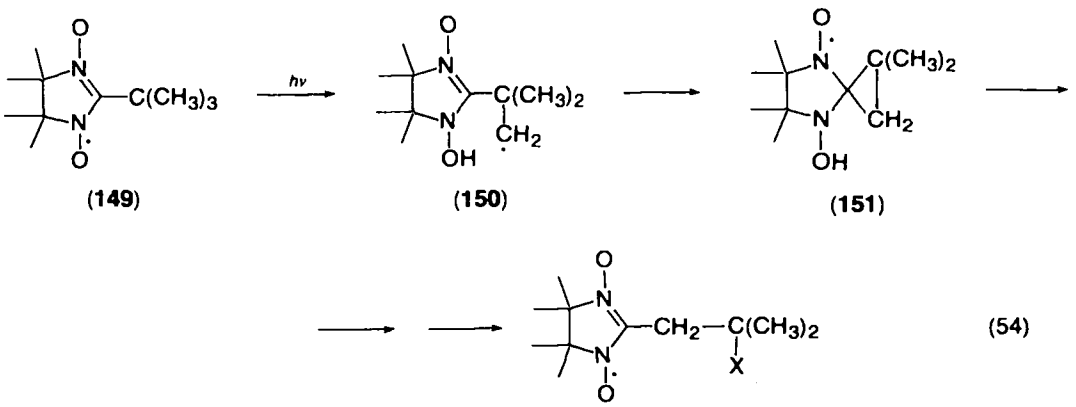


(79) (147) (148) (53)

by photochemically excited dialkyl nitroxides occurs from the n → π* excited state of the radical.

The activation energy for reactions of photochemically excited 2,2,6,6-tetramethyl piperidine-*N*-oxyl is estimated to be in the range 2–3 kcal/mol, indicating that the radical is very reactive in its excited state. The excitation causes the dipole moment to fall from 3.14 D for the ground state to 1.0 D in the excited state[178]. This reflects a shift in electron density from oxygen to nitrogen making the oxygen atom much more electrophilic.

Demethylation at a specific position has been achieved in a steroid molecule labelled with a nitroxide group by a photochemically induced intramolecular oxidation[179]. Another intramolecular hydrogen abstraction by a photochemically excited nitroxide group involves the photochemical conversion of nitronyl nitroxide **149** in aqueous solution, **152a** and **152b** being isolated. It has been suggested that this reaction occurs via the intermediates **150** and **151**[180].



(149) (150) (151) (54)

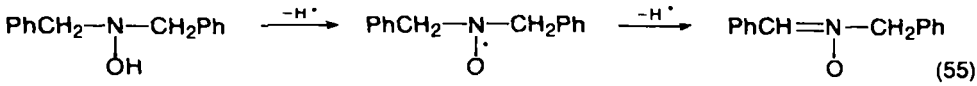
(152)

(a) X = OH
(b) X = OOH

F. Oxidation of the Nitroxide Group

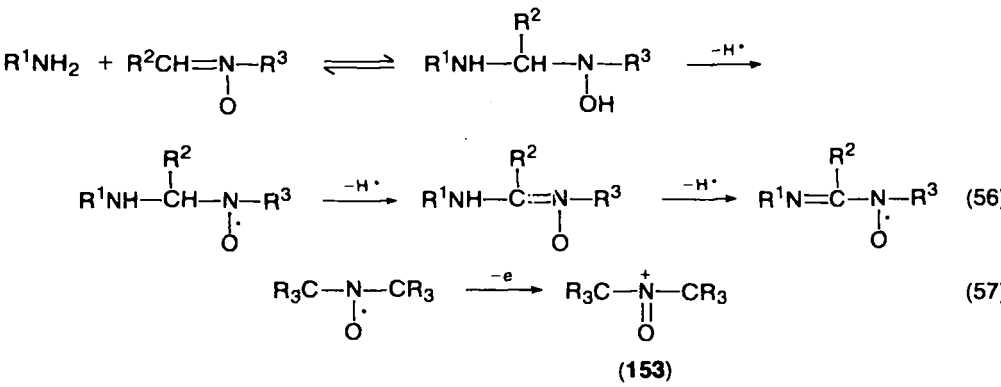
Oxidation of monoaryl and monoalkyl nitroxides affording nitroso compounds has already been discussed in Section V.D. This reaction is part of the oxidative

conversion of hydroxylamines to nitroso compounds, in which the nitroxides are intermediates. An analogous situation arises for the oxidation of disubstituted nitroxides to give nitrones[181]. For instance, *N*-benzylidene benzylamine-*N*-oxide is formed by the oxidation of dibenzyl hydroxylamine via dibenzyl nitroxide (equation



(55)

55)[182]. Frequently, however, the resulting nitrones undergo secondary reactions and cannot be isolated[163,165]. Oxidation of nitroxides beyond the nitrone level yielding αβ-unsaturated nitroxides has been only observed for aminoalkyl nitroxides (equation 56)[183]. Oxidation of di-*t*-alkyl nitroxides gives the oxoammonium salts **153** (equation 57).



(56)

(57)

(153)

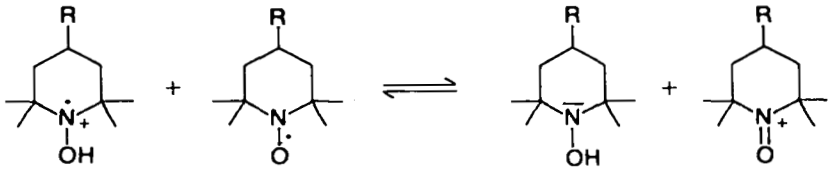
In Table 11 the half-wave potentials determined by electrochemical oxidation of some nitroxides are listed[184] reflecting the trend for the formation of oxoammonium cations.

Oxidation occurs with a variety of oxidizing agents[185]. For instance, 2,2,6,6-tetramethylpiperidine-*N*-oxyl is oxidized by xenon difluoride to afford the corresponding oxoammonium fluoride[186]. Using bromine or chlorine in inert solvents, oxoammonium salts can be isolated in most cases[185]. Oxoammonium salts can also be obtained by the disproportionation of di-*t*-alkyl nitroxides after partial protonation (equation 58)[185].

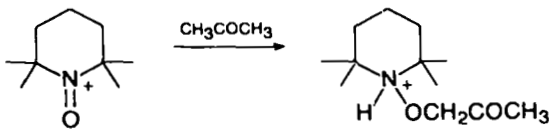
Oxoammonium cations are electron-deficient compounds compared to nitroxides, thus easily undergoing secondary reactions. For instance, reaction with the solvent can occur. The hydroxylammonium cation **155** is formed from **154** in acetone[187].

TABLE 11. Half-wave potentials ($E_{1/2}$) of nitroxides[184]

Nitroxide	$E_{1/2}$(V)
Di-*t*-butyl nitroxide	0.207
Tetramethylpiperidine-*N*-oxyl	0.271
4-Hydroxytetramethylpiperidine-*N*-oxyl	0.331
4-Oxotetramethylpiperidine-*N*-oxyl	0.444
3-Oxo-9-azabicyclo[3.3.1]nonane-*N*-oxyl	0.473
1,5-Dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-*N*-oxyl	0.448
3-Oxo-8-azabicyclo[3.2.1]octane-*N*-oxyl	0.509

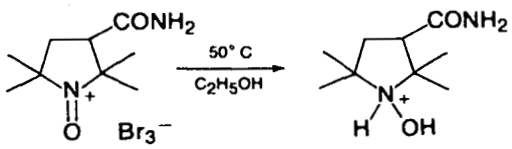


(58)



(59)

(154) (155)

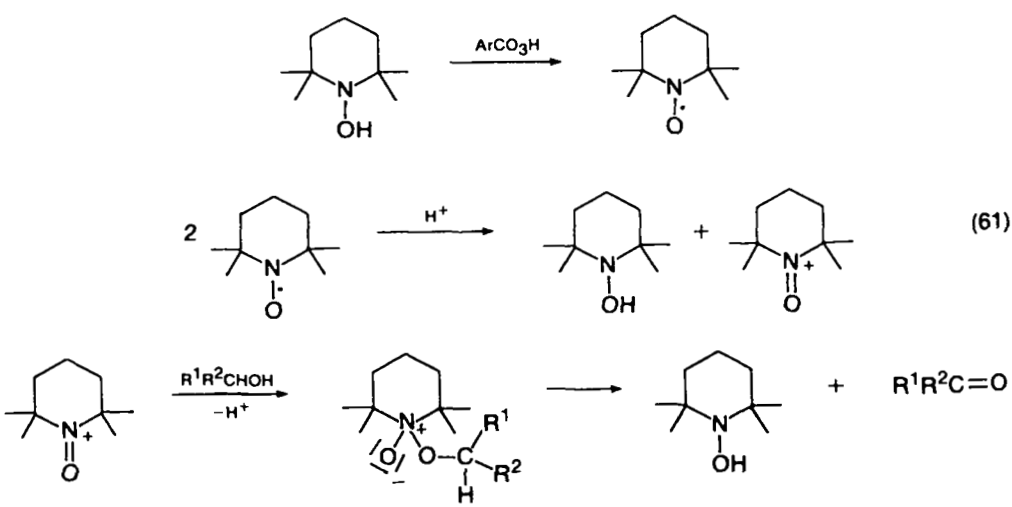


(60)

(156) (157)

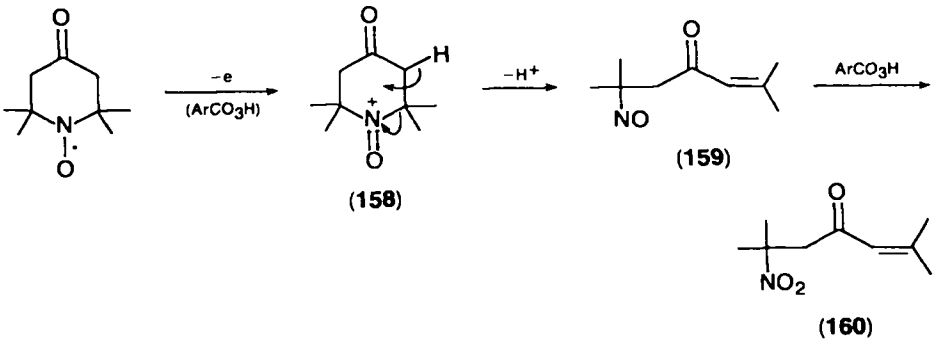
The oxoammonium salt **156** is reduced by warming it in alcohol, to yield **157**, from which the corresponding free hydroxylamine can be obtained by treatment with potassium carbonate[187]. This reaction is used to oxidize secondary alcohols using a mixture of *m*-chloroperbenzoic acid and 2,2,6,6-tetramethylpiperidine-*N*-oxyl to yield ketones[188]. The oxidation does not occur in the absence of the nitroxide but proceeds with only a catalytic amount[189]. Therefore the reaction sequence shown in equation (61) is suggested[188]. The oxidation of methanol in the presence of di-*t*-butyl nitroxide and cupric phenanthroline complexes to yield formaldehyde appears to be more complicated[190].

In some oxoammonium salts, bond cleavage occurs, being favoured by the presence of suitable functional groups within the molecule. Thus the oxoammonium



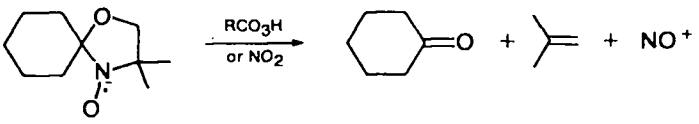
(61)

salt **158**, formed by oxidation of 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl, is cleaved to afford the nitro compound **160** via the nitroso compound **159** (equation 62) whereas the cation obtained from 2,2,6,6-tetramethylpiperidine-*N*-oxyl is stable under these conditions[191].



(158) (159) (160) (62)

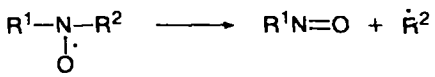
Nitroxide **161** is oxidized by *m*-chloroperbenzoic acid or nitrogen dioxide, and decomposes via its oxoammonium cation to yield cyclohexanone, isobutylene and NO^+ (equation 63)[191]. Molecular rearrangements, accompanying the oxidation of bicyclic nitroxides by silver oxide, are assumed to be induced by cleavage of the primarily formed oxoammonium cations[192,193].



(161) (63)

G. α-Scission of Nitroxides

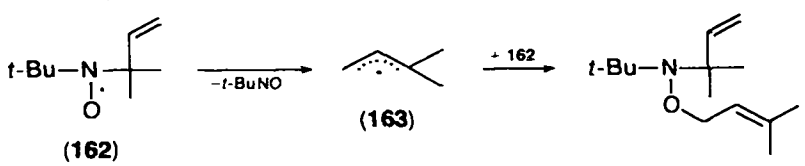
The reverse of spin trapping by nitroso compounds is the α-scission of a disubstituted nitroxide. The α-scission of the N—C bond occurs readily if the resulting radical $\dot{R}^2$ is stabilized (equation 64).



(64)

$R^2 = Ph_3C^{\cdot}$, $H_2C{=}CH{-}\dot{C}(CH_3)_2$, $HC{\equiv}C{-}\dot{C}(CH_3)_2$

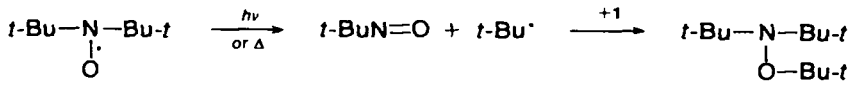
Thus, trityl nitroxides decompose yielding the triphenyl methyl radical and the nitroso compound[194]. This reaction occurs easily if the R^1 group is bulky, as for instance the *t*-butyl group. In solution, radical **162**, decomposes even at 25°C affording the allyl radical **163**, which further attacks the nitroxide **162** to yield the product **164** · (equation 65)[195]. On the other hand, the corresponding



(162) (163) (164) (65)

t-butyl-(1,1-dimethyl) propyne-2-yl nitroxide is only cleaved in refluxing benzene solution, when subsequent reactions yield a bicyclic compound with a complicated structure[196].

Di-*t*-butyl nitroxide (**1**) is only decomposed at temperatures above 125°C, yielding 2-methyl-2-nitrosopropane and tri-*t*-butylhydroxylamine (equation 66),

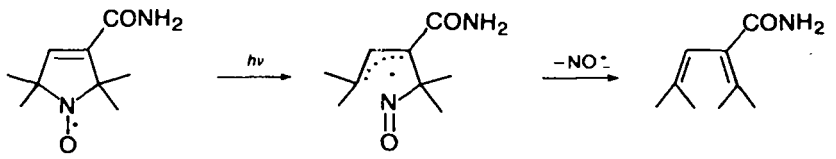


(66)

(**1**)

the latter arising from the trapping of *t*-butyl radicals by unreacted di-*t*-butyl nitroxide. The dissociation energy for the N—C bond has been estimated to be 29 kcal/mol[197]. The same products are formed by the photochemical cleavage of **1** but the reaction requires $\pi \rightarrow \pi^*$ excitation ($\lambda < 320$ nm), the $n \rightarrow \pi^*$ excitation being photochemically inert[198].

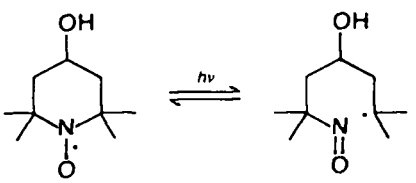
The photochemical decomposition of nitroxide **165** is thought to proceed via the intermediate **166**, which is stabilized by its allylic group. Elimination of nitrogen oxide then affords product **167** (equation 67).



(67)

(**165**) (**166**) (**167**)

On the contrary, photochemically excited 4-hydroxy-2,2,6,6-tetramethyl-piperidine-*N*-oxyl (**79**) does not decompose but abstracts hydrogen in the presence of toluene (equation 68) (see Section V.E). It is suggested that α-scission also occurs in this case, but that the radical **168** not being stabilized is converted reversibly to **79** by intramolecular spin trapping[198].

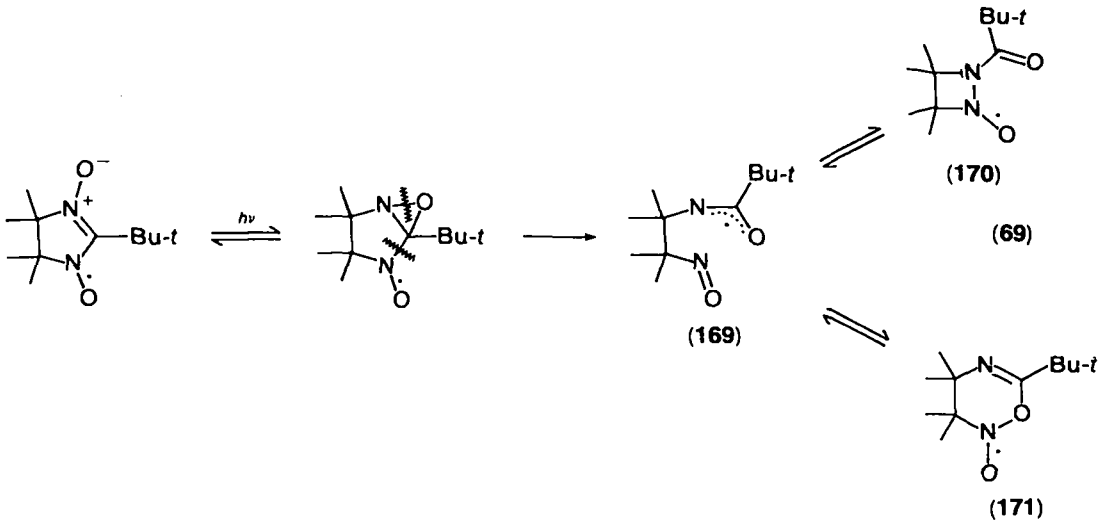


(68)

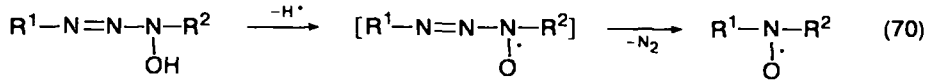
(**79**) (**168**)

The photochemically induced reaction of 2-*t*-butyl-4,4,5,5-tetramethyl-imidazoline-3-oxide-1-oxyl in aprotic solvents follows a rather complicated course[199]. Irradiation at low temperature causes the usual conversion of the nitrone group to an oxaziridine ring. At higher temperatures the NO bond of the oxaziridine ring is broken, inducing α-scission at the nitroxide moiety to afford the intermediate **169**. Finally this undergoes intramolecular spin trapping to yield the nitroxides **170** or **171** (equation 69).

Radicals in which a heteroatom such as nitrogen or oxygen is attached directly to the nitroxide group undergo α-scission much more readily. Until now, the acyclic triazene-*N*-oxyls **172** have not been detected. All attempts at generating these radicals have given only the nitroxides **173**[200]. Their formation is assumed to occur by α-scission of the transient triazeneoxyl giving the nitroso compound and a



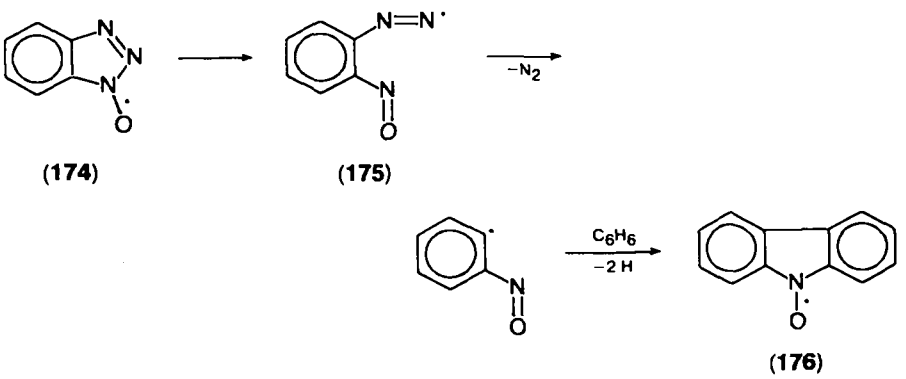
diazonium radical which further decomposes by elimination of nitrogen. The radical $\dot{R}^1$ is then trapped by the nitroso compound yielding the nitroxide **173** (equation 70).



(70)

(172) (173)

On the other hand, benzotriazole-1-oxyl (**174**), is sufficiently persistent to be detected by ESR in several solvents[201]. In aromatic solvents, however, or even in the presence of aromatic compounds, **174** decomposes with the formation of the *o*-nitrosophenyl radical. In, for example, benzene, the reaction of the *o*-nitrosophenyl radical with the solvent affords the carbazole-*N*-oxyl **176** (equation 71). Substituent effects on the persistence of radicals of the type **174** makes it



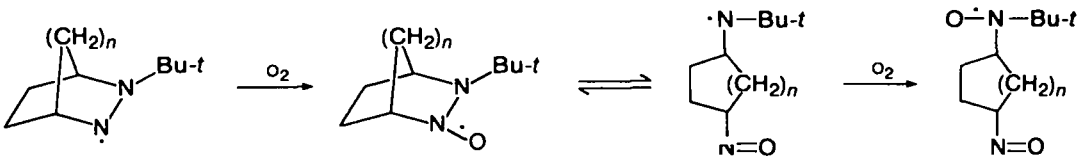
(174) (175) (176)

(71)

probable that in the first step of the reaction α-scission occurs to yield the α-nitrosodiazophenyl radical **175** which subsequently eliminates nitrogen[202].

The conversion of bicyclic hydrazyls **177** in the presence of oxygen is a further example of N—N scission in the α-position of the nitroxide group. Firstly the

oxidation of **177** gives **178**. The latter is assumed to be oxidized via the intermediate **178** to yield **180** (equation 72)[203].



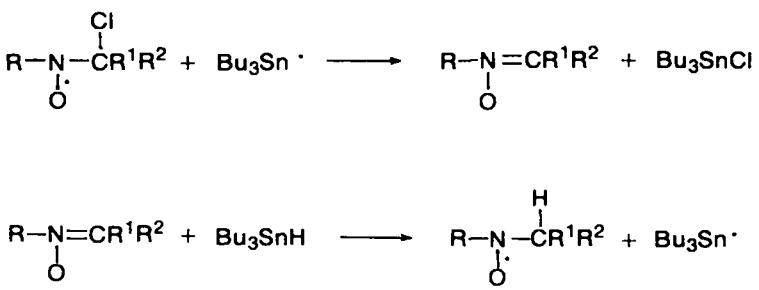
(177) **(178)** **(179)** **(180)**

n = 1 or 2 (72)

The low persistence of alkoxy nitroxides is well documented[204,205]. The activation energy for the α-scission of the N—O bond in alkoxy nitroxides has been determined to be 10 kcal/mol[206], indicating that cleavage of alkoxy nitroxides occurs readily.

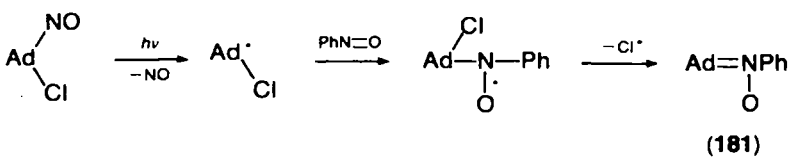
H. β-Scission of Nitroxides

The oxidation of nitroxides to afford nitrones may be considered as a β-scission. Moreover halogen substituents in the β-position of the nitroxide group can be easily eliminated. Thus it has been shown, that the chlorine atom in β-chlorinated nitroxides is substituted by hydrogen after treatment with tri-*n*-butyltin hydride[207]. The reaction is considered to be a radical-chain reaction, the propagation of the chain involving the steps shown in equation (73).



(73)

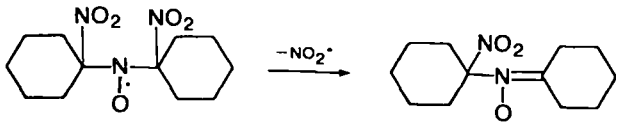
Supposing that intermediate formation of β-chloronitroxides occurs, followed by elimination of chlorine to yield nitrones, several reactions can be reasonably interpreted[208–210] such as the photochemical synthesis of the nitrone **181** from 2-chloro-2-nitrosoadamantane and nitrosobenzene (equation 74)[208].



(181)

Ad = adamantane

Similarly, photolysis of 1-nitro-1-nitrosocyclohexane is assumed to occur via the intermediate **182**. The latter eliminates nitrogen dioxide with the formation of **183** which then reacts further (equation 75)[211].



(182) (183) (75)

I. Miscellaneous Nitroxide Group Reactions

The most reactive nitroxide, bis(trifluoromethyl) nitroxide, is capable of addition to alkenes. A 2:1 adduct **184** is formed with ethylene in 99% yield (equation 76)[212].

$$2\,(CF_3)_2NO^{\cdot} + CH_2{=}CH_2 \longrightarrow (CF_3)_2N{-}O{-}CH_2CH_2{-}O{-}N(CF_3)_2 \quad (76)$$

(184)

Reactions with isobutene, 2-methylbutene-1 and 2-methylbutene-2 also give the corresponding products. On the other hand, hydrogen is abstracted from 3-methylbutene-1, the resulting radical being trapped by a further nitroxide molecule to yield **185** and **186** (equation 77)[173].

$$2\,(CF_3)_2NO^{\cdot} + Me_2CHCH{=}CH_2 \xrightarrow[-(CF_3)_2NOH]{}$$

$$Me_2\underset{\displaystyle ON(CF_3)_2}{\underset{|}{C}}CH{=}CH_2 \quad + \quad Me_2C{=}CH{-}CH_2{-}ON(CF_3)_2 \quad (77)$$

(185) **(186)**

Acetylene and substituted acetylenes can first add two bis(trifluoromethyl) nitroxide molecules, but contrary to the reaction of ethylene very complex reactions occur[213]. In the reaction of bis(trifluoromethyl) nitroxide and benzene, substitution occurs yielding the 1,2,4-tris[*N*,*N*-bis (trifluoromethyl)] aminoxybenzene[214].

Recently some addition reactions of acyl nitroxides have been reported[215].

Nitroxides of usual reactivity can induce homolytic cleavage of weak σ-bonds. It has been found that in di-*t*-butyl nitroxide as the solvent or in molten 4-oxo-2,2,6,6-tetramethyl piperidine-*N*-oxyl, compounds such as benzoyl peroxide, *N*-bromosuccinimide, allyl and benzyl bromide and even the less reactive secondary and tertiary alkyl bromides and iodides can be cleaved. This process, called homosolvolysis[216], can be formulated as in equation (78). If X is bromine, the almost insoluble oxoammonium bromide precipitates; benzyl and allyl bromides afford the

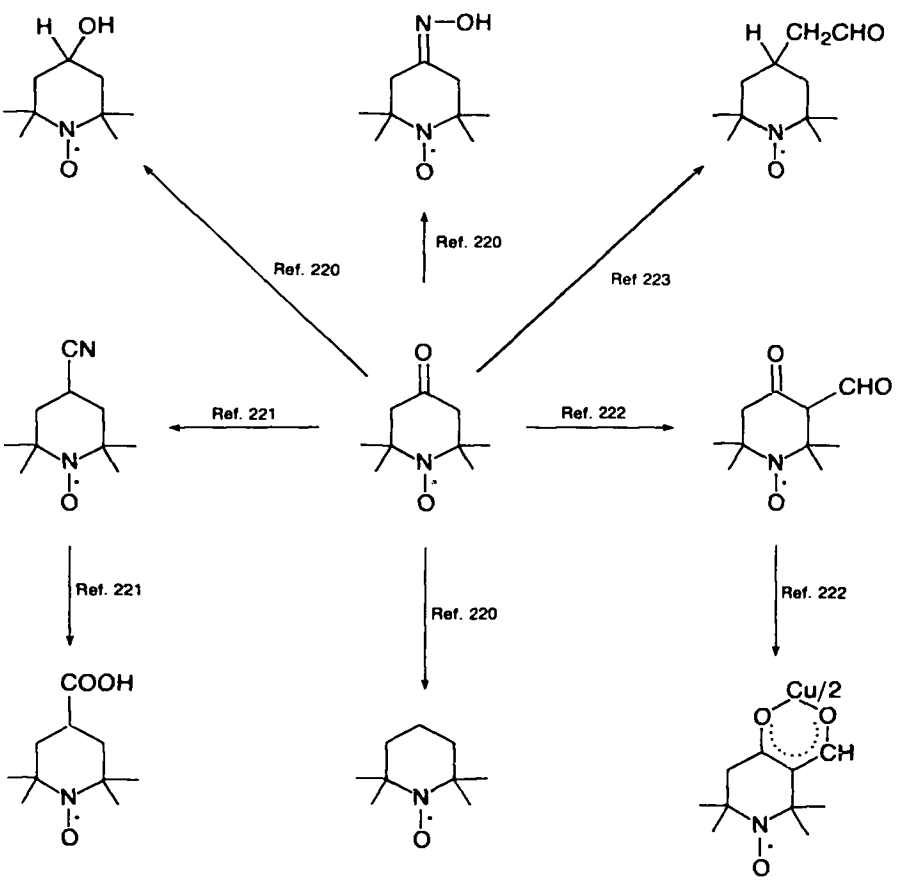
$$\begin{array}{ccccccc} & & & & \dot{R}^1 + \dot{O}NR_2^2 & & \\ & & & & \uparrow & & \\ R^1X + 2\,R_2^2N\dot{O} & \longrightarrow & [\dot{R}^1 \;\; \dot{X}]_{2\,R_2^2NO} & \rightleftharpoons & [\dot{R}^1 \;\; \dot{O}NR_2^2] + [R_2^2N\dot{O} \;\; \dot{X}] & & (78) \\ & & & & \Downarrow & & \\ & & & & R^1ONR_2^2 + R_2^2NOX \text{ or } R_2^2NO^+X^- & & \end{array}$$

corresponding *O*-substituted hydroxylamines, whereas the radicals formed from *N*-bromosuccinimide or benzoyl peroxide abstract hydrogen. Most strikingly, a small amount of di-*t*-butyl nitroxide in an inert solvent is sufficient to induce the dissociation of triphenylmethyl bromide, the triphenylmethyl radical being detected by ESR[217].

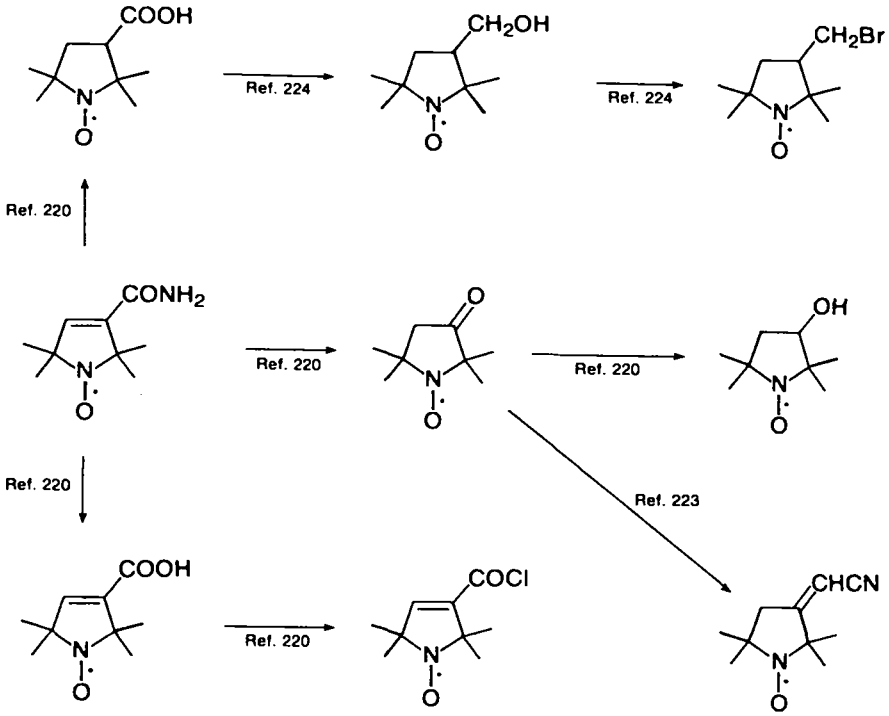
Deoxygenation of nitroxides occurs with a variety of reagents such as triethyl phosphite, methyl iodide or iodine, sodium sulphide in dimethyl sulphoxide, tetramethylthiuram disulphide and sulphur dioxide[218]. The mechanism of this reaction has been discussed for triethyl phosphite only[219]. It is assumed that the reaction begins with the formation of a P—O bond; then scission of the N—O bond follows, yielding triethyl phosphate and an aminyl radical which finally abstracts hydrogen from the solvent to form an amine.

VI. REACTIONS WITHOUT DIRECT INVOLVEMENT OF THE NITROXIDE GROUP

The extraordinary persistence of the di-*t*-alkyl nitroxides makes it possible for various reactions to be performed at other reactive positions of the radical molecule, the nitroxide group itself being unaffected[1–4]. Such reactions were first



SCHEME 5



SCHEME 6

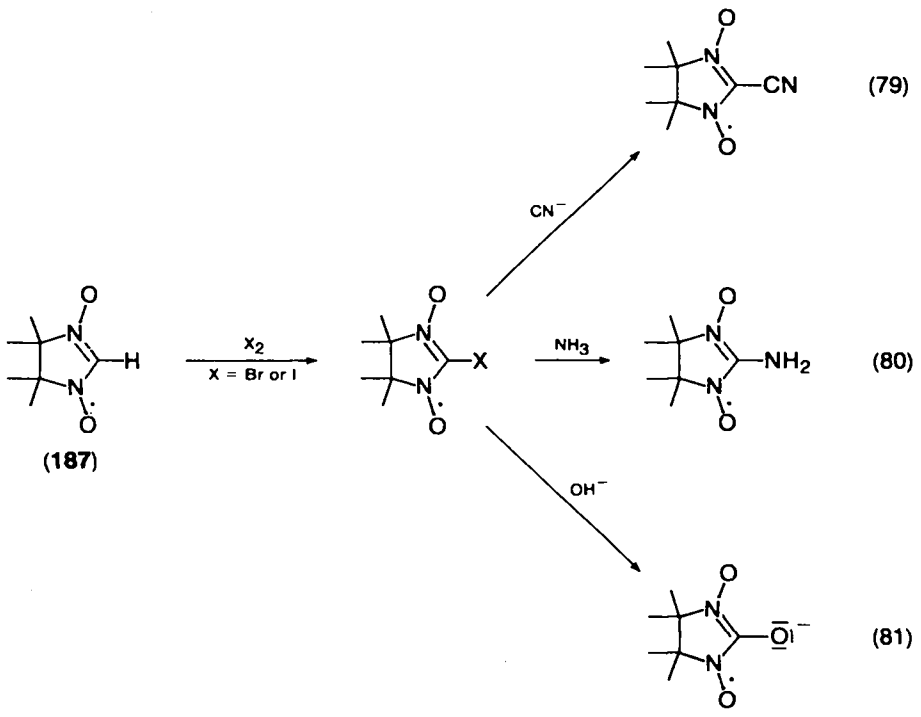
carried out by Rozantsev[2,3] using the carbonyl group reactivity of the 4-oxo-2,2,6,6-tetramethylpiperidine-*N*-oxyl. The great numer of possibilities for the application of such reactions is demonstrated in Schemes 5 and 6[220–224]:

The reactions, occurring at the position 2 of 4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl **187** and its 2-halogeno derivatives, leaving the nitroxide group unchanged (equations 79–81), indicate that the high persistence of the nitroxide group does not originate alone from steric effects[225].

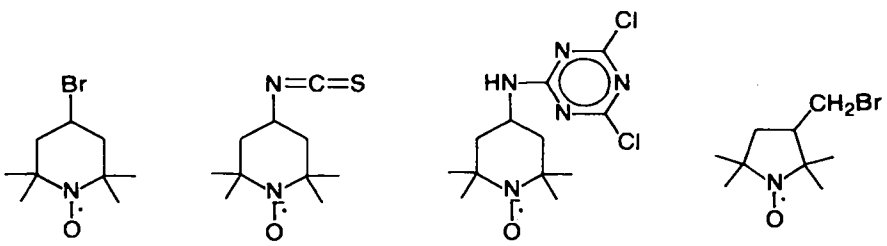
2-Substituted derivatives of **187** can undergo various reactions at the side-chain without loss of the radical properties[225]. Moreover, nitroxides containing chelate-forming groups can form chelate complexes with metal ions[226].

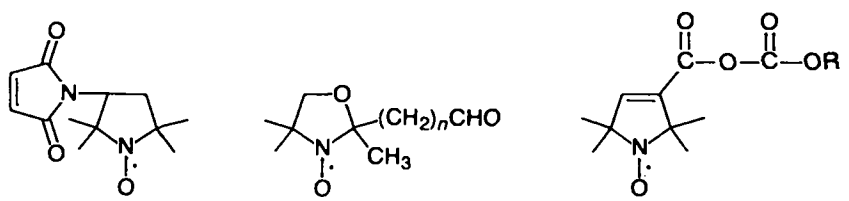
The reactions of nitroxides without direct participation of the nitroxide group have been extensively applied in the field of spin labelling[227,228] during recent years. This technique depends on the fact that a nitroxide which is either covalently or noncovalently incorporated into a biological system can give, via its ESR spectrum, information about its environment. Thus, for instance, the anisotropy of the ESR spectrum of the spin label can give information about the mobility of the biomolecule (see Section III.C.1). Moreover, from the magnitude of the coupling constant a^N, it can be concluded whether the environment of the nitroxide label is polar or nonpolar. Other properties of nitroxides affecting their ESR spectra such as the spin exchange in biradicals, which is dependent on several factors (see Section IV.C) can also be used to gain information about biological systems.

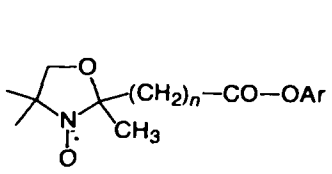
The most important spin labels are 2,2,6,6-tetramethylpiperidine-*N*-oxyls, 2,2,5,5-tetramethylpyrrolidine-*N*-oxyls, 2,2,5,5-tetramethylpyrroline-*N*-oxyls and 4,4-dimethyloxazolidine-*N*-oxyls, substituted by functional groups which are capable



of undergoing chemical reactions with the reactive sites of biomolecules. A selection of alkylating, acylating, sulphonating and phosphorylating spin labels is shown in formulae **188–199**.







