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BY

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CONTENTS

PAGE NO.

PAGE NO.

SUMMARY

A series of 4-substituted isoborneols has been synthesised in order to investigate, by infrared spectroscopy, the field effects of 4-substituents on the hydroxyl group stretching frequency, ν(OH), of isoborneols. The rather low sensitivity to substituent field effects of the free hydroxyl group stretching frequency of the 4-substituted isoborneols is attributed to the separation of the O-H and C-X bonds and to the low polarity of the O-H bond. The corresponding property of the more polar hydrogen-bonded hydroxyl group is about forty times more sensitive to substituent variation.

A range of N-nitroimines in dilute solutions of methyltetrahydrofuran and CD_3OD, exposed to ^{60}Co γ-rays at 77 K, gave the corresponding radical anions, detected by EPR spectroscopy. Analysis of the spectra show that the radical anions of the aliphatic N-nitroimines have the unpaired electron in the π^*-NO_2 molecular orbital and that the radical anion of the aromatic N-nitroimines is delocalised in the aromatic π^* molecular orbitals. The EPR spectra of the radical anions of a range of nitroalkenes, prepared in the solid state by similar methods, have been studied and compared with the radical anions of the N-nitroimines. Analysis of the EPR spectra indicates that the unpaired electron in the radical anions of the N-nitroimines is more centred on the nitro group than in the nitroalkenes.

As a result of the second order Beckmann rearrangement of its camphor oxime ether derivative, the first synthesis of 4-fluoro-3,5-dinitrophenol is reported. As a consequence, 4-trimethylsilylbutan-2-one oxime is investigated as a protected

alcohol species.

The novel compound (+)-α-oximino-5,6-dehydrocamphor has been synthesised. Attempts to oxidise this compound to its α-diketone derivative has thus far been unsuccessful.

The synthesis, characterisation and reactivity are reported for 4-(difluoroiodo)tricyclene, the first isolable compound of the type RIF_2 from an aliphatic iodide.

PART I

FIELD EFFECTS OF 4-SUBSTITUENTS ON THE ν(OH) VIBRATOR OF ISOBORNEOLS[1]

1.1 INTRODUCTION

1.1.1 INFRARED SPECTROSCOPY[2,3,4]

As a field of study, infrared spectroscopy dates back well over one hundred years. This compares with the relatively new field of study, nuclear magnetic resonance, which was first observed in 1939.[5] Infrared spectroscopy is probably the most widely used tool in the world today for the identification of organic compounds.[6] The technique can be used to identify unknown materials since functional group information can be obtained easily from an infrared spectrum and once the nature of the compound is known, a vast amount of reference data is available for direct comparison. Similarly, individual components of a mixture of known compounds can be quantitatively assayed by infrared spectroscopy provided that the spectrum of each pure component is available.

As a first approximation, the total energy of a molecule can be separated into three more important components:[7,8] a) that energy associated with the rotation of the molecule as a whole; b) its vibrational energy, and c) its electronic energy. The basis for this separation lies in the fact that, generally, the electronic mobility is much greater than that of atomic nuclei, the vibration frequency of which is, in turn,

considerably greater than that of the molecular rotations.

If a molecule is placed in an electromagnetic field (*e.g.* light), a transfer of energy from the field to the molecule will occur only when Bohr's frequency condition is satisfied:

$$E_1 - E_2 = h\nu \qquad (1)$$

where E_1 and E_2 are two quantized energy states of this molecule, h is Planck's constant and ν is the frequency of the electromagnetic field (light). The frequency, ν, is converted to the wavenumber, $\bar{\nu}$, through the equation

$$\nu = c\bar{\nu} \qquad (2)$$

where c is the velocity of light.

Because rotational levels are relatively close to each other, transitions between these levels occur at low frequencies. The range in which pure rotational spectra occur is between 1 cm^{-1} and 10^2 cm^{-1}. The separation of vibrational energy levels is greater and the transition occurs at higher frequencies than do rotational transitions. As a result, pure vibrational spectra occur in the range between 10^2 cm^{-1} and 10^4 and cm^{-1}. The electronic energy levels being further apart again, are observed in the range between 10^4 cm^{-1} and 10^6 cm^{-1}. Thus pure rotational spectra are observed in the microwave and far infrared[9] regions, electronic spectra are observed in the visible

and ultraviolet regions and vibrational spectra in the infrared region. The most useful vibrations, from the point of view of an organic chemist occur in the range 4000 cm^{-1} to 625 cm^{-1}.

To understand the vibrational origin of group frequencies one must consider the case of a diatomic molecule where the nuclei are represented by point masses and interatomic bonds are represented by massless springs which follow Hooke's law. During the vibration, the internuclear distance changes sinusoidally with time, but the centre of gravity remains fixed. Therefore, at any time during the vibration, the nuclear displacements are inversely proportional to the masses. The diatomic vibrational frequency $\nu(s^{-1})$ is given by:

$$\nu = \frac{1}{2\pi}\sqrt{F\left(\frac{1}{M_1} + \frac{1}{M_2}\right)} \qquad (3)$$

where the diatomic molecule is represented by two masses, M_1 and M_2 connected by a massless spring and F is the force constant.

If one now considers the case where there are a number of bonded atoms, the simplest case is the linear M-M-M model, which consists of two M-M diatomic oscillators coupled together. Displacement of the central common mass M in such a way as to distort one M-M oscillator, unavoidably distorts the other M-M oscillator, hence coupling occurs. The in-phase and out-of-phase stretching vibrations of the M-M-M model are illustrated in Figure 1(a) and (b). The question then raised is: what happens if the two oscillator components are unequal? If the right-hand force

constant is made zero (no spring), see Figure 1(c), or the right-hand mass is made infinite, see Figure 1(e), the frequency of the right-hand oscillator component will be lowered with respect to that of the left-hand oscillator component. Such out-of-phase vibrations result in the right-hand mass of the low frequency oscillator being motionless ($\Delta X = 0$), although both bond lengths change. In Figure 1(c) this is presumably due to forces on this mass being zero.

In Figure 1(d) and (f), the frequency of the right-hand oscillator component has been raised relative to that of its left-hand counterpart. This is achieved by making the right-hand force constant infinite (rigid bond) in Figure 1(d) and in Figure 1(f) by making the right-hand mass zero. The result of this is that the right-hand frequency oscillator component bond length does not change ($\Delta S = 0$). In Figure 1(f) this is due to the fact that the right-hand spring cannot distort because of the zero inertial mass on its end.

Of course, these cases are extremes and the form of the vibration will be intermediate between those of the symmetrical coupled oscillators, Figure 1(a) and (b), and the unsymmetrical coupled oscillators, Figure 1(c) to (f).

Two assumptions may be drawn from the above discussion:

(1) in the high-frequency vibration of the unequal oscillator combination, the only atoms that move are those of the high-frequency oscillator component;

(2) in the low-frequency vibration of the unequal oscillator combination, the only bond length (or bond angle) that deforms is that of the low-frequency oscillator component.

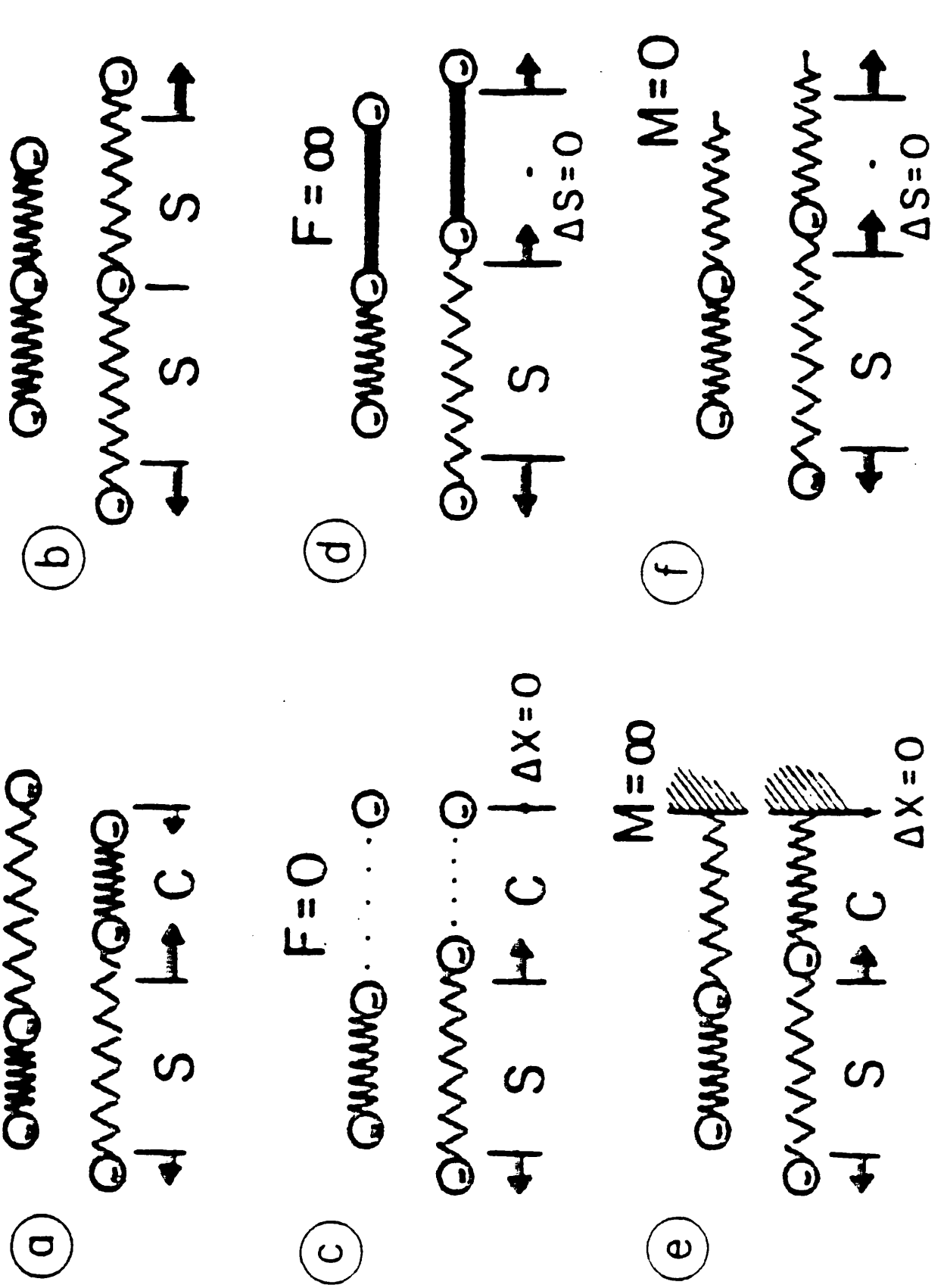


Figure 1

The first approximation above indicates that hydrogen stretching vibrations (X-H, where X is a non-hydrogen atom), triple bond stretching vibrations (C≡C, C≡N) and double bond stretching vibrations (C=C, C=O, C=N, P=O, S=O) should all give rise to good group frequencies when these groups are attached to the rest of the molecule by low frequency X-Y bonds where the attached atom is carbon (or a heavier atom). Indeed, when a spectrum has been taken, the region above 1500 cm^{-1} shows absorption bands assignable to the functional groups mentioned above. Since the attached atom moves only slightly, the vibration is mechanistically insensitive to the nature of the attached atom.

The vibrational frequencies of the X-H bond provide one of the largest and most reliable blocks of group frequencies. X-H frequencies are in general considerably higher than Y-X stretching frequencies where Y is a non-hydrogen atom directly attached to X. X-H stretching frequencies for the first row of the periodic table range from 2500 cm^{-1} (B-H) to 3960 cm^{-1} (F-H).

Because hydrogen stretching frequencies are insensitive mechanistically to the non-hydrogen part of the molecule, it appears that the different values for X-H stretching frequencies are due to the X-H force constant or mass effects. However, simple calculations using Hooke's law show that the mass effects on the X-H stretching frequency will be small. Bernstein[10] found that the stretching frequencies in particular show little sensitivity to mass effects. Lippincott's delta function model[11] incorporates functions which relate ν(X-H) to the radius, to an electronegativity term and to the dissociation energy:

$$V = D_e [1-\exp(-n\Delta R^2/2R)] \quad (4)$$

where V is the potential energy, D_e is the bond dissociation energy, $\Delta R = R-R_e$, where R_e is the equilibrium bond length and n is related to the bond dissociation energy by:

$$D_e = k_e R_e / n \quad (5)$$

where k_e is the bond stretching force constant.

This delta function gives rise to the conclusion that the frequency of the X-H stretching vibration will depend primarily on the bond length and upon the bond strength.

1.1.2 OH STRETCHING FREQUENCY WHEN ATTACHED TO CARBON

The infrared absorption band arising from the O-H valence vibration is one of the earliest known and most studied absorptions. It was first noted by Aschkinass[12] in 1895 that a band near 3300 cm^{-1} appeared to be associated with the hydroxyl group.

Alcohols are characterised by several bands, all of which are sensitive to the nature of the molecule. The hydroxyl group is very highly polar, and therefore associates with any other molecules having some degree of polar interaction, so that it is only in the vapour state and in dilute solution in non-polar solvents that the

absorption of the free OH vibration is observed, *e.g.* in $CC\ell_4$ solution, alcohols absorb near 3640 cm^{-1} as a sharp weak band attributable to the free OH stretch.[13] In the pure liquid or solid state, alcohols and phenols usually exist as hydrogen bonded polymers.[14-16] This is shown by a very strong and broad absorption near 3300 cm^{-1} owing to the stretching of the O-H...O bonds.[13] As illustrated, solvent association, changes of state[17,18] and temperature[19,20] will all influence the position of the OH absorption band.

Previously, it had been usual to attribute the changes within the frequency range of OH to inductive and resonance effects. At a glance, it would appear that inductive effects do have a major effect upon the OH frequencies. The highest values are found with electron donors (Si, Mg) and much lower values for electron withdrawing groups (F). However, it is more likely that any electronegativity effects will be small since in the CH system, they are essentially absent. The high frequencies may be due to donation of electrons into vacant d-orbitals, whilst the low values (*e.g.* in HOF) may well be due to the influence of the fluorine lone pairs lying *trans* to the OH bond. In the alkyl series t-butanol-methanol, the frequency rises as the chain branching is reduced. Normally, chain branching would be expected to reduce the electronegativity, so that the direction of shift is opposite to that which would be expected.

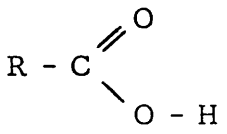
Despite there existing relationships between the OH stretching frequency of phenols and the Hammett σ[21,22] value of substituents (where the inclusion of a σ_I term could imply some dependence on inductive effects) it is thought that the inductive

effects in phenols operate primarily through influence upon the shape of the π-cloud, rather than by influence along the σ-bonds. Laurence and Berthelot[23] added credence to this theory by illustrating little or no change in the OH stretching frequency of substituted benzyl alcohols.

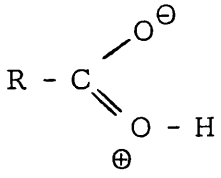
It appears that any part played by electronegativity effects in the OH stretching frequency is small compared to that of resonance. The importance of resonance is shown by the low ν(OH) stretching frequencies of the carboxylic acids and by the dependence of these frequencies and those of the phenols on Hammett σ values[24,25] in which resonance contributions are a major term. In phenols, an increase in σ values corresponding to an increase in the sp^2 contribution (which might be expected to raise the frequency by shortening the OH bond), leads to a more polar OH group and to a frequency decrease.

In $CC\ell_4$ solutions, acid OH frequencies are lower than those of the phenol OH frequencies. Laurence and Berthelot[23] have extensively studied *meta* and *para* substituted benzoic acids and shown that OH stretching frequencies have good linear relationships with Hammett σ values. The dominant factor in determining the frequencies of carboxylic acids is the resonance effect rather than any inductive effect, since the inductive effect of the carbonyl is relatively small. A reasonably good relationship exists between carbonyl frequencies of *meta* and *para* substituted benzoic acids.[26,27] As ν(CO) rises, ν(OH) falls. In the alkyl series, CF_3COOH has the highest carbonyl frequency and the lowest hydroxyl frequency. This can be interpreted in terms of the differing contributions of the canonical forms (1) and (2).

A substituent that raises the carbonyl stretching frequency increases the contribution of (1) at the expense of (2). The charge on the oxygen atom in (2) is greater than that of (1), and it is to be expected that the OH bond will be shorter than in (1). This follows from the hybridisation (sp^2) of the oxygen atom of (2). Any increase in the contribution of (1) that raises the carbonyl stretching frequency will therefore be accompanied by a fall in the hydroxyl stretching frequency.



(1)



(2)

It is now clear that other factors also make considerable contributions to the changes within the frequency range of OH. One such factor is the interaction with lone pairs in the *trans* configuration. Bellamy and Mayo[28] had shown that a CH or NH bond lying *trans* to a lone pair of electrons on the adjacent atom resulted in a fall in the stretching frequency of X-H, attributed to donation into an antibonding orbital in the X-H bond. Evidence to support this in the case of OH can be seen with hydrogen peroxide. The skew configuration that hydrogen peroxide adopts, has no lone pairs *trans* to the OH bond. This absorbs at 3610 cm^{-1}. In the peroxide anion, a lone pair does lie *trans* to the OH bond and as a result, the frequency falls to 3414 cm^{-1}.

Lone pair effects of this kind will not arise very frequently since the

attachment of the oxygen atom to atoms with free lone pairs is limited to a relatively small number of systems and even then, the requirement that the lone pair must be *trans* to the OH bond must also be met if the frequency is to be affected.

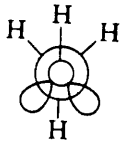
A further factor influencing the OH frequency is that of rotational isomerism. The importance of conformation effects in alcohols was first indicated by Ingold[29] when he showed that dipole moments of alcohols did not change with chain branching as they did with alkyl halides. The band shape of monohydric alcohols varies considerably. In most cases it is broad and asymmetric, sometimes a well defined doublet or even sharp and symmetric as it is with methanol and t-butanol.

Piccolini and Winstein[30] attributed asymmetry to "conformational heterogeneity", whilst Oki and Iwanura[31] noted that the fundamental free OH stretching absorption of alcohols generally results in an unsymmetrical band which they attributed to the presence of isomers corresponding to the rotational conformations of the hydroxyl group. The fact that methanol with only one conformation about the C-O bond shows a sharp symmetrical band gives added weight to the concept of band breadth originating in conformational isomerism.

Based on the observation that an axial hydroxyl group has a fundamental free OH stretching absorption about 5-10 cm^{-1} higher than that of its equatorial epimer,[32] which Cole *et al.*[33] suggested was due to an increase in the force constant of the OH stretching vibration on account of steric opposition of the axial hydrogens, Aaron and Rader[34] used the shape of the OH stretching band for direct conformational assignment in rigid six-membered ring systems: a symmetrical band for an axial and

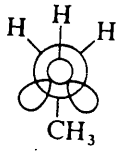
an unsymmetrical band for an equatorial hydroxyl group. Dalton *et al.*[35] concluded that the presence of a methyl group close in space to the OH bond (gauche) lowered the frequency by about 14 cm^{-1}. This is possibly due to a change in the C-O-H bond angle or the field effect altering the polarity. In the skew conformation, the frequency was lowered by 7 cm^{-1}.

Kreuger and co-workers[36] proposed that the broad band of ethanol was made up of two components (Figure 2), one of these would arise from the conformation in which the OH was gauche to two hydrogen atoms and would absorb at the same frequency as methanol (type I),[31] while the other would have the same OH gauche to one hydrogen and one methyl group (type II).[31]



Methanol

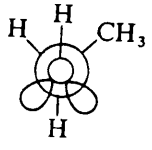
3643 cm^{-1}



(I)

3643 cm^{-1}

Ethanol



(II)

3630 cm^{-1}

Figure 2

The shifts arise from direct interactions between the orbitals of the OH and those of the C-H bond or methyl group. This mechanism is well established in the alkanes, in which, as with OH, the effect of a gauche methyl group is greater than that of a corresponding hydrogen atom. The idea of lowering the frequency by a gauche methyl group has been investigated by Lutz and Van der Maas[37] whose results support the concept. Thus variations in the frequencies of an OH stretching frequency in a series of closely related compounds are due primarily to field effects.

1.1.3 CALCULATION OF σ_F [38,39]

A substituent X can alter the measured property of some other part of the molecule Y (known as the probe site) in the molecule XGY, where G is a molecular framework (consisting of at least one connecting atom) to which X and Y are attached. X=H is generally taken as the standard substituent because of its simplicity; all the bonding interactions are restricted to use of its 1s-orbital.

Changing X may alter the bonding electron energy of the system. There are four primary electronic substituent effects, all of which differ in their origin and mode of transmission:

(1) Field Effects (F). The substituent parameter, σ_F, operates over long ranges and involves no substituent transfer of charge and has origins in charge-charge, charge-dipole or dipole-dipole interactions between substituents, polarised bonds of the framework G and the probe site.

(2) Resonance Effects (R). The substituent parameter, σ_R, is transmitted through π-bonds of G and Y and is interactive over a long range in extended π-systems. It has origins in π-electron bonding and delocalisation between substituent and the framework of G.

(3) Polarisability Effect (P). The substituent parameter, σ_α, has origins in induced dipole or dipole-induced interactions between the substituent and the probe site. The effect is transmitted through space with interaction over a short range.

(4) Electronegativity Effect (χ). The substituent parameter, σ_χ, has origins in the partial ionic character in sigma bonds between the substituent and its bonded atom of the molecular framework of G. The transmission of this effect is as above over a short range (mostly a single atom).

The field effect is based upon the effect of a substituent-induced dipole as felt at a probe site elsewhere in a molecule (Figure 3).

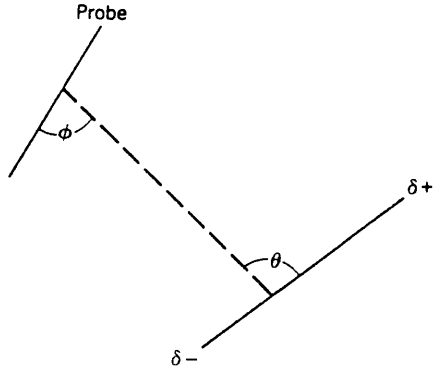


Figure 3

When the reference H-atom substituent is replaced by any substituent, X, there will be a general change in the local dipole interacting with the group, Y. This is due to the fact that the bonds between most atoms are not completely covalent but possess partial ionic characters which impose electrical asymmetry either in the bonds to H or X or in the bonds within X. The through space dipolar interactions with Y are of several kinds, all of which are regarded as electrostatic effects.

The experimental σ_F values are based upon measured dipolar substituent effects on physical properties in either gas phase or in hydrocarbon or similar solvents.[40] The σ-constant can only express the influence of a substituent on the rest of the molecule, and not its intrinsic properties.

Actual molecules have been used to approximate field effects. In one such case, Taft and Topsom[41] employed substituted methylamines as a model, although the probe and the substituent are not well separated; accordingly deviations due to substituent polarisability effects resulted. On the other hand, experimental figures for higher aliphatic amines (*e.g.* substituted ethylamines) are complicated by chelation and conformational ambiguity. To overcome this, calculated values on the fully extended (all *trans*) molecular conformation were employed.[41] However, this did not remove the effects of polarisability.

The contribution of electronegativity effects can be excluded by using the "isolated-molecule" technique which is only possible by theoretical calculations. In this method, the probe site and substituent are placed in separate molecules and thus substituent electronic effects can only be transmitted through space.

Employing such a method, values of ΔE°, for the process in Figure 4, can be calculated and related to σ_F (equation 6).[42]

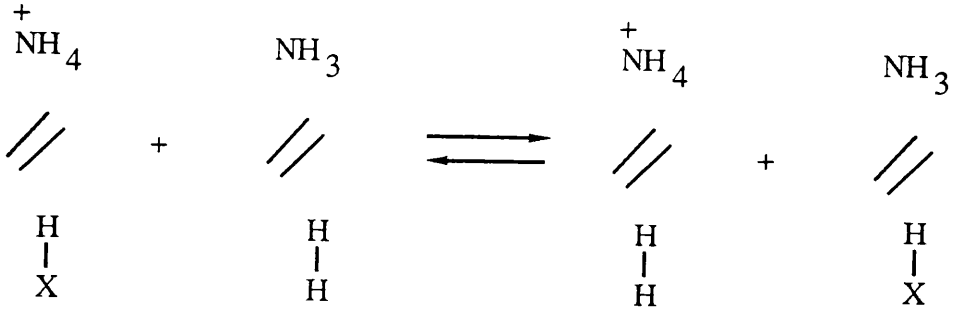


Figure 4

$$\sigma_F = -0.074\ \Delta E^{\circ} \qquad (6)$$

This equation results if the nitrogen of the ammonia, or of the ammonium salt, is on the H-X axis and 4.5 Å from the H-atom. In this case, the authors consider there still to be small contributions from polarisability effects.

A recent advance[39] has been to use electrostatic potentials (EP) obtained from the interaction of a positive charge at a determined geometry from a molecule HX. This leads to the relationship, (equation 7), where the positive charge is on the H-X axis and 4 Å from the H-atom. Here polarisability effects are excluded.

$$\sigma_F = 0.0635\ EP \qquad (7)$$

An alternative approach[42] is to measure the polarisation of a bond produced in an isolated molecule by the molecule HX. For example, the change in atomic population at one of the atoms in the H-H molecule accurately follows the experimental σ_F values. The relationship follows:

$$\sigma_F = -35.5\ \Delta_{q(H)_\alpha} \qquad (8)$$

where the hydrogen atom on H_2 nearest to HX is designated α (Figure 5)

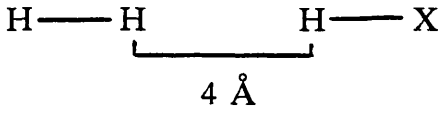


Figure 5

Although the methods mentioned above give good agreement with each other as well as with experimental values, a universal scale of σ_F is not possible for several reasons, even in the absence of specific solvent effects. First of all, even if the substituents are symmetric about the bond joining them to the rest of the molecule and if the point dipole assumption holds true, the relative effect depends on the distance, r, from the probe site to the substituent. The value of r, does not change completely uniformly from one system to another. When a system is changed, the incremental increase in r, is constant but the relative change is not and will vary from

one substituent to another. By electrostatic calculations it is $1/r^2$, that is significant:

$$\Delta E = \frac{q_1 \mu \cos \theta}{Dr^2} \qquad (9)$$

where q_1 is the charge on the probe site, μ is the local dipole, θ is the angle the dipole subtends to the probe site (Figure 3). D is the effective dielectric constant and r is the distance from the centre of the dipole to the probe site.

Secondly, charged substituents cannot be included in a scale for dipolar substituents.[43,44] This is because the effect of a dipole varies as $1/r^2$ (equation 9) while that of a pole varies as $1/r$ (equation 10).

$$\Delta E = \frac{q_1 q_2}{Dr} \qquad (10)$$

where q_2 is the charge on the pole substituent.

A third reason is that for dipolar substituents, the preferred conformation may differ from one system to another.

Finally, the substituent electronic effects may change somewhat depending on the substrate. An example of this is the cyano group. Values for σ_F for CN, range from 0.54 to 0.60. Marriot and Topsom[42] found a theoretical value of 0.45, which was very low. They suggest that the higher experimental values are due to charge transfer (hyperconjugation) that can occur between the CN group and C-H or C-C bonds if the atom attached is sp^3 hybridised.

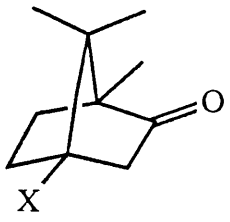
A general order of increasing magnitude of substituent field effects[38] is: Metal (M) < MMe_x < H, alkyl (R) < Ph < OR, SR, COR < halogen < CN < NO_2 < SO_2CF_3.

1.2 RESULTS AND DISCUSSION

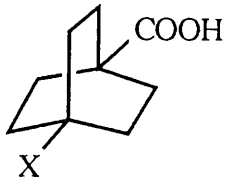
In order to investigate substituent effects on the hydroxyl group stretching frequency of alcohols, it is necessary to remove those factors, *viz.* resonance, steric and conformational effects, that can influence the shape and position of the absorption band of the O-H vibrator.

Previously[40,45] it had been shown that 4-substituted camphors (3) constituted a new model for substituent effects, since the essentially rigid bicyclic skeleton,[46] with its well defined degrees of bond angle strain and intramolecular distances, ensured that a fixed disposition was maintained between the carbonyl group and the C4-X bond and that steric and resonance effects could not operate. Such a system was based upon the pioneering work of Ritchie and Lewis[47] who had employed 4-substituted bicyclo[2.2.2]octane carboxylic acids (4) in an investigation of substituent effects.

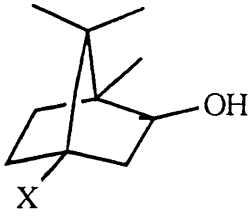
The same bicyclic structure as in (3) is now employed to investigate the influence of field effects on the hydroxyl group stretching frequency. To this end, a series of 4-substituted isoborneols (5), in which the configuration of the hydroxyl group is constant and *exo*, has been prepared.



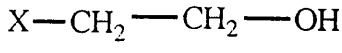
(3)



(4)



(5)



(6)

In Table 1 are presented:

(1) The wavenumbers ν(OH) of the free hydroxyl group of the 4-substituted isoborneols (7)-(15) and 2-substituted ethanols (6) (these are sharp bands, reproducibility ± 0.2 cm^{-1}).

(2) The wavenumbers (ν(OH...) of the 4-substituted isoborneols (7)-(15) hydrogen-bonded to dioxan (these are broad bands, reproducibility ± 2 cm^{-1}).

(3) The carbonyl stretching wavenumbers of the corresponding 4-substituted camphors (3) determined previously.[40]

(4) The value of the substituent field effect constant σ_F. These values are derived from substituent effects on gas-phase acidity and basicity[38] and agree well with values calculated theoretically.[39]

The free hydroxyl stretching frequency, ν(OH), of the 4-substituted isoborneols (7)-(15) is virtually insensitive to the field effect of the substituent; over the range of substituent character investigated, a diminution of only 0.7 cm^{-1} was observed. This contrasts with the carbonyl stretching frequency, ν(CO), of the 4-substituted camphors (3), which increases steadily with increasing electron-withdrawing character of the substituent; a range of 14.2 cm^{-1} was observed between 4-methyl and 4-nitro camphors.