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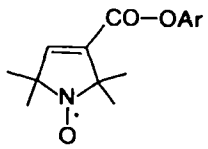

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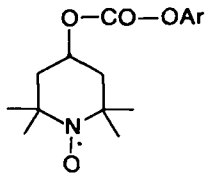
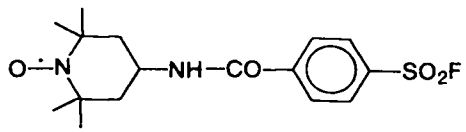


(197)

Ar = $C_6H_4NO_2$-p



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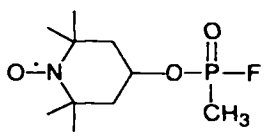

(199)

VII. ACKNOWLEDGEMENTS

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CHAPTER **15**

Enamines and ynamines

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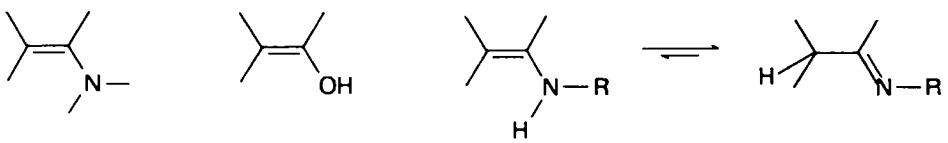
I. INTRODUCTION

The term enamine designates any α,β-unsaturated amine, in analogy with the term enol.

Primary and secondary enamines (1) exist in tautomeric equilibria, in which the imino forms (2) largely predominate, unless other factors, such as for instance an intramolecular hydrogen bond, stabilize the former tautomers. They have been studied extensively by many authors[1].



(1) (2)

Enamine Enol R = H: primary enamine
R = alkyl, aryl: secondary enamine

Our paper, however, will deal only with tertiary enamines whose importance in organic synthesis has grown since the fundamental work of Stork and coworkers[2]. From then onwards many papers have been published together with some reviews[3] and a comprehensive book[4] covering the whole literature up to 1969. Subsequently, about 1500 pertinent papers have appeared, in addition to another book[5] and several reviews[6] concerning acylation[6a,b] and alkylation[6c] of enamines, application of enamines to the synthesis of natural products[6d], dienamines[6e] and enaminones[6f].

Almost simultaneously, ynamines, which are the acetylenic analogues, received attention[7]. Application of ynamines to organic synthesis has been widely developed and reviewed by Viehe[8] and Ficini[9].

In the present chapter are presented the more recent results in the enamine and ynamine fields. Omissions are inevitable and reflect space restrictions and the authors' attempt to avoid duplication with earlier reviews, and obviously do not imply any negative judgement.

II. ENAMINES

A. Preparation

1. Acyclic and cyclic enamines

The most general method of enamine synthesis involves condensation of an aldehyde or ketone with a secondary amine (equation 1). Removal of the water

(1)

formed can be accomplished by azeotropic distillation with aromatic hydrocarbons. Drying agents, such as $CaCl_2$, CaO, K_2CO_3 or $MgSO_4$, are employed under varied conditions[10]. The use of molecular sieves as dehydrating agents has the advantage that very mild conditions can be used, even with rather hindered ketones[11]. Better results have been obtained with added silica–alumina catalysts[12].

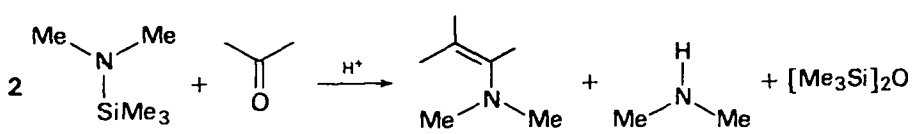
The widely used method of White and Weingarten (W.W. method) using $TiCl_4$ [13] may also be applied to sterically hindered ketones and to cases where side-reactions are possible, as in the synthesis of enamines from substituted acetones[14] and cycloalkenyl methyl ketones (equation 2)[15]. Acyclic as well as cyclic amines can be

$$2\ R^1CH_2COR^2 + 6\ R^3_2NH + TiCl_4 \longrightarrow 2\ R^1CH{=}CR^2NR^3_2 + 4\ R^3_2\overset{+}{N}H_2\bar{C}l + TiO_2 \quad (2)$$

used, and the method has proved successful even with aziridine[16] for which difficulties had been encountered[17].

For a volatile base, such as dimethylamine, a mild method is reported[18] which makes use of the trimethylsilyl derivative of the amine (**3**) and of the carbonyl compound. This method has been also extended to other amines.

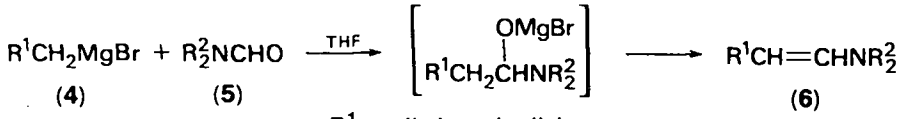
A convenient method for the synthesis of aldehyde enamines* (**6**) from hindered



(**3**)

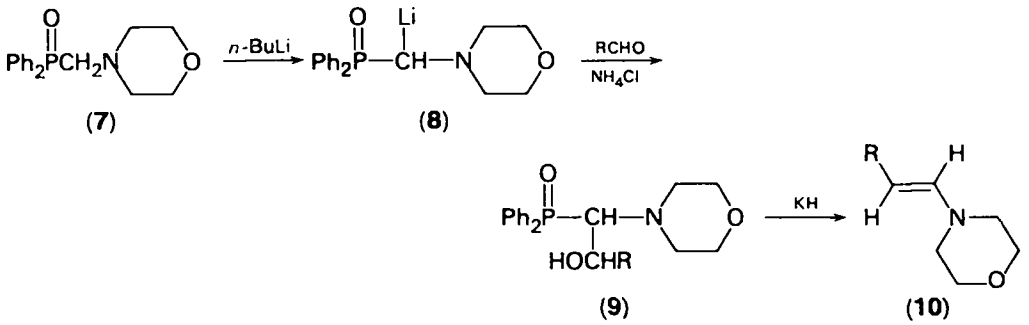
*Aldehyde and ketone enamines are used to designate enamines derived from an aldehyde and a ketone respectively.

amines is that reported by Hansson and Wickberg[19] which involves addition of Grignard reagents (**4**) to *N,N*-dialkylformamides (**5**) in THF.



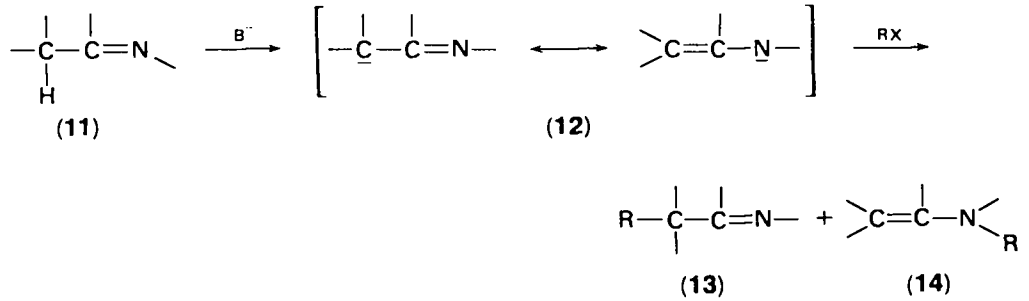
$R^1 = alkyl, aryl, allyl$
$R^2 = n\text{-Bu}, i\text{-Bu}, s\text{-Bu}$

Derivatives of As, B, Hg and P have been also employed in the preparation of particular enamines[20]. Recently aldehyde enamines have been synthesized by the Horner–Wittig reaction[21]. For instance, *N*-morpholinomethyldiphenylphosphineoxide (**7**) was treated with *n*-BuLi in THF at 0°C. The resulting lithiated anion (**8**) reacted with aliphatic and aromatic aldehydes to give an intermediate (**9**) which, by treatment with KH, led to the required enamines (**10**), generally in the *E* configuration.

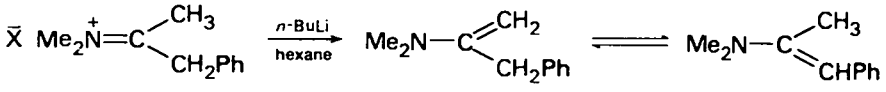


R = alkyl, aryl

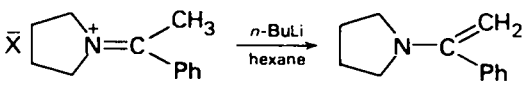
Enamines (**14**) have been prepared by *N*-alkylation of imine anions (**12**), formed by treatment of the parent imines (**11**) with sodium hydride or amide in dimethylcellosolve (DMC) and hexamethylphosphotriamide(HMPT), at 40°C[22]. Suitable solvents, temperature and alkylating agents must be chosen in order to minimize the undesired concomitant formation of the *C*-alkylated product (**13**). Another versatile



synthetic route to enamines involves reaction of iminium salts[23] with *n*-BuLi. For instance, treatment of the iminium salts of benzyl methyl ketone (**15**) and acetophenone (**16**) with *n*-BuLi leads to the formation of the corresponding enamines (**17**) and (**18**) respectively[24].



(15) (17)



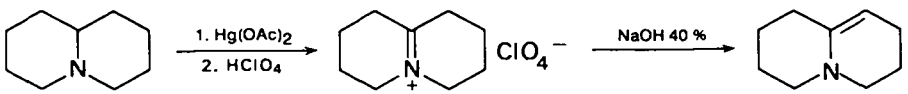
(16) (18)

Many other methods for the synthesis of enamines are reported in the literature; however, they are of less general applicability.

2. Heterocyclic enamines

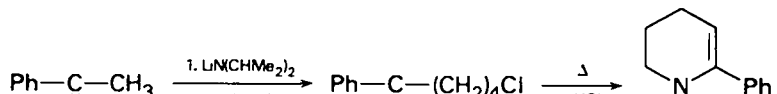
An enamine system in which the N and α-C atoms are part of a cycle is called a heterocyclic enamine[3b,25]. They are particularly interesting as efficient intermediates in the synthesis of natural and synthetic compounds of biological activity[6d,26].

Among the reliable methods used for the synthesis of heterocyclic enamines such as **20**, oxidation of the corresponding tertiary amine (**19**) with mercuric acetate is the most general[27,28].



(19) (20)

2-Substituted Δ^1-pyrrolideine and -piperideine are obtained by intramolecular condensation of γ- and δ-aminoketones and by the use of Grignard reagents on γ- and δ-halogenonitriles and *N*-alkylated lactams[28]. *N*-Methyl-2-phenyl-Δ^1-piperideine (**23**) is prepared[29] by alkylation of the imine anion formed by treatment of the required Schiff's base (**21**) with lithium diisopropylamide (LDA). Subsequent cyclization of the intermediate (**22**) is accomplished by heating.

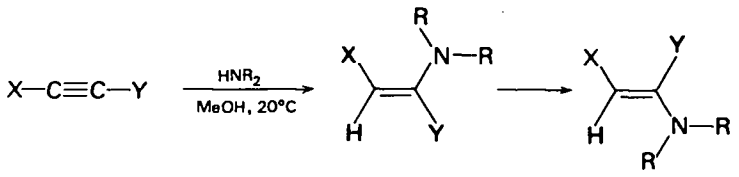


(21) (22) (23)

Partial reduction of quaternary pyridine salts[27,30] has also made available a variety of heterocyclic enamines.

3. Functionalized enamines

C- and *N*- functionalized enamines are represented by those structures in which multiple bonds are linked to either the carbon or the nitrogen atom. Among functionalized enamines of particular interest are dienamines[6e,31] and enaminones[6b,c,f,32] although other systems such as β-aryl-[31k,33], β-heterocyclic[34], β-cyano[35], β-nitro[36] and nitroso-[37] enamines as well as enaminosulphones[15,38], enamides[39] and *N*-nitrosoenamines[40] are known.



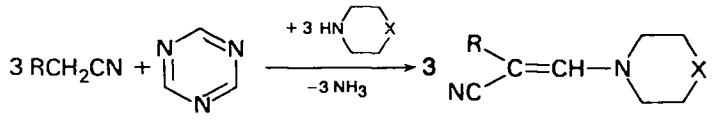
(24) (25)

X = COPh, CO_2Me, CON(Me)Ph, $SOCH_2Ph$, SO_2Ph

Y = H, Me

R, R = Me, Me; CH_2Ph, CH_2Ph; Me, CH_2CO_2Et

A series of *C*-functionalized enamines (**25**) in the *E* configuration has been prepared by addition of a base to activated acetylenes (**24**)[41]. *C*-Difunctionalized enamines (**27**) have been also prepared by aminomethynylation of the appropriate acetonitriles (**26**)[42].

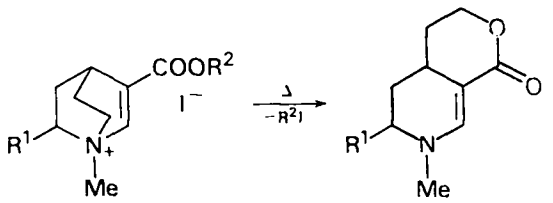


(26) (27)

R = 4-biphenyl, 2-naphthyl, 2-thienyl, 2-benzimidazoyl, benzoyl, 4-F-benzoyl

X = —O—, $—CH_2—$

In the heterocyclic series an interesting sigmatropic rearrangement leading to the enaminones **29** has been carried out starting from the quaternary salt of the dihydroquinuclidine derivatives **28**[43].

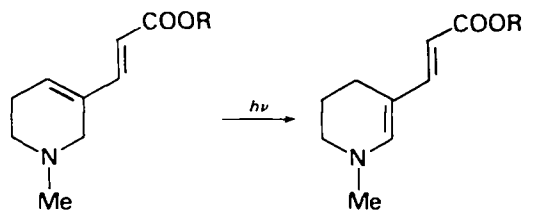


(28) (29)

R^1 = H, Me

R^2 = Me, Et

A case has been reported[44] of photoisomerization of 3-piperideine derivatives (**30**), with formation of the corresponding 2-piperideine derivatives (**31**), otherwise difficult to synthesize.



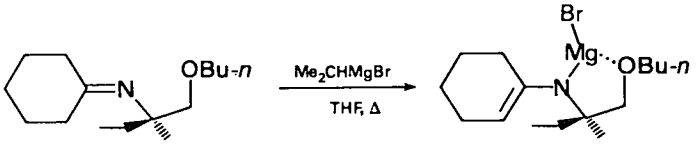
(30) (31)

R = Me, Et

4. Metalloenamines

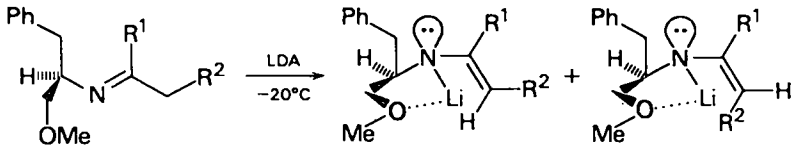
A continuing interest has been taken in the metalloenamine field, since the work of Stork and coworkers[45] on imine anion alkylation. Although they are not generally isolated, but are allowed to undergo further reactions *in situ* with electrophiles, metalloenamines are a versatile and efficient tool especially for the asymmetric synthesis of carbonyl compounds (see Section II.C.4.a).

Magnesium enamines (**33**) have been prepared by the action of Grignard reagents on chiral ketimines such as **32**[46] or α,β-unsaturated aldimines[47].



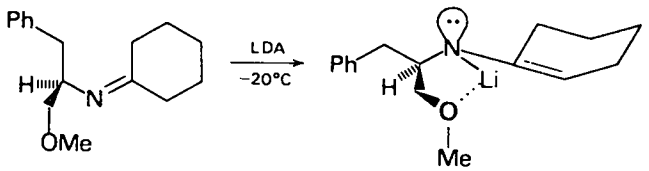
(**32**) (**33**)

Lithioenamines of the type **35**, **36** and **38** have been obtained by lithiation of the required acyclic (**34**) and cyclic (**37**) imines, by LDA at low temperature[48]. In the case of acyclic imines, kinetic ratios of *E*–*Z* lithioenamine isomers can be obtained. Subsequent equilibration affords the thermodynamic mixtures[48c].



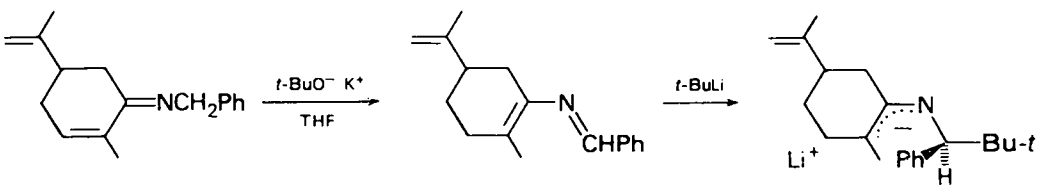
(**34**) (**35**) (**36**)

R^1, R^2 = *n*-Bu, *n*-Pr; *n*-Pr, Et; Et, Me; Ph, Et; Ph, Me; $PhCH_2$, Ph; Ph, Ph

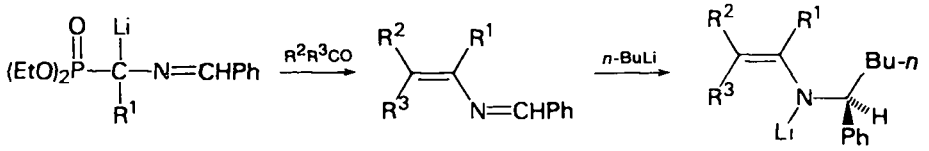


(**37**) (**38**)

Other syntheses involving metalloenamines such as **40** and **43** as intermediates have been carried out on α,β-unsaturated imines (**39**)[49] and on 2-azadienes (**42**)[50], the latter generated from the suitable carbonyl compound and diethyl lithio-*N*-benzylideneaminomethylphosphate (**41**). Both methods are regioselective and rather general.



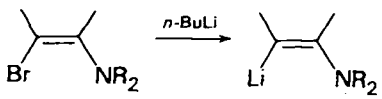
(**39**) (**40**)



(41) (42) (43)

β-Lithioenamines (**45**) which have been proved useful synthetic intermediates, can be prepared by halogen–metal exchange of an organolithium compound with β-bromoenamines (**44**)[51].

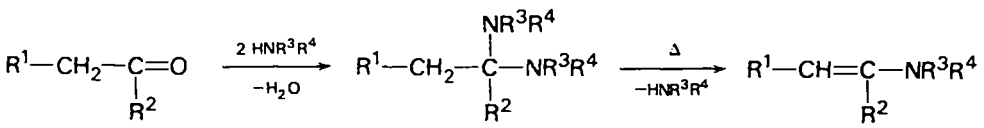
Enamines of Sn[52], Si[53] and P[54] are also known.



(44) (45)

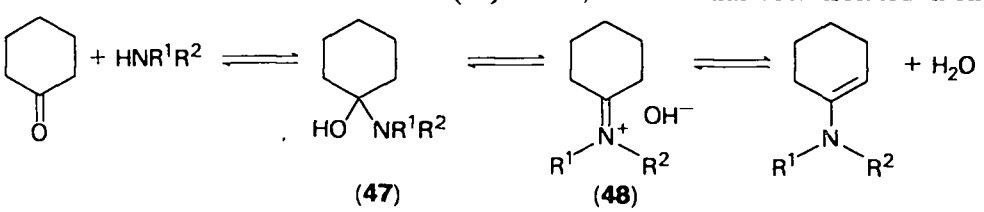
5. *Mechanistic and structural aspects in enamine synthesis*

Aldehyde enamine formation occurs through *N,N*-aminal intermediates (**46**) which have been isolated in some cases[55,56].



(**46**)
R^2 = H, alkyl

On the other hand, the intermediacy of **46** in the formation of ketone enamines has been evidentiated only in a very few cases[14a]. The possible pathway for cyclic enamine formation involves intermediacy of the *O,N*-aminal (**47**) with subsequent formation of the iminium intermediate (**48**). An *O,N*-aminal has been isolated in one

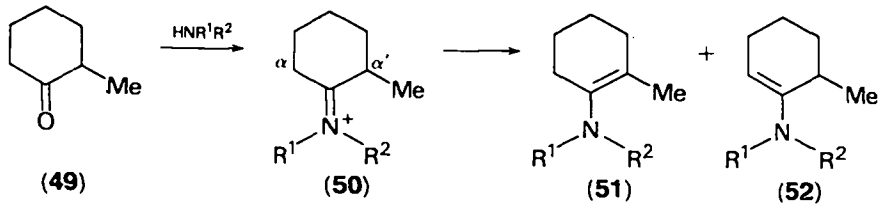


(**47**) (**48**)

case[17], namely in the addition of aziridine to cyclohexanone in benzene. Unfortunately since in this case the reaction does not proceed towards enamine formation, the general presence of *O,N*-aminals can be only postulated.

The rate of formation of enamines is strongly affected by the basicity and steric encumbrance of the base and the nature and environment of the carbonyl group[2b]. The higher reactivity in the formation of pyrrolidinoenamines compared to other acyclic and cyclic amines has been related to the higher stability of the iminium intermediate in accordance with Brown's postulate[57]. When the starting ketone is unsymmetric, as for instance 2-methylcyclohexanone (**49**), double-bond isomerism between the more and less substituted forms **51** and **52** in the resulting enamines is possible[58]. According to Carlson and coworkers[59] they are formed at a different rate

from the corresponding iminium salt intermediate (**50**), owing to the different acidity of the α,α′-protons.



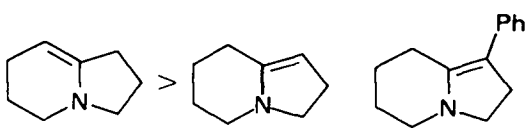
(**49**) (**50**) (**51**) (**52**)

Sometimes the W.W. method has been found to yield the product of kinetic control, namely the less substituted isomer, as in the case of enamines from alkyl methyl ketones[13,15a,60].

Although some data are reported for thermal isomerization[61], it seems that equilibration between the two double-bonded isomeric forms can be achieved only with added acid catalyst[61,62]. The isomeric ratio is affected by both the steric encumbrance of the ketone and the nature of the base. For instance, when the base is *N*-methylaniline, only the more substituted isomer is present[58,62,63]. On the contrary, pyrrolidine favours the less substituted form[2b,64], at least in the absence of other factors, such as extended conjugation[65].

In acyclic enamines derived from both aldehydes and ketones, *E*–*Z* isomerism is possible. Under conditions of thermodynamic control, the *E* isomer is generally the major or exclusive component, as determined by ^{1}H-NMR[41,66] and NOE (Nuclear Overhauser Effect) studies[67]. As usual, the presence of bulky groups may play an important role in determining the isomeric ratio.

In the heterocyclic enamines the double-bond isomerism is greatly influenced by the factors controlling the stability of a double bond in a ring, such as *exo* or *endo* positions[57], the size of the ring itself, and additional conjugation. For instance, the indolizidine system is a mixture of **53** and **54** in which **53** is the major component. The presence of a phenyl group at the enamine β-carbon in the small ring directs towards the exclusive formation of **55**, demonstrating in this case the prevalence of electronic factors over steric ones[68].

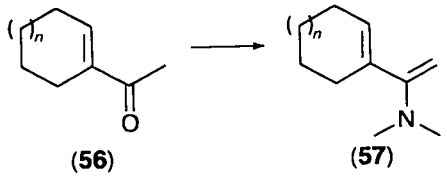


(**53**) (**54**) (**55**)

The syntheses of dienamines from some acyclic ketones such as **56**[15,31f] and from fixed *s-cis* unsaturated cyclohexanones (**58**)[31h,i] have been reported to afford the cross-conjugated isomers* as major (**59** > **60**) or exclusive (**57**) products. However, one case is known[31k] in which the fully conjugated isomer (**62**)* is formed preferentially from the *cisoid* unsaturated ketone **61**.

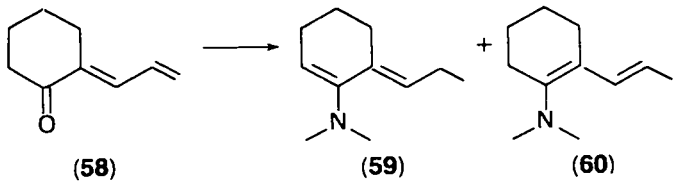
On the contrary, dienamines from fixed *s-trans* unsaturated cyclic ketones, such as **63**, appear as mixtures of fully *exo* (**64**) and *endo* (**65**) forms and cross-conjugated (**66**) forms, the former being predominant or exclusive, depending upon the

*The terms 'cross-conjugated' and 'fully conjugated' dienamines are used to designate the systems C=C–C=C and C=C–C=C–N– respectively.

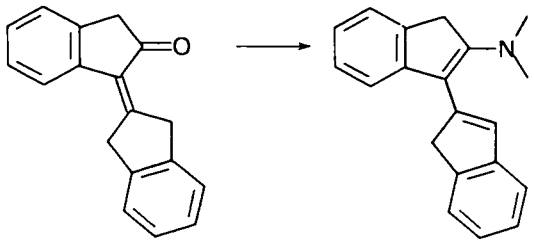


(56) (57)

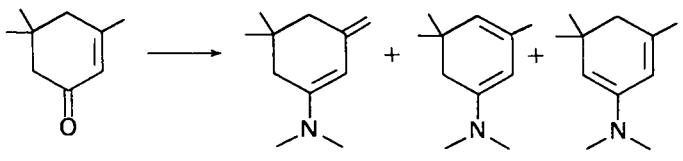
$n = 1, 2$



(58) (59) (60)



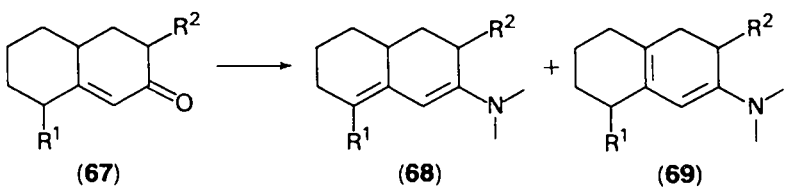
(61) (62)



(63) (64) (65) (66)

base[31a,c,d]. An equilibrium between the forms in the presence of pentacarbonyliron has been demonstrated[69].

In the case of the $\Delta^{1,8a}$-2-octalones (**67**), only the fully conjugated dienamines have been obtained, in which the heteroannular form (**68**) predominates over the homoannular one (**69**)[31a].

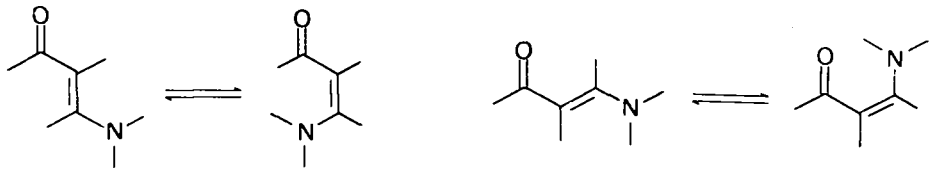


(67) (68) (69)

R^1, R^2 = H, H; H, Me; Me, H

Studies about the relative stability of the fully conjugated forms have shown that the *endo* isomer equilibrates into the *exo* form, in the presence of an acid or a base as a catalyst[70].

Linear enaminones can exist in *s-trans* and *s-cis* conformations, the *trans* and *cis* configurations being possible for each conformation:

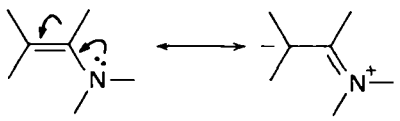


trans-s-trans *cis-s-trans* *trans-s-cis* *cis-s-cis*

The *trans* configuration is clearly indicated as the more stable by spectroscopic evidence, and the *cis* conformation seems to be favoured. Even so, no prediction can be made, since steric factors play an important role in determining the conformation[71].

B. Physical Properties

The extent of p–π delocalization in the N—C=C grouping affects markedly the structural, physical and chemical properties of enamines and their nucleophilic reactivity.



Theoretical studies[72] as well as experimental data of X-ray[73], photoelectron spectroscopy[74], and microwave analysis[75] have argued the degree of pyramidality in the enamine nitrogen atom, depending on the structure of the amine.

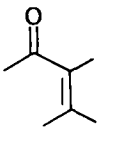
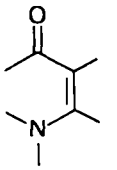
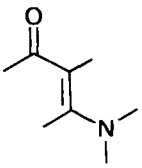
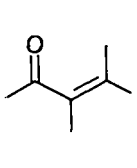
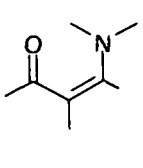
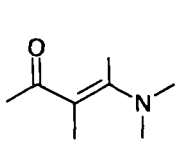
1. Basicity

Unfortunately, correct evaluation of basicity data obtained in aqueous solutions is affected by ambiguities arising from competition between *C*- and *N*-protonation, α- or β-substituent effects in the *C*- or *N*-protonated species, hydrolysis, and formation of by-products[76]. Therefore many authors, starting from different substrates, have arrived at the opposite conclusions. For instance, enamines derived from isobutyraldehyde were found to have aqueous-phase basicities lower than those of the corresponding tertiary amines[77]. This conclusion is opposite to that of Adams and Mahan[78] for pyrrolenine and piperideine systems as well as for cyclohexanone enamines[74b]. Actually, structural modifications in the enamine greatly affect the base strength order. Moreover, different results are obtained in different phases. Gas-phase basicities of some enamines from cyclohexanone and isobutyraldehyde have been measured by PES. Since the ionization energy decreases in the order enamines < related tertiary amines < secondary amines, the base strength increases in the reverse order[74b].

2. Infrared spectroscopy

The enamine double-bond stretching appears in the range 1620–1680 cm^{-1} with intensity varying with substituents. If an electron-withdrawing group is linked to the β-carbon, lowering in frequency is observed[79]. When both double-bond isomers are present, the more substituted form absorbs at higher frequency and lower intensity than the corresponding less substituted one, as a consequence of a minor degree of p–π overlap[79].

TABLE 1. Infrared frequencies, $\nu(cm^{-1})$, for *s-trans* and *s-cis* forms of enaminoketones in $CHCl_3$

	s-trans			*s-cis*		
						
		cis	*trans*		*cis*	*trans*
$\nu_{C=O}$	1660	1615	1595	1685	1640	1620
$\nu_{C=C}$	1635	1585	1550	1620	1565	1530

Like conjugated dienes, dienamines show two absorption bands in the range 1630–1610 and 1600–1575 cm^{-1} (film) for fully and cross-conjugated cyclic dienamines[31d] and 1680–1670 and 1650–1630 cm^{-1} ($CHCl_3$) for linear dienamines[31f]. In both cases, the low-frequency band is more intense.

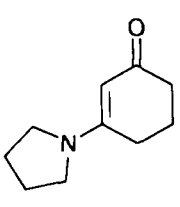
Linear enaminoketones have been studied extensively[71,80]. It has been suggested[71e] that the infrared differences between the *s-cis* and *s-trans* forms (Table 1) are due to a greater coupling between $\nu_{C=O}$ and $\nu_{C=C}$ in the *s-cis* conformer, rather than to a different conjugation. A distinct value for frequency range characterizes each conformation, which can be also applied to fixed forms.

3. *Ultraviolet spectroscopy*

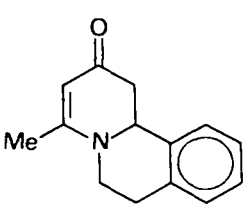
Enamines show an absorption band at about 230 ± 10 nm (ε_{max} 5000–9000). A bathochromic shift to 270–280 nm (ε_{max} 19,000–26,000) is observed for heteroannular dienamines[81].

The $\pi \rightarrow \pi^*$ transitions in enaminoketones with *cis-s-trans* structures occur at longer wavelengths than those of the *trans-s-trans* compounds, the extinction coefficients of the former being ca. 10,000 l mol^{-1} cm^{-1} smaller than those of the latter[71b,d,80b,82]. For instance, fixed *trans-s-trans* structures such as **70** absorb near 305 nm (ε_{max} 30,000–40,000), while the fixed *cis-s-trans* conformations **71** and **72** absorb between 320 and 330 nm (ε_{max} 16,000–17,000).

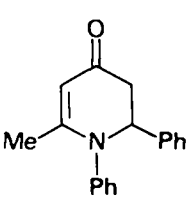
A shift of the highest intensity band to higher wavelengths has been observed for 2-acetyl-1-morpholino-cycloheptene (**73**) and -cyclooctene (**74**)[83].



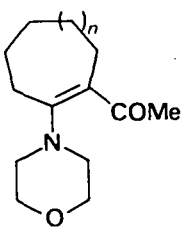
(**70**)



(**71**)



(**72**)



(**73**) $n = 1$

(**74**) $n = 2$

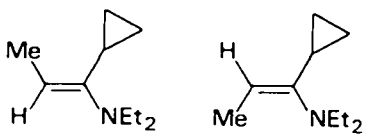
4. Nuclear magnetic resonance spectroscopy

The conformation and degree of p–π interaction between the nitrogen lone pair and the enamine double bond have been studied by ^{1}H-[31a,38f,58,66a,67,70,71a,c,84], ^{13}C-[85] and ^{15}N-NMR[86] spectroscopy. It is generally accepted that the chemical shifts of vinylic protons, of β-carbon and of nitrogen, being correlated with electron density, reflect the degree of p–π overlap.

a. ^{1}H-NMR. The enamine vinylic proton signal is observed in the range 4.0–6.0 δ from TMS as internal standard[87]. In particular, cyclic enamines absorb between 4.0 and 4.75 δ with the exception of *N*-methyl-*N*-phenylaminocyclohexene, whose olefin proton signal appears at 5.4 δ[87].

The observed values within the general range are due to the influence of many factors, such as amine component, steric and electronic effects of the substituents and, for cyclic enamines, to the ring-size effect[58,84d].

The *E* and *Z* isomers in acyclic enamines can be characterized and their ratio determined by ^{1}H-NMR. The vinylic proton signal of the *E* isomer in fact usually resonates at higher field than that of the *Z* form, as a consequence of steric interactions which in the latter prevent extended p–π conjugation[67,84b–e]. For instance in 1-*N*,*N*-diethylamino-1-cyclopropylpropene the vinylic proton of the *E* isomer (**75**) resonates at 4.58 δ, whereas in the *Z* form (**76**) it appears at 4.97 δ.



(**75**) (**76**)

When the α-carbon bears an aryl group, any variation in the aromatic substituent affects the chemical shifts of the vinylic protons in the *Z* isomers to a greater extent than those of the *E* isomers[66a]. As a result, the olefinic protons of the *Z* isomers (**78**) resonate in a much wider range than that of the *E* isomers (**77**).

(**77**) (**78**)

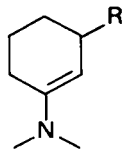
4.44–4.80 δ 4.95–6.00 δ

Ar = Ph, *p*-$MeOC_6H_4$, 2-, 3-, and 4- pyridyl, 2-thienyl, 2-furyl

Among cyclic enamines, the seven-membered ring offers the greatest conformational hindrance to conjugation, due to the high value of the vinyl proton chemical shift, whatever the base. This is in fact the highest value in the whole series[58,84a,87]. As to the effect of the amine, the vinyl proton chemical shift is directly related to the order of increasing nitrogen lone-pair delocalization, i.e. pyrrolidine > NR_2 > piperidine > morpholine > NRAr.

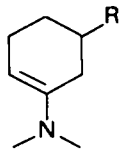
In the 3-substituted cyclohexanone enamines, the olefinic protons of the Δ^1 isomers (**79**) resonate at lower field than those of the Δ^6 isomers (**80**) as a consequence of the electron-releasing effect of the alkyl substituent[88].

In dienamines, β-vinyl proton signals of the *s-trans* isomers such as **81** and **84** are observed at lower field than those of their *s-cis* counterparts **82** and **85**, respectively, both isomers resonating at lower field with respect to the related simple enamines **83** and **86**[31a,d].



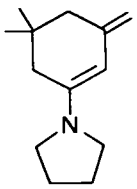
Δ^1

(79)



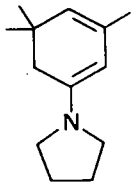
Δ^6

(80)



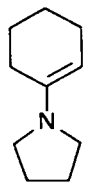
(81)

4.97 δ



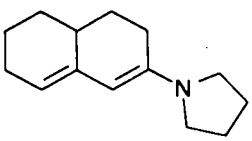
(82)

4.34 δ



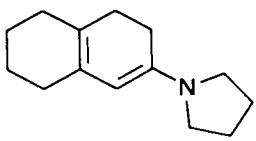
(83)

4.16 δ



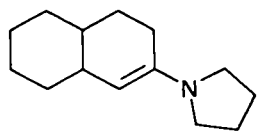
(84)

4.88 δ



(85)

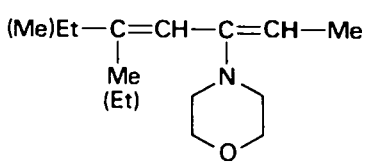
4.23 δ



(86)

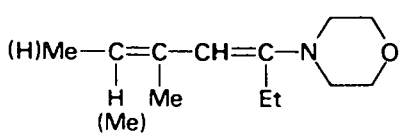
4.13 δ

On the other hand, β-vinylic protons of cross-conjugated enamines, as for instance **87** and **89**, are observed at higher field than their corresponding fully conjugated isomers **88** and **90**, respectively, regardless of the *E*–*Z* configuration, base and solvent used[31d,f,h].



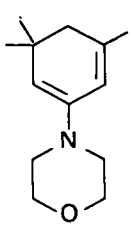
(87)

E 4.54, *Z* 4.50 δ



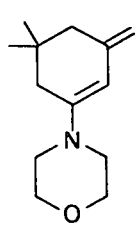
(88)

E 4.86, *Z* 4.74 δ



(89)

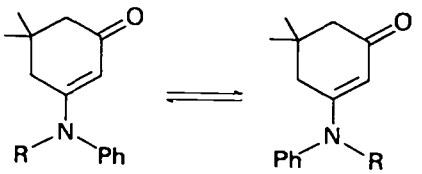
4.37 δ



(90)

5.32 δ

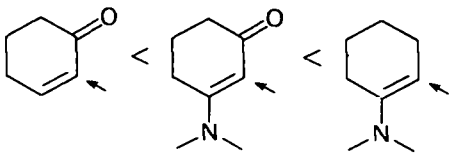
In acyclic, cyclic and heterocyclic enaminoketones, the olefinic proton resonates in the relatively small range 5.0–6.0 δ, differences in chemical shifts being observed even for **a–b** rotamers, as in the case of 5,5-dimethyl-3-(*N*-alkyl, *N*-phenyl)amino-cyclohex-2-en-1-one (**91**)[71d].



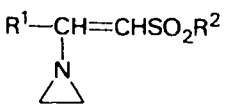
(**91a**) (**91b**)

Studies based on the analysis of J(HH) and $J(^{13}CH)$ coupling constants[71c] and on theoretical calculations[71d] of vinyl proton chemical shift for a series of enaminones, have been carried out. In the latter investigation, the conformations of nonrigid molecules can be deduced from the differences between the calculated and observed δ values.

All the general considerations made for cyclic enamines also hold for cyclic enaminoketones. In general, the vinyl proton signal is observed at lower field than that of the simple enamine, and at higher field than that of the corresponding α,β-unsaturated ketones[82b].



Linear enaminosulphones derived from aziridine show the vinyl proton signal in the range 5.0–6.0 δ, the *E* isomers resonating 0.12–0.19 ppm downfield of the *Z* isomers[38f].



E 5.30–6.03 δ

Z 5.22–5.92 δ

R^1 = H, Me, Et, *i*-Pr, *t*-Bu, Ph

R^2 = *p*-MeC_6H_4

b. ^{13}C-NMR. Several enamines derived from linear aldehydes and ketones have been examined[85a–c]. Among enamines derived from aldehydes with no β-hydrogen, the β-carbons in the morpholino derivatives resonate in the range 120–132 ppm, and in the range 105–126 ppm for the pyrrolidino and piperidino derivatives. Ketone enamines show the β-carbon signal between 90 and 120 ppm.

In both series the *E* isomer β-carbons appear at higher field than those of the corresponding *Z* forms[85a]. The α-effect of the amine varies from +14 to +26 ppm and the β-effect from −5 to −40 ppm, the observed values being affected by substitution at both α- and β-carbon[85c].

The ^{13}C-NMR technique is particularly useful in stereochemical studies. For instance, in 2-methylcyclohexanone enamines, the preferential pseudoaxial conformation of methyl groups in the less substituted isomers has been assigned from a

comparison with the corresponding values of chemical shifts in methylcyclohexenes and cyclohexanone enamines[85d].

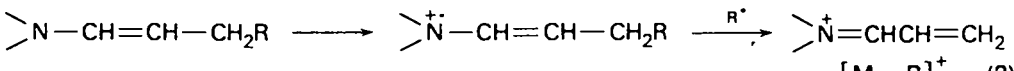
The β-carbons of cyclopentanone and cyclohexanone enamines appear in the range 93–98 and 94–100 ppm respectively, both in the order of decreasing values determined by the decreasing resonance of the base (morpholine < piperidine < diethylamine < pyrrolidine).

c. ^{15}N-NMR. For simple enamines the ^{15}N shifts occur in the range −303 to −348 ppm upfield of $D^{15}NO_3$. In cyclic enamines, the shifts of cycloheptanone enamines are downfield of the other cyclic enamines, consistently with the proton chemical shift[86b]. A low-field shift is observed with increasing electron p–π delocalization. This latter parameter, being correlated with the barrier to rotation around the C—N bond, can be evaluated from the difference in ^{15}N chemical shifts for enamines and related amines[86]. For conjugated enamines, the range extends from −326 to −298 ppm and for enaminoketones from −280 to −235 ppm.

5. Mass spectrometry

Mass spectra of some acyclic and cyclic enamines[89], dienamines[90] and enaminones[89a] have been reported.

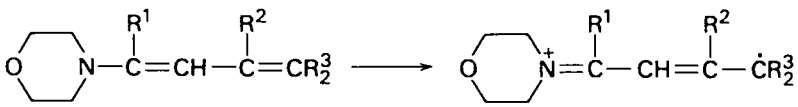
Aldehyde pyrrolidinoenamines afford $[M - R]^+$ ions, corresponding to the iminium ions formed by allyl fission (equation 3). $[M - H]^+$ ions are also present, arising by loss of hydrogen from the β-carbon of the base ring.



$[M - R]^+$ (3)

R = H, Me, Et, *n*-Pr

Cyclic ketone enamines give peaks due to the loss of several hydrogen atoms. At high temperature aromatization also occurs[89], but this does not seem to be a simple electron-impact phenomenon. Linear fully conjugated dienamines give base peaks due to the eniminium ion (equation 4). Cyclic dienamines derived from isophorone



(4)

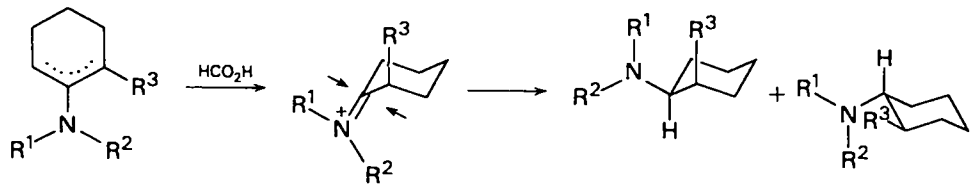
show, besides other characteristic peaks, a very strong $[M - Me]^+$ ion, which forms the base peak. Cross-conjugated dienamines show both the allylic and vinyl fissions, the latter giving rise to the $[M - Pr]^+$ ion as the base peak[90].

C. Reactions

1. Reduction

Reduction of enamines to the corresponding tertiary amines can be achieved in many ways, e.g. by catalytic hydrogenation[91], by sodium borohydride[91,92], diborane[91,93], formic[91,94] and hypophosphorous acid[95]. Reduction by sodium in liquid ammonia has been performed with success in the case of acyclic enamines[96] and dienamines[31c], but failed with cyclic enamines[31c]. Less familiar hydrides such as carbonyl hydridoferrates, $Fe_nH(CO)_m$ have also been used[97]. With aluminium hydrides or diborane, under suitable conditions, hydrogenolysis takes place instead of reduction, leading to alkenes[98]. Reduction by hydrides as well as by formic acid

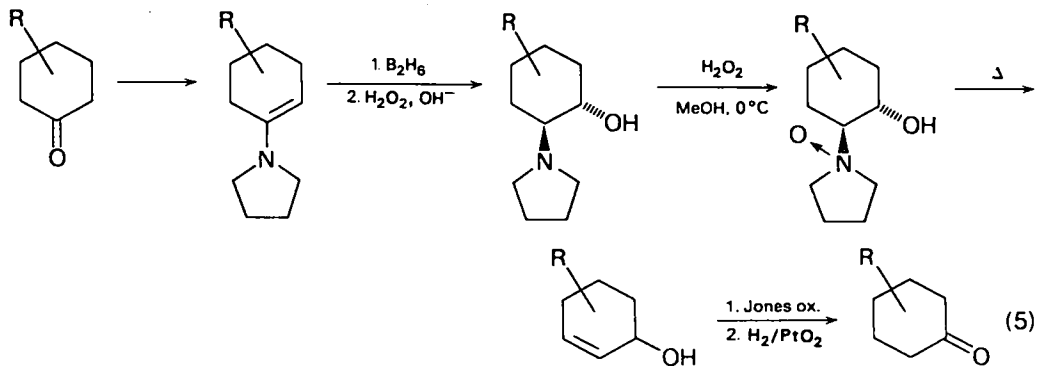
needs the prior formation of an iminium salt, such as **92**, to take place. Furthermore, formic acid operates with high stereoselectivity, the hydride transfer agent, namely the formate anion, approaching from the sterically less hindered side of **92**, to give the corresponding mixtures of tertiary amines **93** and **94**, in which the former predominate[94].



(92) (93) (94)

NR^1R^2 = piperidino, pyrrolidino; R^1, R^2 = Me, Me; R^3 = Me

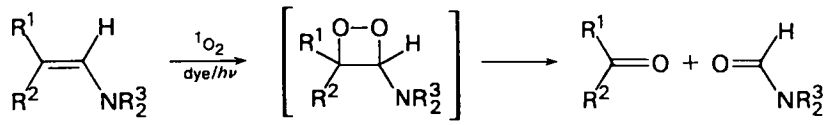
Hydroboration also allows a 1,2-carbonyl shift[93], as depicted in equation (5). The reaction is particularly useful in the steroid enamine field.



(5)

2. Oxidation

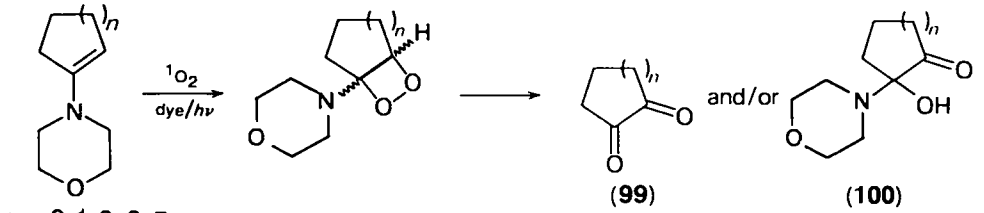
Enamines are generally very sensitive to oxidation. Besides metal oxidants[99,100], hydrogen peroxide[99,101], peracids[101], and electrochemical methods[102], photosensitized oxygenations have been studied carefully. By photooxygenation, acyclic enamines of the type **95** give the corresponding carbonyl (**97**) and amide (**98**) fragments[103]. The mechanism, involving formation of a dioxetane intermediate **96**, followed by C—C bond cleavage, has been proposed by Huber[104], and further demonstrated by Foote and coworkers[103b].



(95) (96) (97) (98)

R^3 = Me; NR_2^3 = piperidine R^1, R^2 = Me, Me; Ph, Ph; Ph, H

Several dioxetane intermediates have been isolated in the photooxidation of cyclic enamines, for which the major product is an α-diketone (**99**), in some cases accompanied by a keto alcohol (**100**)[105].



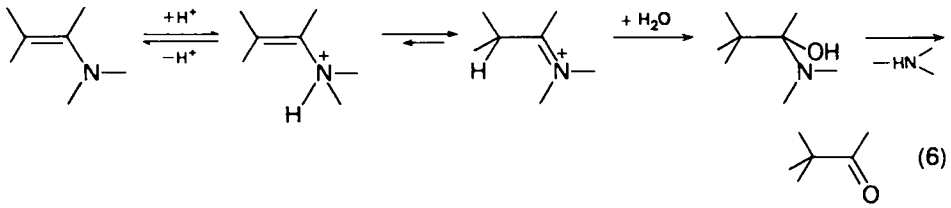
(99) (100)

$n = 0,1,2,3,7$

Opening of the dioxetane ring has been postulated to occur by a two-step biradical mechanism[106], although theoretical studies are in favour of a symmetry-forbidden nonradical mechanism through a zwitterion intermediate[107].

3. *Protonation and hydrolysis*

In the theoretical studies of protonation, vinylamine has been taken into account as the simplest model of enamines[72a,b]. These studies support the experimental observation that protonation of enamines first occurs at nitrogen[108]. The resulting enammonium salts have been isolated in some cases, under suitable conditions[109]. Their rearrangement into the corresponding iminium salts* has been followed by means of ^{1}H-NMR and IR techniques[109]. Finally, they undergo hydrolysis to the corresponding carbonyl compounds (equation 6).



(6)

Kinetic studies on the hydrolysis of acyclic enamines have been carried out in the range H_0 −3 to pH +14, at 25°C[111]. The rate-determining step has been found to be the general acid-catalysed *C*-protonation, above pH 5. From pH 5 to 0, hydration of the iminium ion is rate-determining, and for $H_0 < -1.3$, deamination becomes rate-limiting. The rate of hydrolysis is affected by the buffer used[111] as well as by steric effects present in the molecule[112].

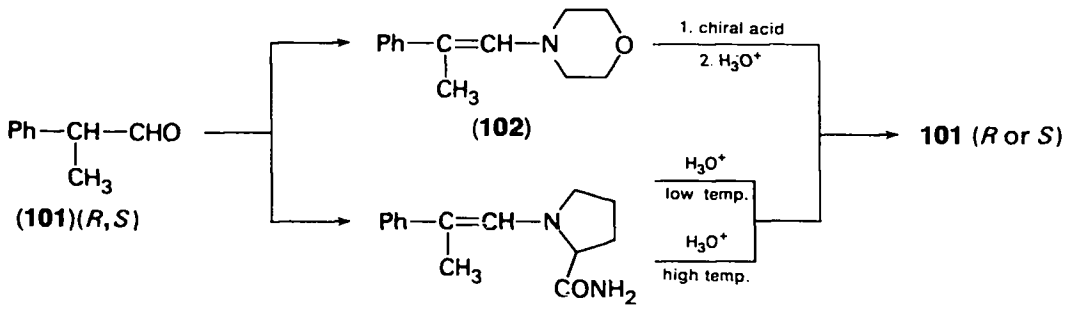
The stereochemical implications relative to the possible diastereoisomerism in the final carbonyl compounds have been studied carefully. If the two stereoisomers are formed in equal amounts, this could be ascribed to the low stereoselectivity in the *C*-protonation of the parent enamine, which would reflect the low degree of rehybridization of the β-carbon in the transition state[113]. This latter would be reactant-like, as in the case of 2-methyl-4-*t*-butylcyclohexanone and 2,6-dialkylcyclohexanone enamines[62].

On the other hand, high stereoselectivity is observed if the transition state is product-like. As a consequence, the resulting carbonyl products would reflect the stability of their related iminium salts[114]. This different stability of the iminium salts has been exploited to prepare enamines under kinetic control, by regioselective deprotonation of the salts themselves[59].

*Stable iminium salts have been treated extensively by Paukstelis in a review concerning especially their nucleophilic reactivity[110]. A comprehensive book, surveying their synthesis, structural aspects, physical properties, and reactivity has also been published[23b].

For dienamines a generally accepted mechanism involves initial *N*-protonation, followed by successive proton shift to β- and δ-carbons. However, in this rearrangement, an important role is played by both the substrate and the acid[6e]. On the contrary, conjugated enaminoketones are generally protonated on oxygen[6f], although some cases are reported[115] in which *C*-protonation occurs. The kinetics of their hydrolysis is however much more complex than that of simple enamines[116].

Optical activation of carbonyl compounds has been achieved by enantioselective protonation of the morpholinoenamine (**102**) of racemic α-phenylacetaldehyde (**101**) by means of chiral acids[117,118] or by protonation of a chiral enamine, such as **103**, by achiral acids, followed by hydrolysis[119].



Two mechanisms are invoked to account for the strong dependence of the reactions on temperature and solvent. At low temperatures, the optical activation is controlled kinetically at the enammonium salt stage, whereas at high temperatures it is controlled thermodynamically at the iminium salt stage[118b,119]. Furthermore, the asymmetric induction has been shown to depend on the geometric isomerism of the parent enamines[118a].

4. Alkylation

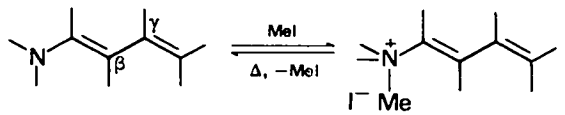
The main goal of alkylation of enamines is to obtain monoalkylated carbonyl compounds. To achieve this a suitable choice of the amine component in the parent enamine, temperature, solvent and stoichiometry of the electrophile must be made[2b,6a].

a. Reaction with alkyl halides. Since there is a competition between *N*- and *C*-alkylation, only alkylations by activated electrophiles, such as benzylic[6a,120], allylic[6a], propargylic[6a,121] and other unsaturated halides[122], as well as α-halocarbonyl compounds[6a,123] are satisfactory in affording the desired *C*-alkylated products. In the latter case, however, some caution must be taken when an additional electrophilic centre is present[124].

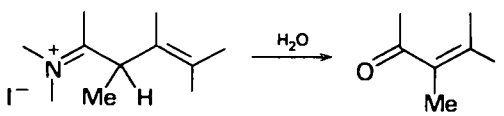
With unactivated halides, and with aldehyde enamines in particular, only *N*-alkylation is observed[6a,125]. However, formation of *N*-alkylated products can be minimized or avoided by the use of alkyl halides or trialkyloxonium salts and enamines in which the amine component is sterically hindered[6a,126]. In cyclic enamines, the size of the rings of both the olefin and amine play an important role in determining the *C*/*N* alkylation ratio[127].

In some cases and under certain conditions, *N*-alkylation is reversible. The *C*-alkylated product can in fact be formed from the *N*-alkylated product, obtained from propargylic or allylic halides, by a [3,3]sigmatropic rearrangement[6a,121b] and by an N → C shift, promoted in other cases by strong heating[125,127–129].

Alkylation of dienamines (**104**) by methyl iodide takes place at nitrogen exclusively[130]. Subsequent heating under very drastic conditions affords the β-alkylated derivative. In this case, mechanistic considerations concerning the N → C alkyl transfer are in favour of the reversibility of formation of the dienammonium salt (**105**), to give the corresponding iminium salt (**106**). Hydrolysis leads to the α-substituted α,β-unsaturated ketone (**107**)[130].



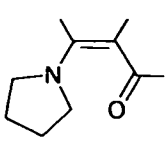
(**104**) (**105**)



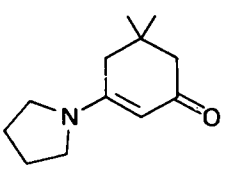
(**106**) (**107**)

Reactions of dienamines with allylic halides are strongly dependent on the base. With pyrrolidinodienamines direct *C*-alkylation occurs, whereas in the morpholino and piperidino systems, *N*-alkylation takes place, followed by aza-Cope rearrangement leading to the β-*C*-alkylated products and in some cases also to the δ-*C*-alkylated product, by a second rearrangement accompanied by double δ-*C*-alkylation product[131].

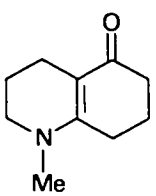
As to enaminoketones, only acyclic systems (**108**)[132] afford the *C*-alkylated products with certain alkyl halides, since they can assume the *s-cis* conformation. In fact, cyclic[133] and heterocyclic[134] enaminones (**109**) and (**110**) respectively, which are in *trans* geometry, exhibit *O*-alkylation as the sole path of reaction, regardless of the type of solvent. *Cis* heterocyclic enaminones (**111**) may undergo both *C*- and *O*-alkylation, depending upon the solvents.



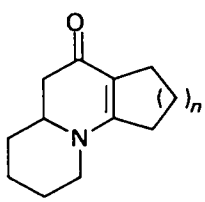
(**108**)



(**109**)



(**110**)

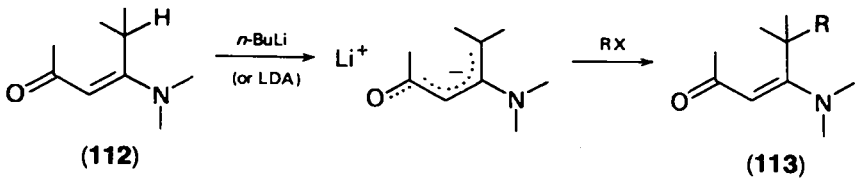


(**111**)

n = 1, 2

Among alkylations of particular interest is the allylic alkylation of acyclic and cyclic enaminoketones (**112**), performed by successive treatment with *n*-butyllithium[135] or lithium diisopropylamide(LDA)[136] and an alkylating agent, at low temperature, to give allylic substituted enaminones (**113**).

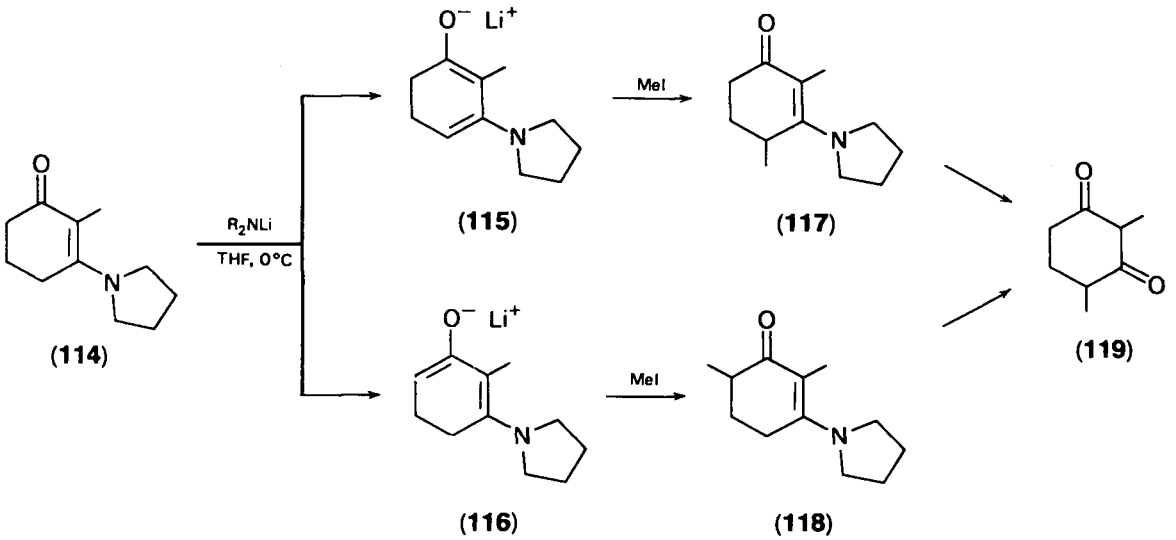
Controlled alkylations of enaminones, such as **114**, have been carried out by Reusch and collaborators[137] by the use of lithium isopropylcyclohexylamide in various amounts. Its excess, for instance, favours the formation of the cross-conjugated



(112) (113)

R = Me, *n*-Pr, allyl, benzyl

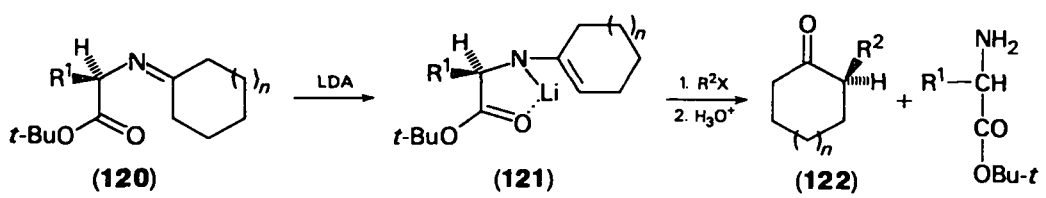
O-lithiated enamine (**115**) over the fully conjugated one (**116**). Alkylation by methyl iodide leads to **117**. Enamine **118** would be formed preferentially with an excess of the parent enaminone[137]. Both **117** and **118** afford by hydrolysis the same substituted β-diketone (**119**).



(114) (115) (116) (117) (118) (119)

Earlier studies on the reactivity towards electrophiles of the allylic position in acyclic enaminones had been already reported[138].

The first enantioselective alkylations were carried out by Horeau[139] and Yamada[140]. The former used a metalloenamine, while the latter employed chiral[140a] or lithiated[140b] enamines. Modifications of these methods have led successively to a high degree of asymmetric induction[141], whose efficiency has been still increased by the use of chiral metalloenamines. Asymmetric alkylations of acyclic[48a,c] and cyclic carbonyl compounds[48b,142] have been accomplished via chiral lithiated enamines. The key step in these syntheses appears to be the rigidity of the chiral metalated enamines **121**, obtained from the suitable ketimine **120**[48b,142]. This rigidity is in fact



(120) (121) (122)

n = 0, 1; R^1 = *i*-Pr, *t*-Bu

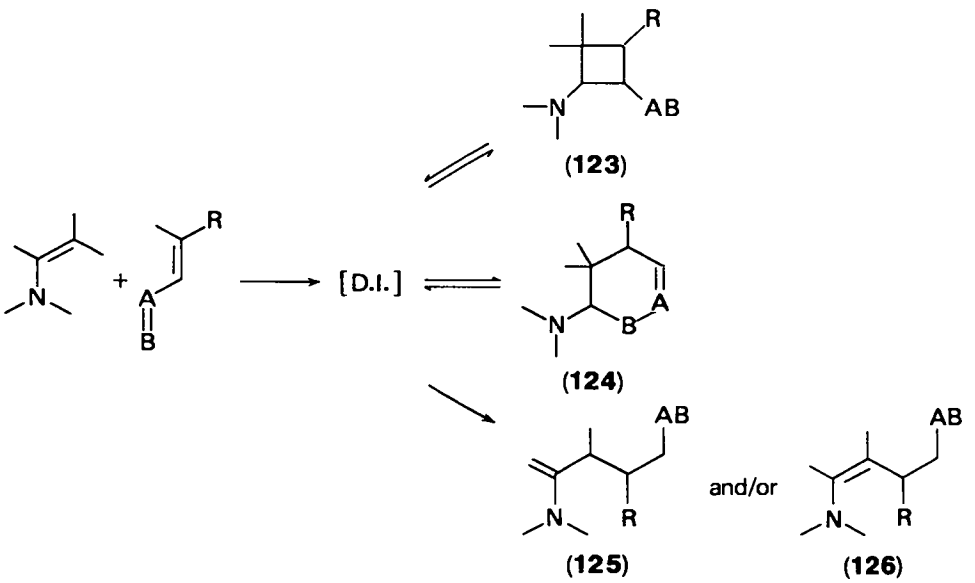
TABLE 2. Asymmetric synthesis of α-alkylated cyclohexanones (122)[a]

R^1	R^2X	Isolated yield (%)	α_D^{25} (degrees) (obs., in MeOH)	Optical yield (%) (config.)
i-Pr	Me_2SO_4	59	+11.7	84(*S*)
i-Pr	$CH_2{=}CHCH_2Br$	71	+11.6	73(*R*)
t-Bu	Me_2SO_4	65	+12.4	98(*S*)
t-Bu	MeI	57	+12.3	97(*S*)
t-Bu	$CH_2{=}CHCH_2Br$	75	+12.0	84(*R*)
t-Bu	*n*-PrI	70	+24.7	97(*S*)

[a]Reproduced by permission of Pergamon Press Ltd. from S. Hashimoto and K. Koga, *Tetrahedron Letters*, 573 (1978).

responsible for the stereoselective attack of the alkyl halide and hence for the enantiomeric excess in the final alkylated ketone (**122**) (see Table 2). This method has also been applied to the asymmetric induction of 2-methyl-2-phenyl-cycloalkanones[48b].

b. Reaction with electrophilic olefins. Reaction with olefins activated by the presence of electron-withdrawing groups may result in the formation of several products, such as [2 + 2]- and [4 + 2]-cycloaddition adducts, **123** and **124**, respectively, or substituted linear enamines **125** and/or **126**, sometimes simultaneously, depending on the substrate, the electrophile, temperature and solvent[6a,143].



D.I. = dipolar intermediate

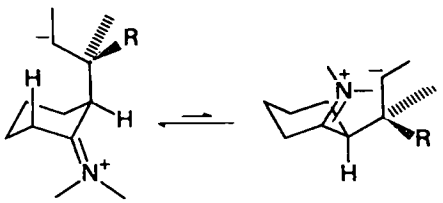
According to Stork[2b], *N*-alkylation, if present, is reversible and hence has no effect on the final isomeric ratio. A stepwise mechanism is generally accepted for the formation of both the [2 + 2][144]- and the [4 + 2][144b 145]-adducts, although a more or less degree of concertedness has been postulated by Epiotis[146] for the majority of the cyclization reactions, to explain the origin of stereoselectivity in the products. In

some cases there is evidence for dipolar intermediates – by their trapping by an excess of the electrophile[144c,147] or by the use of tetracyanoethene (TCNE)[148] with formation of carbocyclic compounds. However, according to some authors[144b,149] this does not provide a conclusive proof about the exact position of such an intermediate in the reaction profile.

Formation of Michael-type adducts proceeds through dipolar intermediates and is regarded as irreversible[143]. However at least one case is reported[150] for which the reversibility of a trisubstituted nitroalkylated enamine is proved. Another case is known[151] in the reaction of aminocycloalkenes with 2-phenyl-3*H*-indol-3-one.

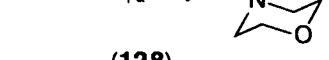
On the contrary, most of the [2 + 2]- and [4 + 2]-adducts undergo retrocyclization[143,145,152] and interconversion[148,153] reactions, under appropriate conditions.

The stereochemical course of the alkylation of unhindered cyclic enamines by electrophilic olefins is strongly affected, *inter alia*, by the steric situation of the electrophilic centre in the olefin itself[154]. In fact, if a bulky group is present, the initially formed dipolar intermediate is forced into that conformation (**127**) (ax.) in which the steric interactions are minimized, i.e. axial orientation of the entering group [to avoid the $A^{(1,3)}$ strain[155] with the base, present in **127** (eq.)], with the bulky group *exo* and the carbon anion *endo* to the carbocyclic ring[156].



(**127**)(ax.) (**127**)(eq.)

This conformation accounts for the formation of trisubstituted enamines, via a six-membered cyclic transition state. The same situation applies also to biased enamine systems, in which the stereoelectronically favoured β-attack occurs[156b,d]. However, 4-*t*-butylmorpholinocyclohexene (**128**) undergoes both α and β-attack by the electrophile, even if the former attack is less usual[156c].

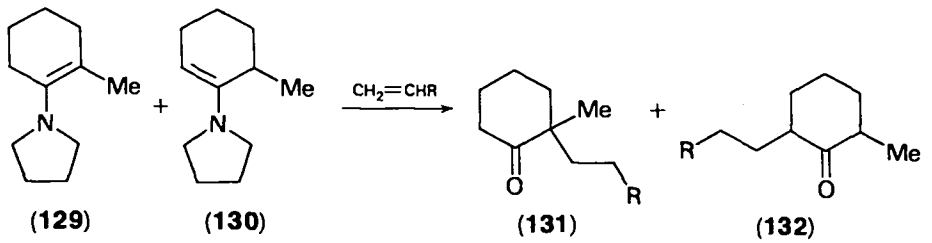


(**128**)

All these facts, however, do not exclude the formation of cyclic adducts for sterically hindered electrophiles also, as verified in some cases[145,149,156b,157].

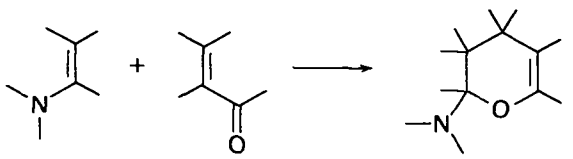
All these considerations can be applied to mild reaction conditions. Under forcing conditions, the stereochemical course appears to be more complex. For instance, pyrrolidinoenamines from 2-methylcyclohexanone, **129** and **130**, react with methyl acrylate and acrylonitrile, under reflux of the solvent, to give a mixture of 2,2- and 2,6-disubstituted products, **131** and **132** respectively, in both cases[158]. The ratio of the resulting products is related to the polarity of the solvent.

Reactions of α,β-unsaturated aldehydes and ketones with enamines result in the initial formation of dihydropyrane intermediates (**133**), which have been isolated in some cases[144b,145,159]. With α,β-unsaturated esters, cyclobutane adducts or alkylated enamines are formed[159].



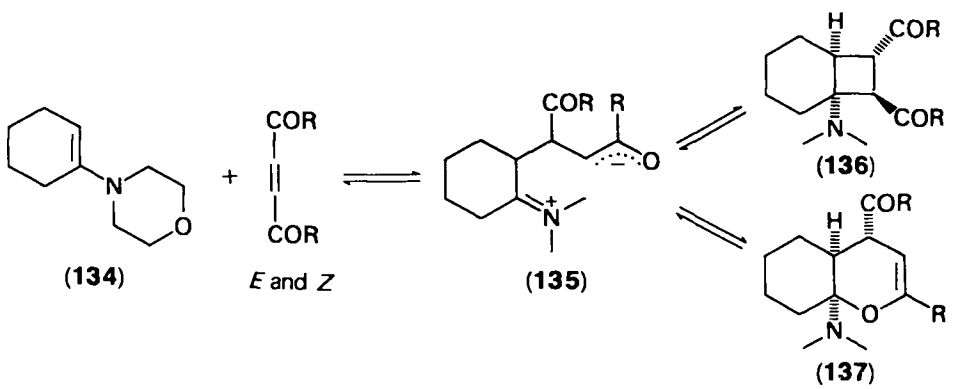
(129) (130) (131) (132)

R = CO_2Me, CN



(133)

The intermediacy of a zwitterion, such as **135**, in the reaction of α,β-unsaturated carbonyl compounds with morpholinocyclohexene (**134**) has been proved by Risaliti and collaborators[144a,145]. The same [2 + 2] adducts (**136**) have been obtained from dialkylmaleate and fumarate, while the same dihydropyrane systems (**137**) are formed from both the *E* and *Z* isomers of dibenzoylethene. Chemical methods[145] as well as X-ray analyses[152,156d,160] have shown the stereochemical features of these types of cyclic adducts.

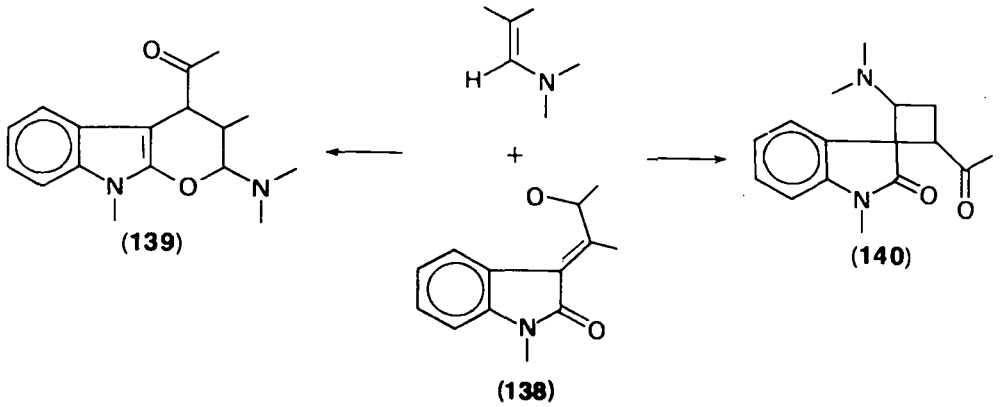


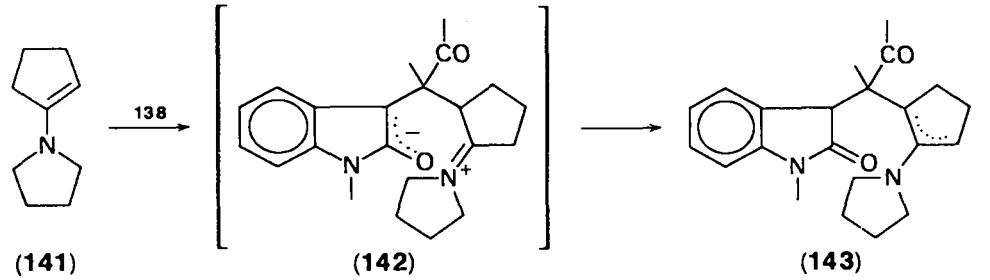
(134) *E* and *Z* (135) (136) (137)

R = OAlk, Ph

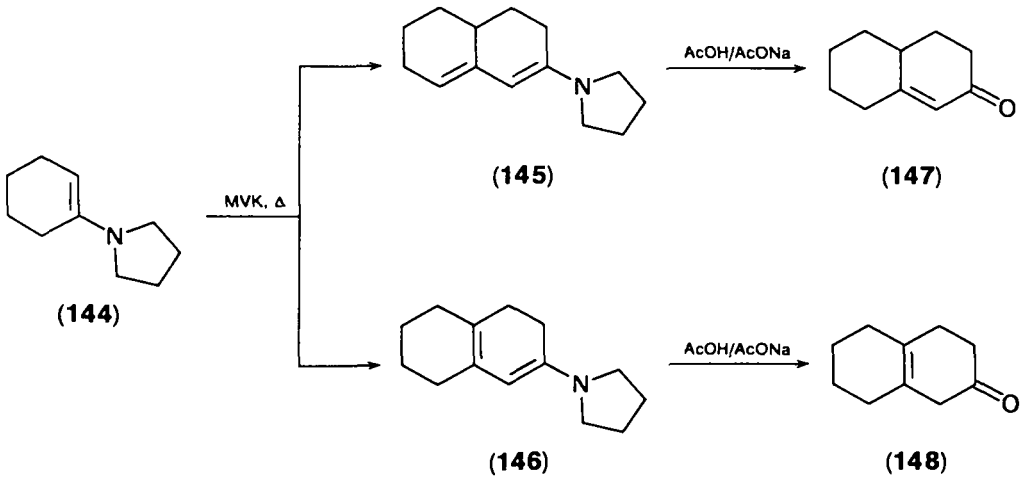
α,β-Unsaturated carbonyl systems bound to a heterocyclic ring, such as **138**, also react with enamines affording dihydropyrane derivatives (**139**), spiro compounds (**140**) or Michael-type adducts (**143**), depending upon the substituents present in the electrophile, the substrate and the solvent. Intermediacy of a zwitterion (**142**) in the formation of **143** from pyrrolidinocyclopentene (**141**) has been also supported by FO methods[144b,148c,d]. In polar solvents both **139** and **140** open into the corresponding Michael-type adducts through dipolar intermediates[148c].

Reactions between enamines and 4-arylmethylene-3-phenyl-isoxazolones and 4-arylmethylene)1,3-diphenylpyrazolones have led to Michael-type adducts as sole products[161].

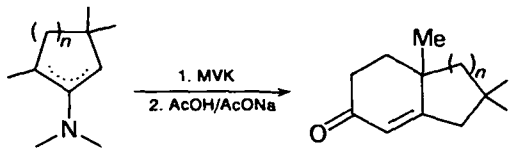




A particular modification to the Robinson annulation reaction has been brought about by Stork and coworkers[2b]. The condensation between pyrrolidinocyclohexene (**144**) and methyl vinyl ketone (MVK), carried out in refluxing benzene, leads to the formation of a mixture of $\Delta^{1,8a}$- and $\Delta^{4a,8a}$-octalones, **147** and **148** respectively, after hydrolysis of the resulting enamine mixture, **145** and **146**[2b,162].



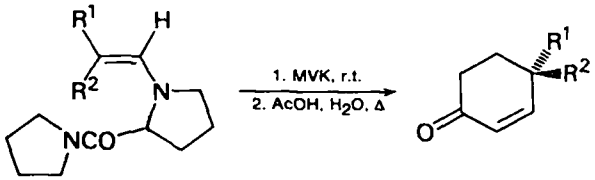
This reaction has been extended with success to the synthesis of natural products, such as alkaloids[163], terpenes[65a,164], and steroids[165]. An anomalous annulation reaction between 2-substituted cycloalkanone enamines (**149**) and alkyl vinyl ketones resulted in the main or exclusive formation of angular substituted octalones (**150**)[164c].



(149) (150)

$n = 1, 2, 3$

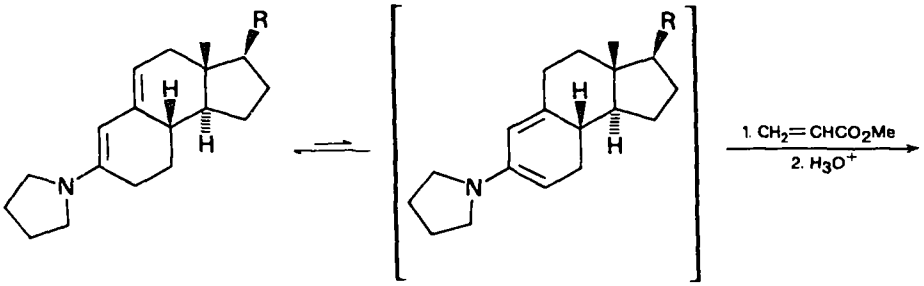
The Stork condensation has been also applied to asymmetric syntheses by Hiroi and Yamada[166]. In fact a series of chiral 4,4-disubstituted-2-cyclohexenones (**152**) has been prepared from MVK and a chiral enamine, such as **151**, and their absolute configurations determined[167]. By this method numerous optically active natural compounds have been synthesized[168].