It has been previously demonstrated[40] that there exists a linear correlation between the carbonyl stretching frequency, ν(CO), of the series of 4-substituted camphors (3) and the parameter σ_F that measures the electrostatic field effect of the dipole C4-X (Graph 1). For the nine substituents considered in this study, the correlation involving ν(CO) in cm^{-1} for 4-substituted camphors (3) takes the form shown in equation (11):

$$\nu(CO) = 1744.9 + 20.7\ (\pm 1)\ \sigma_F \qquad (11)$$

$$n = 9,\ r = 0.992,\ s = 0.7\ cm^{-1},$$

where r is the correlation coefficient and s is the standard deviation of the estimate. This equation demonstrates that the variation of the carbonyl stretching frequency derives mainly from electrostatic factors, and these are exerted longitudinally on the C=O dipole by the C-X dipole. A quantitative study[48] has shown that the variation

in frequency, $\Delta\nu$(CO), is a function of the product of the dipoles $\mu_{C=O}$ and μ_{C-X} and their separation, r:

$$\Delta\nu(CO) = f(\mu_{C=O} \times \mu_{C-X}, r^{-3}) \qquad (12)$$

Other factors, such as angular dependence, are not considered.

The same calculation applied to the hydroxyl group stretching vibration shows that changes of the stretching frequency, $\Delta\nu$(OH), respond in a similar way to changes brought about by the field effect of the substituents and the changes can be expressed by a related equation:

$$\Delta\nu(OH) = g(\mu_{O-H} \times \mu_{C-X}, r'^{-3}) \qquad (13)$$

Again, other factors such as angular dependence are not considered.

Comparison of equation (12) and equation (13) indicates that the weaker sensitivity of the O-H vibrator to field effects would have origins in:

(a) the fact that the separation of r' of the dipoles C4-X and O-H in the isoborneols (7)-(15) is greater than the corresponding separation r between the dipoles C4-X and C=O in the 4-substituted camphors (3). If one crudely assesses this distance between the dipoles by the number of bonds between them, one can estimate that the sensitivity to substituent effects diminishes by a factor of about $(2/3)^3$, approximately 0.3;

(b) the greater polarity of the carbonyl dipole ($\mu_{C=O}$ ~ 2.5 Debye) with respect to the hydroxyl dipole (μ_{O-H} ~ 1.5 Debye).[49]

In order to examine the first hypothesis, the effects of substituents on the hydroxyl stretching frequency, ν(OH), of 2-substituted ethanols (6) was studied. For non-alkyl substituted ethanols, X is generally a hydrogen bond acceptor, and consequently an intramolecular hydrogen bond O-H...X is formed in the gauche staggered conformation (17).[50] Kreuger and Mettee[51,52] had studied a number of 2-substituted ethanols and found there to be two or three bands present, the lowest of which they assigned to the gauche rotamer, which exhibited hydrogen bonding.

The ν(OH) band corresponding to the hydrogen bonded form (17) must always be broader and at lower frequencies than the free band corresponding to (16). It is therefore tempting to attribute the higher frequency ν(OH) band to rotamer (16) and also to believe that over the range of substituent character from alkyl to nitro, one will be able to observe the field effect of substituent X in a series of ethanols of the same staggered conformation. However, in the conformation (16), the molecules XCH_2CH_2OH remain highly flexible with geometry that can vary according to the electrical and steric nature of the substituent X.[53]

It is not altogether surprising that the quality of the correlation between the frequency of the non-intramolecular hydrogen-bonded ν(OH) vibrator of ethanols and σ_F (equation 14) is poor:

$$\nu(OH) = 3636.6 - 12.7\ (\pm 3)\ \sigma_F \qquad (14)$$

$$n = 13,\ r = 0.78,\ s = 2.5\ cm^{-1}$$

This correlation still has some statistical significance, and the coefficient of sensitivity, 12.7 ± 3 of the ν(OH) vibrator of ethanols (16) with respect to field effects is appreciably higher than that of the isoborneols (7)-(15), 1.0 ± 0.7 (equation 15), ν in cm^{-1}, in which the rather meagre value of the correlation coefficient derives, in part, from the low value of the regression coefficient. A plot of ν(OH) for the isoborneol derivatives versus σ_F is shown in Graph 2.

$$\nu(OH) = 3629.1 - 1.0\ (\pm 0.7)\ \sigma_F \qquad (15)$$

$$n = 9,\ r = 0.51,\ s = 0.5\ cm^{-1}$$

A comparison of equations (14) and (15) in the context of the associated discussion, demonstrates the significance of the distance between the substituent and the O-H bond on the sensitivity of the value of ν(OH) to the substituent field effect.

The second hypothesis was studied by increasing the polarity of the O-H bond of the isoborneol derivatives (7)-(15) by association with dioxan, a well-recognised hydrogen bond acceptor. It is well known that formation of a hydrogen bond of the type O-H...O results in a 0.3-0.6 Debye increase in the polarity of the O-H bond.[54] In the hydrogen-bonded complexes between the isoborneol derivatives (7)-(15) and dioxan, a sensitivity of ν(OH...), the frequency of the hydrogen-bonded O-H stretch, to field effects that is considerably more than an order of magnitude greater than that of ν(OH), the frequency of the free O-H stretch is observed. This is readily apparent from a comparison of the regression coefficients of equations (15) and (16) (Graph 3).

$$\nu(OH...) = 3504.9 - 42.7\ (\pm 3.5)\ \sigma_F \qquad (16)$$

$$n = 9,\ r = 0.977,\ s = 2.4\ cm^{-1}$$

It has been demonstrated that the sensitivity to substituent field effects of the hydrogen-bonded hydroxyl group stretching frequency ν(OH...) of isoborneol derivatives (7)-(15) is about forty times greater than that of the corresponding, less polar, free hydroxyl group.

A pertinent aspect of Graphs (1)-(3) (which derive from the data in Table 1) is that whereas the slopes of Graphs (2) and (3) are negative, that of Graph (1) which relates to carbonyl stretching frequencies, is positive. The action of an

electron withdrawing substituent *e.g.* nitro, on the hydroxyl stretching frequency is normal and operates *via* removal of electron density from the O-H bond; this is achieved by means of a field effect of the substituent operating principally through space.

In the case of a carbonyl group, the same effect is no doubt operative on the electrons of the σ and π bonds. This effect however is overridden by the field effect of the substituent on the lone pair electrons of (19). Accordingly for 4-nitrocamphor, the contribution of (18) to the carbonyl structure is greater than is the case for camphor itself.

$$>C = O \qquad\qquad >\overset{\oplus}{C}-\overset{\ominus}{O}$$

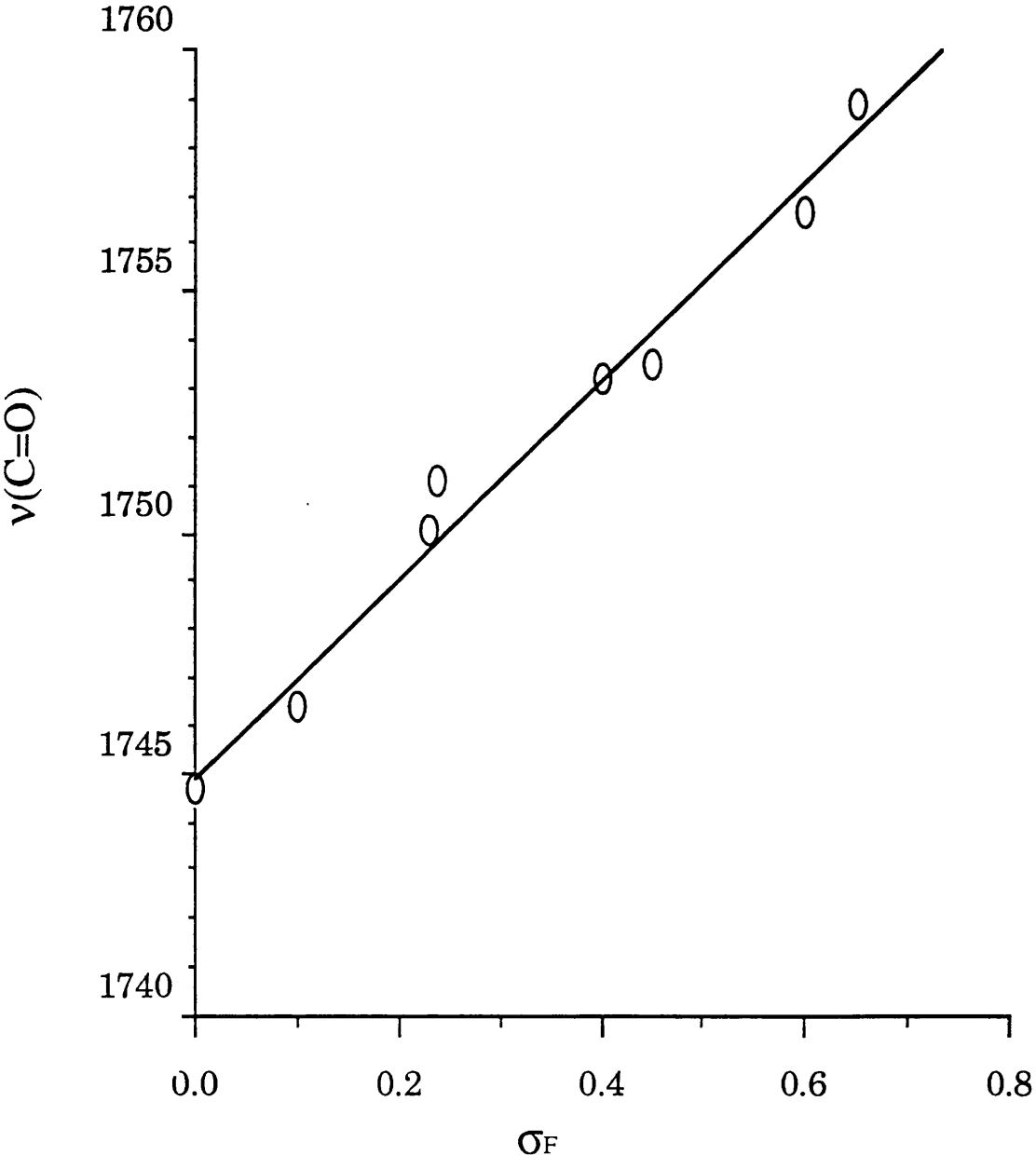
(18) (19)

The consequence is that 4-nitrocamphor has a higher stretching vibration frequency than has camphor. Similar arguments have been proposed previously to account for the greater shielding experienced by the carbonyl carbon of 4-nitrocamphor with respect to camphor in the ^{13}C n.m.r. spectrum[55] and of carbonyl groups bearing electron withdrawing substituents in other systems.[56,57]

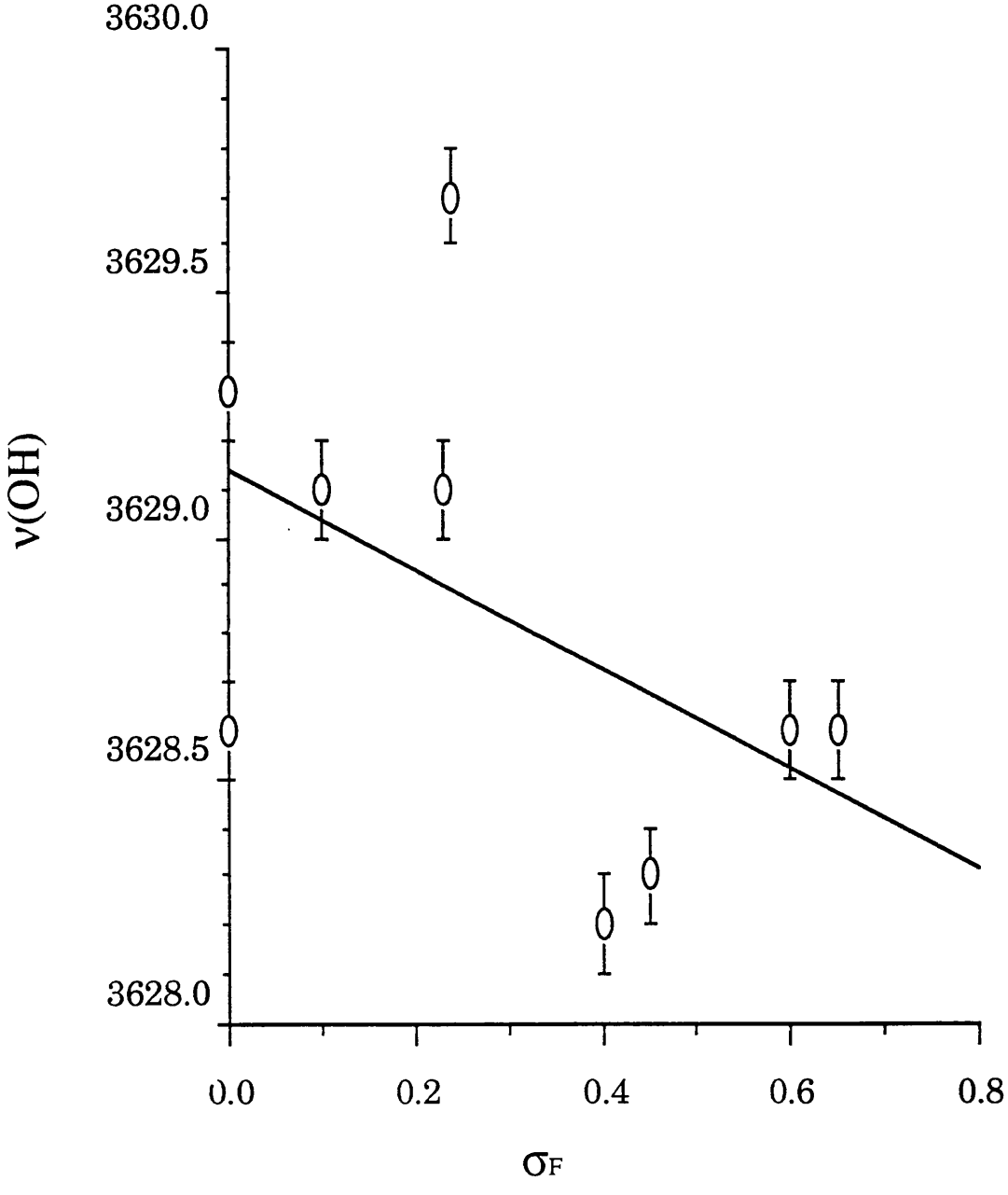
Table 1. Vibrational frequencies ν(OH), ν(C=O) of substituted camphors (3), isoborneols (5) and ethanols (6) and substituent constants σ_F

Substituent	ν(C=O) camphors	ν(OH) isoborneols	ν(OH...) isoborneol-dioxan complexes	ν(OH) ethanols	σ_F
Et				3628.1	0
Me (7)	1744.7	3629.3	3507	3637.9	0
Pr				3637.2	0
H (8)	1744.7	3628.6	3502	3634.2	0
Ph (9)	1746.4	3629.1	3500	3634.1	0.10
C≡CH (10)	1750.1	3629.1	3496		0.23
COOMe (11)	1751.1	3629.7	3498		0.24
OEt				3635.6	0.25
SH				3633.0	0.28
OPh				3633.7	0.38
I (12)	1753.2	3628.2	3484	3625.7	0.40
Br				3629.5	0.45
Cℓ (13)	1753.5	3628.3	3486	3631.6	0.45
C≡N (14)	1756.6	3628.6	3479	3623.3	0.60
NO_2 (15)	1758.9	3628.6	3478	3627.5	0.65

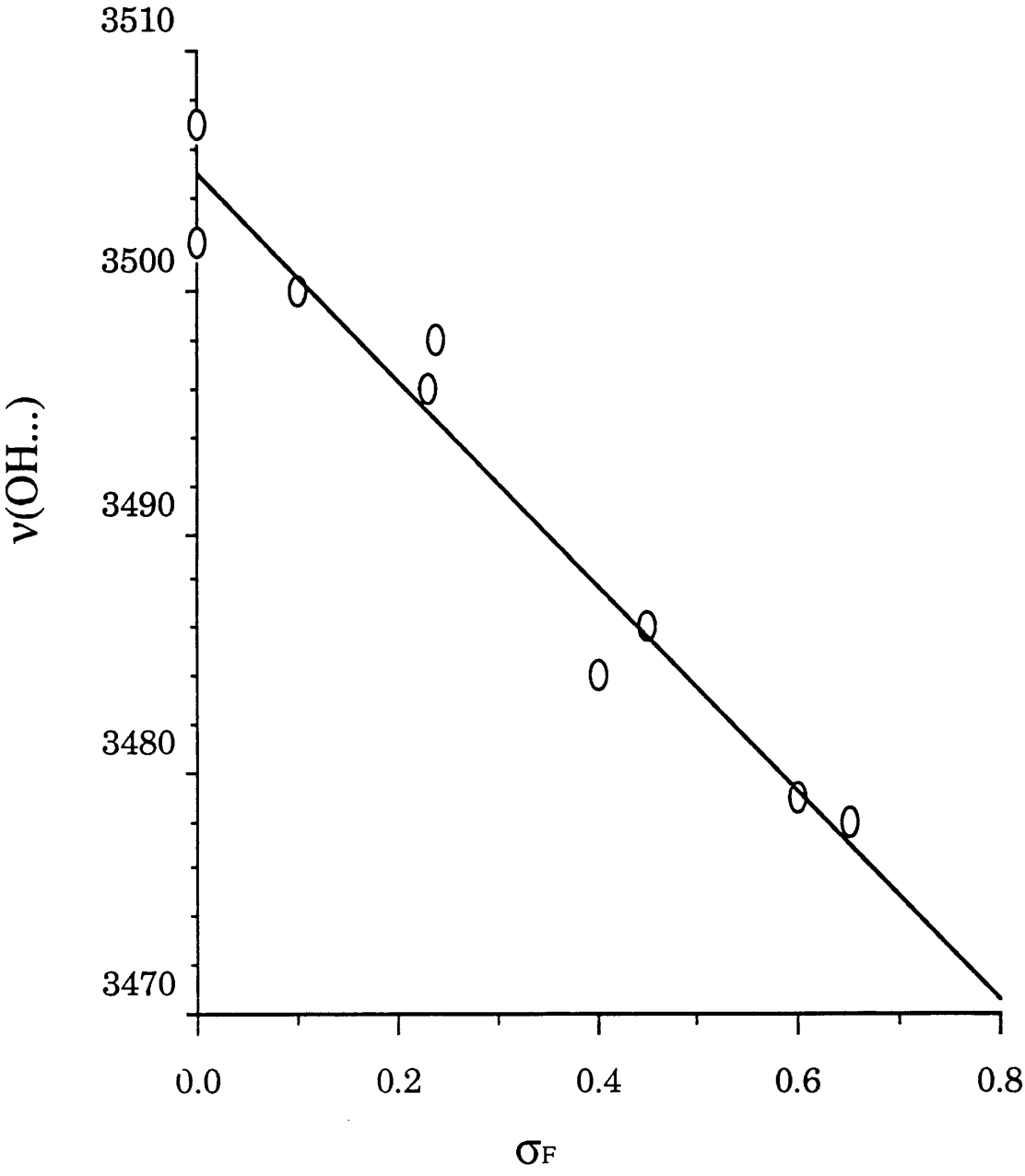
Graph 1
Plot of ν(C=O) for 4-substituted camphors against the substituent field effect constant σ_F



Graph 2
Plot of ν(OH) for 4-substituted isoborneols against the substituent field effect constant σ_F



Graph 3
Plot of ν(OH...) for hydrogen-bonded 4-substituted isoborneols against the substituent field effect constant σ_F



1.3 EXPERIMENTAL

1.3.1 GENERAL EXPERIMENTAL

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded either on a Perkin Elmer R32 spectrometer operating at 90 MHz with either deuteriochloroform or d_6-acetone solutions containing tetramethylsilane as an internal standard (assignments are in p.p.m. downfield from tetramethylsilane), a Bruker WP 200 SY spectrometer or a Bruker AM 200 spectrometer, both operating at 200.132 MHz. ^{13}C NMR spectra were recorded on the aforementioned Bruker instruments operating at 50.32 MHz. With the Bruker instruments, all spectra were recorded using deuteriochloroform or d_6-acetone as solvent and internal standard. ^{19}F NMR were recorded on the aforementioned Bruker instruments operating at 188.31 MHz as solutions in deuteriochloroform or d_6-acetone with $CFC\ell_3$ as internal standard. The following abbreviations are used: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, dd - double doublet, dm - double multiplet. Infrared spectra were determined with either a Perkin Elmer 580 or 953 spectrometer. Low resolution mass spectra were determined using a VG updated MS 12 spectrometer while high resolution mass spectra were determined on a modified Kratos MS9 instrument. Microanalyses were carried out by Mrs. K. Wilson at the Department of Chemistry, University of Glasgow.

Solvents were distilled before use: Et_2O and THF from sodium-benzophenone ketyl, $CH_2C\ell_2$ from P_2O_5, acetone from anhydrous K_2CO_3, EtOH and MeOH from Mg/I_2 and EtOAc from CaO.

Unless otherwise stated, all organic extracts were dried over anhydrous $MgSO_4$ prior to evaporation.

Thin layer chromatography (t.l.c.) was carried out using Kieselgel G (Merck) for analytical purposes and Kieselgel HF_{254} for preparative work.

1.3.2 INFRARED MEASUREMENTS

Infrared measurements were made on very dilute (*ca.* 0.01 M) solutions of isoborneols and ethanols in a 1 cm path-length cell; in this way self-association of the substrates was prevented. Hydrogen-bonded complexes of isoborneols were obtained by addition of 0.25 M dioxan to the carbon tetrachloride. Spectra were recorded with a Bruker IFS45 WHR FTIR spectrometer with 256 scans at a resolution of 0.25 cm^{-1}.

1.3.3 PREPARATION OF ISOBORNEOLS (7) - (15)

4-Methyl Isoborneol (7)

Methyl iodide (22.8 g, 0.161 mol) was added portionwise and continuously to a stirred solution of magnesium (3 g, 0.125 mol) in anhydrous ether (20 ml) under an atmosphere of nitrogen. Once all the magnesium had reacted, camphor (80)

(6.08 g, 0.04 mol) in anhydrous ether (20 ml) was added and the mixture left to stir for 2 days, after which time a saturated aqueous solution of ammonium chloride was added cautiously. After extraction into ether and drying, the crude alcohol was placed on an alumina column with petroleum ether (40-60 °) as eluent. Due to dehydration on the column, 1-methylcamphene (3.66 g, 61%) was obtained, m.p. 41-42 °C (lit.,[58] 43 °C).

1-Methylcamphene (3.66 g, 0.024 mol) was heated at 80 °C for 16 h with trichloroacetic acid (11 g, 0.067 mol). Conventional work-up[55] afforded the crude trichloroacetate (6.72 g, 89%).

Saponification of the crude trichloroacetate (6.22 g, 0.021 mol) was effected with potassium hydroxide (2.36 g, 0.042 mol) in methanol (10 ml) stirred for 16 h at room temperature. The solution was neutralised (2 M hydrochloric acid) and extracted with ether. After washing with water and saturated aqueous brine solution and drying, removal of the ether yielded crude 4-methyl isoborneol (7). Recrystallisation from petroleum ether (80-100 °) gave pure 4-methyl isoborneol (7) (3.10 g, 86%); m.p. 196-197 °C (lit.,[59] 195-196.5 °C); ν_{max} ($CC\ell_4$) 3640, 1395 and 1375 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.70 (3 H, s), 0.83 (3 H, s), 0.88 (3 H, s), 0.93 (3 H, s), 1.07-1.90 (6 H, m), 1.70 (1 H, s), 3.57 (1 H, dd, *J* 8 and 4 Hz).

4-Phenyl Isoborneol (9)

2-Phenyl isoborneol was prepared by the literature method[60] from camphor (80) (7.5 g, 0.05 mol). 2-Phenyl isoborneol (9.2 g, 0.040 mol) was stirred with

trichloroacetate acid (17.7 g, 0.108 mol) at 80 °C overnight. The cooled mixture was worked up in the usual manner.[55] The crude trichloroacetate was taken through to the next stage directly. Hydrolysis of the trichloroacetate (11.4 g, 0.030 mol) was effected with potassium hydroxide (3.42 g, 0.060 mol). After neutralisation and extraction, crude (9) was obtained. Recrystallisation from petroleum ether (80-100 °) yielded pure 4-phenyl isoborneol (9) (4.37 g, 63%); m.p. 113-115 °C (lit.,[61] 115 °C); ν_{max} ($CC\ell_4$) 3340 and 1600 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.70 (3 H, s), 0.85 (3 H, s), 1.00 (3 H, s), 1.30-2.45 (6 H, m), 1.70 (1 H, s), 3.75 (1 H, dd, *J* 8 and 3.5 Hz); M^+ 230 (41.4%).

4-Ethynyl Isoborneol (10)

2-Ethynyl isoborneol was prepared by the literature method[62] from camphor (80) (2.5 g, 0.015 mol). 2-Ethynyl isoborneol (5 g, 0.028 mol) was stirred with trichloroacetic acid (12.1 g, 0.074 mol) at 60 °C for 4 days, after which time, the cooled reaction mixture was worked up in the usual way[55] yielding the crude trichloroacetate (6.16 g, 68%).

Column chromatography on alumina (40% ethyl acetate/petroleum ether (40-60 °)) gave the title compound (10) which on purification by sublimation gave white crystals (2.33 g, 63%); m.p. 86-90 °C (lit.,[63] 122 °C); ν_{max} ($CC\ell_4$) 3400, 3300 and 2100 cm-1; δ_H ($CDC\ell_3$) 90 MHz, 0.83 (3 H, s), 1.00 (3 H, s), 1.08 (3 H, s), 1.15-2.08 (6 H, m), 1.62 (1 H, s), 3.63 (1 H, dd, *J* 7.6 and 3.6 Hz); M^+ 178 (16.9%).

4-Acetyl Isoborneol (11)

Camphene-1-carboxamide was prepared by the literature method[64] from camphor N-nitroimine (27).

A solution of camphene-1-carboxamide (10.52 g, 0.058 mol) and potassium hydroxide (12.99 g, 0.32 mol) in methanol (100 ml) was refluxed for 20 h. The solution was cooled and brought to pH 8-9 at which point unsaponified amide precipitated out. Upon removal of this precipitate, an excess of 2 M hydrochloric acid was added, resulting in a precipitate. This precipitate was dissolved in petroleum ether (60-80 °), washed with water and brine and dried. Recrystallisation from petroleum ether (60-80 °) gave pure camphene-1-carboxylic acid (3.66 g, 34%); m.p. 82-83 °C (lit.,[65] 83-84 °C, lit.,[66] 81-82.5 °C); ν_{max} ($CC\ell_4$) 3300-2550, 1750 and 1702 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 1.10 (6 H, s), 1.50-2.15 (7 H, m), 4.76 (1 H, s), 5.01 (1 H, s), 11.51 (1 H, s).

Camphene-1-carboxylic acid (2.66 g, 0.0149 mol) and trichloroacetic acid (9 g, 0.055 mol) were heated together under an atmosphere of nitrogen, at 60-70 °C. The solution that formed was stirred for 4 h. Conventional work-up[64] gave the crude trichloroacetate (4.92 g, 96%).

Without purification, the crude trichloroacetate (4.92 g, 0.0143 mol) obtained, was saponified by refluxing for 1 h with a solution of potassium hydroxide (2.50 g, 0.044 mol) in methanol (10 ml). On cooling, the solution was made acidic with 2 M hydrochloric acid, yielding a highly insoluble alcohol, which was recrystallised from boiling xylene (0.7 g, 24%); m.p. 230-231 °C (lit.,[64] 230-231, lit.,[67] 216-220 °C); ν_{max}

($CC\ell_4$) 3620, 3530,1740 and 1690 cm^{-1}.

To a solution of 4-carboxylic acid isoborneol (0.7 g, 0.0035 mol) in anhydrous ether (25 ml) maintained at 0 °C, was added diazomethane.[68] Excess diazomethane was destroyed using acetic acid. The resultant acidic solution was neutralised with sodium bicarbonate solution, washed with water and dried. The ether was removed leaving yellow crystals which were dissolved in petroleum ether (60-80 °). The precipitate that formed was filtered off and recrystallised from ethyl acetate/petroleum ether (60-80 °) giving the title compound (11) (0.24 g, 32%); ν_{max} ($CC\ell_4$) 3500, 2960, 1705 and 1110 cm^{-1}; M^+ 212 (5.1%).

4-Iodo Isoborneol (12)

Camphor hydrazone (78) was prepared by the method of Reusch[69] and recrystallised from petroleum ether (80-100 °) to give white crystals which melted at 53-55 °C (lit.,[69] 55 °C). These were used within one day of preparation owing to their hygroscopic nature.

To a stirred solution of camphor hydrazone (78) (10 g, 0.06 mol) in anhydrous ether (30 ml) and triethylamine (70 ml) was added slowly, a saturated solution of iodine in anhydrous ether (> 30 g of iodine to 200 ml of ether).[70] On completion of the reaction, as judged by the cessation of nitrogen evolution and the persistence of the iodine colour, the mixture was diluted with ether (200 ml), washed consecutively with 5% sodium thiosulphate solution, 2 M hydrochloric acid, brine, sodium carbonate solution and brine. After drying and evaporation of the solvent,

a dark brown oil, 14.5 g, was recovered. Purification on an alumina column (petroleum ether (40-60 °)) gave 1-iodocamphene (109) as a colourless oil (5.7 g, 36%); ν_{max} (film) 1662, 1145, 975, 950 and 895 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 1.10 (3 H, s), 1.15 (3 H, s), 1.80-2.75 (7 H, m), 4.80 (1 H, s), 5.20 (1 H, s).

1-Iodocamphene (109) (5.3 g, 0.02 mol) was stirred with trichloroacetic acid (14 g, 0.087 mol) at 80 °C for 21 h under an atmosphere of nitrogen. Conventional work-up[61] afforded the crude trichloroacetate (121) (7.41 g, 88%).

To a vigorously stirred solution of the trichloroacetate (121) in methanol (25 ml) was added a solution of potassium hydroxide (1 equiv. in minimum amount of water). After stirring overnight, the reaction was poured into water, extracted with ether and washed several times with brine. Ethereal extracts were dried and evaporated to yield crude 4-iodo isoborneol (12). Recrystallisation from petroleum ether (80-100 °) gave pure (12) (4.5 g, 80%); m.p. 136-138 °C; ν_{max} ($CC\ell_4$) 3370 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.85 (3 H, s), 1.05 (3 H, s), 1.10 (3 H, s), 1.45-2.55 (6 H, m), 1.78 (1 H, s), 3.65 (1 H, dd, *J* 7.8 and 3.7 Hz); M^+ 280 (1.3%).