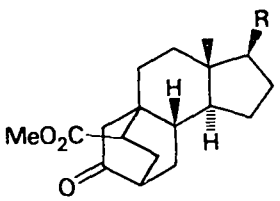
(151) (152)

Fluorinated carbonyl compounds with therapeutical properties have been prepared through reaction of acyclic and cyclic enamines with fluorinated alkyl vinyl ketones[169].

Michael-type addition reactions on heteroannular dienamines occur at the δ-carbon[165]. On the other hand, Diels–Alder-type cyclization reactions, with formation of **155**, have been observed[170] for fully conjugated heteroannular dienamines (**153**) in their reaction with methyl acrylate, through intermediacy of the homoannular form (**154**), as already found in the isophorone dienamines[171].



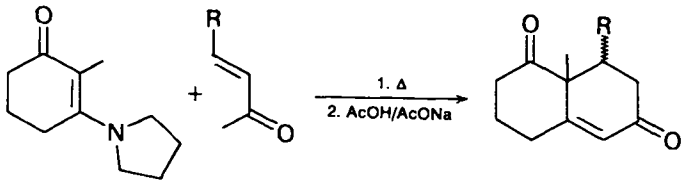
(153) (154)



(155)

Diels–Alder reactions on dienamines and α,β-unsaturated carbonyl compounds, as well as on enamines and electrophilic dienes have been carried out at high pressure (8–20 kbar)[172]. They proceed at room temperature and generally in higher yield and shorter time than the analogous thermally induced reactions.

Enaminoketones, such as 2-methyl-3-pyrrolidinocyclohex-2-en-1-one (**114**), undergo easy reaction with α,β-unsaturated ketones at the β-position, affording the bicyclic diketones **156**, after hydrolysis of the reaction mixture[65a].



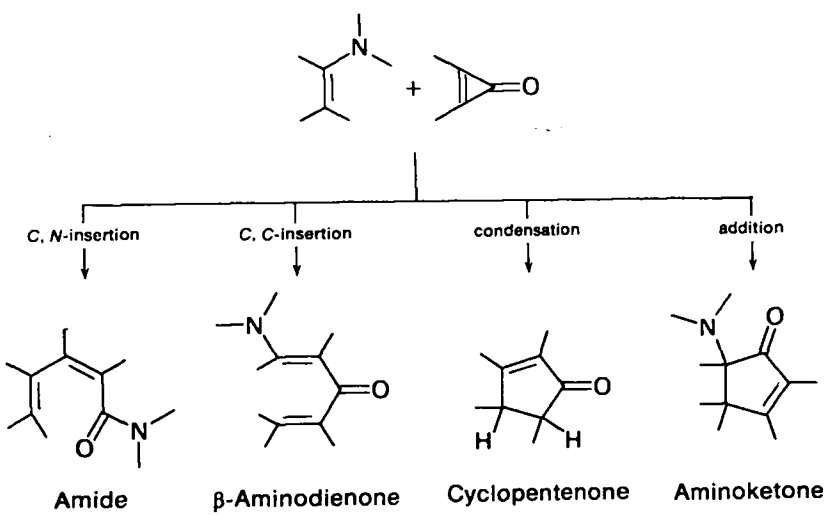
(**114**) (**156**)

Among the cyclic α,β-unsaturated carbonyl compounds, cyclopropenones[173], quinones[174] and tropones[175] have been examined in their reactions with enamines.

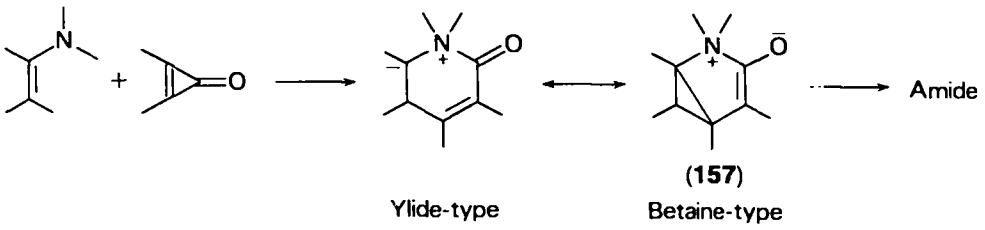
The first studies on the reactions of diphenyl cyclopropenone with enamines[173] were later extended to the study of a novel *C,N*-insertion reaction in a macrocyclic enamine by Dreiding and coworkers[176]. This group also found that substituted cyclopropenones with acyclic and cyclic enamines afford a variety of products, arising via *C,N*- or *C,C*-insertion, condensation and addition reactions (Scheme 1)[177].

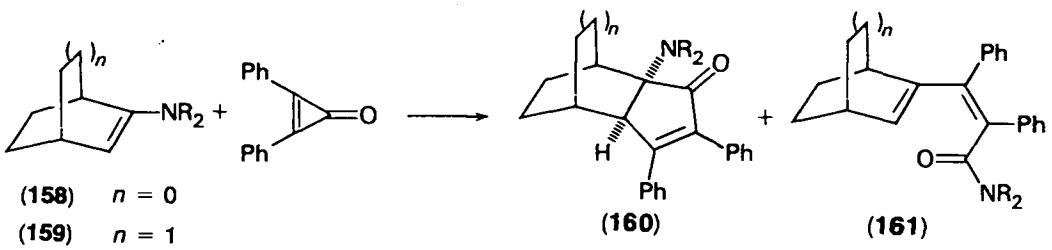
The presence of the betaine-type intermediates **157** in the formation of the *C,N*-insertion products was postulated[177a] and supported later by spectral analysis and chemical reactions[178].

Bicyclic enamines, such as 2-piperidino-2-norbornene (**158**) or 2-piperidinobicyclo[2.2.2]oct-2-ene (**159**), afford *exo* fused aminoketones (**160**) exclusively or in mixture with amides (**161**), in their reaction with diphenylcyclopropenone[179]. Enaminoketones also react with diphenylcyclopropenone to yield only *C,N*-insertion products[180].

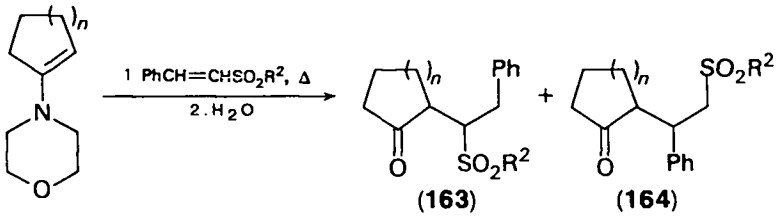


SCHEME 1





α,β-Unsaturated sulphones $R^1—CH=CH—SO_2R^2$ have been shown to react with enamines[181] affording cyclobutane and Michael-type adducts by attack of their electrophilic β-carbon onto the enamine β-carbon (R^1 = H, R^2 = Me, Ph). When R^1 = Ph, lack of regiospecificity is observed[182], since both the α- and β-carbon atoms of the sulphone undergo nucleophilic attack by the enamines, affording **163** and **164** respectively, in ratios varying with the solvent, reaction time and configuration of the olefin.

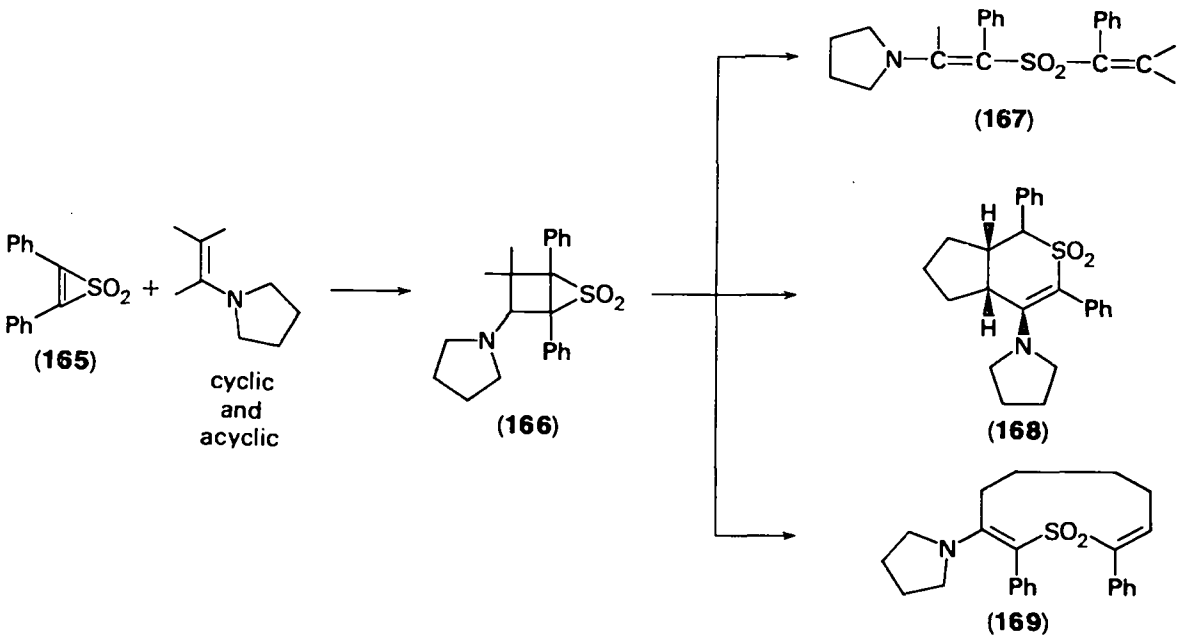


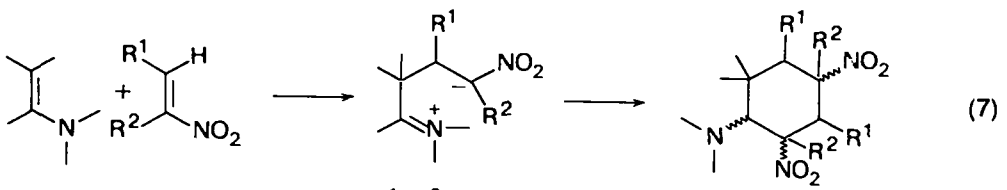
(**162**) n = 1
(**134**) n = 2

The reaction of 2,3-diphenylthiirene-1,1-dioxide (**165**) with acyclic and cyclic enamines is postulated to proceed via a stepwise mechanism, with initial formation of a cyclobutane intermediate (**166**), followed by opening to Michael-type adducts (**167**), heterocyclic systems (**168**) or ring-enlargement products (**169**), depending on the substrate[38a].

A variety of products can be formed in the reaction of enamines with nitro olefins[183] such as cyclobutanes[147a,156b,184], oxazines[15a,147b,150,157], Michael-type adducts[15a,147b,156,157,184] and also cyclohexane derivatives[147b,156a,184], the latter by double addition of the olefin (equation 7).

With cross-conjugated dienamines, derived from methylcycloalkenyl ketones, β-nitrostyrene yields 1:1 carbocyclic adducts as major products, together with small amounts of Michael-type adducts[15]. The structure of the resulting cycloaddition products is strongly affected by the size of the cycloalkene group and by the polarity of the solvent. The latter fact and the isolation of cyclic double-addition products would account for a stepwise mechanism[15b].



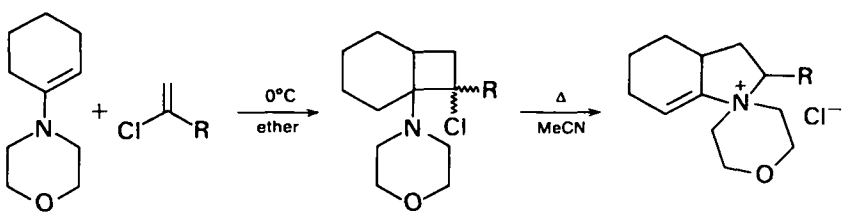


(7)

R^1, R^2 = H, Me; Ph, H

The expected stereochemistry but unusual regioselectivity has been observed in the reaction of β-nitrostyrene with pyrrolidino- and morpholino-enamines of 2-tetralone[185]. The exclusive formation of the 3-substituted pyrrolidino derivative and the main formation of the 1-substituted morpholino derivative has been explained in terms of a rapid equilibrium in the starting pyrrolidinoenamine and a slow equilibrium in the morpholino system[185].

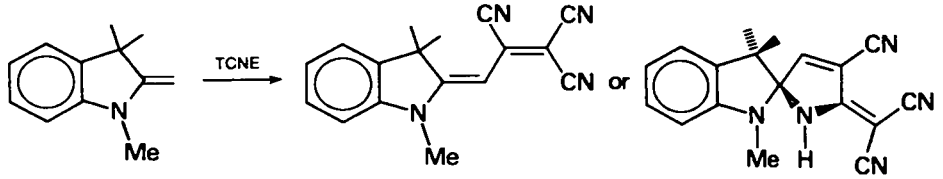
Some hyperactivated electrophilic olefins, such as α-chloroacrylonitrile and methyl α-chloroacrylate react with morpholinocyclohexene (**134**). Hexahydroindolium salts of the type **171** have been isolated in polar solvents, whereas cyclobutane adducts (**170**) were formed at low temperature in ether solution. The latter compounds are thermally unstable and easily convert into the former ones[186].



(134) (170) (171)

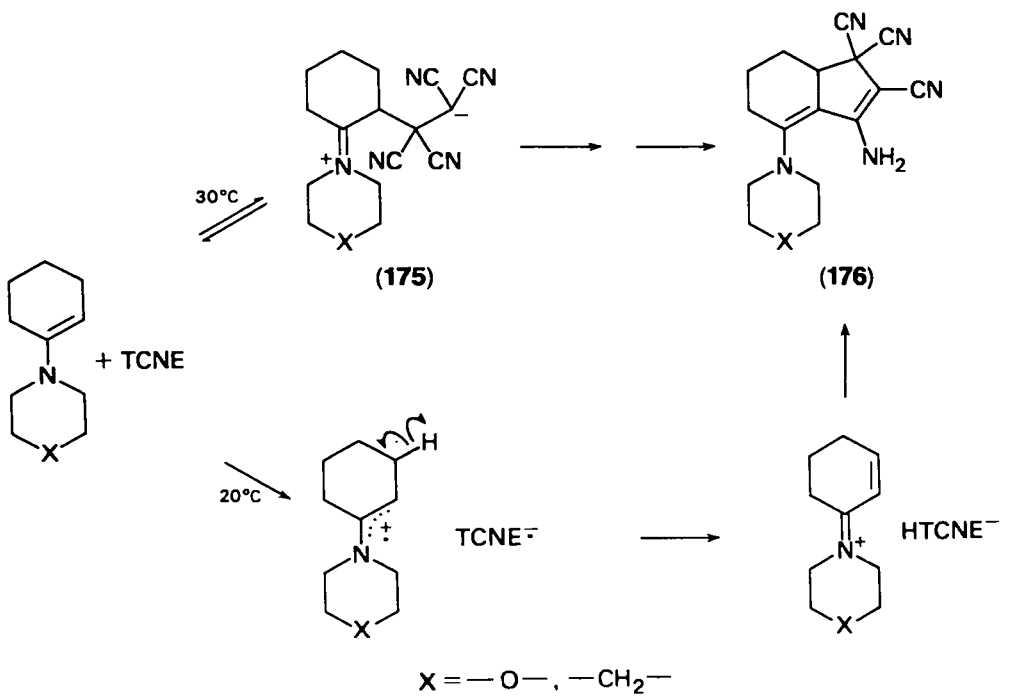
R = CN, CO_2Me

TCNE shows a varied reactivity towards enamines, dependent even on the order of addition of the reactants. In fact Fischer's base, i.e. 1,3,3-trimethyl-2-methylideneindoline (**172**), reacts with TCNE to give either a tricyanovinylation product (**173**) or a spiro compound (**174**)[187].



(**172**) (**173**) (**174**)

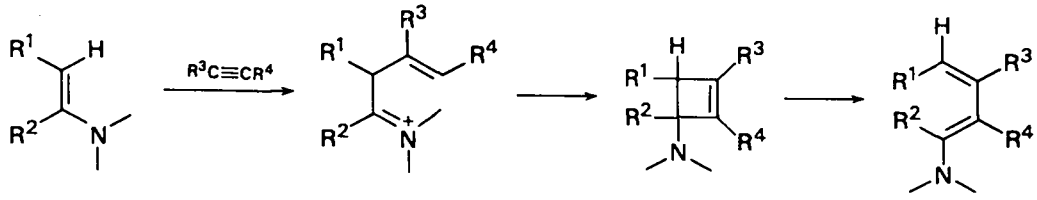
With cyclohexanone enamines, TCNE affords substituted tetrahydroindenes (**176**), via an unusual attack on the γ-position of enamines. Two mechanisms are envisioned, a stepwise and an electron-transfer one, at low and room temperature respectively[188]. In the former case, the zwitterion intermediate (**175**) has been proven by spectroscopic methods.



(**175**) (**176**)

c. Reaction with electrophilic alkynes. Activated alkynes react with enamines in apolar solvents to give cyclobutene adducts (**177**), through a [2 + 2]cycloaddition[189]. Subsequent rearrangement of **177** affords fully conjugated dienamines (**178**), which in the case of cyclic enamines are ring-enlargement products. Evidence exists of the presence of zwitterion intermediates[190], although a concerted mechanism is also possible, particularly in apolar and aprotic solvents[189b,c].

In polar solvents, such as methanol or acetonitrile, the reaction of acyclic and cyclic enamines with dimethyl acetylenedicarboxylate (DMAD) proceeds in a different manner, giving mixtures of ring-enlargement products (**178**) and pyrrolizine

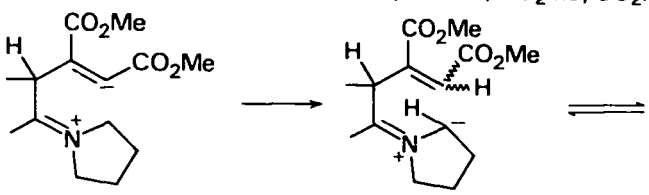


(177) (178)

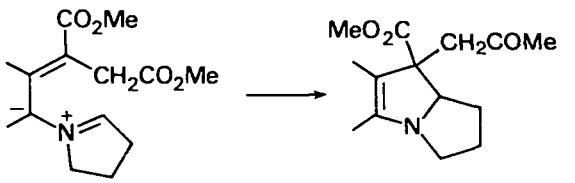
R^1 = SPh, OPh, Ph; R^2 = Ph

R^1, R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$

R^3, R^4 = H, CO_2Me; CO_2Me, CO_2Me



(179)

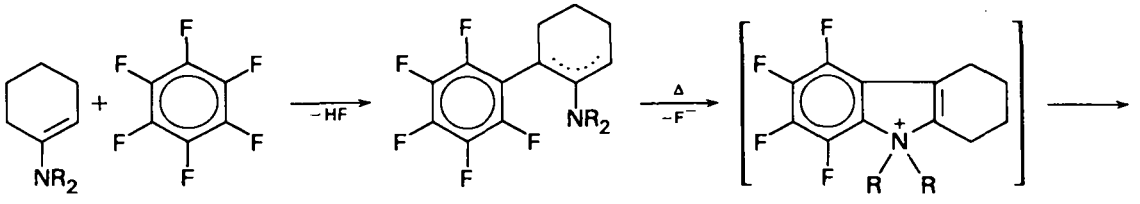


(180) (181)

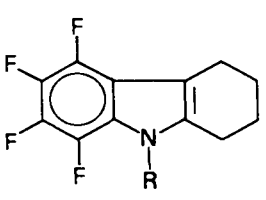
derivatives (**181**). The mechanism involves initial formation of an azomethine ylide (**179**) and subsequent intramolecular 1,5-cycloaddition in **180**[189c]. The enlargement reaction has been also applied to the synthesis of products of biological interest[191].

Perfluoroacetylenes have been employed in the reactions of enamines in a mixture of trifluorotrichloroethane and chloroform to give linear dienamines, detected by ^1H- and ^{19}F-NMR spectroscopy[192].

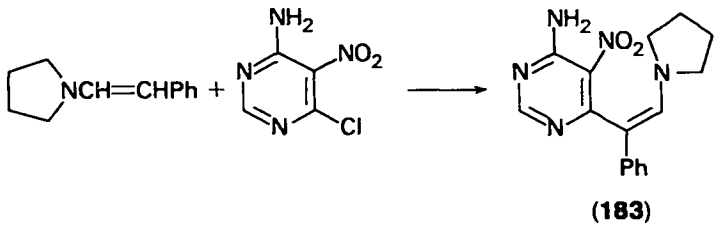
d. Arylation. Arylation of enamines with activated aromatic[193] and heteroaromatic[194] halides, *p*-benzoquinone derivatives[193a,195] and benzyne[193a,196,197] have been reported. Linear **182** and **183** and cyclic products **184** and **185** have been



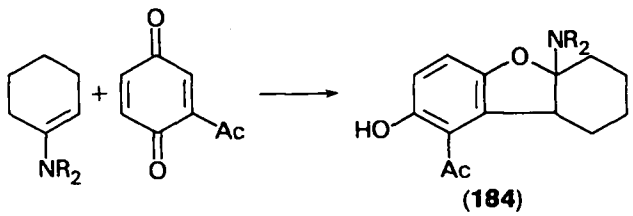
(182)



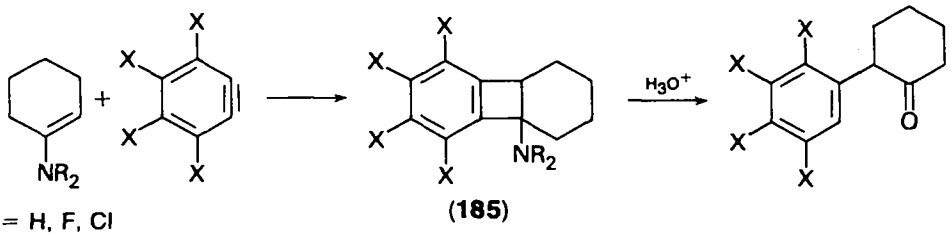
R = Me, Et, $-(CH_2)_4-$



(183)

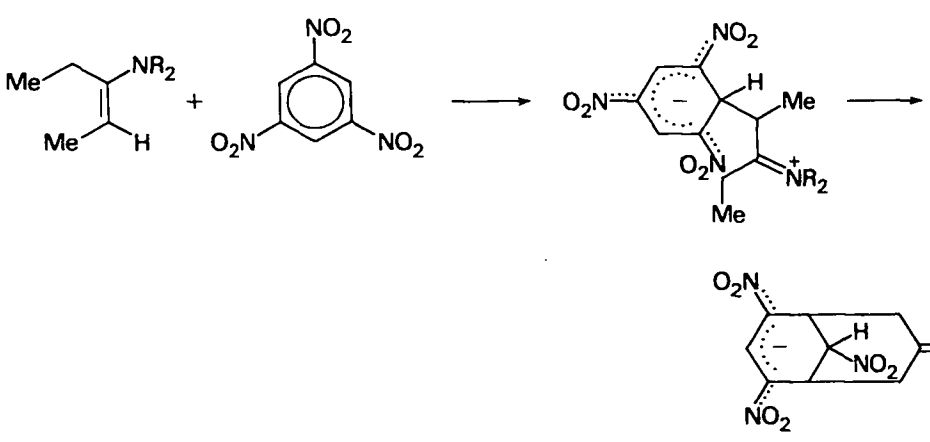


(184)



X = H, F, Cl

(185)

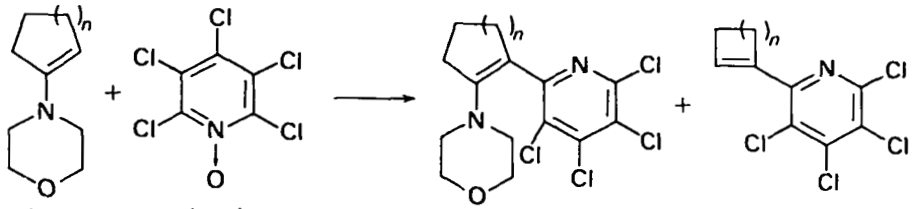


R = Et; NR_2 = pyrrolidine

(186)

obtained from some of these reactions. In one case[198] stable bicyclic iminium zwitterions (**186**) were isolated.

Arylation of enamines has also been carried out with pyridine[199], pyrimidine[200] and quinoline *N*-oxides[201], in the presence or absence of acylating agents. An interesting ring-contraction by-product (**189**) has been observed in the reaction of pentachloropyridine *N*-oxide (**187**) with morpholino-cyclopentene and -cyclohexene, together with the usual open enamine adducts (**188**)[202].

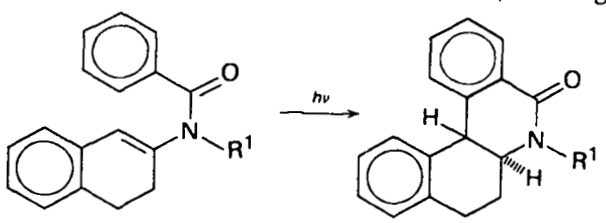


(162) $n = 1$ (187) (188) (189)

(134) $n = 2$

Intramolecular stereoselective photoarylations of acyclic[189b,203] and cyclic[203] *N*-arylenamines, as well as of cyclic *N*-arylenaminones[204], under mild conditions, are reported to yield heterocyclic compounds of biological interest.

Some enamides (**190**)[205], e.g. the *N*-aroyl-substituted enamines from 2-tetralone afford saturated heterocyclic systems, such as **191**, through stereospecific

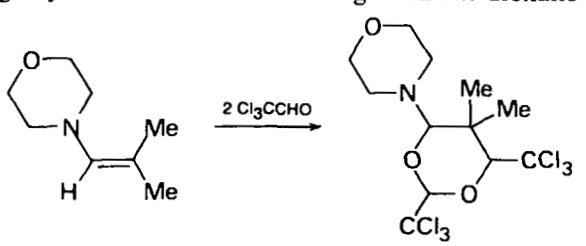


(190) (191)

$R^1 = -CH_2-CH=CH_2$; Me; $-CH_2Ph$; $-(CH_2)_3Me$

intramolecular arylation under UV irradiation[205]. Several natural products have been synthesized by this method[206].

e. Reaction with saturated carbonyl compounds. Cyclic compounds as well as Michael-type adducts can be formed in the reaction between enamines and aldehydes. Unlike acyclic enamines[195a], such as 1-morpholino-2-methylpropene (**192**), which undergo cyclization with chloral to give the *m*-dioxane derivative (**193**),



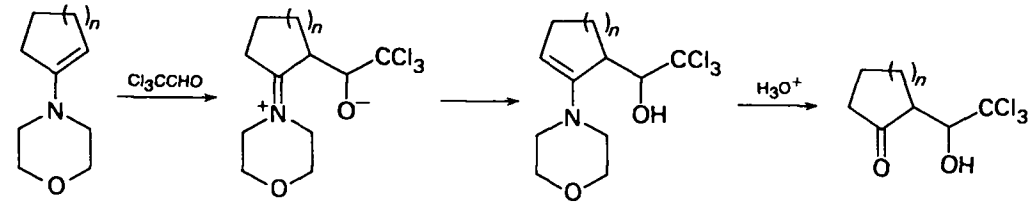
(192) (193)

regardless the ratio of the reactants, aminocycloalkenes such as **162** and **134** afford the corresponding 2-(α-hydroxy-β,β,β-trichloro)ethylcycloalkanones (**195**), after hydrolysis of the less substituted alkylated enamines (**194**)[207].

Aliphatic and aromatic aldehydes react with morpholinocycloalkenes to give 2-*R*-methylenecycloalkanones (**196**), after hydrolysis. Double-addition products have been also isolated[208a]. With aminocyclohexenes and benzaldehyde, substituted decahydroxanthene derivatives have been isolated[208b].

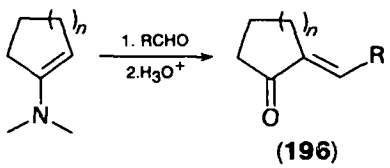
The reaction of cyclic enamines with *ortho*-substituted aromatic aldehydes (**197**) results in the formation of xanthene derivatives (**198**)[209].

[3 + 2]Cyclocoupling reactions between enamines and α,α′-dibromoketones



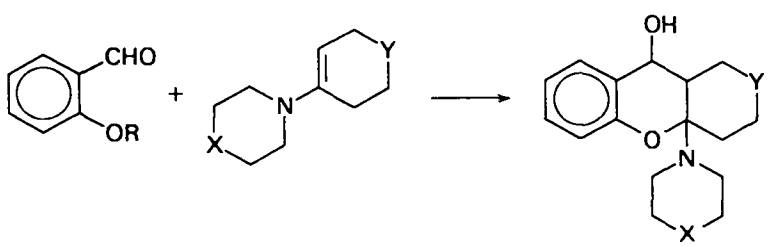
(162) $n = 1$
(134) $n = 2$

(194) **(195)**



(196)

$n = 1, 2$; R = Me, Et, *n*-Pr

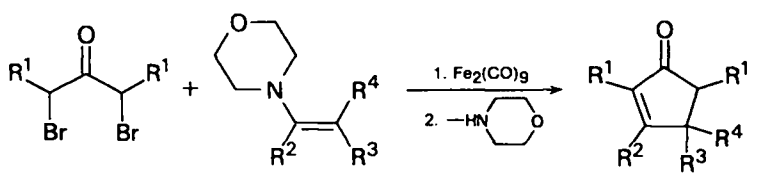


(197) **(198)**

X = —O—; —CH_2—; —Y = —CH_2—; R = H, acyl[209b]

X = —O—; Y = —N.(CH_2Ph)—; R = H[209c]

(**199**), in the presence of $Fe_2(CO)_9$ have afforded a series of 2-cyclopentenones (**200**), including spiro compounds in high yields[210]. The method is general both for aldehyde and ketone enamines.



(199) **(200)**

R^1 = Me, Et, *i*-Pr

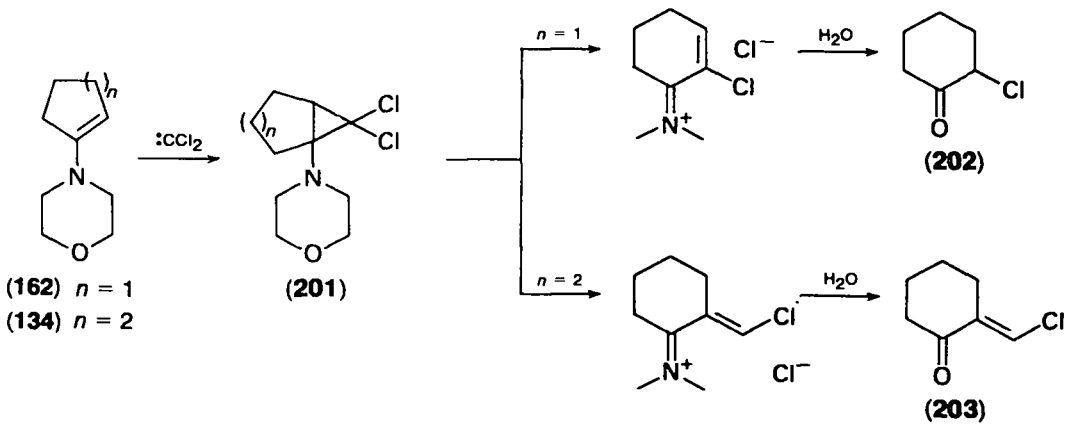
R^2, R^3, R^4 = H, Me, Me; Ph, H, H; Et, H, Me

R^2, R^3 = —$(CH_2)_3$—; —$(CH_2)_5$—; —$(CH_2)_{10}$—; R^4 = H

R^2 = H; R^3, R^4 = —$(CH_2)_5$—; —$(CH_2)_{11}$—

f. Reaction with carbenes and thiocarbenes. Reaction of carbenes with enamines results in the formation of aminocyclopropyl adducts of the type **201**[211,212]. Products

from cyclic enamines, such as **162** and **134**, can rearrange into many systems, namely a ring-expanded product (**202**) and an α-chloromethylene ketone (**203**) respectively, besides other more complex compounds. The structure of the base in the parent enamine, the type and source of the electrophile, as well as the ratio of the reactants are determining factors[212].



A series of conjugated enamines, such as **204** and **205**, derived from α- and β-tetralone, and **206**, derived from the $\Delta^{1,8a}$-octalone system, have been examined as regards to their reactivity with a number of carbenes.

While the morpholinoenamines (right-hand side of Scheme 2) furnish the aminocyclopropyl derivatives as main products, the corresponding pyrrolidino systems (left-hand side of Scheme 2) afford various products, those arising from ring-insertion or -opening prevailing.

The preferential formation of ring-expanded products from pyrrolidinoenamines has been attributed[212c] to the greater decrease in energy of the ring-opening transition state by the pyrrolidine as compared to the morpholine ring, based on Brown's postulate[57].

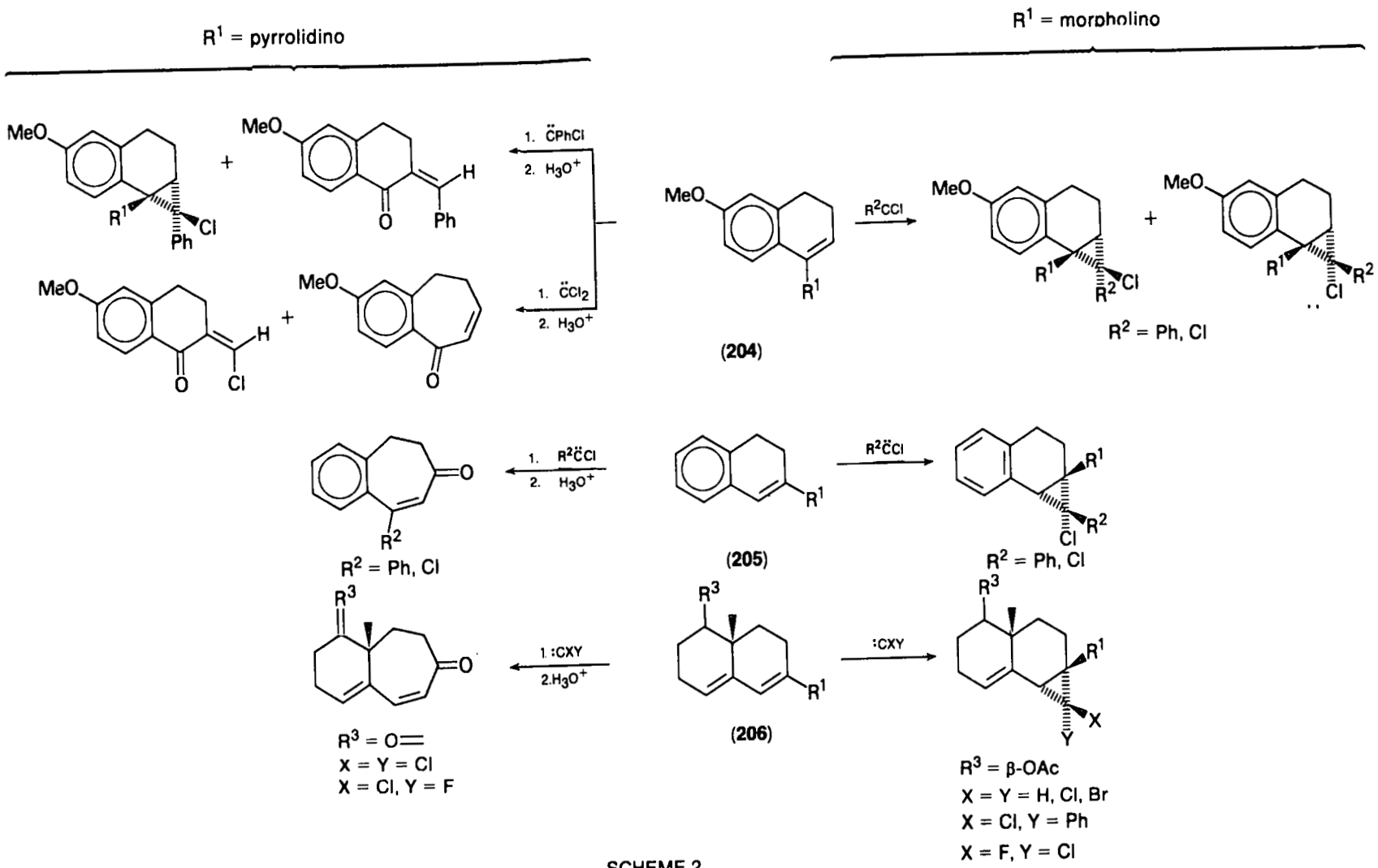
The reaction of enamino esters **207** and **210** with carbene and dichlorocarbene, followed by hydrolysis, yields γ-keto esters **208** and **211**, and α-halogenated α,β-unsaturated esters **209** and **212** respectively, as a result of a regiospecific carbene insertion[32c].

Thiocarbenes add to acyclic (**213**) and cyclic (**214**) enamines in excess of the latter, to give mixtures of diastereoisomeric aminocyclopropyl sulphides **215** and **216** respectively[213]. Successive treatments furnish functionalized sulphones, via a zwitterion intermediate.

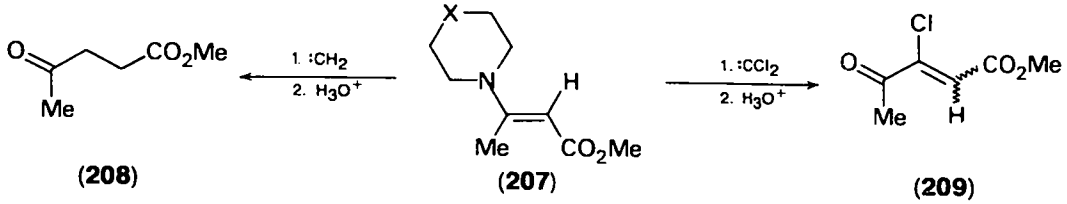
5. Acylation

One of the most widely used syntheses of 1,3-dicarbonyl compounds involves acylation of enamines[6b,c,214]. This can be performed by means of anhydrides, acid chlorides, ketenes, formic and carbonic acid derivatives (such as alkyl chloroformates and phosgene), isocyanates, isothiocyanates, the Vielsmeier–Haack–Arnold reaction[23b,214], carbon disulphide and other sulphur derivatives[6b]. *C*-functionalized enamines, namely dienamines and enaminones, show as high a reactivity as simple enamines towards acylating agents, although sometimes the reaction course is different.

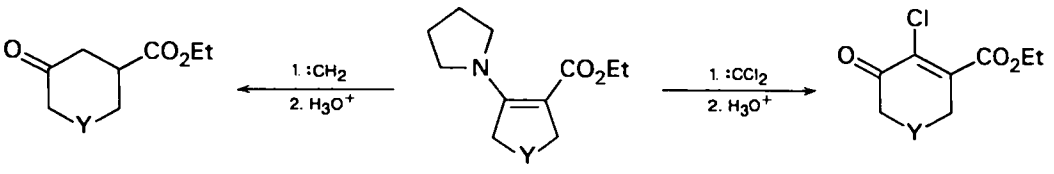
a. Reaction with phosgene and alkyl chloroformates. Acylation reactions with


R1 = pyrrolidino
R1 = morpholino
MeO
1. ĊPhCl
2. H3O+
1. ĊCl2
2. H3O+
R1
Cl
Ph
H
O
(204)
R2CCl
R2 = Ph, Cl
1. R2ĊCl
2. H3O+
(205)
R3 = O=
X = Y = Cl
X = Cl, Y = F
1. :CXY
2. H3O+
(206)
:CXY
R3 = β-OAc
X = Y = H, Cl, Br
X = Cl, Y = Ph
X = F, Y = Cl

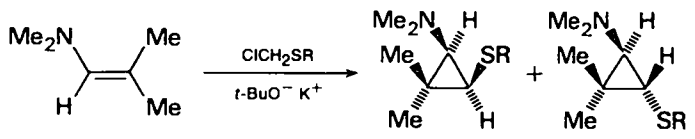
SCHEME 2



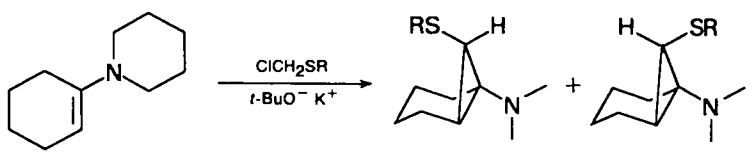
(208) (207) (209)



(211) (210) (212)



(213) (215)



(214) (216)

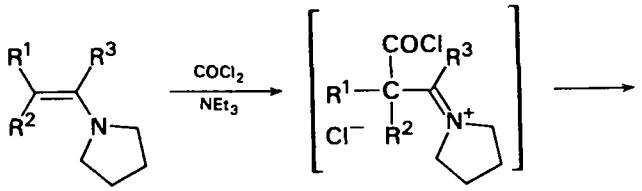
phosgene have been performed on a series of acyclic and cyclic pyrrolidinoenamines (**217**)[215]. The resulting enaminoacyl chlorides (**219**) cannot however be isolated but are treated with alcohols or amines to give the corresponding enamino esters (**220**) and vinylogous amides (**221**) respectively. With enamines bearing no β-hydrogens, only the unstable iminium salt of the type **218** can be obtained and allowed to react with bases and water to give 2-amidocarbonyl compounds[215].

With particular *N*-arylenamines, such as **222**, an intramolecular Friedel–Crafts acylation occurs, under mild conditions, in the β-(chloroformyl)enamine intermediate (**223**), to yield the 4-chloroquinolinium salt (**224**)[216].

Phosgenation of morpholinocyclopentene (**162**) results in the formation of **225** and **226**, the latter deriving from the former by intramolecular dehydration[217]. The same reaction carried out on morpholinocyclohexene (**134**) leads to many products, among which **227** and **228** are also detected[217].

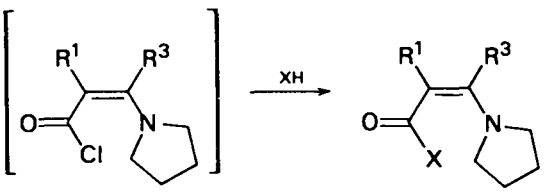
Enamino esters such as **220** can also be obtained from the reaction of the suitable alkyl chloroformate with enamines in the ratio 1:2, or in stoichiometric ratio, in the presence of *N,N*-diethylaniline[2b].

Enamino esters derived from aminocycloalkenes are in tautomeric equilibrium.

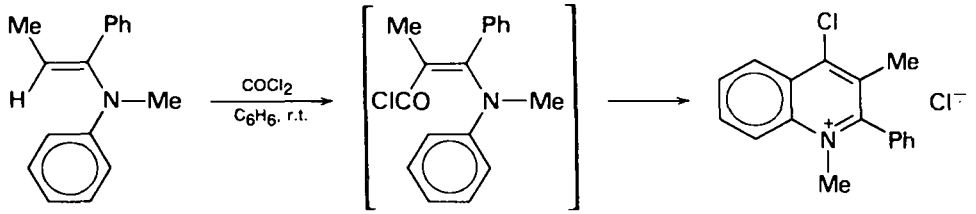


(217) (218)

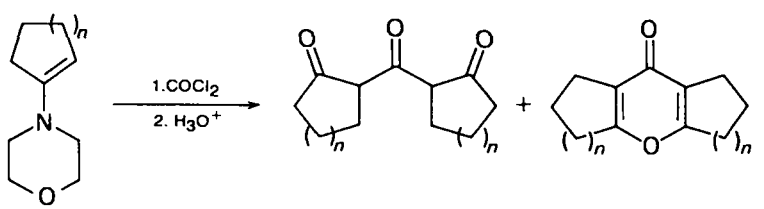
$R^2 = H$



(219) (220) X = RO (221) X = R_2N



(222) (223) (224)



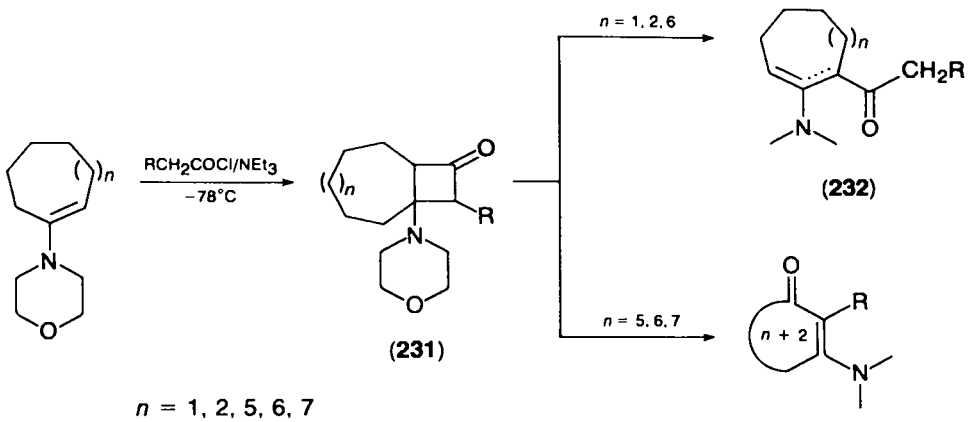
$n = 1$	(162)	(225)	(226)
$n = 2$	(134)	(227)	(228)

The ratio of the conjugated and nonconjugated forms **229** and **230** respectively depends as usual on the ring size and on the structure of the base. For instance, while 2-carbethoxymorpholinocyclopentene[218] exists only as the conjugated form, in the analogous morpholinocyclohexene derivative, the trisubstituted isomer is predominant[65b,218]. As to the effect of the base, in the pyrrolidino derivatives the

(229) (230)

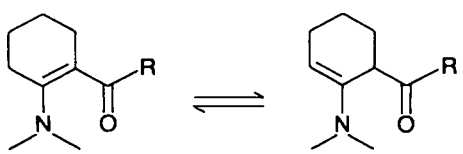
conjugated forms are always more prevalent than in the corresponding morpholino systems[65b].

b. Reaction with acyl chlorides. Acyl chlorides have been found to react with enamines in varying ways depending on the base used. In the presence of triethylamine, acyl chlorides having an α-hydrogen atom form a ketene which undergoes 1,2-cycloaddition with enamines with consequent formation of an aminocyclobutanone intermediate (**231**). This latter has been isolated in some cases under suitable conditions, as for instance in the reactions between morpholinoenamines of some cyclic ketones with acyl chlorides. Opening of **231** affords isomeric mixtures of acylated enamines (**232**)[6b]. For larger members of the series, namely those derived from 11-, 12- and 13-membered ring ketones, ring-expanded products (**233**) have also been isolated in good yields[83]. Some data are



also reported about direct acylation of enamines occurring in the absence of triethylamine, in particular with the morpholinoenamine of isobutyraldehyde (**192**)[219].

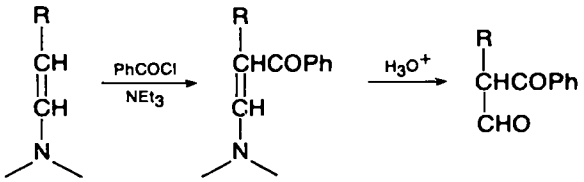
Like enamino esters, enaminoketones derived from cyclic ketone enamines exist as isomeric mixtures of conjugated (**234**) and nonconjugated (**235**) forms, the equilibrium composition being strongly dependent on the ring size, on the amine component, and on the substituent at the carbonyl group[65b,80c,218].



(**234**) (**235**)

Enaminoketones are structurally similar to enamino esters[65b,80c,218]. In particular, morpholinoenamines afford isomeric mixtures in which the form **235** predominates over **234**, whereas in the pyrrolidino derivatives virtually only the tetrasubstituted isomer is present[65b,80b]. Interestingly, when the substituent at the carbonyl group is a 5- or 6-membered saturated ring, only the conjugated isomer is detected, regardless of the base[80c].

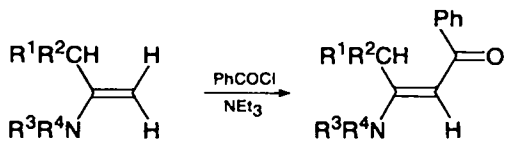
Benzoylation of enamines has been widely investigated[6b,c,214,220]. Aldehyde



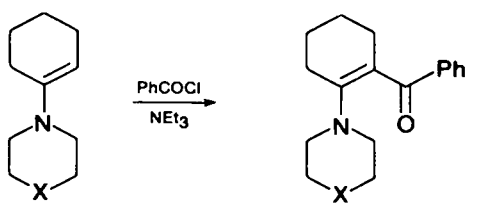
(236) (237) (238)

enamines (**236**) yield conjugated enamines (**237**), which afford the corresponding β-keto aldehydes (**238**), on hydrolysis[214].

Ketone enamines also undergo easy benzoylation. Enamines derived from unsymmetric linear ketones (**239**) afford conjugated acylated enamines (**240**) for which the *trans -s- trans* conformation seems the most plausible[220]. Also cyclic ketone enamines **134**, **214** and **144** afford the conjugated enamines **241**, **242** and **243**,



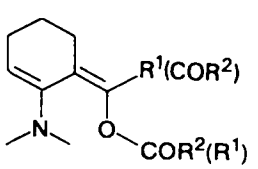
(239) (240)



X = —O— (134) (241)
X = —CH_2— (214) (242)
X = — (144) (243)

respectively, as the sole products[65b]. From the reaction between **144** and benzimidoyl chloride, the conjugated isomer has been isolated as the only product, namely benzimidoyl-1-pyrrolidino-1-cyclohexene[221].

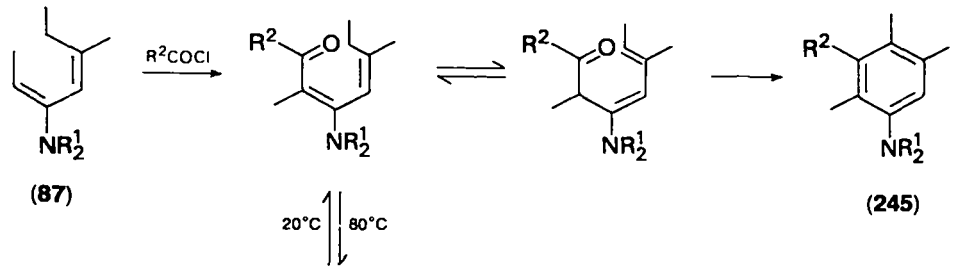
Unlike alkylations, acylations by acyl chlorides easily give double acylation products. The monoacylated products undergo further acylation[214,222] at the oxygen atom affording enamine enol esters of the type **244** which have been isolated, in some cases, as *Z* isomers[222].

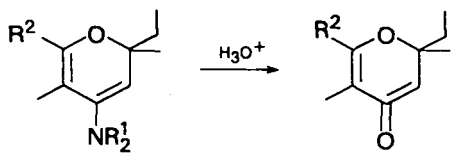


(244)

$R^1 = R^2 = Ph$
R^1 = Ph, R^2 = Me

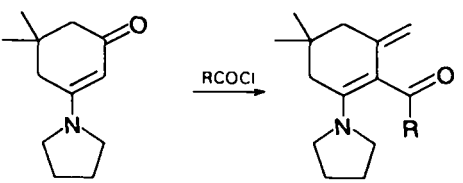
Acyclic cross-conjugated dienamines such as **87** react with aliphatic and aromatic acid halides to give either polysubstituted benzenes (**245**) or dihydro -γ- pyrones (**246**), on hydrolysis, depending on the reaction conditions[223].





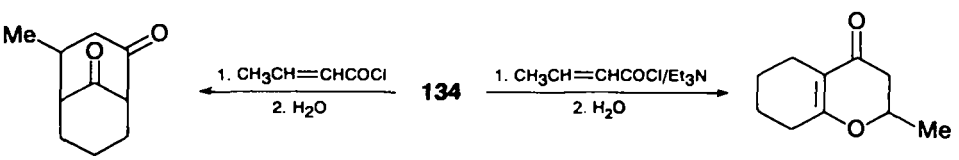
NR^1_2 = morpholino: R^2 = alkyl, aryl

In some enaminoketones exclusive *C*-acylation takes place instead of the usual *O*-acylation. For example, this is the case for the pyrrolidinoenamine of dimedone (**109**), which reacts with acetyl chloride, as well as with pivaloyl chloride, to give the corresponding *C*-acylated product (**247**)[224]. (It is worth noting that the presence of triethylamine prevents this reaction from occurring).



R = Me, *t*-Bu

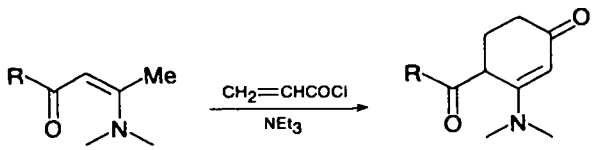
α,β-Unsaturated acid chlorides have also been employed in the acylation of enamines[6c]. When morpholinocyclohexene (**134**) is allowed to react with crotonoyl chloride, bicyclo[3.3.3]nonan-2,9-dione (**248**) is obtained on hydrolysis[225]. In the presence of triethylamine, however, tetrahydrochromanone (**249**) is formed[226]. When the substrate is a biased enamine, such as 2- and 6-methyl-4-*t*-butyl-morpholinocyclohexene, the reaction with crotonoyl chloride leads to a mixture of



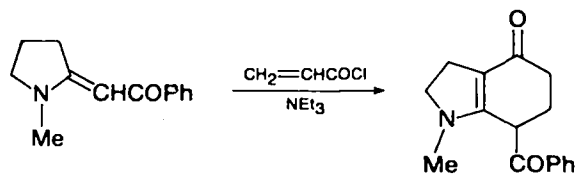
(**248**) (**249**)

two isomers, the major product deriving from β-attack of the electrophile onto the enamine, as proved by X-ray analysis[227].

With enamines derived from acetylacetone (**250**) and benzoylacetone (**251**), reaction with acryloyl chloride leads to fixed *s-trans*-enaminone derivatives, **252** and **253** respectively[228]. Analogous behaviour has also been found in the reactions of heterocyclic enaminones such as **254** with acryloyl chloride, in the presence of triethylamine, leading to **255**[229].

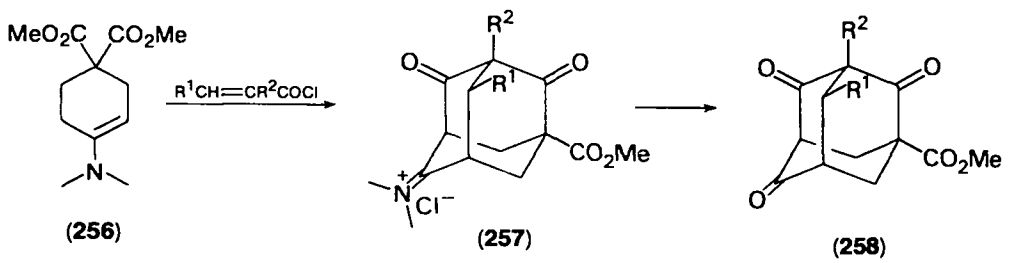


(**250**) R = Me (**252**)
(**251**) R = Ph (**253**)



(**254**) (**255**)

Reactions of α,β-unsaturated acid chlorides and enamines derived from 4,4-dicarbethoxycyclohexanone (**256**) result in the formation of adamantane trione derivatives (**258**), after hydrolysis of the iminium salt intermediate (**257**)[230].



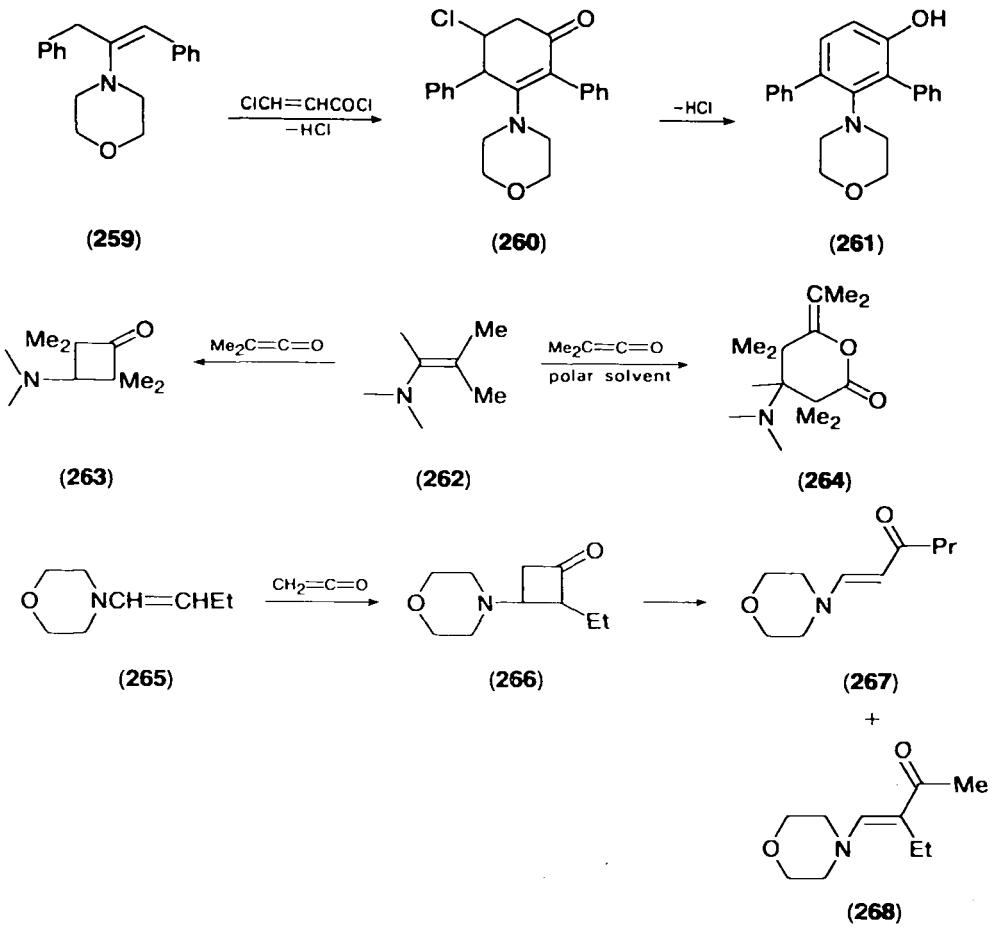
(**256**) (**257**) (**258**)

R^1 = H, R^2 = Me
R^1 = Me, R^2 = H

Substituted adamantan-2,4-diones have also been obtained from the reaction of 4-methyl- and 4-benzoyl-cyclohexanone enamines with α,β-unsaturated acid chlorides, while 4-acetyl-, 4-phenyl- or 4-ethoxycarbonyl-cyclohexanone enamines lead to substituted amino[2.2.2]octane-2-ones as main products[231].

The reaction between the enamine **259** and β-chloroacryloyl chloride results in the formation of *m*-aminophenol (**261**), through dehydrochlorination of the enaminoketone intermediate (**260**)[232].

c. Reaction with ketenes. The reaction of substituted ketenes and β,β'-disubstituted enamines (**262**) leads to stable cyclobutanones (**263**). In polar solvents however, α-pyrones (**264**) are also formed as a result of a double addition of the electrophile onto the enamine, via formation of a dipolar intermediate[6b,214]. Linear enamines having α-hydrogen atoms, such as **265**, react with ketene to give an



(259) (260) (261)

(263) (262) (264)

(265) (266) (267)

+

(268)

isomeric mixture of enaminones, **267** and **268**, owing to two possible opening modes of the unstable cyclobutanone intermediate (**266**)[233].

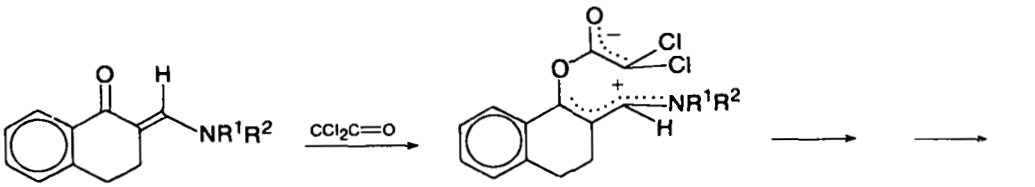
In the analogous reaction of aminocycloalkenes opening of the cyclobutanone intermediate depends upon the ring size of the cycloalkanone. With 5- and 6-membered ring ketones, the main products are linear enaminones, whereas with larger ring ketones, formation of ring-enlarged products occurs preferentially[234].

The 1,4-cycloaddition reaction between dichloroketene and 2-aminomethylenecycloalkanones, such as **269**, has been observed to afford α-pyrone derivatives (**270**)[235].

Vinylketenes such as **271** react with β,β′-disubstituted enamines (**262**) via dipolar intermediates yielding cyclobutanones (**272**). A cyclohexenone derivative has been obtained under more drastic conditions. With vinylketene morpholinocyclohexene undergoes the usual β-acylation[236].

Reactions with diketene have been applied to the synthesis of both chromones[6b] and azachromones[237], depending on the structure of the parent enamines.

d. Intramolecular acylation. The pyrrolo[1,2-a]indole derivative **273** can be obtained via intramolecular acylation of enamines in which the amine component is methyl or ethyl prolinate[238]. The same reaction applied to enamines derived from seven and eight-membered ring ketones, from some acyclic ketones and from



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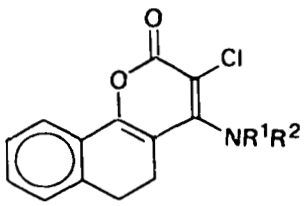
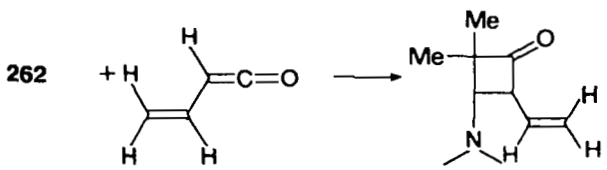
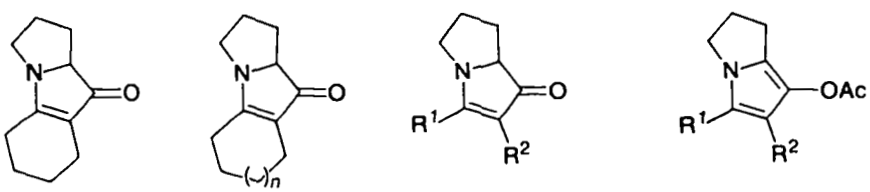


(270)



(271) (272)

β-diketones and β-keto esters, affords the corresponding substituted pyrrolizines **274**, **275** and **276** respectively[239]. In contrast, cyclic dienamines fail to undergo the cyclization reaction[239].



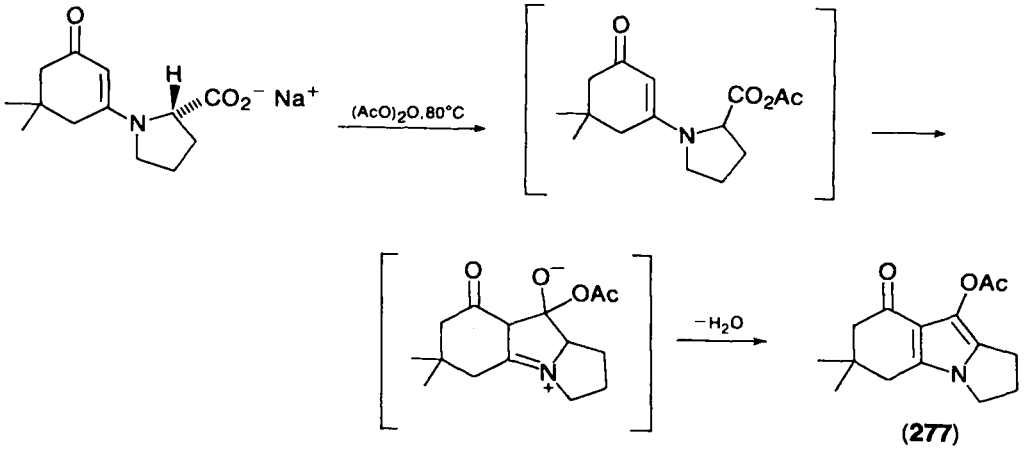
(273) (274) (275) (276)

$n = 2, 3$

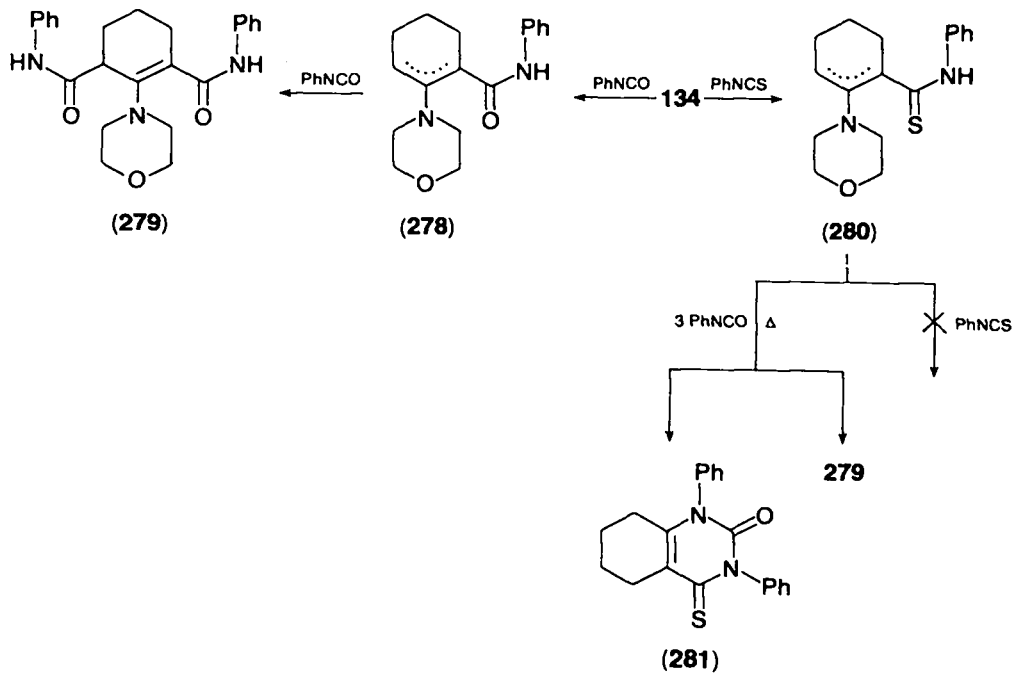
Intramolecular acylations at the β-carbon of enamines with formation of pyrrolo[1,2-a]indole derivatives (**277**) have also been found in enamines derived from dimedone and proline derivatives[240].

e. Reaction with isocyanates and isothiocyanates. Linear, cyclic and heterocyclic enamines react with alkyl and aryl isocyanates to yield cycloaddition products or carboxamides, depending upon the structure of the parent enamines, the electrophile and the reaction conditions[6b,241].

Double acylation by isocyanates can occur particularly with aminocycloalkenes, such as **134**, but the second acylation reaction takes place on the less substituted β-carbon of **278** to give **279** unlike acyl halides which add to the oxygen atom. Isothiocyanates afford only monoacylated products (**280**). The latter gives

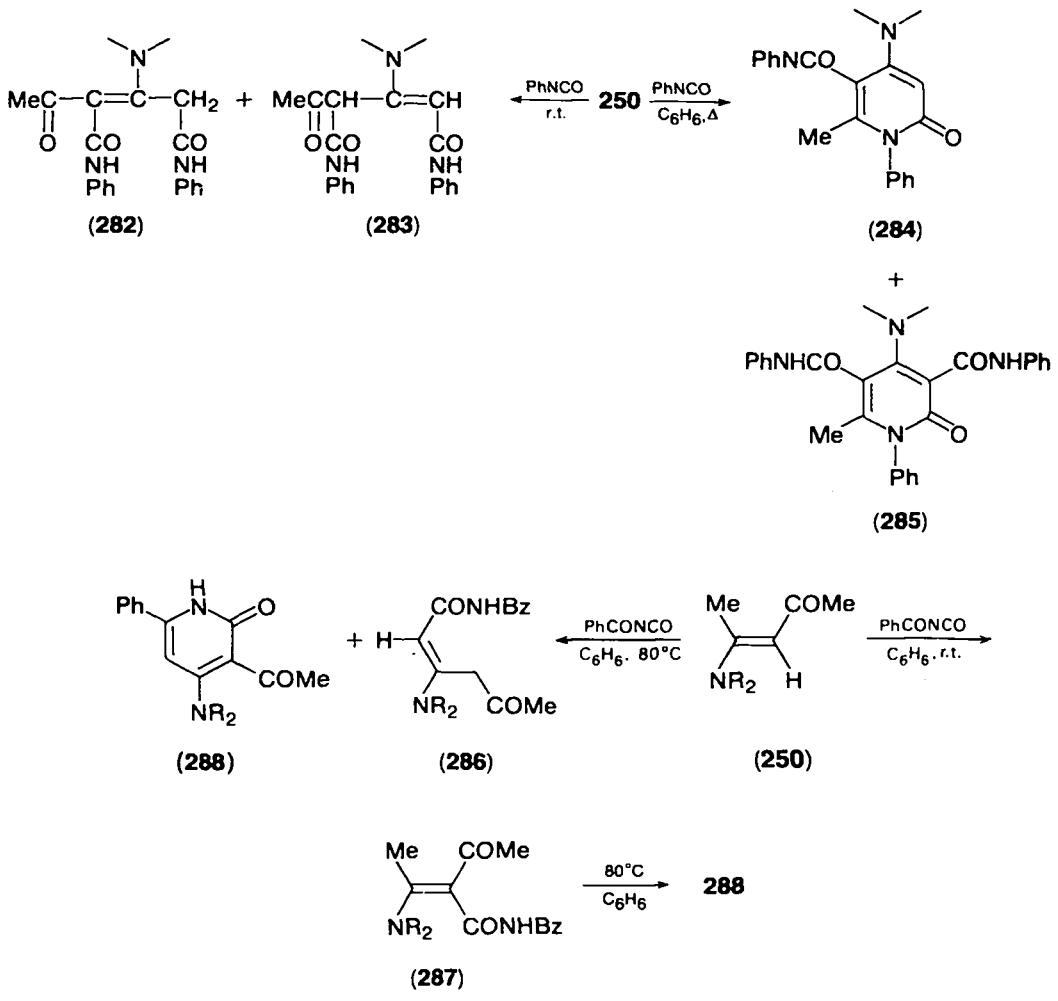


transacylation with phenyl isocyanate to the corresponding dicarboxamide (**279**)[242]. From the same reaction a quinazoline derivative (**281**) has also been separated[242].



Enaminones derived from acetylacetone show high reactivity towards aryl isocyanates[243]. Thus, 4-(1-amino)-3-penten-2-ones (**250**) react with phenyl isocyanate, at room temperature, to give tautomeric mixtures of 1:2 enamine adducts **282** and **283**, even with excess **250**. When the reaction is performed in refluxing benzene, mixtures of *N*-phenyl-2-pyridone derivatives **284** and **285** are obtained after loss of water. Phenyl isothiocyanate is less reactive, since with the piperidino-enamine of acetylacetone only the 1:1 adduct can be isolated, even on heating[244].

Benzoyl and sulphonyl isocyanates and isothiocyanates react with linear enaminoketones to give various products[245]. For example, benzoyl isocyanate reacts



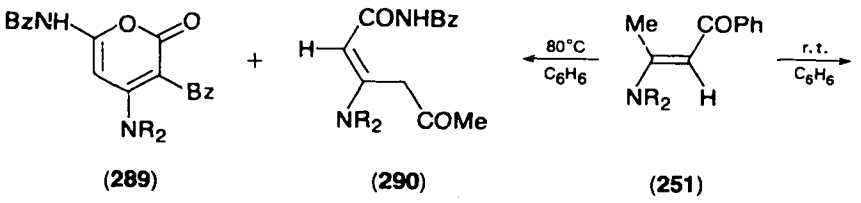
with **250** to give carboxamides **286** and **287** and/or α-pyridone derivatives **288**, depending upon the temperature.

Analogous behaviour is shown by the enamines derived from benzoylacetone (**251**), which afford α-pyrone derivatives (**289**), together with the carboxamides **290** and **291**, under different conditions. Thermal reversibility of **291** into the starting materials has been proven[245].

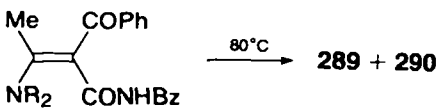
Reactions of linear enaminones and benzoyl isothiocyanate afford mixtures of linear and heterocyclic compounds, but the yields are low[246].

Arylsulphonyl isocyanates and isothiocyanates react with ketene *S,N*-acetals and cyclic and heterocyclic enamines to yield the corresponding zwitterionic products **292**, **293** and **294**[247].

With β,β'-disubstituted linear enamines (**262**) dipoles (**295**) are formed, which can be in equilibrium with the corresponding β-lactams (**296**). They can also add a second molecule of isocyanate to give dihydrouracil derivatives (**297**)[248].

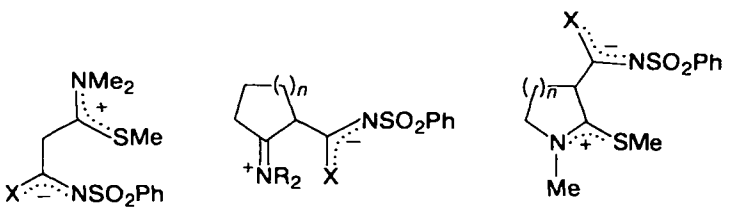


(289) (290) (251)



(291)

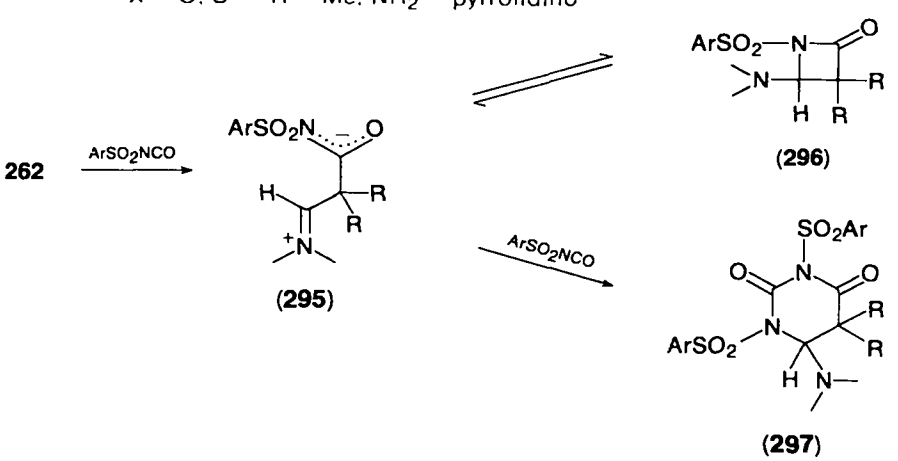
NR_2 = pyrrolidino



(292) (293) (294)

n = 1, 2 *n* = 1, 2

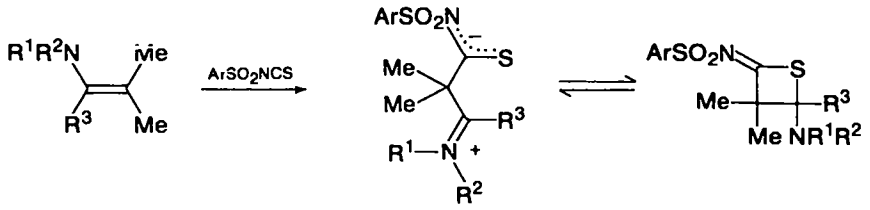
X = O, S R = Me, NR_2 = pyrrolidino



(295) (296) (297)

Only dipolar structures (**299**) have been isolated in the analogous reaction of arylsulphonyl isothiocyanates with β,β′-dimethylenamines (**298**)[249]. In nonpolar solvents an equilibrium between **299** and the corresponding thietane form (**300**) can be detected by NMR. This latter is the only isomer when one of the substituents at the enamine β-carbon is phenyl[249].

f. Reaction with sulphonyl halides. Like acyl chlorides, sulphonyl chlorides having α-hydrogen atoms react with enamines, in the presence of triethylamine, to give

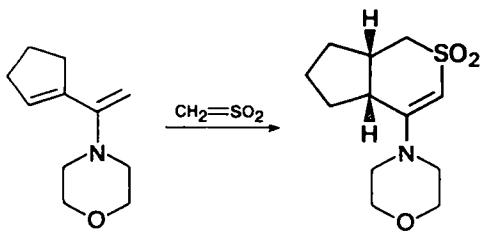


(298) (299) (300)

$R^1 = R^2 = Me$; $R^3 = H$, Me, *i*-Pr, Ph

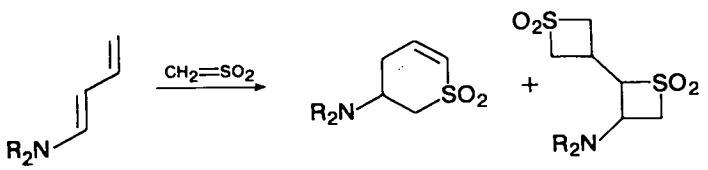
[2 + 2]cycloadducts as main products[189b,250], via a transient sulphene. In some cases, however, open-chain products are also formed[15,251,38d].