4-Chloro Isoborneol (13)

1-Chlorocamphene was obtained as a colourless oil from camphor (80) according to the method of Joshi and Warnhoff.[71]

1-Chlorocamphene (20.5 g, 0.12 mol) and trichloroacetic acid (80 g, 0.49 mol) were heated at 90 °C, with stirring, under an atmosphere of nitrogen, overnight. After cooling, the mixture was diluted with water and neutralisation effected with the

slow addition of sodium hydroxide (17 g). After extraction into ether, the combined extracts were washed with sodium carbonate solution and dried. Evaporation of the ether yielded the crude trichloroacetate as an oil (37.6 g, 94%); ν_{max} (film) 1760 cm^{-1}.

Without further purification, the trichloroacetate was saponified by refluxing for 30 min with a 30% aqueous solution of potassium hydroxide (40 ml) in methanol (80 ml). After addition of water to the cooled reaction mixture, the resultant precipitate was filtered off and dissolved in ether. After washing with water and drying, evaporation of the ether and recrystallisation (petroleum ether (80-100 °)) pure 4-chloro isoborneol (13) was obtained (12.5 g, 60%); m.p. 233-234 °C (lit.,[71] 202-203, lit.,[72] 235-236 °C); ν_{max} (nujol) 3350 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.86 (3 H, s), 1.00 (3 H, s), 1.05 (3 H, s), 1.51-2.50 (6 H, m), 1.80 (1 H, s), 3.65 (1 H, dd, *J* 8 and 3.8 Hz).

4-Cyano Isoborneol (14)

1-Cyanocamphene was prepared from camphene-1-carboxamide according to the literature method.[72]

1-Cyanocamphene (8.5 g, 0.053 mol) was stirred with trichloroacetic acid (22.4 g, 0.14 mol) at 80 °C for 50 h under an atmosphere of nitrogen, after which time the cooled reaction mixture was worked up as for (13) to give the crude trichloroacetate (14.6 g, 85%). This was saponified directly using potassium hydroxide (2.56 g, 0.045 mol) in methanol (40 ml), at 50 °C, under an atmosphere of nitrogen, with stirring for 3.5 h. Upon cooling, the reaction mixture was acidified to pH 3 using 2 M

hydrochloric acid. The ethereal extractions were washed with brine, saturated sodium bicarbonate solution, water and dried. After evaporation of the ether, the crude product was recrystallised from petroleum ether (80-100 °) to give pure 4-cyano isoborneol (5.37 g, 67%); m.p. 218-220 °C; ν_{max} ($CC\ell_4$) 3610, 2960, 2230, 1390 and 1370 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.97 (6 H, s), 1.15 (3 H, s), 1.27-2.17 (6 H, m), 1.78 (1 H, s), 3.63 (1 H, dd, *J* 7.5 and 3.6 Hz).

4-Nitro Isoborneol (15)

1-Nitrocamphene[73] (15 g, 0.083 mol) and trichloroacetic acid (65 g, 0.4 mol) were heated, under an atmosphere of nitrogen, at 100 °C for 15 h. Upon cooling, partial neutralisation was effected by addition of a solution of sodium hydroxide (13.2 g) in water (300 ml). The ethereal extracts were washed with sodium bicarbonate solution until neutral. Drying and evaporation of the ether yielded the crude trichloroacetate (24.7 g, 87%).

The crude trichloroacetate (13 g, 0.038 mol) and potassium hydroxide (6.4 g, 0.11 mol) in methanol (60 ml) were refluxed for 2 h under an atmosphere of nitrogen. After cooling, the solution was concentrated on a rotary evaporator and the residue extracted into ether. The ethereal extracts were washed with water, brine and dried. Upon removal of the ether, the crude product was recrystallised from ethanol to give pure 4-nitro isoborneol (15) (5.8 g, 78%); m.p. 266-267 °C; ν_{max} (nujol) 3430, 1540 and 1395 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.90 (3 H, s), 0.92 (3 H, s), 1.07 (3 H, s), 1.40-2.70 (6 H, m), 1.87 (1 H, s), 3.75 (1 H, dd, *J* 7.5 and 4 Hz); M^+ 153 ($M-NO_2$, 16.8%).

PART II

ELECTRON PARAMAGNETIC RESONANCE STUDIES OF ELECTRON CAPTURE PROCESSES. RADICAL ANIONS OF N-NITROIMINES AND NITROALKENES[74]

2.1 INTRODUCTION

2.1.1 E.P.R. SPECTROSCOPY[75,76,77]

The first basic experiment into electron spin resonance (e.s.r.) was performed by Zavoisky[78] and by Bleaney and Penrose[79] just after the Second World War. Electron spin resonance can only occur for molecules with unpaired electrons and as a result, the technique is an important tool for studying the structure of paramagnetic transition metal complexes and also for the study and detection of a wide range of organic and inorganic radicals. An important development was the discovery that normally unstable radicals could be stabilised for indefinite periods simply by their preparation in a rigid medium.[80,81] Electron spin resonance involves magnetic dipolar interactions where the dipole attributable to electrons arises from a combination of mainly spin angular momentum and some orbital angular momentum. Resonant absorption of radiation in a static magnetic field by such systems is variously called "electron spin resonance", "paramagnetic resonance" or a term introduced by H.E. Weaver of Varian Associates,[82] "electron paramagnetic resonance". This term was introduced to account for contributions from orbital as well as spin angular momentum.

It should be noted that even if a compound is paramagnetic, it will not necessarily give rise to a detectable absorption.[80]

E.P.R. EXPERIMENT

An electron possesses spin angular momentum and because of this momentum, a spin magnetic moment. By virtue of its intrinsic angular momentum (spin) an electron behaves as a tiny bar magnet. In the presence of an externally applied magnetic field, the electrons (magnets) will align themselves in a preferred direction. From quantum mechanics it may be deduced that an electron has a spin quantum number of ½ and that it can only have two orientations with respect to a given axis *i.e.* the electron (magnet) is aligned effectively with the direction of the external field or against it.

The difference in energy between the two directions of spin depends on the strength of the external field shown in Figure 6.

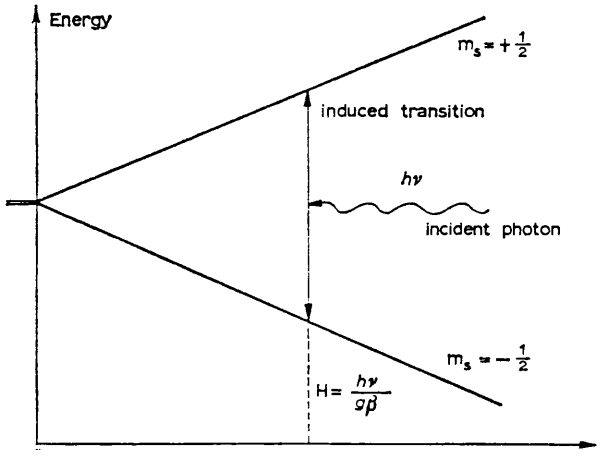


Figure 6

The energy required to reverse the spin of an electron in an externally applied magnetic field is given by:

$$E = h\nu = g_e\beta H \qquad (17)$$

where ν is the microwave frequency, h is Planck's constant, β is the Bohr magneton, H is the magnetic field strength and the Landé g-factor may be taken as a parameter which governs the position of the resonance absorption. When the condition is satisfied the energy levels are in resonance with the surrounding radiation and the spins may absorb its energy strongly. There will be net absorption only if there is greater population of the lower energy state.

Molecules of different kinds come into resonance at different applied magnetic fields. The reason for this is that the g-value of the electron depends on the molecule under study. The expected g-value for an electron with no angular momentum except that due to its spin is 2, the actual "free spin" value is 2.0023. The reason for the differing g-values is that the electron spin magnetic moment interacts with the local magnetic field and this local field differs from the applied field. This is because the applied field can force the electron to circulate through the molecular framework and the orbital motion sets up a small additional magnetic field, δH. The magnitude of δH is proportional to H itself, so the total local field $H + \delta H$ could be written as $H-\sigma H$ where σ is some constant. The resonant condition in equation (17) is satisfied when

$$h\nu = g\beta(1-\sigma)H \qquad (18)$$

where the constant σ may be positive or negative and as such, the g-factor may be more or less than 2.0023. The value of g depends upon the electronic structure of the species and also upon its dependence on direction, and as such, is written as a tensor.

It is rare for EPR spectra to consist of only a single signal. EPR spectra are characterised by three constants: the g-factor, the coupling constants of nuclei with a non-zero nuclear spin (especially the nitrogen nucleus) and the line width. The extra lines seen may be due to species with different g-values but a mechanism to explain multiplet spectra invokes hyperfine interactions. The interaction of an unpaired electron and a magnetic nucleus is called nuclear hyperfine interaction.

In a molecule containing one or more nuclei, the electron will experience not only the externally applied field, but also that of the magnetic nuclei. The nuclear magnetic moments are small but the unpaired electron approaches them closely. The result of this hyperfine splitting is that the spectrum is now a number of lines centred on the single resonance position.

A nucleus of spin I has an associated magnetic quantum number m_I that can take the values m_I = I, I-1, ... , -I. The nuclear moments are small and thus the energy difference between the orientations is small. To an approximation, the different states can be said to be equally populated. In practice, the small population differences actually present will be detected in nuclear magnetic resonance.[83]

Due to the presence of these nuclear magnetic moments, the spectrum will show a multiplet of 2I + 1 lines of equal intensity for a nucleus of spin I. When the unpaired electron interacts with more than one nucleus, more complex splitting patterns are observed. The electron will experience a field that is the vector sum of the applied field and all the nuclear fields. Thus for two nuclei of spin $I_A = 3/2$ and $I_B = 1/2$, a quartet of doublets is observed. If all the nuclei are equivalent, symmetrical patterns following the binomial intensity distribution of Pascal's triangle are observed.

There are two types of interaction between the unpaired electron and the magnetic nuclei. The hyperfine interaction may be either anisotropic (orientation dependent) or isotropic (independent of the orientation of H with respect to a molecular axis).

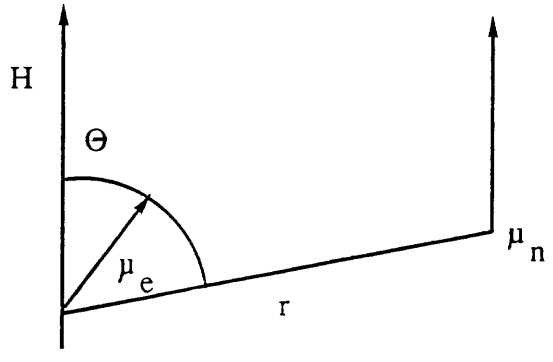


Figure 7

In Figure 7, the electron and nucleus are precessing about the direction of the applied field H, but at different frequencies. The direct dipolar magnetic field

generated by the nucleus at the electron is:

$$(\mu_z)_n < \frac{(3\cos^2\theta - 1)}{r^3} \qquad (19)$$

Here only the z-component is contributing. This equation involves a binomial expansion, valid if $r >> 0$. Values of $<r^{-3}>$ are normally calculated directly from the wavefunctions of the free atom by integration. For Slater orbitals $<r^{-3}>$ may be calculated from:

$$<r^{-3}>_{np} = 2Z_{np}[n^4(n-1)(2n-1)]^{-1} \qquad (20)$$

where Z_{np} is the effective atomic number for the orbital concerned. A better method is to use self-consistent field (SCF) wavefunctions.[84]

A good description of the nuclear field is obtained if the electron is in a p-, d- or f-orbital. In one of these orbitals the electron does not approach the nucleus very closely, and so it experiences a magnetic dipole that appears to arise from a point magnetic dipole. This is the dipole-dipole interaction. A characteristic of this type of interaction is that it is anisotropic. Equation (19) does not give a good description if the electron is in an s- or σ-orbital since these have no nodes at their own nucleus, and therefore there is no dipolar interaction. The s-orbital does not vanish at the nucleus and so an s-electron may approach the nucleus so closely that it is no longer correct to treat the latter as a point magnetic dipole. Another

magnetic interaction comes into play called the Fermi contact contribution, given by:

$$8\pi/3\ \mu_n |\psi_e(0)|^2 \qquad (21)$$

where $\psi_e(0)$ is the electronic orbital wavefunction at the nucleus; this interaction is isotropic.

The total hyperfine splitting constant, A, is the sum of the dipole-dipole interaction, A_{dip}, and the Fermi contact interaction, A_{iso}. For an electron interacting with an applied field H, and more than one magnetic nuclei:

$$E = g_e\beta_e m_s H + (g_e\beta_e m_s)\Sigma\, g_n\beta_n m_I \left\langle \frac{3\cos^2\theta - 1}{r^3} \right\rangle$$

$$+ (g_e\beta_e m_s)\Sigma\, g_n\beta_n m_I \frac{8\pi}{3} |\psi_e(0)|^2 \qquad (22)$$

Averaging over all motions, in fluids, the direct dipolar interactions become zero. Therefore, in fluids

$$E = g_e\beta_e m_s H + \frac{8\pi}{3}(g_e\beta_e m_s)\Sigma\, g_n\beta_n m_I |\psi_e(0)|^2 \qquad (23)$$

The magnitude of the Fermi contact interaction can be interpreted in terms of the s-character of the unpaired spin, while the dipole-dipole interactions can be interpreted in terms of p-, d- and f-character. These isotropic and anisotropic

hyperfine coupling constants can be used to obtain structural information such as spin density and often bond angles.

The electron spin density at nucleus X in a molecule is the difference between the total probability densities of all electrons with spin α and with spin β at nucleus X.[85] However, in the first approximation, the α and β spins in closed shells cancel and only the spin density of the unpaired electrons contributes. The spin density can be divided into the contributions from s-, p-, d- *etc.* electrons. The unpaired electron spin population is obtained from

$$\rho_s X = \frac{A_{iso} X \text{ (molecule)}}{A_{iso} X \text{ (atom)}} \qquad (24)$$

and

$$\rho_p X = \frac{A_{dip} X \text{ (molecule)}}{A_{dip} X \text{ (atom)}} \qquad (25)$$

A_{iso} (molecule) and A_{dip} (molecule) are obtained from the observation of hyperfine splitting in the molecular spectra but A (atom) values are obtained from tables[86] with A_{iso} (atom) including a relativistic correction factor suggested by Mackey and Wood.[87] A_{dip} (atom) is obtained from the free atom value of:

$$P = g_e\beta_e g_I\beta_n \langle r^{-3} \rangle \qquad (26)$$

by multiplying it by the appropriate angular factor, $\overline{\alpha}$,[86] which for p-electrons is 2/5. The p:s ratio, estimated for the calculated 2s- and 2p- characters, can give a value to the extent of hybridisation of the atomic orbitals occupied by the unpaired electron.

If one assumes that the bonds formed from the hybridisation of s- and p-orbitals on an atom are orthogonal to each other, it is possible to estimate the bond angle from the hybridisation ratio. The bond angle can only be calculated in this manner if the unpaired electron is in an sp^n-hydrid, not a pure π-level.

Hyperfine structure also arises from atoms bonded directly to an atom bearing an unpaired electron. The discovery of hyperfine coupling to α-atoms in atomic radicals was made by Lipkin.[88] If one considers the benzene radical anion where the unpaired electron occupies a π-orbital which has a node in the plane containing the C-H bond, an unexpected hyperfine splitting is observed. Work by McConnell,[89] amongst others, showed that this was due to mixing of excited states involving σ-π exchange of electrons and not out-of-plane bending vibrations of the C-H bond, as had previously been considered.

The pair of electrons in the C-H bond are slightly influenced by the magnetic field arising from the proton, such that an electron of the same spin orientation of the proton has a tendency to be found more often in the vicinity of the proton than the other electron. The latter electron is more likely to be found in the vicinity of the unpaired electron in a π-orbital. This "π-electron" detects the magnetic orientation of the proton even though there is no direct coupling. McConnell *et al.*[90] showed that the positive spin density in p_x (Figure 8) on carbon induces a small spin

polarisation in the $sp^2\sigma(y)$ carbon orbital, which will also be positive (Hund's Rule). Hence the spin on the proton tends to be negative since it must remain antiparallel according to Pauli's principle.

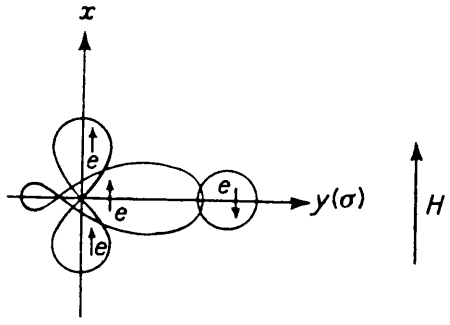


Figure 8

For aromatic π-electron radicals, all the protons couple with the unpaired electron and the coupling constant for each maps out the spin density in the system. McConnell[89] showed there is a simple linear relationship between the spin density on the carbon and this coupling constant.

$$A_H = Q_H P_C \qquad (27)$$

Q is a "constant" generally taken as -23 Gauss,[91,92] but the real value was found to be dependent upon the excited triplet states of the σ-bonds.[93]

The situation in which β-atoms play a significant role in hyperfine interactions is encountered frequently in organic systems. Isotropic hyperfine coupling to β-

atoms is known as hyperconjugation. The fundamental concept of hyperconjugation is that of overlap between one or more of the σ(C-H) bonds and the p-orbital of the unpaired electron. This will result in some redistribution of electron spin onto the β-proton.

The interaction between an unpaired electron and β-H's is a function of the angle, θ, between the plane of the C-H bond and the nodal plane of the p-orbital containing the unpaired electron.[94] From Figure 9, such an interaction will be at a maximum when the density axis of the p-orbital and the C-H bond are co-planar, and close to zero when the C-H bond lies in the nodal plane of the p-orbital containing the unpaired electron.

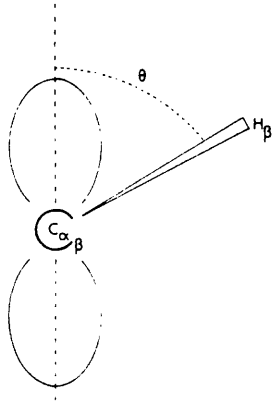


Figure 9

A relationship of the form shown in equation (28)[95,96] has been postulated for the almost isotropic interaction due to β-protons.

$$A = B_0 + B_1 \cos^2\theta \qquad (28)$$

B_0 is a constant that includes contributions from spin density which arise from a conformation-dependent mechanism. Stone and Maki[97] attribute B_0 to residual torsional motion of β-protons in the crystal lattice; B_1 is the hyperconjugative factor. In the case of rapid free rotation about the C-C bond, an average coupling is observed such that

$$< A > = B_0 + \tfrac{1}{2} B_1 \qquad (29)$$

The interaction can be quite large and gives rise to positive spin density at the proton (in contrast to α-protons in π-radicals).

The remaining unexplained features of an EPR spectrum are the intensities and shapes of the resonance lines. The observed intensity is proportional to the difference in population between the different spin levels, α and β. If the population of the two levels were the same, radiations would induce as many transitions from α to β from β to α and hence no net absorption or emission. The difference in population is given by:

$$(g\beta H)\backslash 2kT \qquad (30)$$

where T is the temperature and k is the Boltzmann constant. At room temperature and in a typical experiment (H = 0.3T), an imbalance of populations of approximately 0.07% is present. One might expect the absorption to fall to zero

when the population imbalance has been overcome. However, a mechanism exists whereby spins can be returned to the lower energy state. This is called a relaxation process. If such processes are fast enough, the original population distribution is maintained. The absorbed energy is given up by the returning spins and dissipated as thermal energy in the rest of the sample.

Relaxation processes affect line widths of absorption lines due to the lifetimes of spin levels shortening when relaxation occurs. As a result their energy is made imprecise, and transitions then come into resonance over a range of applied fields and hence the line broadens.

There are two types of relaxation:

(i) spin-lattice relaxation (T_1) - this depends upon fluctuating magnetic fields close to the unpaired electron due to lattice vibrations causing oscillation of local electrically charged particles. These fields couple with the spin magnetic moment of the electron and thus induce transitions;

(ii) spin-spin relaxation (T_2) - this depends upon local magnetic nuclei or unpaired electrons affecting the field at the unpaired electron. Although anisotropic interactions average to zero in fluids, if there is a random distribution of fields, the energy level of the unpaired electron will be blurred and the line broadens.

The linewidths are inversely proportional to T_1 and T_2, thus short relaxation times imply broad lines.

Another process which can broaden lines is when the wavefunction of the unpaired electron is distributed over a large number of magnetic nuclei, but does not overlap with the wavefunction of the other unpaired electrons. This is called a "superhyperfine interaction"; the splitting is generally not resolvable but leads to a broad line. The line is said to be inhomogeneously broadened, but the process by which it occurs is not a relaxation.

2.1.2 MATRIX ISOLATION TECHNIQUE

Matrix isolation of radical anions has proved that by using solvents such as CD_3OD and 2-methyltetrahydrofuran (MeTHF), the major reaction shown by solutes is electron capture.[98]

The low temperature technique often allows the observation of first formed species, and for strongly coupled nuclei, anisotropic coupling constants are obtained which can be used to obtain estimates of spin densities. However, the lines are broad and in many cases smaller hyperfine splittings are not fully resolved.

2.1.3 $S_{RN}1$ REACTIONS

The electron acceptor properties of the nitro group are well documented and indeed it has been described as "the best one-electron group in organic chemistry".[99] This is due to the presence of a low energy π^* molecular orbital which allows the formation of a relatively stable radican anion. The radical anions of a wide variety of nitro compounds with C-NO_2 groups have been studied using EPR spectroscopy.[100]

These include nitroarenes,[100,101] nitroalkenes[100,102] and nitroalkanes.[100,103] In the case of 1-nitro-olefins,[102] the lifetimes of the radicals lie between a few minutes and some hours according to the nature of the substrate.

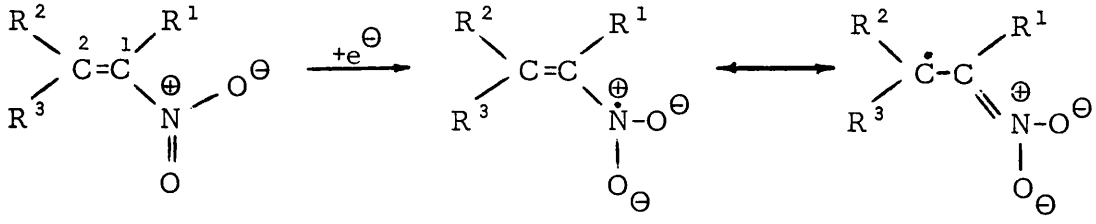


Figure 10

The nature of R^1 has little influence upon the lifetime of the newly formed radical anion. Groups R^2 and R^3 that contribute to delocalisation of the unpaired electron or, by their steric properties, reduce the reactivity of C-2 are particularly effective in prolonging the lifetime of radicals. If R^1=R^2=H, no radical anions are observed.

Studies by Symons and Bowman[104] have included the radical anions of a variety of substituted nitroalkanes, many of which are able to fragment to radicals and anions. One such study was conducted on nitroimidazoles.[104] Such compounds are important antimicrobial drugs with a wide range of activity. Previously it had been suggested that 5-nitroimidazoles (one of the market leading brands is the 5-nitroimidazole,metronidazole) are reduced by electrons donated by pyruvate/NADH *via* the hydrogenosomal enzyme pyruvate-ferrodoxin oxidoreductase.[105] The resultant reduced species attacks DNA causing, amongst other things, loss of helical structure

and consequent impairment of function as an enzyme template. Detection of the radical anions of nitroimidazoles by EPR spectroscopy in protozoal and anaerobic bacterial cells treated with nitroimidazoles suggests that the radical anions may be the reactive species.[106] Symons and Bowman[106] found that the EPR spectra of 4- and 5-nitroimidazoles showed that they had similar structures and distributions of spin densities with respect to the biologically active 2-nitroimidazoles and concluded that the differences in biological activity cannot be readily explained by differences in radical anion structure and other factors must be considered.

A nitro compound and a nucleophile (able to act as an electron donor) reacting is likely to lead to electron transfer, shown in equation (31):

$$R\text{-}NO_2 + Nu^- \xrightarrow{s.e.t.} [R\text{-}NO_2]^{-\bullet} + Nu^{\bullet} \qquad (31)$$

The most common course of reaction is dissociation of the radical anion to yield a radical and an anion with further reaction of the radical. α-Substituted nitro compounds commonly undergo substitution reactions while β-substituted compounds undergo elimination.

In 1940, substitution of α-halogenonitroalkenes was observed by Hass and Siegle:[107]

$$Me_2C(X)NO_2 + Me_2C{=}NO_2^- \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + X^-$$

$X^- = I, C\ell, Br$

Figure 11

The mechanism for this reaction (Figure 12) was postulated by Russell and Dannen[108] who had carried out work on other aliphatic nitro compounds.

$$RX + A^- \xrightarrow{s.e.t.} [RX]^{-\bullet} + A^\bullet \quad (32)$$

$$[RX]^{-\bullet} \longrightarrow [R^\bullet] + X^- \quad (33)$$

$$[R^\bullet] + A^- \longrightarrow [RA]^{-\bullet} \quad (34)$$

$$[RA]^{-\bullet} + RX \xrightarrow{s.e.t.} [RX]^{-\bullet} + RA \quad (35)$$

Figure 12

Equation (32) is the initiation step; equations (33), (34) and (35) are the propagation steps; summarising these three steps one obtains:

$$RX + Y^- \longrightarrow RY + X^- \quad (36)$$

The mechanism involves radical and radical anion intermediates and single electron transfer steps. The overall result is, however, nucleophilic substitution. For this reason, Bunnett[109,110] termed the mechanism $S_{RN}1$ (substitution, radical nucleophilic, unimolecular). The mechanism is unimolecular in the same sense as an S_N1 reaction (Figure 13), except that in the $S_{RN}1$ reaction, the substrate derived species are one electron richer.

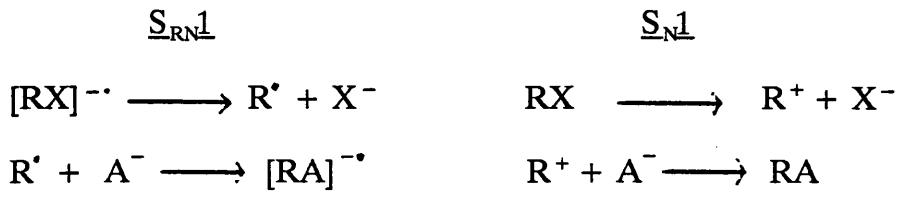


Figure 13

$S_{RN}1$ reactions are initiated by light, catalysis, thermal or electrochemical means. The role of light, for example, is to energise the charge transfer complex between the substrate and the nucleophile, thereby enhancing single electron transfer. In most $S_{RN}1$ reactions of $R_2C(X)NO_2$, neither the substrate nor the nucleophile absorb visible light, but with many of these substrates, Bowman and co-workers[111] observed colours that would disappear upon completion of the reaction, indicating that charge-transfer complexes are present during the reaction.

$S_{RN}1$ reactions proceed with substitution of either the α-substituent (X), as in equation (38a), or nitrite in equation (38b) (Figure 14). Initial single electron transfer between (A^-) and the α-substituted nitroalkanes, equation (37), leads to an intermediate radical anion which dissociates to a radical and an anion, equations (39a) and (39b), thereby initiating the $S_{RN}1$ chain mechanism.

The direction of the $S_{RN}1$ reaction is determined by the dissociation of the radical anion intermediate *i.e.* loss of X^- or NO_2^-. EPR spectroscopy at low temperatures has been used to obtain evidence for the structures and identification of intermediates as well as mechanisms for the various steps in certain $S_{RN}1$ reactions.

$$R_2C(X)NO_2 + A^- \xrightarrow{s.e.t.} [R_2C(X)NO_2]^{-\cdot} + A^{\cdot} \quad (37)$$

$$R_2C(X)NO_2 + A^- \longrightarrow R_2C(A)NO_2 + X^- \quad (38a)$$

$$[R_2C(X)NO_2]^{-\cdot} \longrightarrow R_2\dot{C}NO_2 + X^- \quad (39a)$$

$$R_2\dot{C}NO_2 + A^- \longrightarrow [R_2C(A)NO_2]^{-\cdot} \quad (40a)$$

$$[R_2C(A)NO_2]^{-\cdot} + R_2C(X)NO_2 \longrightarrow [R_2C(X)NO_2]^{-\cdot} + R_2C(A)NO_2 \quad (41a)$$

X = I, Br, Cℓ, SCN, SR, SO_2R, N_3, NO_2.

$$R_2C(X)NO_2 + A^- \longrightarrow R_2C(A)X + NO_2^- \quad (38b)$$

$$[R_2C(X)NO_2]^{-\cdot} \longrightarrow R_2\dot{C}X + NO_2^- \quad (39b)$$

$$R_2\dot{C}X + A^- \longrightarrow [R_2C(A)X]^{-\cdot} \quad (40b)$$

$$[R_2C(A)X]^{-\cdot} + R_2C(X)NO_2 \xrightarrow{s.e.t.} [R_2C(X)NO_2]^{-\cdot} + R_2C(A)X \quad (41b)$$

X = CN, COR, CO_2R, N_3, NO_2, <u>O</u>- , <u>m</u>-, <u>p</u>-$NO_2C_6H_4$.

<u>Figure 14</u>

EPR data indicate an overlap of spin density from the nitro π^* molecular orbital into the C-X σ^* molecular orbital. The favoured structure is shown in Figure 15.[112]

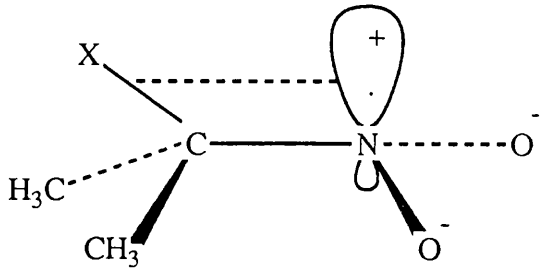


Figure 15

The location of spin density could be an important factor in the rate of dissociation if there is no overlap between C-X and NO_2 molecular orbitals or when the nucleofugicities are similar *e.g.* I > Br > Cℓ, are also responsible for the direction of dissociation.

Dissociation of $[R_2C(X)NO_2]^{\cdot -}$ radical anions proceeds with smooth reorganisation of the π^* and σ^* molecular orbitals to the required transition state for the loss of NO_2^- and X^- anions.

EPR spectroscopy has also been used to show evidence for the third step in the propagation sequence *viz.* equations (41a) and (41b).

Inhibition of the $S_{RN}1$ mechanism is carried out by exclusion of light, use of radical traps *e.g.* nitroso compounds and p-dinitrobenzene or strong electron acceptors such as oxygen.

2.1.4 N-NITROIMINES

Although N-nitroimines (nitrimines) have been known for some time, they have been little investigated. Several examples of these compounds exist in the steroid and terpenoid fields as well as certain aromatic derivatives, exemplified by the N-nitroimines of benzophenone and fluorenone.[113]

There are three methods of making N-nitroimines, (i) condensation of nitramide with an aldehyde, (ii) the action of nitric oxide (NO) on aryl or diaryl diazoalkenes, and (iii) reaction of an oxime with nitrous acid.

The first route has only been reported for a single example[114] shown in Figure 16. The reaction would not take place with solvent present. The nitramide probably reacted as it did because it could not be replaced by hyponitrous acid, a possible contaminant.

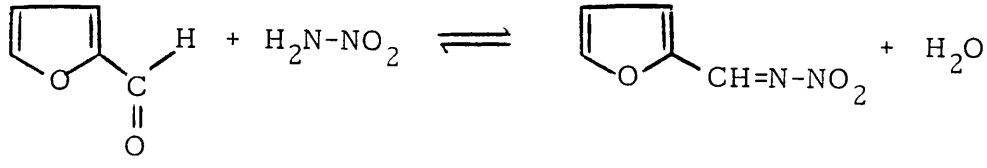


Figure 16

The second method was reported by Horner *et al.*[113] The route is shown in Figure 17. In this case the intermediates would seem to be free-radical although the authors were unable to detect them by EPR spectroscopy.

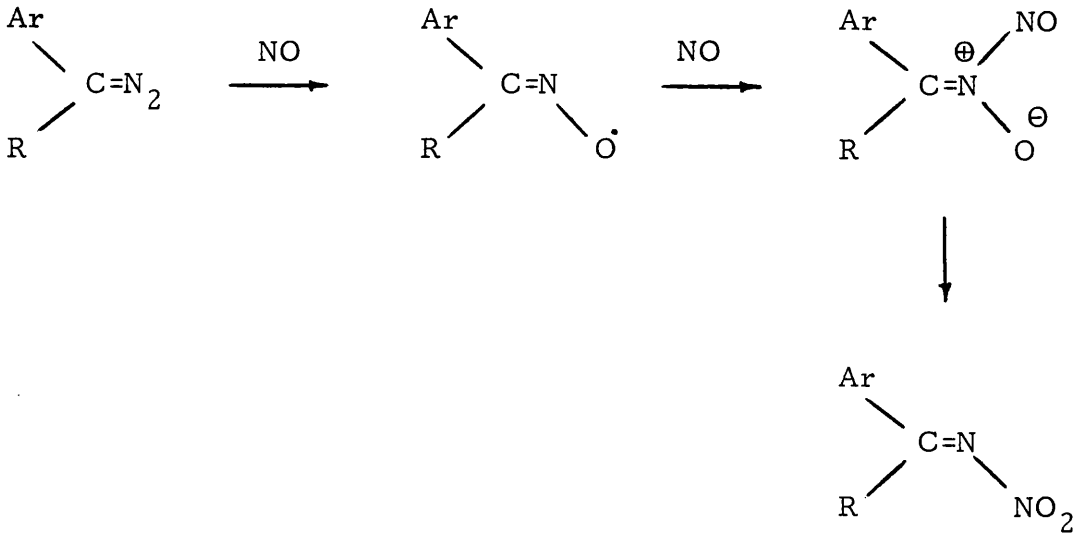
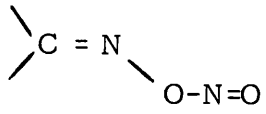


Figure 17

The third and most frequently used method involves reaction of an oxime with nitrous acid. This method has been used previously for degradation of oximes to ketones.[115] However, when the site of the oxime is sterically hindered, 'pernitroso-ketones' or nitrimines are formed. In aliphatic systems they are generally stable if the imine carbon is adjacent to at least one quaternary carbon atom, although exceptions are known[116] *e.g.* 'pernitroso'-di-isopropyl ketone.

The structure of these compounds has provoked much discussion. Early proposals included oxime nitrite[117] (20) and N-nitrosonitrone[118] (21). X-ray crystallography,[119] spectral and chemical evidence[120] have been employed to confirm the structure (22) for nitrimines first proposed by Scholl.[121]



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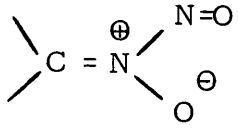

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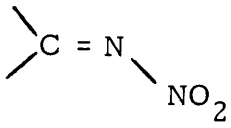


(22)

The structure of nitrimines of t-alkyl ketones was investigated by Freeman.[120] His results with ultra-violet and infrared spectra suggest that the imine and nitro group are not conjugated in the conventional sense. The nitro group stretching frequencies of nitrimines are found in the same region as saturated C- and N-nitro compounds. In nitro-olefins[122] this frequency is lowered by about 30 cm^{-1}. The nitro group has little effect upon the position of C-H and C=C bonds although the intensities are increased in α- and β-nitro-olefins. Without giving an explanation, Haszeldine[123] stated that the unshared pair of electrons on the amino-N of nitroamines cannot interact with the nitro group. It would appear that in these systems, the nitrogen acts as an insulator to electron delocalisation.

Although the structure of nitrimines is agreed upon, the exact mechanism for the conversion of oximes to the nitrimines has been the centre of much discussion without universal agreement being reached. The problem lies in explaining the replacement of an N-O bond with an N-N bond. Freeman[120] suggested that the nitrosonitrone (21) is formed initially with subsequent rearrangement to (23) in Figure 18(a). Cameron *et al.*[119] objected that this mechanism would place the nitro

group in the geometrical orientation opposite to that of the oxime. This was contrary to what had been observed with the nitrimine of camphor. The mechanism proposed by Cameron *et al.*[119] (Figure 18b) involves formation of an oxime nitrite (20), dissociation into free radicals followed by combination to give the nitrimine (22)

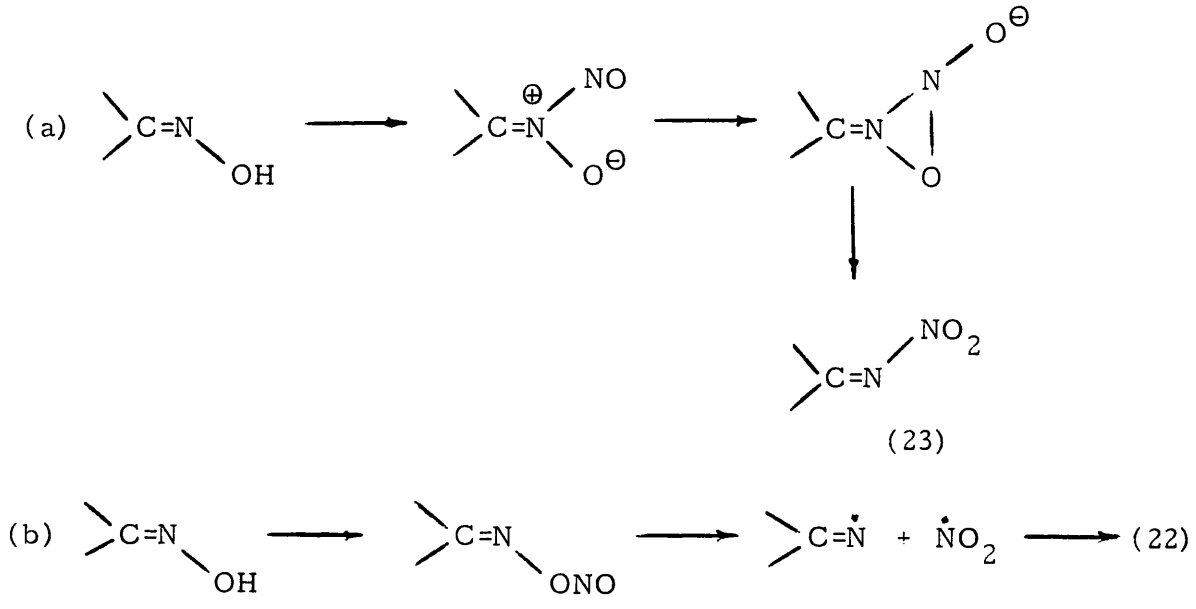
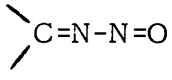


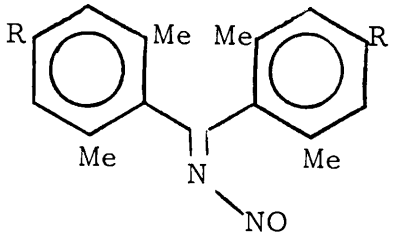
Figure 18

Although this mechanism appears plausible, the radical intermediates have not been detected by EPR spectroscopy. It is therefore thought that the reaction may proceed *via* an ionic pathway. Coulton *et al.*[116] are unwilling to propose a full mechanism, although they propose that a nitrosimine (24) is an intermediate. There are few examples of nitrosimines in the literature; two of the most stable are diaryl derivatives (25) and (26), reported by Zimmerman and Paskovich.[124] Deep red or

purple colours are observed with compounds of this type. When at least one equivalent of nitrous acid is present, the oxime to nitrimine reaction mixture exhibits a pink/purple colour.



(24)

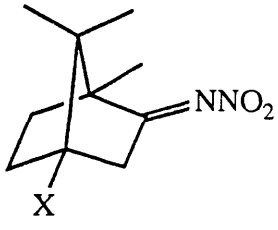


(25) R=Me

(26) R=OMe

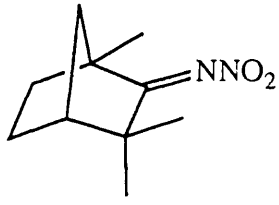
2.2 RESULTS AND DISCUSSION

A series of N-nitroimines (27-30), derived from camphor, 4-chlorocamphor, fenchone and fluorenone, respectively, were studied and compared with nitroalkenes (31)-(34). 2,2-Dimethyl-3-nitromethylene bicyclo[2.2.1]heptane (31) was chosen as one of the nitroalkenes because it is a close analogue of the N-nitroimine derived from fenchone (29) and is particularly useful for comparing the radical anions derived from a C=C-NO_2 group and those from a C=N-NO_2 group.

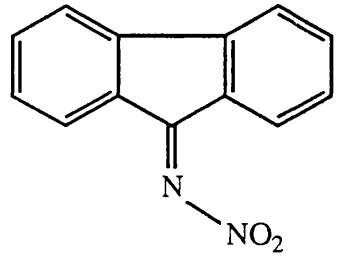


(27) X = H

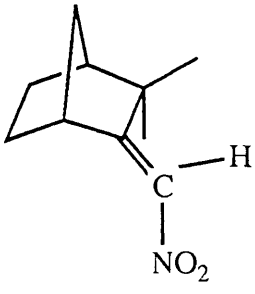
(28) X = Cl



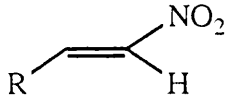
(29)



(30)

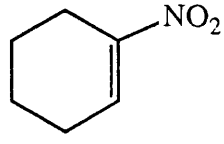


(31)



(32) R = Me

(33) R = i-Pr



(34)

Synthesis of (31) gave an unexpected result. Upon purification of the crude product on a gravity alumina column, subsequent recrystallisation of two successive

fractions (petroleum ether 40-60 °) yielded two sets of crystals with different melting points. The first fraction gave crystals with a melting point of 62-65 °C (lit.,[125] 62-64 °C), while the crystals obtained from the second fraction had a melting point of 75-77 °C (lit.,[126] 75 °C). The two literature melting point values both refer to (31). Infrared, ^{1}H and ^{13}C n.m.r. spectroscopy gave no clues as to the source of the difference.

Reheating crystals of the second fraction gave a melting point range of 62-77 °C. The melting point of the crystals from the first fraction stayed constant. This suggests that there is a different crystal packing between the two sets of crystals. Unfortunately, crystals that were small enough, could not be obtained for X-ray analysis.

Interpretation of the Spectra of Nitroalkenes

The results are given in Table 2, and a typical EPR spectrum is shown in Figure (19a). For solutions in MeTHF, well-defined features characteristic of nitro anions were revealed after annealing between 70 K and 140 K to remove signals from solvent radicals. Proton coupling to hydrogen or methyl groups on C(2) (*i.e.* the β-carbon of $C_{\beta}=C_{\beta}NO_2$) of about 9 G was resolved, but the smaller splitting for C(1) protons was not. From simulation studies, Figure (19b), splittings of 2-2.5 G, but certainly less than 3 G are found. For solutions in CD_3OD, features for $^{\bullet}NO_2$ radicals were also detected, and it was not possible to remove central features due to solvent radicals. Hence the overall spectra were poorly defined, but a clear

secondary splitting of *ca.* 3 G was displayed on the ±1 lines, which is assigned to protons associated with C(1). In no case could any of the ^{14}N perpendicular splittings be resolved. In all cases the glasses were a strong yellow colour after exposure. This is assigned to the radical anions: absence of a violet colour (from 'trapped' electrons) shows that electron capture by the solutes was very efficient.

Interpretation of the Spectra of N-Nitroimines

Again, these were better defined in THF (Figure 20). In these cases, definite perpendicular (^{14}N) features were resolved, the spectra closely resembled those for saturated nitroalkane radical anions.[98,103] For solutions in CD_3OD the resolution was better but features from $^{\bullet}NO_2$ and solvent radicals made interpretation more difficult. In the case of the N-nitroimine of camphor (27) and its chloro derivative (28) a well-defined doublet splitting of *ca.* 7 G was observed (Table 3). This is assigned to an axial proton (*endo*-H at C(3)). The other proton (equatorial, *exo*-H at C(3)) gave no resolved splitting.

The EPR spectrum of the radical anion of N-nitrofluorenone 2-imine (30) showed a singlet in both MeTHF and CD_3OD, *i.e.* the unpaired electron is mainly in an aromatic π^* molecular orbital rather than the nitro π^* molecular orbital. Therefore, electron capture by the aromatic ring system is preferred over the nitro group. The nitro group is conjugated to the aromatic system and may simply indicate complete delocalisation of the unpaired electron. On annealing, no clear features could be distinguished.

The results for the radical anions of the nitroalkenes agree reasonably well with those of Berndt,[102] for similar species in fluid solution. Using the ^{14}N parallel data obtained and Berndt's isotropic coupling, perpendicular splittings of *ca.* 2 G for C(1) protons (α-H) using MeTHF is less than the coupling noted by Berndt[102] (3 G) but for CD_3OD solutions a coupling of 3 G was observed. Reasons for this are not clear.

There is a remarkable difference between the results for the $C{=}C\text{-}\dot{N}O_2^-$ system and the $C{=}N\text{-}\dot{N}O_2^-$ system. For the former, $A_\perp$ is very small, the isotropic coupling is low and the p:s ratio, estimated for the calculated 2s- and 2p- characters on nitrogen (*ca.* 27) shows that the $-NO_2$ units must be planar. Indeed they are the only $R\text{-}\dot{N}O_2^-$ species that have been discovered that seem to be planar.

In marked contrast, the $-NO_2$ units for the $\rangle C{=}N\text{-}\dot{N}O_2^-$ species have p:s ratios (*ca.* 10) that are actually less than those for typical $R\text{-}NO_2^-$ species (R=Alkyl) (*ca.* 11). The difference is due to the effect of changing one of the atoms from carbon to nitrogen. The increase in electronegativity is expected to induce greater bending on electron addition. Thus, for example, for $\dot{N}O_3^{2-}$ radicals, p:s ratios of *ca.* 8 are found.

This increased pyramidality results from a greater admixture of 2s character with the wavefunction on nitrogen, and this should induce a shift of spin density onto the nitrogen unit. For both types of radical an 'allylic' structure is expected, with a node close to the 'central' atom, as in Figure (21). This is only an approximation, but it fits the fact that protons associated with C(2) have much greater coupling

constants than those for C(1). The fall in coupling for the β-proton in the camphor N-nitroimine (27) is marked, relative to those for the $C=C-\dot{N}O_2^-$ species, especially since this must be an equatorial proton which is expected to give a large splitting. It is difficult to quantify this result, but qualitatively, this is a clear shift of spin density away from the outer carbon (β) (of $C_\beta=C_\alpha-NO_2$) towards the $-NO_2$ unit.

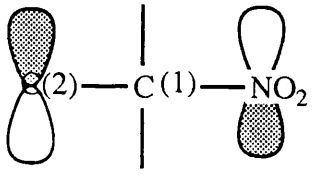
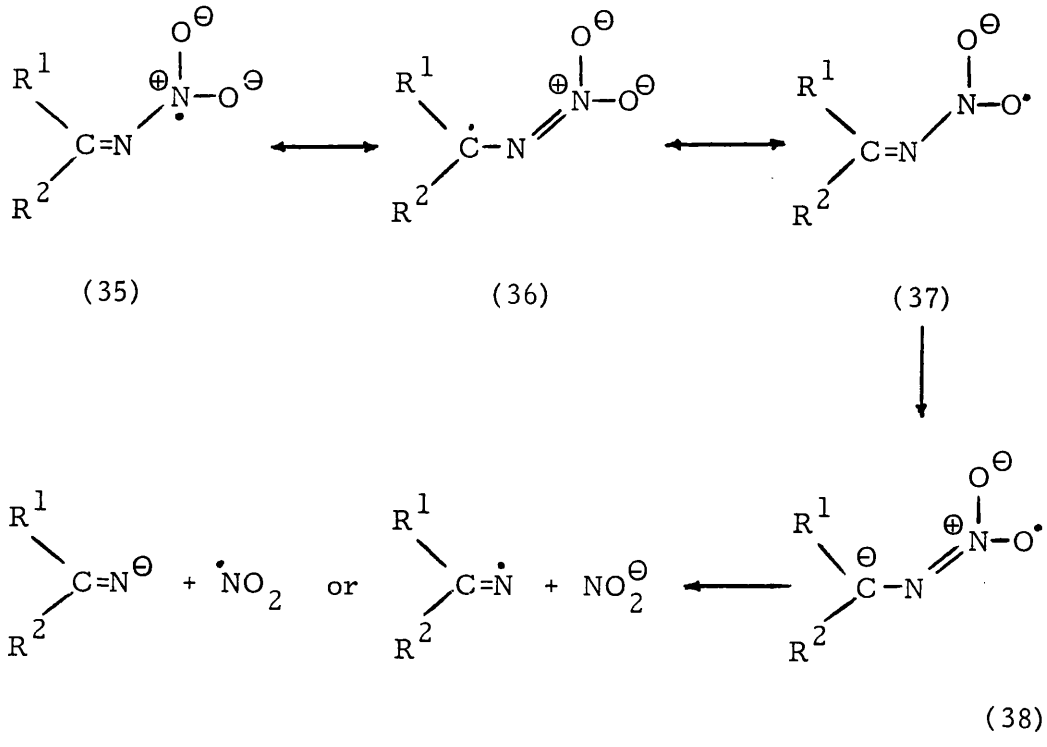


Figure 21

Dissociation of N-Nitroimine Radical Anions

Dissociation of the radical anions of N-nitroimines is predicted to yield nitrite anions and iminyl radicals ($R^1R^2C=\dot{N}$) (Figure 22). Iminyl radicals [127] are unusually stable due to very strong hyperconjugation and therefore dissociation would give thermodynamically favourable products. Features in the EPR spectra due to iminyl radicals are easy to observe. However, no such features assignable were detected in any of the spectra; this indicates that at temperatures of the study (77 K - *ca.* 150 K) dissociation does not take place. However, for the spectra in CD_3OD, features for $^{\bullet}NO_2$ were observed, in accord with the alternative dissociation in methanol (Figure 22) to yield NO_2 and imine anion.



(35) (36) (37) (38)

Figure 22

Consideration of the canonical forms (35)-(38) (Figure 22) of the radical anions of N-nitroimines and the deductions from the EPR spectra indicate considerable double bond character for the N-N bond; therefore it is not surprising that dissociation, as shown in Figure (22), does not take place. No dissociation of the corresponding C-NO_2 bond in the radical anions of nitroalkenes has been observed in solid or liquid phase studies at 300 K. However, the presence of $\dot{N}O_2$ in the CD_3OD spectra is possibly of significance.

Figure 19 (a) First derivative EPR spectrum of a dilute solution of 1-nitrocyclohex-1-ene (34) in MeTHF after exposure to ^{60}Co γ-rays at 77 K showing features assigned to the radical anion. (b) Simulation of the EPR spectrum using the parameters in Table 2.

Figure 20 (a) First derivative EPR spectrum of a dilute solution of (E)-1,7,7-trimethyl-N-nitrobicyclo[2.2.1]heptane-2-imine (29) in MeTHF after exposure to ^{60}Co γ-rays at 77 K showing features assigned to the radical anion. (b) Simulation of the EPR spectrum using the parameters in Table 3.

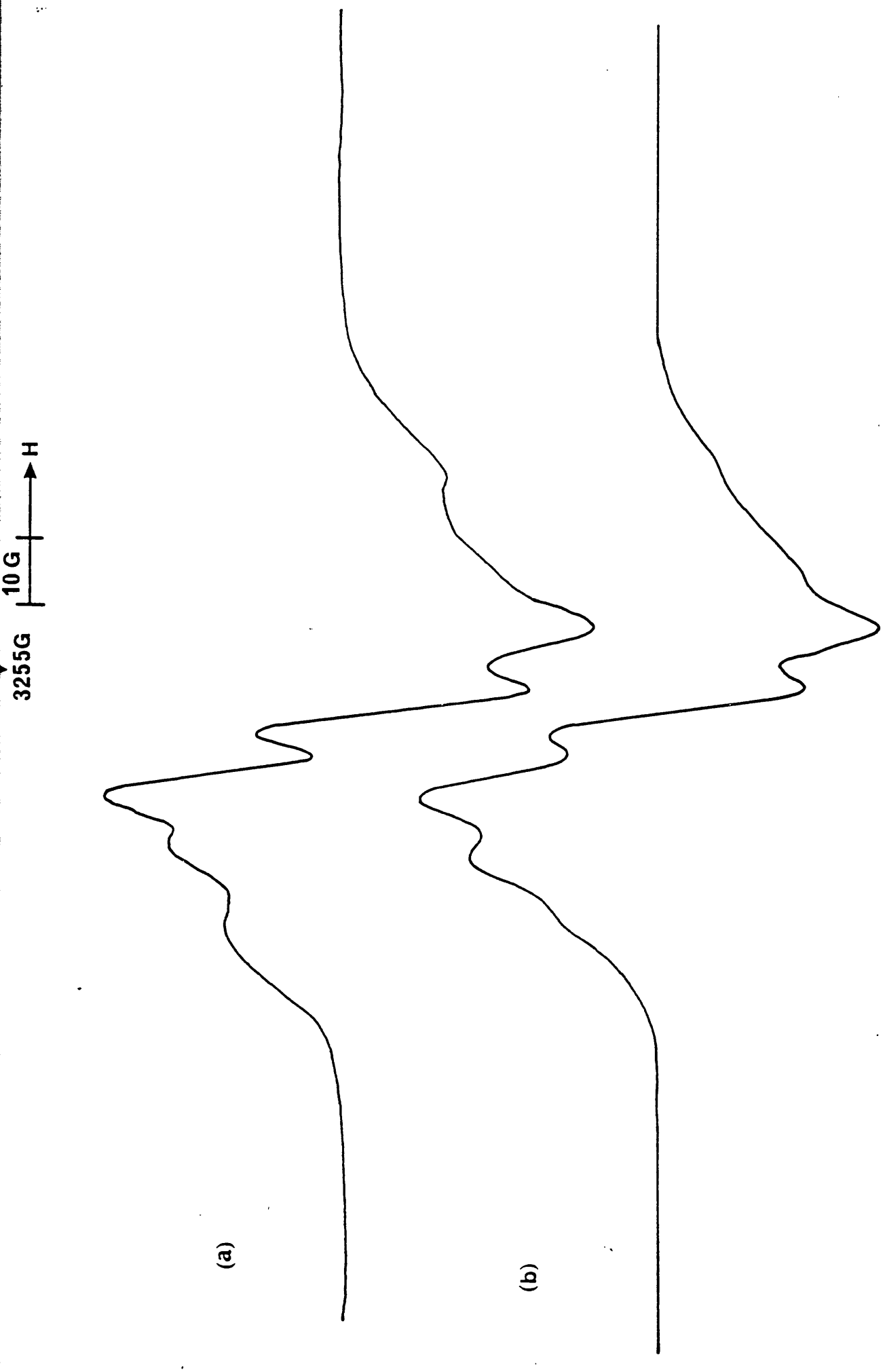


Figure 19

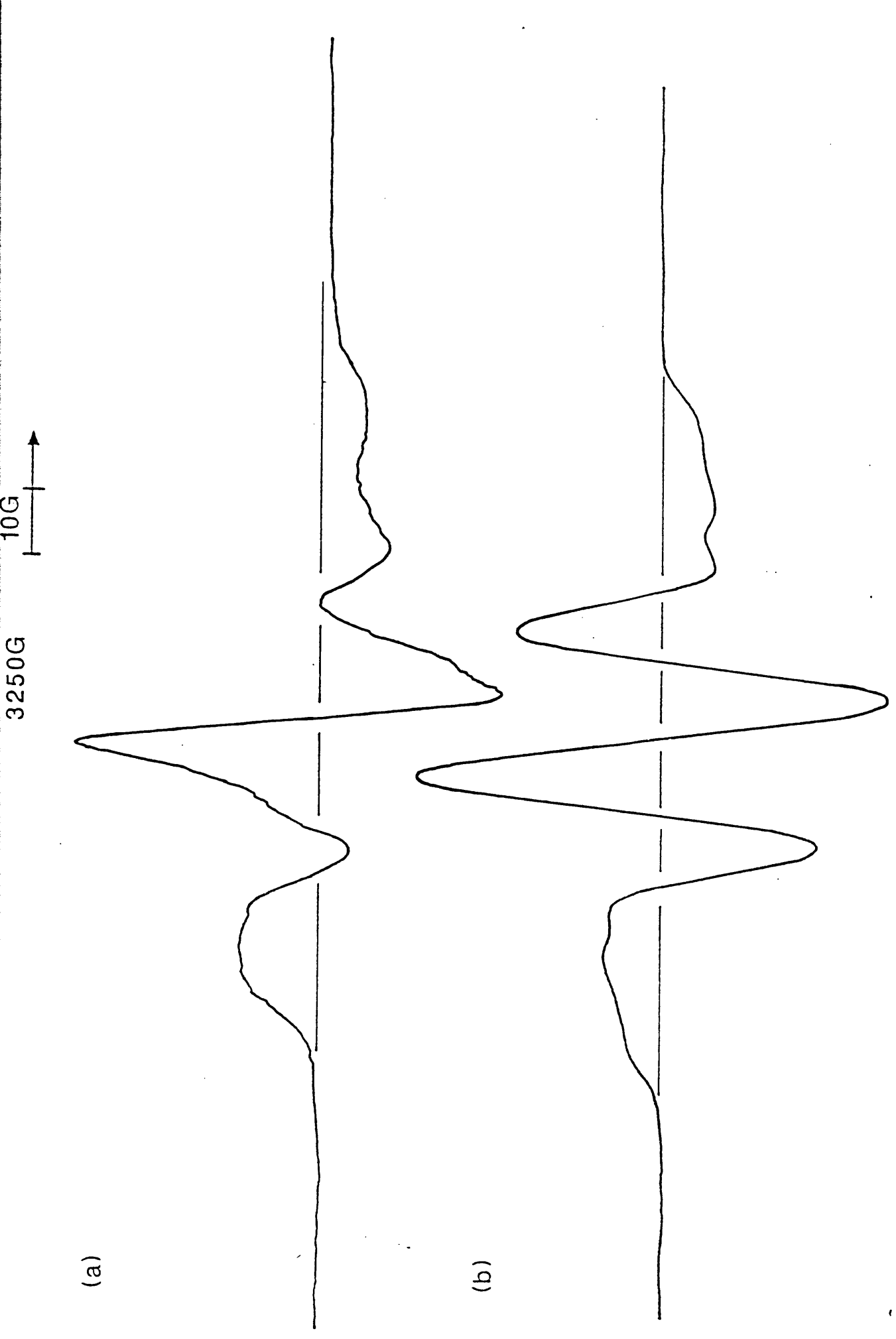


Figure 20

Table 2. EPR parameters of radical anions formed by electron capture in the radiolysis of nitroalkene solutions at 77 K.

Nitroalkene	Solvent	^{14}N Hyperfine coupling/G[a]			^{1}H (G)[a]
		A_{11}	$A_{\perp}$	A_{iso}	
2-Nitrobut-2-ene (13)	MeTHF	30	0	10	9 (4H), 2 (3H)
	CD_3OD	33	0	11	9 (4H), 3 (3H)
4-Methyl-5-nitropent-2-ene (14)	MeTHF	30	0	10	9 (1H), 2 (3H)
	b				
2,2-Dimethyl-3-nitromethylene-bicyclo[2.2.1]heptane (12)	MeTHF b	30	0	10	-
1-Nitrocyclohex-1-ene (15)	CD_3OD	33	0	11	18(1H), 9 (1H)
	MeTHF				5 (2H)
2-Methyl-1-nitroprop-1-ene	CH_3CN[c]	-	-	11.6	9 (3H), 3.2 (1H)
2,3,3-Trimethyl-1-nitropent-1-ene	CH_3CN[c]	-	-	11.9	8.7(3H),3.5(1H)
2,2-Diphenyl-1-nitroethene	CH_3CN[c]	-	-	7.0	3.5(1H)
2-C_6D_5-1-Nitroprop-1-ene	CH_3CN[c]	-	-	7.9	9.3(3H),2.8(1H)

[a] G = 10^{-4} T. [b] Very poor spectrum in CD_3OD, possibly due to low solubility. [c] Ref. 29.

Table 3. EPR parameters of radical anions formed by electron capture in the radiolysis of N-nitroimine solutions at 77 K.

N-Nitroimine	^{14}N Hyperfine coupling/G[a,b]				^{1}H (G)[a,b]
	A_{11}	$A_{\perp}$	A_{iso}	2B	
Camphor (8)	39	17	24.3	14.7	7 (1H)
4-Chlorocamphor (9)	39	17	24.3	14.7	7 (1H)
Fenchone (10)	43	19	27	16	-

[a] G = 10^{-4} T. [b] Results were about the same for MeTHF and CD_3OD.