Another method for generating sulphenes is the reaction of diazoalkanes with sulphur dioxide[250b,252]. Also, a [4 + 2]cycloaddition reaction has been found to occur with sulphene and a cross-conjugated enamine such as **301**, leading to the cyclic vinylogous sulphonamide (**302**)[15b].

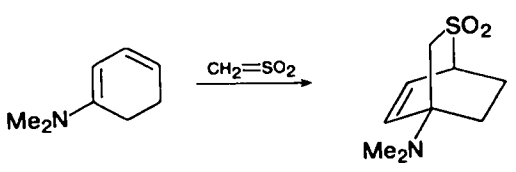


(301) (302)

[4 + 2]Cycloaddition also takes place with linear (**303**)[253] and cyclic (**306**)[250b] fully conjugated dienamines, to give **304** and **307** respectively. In the former case there is competition with the double [2 + 2]cycloaddition reaction which leads to **305**.

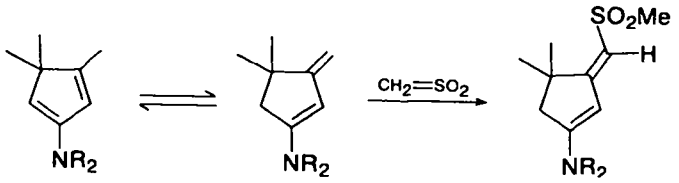


(303) (304) (305)



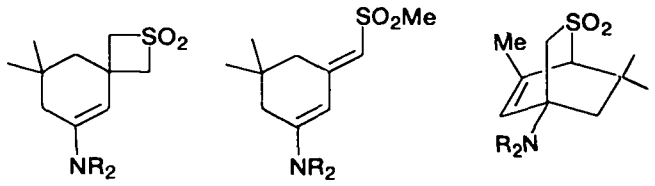
(306) (307)

With dienamines derived from 3,4,4-trimethylcyclopenten-2-one, i.e. (**308**), only the dienaminosulphone (**309**) is obtained on reaction with sulphene[254], while a mixture of **310**, **311** and **312** is obtained with enamines derived from isophorone.



(308) (309)

NR_2 = morpholino

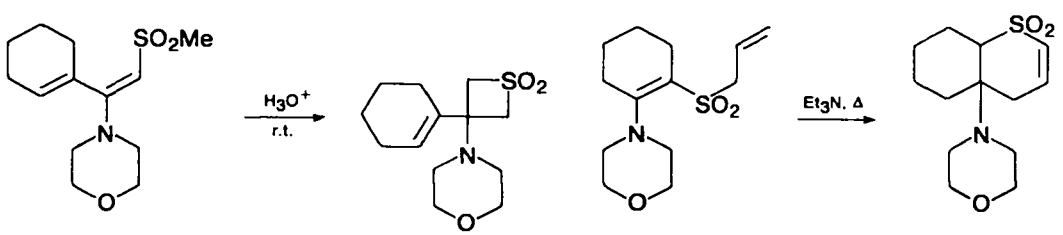


(310) (311) (312)

NR_2 = morpholino, piperidino, *N*-methylpiperazine

Thietane-1,1-dioxides are very stable and open into the corresponding enaminosulphones only at high temperatures and after long reaction times. Analogous forcing conditions as well as the presence of a secondary base as a trapping agent favours their reversibility into the starting materials[15]. On the other hand, open-chain enaminosulphones are the favoured products when the sulphene nucleophilic carbon bears an electron-withdrawing group[255], or when the number of substituents is increased at the α-carbon of both the sulphene and the enamine.

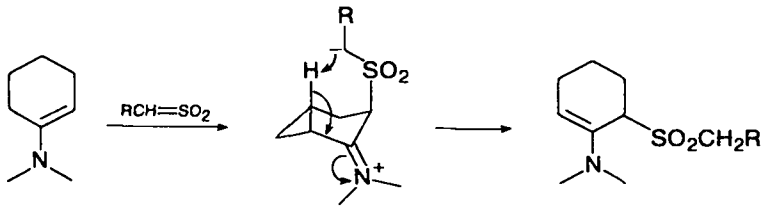
Some open-chain sulphonylenamines, such as **313** and **315**, show unusual behaviour, as they cyclize into the thietane 1,1-dioxide (**314**)[15a] and thiopyrane 1,1-dioxide (**316**)[38d] respectively, under suitable conditions.



(313) (314) (315) (316)

The mechanism of 1,2-cycloaddition of sulphene to enamines is not yet definitely resolved, since data are available supporting both the concerted[250c,256] and the stepwise[252,256] mechanism.

The high stereoselectivity observed in the reaction of sulphenes with (*E*)-β-morpholinostyrene[251b] and *N*-methyl-*N*-phenyl-2-butene, as well as the results of the asymmetric induction[250], are in favour of a concerted mechanism. On the other hand, a stepwise process via a dipolar intermediate must be envisaged for the formation of enaminosulphones which often accompanies the production of cyclic sulphones[252]. For instance, formation of cyclic enaminosulphones (**318**), which are



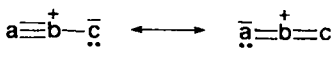
(317) (318)

R = CN, COPh

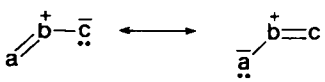
formed as trisubstituted isomers, must take place through a zwitterion intermediate (317)[255a,b].

6. 1,3-Cycloaddition

Numerous octet-stabilized 1,3-dipoles of both propargyl–allenyl anion-type (319) and allyl anion-type (320) are known to react with enamines to give



(319)

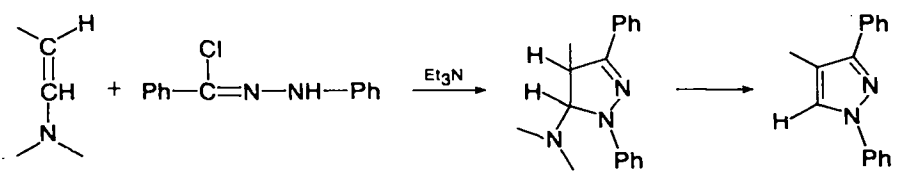


(320)

[3 + 2]cycloaddition products[257]. Nitrile imines, nitrile oxides, diazoalkanes and azides fall into the former category, and nitrones, thione-*S*-imides and azomethine imines into the latter[257b].

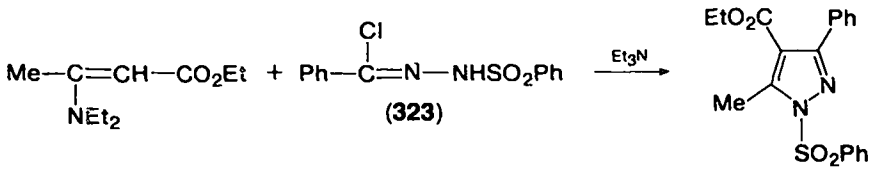
The resulting five-membered heterocyclic systems are generally obtained in a regiospecific manner, as supported also by FO method calculations[258]. They can be stable or undergo 1,3-dipolar cycloreversion[259] depending on the substituents in the reactants and on the conditions used. For this type of cycloaddition, a concerted mechanism is generally accepted[260], although arguments have been advanced for a biradical stepwise one[261].

Nitrile imines, generated *in situ* by dehydrohalogenation of hydrazidoyl halides, undergo 1,3-cycloaddition with enamines and enaminones to give pyrazole derivatives (322), through the intermediacy of a 5-amino-Δ^2-pyrazolino system (321)[257a,262].



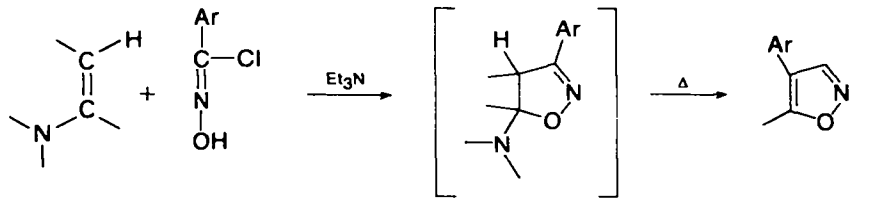
(321) (322)

On the contrary, *N*-(arylsulphonyl)benzohydrazonoyl chloride (323) reacts with some enamines through a two-step process[263], the reaction giving better results with



enaminones than with cyclic enamines, for which formation of by-products predominates.

The reaction of enamines with nitrile oxides, generated *in situ* from hydroxamoyl chlorides and a base, leads to 5-amino-Δ^2-isoxazolines (**324**) as intermediates. Successive base elimination affords the corresponding isoxazoles (**325**)[14a,262,264]. With

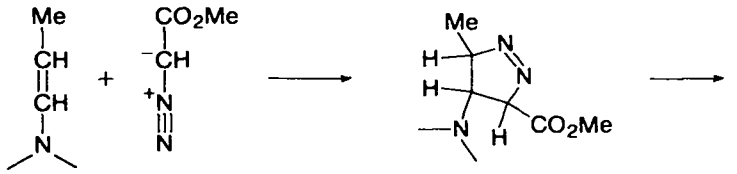


(**324**) (**325**)

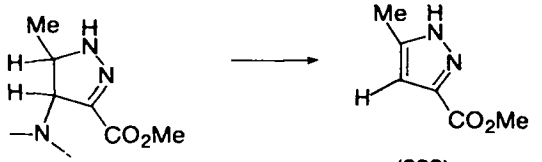
aryl-substituted furan nitrile oxides and aminocyclopentenes, isoxazoline intermediates of type **324** are particularly stable and no amine elimination occurs[265].

In the reaction of acyclic fully conjugated dienamines with benzonitrile oxide both double bonds undergo 1,3-cycloaddition, leading to monoadducts, and also simultaneously affording isomeric mixtures of 4,5-diisoxazole derivatives[266].

α-Diazocarbonyl compounds (**326**) react regiospecifically with enamines, to give Δ^2-pyrazolino derivatives (**327**), which isomerize and aromatize to **328**[267,268]

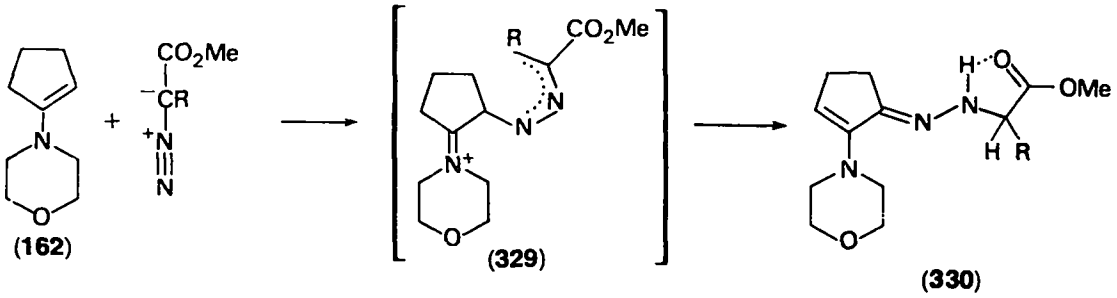


(**326**) (**327**)



(**328**)

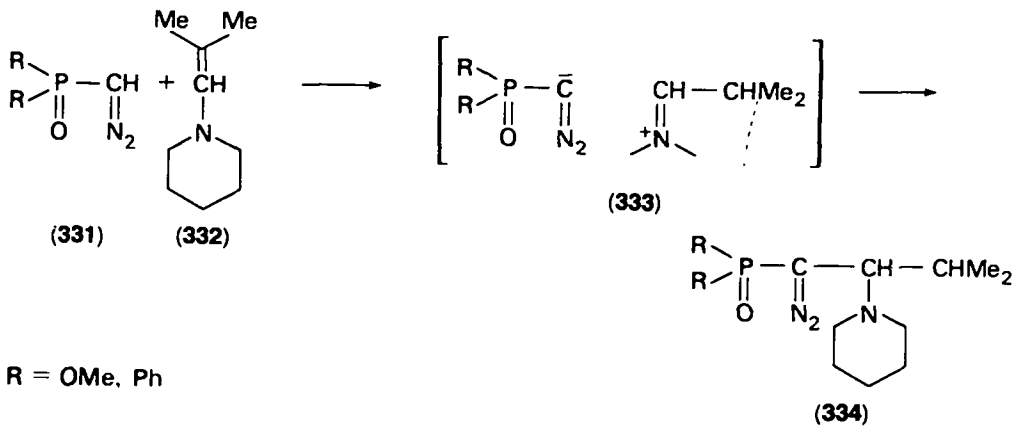
However, unusual behaviour has been shown in the reactions of α-diazocarbonyl compounds with aminocyclopentenes[269]. Thus, azocoupling products (**330**) have been isolated as *syn–anti* isomeric mixtures in the reaction of **162** with methyl diazoacetate and malonate, via formation of dipolar intermediates (**329**). Compound **141** and dimethyldiazomalonate afford a zwitterionic compound analogous to **329**, which has been characterized spectroscopically, and has been found to be in equilibrium with the stereoisomeric mixture of the corresponding azocoupling compounds.



(162) (329) (330)

R = H, CO_2Me

β,β-Disubstituted enamines (e.g. **332**) react with phosphoryldiazomethanes (e.g. **331**) to give β-amino-α-diazophosphoryl compounds (**334**), probably through an iminium salt intermediate (**333**), rather than through formation of the usual pyrazoline derivatives[270].

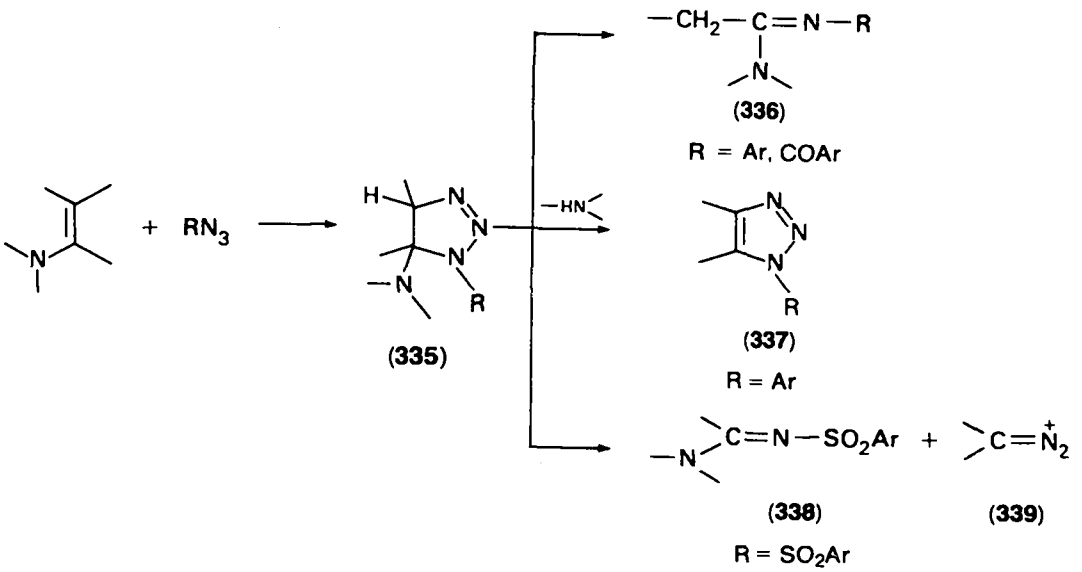


(331) (332) (333) (334)

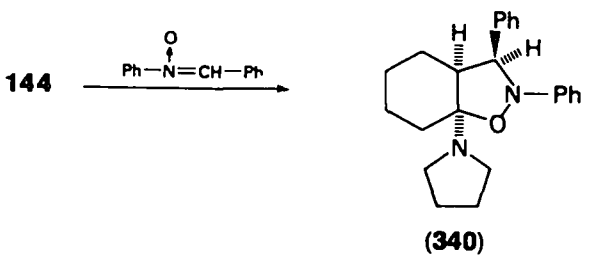
R = OMe, Ph

1,3-Cycloaddition reactions between enamines and azides have been widely investigated[257,271]. They are regiospecific, since the terminal nitrogen of the azides always adds to the enamine β-carbon, with formation of Δ^2-1,2,3-triazolines (**335**). The latter react subsequently depending upon the type of reactant. With 3,β'-dialkylenamines stable 1,2,3-triazolines are formed[271c], while with aldehyde enamines and aryl and acyl azides, the 1,2,3-triazolines easily open into the corresponding amidines (**336**), with loss of nitrogen[272].

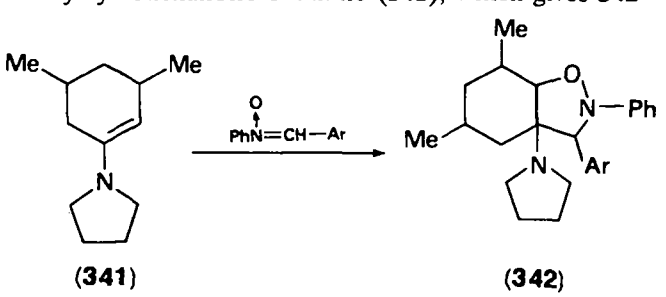
Enaminones, enaminosulphones and β-nitroenamines afford with aryl azides the corresponding 1,2,3-triazoles (**337**) with elimination of base from **335**[272]. With acyclic enamines and sulphonyl azides the 1,2,3-triazoline is very unstable and opens into a zwitterionic intermediate to give several products, including amidines (**338**) and diazo compounds (**339**)[271d,272]. In one case however, a different fragmentation has been observed[271f]. In the reaction with cyclic fully conjugated dienamines, a stable 1,2,3-triazoline derivative has been isolated[271e]. Δ^2-1,2,3-Triazolines have also been obtained from cyclic enamines. Subsequent aromatization with loss of base affords 1,2,3-triazole derivatives, analogous to **337**[257a]. The concerted polar mechanism in the 1,3-cycloaddition of azides to acyclic and cyclic enamines has been supported by many experimental results[271a,273] as well as by theoretical calculations[257b,271a].



Regio- and stereo-specific 1,3-cycloaddition reactions of nitrones to enamines are known to yield 5-aminoisoxazolidine derivatives[257a,274], as for instance in the reaction of pyrrolidinocyclohexene (**144**) with α-*N*-diphenyl nitrone, which affords **340**[275].

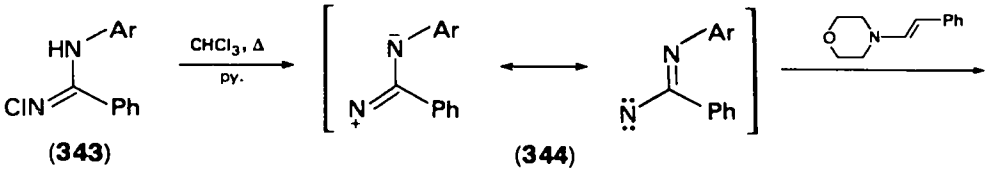


However, with hindered enamines, a reverse-oriented cycloaddition occurs, as in the case of 3,5-dimethylcyclohexanone enamine (**341**), which gives **342**[276].

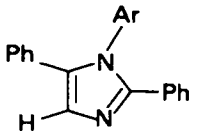


A new synthesis of imidazole derivatives, such as **345**, has been reported[277], starting from *N*-chloro-*N'*-arylamidines (**343**) and aldehyde enamines, with the intermediate formation of the dipolar species **344**. With β,β'-dialkyl aldehyde enamines or with linear ketone enamines, the same reaction yields open-chain products[277].

Thione-*S*-imides also behave as 1,3-dipoles towards enamines. In fact

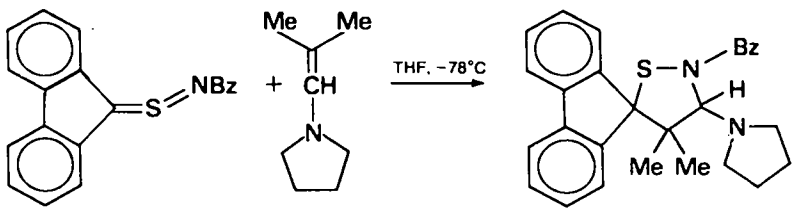


(343) (344)



(345)

9-fluorenthione-*S*-imides such as **346** react with **347** to give the isothiazolidino derivative (**348**)[278a]. Thione-*S*-tosylimide reacts in the same manner with **347**, whereas with aminocyclohexenes only open-chain products are formed[278b].



(346) (347) (348)

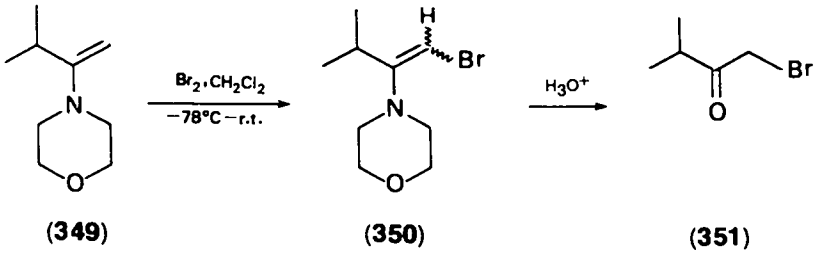
Linear dienamines have been found to react with thione-*S*-imides. In particular, **303** and **346** easily react at −78°C to give the isothiazolidine derivative as the sole product by [3 + 2]cycloaddition of the heterocumulene on the terminal double bond of the dienamine[278a].

Among the allyl anion-type 1,3-dipoles, azomethine imino derivatives add to enamines, such as for instance pyrrolidino cyclopentene (**141**), to afford pyrazole systems[279].

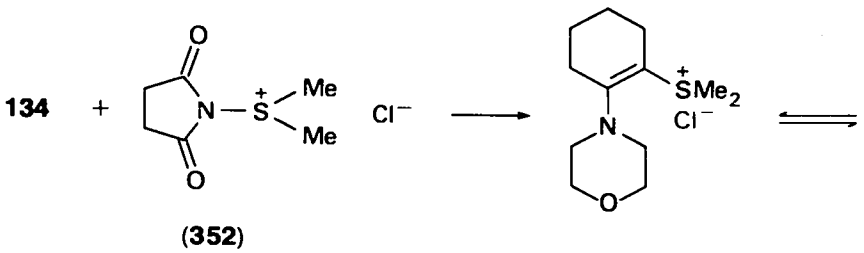
7. Halogenation

Bromination and chlorination of enamines can be carried out by means of halogens[280], *N*-halosuccinimides[281] or sulphuryl chloride[280,282]. The resulting monohalogenated ketones are often contaminated by polyhalogenated by-products. Nevertheless, halogenation of ketones through enamines is by far the best available method, since direct halogenation of ketones generally leads to substantial amounts of undesired products. Carlson and Rappe[283] have prepared bromomethyl isopropyl ketone (**351**), in good yield and purity, by bromination of 1-morpholino-1-isopropylethene (**349**)[60] followed by hydrolysis. The β-bromoenamine intermediate (**350**) is a 3:2 mixture of *E*–*Z* isomers[284]. Using the same procedure, 1-bromo-1-chloro-3,3-dimethyl-2-butanone can also be prepared[285].

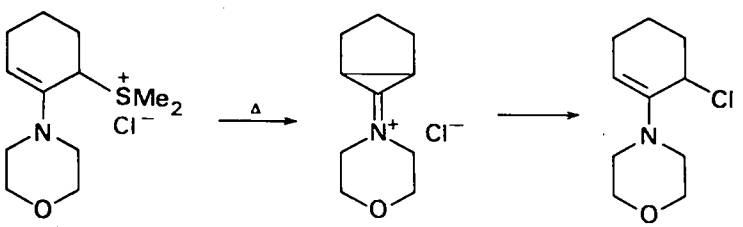
Halogenations of aminocycloalkenes by *N*-chlorosuccinimide afford di- and tri-chlorinated enamines[281]. However, the use of succinimidodialkylsulphonium chloride (**352**) on **134** in the ratio 1:1, followed by heating, leads to the monohalogenated 6-chloromorpholinocyclohexene (**353**), as determined by



(349) (350) (351)



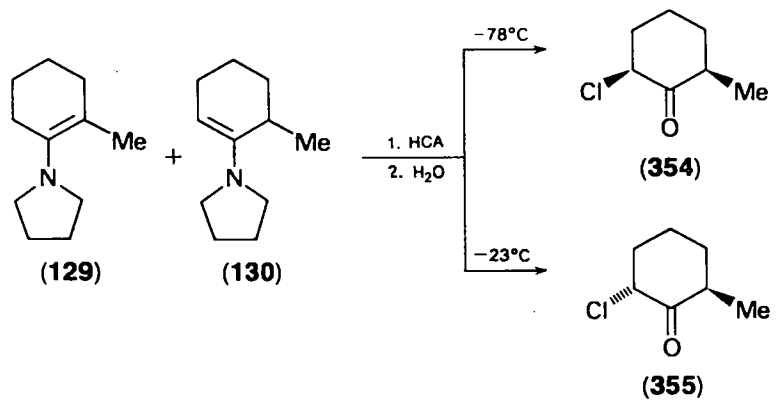
(352)



(353)

^{1}H-NMR[286]. The presence of **353** has also been detected, by ^{13}C-NMR, in the reaction of **134** with hexachloroacetone (HCA), at −9°C[287].

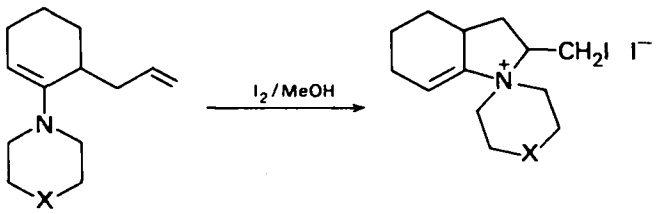
HCA shows regioselective reactivity towards the pyrrolidinoenamines of 2-methylcyclohexanone (**129** + **130**). At different temperatures, both the 2,6-disubstituted stereoisomers **354** and **355** can be isolated in very good yields; this



(129) (130) (354) (355)

contrasts with other halogenating agents which give the 2,2-disubstituted cyclohexanone preferentially[287].

Few data are available on the iodination of enamines. Iodocyclization occurs with the 2-allylcyclohexanone enamine **356**, affording Δ^7-hexahydroindolium salts **(357)**[288].



(356) **(357)**

X = O, CH_2

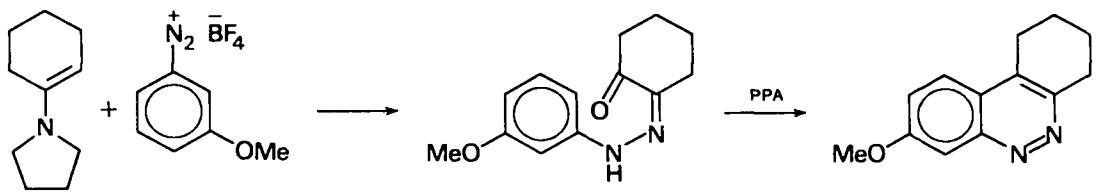
α-Fluorocycloalkanones can be obtained by oxidative fluorination of morpholinocycloalkenes by means of difluorodiazine[289]. Perchloryl fluoride can also be used to introduce a fluorine adjacent or vinylogous to a carbonyl group[290].

a. α-Haloenamines and β-haloenamines. α-Chloroenamines can be easily obtained by addition of an acid chloride to ynamines[291], and from the reaction of tertiary amides and phosgene, followed by dehydrochlorination[292]. They show high reactivity towards nucleophiles[293], as illustrated by the displacement reactions with F^- and I^- [294], by the reaction with sodium azide leading to aminoaziridines[295] and by reactions with electron-rich aromatics[296] and olefins[297]. Moreover, like enamines, α-chloroenamines react with electrophiles at the β-carbon[293].

Few data have been reported on the direct β-halogenation of enamines[280,285,298]. Acyclic β-haloenamines have been prepared by condensation reactions of α-halo-aldehydes and -ketones[299–301] with secondary bases, in the presence of a Lewis catalyst. Heterocyclic β-haloenamines have been obtained as intermediates in ring-contraction reactions[302].

8. Miscellaneous reactions

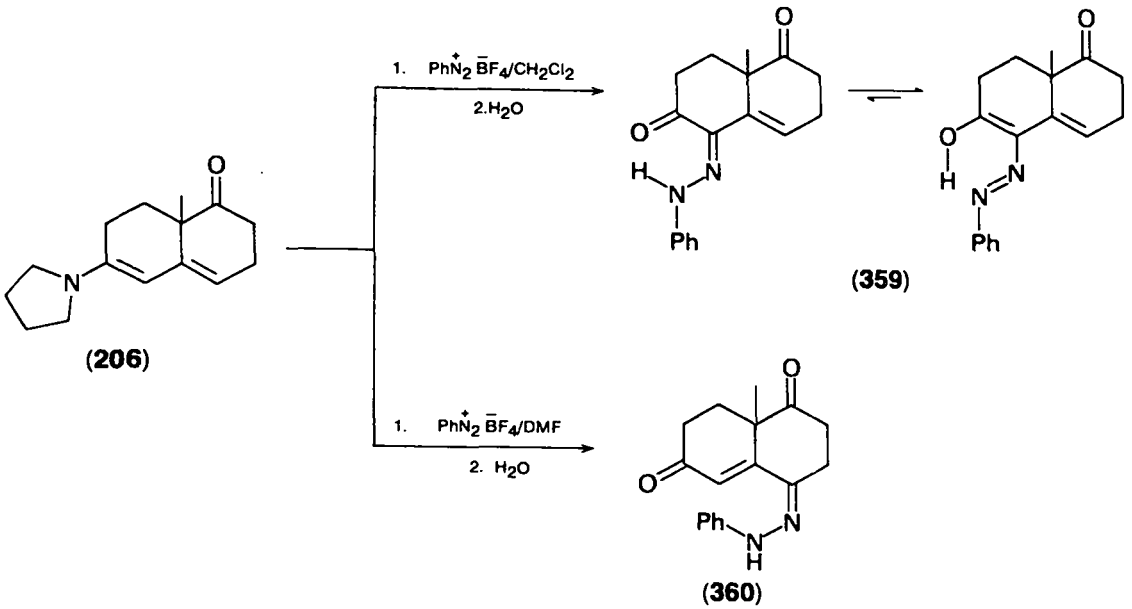
a. Reaction with diazonium salts. Monoaryl hydrazones of α-diketones and α-keto aldehydes have been obtained from the reactions of aromatic diazonium salts with enamines derived from ketones and aldehydes respectively[303]. This reaction has been extended to the synthesis of tetrahydrobenzo[*c*]cinnoline derivatives **(358)**[31m].



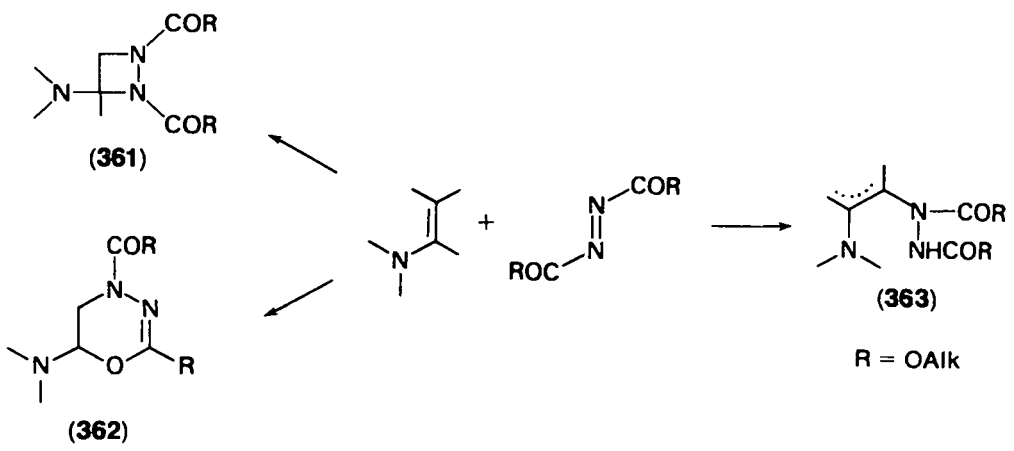
(144) **(358)**

Functionalized enamines, such as dienamines and enaminoesters have also shown a facile reactivity towards diazonium salts, to afford heterocyclic compounds, after suitable treatments of the aryl hydrazone intermediates. Thus indazoles[31m], cinnolines[31m], indoles[304] and imidazoazacycloalkanes[305], have been obtained. The type of solvent used is important however, as, for example, dienamines such as **206** undergo attack by the electrophile at the β-position to give **359** after hydrolysis, if the

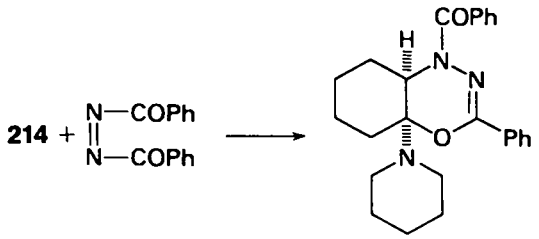
reaction is carried out in methylene chloride. In dimethylformamide, **206** reacts at the δ-position to give **360**[31m]. Using this type of reaction, syntheses of steroid systems have been successfully performed[31m,304,306].



b. Reaction with azodicarbonyl compounds. Azodicarbonyl compounds react with enamines to give either 1,2-diazetidines (**361**) or 1,3,4-oxadiazino derivatives (**362**)[307]. With azo esters, enamines possessing a poor electron donor nitrogen or two substituents at the β-carbon form 1,2-cyclic adducts, whereas cyclic ketone enamines give the open-chain adducts (**363**)[308].

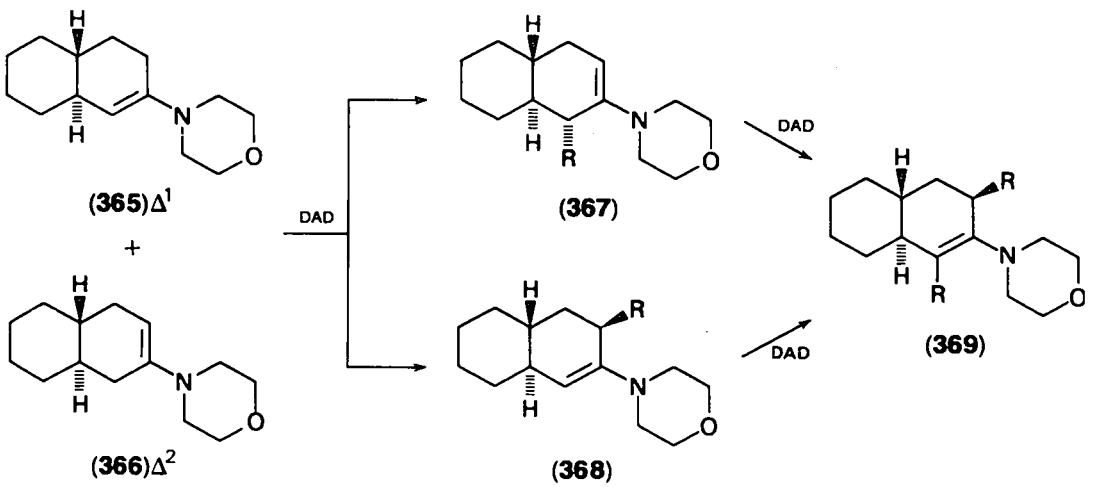


On the contrary, azoketones prefer 1,4-cycloaddition, both with linear[307b] and cyclic[309] ketone enamines. The *cis* fusion between the rings in the 1,3,4-oxadiazine **364** has been demonstrated by X-ray analysis[310].



(364)

The stereochemistry of addition of azo esters to cyclic enamines has been widely investigated, with particular attention to open-chain products[311]. Attack of diethyl azodicarboxylate (DAD) onto the enamine mixture derived from *trans*-2-decalone (**365** + **366**), occurs from the less hindered side of the molecules, i.e. from the β-side of the Δ^2-isomer and from the α-side of the Δ^1-isomer, to give **367** and **368** respectively. Further addition of DAD affords enamine **369** in both cases[311]. The reaction of DAD with nonequilibrium enamine mixtures has proved useful in determining the composition of the double-bond isomers[312].

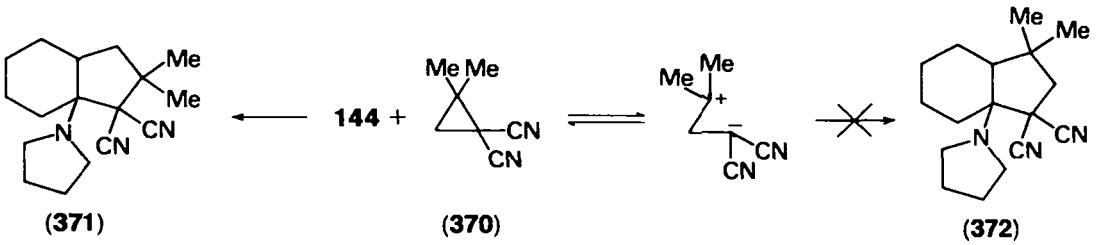


A [2 + 2]cycloaddition takes place between linear enamines and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione, in which the azodicarbonyl grouping is in a fixed *Z* configuration[313], to give 1,3,5-triazabicyclo[3.2.0]heptane-2,4-dione derivatives.

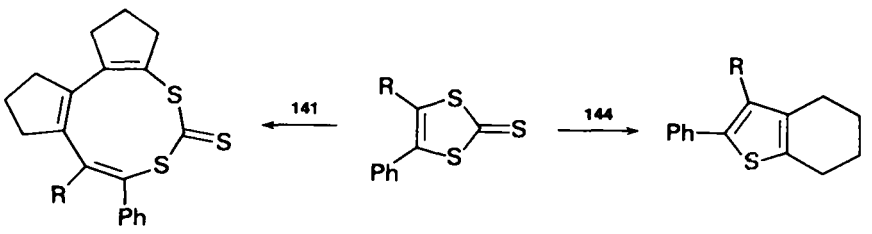
c. Reaction with activated cyclopropanes. Cyclopropane derivatives, such as 1-carbethoxy-1-cyanocyclopropane, give cycloaddition products with enamines[314]. With 1,1-dicyano-2,2-dimethylcyclopropane (**370**) and **144**, the reaction has been seen to proceed via an S_N2 mechanism, with formation of **371**, and not by preliminary opening of the cyclopropane adduct, which would lead to **372**[315].

d. Reaction with sulphur compounds. Sulphur and carbon disulphide have been widely employed in the synthesis of sulphur heterocyclic compounds starting from enamines[316].

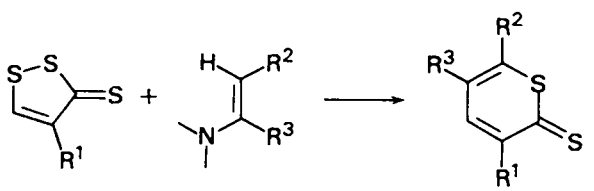
Heterocyclic sulphur compounds, such as **373**, react with enamines, leading to 1,3-dithionin-2-thiones (**374**) with pyrrolidinocyclopentene (**141**) and to tetrahydrobenzothiophene derivatives (**375**) with pyrrolidinocyclohexene (**144**)[317].



(371) (370) (372)



(374) (373) (375)



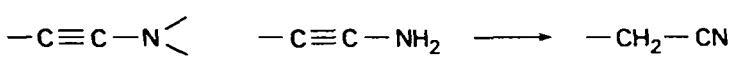
(376) (377)

R^1 = H, alkyl, aryl

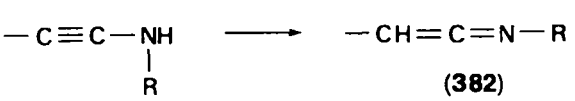
Different reactivity has been shown by 1,2-dithiole-3-thiones (**376**) unsubstituted at carbon 5 in their reactions with linear and cyclic enamines, in which α-thiopyranthiones (**377**) are always obtained[318].

III. YNAMINES

The *N,N*-disubstituted 1-ethynylamines, namely acetylenic systems possessing a tertiary nitrogen atom, are named ynamines (**378**). Primary (**379**) and secondary (**381**) acetylenic amines are expected to be more stable in the nitrile (**380**) and imine (**382**) form respectively.



(378) (379) (380)



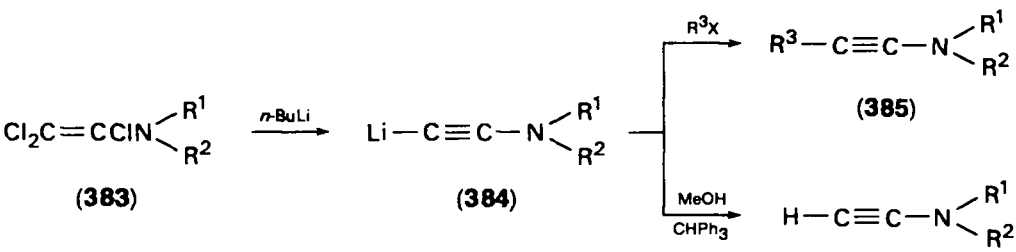
(381) (382)

A. Preparation

Ynamines can generally be prepared by substitution, elimination and isomerization reactions[8], and in some cases by special, unique methods.

1. Ynamines from activated alkynes

A general route to substituted ynamines (**385**) is the alkylation of lithium ynamines (**384**) by alkyl bromides or alkyl tosylates in HMPT[319]. The appropriate lithium ynamines (**384**) can be prepared from trichloroenamines (**383**) and *n*-butyllithium. The so-called free ynamines (**386**) are obtained from **384** by the action of mild acids, such as methanol[8] or triphenylmethane[319a].

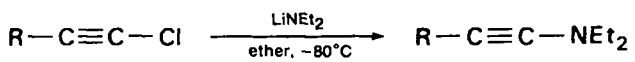


(**383**) (**384**) (**385**) (**386**)

R^1, R^2 = Alk, Alk; Alk, Ar

R^3 = Alk; X = Br, OTs

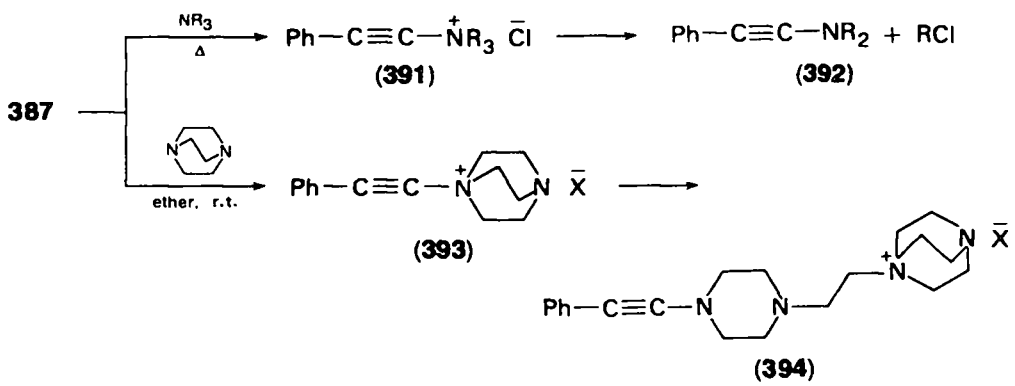
Chloroalkynes **387** and **388** give the corresponding ynamines **389** and **390** in high yield when treated with *N,N*-dialkyllithium amides[8]. Essential, however, is the presence of an electron-withdrawing group, such as phenyl or cyclohexen-1-yl[320]. Higher temperatures and complexing solvents, such as HMPT, are necessary if the alkyl group is *t*-butyl[320].



(**387**) R = Ph (**389**)

(**388**) R = C-C_6H_9 (**390**)

Haloalkynes, such as **387**, can also react with tertiary aliphatic[321] and bridgehead[322] amines to form the corresponding ynamines **392** and **394** through the unsaturated ammonium salts **391** and **393**.



(**391**) (**392**)

(**393**)

(**394**)

Several mechanistic possibilities have been proposed for these reactions[8,322]; the most probable involves α-addition of the base, followed by elimination of the halogen (equation 8).

$$-C\equiv C-X \xrightarrow{B^-} -\bar{C}=C\begin{matrix}X\\B\end{matrix} \xrightarrow{-X^-} -C\equiv C-B \qquad (8)$$

Easily accessible acetylenic ethers (**395**) have also been used, in particular for the synthesis of *C*-alkylynamines (**396**) (except when R^1 is methyl), by heating with lithium dialkylamides[323]

$$R^1-C\equiv C-OEt \xrightarrow[\Delta]{LiNR_2^2} R^1-C\equiv C-NR_2^2$$

(**395**) (**396**)

2. *Ynamines from haloethenes*

Ynamines can be prepared by the action of lithium dialkylamides on the appropriate dihaloethenes[324] or dihaloenamines[319a]. By this method, *t*-butylynamines (**397**) and phenylynamines (**398**) can be prepared. α-Chloroenamines can undergo dehydrochlorination by a weak base, at room temperature, to yield the corresponding ynamines[293].

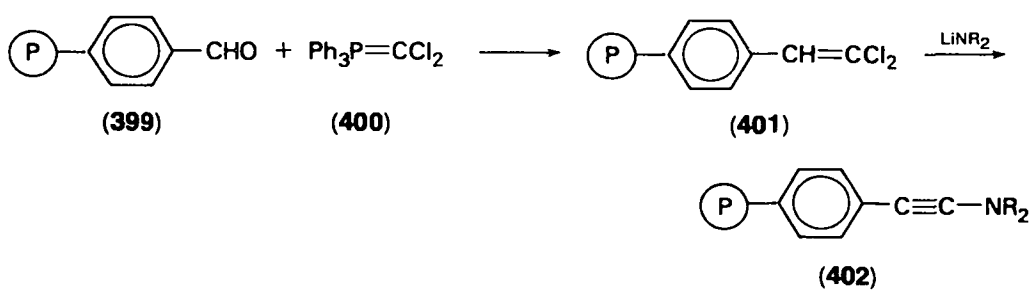
$$t\text{-Bu}-CCl=CHF \xrightarrow{LiNR_2} t\text{-Bu}-C\equiv C-NR_2$$

(**397**)

$$Ph-CCl=CCl-NEt_2 \xrightarrow{LiN(Bu\text{-}n)_2} Ph-C\equiv C-N(Bu\text{-}n)_2$$

(**398**)

A polymeric β-dichlorostyrene derivative (**401**) has been prepared from a formylated resin (**399**) and dichloromethylenetriphenylphosphorane (**400**). Treatment of **401** with lithium dialkylamide affords the resin-bound ynamine **402**[325].



(**399**) (**400**) (**401**)

(**402**)

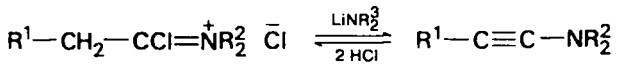
3. *Miscellaneous methods*

A prototropic isomerization of *N,N*-dialkylprop-2-ynylamines, such as **403**, has been found to give the corresponding ynamines (**404**) in good yield[326].

$$HC\equiv C-CH_2-NR_2 \xrightarrow[C_6H_6]{KNH_2/Al_2O_3} Me-C\equiv C-NR_2$$

(**403**) (**404**)

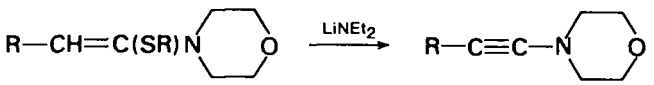
Among eliminations, the dehydrohalogenation of α-haloiminium salts[23b], such as **405**, by means of lithium dialkylamides is reported[327].



(405)

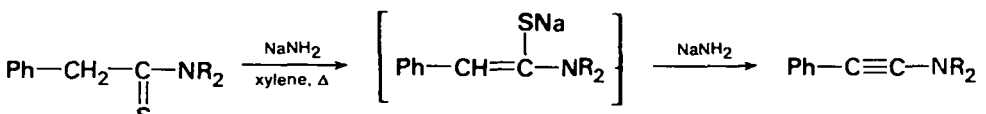
R^1 = H, Me, *n*-Pr; R^2 = Et, NR^2_2 = pyrrolidino; R^3 = Me, Et, *c*-C_6H_{11}

Thiol elimination with base from ketene *S,N*-acetals (**406**)[327] or elimination of sulphur hydride from phenyl thioacetamides (**407**) by sodium amide are also successful methods.[328]



(406)

R = H, Ph



(407) **(392)**

R = Me, Et; NR_2 = morpholino

B. Physical Properties

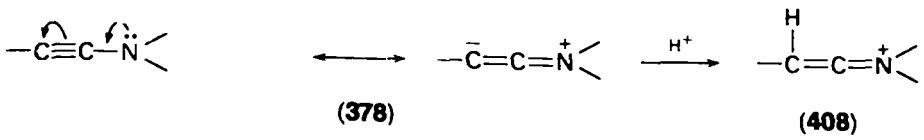
Unlike enamines, ynamines are stable, particularly when substituted at the β-carbon. Their stability is also dependent on the type of substitution at nitrogen, *N*-aryl-substituted ynamines being more stable than the corresponding *N*-alkyl ones[319a].

The IR spectrum of ynamines shows the triple-bond stretching at 2220–2240 cm^{-1} as a strong band. Additional conjugation with C=O and C=C double bonds causes a bathochromic shift to 2160–2190 cm^{-1} [8]. A bathochromic shift towards 2130 and 2050 cm^{-1} is also observed when the β-carbon bears SR, H and Li respectively. The ≡C—H stretching band of free ynamines absorbs at about 3280–3295 cm^{-1} [8], depending upon the nature of the substituents at nitrogen.

The ^{1}H-NMR spectrum of free ynamines is characterized by the presence of a singlet at about 2.3 δ if the substituents at nitrogen are both alkyl groups, and at about 2.7 δ, if one of them is an aryl group[8].

C. Reactions

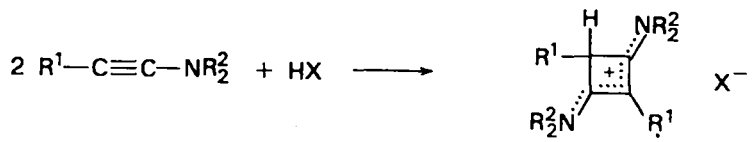
As for enamines, the reactivity of ynamines can be ascribed to the conjugation of the nitrogen lone pair with the π-electrons of the multiple bond. Therefore ynamines can undergo electrophilic attack on the β-carbon. Nucleophilic attack on the α-carbon of the ketene iminium form (**408**) can also take place, e.g., in the presence of an acid catalyst.



(378) (408)

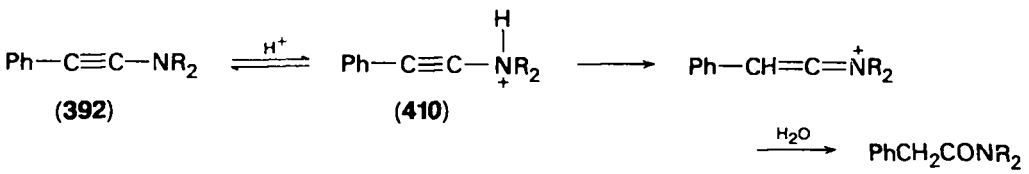
1. Protonation and hydration

The nonaqueous protonation of ynamines generally leads to the cyclobutenylcyanines **409** whose structures have been proved by spectral data and chemical reactivity[329,330]. The simplest method of protonation involves treatment of ynamines with salts of weak tertiary amines, such as *N,N*-dimethylaniline[331].



(409)

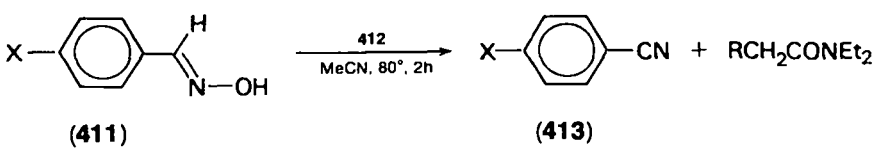
In aqueous solution, ynamines are protonated at nitrogen, with a reversible initial formation of an unsaturated ammonium salt (**410**)[332]. For the subsequent



(392) (410)

rate-determining *C*-β-protonation, a concerted process is postulated, in which both proton removal and donation occur, at least in acetic acid–sodium acetate buffer and for 1-amino-2-phenylacetylenes[332].

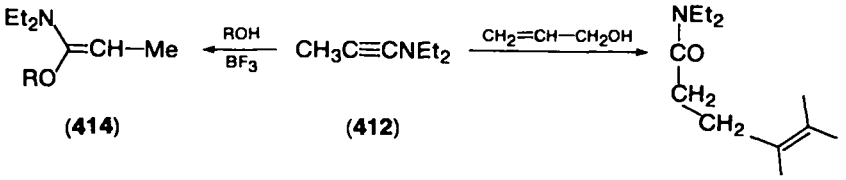
By the use of ynamines as dehydrating agents in the synthesis of peptides it is possible to avoid racemization[8]. Removal of water by ynamines is so efficient that formation of acid anhydrides and esters is readily achieved[320]. Also, benzonitriles (**413**) in good yield can be obtained from the corresponding benzaldoximes (**411**) with *N,N*-diethylaminopropyne (**412**)[333].



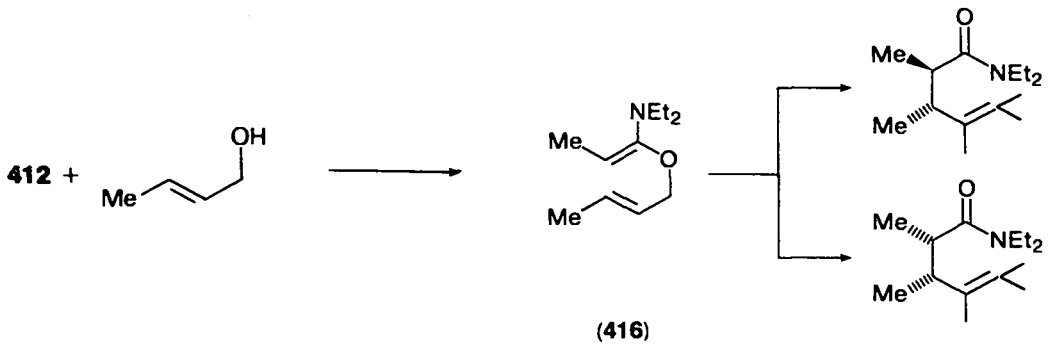
(411) (413)

X = H, Cl, NO_2, COMe

Alcohols also add to the carbons of ynamines, such as **412**, in the presence of BF_3 to give the corresponding *N,O*-ketene acetals (**414**)[329]. With allylic alcohols, however, the final product is a γ-unsaturated amide (**415**), derived through Claisen rearrangement. The mechanism of the ynamine–Claisen rearrangement in the reaction between crotyl alcohol and **412** has been proved to proceed via the kinetically formed (*E*)-ketene *N,O*-acetal **416**[334].



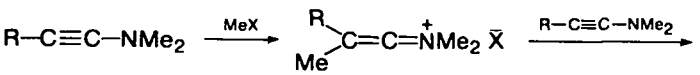
(414) (412) (415)



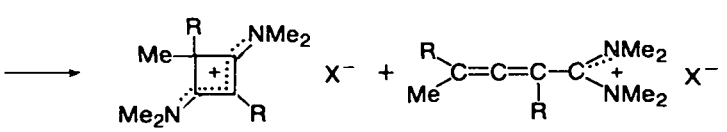
(416)

2. Alkylation

Direct alkylation at the β-carbon of ynamines by alkyl halides does not occur, contrary to the case with enamines. The reaction is in fact more complex, since the mechanism involves attack of a second molecule of the parent ynamine on the alkylated ketene iminium intermediate (**417**), followed by intramolecular *C*- and/or *N*-transalkylation[329,331]. When R is *t*-butyl, both **418** and **419** are formed, whereas only 418 is obtained for R = phenyl[331]. This different behaviour between enamines and ynamines could be ascribed to the different stability of the respective iminium salt intermediates, being greater for ynamines than for enamines.



(417)



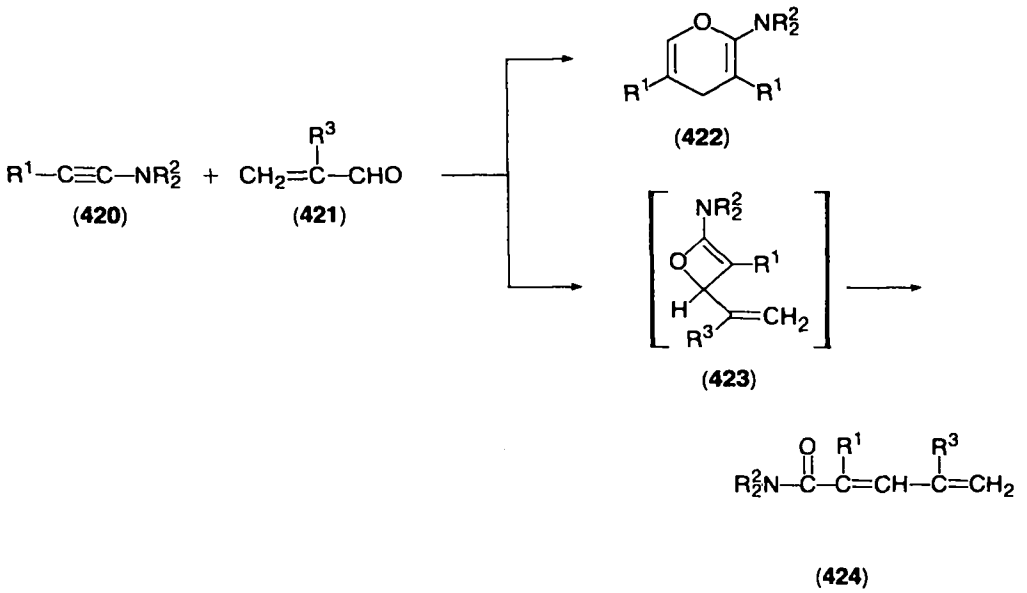
(418) (419)

R = *t*-Bu, Ph; X = Br, I

3. Reaction with electrophilic olefins

The reaction of electrophilic alkenes with ynamines produces one or both of the 1,2- and 1,4-cycloaddition products[9].

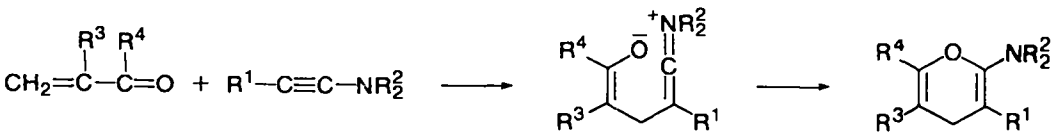
The treatment of ynamines (**420**) with α,β-unsaturated aldehydes (**421**) results in the formation of γ-pyranes (**422**) as well as compounds (**424**), the latter through a



(420) (421) (422) (423) (424)

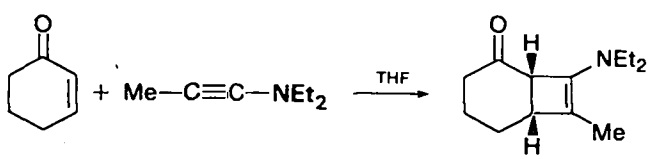
probable oxetene intermediate (**423**) derived from 1,2-cycloaddition of the carbonyl group to the ynamine[335,336].

Linear α,β-unsaturated ketones (**425**) with no bulky group at the β-position add to ynamines to give amino-γ-pyranes (**427**), through a ketene iminium intermediate (**426**)[335–337]. A concerted mechanism has also been postulated for this 1,4-cycloaddition reaction[144b].



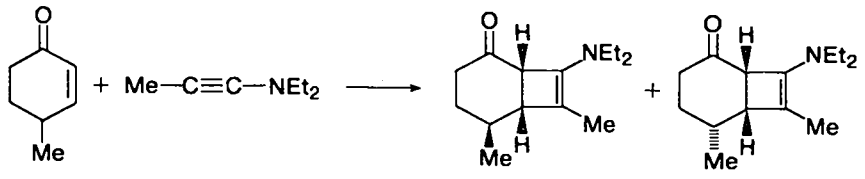
(425) (420) (426) (427)

On the other hand, cyclic α,β-unsaturated ketones, e.g. 2-cyclohexenone (**428**), which are in fixed *s-trans* geometry, give 1,2-cycloaddition compounds (**429**) as the sole products[338].



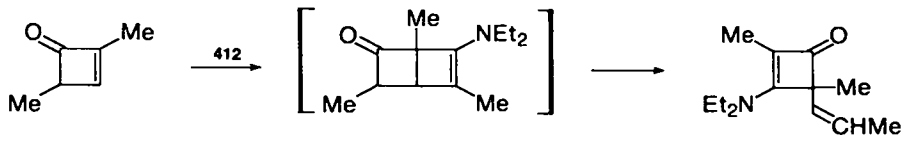
(428) (412) (429)

These reactions are of interest from the stereochemical point of view, being stereospecific as far as the fusion between the rings. Thus, reaction of 4-methylcyclohex-2-en-1-one (**430**) with *N,N*-diethylaminopropyne (**412**) leads to a 4:1 mixture of stereoisomeric *cis*-fused bicyclo[4.2.0]octane systems **431** and **432**[339]. The mechanism involves a two-step process through a zwitterion intermediate[338c]. In the presence of $MgBr_2$, the carbonyl group becomes the exclusive site of attack by the ynamines, affording dienamide compounds[9].



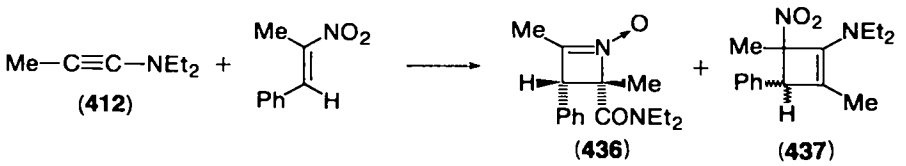
(430) (412) (431) (432)

The cyclobutenone **433** affords the aminocyclobutenone **435**, through the probable intermediacy of the bicyclo[2.2.0]hexenone **434** and subsequent concerted rearrangement[340].



(433) (434) (435)

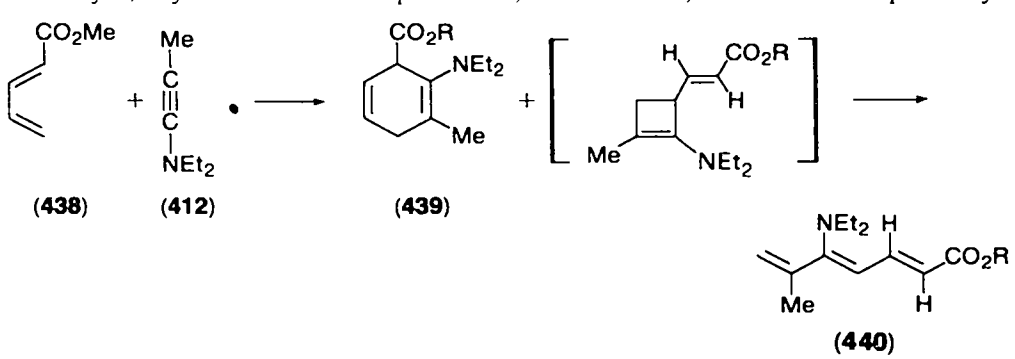
Acyclic α,β-unsaturated esters react with ynamines to give cyclobutene derivatives as well as γ-pyranes[341]. Cyclobutene enamine systems are also produced by 1,2-cycloaddition of α,β-unsaturated nitriles to ynamines[342], as well as by reaction of nitro olefins[343]. In this latter case stable cyclic nitrones, such as **436**, have been separated, together with a certain amount of **437**.



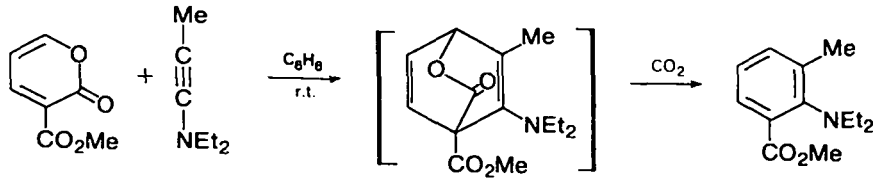
(412) (436) (437)

4. *Reaction with electrophilic dienes*

With electrophilic dienes ynamines undergo 1,2- as well as 1,4-cycloaddition, depending on the steric arrangement of the dienes. The *cisoid* conformation of the diene is essential to its reactivity, as demonstrated by the lack of reactivity shown by fixed *transoid* activated dienes[9]. The 1,2-cycloaddition predominates over the 1,4-cycloaddition in the reaction with linear dienes (**438**), whereas with cyclic diene **441** only 1,4-cycloaddition takes place[9,344b], to afford **439**, **440** and **442** respectively.

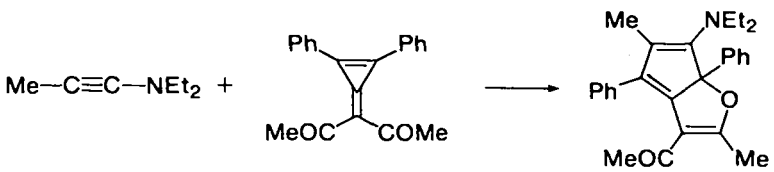


(438) (412) (439) (440)

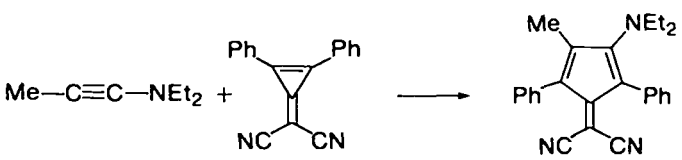


(441) (412) (442)

Also known are the 1,2-cycloadditions of particular activated dienes such as **443** and **445** to ynamine (**412**)[345]. Formation of bicyclic[2.1.0]pentene intermediates is followed by rearrangement to the corresponding heterocyclic (**444**) and fulvene (**446**) derivatives.



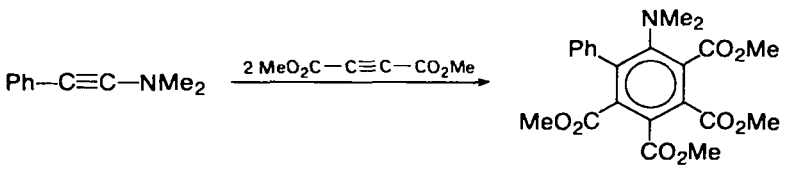
(412) (443) (444)

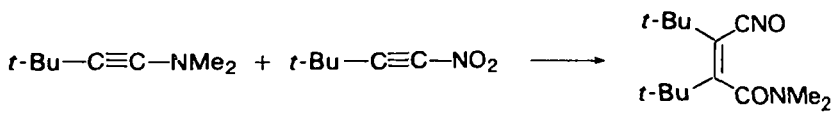


(412) (445) (446)

5. *Reaction with activated acetylenes*

Polysubstituted benzenes are formed by condensation of two moles of DMAD with one mole of ynamines[8]. In contrast, the nitroacetylene **448** adds to the ynamine **447** to give the nitrile oxide derivative **449**[346].



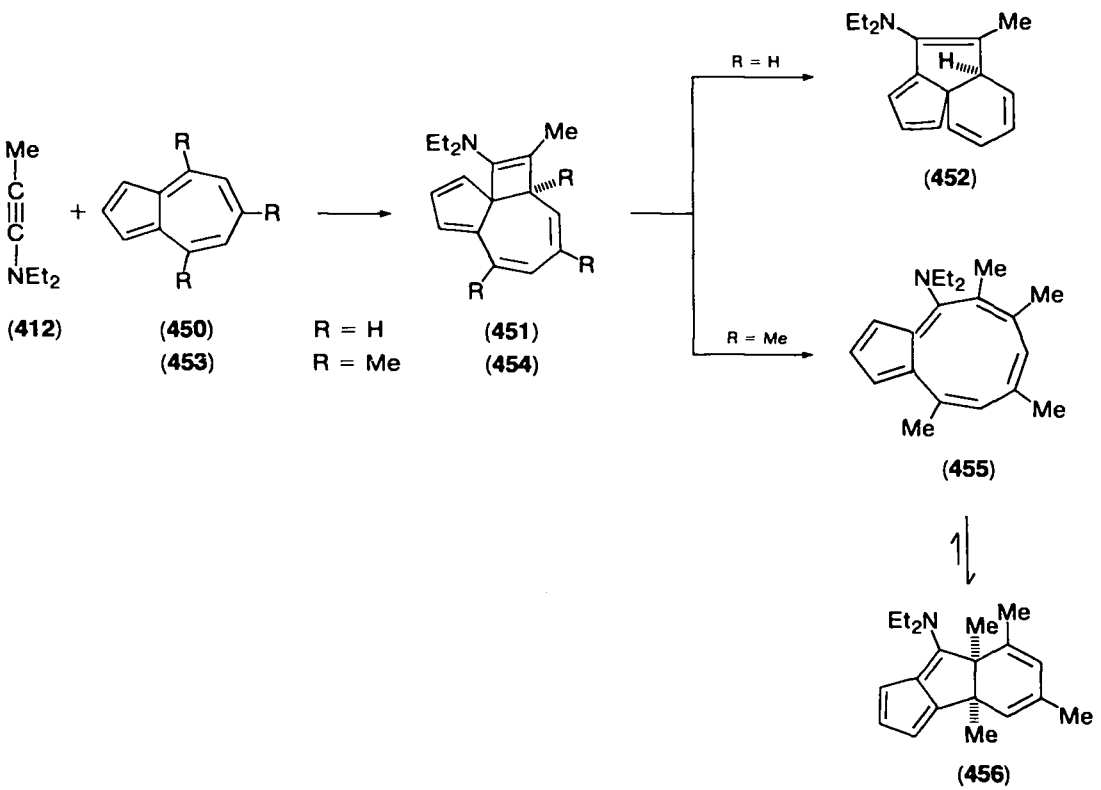


(447) (448) (449)

6. *Reaction with aromatic systems*

Reactions of ynamines with azulene and its derivatives are accompanied by either sigmatropic rearrangement or valence isomerization, depending upon the type of

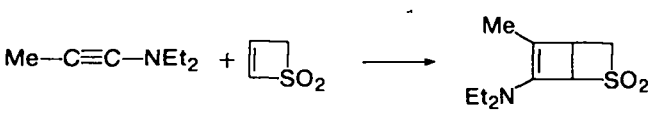
substitution in the aromatic compound. Thus azulene (**450**) and 4,6,8-trimethylazulene (**453**) react with **412** to give a bridged spiro[4,5]decatetraene (**452**) and a dihydrocyclopentaindene derivative (**456**) respectively, via the intermediacy of 1,3-diene bridged spiro[3,4]octa-1,5,7-triene derivatives **451** and **454**. Compound **452** derives from the intermediate **451** by a sigmatropic ring-enlargement, while **456** is formed from the cyclopentacyclononene derivative **455**, by a valence isomerization reaction[347]. The reaction conditions are different, as **450** reacts even at room temperature, whereas **453** needs boiling tetraline to react.



(412) (450) (453) R = H R = Me (451) (454) (452) (455) (456)

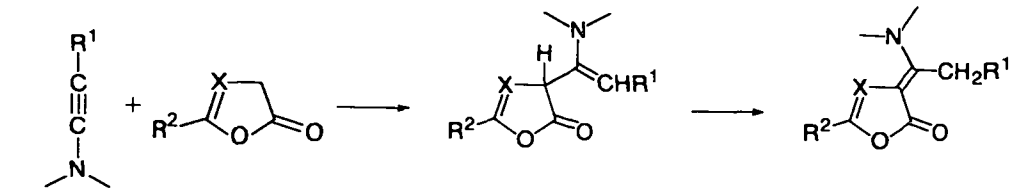
7. *Reaction with activated heterocycles*

Ynamines react with α,β-unsaturated sulphones, such as thietene-1,1-dioxide (**457**), to yield cycloaddition products, such as **458**[348].



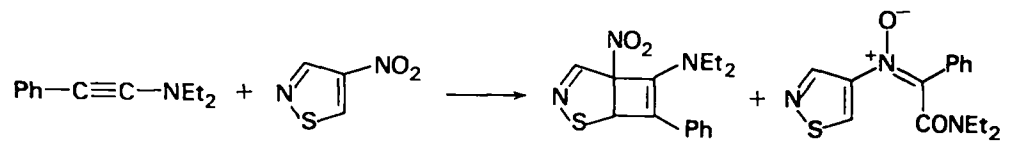
(412) (457) (458)

Unlike δ-enol lactones (see Section III.A.8), γ-enol lactones (**459**)[349] as well as 5-oxazolones (**462**)[350], possessing a methylene group α to the carbonyl group, react with ynamines at C-4 to give enaminones **461** and **464** respectively, through prototropic isomerization of the enamine intermediates **460** and **463**.



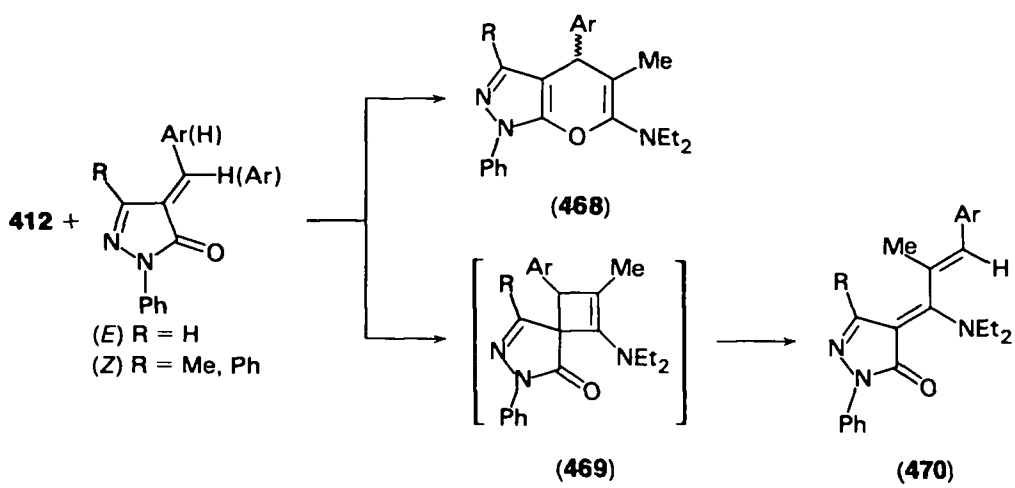
R^1 = Me, Ph (459) R^2 = Me, X = CH (460) (461)
(462) R^2 = Ph, X = N (463) (464)

A 1,2-cycloaddition occurs between ynamines such as diethylaminophenylacetylene (**389**) and 4-nitroisothiazole (**465**) to yield **466**[351]. A concomitant addition to the nitro group, favoured by polar solvents, with successive opening to nitrone **467** is also observed.



(389) (465) (466) (467)

The reaction of diethylaminopropyne (**412**) with 4-arylmethylene-5-pyrazolones leads to mixtures of [4 + 2]cycloaddition products (**468**) and open-chain adducts (**470**), the latter deriving from opening of the [2 + 2]adduct intermediate (**469**)[352]. Compounds **470** have been assigned the (4*Z*–2′*E*) configuration, on the basis of ^{1}H-NMR and NOE analyses, together with the X-ray analysis of one of them.

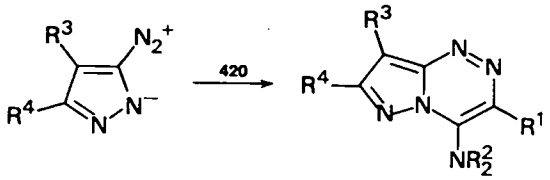


(*E*) R = H
(*Z*) R = Me, Ph

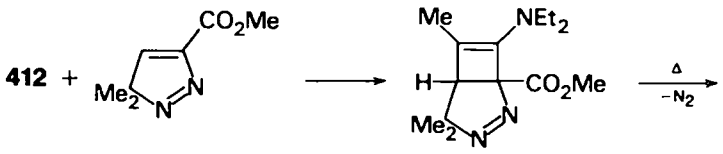
(468) (469) (470)

Numerous diazo-azolo derivatives (**471**) have been allowed to react with ynamines to give 4-aminoazolo[5,1-*c*][1,2,4]triazines (**472**), through a [4 + 2]cycloaddition reaction[353].

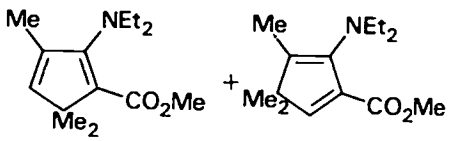
A rapid [2 + 2]cycloaddition reaction takes place at room temperature between ynamines such as **412** and methyl 3,3-dimethyl-3*H*-pyrazole-5-carboxylate (**473**) affording **474** in quantitative yield[354]. Thermolysis of **474** gives the cyclopentadiene derivatives **475** and **476** in ratio 6:1, by loss of nitrogen and rearrangement.