2.3 EXPERIMENTAL

For general experimental details, see Section 1.3.1.

2.3.1 EPR SPECTROSCOPY

De-gassed samples were irradiated as dilute solutions (*ca.* 1% v/v) in methanol (CD_3OD was used to avoid overlap with solvent features) or MeTHF. They were frozen as small beads in liquid nitrogen and irradiated at 77 K in a Vickrad ^{60}Co γ-ray source to doses of up to 1 Mrad. EPR spectra were measured on a Varian E109 spectrometer. Samples were annealed to selected temperatures or until significant changes occur in the EPR spectra, and recooled to 77 K for study.

2.3.2 PREPARATION OF COMPOUNDS (27)-(34)

Camphor N-Nitroimine (27)

Camphor (80) (5 g, 0.033 mol) in ethanol (15 ml), hydroxylamine hydrochloride (5 g, 0.071 mol) in water (10 ml) and sodium acetate trihydrate (6.15 g, 0.045 mol) were refluxed together for five hours. The cooled solution was poured into water (75 ml) and the product filtered and washed with water until neutral to give crude camphor oxime, which was recrystallised from ethanol; pure camphor oxime (60) was obtained (6.63 g, 79%); m.p. 119 °C (lit.,[128] 118 °C).

Camphor N-nitroimine (27) was prepared from camphor oxime (60) (6.63 g, 0.040 mol) according to the method of Brooks *et al.*[129] Recrystallisation from ethanol

gave pure camphor N-nitroimine (27) (2.82 g, 36%); m.p. 41-43 °C (lit.,[130] 41-43 °C); ν_{max} (KBr) 1635, 1550 and 1300 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 1.22 (3 H, s), 1.32 (3 H, s), 1.35 (3 H, s), 1.45-1.95 (7 H, m).

4-Chlorocamphor N-nitroimine (28)

To an ice-cooled solution of 4-chloroisoborneol (13) (10.52 g, 0.056 mol) in dry acetone (70 ml) was added dropwise, over 5 min, a freshly prepared solution of Jones' reagent[131] (25 ml). The mixture was stirred for 30 min, after which time a green precipitate had formed. The reaction mixture was poured onto heavily salted water (1 ℓ) and extracted with ether (30 x 20 ml). The combined ethereal extracts were washed with water, brine and dried. After evaporation of the ether, the residue was placed on an alumina column (petroleum ether (40-60 °)) resulting in pure 4-chlorocamphor (8.97 g, 86%); m.p. 197-198 °C (lit.,[71] 198-199 °C).

4-Chlorocamphor oxime was prepared from 4-chlorocamphor in a manner analogous to that employed in the preparation of camphor oxime (60).

4-Chlorocamphor N-nitroimine was prepared directly from 4-chlorocamphor oxime (5 g, 0.030 mol) according to the literature method.[129] Recrystallisation from ethanol, gave pure 4-chlorocamphor N-nitroimine (28) (4.24 g, 61%); m.p. 83-84 °C (lit.,[130] 84-85 °C); ν_{max} (KBr) 1649, 1570 and 1313 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.87 (3 H, s), 0.95 (3 H, s), 1.07 (3 H, s), 1.20-2.20 (4 H, m), 2.71 (1 H, d, *J* 18.4, 3-H_{endo}), 2.91 (1 H, dd, *J* 18.4 and 3 Hz, 3-H_{exo}).

Fenchone N-Nitroimine (29)

Fenchone oxime was prepared by the method of Cottingham[132] from fenchone.

To fenchone oxime (3.3 g, 0.019 mol) in acetic acid (30 ml) was added, with stirring, a 5% aqueous solution of sodium nitrite (45 ml). After 2 h stirring, the precipitate obtained by addition of water was filtered, dried and recrystallised from ethanol to give pure fenchone N-nitroimine (29) (2.1 g, 56%); m.p. 52-57 °C (lit.,[133] 52-58 °C); ν_{max} (KBr) 1625, 1540 and 1290 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 1.20 (3 H, s), 1.27 (3 H, s), 1.30 (3 H, s), 1.40-1.97 (6 H, m).

Fluorenone N-nitroimine (30)

Diazofluorene was prepared from fluorenone hydrazone (4.2 g, 0.022 mol) by stirring as a suspension in dry ether (300 ml) overnight with excess mercuric oxide (red, 12 g, 0.056 mol) in the presence of 4 drops of a concentrated solution of sodium methoxide in methanol. After filtration to remove mercury residues and evaporation of the ether solvent, diazofluorene was obtained as lustrous red crystals (2.98 g, 70%).

To a solution of diazofluorene (1.2 g, 0.006 mol) in benzene (50 ml) in a gas burette was added (after evacuation of air and filling with dry nitrogen, a sequence that was repeated three times) nitric oxide. The solution was stirred and a colour change from red to yellow took place over *ca.* 40 min. On stopping stirring evolution of small bubbles could be observed. Since nitrogen is evolved and nitric oxide consumed the reaction was monitored by colour change and at intervals the gas burette was emptied of gases and the system replenished with fresh nitric oxide.

Work up by removal of the solvent and recrystallisation from ethanol gave pure fluorenone N-nitroimine (30) (0.41 g, 31%); m.p. 140-141 °C (lit.,[113] 141 °C).

2,2-Dimethyl-3-nitromethylbicyclo[2.2.1]heptane (31)

To a stirred, ice-cooled solution of camphene (8.16 g, 0.06 mol), petroleum ether (40-60 °) (20 ml) and sodium nitrite (66 g, 0.95 mol) in water (40 ml) was added, at the rate of 1 ml per hour, a mixture of acetic acid and water (40 ml and 0.4 ml). The reaction mixture was then placed in a fridge for 48 h. The organic layer was removed, and the aqueous layer extracted with petroleum ether (40-60 °). The combined organic extracts were dried and the solvent removed under reduced pressure. Purification on an alumina column (10% ethyl acetate/petroleum ether (40-60 °)) gave the title compound (31) (3.47 g, 32%); m.p. 62-65 °C (lit.,[125] 62-64 °C, lit.,[126] 75 °C, lit.,[134] 64-66 °C); ν_{max} (KBr) 1640, 1505 and 1340 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 1.10 (6 H, s), 1.16-1.95 (7 H, m), 3.97 (1 H, d, *J* 5.5), 6.75 (1 H, s).

(Z)-2-Nitrobut-2-ene (32)

This compound was prepared from 2-nitro-butan-2-ol by the method of Melton and McMurray.[135]

(Z)-4-Methyl-2-nitropent-2-ene (33)

This compound was prepared from 4-methyl-2-nitropentan-2-ol by the method of Melton and McMurray.[135]

1-Nitrocyclohex-1-ene (34)[136]

Cyclohexene (5 g, 0.061 mol) was treated with mercuric chloride (16.53 g, 0.061 mol) and an aqueous solution of sodium nitrite (8.42 g, 0.122 mol). The reaction mixture was stirred at 25 °C for 30 h. After this time, the resultant precipitate was taken up in methylene chloride (30 ml) and treated with 2.5 M aqueous sodium hydroxide (25 ml) at 25 °C for 5 min with stirring followed by acidification (1 M, hydrochloric acid). After filtration through Celite, extractive isolation with methylene chloride and distillation, 1-nitrocyclohex-1-ene (34) was obtained (8.6 g, 80%); b.p.$_2$ 71-73 °C (lit.,[137] b.p.$_1$ 60-61 °C); ν_{max} (film) 1670, 1520 and 1315 cm^{-1}; δ_H (CDCℓ_3) 90 MHz, 1.75 (4 H, m), 2.52 (4 H, m), 7.40 (1 H, t, *J* 6).

PART III

SYNTHESIS OF 4-FLUORO-3,5-DINITROPHENOL (39)

3.1 INTRODUCTION

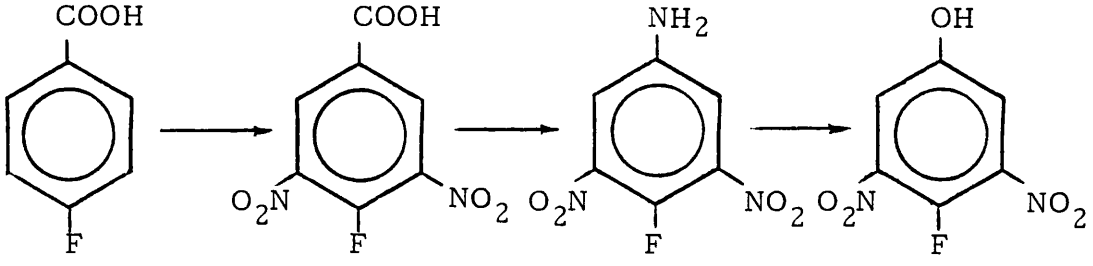
In connection with an investigation on hydrogen bonding, the synthesis of the unknown compound 4-fluoro-3,5-dinitrophenol (39) was undertaken. This particular compound was sought in order to monitor hydrogen bonding by variations in both the O-H stretching frequency of (39) and also in the ^{19}F chemical shifts in this compound.

3.2 RESULTS AND DISCUSSION

A convenient starting material for the synthesis was thought to be 4-fluorobenzoic acid (40). Dinitration of (40) would yield 4-fluoro-3,5-dinitrobenzoic acid (41), which upon a Schmidt reaction,[144] would give 4-fluoro-3,5-dinitroaniline (42). Introduction of the hydroxyl group would be carried out by nucleophilic aromatic substitution (S_N Ar) *via* the diazonium salt. The intended synthesis of phenol (39) is shown in Figure (23).

First attempts to dinitrate 4-fluorobenzoic acid (40) resulted in only mono-nitration to give 4-fluoro-3-nitrobenzoic acid (m.p. 122 °C). This reaction was carried out using concentrated nitric acid and concentrated sulphuric acid. That only mono-nitration occurred was not altogether surprising when one considers the nature of the ring substituents. The carbonyl group of the acid destabilises the benzonium

ion and the halogen atom will deactivate all positions of the ring, but most of all the *meta* position. Fluorine is the most deactivating of the halogen atoms,[138] and of course after nitration, the ring will be even more deactivated due to the newly introduced, powerfully deactivating, nitro substituent.



(40) (41) (42) (39)

Figure 23

It was obvious that more vigorous conditions would have to be employed in order to introduce the second nitro substituent. There is no ambiguity as to the position at which the second nitro group would be placed on account of the *meta*-directing acid and nitro substituents and the *ortho-para*-directing fluorine substituent.

The new, more vigorous conditions employed were based upon those of Nielsen *et al.*[139] Here oleum (20% SO_3) replaces concentrated sulphuric acid and 90% nitric acid is employed.

The concentration of the nitronium ion (NO_2^+) is increased markedly by the addition of sulphuric acid.[140] The conversion of nitric acid to nitronium ion proceeds according to equation (42) and is complete in 90% sulphuric acid.[141] The sulphuric acid catalyses nitration by first protonating the nitric acid to give the nitric acidium ion, equation (43). The nitric acidium ion is then heterolysed slowly to give water and nitronium ion, equation (44).

$$HNO_3 + 2\,H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2\,HSO_4^- \quad (42)$$

$$H_2SO_4 + HNO_3 \rightleftharpoons H_2NO_3^+ + HSO_4^- \quad (43)$$

$$H_2NO_3^+ \rightleftharpoons NO_2^+ + H_2O \quad (44)$$

Figure 24

Oleum is used since it is better able to absorb water without reducing the nitronium ion concentration.[142] Overall in oleum, nitric acid ionises in the following way:[143]

$$HNO_3 + 2H_2S_2O_7 \rightleftharpoons NO_2^+ + HS_2O_7^- + 2H_2SO_4 \quad (45)$$

One problem that results from the use of solutions of nitric acid in sulphuric acid or oleum is that of sulphonation; however this reaction is rarely significant, for nitration is generally a more rapid process than sulphonation.[138] 4-Fluoro-3,5-dinitrobenzoic acid (41) was obtained in 73% yield.

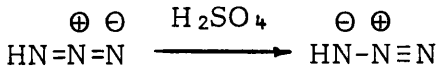
The next step of the synthesis was conversion of 4-fluoro-3,5-dinitrobenzoic acid (41) into 4-fluoro-3,5-dinitroaniline (42). To achieve this, sodium azide and the acid (41) were refluxed in oleum and chloroform in a Schmidt reaction.[144]

The reaction between equimolar quantities of hydrazoic acid (43) and carbonyl compounds in the presence of strong mineral acids has become known as the Schmidt reaction. It affords a convenient method for the preparation of amines from acids according to equation (46):

$$RCO_2H + HN_3 \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2 \qquad (46)$$

Work of McNamara and Strothers[145] showed that yields in a Schmidt reaction were greatly improved when 20% oleum was employed instead of concentrated sulphuric acid, even on compounds with two strong electron withdrawing groups, such as nitro.

The mechanism for the Schmidt reaction is shown in Figure (25). Hurd[146] proposed the activation of hydrazoic acid (43) by concentrated sulphuric acid to form an active species (44) which adds to the carbonyl, forming (45). Molecular nitrogen is then lost from (45) to form an unstable derivative (46) which rearranges with migration of an R-group (the R-group that migrates is the one better able to stabilise a positive charge), to yield an amide (47). In this case, where the R'-group in Figure (25) is hydroxyl, the amide (or carbamic acid) decomposes readily to the amine and carbon dioxide.



(43) (44)

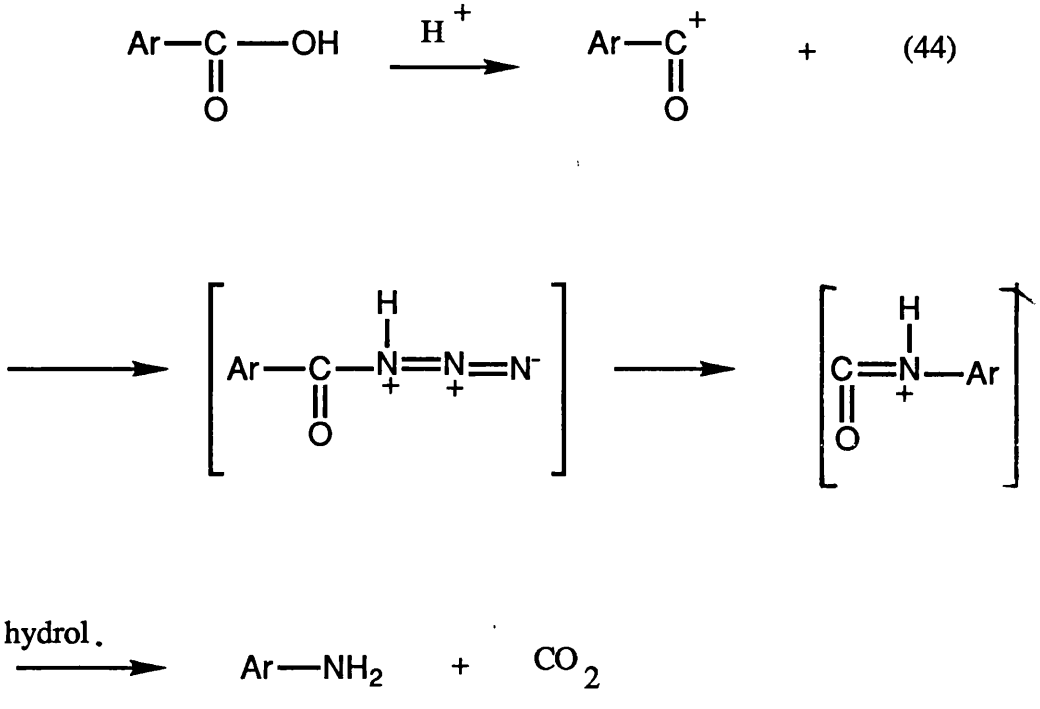


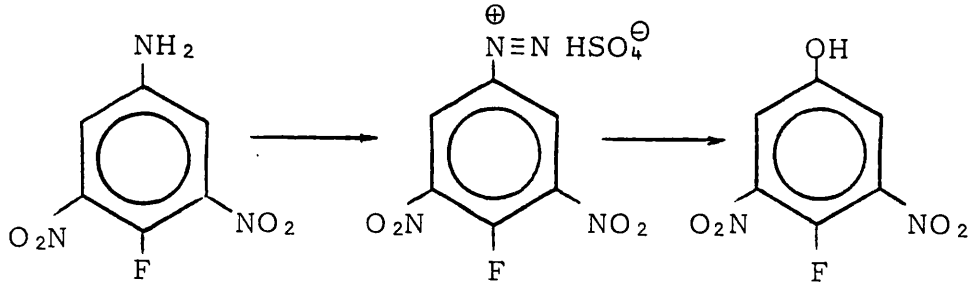
Figure 25

It is thought that aromatic amination by hydrazoic acid can be explained by a slightly different mechanism.[147] It appears that this reaction proceeds *via* an (NH) or (NH_2^+) fragment. Evidence for the difference in mechanism comes from the fact that higher temperatures are needed for the aromatic acids than for the aliphatic

ketones and amination of aromatic nuclei is always accompanied by the formation of one or more of the decomposition products of (NH), *viz.* NH_3, N_2H_4 and NH_2OH.

The Schmidt reaction on 4-fluoro-3,5-dinitrobenzoic acid (41) gave the desired product, 4-fluoro-3,5-dinitroaniline (42) in 56% yield.

The final step involved conversion of the amine (42) to the desired phenol (39) by employing water as the nucleophile in an aromatic nucleophilic substitution on the intermediate diazonium salt (48), Figure (26):



(42) (48) (39)

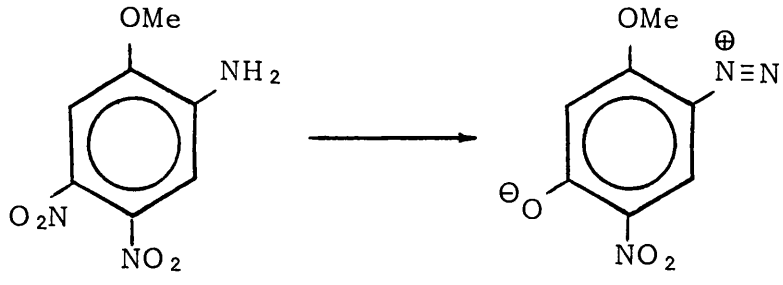
Figure 26

To make the diazonium salt, the amine (42) was reacted with nitrous acid (from sodium nitrite and concentrated sulphuric acid). Here the effective nitrosating agent is probably not HNO_2 itself but, in quite strong acid medium it is more likely to be $H_2\overset{+}{O}$-NO and finally the nitrosonium ion, NO^+.

Upon reaction, the diazonium salt did appear to be formed; this was indicated by a bright yellow colour in the reaction mixture. However, the attempt at nucleophilic substitution using water did not appear to give the desired product, *viz.* 4-fluoro-3,5-dinitrophenol (39). The products were assayed primarily by mass spectrometry. As well as the presence of starting material ($m/z = 201 = M^+$), there were significant peaks present at values as high as $m/z = 356$; this suggests some kind of coupled reaction product. These products were not investigated further.

The lack of success of this reaction was unfortunate though not entirely surprising in view of the work carried out by Bunnett and Zahler.[148] The diazonium group (N_2^+) is the strongest of the activating groups for nucleophilic aromatic substitution. During diazotisation of anilines, a nitro, methoxy or halogen group *ortho* or *para* to the amino group is sometimes replaced by hydroxy owing to the reaction with water. This effect is even more pronounced if there is a second activating structure (*e.g.* a nitro group) suitably oriented to the displaceable substituent. An example of such a reaction is shown in the diazotisation of 6-methoxy-3,4-dinitroaniline (49) in glacial acetic acid. This resulted in 6-methoxy-3-nitrobenzene-1,4-diazo-oxide (50).[149]

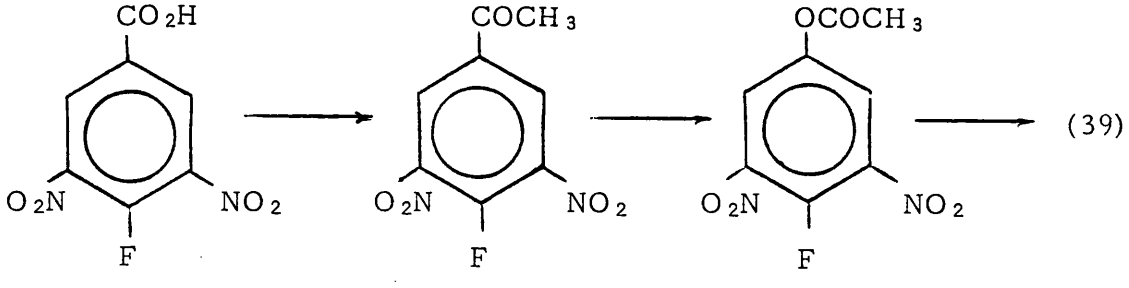
Due to the failure of this deamination, a different route to the phenol (39) was envisaged.



(49) (50)

Figure 27

The new route to the phenol (39) also employed 4-fluorobenzoic acid (40) as the starting material. Once again, after dinitration, (41) was obtained. It was at this point that the new route to (39) is employed. An outline of the reaction pathway is shown in Figure (28).



(41) (51) (52)

Figure 28

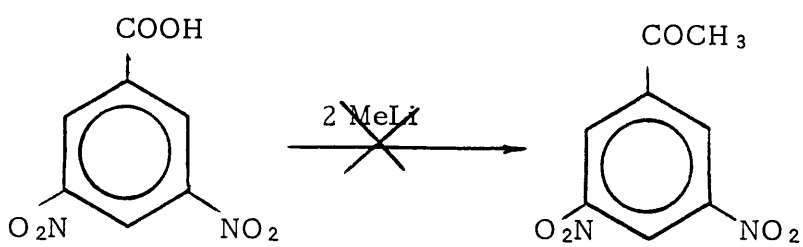
This new route was based upon work carried out by De Puy *et al.*[150] in which the acid (41) is converted to the methyl ketone (51) upon reaction with methyl lithium,[150] the ketone (51) undergoes Baeyer-Villiger oxidation[151,152] yielding the ester (52) and finally, again employing methyl lithium,[150] ester (52) is cleared to give the phenol (39).

The overall equation for the reaction of methyl lithium with an acid is shown in equation (47).

$$RCO_2H + 2\,MeLi \longrightarrow RCOCH_3 + Li_2O + CH_4 \qquad (47)$$

Work carried out by Gilman and Van Ess[153] showed that the intermediate in this reaction is a di-lithium salt. If the intermediate were a ketone, the second mole of methyl lithium would yield a tertiary alcohol.

However, reaction of methyl lithium with 4-fluoro-3,5-dinitrobenzoic acid (41) yielded detectable amounts of starting material only. This result had been predicted by Kieboom[154] who had noticed that reaction between 3,5-dinitrobenzoic acid (53) and methyl lithium did not yield any detectable amount of 3,5-dinitroacetophenone (54).

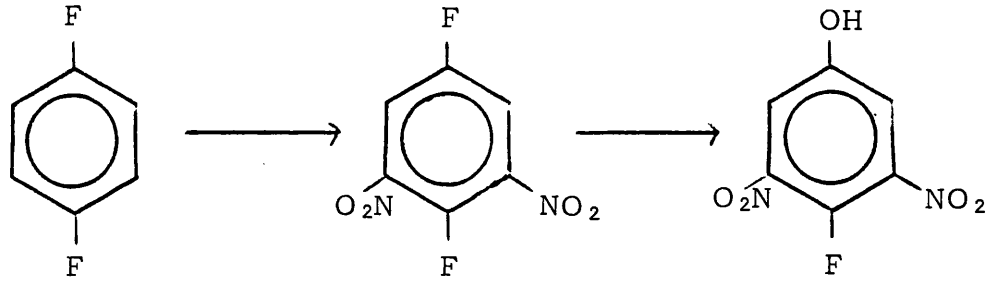


(53) (54)

Figure 29

Failure of this synthetic route meant that a new strategy had to be employed in order to obtain the phenol (39).

Since the phenol (39) contains three adjacent, strongly electron withdrawing groups, it was felt that the hydroxyl group could be introduced into the aromatic ring by nucleophilic substitution. The outline of the pathway is shown in Figure (30).



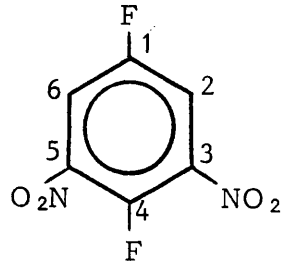
(55) (56) (39)

Figure 30

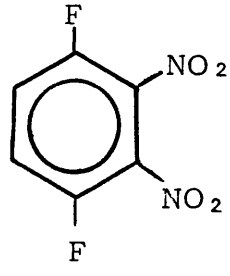
The starting material for this new route is 1,4-difluorobenzene (55). Dinitration of this compound was carried out using the milder nitrating conditions of Hammond and Modic,[155] who had previously dinitrated the analogous dichloro compound, 1,4-dichlorobenzene.

Upon dinitration, as expected, three isomeric products were formed. These were 3,5-dinitro-1,4-difluorobenzene (56), 2,3-dinitro-1,4-difluorobenzene (57) and 3,6-dinitro-1,4-difluorobenzene (58). The three isomers were painstakingly separated by thin layer chromatography.

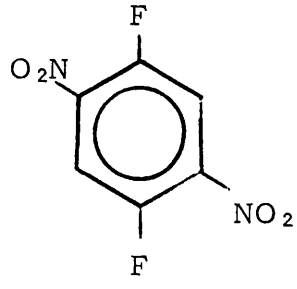
The major isomer was found to be 3,5-dinitro-1,4-difluorobenzene (56), the middle band on the t.l.c. plate. This is not surprising in view of the directing tendencies of the fluorine atoms and the first nitro group.



(56)



(57)



(58)

Assignment and identification of the three isomers was carried out using ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. The desired isomer (56) was identified by two fluorine signals in the ^{19}F NMR spectrum at -109 p.p.m. and -130 p.p.m. (with respect to $CFC\ell_3$ at 0 p.p.m.). Each signal is a doublet of triplets. One fluorine atom is coupled to the other non-equivalent fluorine atom (J_{FF} = 17.5 Hz) and further coupled to the two equivalent protons. The H-F coupling constants were used to assign the fluorine atoms. C(1)-F was found at -109 p.p.m. (J_{HF} = 6.7 Hz) and C(4)-F at -130 p.p.m. (J_{HF} = 5.2 Hz). The *ortho* coupling constant is larger than the *meta* coupling constant. In aromatic systems, the *ortho* H-F coupling constant range overlaps with the *meta* H-F coupling constant range.[156] Also (56) is the only isomer to show four individual chemical shifts in the ^{13}C NMR spectrum (Table 4).

Isomers (57) and (58) were assigned and identified primarily from comparison

of the observed carbon chemical shifts with those calculated[157] (Table 4).

Despite the susceptibility of aromatic ^{13}C chemical shifts to influences such as ring current,[158] solvent and steric effects, the substituent effects are remarkably additive.[157] The main difference between the two isomers lay in the chemical shifts of the carbon atoms carrying the nitro groups.

The t.l.c. bands with the largest and smallest R_f values were thus assigned to (58) and (57), respectively.

Overall, dinitration was achieved in a 20% yield with isolation of (56) in 12% yield.

Having isolated (56), the next step was to replace, selectively, the fluorine atom *meta* to the two nitro groups with the hydroxyl functionality. Use of hydroxide ion as the nucleophile did not yield 4-fluoro-3,5-dinitrophenol (39). It is known that nitro substituents activate the aromatic ring towards $S_N Ar$ displacement reactions *ortho* (and *para*) to themselves.[149]

In order to achieve the desired displacement, it was decided to introduce the hydroxyl functionality by means of a large bulky base. Although the carbon atom adjacent to both the nitro groups is more activated towards nucleophilic attack, it is also more hindered to attack than the other carbon atom bearing fluorine due to the large bulky nitro groups.

The choice of the base to deliver the hydroxyl functionality was the anion of camphor oxime (59). There are three reasons for this choice of anion: (i) it is bulky and therefore not predisposed to attack the more active carbon carrying fluorine

atom, C(4), (ii) as an oximate anion, (59) is a reactive alpha-effect nucleophile,[159,160] and (iii) the oxime ether so formed is capable of releasing the phenol readily in a second order Beckmann reaction[161] that is characteristic of certain oxime derivatives.

Excess reactivity is shown by nucleophilic reagents such as peroxide, hydroxylamine, hydrazine, hydroxamic acids and oxime anions. The one theme that links these compounds is the presence of an electronegative atom containing one (or more) pair of unpaired electrons adjacent to the nucleophilic atom - the alpha effect. Much work has been carried out on the alpha effect, although the mechanism by which the 'alpha electrons' influence nucleophilicity is not yet fully understood.[162]

Edwards and Pearson[159] gave an explanation of the mechanism of the alpha effect by considering the case of nucleophilic substitution. A pair of electrons leaving the nucleophile (Nu) for a substrate some distance away (equation 48) would resemble the ionisation of a halide from an organic halide to form a carbonium ion (equation 49).

$$Nu \longrightarrow Nu^{2+} + 2e^{-} \qquad (48)$$

$$RX \longrightarrow R^{+} + X^{-} \qquad (49)$$

Figure 31

So by analogy, any factor that would stabilise the carbonium ion, R^+, should also stabilise the denuded nucleophile, Nu^{2+}. One such factor could be an unused pair of electrons on the adjacent atom. In the transition state, whereby some of the electron pair of the reactive atom is removed, the π-bonding shown in equation (50) will improve the stability of the system.

$$\rangle C{=}N\text{-}O^{\ominus} \longrightarrow C{=}\overset{\oplus}{N}{=}O + 2e^- \qquad (50)$$

The first-order Beckmann rearrangement[163,164] of a simple ketoxime involves the simultaneous departure of the hydroxyl or acylated hydroxyl, X, with its bonding pair of electrons and the 1,2-shift of the group, R, originally *trans* to X, with its bonding pair (Figure (32)). The reaction is completed upon reaction of the intermediate cation with, for example, a hydroxide anion or water.