(471) (472)



(473) (474)

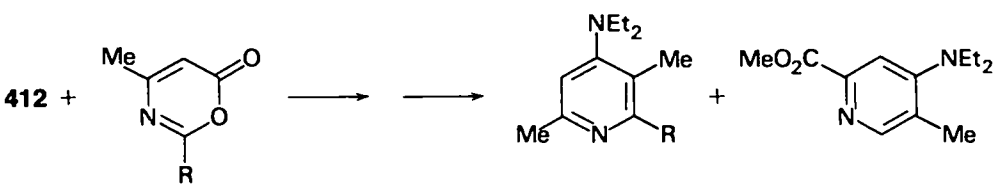


(475) (476)

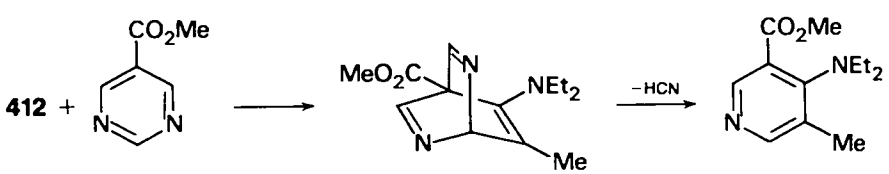
1,3-Oxazin-6-ones (**477**)[355], pyrimidines (**480**)[356], 1,2,4-triazines (**482**)[357] and tetrazines (**484**)[358] have been found to react regiospecifically with ynamines such as **412**. Aromatic heterocycles **478**, **479**, **481**, **483** and **485** are the resulting products, derived by retro-Diels–Alder reactions of the intermediates, which in some cases have been proposed to have azabicyclo structures.

8. *Acylation*

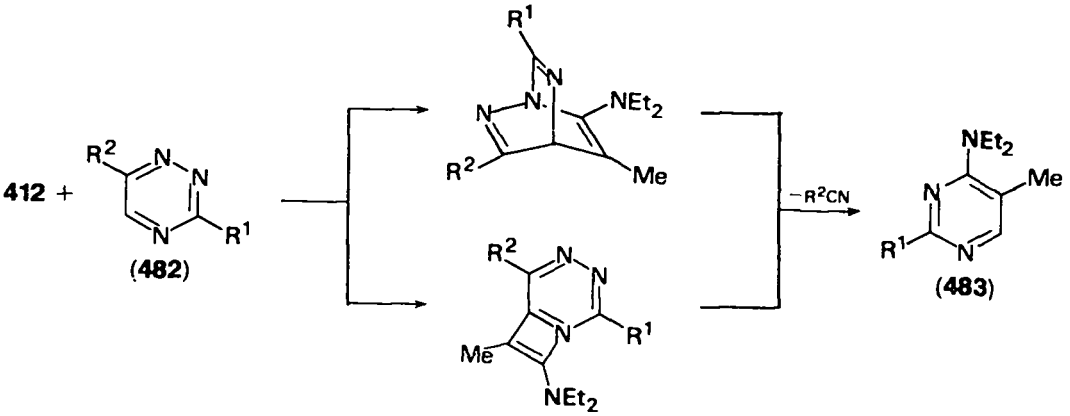
Linear acylating agents, such as carboxylic acid chlorides[291,329], phosgene[291], thiophosgene[291], thionyl chloride[359] and aromatic sulphonyl chlorides[359] add to

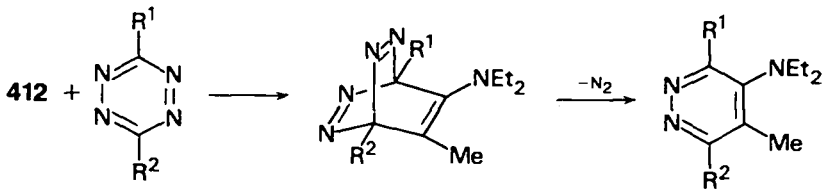


(477) (478) (479)

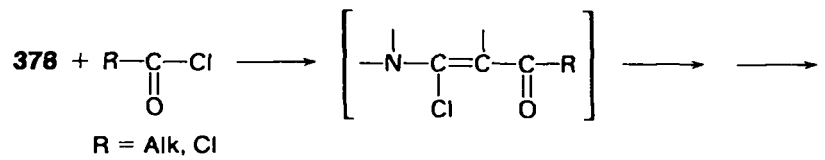


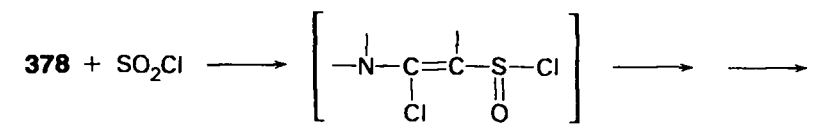
(480) (481)

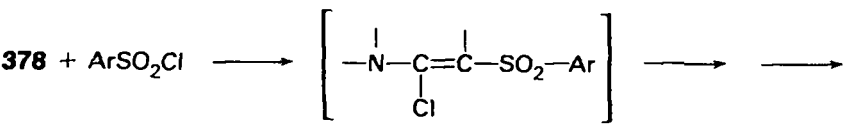




ynamines to give α-chloroenamine derivatives, which cannot be isolated but undergo further reactions with bifunctionalized nucleophiles to give heterocyclic compounds, such as pyrazolones, isoxazoles and pyrimidines[359].

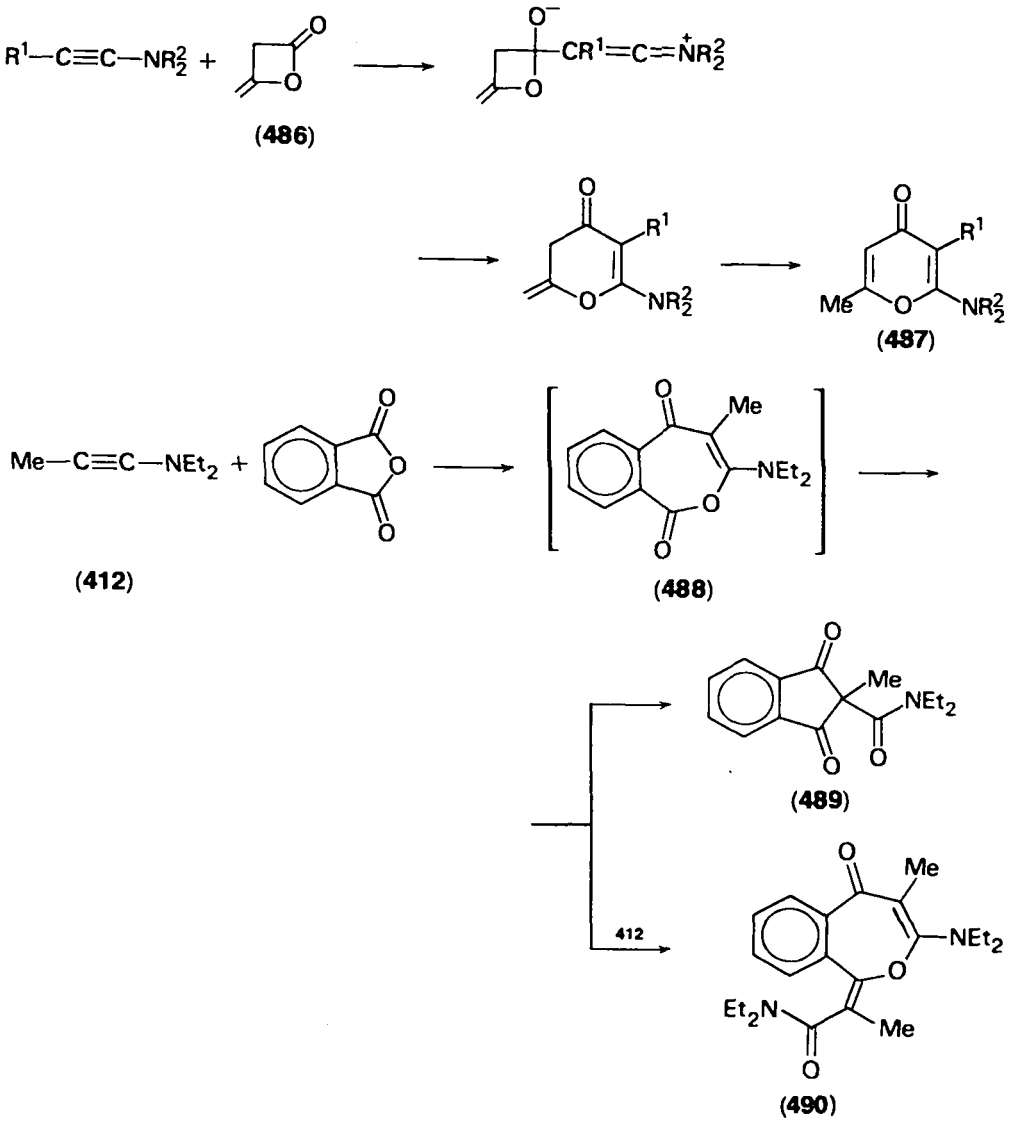






In the case of cyclic acylating agents, such as ketene dimers and six-membered enol lactones[360,361], the initial β-attack is followed by an intramolecular α-attack to give heterocyclic compounds. For instance diketene (**486**) reacts with ynamines to afford the γ-pyrone derivative **487** as the main product.

With phthalic anhydride and **412**, the indandione derivative **489** is obtained by rearrangement of the benzoxepinone intermediate **488**. The intermediate **488** can add a second molecule of ynamine to give **490**.

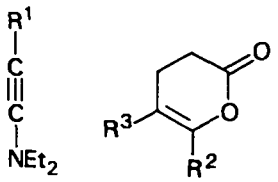


When a δ-lactone such as **491** is allowed to react with an ynamine, a variety of products can be obtained from the initially formed dipolar intermediate (**492**)[362].

The α,β-unsaturated amide **494** derives from electrocyclic-opening of the spiro compound **493**, while the enaminoketone **496** is formed by intramolecular cyclization of the linear ketene iminium intermediate **495**. The ratio of the final products **494** and **496** is dependent on the nature of the parent ynamine as well as on the solvent[362].

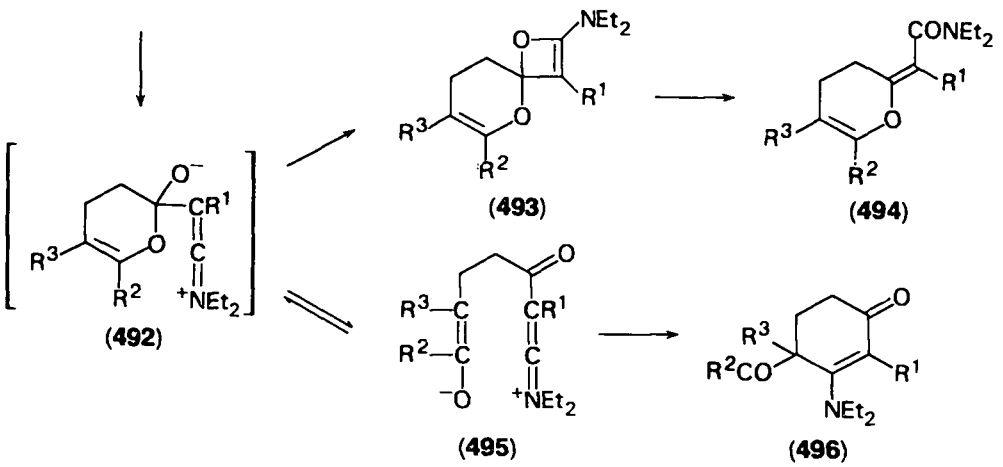
Acylating agents of interest are the α- and β-amino esters such as **497**, which add to ynamines (**420**) to give the enediamine intermediate **498**. Intramolecular acylation leads to the desired heterocyclic compounds (**499**)[363].

On the other hand, ynamines themselves can act as acylating agents towards, for example, γ-lactones (**459**)[349] and oxazolones (**462**)[350], through hydrolysis of the

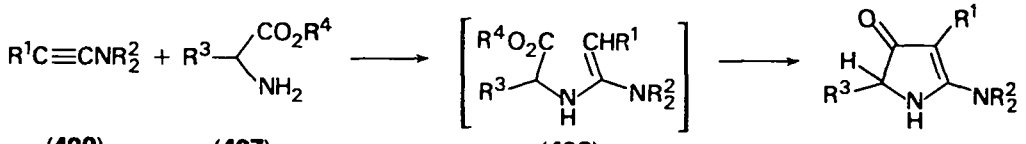


(491)

R^1 = Me, Ph; R^2 = Me, Ph; R^3 = H, Me



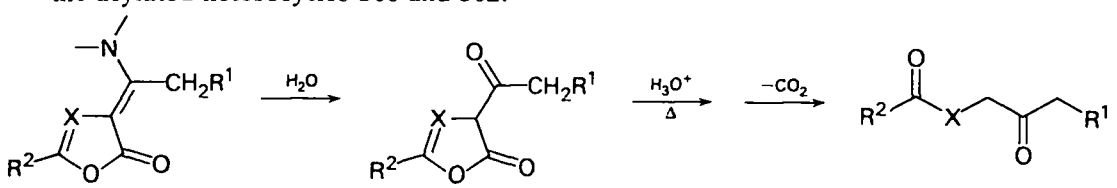
(492) (493) (494) (495) (496)



(420) (497) (498) (499)

R^1 = Me, Ph; R^2 = Me, Et; R^3 = H, Me; *i*-Pr, *i*-Bu; R^4 = Me, Et

enamine intermediates **461** and **464**. These latter are precursors of 1,4-dicarbonyl compounds **501** and **503** respectively, formed by hydrolysis and decarboxylation of the acylated heterocycles **500** and **502**.



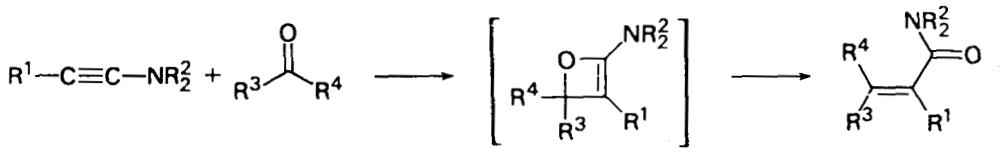
(**461**) R^2 = Me, X = CH (**500**) (**501**)

(**464**) R^2 = Ph, X = N (**502**) (**503**)

R^1 = Me, Ph

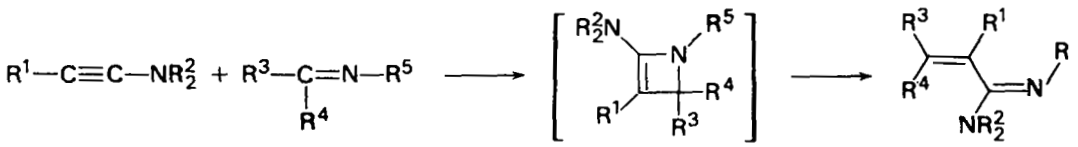
9. *Reaction with carbonyl and azomethine derivatives*

The carbonyl groups of saturated aldehydes, ketones, esters and lactones undergo 1,2-cyclization in the presence of Lewis acids such as BF_3 or $MgBr_2$. The initially formed intermediates (**504**) open to α,β-unsaturated amides (**505**)[364,365].

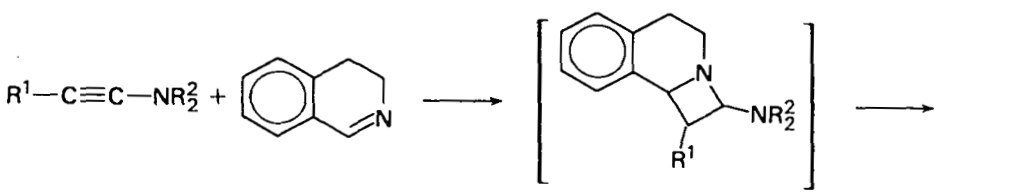


(420) (504) (505)

1,2-Cycloaddition reactions of ynamines to the azomethine groups of ketimines[366] are also known. In the case of linear systems (**506**), α,β-unsaturated amidines (**508**) are formed via an azetine intermediate (**507**). When the C=N group is part of a ring, as for example in **509**, ring-enlargement takes place giving **510**.



(420) (506) (507) (508)



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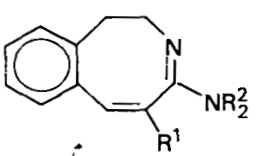
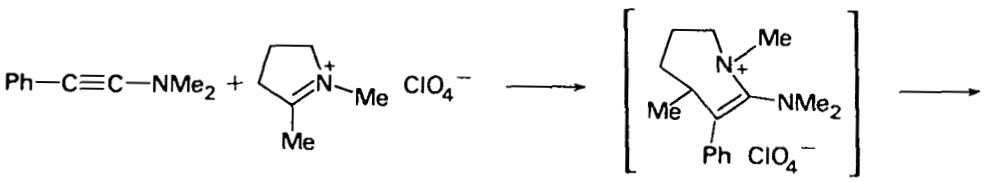
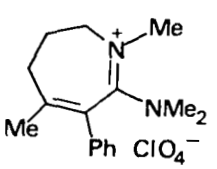


(510)

Iminium salts also react with ynamines[367]. For instance, from a heterocyclic system such as **512**, an expanded ring product (**513**) is obtained with **511**.



(511) (512)

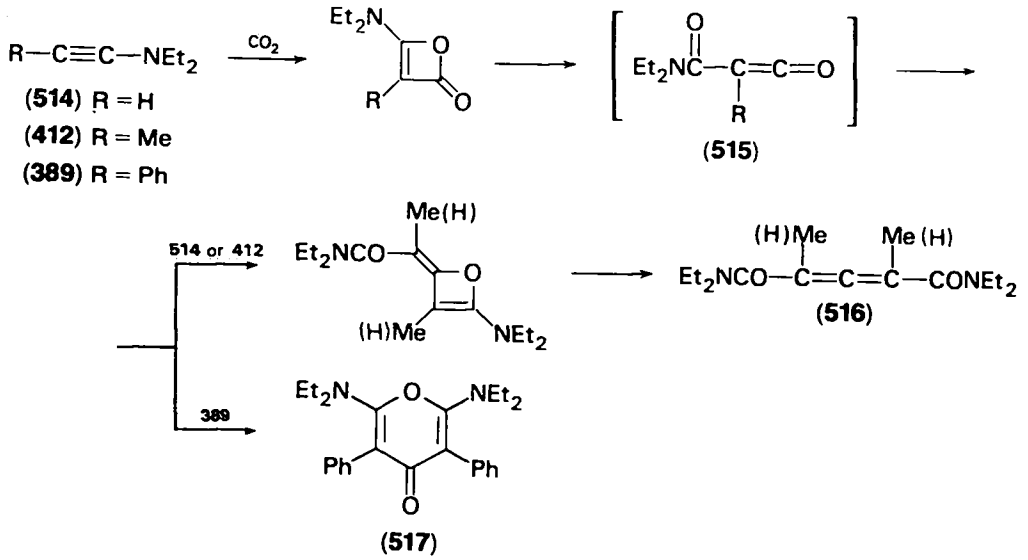


(513)

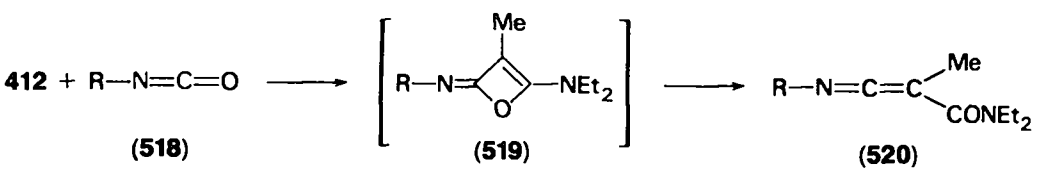
10. Reaction with heterocumulenes

Heterocumulenes such as carbon dioxide, alkyl and aryl isocyanates, ketenes and sulphenes undergo cyclization with ynamines.

Carbon dioxide[9] reacts with ynamines to give double-addition products. From free or aliphatic ynamines **514** and **412**[368] allenedicarboxylic diamides (**516**) are formed by addition of a second molecule of ynamine to the ketene-amide intermediates (**515**). With aromatic ynamines such as **389**[369], α,α′-diamino-γ-pyrones (**517**) are the major products, derived from [4 + 2]cycloaddition of the parent ynamine to **515**.



Alkyl isocyanates (**518**) undergo 1,2-cycloaddition followed by opening of the four-membered ring adducts (**519**) to give carbamoyl ketene imines (**520**)[370a].

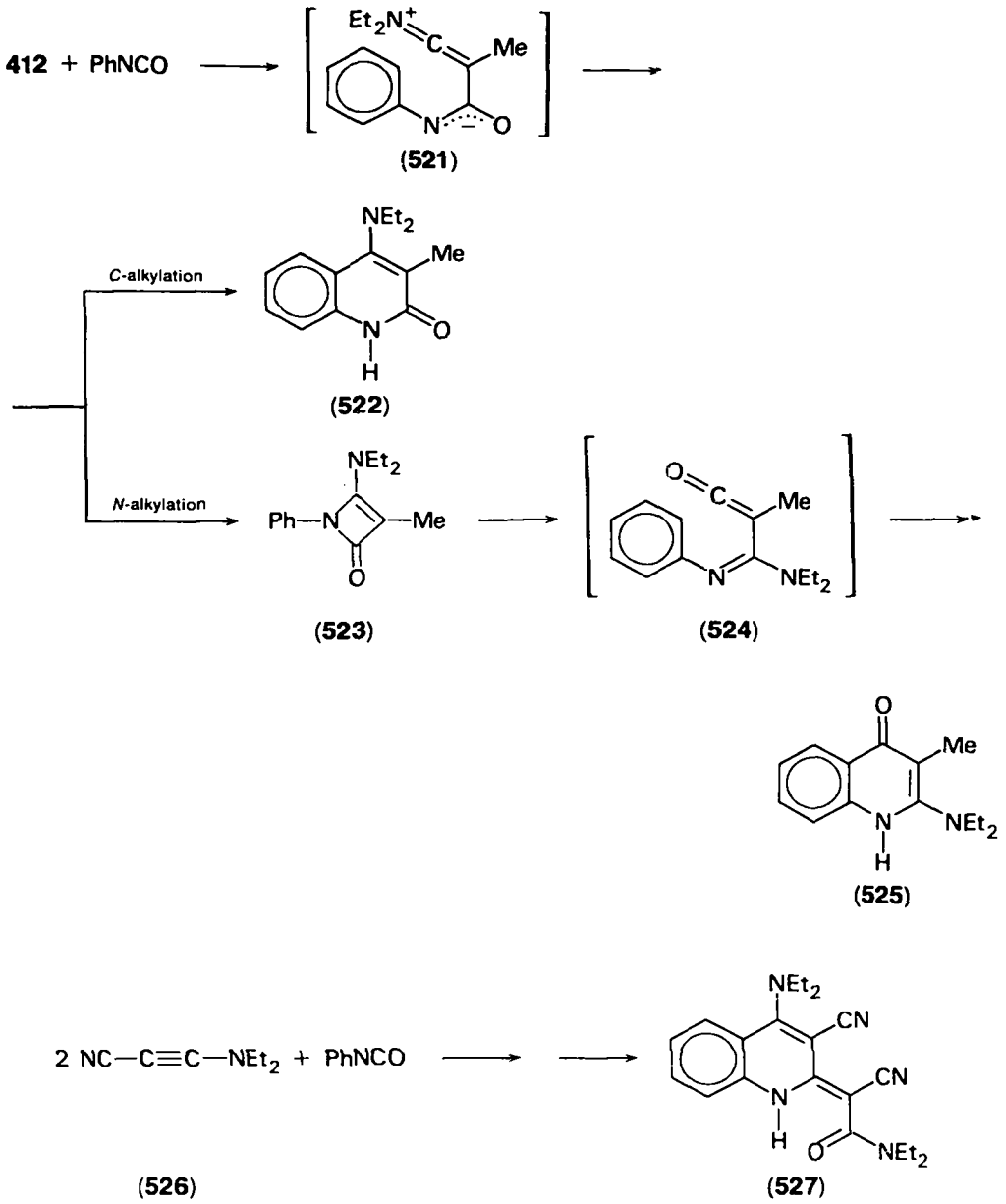


On the other hand, aryl isocyanates lead to mixtures of products deriving from intramolecular *N*- and *C*-alkylation[9,370b]. For example, **412** reacts with phenyl isocyanate to give 4-amino-2-quinolone (**522**), by 1,4-addition, together with 2-amino-4-quinolone (**525**), by initial 1,2-addition, followed by ring-fission in the heterocycle **523** and final cyclization via the imino-ketene form **524**[370d].

With aryl isocyanates, the reactions are solvent-dependent, both for products and for rate, thus supporting the existence of the dipolar intermediate **521**[370b].

In the reaction between *N*,*N*-diethylcyanoynamine (**526**) and phenyl isocyanate the major product is the 2:1 adduct **527**[371]. Its formation is postulated to occur via [2 + 2]cycloaddition of the ynamine to the carbonyl group of the electrophile followed by ring-opening and further addition of a second molecule of the parent ynamine.

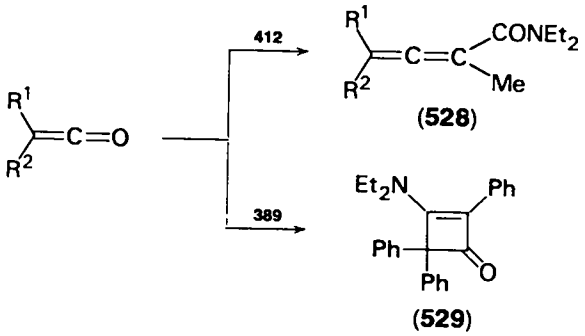
The reactions of ketenes with ynamines follow a different course, depending on whether ynamines are aliphatic or aromatic. The main product seems to be an allene



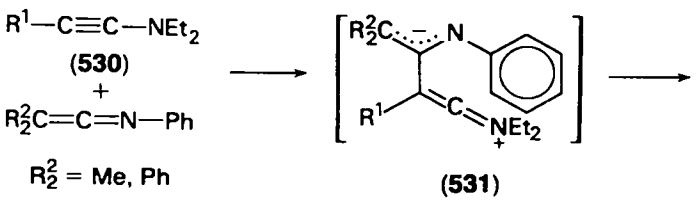
carboxylic amide (**528**) in the former case, and an enaminocyclobutenone system (**529**) in the latter[9,372] although a different interpretation of the results has been reported[370d].

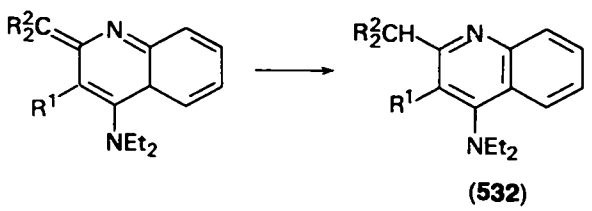
Ketene imines undergo slow reaction with ynamines (**530**), to furnish 4-aminoquinoline derivatives (**532**), through a dipolar intermediate (**531**), as indicated by the solvent dependence of the reaction[373].

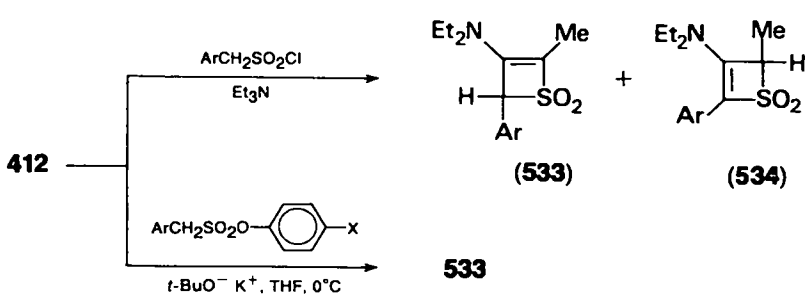
Sulphenes, generated *in situ* from alkanesulphonyl chlorides[370d,374] and a base, react with ynamines, such as **412**, to give isomeric mixtures of 3-aminothieten-



R^1 = Ph; R^2 = H, Ph
R^1 = Me; R^2 = $CONEt_2$





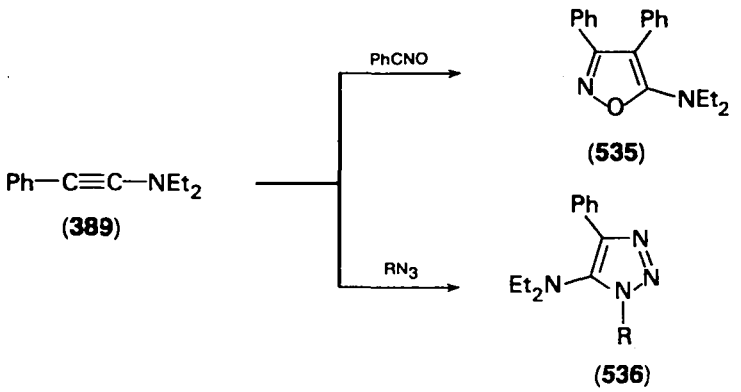


1,1-dioxides **533** and **534**. The use of aryl methanesulphonate derivatives leads to the exclusive formation of isomer **533**[375].

11. 1,3-Cycloaddition

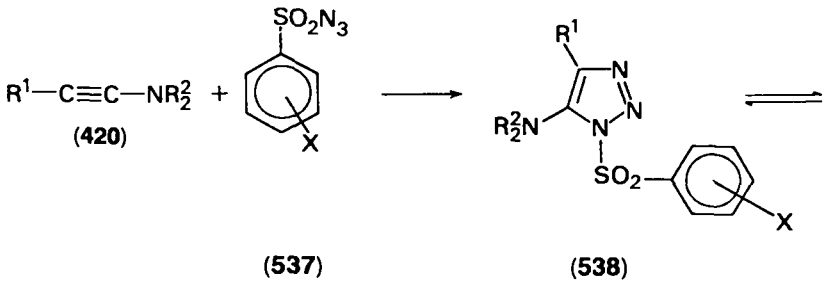
Unlike enamines, few examples are reported in which ynamines react as dipolarophiles towards 1,3-dipoles[370d,376]. They react in a regiospecific manner, probably with a concerted mechanism.

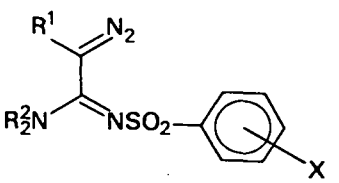
For instance, ynamine **389** reacts with benzonitrile oxide to give the corresponding isoxazole derivative **535**. In a similar manner, aryl and aroyl azides undergo 1,3-cycloaddition with **389** to yield triazole derivatives **536**[370d].



R = Ar, ArCO

The reactions of ynamines with arylsulphonyl azides (**537**) lead to 1,2,3-triazoles (**538**) and/or α-diazoamidines (**539**)[377,378]. A ring-chain tautomerism between **538** and **539** has been observed, its composition depending upon the substituents of both the ynamines and 1,3-dipoles. In particular the open-chain forms (**539**) are favoured by the presence of electron-withdrawing groups in the sulphonyl aryl group. The





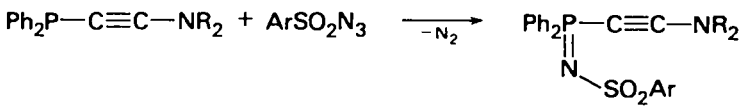
R^1 = H, alkyl, aryl, acyl, $-\overset{O}{\overset{\|}{P}}Ph_2$, $-\overset{S}{\overset{\|}{P}}Ph_2$, $-\overset{Se}{\overset{\|}{P}}Ph_2$

R^2 = alkyl, aryl

X = *p*-Me, *p*-NO_2, *p*-NMe_2, *p*-OMe, *p*-Cl

stability of the cyclic form (**538**) is also influenced by substituents at the β-carbon of the ynamine. Free ynamines for instance afford only the diazoamidine isomers.

Similarly, phosphoryl-, thiophosphoryl- and selenophosphoryl-ethynylamines react with arylsulphonyl azides to give 1:1 adducts, which can be either 5-amino-1,2,3-triazoles or diazoamidines. On the contrary, phosphinoethynylamines (**540**) react with the same 1,3-dipoles, regiospecifically at phosphorus, leading to phosphorimidoethynylamino derivatives (**541**)[377c].

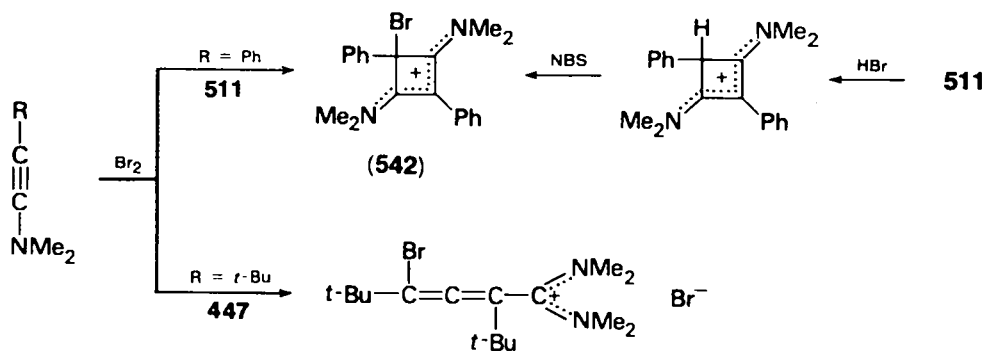


(**540**) (**541**)

The diazoamidine forms largely predominate in the equilibrium mixtures when the starting ynamines are metallated ynamines, such as silylethynyl-, germylethynyl- and stannylethynyl-amines[379].

12. Reaction with halogens

Only the bromination of ynamines has been studied by Fuks and Viehe. This reaction is influenced by the nature of the substituent at the β-carbon of the ynamine. In fact, reaction of **511** with the dioxane–dibromide complex affords as the exclusive product the bromocyclobutenylcyanine **542**, which can also be prepared by a different route. In contrast, **447** yields the bromoallenamidinium bromide **543** quantitatively[331].



(**542**)

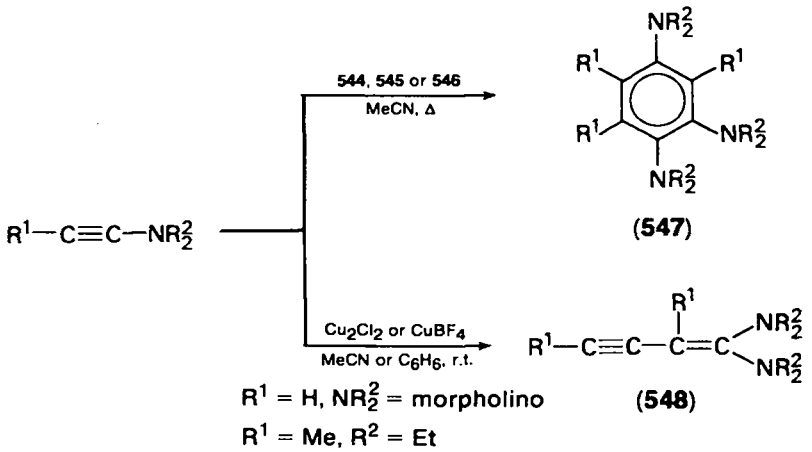
(**543**)

13. Reactions catalysed by coordination and organometallic compounds

The oligomerization of ynamines has been carried out in the presence of transition metal complexes. With $Ni(CO)_2(PPh_3)_2$ (**544**), $NiCl_2(PPh_3)_2$ (**545**) or $Ni(Acac)_2$ (**546**), cyclotrimerization occurs, leading to nonsymmetric benzenes (**547**) in a regioselective manner, whereas in the presence of Cu_2Cl_2 or $CuBF_4$, ynamines dimerize, with formation of alkynylketene aminal derivatives (**548**)[380].

A cycloaddition between ynamines and butadiene has been performed with success in the presence of Fe[O] complexes at 25°C. This provides a new synthetic route to 2-substituted 1-amino-1,4-cyclohexadienes (**549**)[381].

Insertion of ynamines into the metal–carbene bond has been found to occur in the



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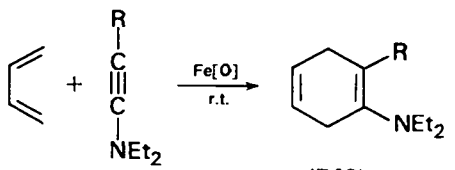
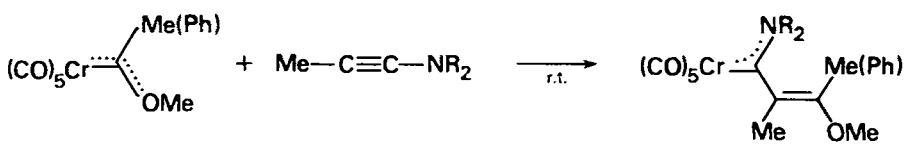


(549)

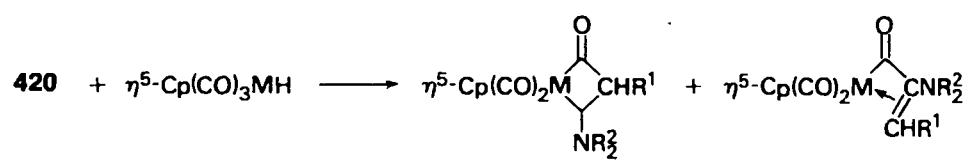
R = Me, *i*-Pr, Pe, Ph

reaction of aliphatic ynamines (**404**) with pentacarbonyl[methoxymethyl (or phenyl)]carbenechromium (**550**). *E*–*Z* organometallic compounds (**551**) are formed in a stereoselective manner[382].

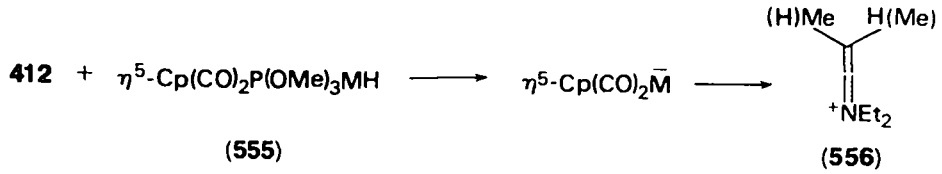


(**550**) (**404**) (**551**)

Several ynamines have been allowed to react with carbonyl-η^5-cyclopentadienyl hydrides of Mo and W (**552**)[383], to yield 1:1 adducts, which are in the form of carbene acyl chelates (**553**) when the metal is W and the substituent at the ynamine β-carbon is Me. When the metal is Mo and the substituent at the β-carbon is H, Me or CO_2Et, or M = W and R = H, Ph and CO_2Et the aminoacryloyl complexes (**554**) are obtained quantitatively. Ketene iminium complexes such as **556** are formed in the reaction of diethylaminopropyne and phosphite-substituted hydrides $(C_5H_5)(CO)_2P(OMe)_3MH$ (**555**), when M is Mo or W[383].



(**552**) (**553**) (**554**)



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IV. ACKNOWLEDGEMENTS

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