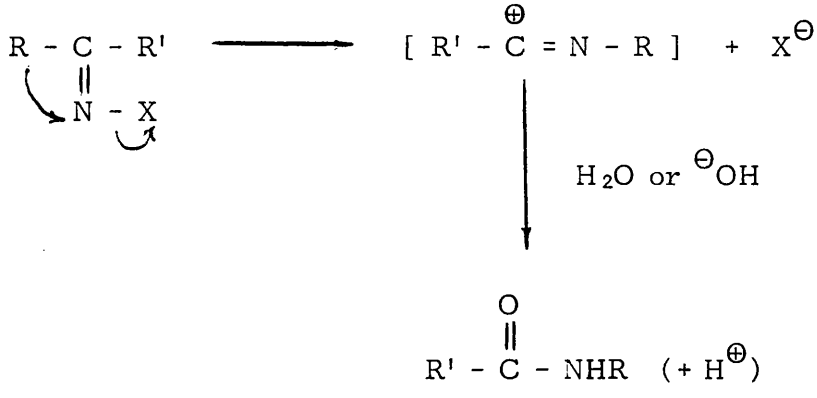


Figure 32

The second Beckmann rearrangement may be described similarly except that the departure of X is accompanied by the shift of an electron pair (Figure (33)). This reaction may also be regarded as the attack of the electron-deficient nitrogen atom on the electron pair of the *trans* group.[165] Once again, the intermediate cation combines with an hydroxide anion or water.

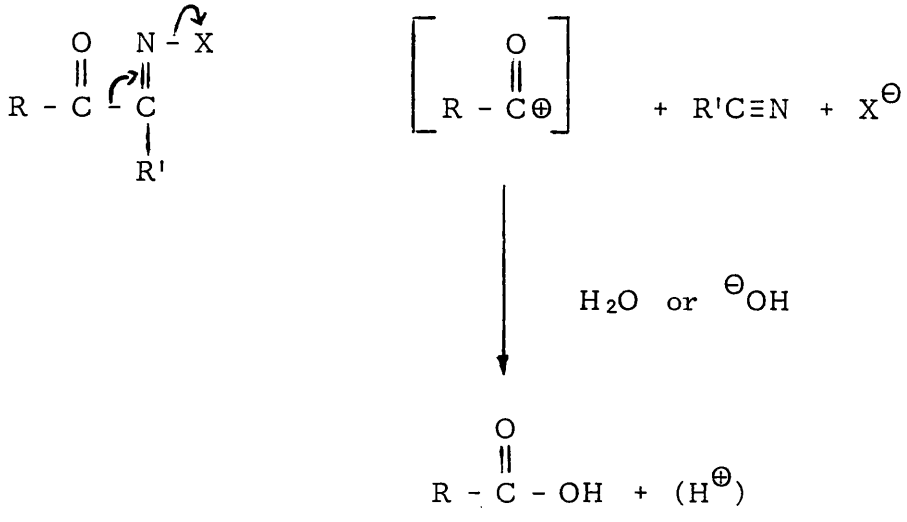


Figure 33

Simple definitions result if the first-order rearrangement is considered as one which involves shift of an organic group with its pair of electrons, and the second-order rearrangement as one which involves shift of an electron pair only.[161]

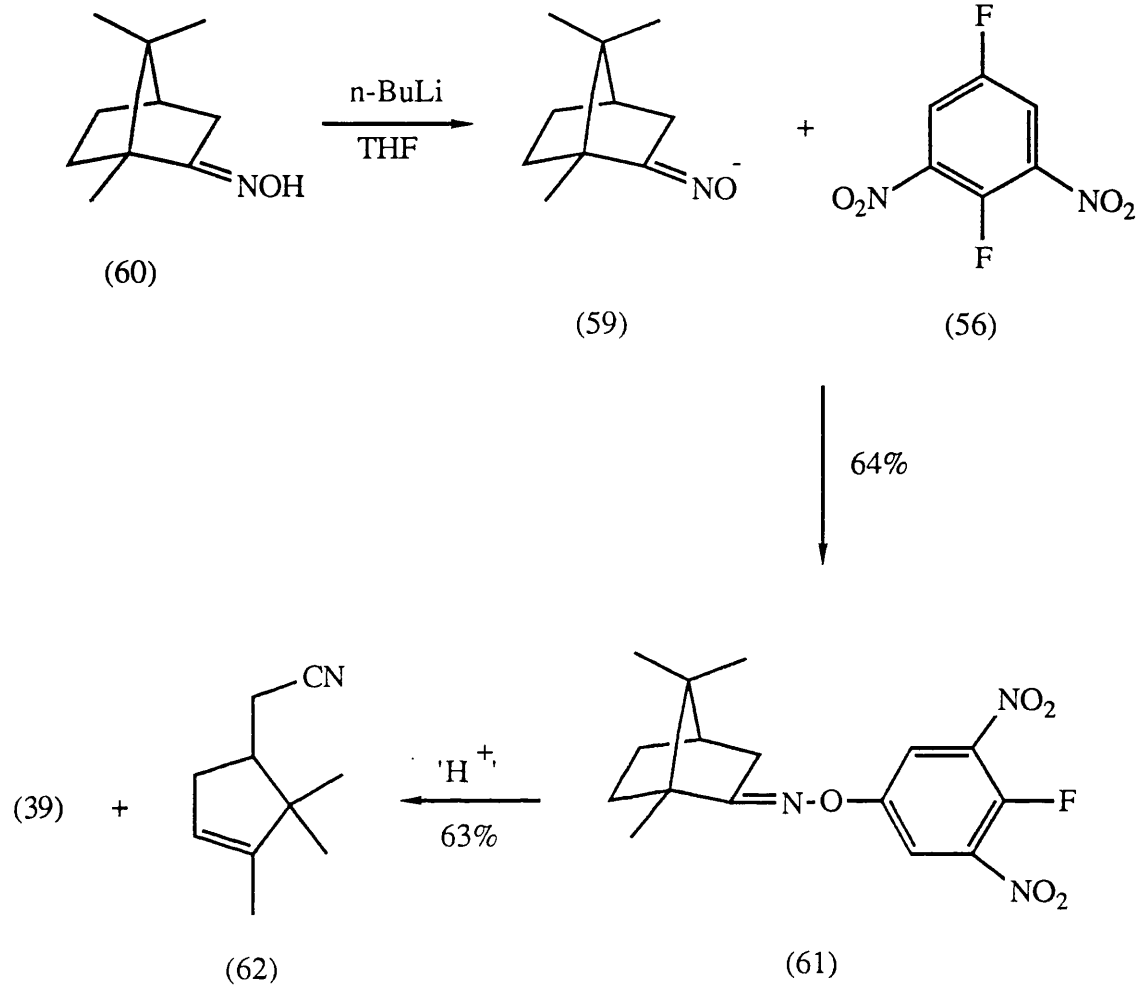
It should be noted that the second-order Beckmann rearrangement is a sub-class of the Grob fragmentation.[166]

A solution of the camphor oximate anion (59) (prepared from camphor oxime (60) and n-BuLi) in dry tetrahydrofuran was treated with 3,5-dinitro-1,4-difluorobenzene (56) resulting in a 64% yield of the oxime ether (61). ^{19}F NMR showed only one signal at -114 p.p.m. (1 F, t, J_{HF} 7.1), while correspondingly, ^{1}H n.m.r. showed only one signal, 7.7 p.p.m. (2 H, d, J_{HF} 7.1). A doublet at 155 p.p.m. for the carbon atom bearing fluorine compared favourably with that of the calculated value[157] (157 p.p.m.).

The second-order Beckmann reaction of oxime ether (61) was carried out by refluxing with aqueous hydrochloric acid in methanol to give a 63% yield of 4-fluoro-3,5-dinitrophenol (39). This reaction was accompanied by the characteristic smell of α-campholenonitrile (62). This is the product of an intramolecular second-order Beckmann rearrangement, where a proton is lost to form a cyclopentene ring. This product (62) was not investigated further.

The mechanism for the second-order Beckmann rearrangement of (61) to (39) and (62) can be shown in Figure (35) where the aromatic part of the oxime ether (61) has been replaced by X, where X is a good leaving group.

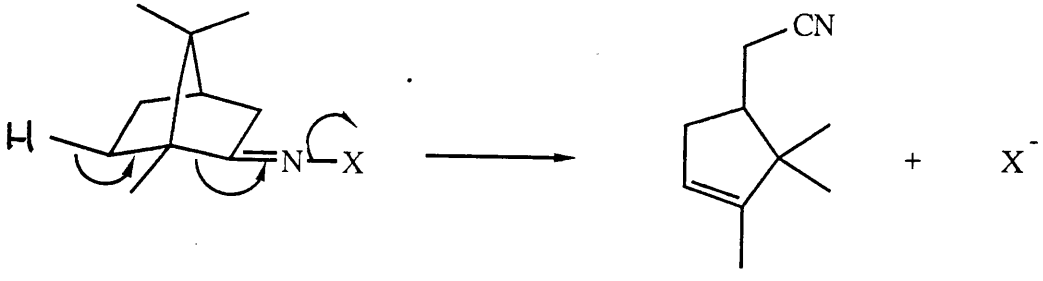
Comparison of the observed ^{13}C chemical shifts with those of the calculated values[157] and also with the observed chemical shifts of the structurally isomeric phenol, 4-fluoro-2,6-dinitrophenol (63), prepared from an independent synthesis from a method by Clewley *et al.*,[167] (Table 5) showed that the desired phenol, 4-fluoro-3,5-dinitrophenol (39) had been synthesised.



(60) (59) (56)

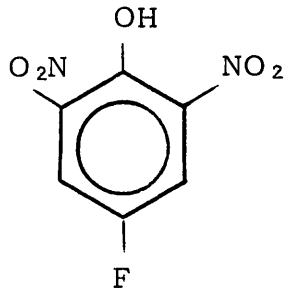
(62) (61)

Figure 34



(62)

Figure 35



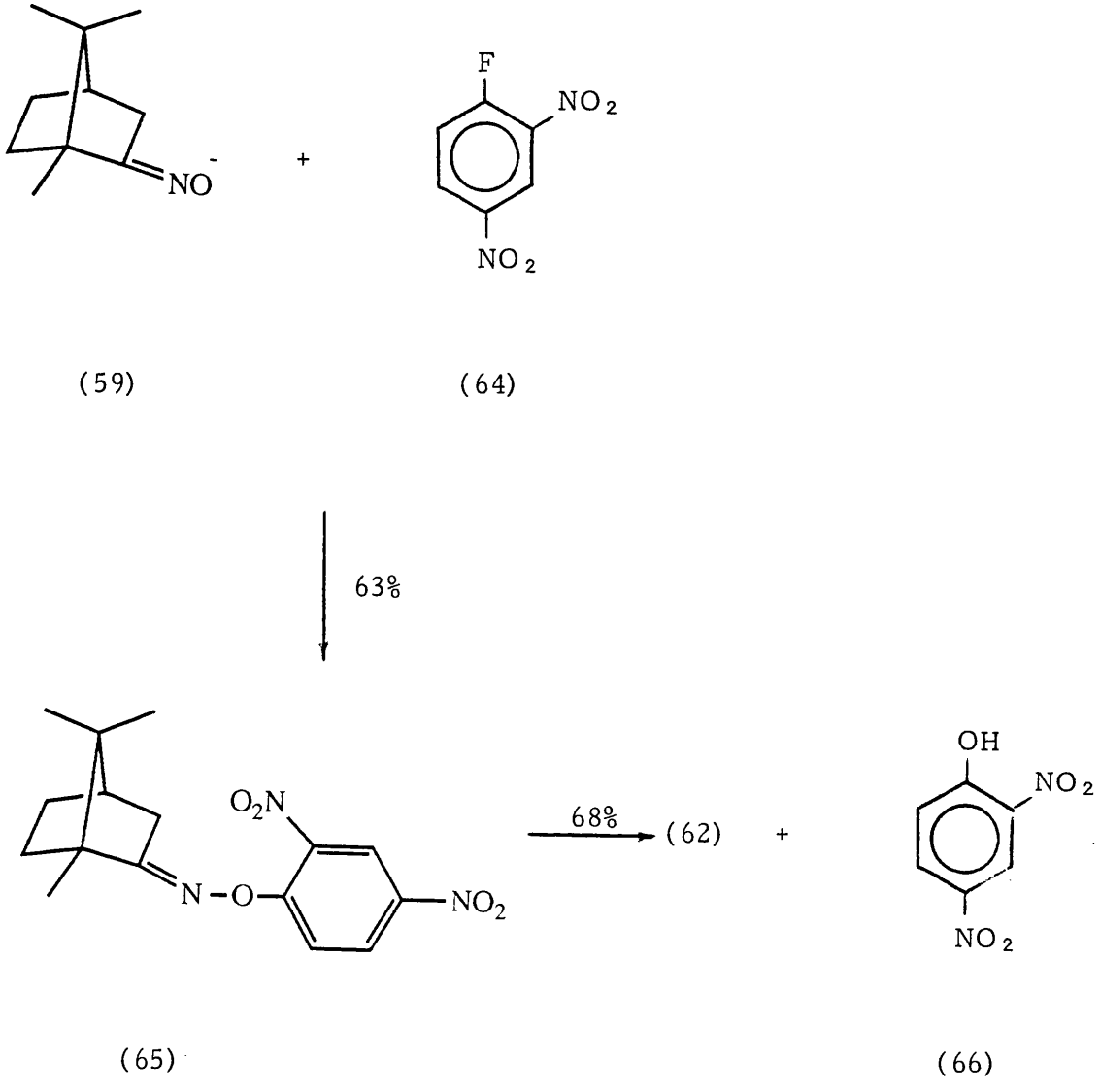
(63)

Previously, the above method had been tested on 2,4-dinitrofluorobenzene (64). The oxime ether (65) was produced in 63% yield. As a result of the second-order Beckmann rearrangement, 2,4-dinitrophenol (66) was formed in 76% yield. The ^{1}H NMR values of this phenol (66) corresponded to those found by Stephens and co-workers.[168]

This method may find application in the synthesis of other phenols with strong electron-withdrawing groups. Clearly though, this method is limited to those molecules without acid sensitive moieties due to the vigorous conditions employed in the cleavage of the oxime ether. Ideally it would be advantageous if the oxime ether could be cleared under milder and more selective conditions.

One such solution to this problem is to incorporate similar methodology to that developed by Lipshutz and Pegram,[169] who developed β-(trimethylsilyl)ethoxy-methyl chloride (SEM-Cℓ) as a new reagent for the protection of the hydroxyl group:

$$\text{R-OH} + \text{C}\ell\text{CH}_2\text{OCH}_2\text{CH}_2\text{SiMe}_3 \xrightarrow{(\text{>-})_2\text{NEt}} \text{ROCH}_2\text{O-CH}_2\text{-CH}_2\text{-SiMe}_3 \qquad (51)$$



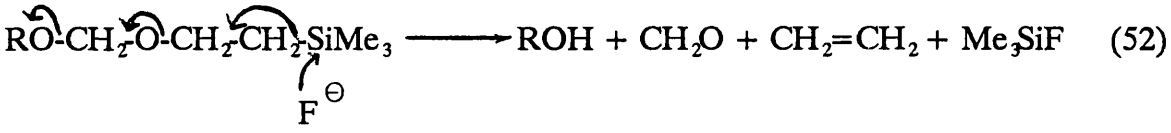
(59) (64)

(65) (66)

Figure 36

Such hydroxyl derivatives are stable over a wide range of conditions, yet can be cleaved in the presence of fluoride ion. The use of fluoride ion in such a process was suggested essentially by the high value of the Si-F bond energy.[170] One method of removal of the SEM-group is to use tetrabutylammonium fluoride (TBAF),[171] as the fluoride ion source.

On reaction of the SEM-protected alcohol with fluoride ion, a cascade effect is observed, resulting in trimethylsilyl fluoride, ethene, formaldehyde and the alcohol being formed as products as in equation (52).



(52)

To utilise this methodology, 6-trimethylsilyl camphor oxime (67) would have to be synthesised. Upon reaction of the resultant oxime ether (68) with fluoride ion, a cascade effect analogous to that observed with the SEM-protected alcohol would result, with products similar to that of the acid cleaved oxime ether (61), namely, α-campholenitrile (62) and the phenol (39) as well as trimethylsilyl fluoride (Figure (37)).

However, the trimethylsilyl group is not readily incorporated at the 6-*exo* position of the bornane skeleton.

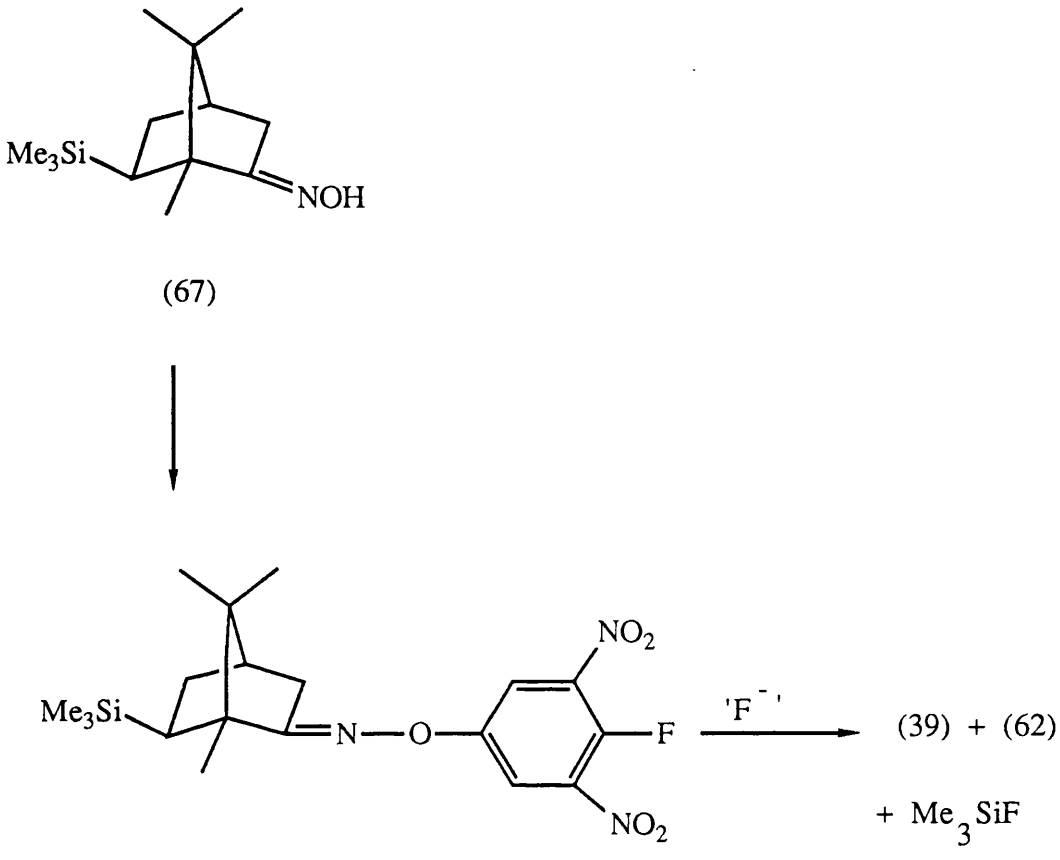


Figure 37

The problem of combining both the silyl group and the oxime functionalities was overcome by synthesising 4-trimethylsilyl butan-2-one oxime ether (69) as shown in Figure (38).

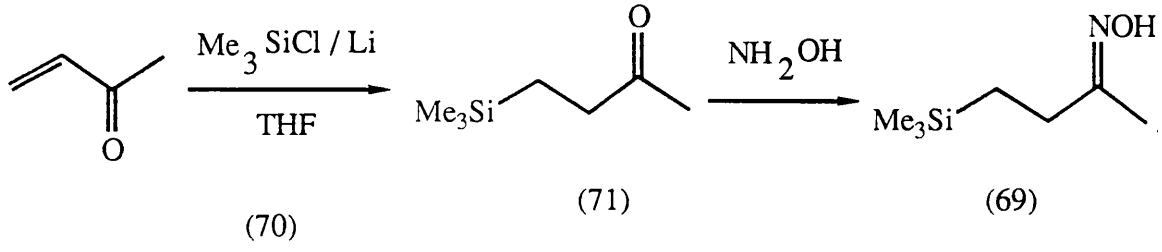


Figure 38

Reaction of methylvinyl ketone (70) with excess trimethylsilyl chloride and excess lithium gave the ketone (71) in 65% yield. The yield of C-silylated product is optimised if the reaction mixture is kept between 0 °C and 10 °C for the duration of the reaction.[172] The desired oxime (69) was obtained in 63% yield as geometric isomers upon reaction of the ketone (70) with excess hydroxylamine hydrochloride according to the method of Brooks *et al.*[129]

The oximate anion of (69) (prepared as with (59)) was treated with 2,4-dinitrofluorobenzene (64) in dry tetrahydrofuran and gave the oxime ether (72). This oxime ether was cleaved after reaction with TBAF in refluxing tetrahydrofuran to give 2,4-dinitrophenol (66) in 86% yield, the other products of the reaction being, acetonitrile, ethene and trimethylsilyl fluoride (Figure (39)).

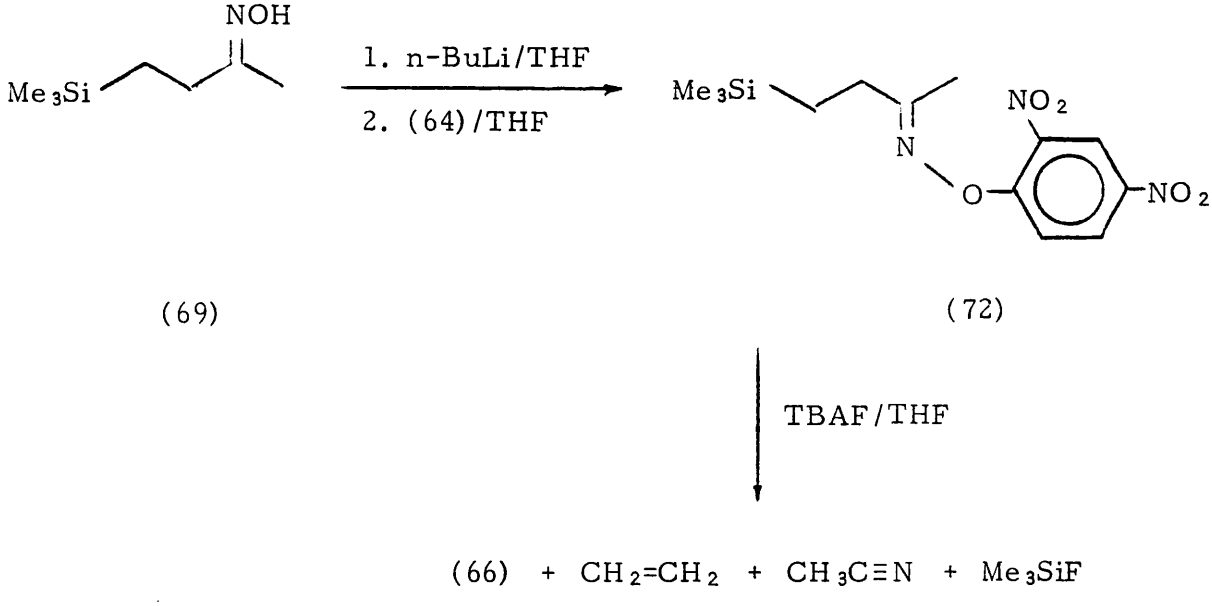
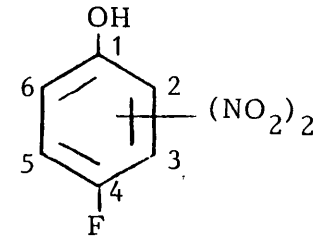


Figure 39

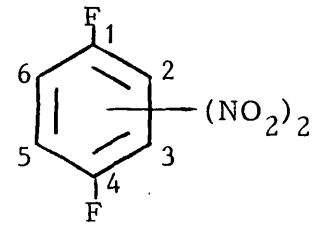
Table 5. Calculated and observed ^{13}C chemical shifts for 4-fluoro-3,5-dinitrophenol (39) and 4-fluoro-2,6-dinitrophenol (63).



Isomer	C(1)		C(2)		C(3)		C(4)		C(5)		C(6)	
	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.
(39)	152.7	157.2	118.2	119.6	137.9	141.6	146.4	147.6	137.9	141.6	118.2	119.6
(63)	141.3	145.9	138.1	138.9	118.0	119.2	157.8	153.4	118.0	119.2	138.1	138.9

All values are in parts per million, relative to internal TMS and using δ_C = 128.5 for benzene.

Table 4. Calculated and observed ^{13}C chemical shifts for dinitro-1,4-difluorobenzenes



Isomer	C(1)		C(2)		C(3)		C(4)		C(5)		C(6)	
	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.
(56)	160.6	155.8	118.0	118.5	137.9	139.2	149.2	146.2	137.9	139.2	118.0	118.5
(57)	154.9	150.1	132.2	132.9	132.2	132.9	154.9	150.1	123.7	122.2	123.7	122.2
(58)	154.9	150.5	113.1	116.6	142.8	140.1	154.9	150.5	113.1	116.6	142.8	140.1

All values are in parts per million, relative to internal TMS and using δ_C = 128.5 for benzene.

As can be seen, the conditions for the oxime ether cleavage by fluoride ion are milder and potentially more selective than with the acid induced second-order Beckmann rearrangement.

It is hoped to extrapolate this methodology to alkyl groups with the result that aliphatic alcohols rather than (66) would be produced. Thus the anion of (69) would serve to introduce a hydroxyl group in pre-protected form both in the general case and also by virtue of being an alpha effect nucleophile in cases in which nucleophilic attack would be slow

3.3 EXPERIMENTAL

For general experimental details see Section 1.3.1.

3.3.1 PREPARATION OF COMPOUNDS

4-Fluoro-3,5-dinitrobenzoic acid (41)[139]

To an ice-cooled, stirred solution of oleum (20% SO_3, 63 ml) and concentrated nitric acid (90%, 56 ml) was added, over a period of 10 min, p-fluorobenzoic acid (40) (14 g, 0.1 mol). After the initial exotherm had subsided, the reaction mixture was heated at 85 °C for 24 h. On cooling, the reaction mixture was poured onto ice, filtered and washed several times with water, yielding the title compound (41) (19.07 g, 73%) as a pale yellow solid; m.p. 220-235 °C (lit.,[139] 235-237 °C, lit.,[173] 220-232 °C); ν_{max} (KBr) 3200-2500, 1710, 1630, 1560 and 1345 cm^{-1}; δ_H (d_6-acetone) 90 MHz, 8.81 (2 H, d, *J* 6).

4-Fluoro-3,5-dinitroaniline (42)[139]

To a solution of 4-fluoro-3,5-dinitrobenzoic acid (41) (9.72 g, 0.042 mol) in oleum (20% SO_3 , 26 ml) was added chloroform (40 ml). Whilst stirring and keeping the reaction flask temperature below 25 °C, sodium azide (3.16 g, 0.049 mol) was added in small quantities over 10 min. After refluxing for 1 h, the reaction mixture was allowed to cool and poured onto ice, resulting in a yellow precipitate. The precipitate was filtered and washed with water leaving pure 4-fluoro-3,5-dinitroaniline (42) (4.72 g, 56%); m.p. 146-148 °C (lit.,[139] 146-148 °C); ν_{max} (KBr) 3505, 3405, 3100, 1605, 1590, 1550 and 1355 cm^{-1} ; δ_H (d_6-acetone) 200 MHz, 5.75 (2 H, br s), 7.65 (2 H, d, *J* 5.4).

3,5-Dinitro-1,4-difluorobenzene (56)[155]

1,4-Difluorobenzene (55) (10 g, 0.0877 mol) was added to an ice-cooled solution of oleum (20% SO_3, 80 ml) and concentrated sulphuric acid (100 ml) with stirring. After 10 min, a mixture of concentrated nitric acid (25 ml) and concentrated sulphuric acid (33 ml) was added dropwise over 15 min to the cold mixture.

The resultant mixture was heated to 70 °C over ½ h and for 1¼ h to 75 °C. After such time, the reaction mixture was allowed to cool before being carefully poured onto ice. The combined ethereal extracts (4 x 100 ml) were washed with water (5 x 100 ml) and saturated brine solution and dried. Evaporation of the ether gave a yellow solid (3.58 g). 3,5-Dinitro-1,4-difluorobenzene (56) was separated

(2.15 g, 12%) by preparative t.l.c. with 10% ethyl acetate/petroleum ether (40-60 °) as eluent (run twice) as the middle band; m.p. 80-82 °C; ν_{max} (KBr) 3100, 1605, 1545 and 1350 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 8.11 (2 H, dd, *J* 6.7 and 5.2 Hz); δ_C ($CDC\ell_3$) 50 MHz, 118.5 (Ar-H), 139.2 (q), 146.2 (dd, *J* 279.8 and 4.4 Hz), 155.8 (dd, *J* 255 and 4.9 Hz); δ_F ($CDC\ell_3$) 188 MHz, -109.9 (1 F, t, *J* 17.5 and 6.7 Hz), -130.2 (1 F, t, *J* 17.5 and 5.2 Hz); (Found: C, 35.31; H, 1.14; N, 13.59. $C_6H_2F_2N_2O_4$ requires C, 35.29; H, 0.98; N, 13.78%).

3,6-Dinitro-1,4-difluorobenzene (58)

This isomer was obtained by preparative t.l.c. with 10% ethyl acetate/petroleum ether (40-60 °) as eluent (run twice) as the top band (0.94 g, 5%); m.p. 110-112 °C (lit.,[174] 104-105 °C); ν_{max} (KBr) 3090, 1550 and 1345 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 8.08 (2 H, t, *J* 7.53); δ_C ($CDC\ell_3$) 50 MHz, 116.6 (Ar-H), 140.1 (q) 150.5 (dd, *J* 269 and 5.4 Hz); δ_F ($CDC\ell_3$) 188 MHz, -118.0 (1 F, t, *J* 7.5); (Found: C, 35.03; H, 1.08; N, 13.68. $C_6H_2F_2N_2O_4$ requires C, 35.29; H, 0.98; N, 13.78%).

2,3-Dinitro-1,4-difluorobenzene (57)

This isomer was obtained by preparative t.l.c. with 10% ethyl acetate/petroleum ether (40-60 °) as eluent (run twice) as the bottom band (0.49 g, 3%); m.p. 52-54 °C; ν_{max} (KBr) 3100, 1545 and 1350 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 7.58 (2 H, t, *J* 6.25); δ_C ($CDC\ell_3$) 50 MHz, 122.2 (Ar-H), 132.9 (q), 150.1 (dd, *J* 264.3

and 4.2 Hz); δ_F ($CDC\ell_3$) 188 MHz, -121.9 (1 F, t, *J* 6.25); (Found: C, 35.02; H, 0.96; N, 13.68. $C_6H_2F_2N_2O_4$ requires C, 35.29; H, 0.98; N, 13.78%).

Camphor oxime, 4-fluoro-3,5-dinitrophenyl ether (61)

To a stirred solution of camphor oxime (60) (0.35 g, 2.1 x 10^{-3} mol) in tetrahydrofuran (10 ml) at -78 °C under an atmosphere of nitrogen, was added n-BuLi (1.6 M, 1.3 ml). After 5 min, 3,5-dinitro-1,4-difluorobenzene (56) (0.43 g, 2.1 x 10^{-3} mol) in tetrahydrofuran (5 ml) was added and the resultant mixture stirred at -78 °C for 1 h. After warming to room temperature, the mixture was poured onto ice and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with water and brine and dried. Recrystallisation from chloroform yielded the pure title compound (61) (0.47 g, 64%); m.p. 104-106 °C; ν_{max} (KBr) 3100, 2960, 1545 and 1350 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 0.85 (3 H, s), 0.91 (6 H, s), 1.25-1.66 (2 H, m), 1.67-2.01 (3 H, m), 2.23 (1 H, d, J_{AB} 18.5), 2.63 (1 H, dm, J_{AB} 18.5), 7.69 (2 H, d, *J* 7.1); δ_C ($CDC\ell_3$) 50 MHz, 10.47 (CH_3), 17.91 (CH_3), 19.41 (CH_3), 26.96 (CH_2), 32.39 (CH_2), 34.81 (CH_2), 43.54 (CH), 48.99 (q), 53.81 (q), 116.21 (Ar-H), 138.56 (q), 143.2 (q), 143.7 (q), 155.20 (d, *J* 251.5), 177.10 (q); δ_F ($CDC\ell_3$) 188 MHz, -114.10 (1 F, t, *J* 7.1); MS, Found: 351.1309. Required: 351.1630.

4-Fluoro-3,5-dinitrophenol (39)

A mixture of oxime ether (61) (0.17 g, 4.96 x 10^{-3} mol) dissolved in ethanol (30 ml) and hydrochloric acid (0.1 M, 5 ml) were refluxed for 24 h. The cooled mixture

was placed on a rotary evaporator and the ethanol and water removed. The residual solid was recrystallised from 1-chlorobutane and ethyl acetate to give the title compound (39) (0.063 g, 63%) as a yellow powder; ν_{max} (KBr) 3740, 3090, 1535 and 1340 cm^{-1}; δ_H (d_6-acetone) 200 MHz, 7.85 (2 H, d, *J* 8.4); δ_C (d_6-acetone) 50 MHz, 119.62 (Ar-H), 141.64 (q), 147.59 (d, *J* 234), 157.15 (q); δ_F (d_6-acetone) 188 MHz, -131.73 (1 F, t, *J* 8.4); MS; Found: 202.0026. Required: 202.0985.

4-Fluoro-2,6-dinitrophenol (63)[167]

The title compound was prepared from p-fluorophenol (6.32 g, 0.056 mol) according to the method of Clewley *et al.*[167] and obtained in 50% yield (5.63 g); m.p. 49-50 °C (lit.,[167] 49-50 °C); ν_{max} (KBr) 3200, 3100, 1550 and 1365 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 8,10 (2 H, d, *J* 7.2), 11.15 (1 H, s); δ_C ($CDC\ell_3$) 50 MHz, 119.02 (Ar-H), 137.32 (q), 146.15 (q), 152.70 (d, *J* 224.0); δ_F ($CDC\ell_3$) 188 MHz, -118.13 (1 F, t, *J* 7.2).

Camphor oxime, 2,4-dinitrophenyl ether (65)

After employing the same method as for the oxime ether (61), the title compound (65) was obtained, from 2,4-dinitro-fluorobenzene (64) (4.62 g, 0.025 mol) in 64% yield (5.31 g) after recrystallisation from ethyl acetate/petroleum ether (40-60 °); m.p. 116.5-117.5 °C; ν_{max} (KBr) 3120, 2960, 1600, 1535 and 1350 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 0.84 (3 H, s), 0.96 (3 H, s), 1.12 (3 H, s), 1.26-1.56 (2 H, m), 1.81-2.02 (3 H, m), 2.33 (1 H, d, J_{AB} 18.6), 2.79 (1 H, dm, J_{AB} 18.6), 7.93 (1 H, d, *J* 9.4),

8.38 (1 H, dd, *J* 9.4 and 2.8 Hz), 8.83 (1 H, d, *J* 2.8); δ_C ($CDC\ell_3$) 50 MHz, 10.89 (CH_3), 18.35 (CH_3), 19.44 (CH_3), 26.93 (CH_2), 32.55 (CH_2), 35.20 (CH_2), 43.47 (CH), 48.94 (q), 53.47 (q), 117.15 (Ar-H), 121.96 (Ar-H), 129.21 (Ar-H), 135.65 (q), 140.08 (q), 159.94 (q), 178.45 (q) (Found: C, 57.55; H, 5.77; N, 12.78. $C_{16}H_{19}N_3O_5$ requires C, 57.65; H, 5.75; N, 12.61%).

2,4-Dinitrophenol (66)

The oxime ether (65) (1.00 g, 3 x 10^{-3} mol) was reacted with hydrochloric acid (0.1 M, 30 ml) in an analogous method to that employed for the synthesis of (39). Recrystallisation from ethanol gave the title compound (66) (0.42 g, 76%); m.p. 114-115 °C (lit.,[175] 113-114 °C); δ_H ($CDC\ell_3$) 90 MHz, 7.22 (1 H, d, *J* 9.0), 8.40 (1 H, dd, *J* 9 and 2.3 Hz), 9.01 (1 H, d, *J* 2.3) (Found: C, 38.94; H, 2.07; N, 2.07. $C_6H_4N_2O_5$ requires C, 39.13; H, 2.17; N, 15.22%); M^+ 184 (70.5%).

4-Trimethylsilylbutan-2-one (71)[172]

The title compound was prepared from methyl vinyl ketone (70) (4.86 g, 0.069 mol) according to the method of Donogues *et al.*[172] in a 60% yield (6.00 g); $b.p._{20}$ 50 °C (lit.,[172] 60 °C); ν_{max} (film) 2950 and 1720 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, -0.22 (9 H, s), 0.45 (2 H, t, *J* 6), 1.84 (2 H, t, *J* 6), 2.11 (3 H, s).

2,4-Dinitrophenol (66)

4-Trimethylsilyl butan-2-one (71) was converted to its oxime derivative (69) by the method of Brooks *et al.*[129]; ν_{max} (film) 1655 cm^{-1}.

To a stirred solution of the oxime (69) (170 mg, 1.08 x 10^{-3} mol) in tetrahydrofuran (5 ml) at -78 °C under an atmosphere of nitrogen, was added n-BuLi (1.6 M, 0.75 ml). After 5 min, 2,4-dinitrofluorobenzene (64) (0.2 g, 1.08 x 10^{-3} mol) in tetrahydrofuran (5 ml) was added and the resultant mixture stirred at -78 °C for 1 h. After warming to room temperature, the mixture was poured onto ice and extracted with ethyl acetate. The organic extracts were washed with water, brine and dried. Evaporation of the solvent left a dark red oil (0.11 g, 31%) identified as the oxime ether (72); δ_H ($CDC\ell_3$) 90 MHz, -0.1 (9 H, s), 0.60 (2 H, t, *J* 6), 2.10 (3 H, s), 2.35 (2 H, t, *J* 6), 7.73 (1 H, d, *J* 9), 8.10 (1 H, dd, *J* 9 and 3 Hz), 8.76 (1 H, d, *J* 3).

A mixture of the oxime ether (72) (0.11 g, 3.3 x 10^{-4} mol) and tetrabutylammonium fluoride (100 mg, 39 mmol) in tetrahydrofuran (5 ml) was heated at 50 °C, with stirring, for 15 h. Upon cooling, the reaction mixture was poured onto ice and the organic layer separated. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ethyl acetate. After washing the ethyl acetate extracts with water and brine, the extracts were dried. Evaporation of the solvent, followed by recrystallisation from ethanol gave pure 2,4-dinitrophenol (66) (0.52 g, 86%). The sample thus obtained exhibited spectral properties identical to the sample of 2,4-dinitrophenol (66) obtained previously.

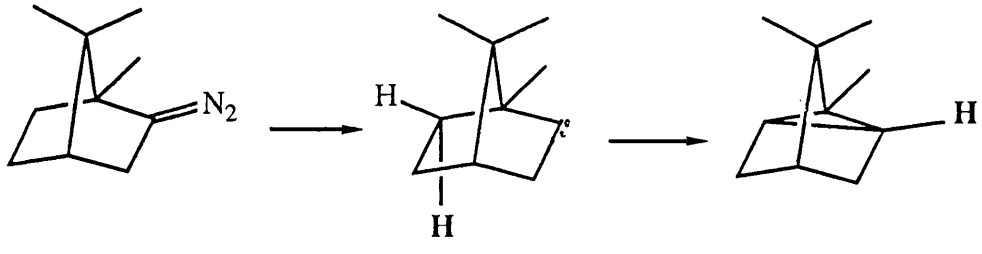
PART IV

SYNTHETIC APPROACH TO (+)-3-DIAZO-5,6-DEHYDROCAMPHOR (73)

4.1 INTRODUCTION

The synthesis of (+)-3-diazocamphor (74) and (+)-3-diazo-5,6-dehydrocamphor (73) was undertaken to investigate and compare their Optical Rotatory Dispersion (O.R.D.) and Circular Dichroism (C.D.) values and the effect of different solvents on these values.

It has been reported[68] that thermal decomposition of 2-diazocamphane (75) leads to tricyclene (76), which results from intramolecular insertion of the intermediate carbene species (77), shown in Figure (40).

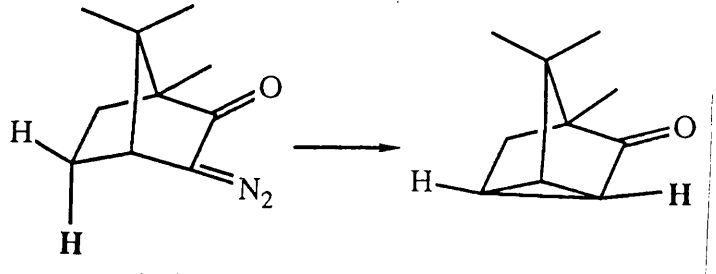


(75) (77) (76)

Figure 40

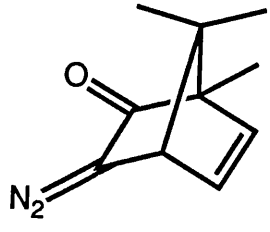
It has also been shown that use of aprotic solvents in the oxidation of camphor hydrazone (78) by mercuric oxide leads to tricyclene (76) as the major product.[176]

It is known[177] that (+)-3-diazocamphor (74) will decompose by the same mechanism to give tricyclanone (79). In both cases the C(6)-*endo*-hydrogen, as indicated in Figures (40) and (41), is transferred.



(74) (79)

Figure 41



(73)

In the case of (+)-3-diazo-5,6-dehydrocamphor (73), there are no such hydrogen atoms available by which such a mechanism could occur. Therefore, a further reason for the synthesis of (+)-3-diazo-5,6-dehydrocamphor (73) was to investigate the fate of its carbenic decomposition.

4.2 RESULTS AND DISCUSSION

The synthesis of (+)-3-diazocamphor (74) was carried out in three steps, shown in Figure (42). It was hoped that an analogous sequence could be employed in the synthesis of (+)-3-diazo-5,6-dehydrocamphor (73).

Readily available (+)-camphor (80) was chosen as the starting material. Oxidation of (80) yielded camphor quinone (bornane-2,3-dione) (81). After

conversion of the α-diketone (81) to the monotosylhydrazone (82), base was used to give the diazoketone (74).

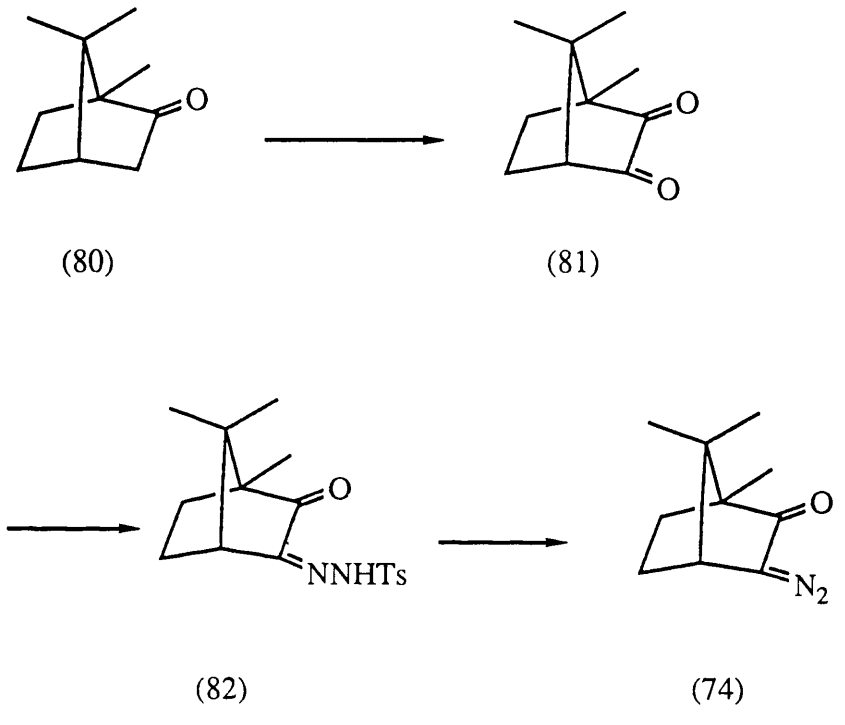


Figure 42

Oxidation of (+)-camphor (80) was effected using selenium dioxide.[178] Until 1976, the mechanism for this reaction had been in some doubt. Corey and Schaefer[179] proposed that the mechanism involved a selenate ester of the enol (83). It was concluded that the enol selenate ester (83) was formed by direct attack on the ketone by an electrophile-nucleophile pair, *viz.* $H_3SeO_3^+$ and H_2O (these reactions were carried out in 70% acetic acid). The enol selenate ester (83) was presumed

to rearrange to an α-substituted selenium (II) ester (84), which upon rapid decomposition was converted into the diketone, selenium and water, illustrated in Figure (43).

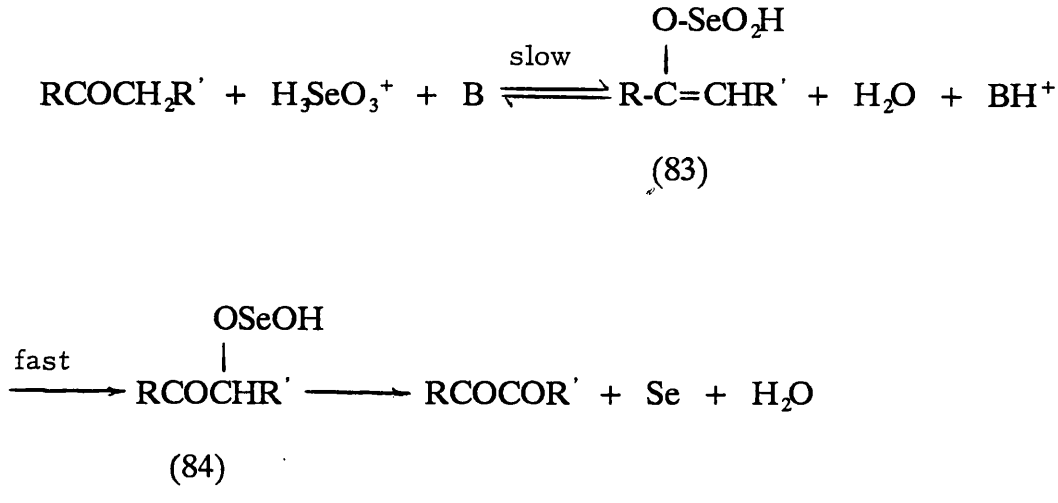
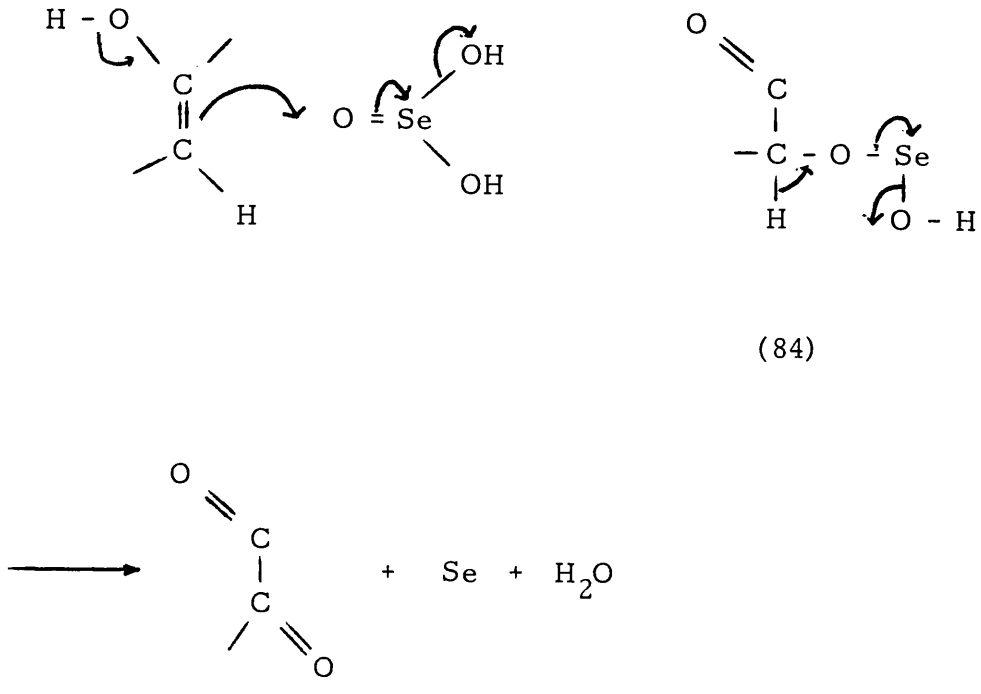


Figure 43

Waters *et al.*[180] proposed a mechanism in which they suggested that the oxidation proceeded *via* rapid and concerted reaction of the enol resulting in a hypothetical selenium (II) ester (84) of the ketone which, upon decomposition, gave the diketone shown in Figure (44).

The principal objection to the above mechanisms is the presence of the selenium (II) ester (84). Arigoni and co-workers[181] found that such species hydrolyse very rapidly to alcohols.



(84)

Figure 44

In 1976, Sharpless and Gordon[182] proposed that the principal intermediate in the oxidation was a β-ketoseleninic acid (85). The proposed pathway is shown in Figure (45).

The β-ketoseleninic acid (85) is formed by electrophilic attack of selenous acid. (85) Then undergoes a Pummerer-like rearrangement resulting in a selenine (86). The short-lived selenine (86) decomposes either by attack of water at the α-carbon or by intramolecular transfer of oxygen *via* closure of the selenine (86) to an oxaselenirane, followed by expulsion of selenium.

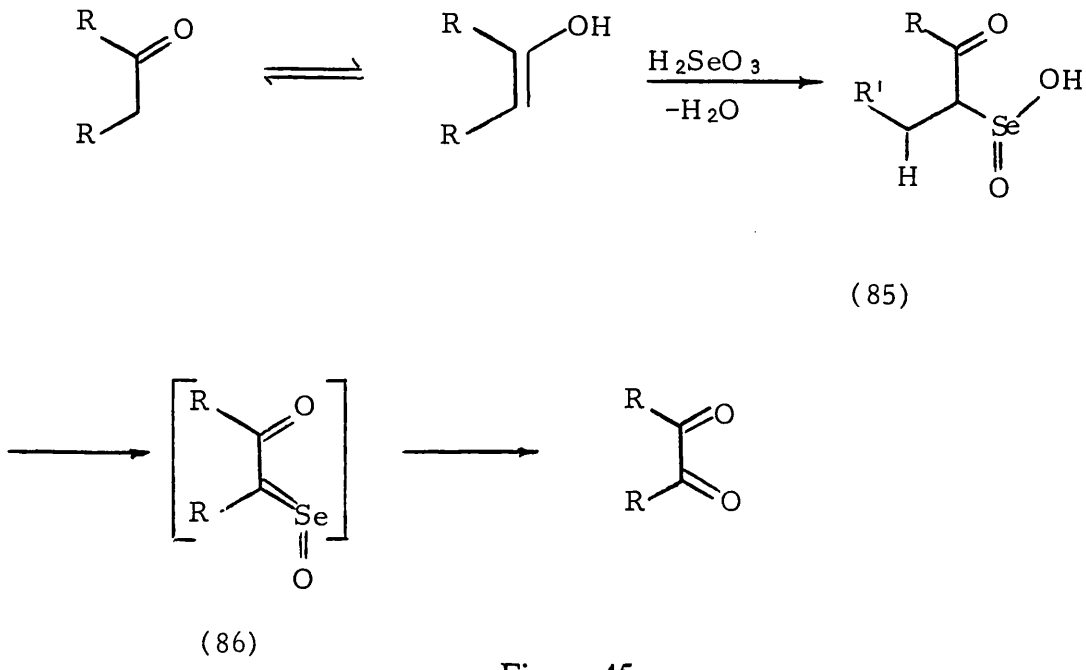


Figure 45

By the method of Evans *et al.*[183] the selenium dioxide oxidation was carried out in acetic anhydride to give (+)-camphor quinone (81) in 47% yield.

The monotosylhydrazone (82) was obtained in 57% yield after treatment of (+)-camphor quinone (81) with p-toluene-sulphonylhydrazine by the method of Cava *et al.*[184]

That only a monotosylhydrazone is formed is due to the fact that only equimolar quantities of the hydrazine derivative and (82) were employed; this contrasts with the method of Hinman[185] who carried out reactions with large excesses of hydrazine in order to obtain hydrazones. The regiospecificity observed is due to the carbonyl moiety at C(3) being less sterically hindered than the corresponding functionality at C(2) and therefore more reactive.

The monotosylhydrazone (82) was treated with aqueous sodium hydroxide[184] to give (+)-3-diazocamphor (74) in 85% yield. The mechanism for this conversion is outlined in Figure (46).

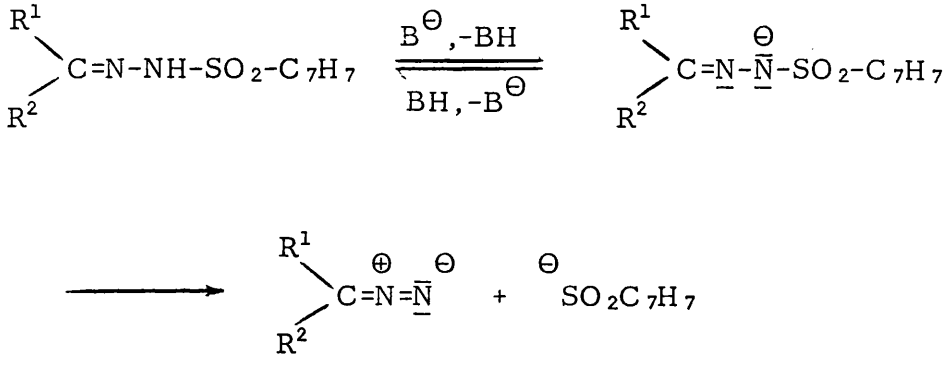


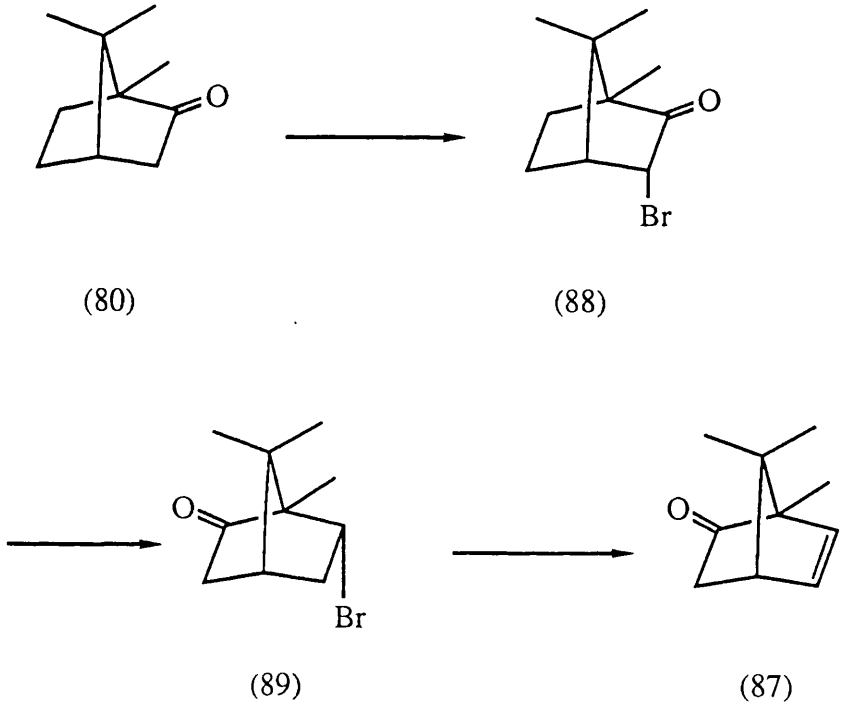
Figure 46

One advantage of this method is that synthesis of α-diazocarbonyls can be carried out under mild conditions; this is highlighted in the cleavage of tosylhydrazones by basic alumina.[186] Essential for the success of this reaction is the admixture of at least a stoichiometric amount of base; otherwise unreacted hydrazone acting as a proton donor, promotes decomposition of the diazo-compound resulting in N-alkylated tosylhydrazones.[187]

Chamberlain and Bond[188] employed 2,4,6-tri-isopropylbenzenesulphonyl-hydrazine as a reagent in aprotic Bamford-Stevens reactions with the advantage that lower temperatures were required for decomposition of the sulphonylhydrazone salts.

In order to utilise the above methods in the synthesis of (+)-3-diazo-5,6-

dehydrocamphor (73), (+)-5,6-dehydrocamphor (87) had to be prepared (Figure (47)). Once again a convenient starting material is (+)-camphor (80). After use of the method of Shive *et al.*[189] with a catalytic amount of aluminium trichloride present,[190] reaction of (+)-camphor (80) with bromine resulted in a 30% yield of (+)-*endo*-3-bromocamphor (88).



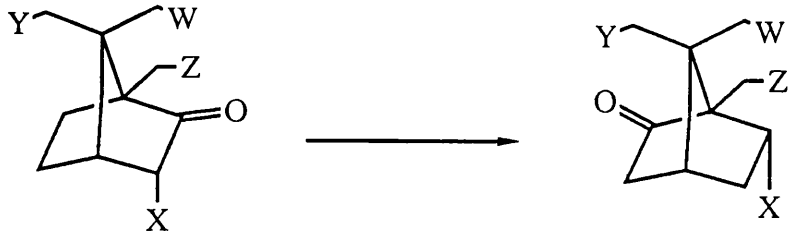
(80) (88)

(89) (87)

Figure 47

Conversion of (+)-*endo*-3-bromocamphor (88) into (+)-5,6-dehydrocamphor (87) follows a method developed by Money and co-workers,[191] that involves acid-catalysed rearrangement of (+)-*endo*-3-bromocamphor (88) to (-)-*endo*-6-bromo-

camphor (89) followed by dehydrohalogenation by base. This transformation is an extension of the work carried out by Nishikawa and co-workers[192] who described the rearrangement of (+)-3,9-dibromocamphor (90) to (-)-6,9-dibromocamphor (91) in fuming sulphuric acid shown in Figure (48).



(90) X=Y=Br, Z=W=H

(91) X=Y=Br, Z=W=H

(80) X=Y=Z=W=H

(92) X=Y=Z=W=H

(93) X=Br, Y=W=H, Z=D

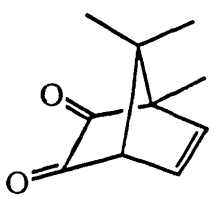
(94) X=Br, Y=D, Z=W=H

Figure 48

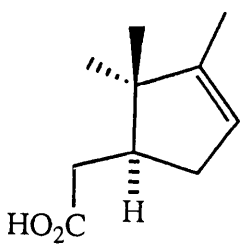
Treatment of (+)-*endo*-3-bromocamphor (88) with chlorosulphonic acid at 55 °C for 15 min produced (-)-*endo*-6-bromocamphor (89) in 30-40% yield. During this transformation, the camphor framework is inverted by a mechanism that consists of a series of Wagner-Meerwein rearrangements, 3,2-methyl shifts and 6,2-hydride shifts. This mechanism is analogous to that proposed by Money *et al.*[191] for the acid-catalysed transformation of (+)-camphor (80) to (-)-camphor (92) (Figure (49)). Experimental support for this mechanism is provided by deuterium-labelled studies;

(+)-*endo*-3-bromo-10-deuteriocamphor (93) rearranges to (-)-*endo*-6-bromo-8-deuteriocamphor (94).[191]

Treatment of (-)-*endo*-6-bromocamphor (89) with potassium hydroxide in a DMSO/H_2O (7:1) mixture at 70 °C for 96 h[193] produced (+)-5,6-dehydrocamphor (87) in 40-50% yield. A major side product (40%) of the dehydrohalogenation is (-)-α-campholenic acid (95). On treatment of (-)-*endo*-6-bromocamphor (89) with KOBu^t/Bu^{t}OH, (-)-α-campholenic acid (95) becomes the major product, a fact that Clase and Money[194] have employed in their enantiospecific route to C, D rings of steroids.

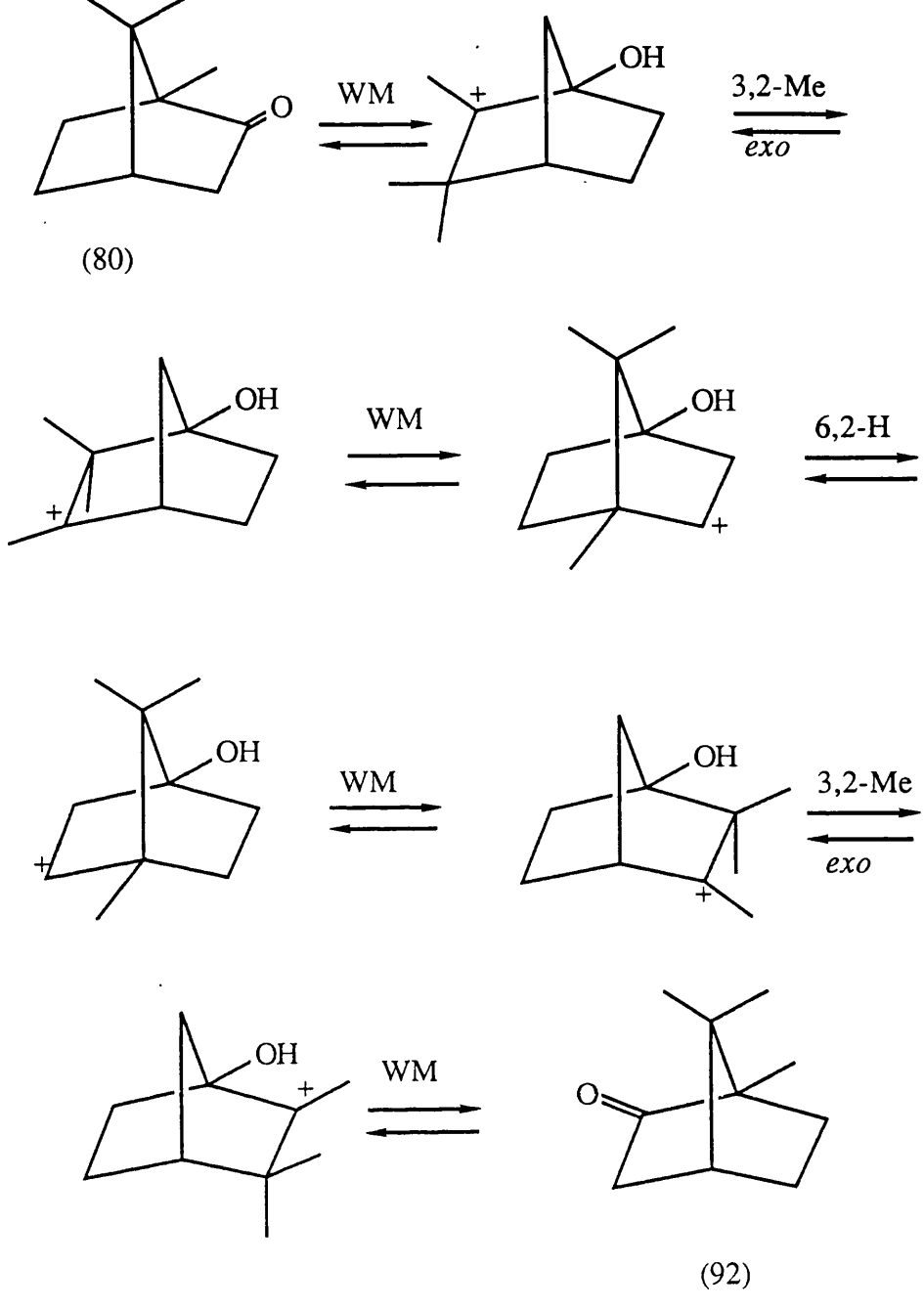


(96)



(95)

The next step was to synthesise the α-diketone (96) from (+)-5,6-dehydrocamphor (87) using selenium dioxide as before. Unfortunately, reaction with selenium dioxide in acetic anhydride did not yield any of the desired α-diketone (96). Various relative molar quantities of selenium dioxide, reaction times and solvent systems were employed including acetic anhydride,[183] bromobenzene[195] and xylene[196]



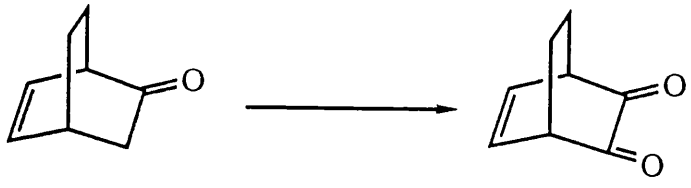
WM = Wagner-Meerwein rearrangement; 3,2-Me-*exo* = 3,2-*exo*-methyl shift; 6,2-H = 6,2-hydride shift.

Figure 49

but all without success.

It is unclear why this method proved unsuccessful since Russell and co-

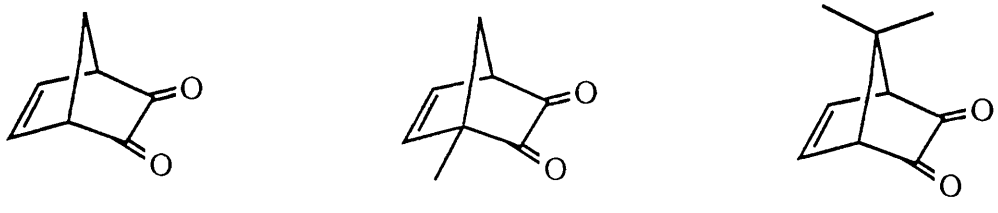
workers[196] successfully oxidised a similar compound *viz.* bicyclo[2.2.2]oct-5-en-2-one (97) to the corresponding α-diketone, bicyclo[2.2.2]oct-5-en-2,3-dione (98), Figure (50), using selenium dioxide in xylene, although the yield was low.



(97) (98)

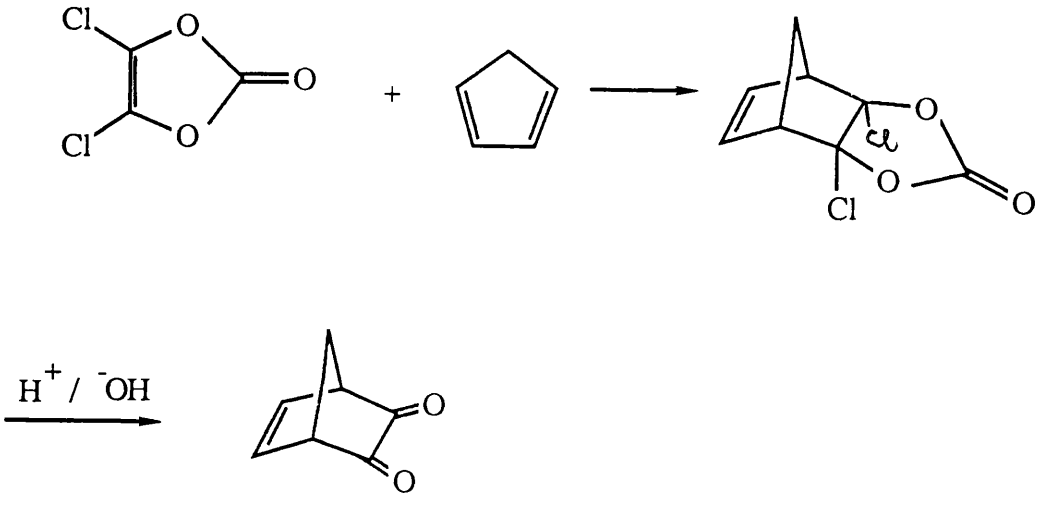
Figure 50

Doubts arising from the stability of the α-diketone (96) appear to be unfounded due to the presence of a series of substituted bicyclo[2.2.1]hept-5-en-2,3-diones (99), (100) and (101) in the literature.[197,198]



(99) (100) (101)

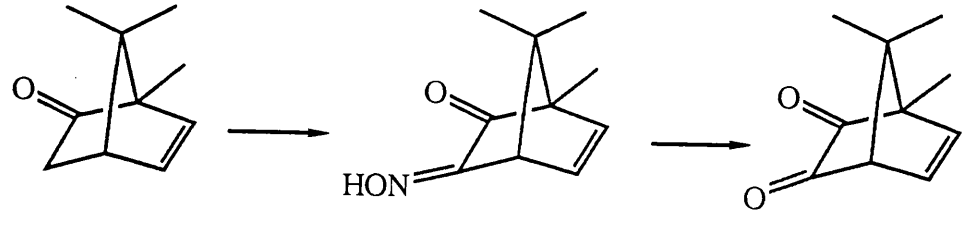
However, these compounds are prepared by the hydrolysis of their cyclopentadiene-dichlorovinylene carbonate Diels-Alder adducts, *e.g.* Figure (51).



(99)

Figure 51

Failure of the selenium dioxide reaction meant a new route, Figure (52), to the α-diketone (96) had to be employed.

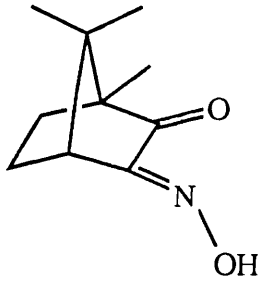


(87) (102) (96)

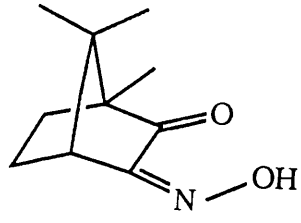
Figure 52

This new route involves conversion of (+)-5,6-dehydrocamphor (87) into the α-diketone (96) *via* (+)-α-oximino-5,6-dehydrocamphor (102). This method was first of all tested on (+)-camphor (80).

Conversion of (+)-camphor (80) to its sodium salt upon treatment with sodium amide, and subsequent reaction with t-butyl nitrite gave (+)-α-oximino-camphor as a mixture of two geometric isomers, (103) and (104) in a 5.4:1 ratio.



(103)



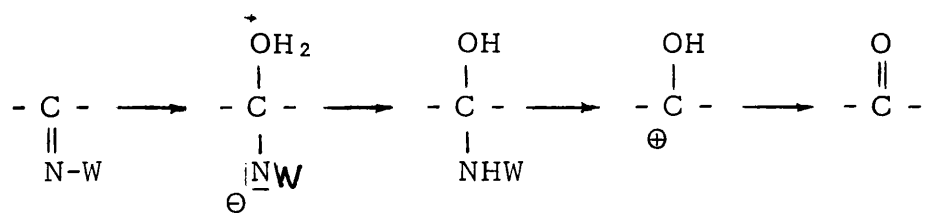
(104)

The *syn* isomer (104) which is internally bonded is much less stable than the *anti* isomer (103). The *syn* isomer isomerises easily and hence, great difficulty arises when attempting to separate the two isomers. The intramolecular bonding in (104) causes a marked lowering of the OH (3248 cm^{-1}) and C=O (1710 cm^{-1}) stretching frequencies compared with the *anti* isomer OH (3576 cm^{-1}) and C=O (1758 cm^{-1}) stretching frequencies. In the *anti* isomer, intermolecular bonding persists even at low concentrations. Cherry and co-workers[199] have shown that the hydroximino-proton signal in deuteriochloroform moves to higher field as concentrations are lowered; this is the expected consequence of disrupting the intermolecular

hydrodgen-bonding of oximes.[200] The preferred intramolecular hydrogen-bonding of (104) results in a signal that is at very low field and is relatively insensitive to concentration.

Without separation, the (+)-α-oximinocamphor (103) and (104), obtained in 47% yield, were hydrolysed to (+)-camphor quinone (81) by means of oxalic acid in ethanol. This sequence was based upon work carried out by De Puy and Ponder,[201] who had previously employed levulinic acid for hydrolysis of oximes to ketones.

The hydrolysis of carbon-nitrogen double bonds involves initial addition of water and subsequent elimination of a nitrogen moiety, illustrated in Figure (53).



W = OH, NHAr, $NHCONH_2$

Figure 53

This sequence is only general; variations in the order of steps may depend on whether the reaction is acid or base catalysed. The rate-determining step can also vary according to the nature of W and of the groups attached to the carbonyl.[202]

Attainment of the transition state for hydrolysis involves a decrease of unsaturation and therefore, substituents that contain unsaturated bonds conjugated

to the imine moiety, will stabilise by resonance the starting material more than the transition state and retard hydrolysis. It should also be noted that hydrolysis is strongly hindered by bulky substituents close to the nitrogen bearing carbon atom.

(+)-α-Oximinocamphor (103) and (104) upon hydrolysis, yielded (+)-camphor quinone (81) in 50% yield and the sample thus obtained showed spectral properties identical to the sample of (81) obtained from selenium dioxide oxidation of (+)-camphor (80).

Oximination of (+)-5,6-dehydrocamphor (87) gave (+)-α-oximino-5,6-dehydrocamphor (102) in 47% yield. In this case, oximination resulted in the production of only the *syn*-form isomer, indicated by the low field hydroximino-proton signal (10.94 p.p.m.) and the low value for the OH stretching frequency (ν_{max}, 3300 cm^{-1}).

Attempts to hydrolyse (102) employing an aqueous solution of oxalic acid proved unsuccessful. Moreover, addition of small amounts of dilute hydrochloric acid gave no detectable amount of the desired diketone (96). Care had to be taken with such acid hydrolysis in case of addition to the double bond of (96) and for this reason, a new method of converting the oxime to the ketone was sought.

As mentioned above, we were constrained to operating under mild conditions, on account of the double bond, in our attempts to transform the α-oximinoketone (102) into the α-diketone (96).

Such a method was devised by Timms and Wildsmith,[203] who found that oximes of several aliphatic ketones and aldehydes undergo rapid hydrolysis in an

aqueous medium (pH ~ 5), in the presence of tervalent titanium, with or without buffers present, to give ketones and aldehydes in good yields, under mild conditions, Figure (54).

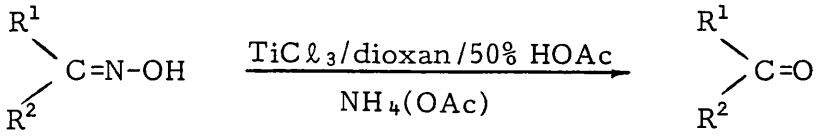


Figure 54

Advantages of this system are that in all cases studied, the reaction was carried out at room temperature and complete within 1 h. Additionally, aqueous titanium trichloride solution is commercially available and the reaction may be conveniently followed by loss of the dark colour of the titanium (III) complexes. Further advantages may be seen when compared to a system developed by Corey and Richmann[204] for deoximation, Figure (55); this involves conversion of the oxime to its O-acetate derivative followed by reduction with chromous acetate.

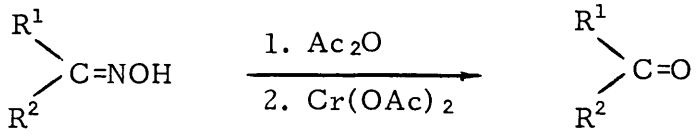


Figure 55

The method of Timms and Wildsmith does not require prior acetylation and has been shown[203] to be successful for aldehydes and di-aryl species where the chromous acetate method fails. Indeed, the limitations of the chromous acetate method were noted by Corey and Richman[204] themselves, who observed that acetoximes derived from di-aryl ketones or α-diketones were not deoximated by chromous acetate, but instead underwent imine reduction to basic products. The acetoximes of aliphatic aldehydes were largely converted to nitriles.

However, we found the reaction of (102) with tervalent titanium, did not yield any detectable amount of the α-diketone (96).

Previously, a simple, inexpensive and mild procedure for reduction of oximes to carbonyls had been found by Pines and co-workers[205] based upon a reaction first described by von Pechman.[206] Reaction of the oxime with 3.5 molar equivalents of sodium bisulphite is carried out under neutral and irreversible conditions; brief exposure to dilute hydrochloric acid is required only for the isolation of the carbonyl compound, Figure (56).

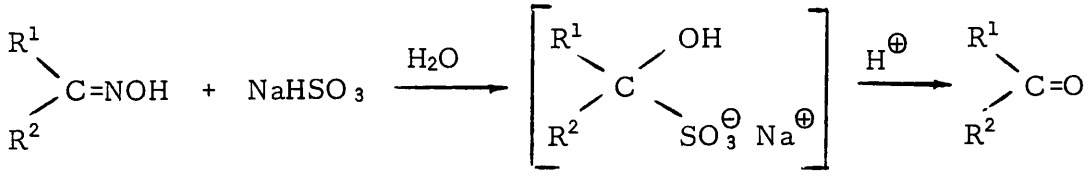


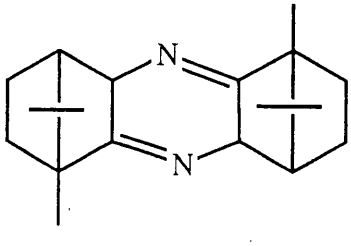
Figure 56

Although the fate of the nitrogenous part of the oxime was not studied, the work of Sisler and Andrieth[207] suggests it is converted to sulphamic acid, NH_2SO_3H.

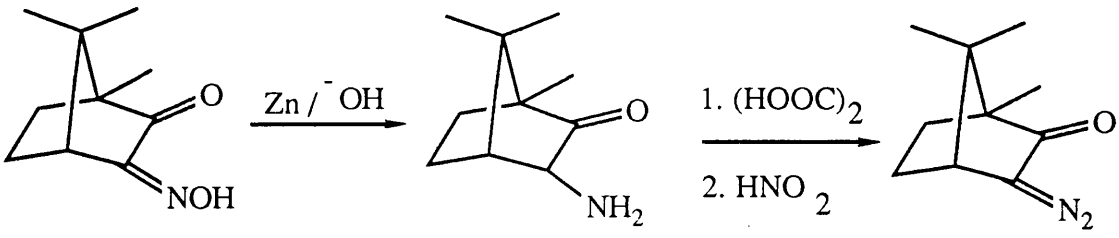
Upon reaction of (102) with sodium bisulphite according to the method of Pines *et al.*,[205] no α-diketone (96) was observed.

It has been known for some time[208] that oximes can be converted to the corresponding amine by reaction with alkaline zinc. In the case of (+)-3-aminocamphor (105) the freshly distilled amine must be converted quickly into its neutral oxalate salt, so as to avoid dimerisation to dihydrodicamphenpyrazin (106).

Treatment of the oxalate salt of (+)-3-aminocamphor (105) with cold nitrous acid[209] yielded (+)-3-diazocamphor (74), Figure (57). This sample of (+)-3-diazocamphor (74) was identical to that obtained upon the cleavage of the monotosylhydrazone (82).



(106)



(103), (104) (105) (74)

Figure 57

Attempts at such a reaction sequence on (+)-α-oximino-5,6-dehydrocamphor (102) resulted in no detectable amounts of (+)-3-diazo-5,6-dehydrocamphor (73). This is possibly due to there being no *endo*-hydrogens at C(5) and C(6) due to unsaturation. Consequently, there will be less steric hindrance and therefore the amino derivatives of (102) will be more likely to combine to form the analogue of (106) than the saturated amine (105).

Recently, a number of other reagents have been employed to cleave oximes, in particular they have been converted to the corresponding aldehyde or ketone by treatment with, among other reagents, thallium nitrate,[210] iron pentacarbonyl and BF_3,[211] $(PhSeO)_2O$,[212] NOCℓ,[213] lead tetra-acetate,[214] cerium (IV) ions,[215] triethylammonium chloroformate[216] and aluminium isoperoxide in isopropyl alcohol.[217]

It is hoped that one of these methods may, in the future, be employed with success in converting the α-oximino ketone (102) to (+)-5,6-dehydrocamphor quinone (96) and, as a result, the synthesis of (+)-3-diazo-5,6-dehydrocamphor (73) may be completed.

4.3 EXPERIMENTAL

For general experimental details, see Section 1.3.1.

PREPARATION OF COMPOUNDS

(+)-Camphor quinone (81)[183]

A solution of (+)-camphor (80) (5 g, 0.033 mol) and selenium dioxide (6 g, 0.054 mol) in acetic anhydride (5 ml) was refluxed for 4 h. The cooled mixture was filtered through florisil to remove deposited selenium. The florisil was washed with acetic acid and the orange/yellow filtrate carefully neutralised with dilute aqueous potassium hydroxide solution. This resulted in yellow crystals precipitating out. Filtration and recrystallisation of these crystals from petroleum ether (60-80 °) gave pure (+)-camphor quinone (81) as yellow crystals (2.57 g, 47%); m.p. 197-198 °C (lit.,[183] 198 °C); ν_{max} (KBr) 1770 and 1745 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.88 (3 H, s), 1.01 (3 H, s), 1.05 (3 H, s) 1.45-1.70 (2 H, m), 1.71-2.35 (2 H, m), 2.58 (1 H, d, *J* 5.3).

(+)-Camphor-3-tosylhydrazone (82)[183]

A solution of (+)-camphor quinone (81) (1.53 g, 9.22 x 10^{-3} mol) and p-toluenesulphonylhydrazine (1.73 g, 9.30 x 10^{-3} mol) in methanol (14 ml) was refluxed for 1 h. The cooled solution was diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dried and concentrated to

a small volume. Upon gradual addition of petroleum ether (40-60 °) powdery crystals were deposited. After washing the crystals with petroleum ether (40-60 °) and drying under suction gave the title compound as a pale yellow powder (1.74 g, 57%); m.p. 110-112 °C (lit.,[183] 110-113 °C); ν_{max} (KBr); δ_H ($CDCl_3$) 90 MHz, 0.80 (3 H, s), 1.00 (3 H, s), 1.05 (3 H, s), 2.45 (3 H, s), 7.40 (2 H, d, *J* 9), 7.90 (2 H, d, *J* 9), 8.3 (1 H, s).

(+)-3-Diazocamphor (74)[184]

A solution of the tosylhydrazone (82) (1.71 g, 5.12 x 10^{-3} mol) in aqueous 0.1 M sodium hydroxide solution (52 ml) was covered with petroleum ether (40-60 °) (26 ml) and the mixture stirred at room temperature for 2 h. Evaporation of the dried organic phase gave yellow crystals (0.55 g). Stirring the aqueous layer with petroleum ether (40-60 °) for an additional 24 h gave a further 0.33 g of the same yellow crystals. The combined crystals were recrystallised from petroleum ether (60-80 °) to give pure (+)-3-diazocamphor (74) (0.78 g, 86%); m.p. 72-74 °C (lit.,[184] 70-74 °C); ν_{max} (KBr) 2080 and 1685 cm^{-1}; δ_H ($CDCl_3$) 90 MHz, 0.90 (3 H, s), 0.95 (3 H, s), 0.97 (3 H, s), 1.61 (3 H, m), 2.17 (1 H, m), 2.94 (1 H, d, *J* 3.3) (Found: C, 67.35; H, 7.94; N, 15.96. $C_{10}H_{14}N_2O$ requires C, 67.38; H, 7.92; N, 15.72%).

(+)-3-Diazocamphor (74)[208,209]

(+)-α-Oximinocamphor (103) (0.8 g, 4.42 x 10^{-3} mol) was dissolved in aqueous sodium hydroxide solution (25%, 3.2 ml) and water (10 ml). The resultant clear solution was treated with zinc powder (0.96 g, 0.015 mol) and stirred vigorously for

3 h at room temperature. After dilution with water, the zinc was filtered off and the aqueous mixture extracted with ether. The ether extracts were dried and evaporated off to yield the amine (105) as a yellow oil (0.41 g, 56%). The amine (105) was immediately converted to its oxalate salt by addition of one equivalent of oxalic acid in ethanol to avoid dimerisation.

The oxalate salt of (+)-3-aminocamphor (105) (0.63 g, 2.46 x 10^{-3} mol) was suspended in an ice-cooled solution of aqueous sodium nitrite (0.19 g, 2.8 x 10^{-3} mol) and covered with petroleum ether (40-60 °). With vigorous stirring, dilute acetic acid (0.17 g in 1.8 ml H_2O) was added. After 24 h the dried organic phase was evaporated and the residue recrystallised from petroleum ether (60-80 °) to give pure (+)-3-diazocamphor (74) (0.25 g, 57%). The sample thus obtained showed spectral properties identical to the sample of (+)-3-diazocamphor (74) obtained from the cleavage of the tosylhydrazone (82).

(+)-α-Oximinocamphor (103) and (104)[219]

(+)-Camphor (80) (3 g, 0.02 mol) was transformed into its sodium derivative by treatment with sodium amide (0.82 g, 0.021 mol) in dry benzene (15 ml) under an atmosphere of nitrogen. To this, excess freshly prepared t-butyl nitrite[218] (3.0 g, 0.03 mol) was added slowly. After stirring for 24 h, at room temperature, the mixture was poured onto an ice/water slurry and the organic layer removed. The aqueous layer was acidified with dilute acetic acid and extracted with ether (3 x 50 ml). The ethereal extracts were washed with water, brine and then dried. Removal of the

solvent and recrystallisation from 1-chlorobutane of the residue gave (+)-α-oximino-camphor as a mixture of *syn*- (104) and *anti* (103) isomers (1.51 g, 42%); m.p. 149-153 °C (lit.,[219] 155-157 °C (*anti*), lit.,[220] 152-153 °C (*anti*), lit.,[199] 155 °C (*anti*), lit.,[199] 117 °C (*syn*)); ν_{max} ($CC\ell_4$) 3580 (free OH stretch), 3260 (OH stretch, H-bonded), 1755 (*anti*) and 1710 cm^{-1} (*syn*); δ_H ($CDC\ell_3$) 200 MHz, *anti*-isomer (103), 0.85 (3 H, s), 0.97 (3 H, s), 1.00 (3 H, s), 1.54-2.20 (4 H, m), 3.24 (1H, d, *J* 4.5), 9.40 (1 H, s); *syn*-isomer (104), 0.89 (3 H, s), 0.99 (3 H, s), 1.00 (3 H, s), 1.54-2.20 (4 H, m), 2.76 (1 H, d, *J* 4.5), 11.85 (1 H, s) (Found: C, 66.27; H, 8.27; N, 7.68. $C_{10}H_{15}NO_2$ requires C, 66.30; H, 8.29; N, 7.73%).

(+)-Camphor quinone (81)

This compound was prepared from (+)-α-oximinocamphor (103) and (104), and treated with oxalic acid according to the method of De Puy and Ponder.[201]

(+)-*endo*-3-Bromocamphor (88)[189]

(+)-Camphor (80) (15 g, 0.0987 mol) and a small amount of aluminium trichloride were placed in a three-necked round bottomed flask (250 ml) equipped with a condenser and a dropping funnel. To the camphor was added bromine (32 g, 0.2 mol) *via* the dropping funnel over 6 h. The mixture was heated at 100 °C for 1 h. After such time as all the HBr gas had been evolved, H_2O (5 ml) was added and enough glacial acetic acid was added to effect a homogeneous phase. After this, the reaction mixture was heated for a further 2 h at 100 °C and allowed to cool

overnight. After pouring onto ice, the crude product was filtered off and dried under suction. Recrystallisation from ethanol gave pure (+)-*endo*-3-bromocamphor (88) (6.02 g, 27%); m.p. 75 °C (lit.,[189] 76 °C); ν_{max} (KBr) 1750 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.89 (3 H, s), 0.93 (3 H, s), 1.04 (3 H, s), 1.38 (1 H, m), 1.64 (1 H, m), 1.72 (1 H, m), 2.05 (1 H, m), 4.58 (1 H, d, *J* 4.8).

(-)-*endo*-6-Bromocamphor (89)[191]

(+)-*endo*-3-Bromocamphor (88) (6.00 g, 0.026 mol) in chlorosulphonic acid (30 ml) was stirred at 50 °C for 15 min, then poured carefully onto ice. After extraction with ether (6 x 50 ml), the combined ether layers were washed with sodium bicarbonate solution, twice with water and finally brine. After drying, the ether was removed to give a dark semi-crystalline product. Column chromatography on alumina with petroleum ether (40-60 °) and ether (9:1) as eluent gave pure (-)-*endo*-6-bromocamphor (89) (2.28 g, 38%); ν_{max} ($CHC\ell_3$) 1750 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 0.88 (3 H, s), 0.93 (3 H, s), 0.96 (3 H, s), 1.85 (1 H, dd, *J* 14.3 and 3.4 Hz), 2.00 (1 H, d, *J* 18.4), 2.20 (1 H, m), 2.36 (1 H, m), 2.80 (1 H, m), 4.19 (1 H, dd, *J* 10.1 and 3.4 Hz).

(+)-5,6-Dehydrocamphor (87)[193]

(-)-*endo*-6-Bromocamphor (89) (6.5 g, 0.028 mol), potassium hydroxide (7.89 g, 0.14 mol), dimethylsulphoxide (280 ml) and water (40 ml) were stirred at 70 °C for 96 h. The mixture was diluted with water and extracted with ether (6 x 50 ml).

The combined organic extracts were washed with water, saturated aqueous brine solution and dried. Flash column chromatography on silica gel (petroleum ether (40-60 °)/ether (9:1)) afforded (+)-5,6-dehydrocamphor (87) (1.81 g, 43%) as a volatile white solid; ν_{max} ($CHC\ell_3$) 3020, 1735 and 720 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 0.87 (3 H, s), 0.96 (3 H, s), 1.03 (3 H, s), 1.88 (1 H, d, *J* 16.7), 2.17 (1H, dd, *J* 16.7 and 3.4 Hz), 2.63 (1 H, s), 5.53 (1 H, d, *J* 5.7), 6.41 (1 H, dd, *J* 5.7 and 3 Hz).

(-)-α-Campholenic acid (95)[193]

The aqueous phases from the above reaction were acidified with 1 M hydrochloric acid then extracted with ether (5 x 200 ml). The combined extracts were washed with brine and removal of the solvent gave pure (-)-α-campholenic acid (95) (2.21 g, 47%); ν_{max} (film) 3020, 2950 and 1710 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 0.78 (3 H, s), 1.60 (3 H, s), 1.95 (1 H, m), 2.34 (4 H, m), 5.22 (1 H, s), 11.05 (1 H, s).

(+)-α-Oximino-5,6-dehydrocamphor (102)[219]

(+)-α-Oximino-5,6-dehydrocamphor5 (102) (0.56 g, 47%) was prepared from (+)-5,6-dehydrocamphor (87) (0.99 g, 6.7 x 10^{-3} mol) by the method of Hassner *et al.*[221] M.p. 118-119 °C; ν_{max} ($CC\ell_4$) 3300 and 1715 cm^{-1}; δ_H ($CDC\ell_3$) 200 MHz, 1.03 (3 H, s), 1.10 (3 H, s), 1.12 (3 H, s), 3.14 (1 H, d, *J* 3.2), 5.85 (1 H, d, *J* 5.5), 6.59 (1 H, dd, *J* 5.5 and 3.2 Hz), 10.94 (1 H, s); δ_C ($CDC\ell_3$) 50 MHz, 5.91 (CH_3), 17.95 (CH_3), 19.71 (CH_3), 54.81 (CH), 62.19 (q), 66,39 (q), 66.39 (q), 137.06 (CH), 140.76

(CH), 151.97 (q), 204.11 (q) (Found: C, 67.06; H, 7.37; N, 7.82. $C_{10}H_{13}NO_2$ requires C, 67.04; H, 7.26; N, 7.82%).

PART V

4-(DIFLUOROIODO)TRICYCLENE (107), AN ISOLABLE COMPOUND OF THE TYPE RIF_2 FROM AN ALIPHATIC IODIDE[221]

5.1 INTRODUCTION

Although there are examples of difluoroiodo compounds in the literature such as $C_6H_5IF_2$[222] CF_3IF_2[223] and CH_3IF_2[223] the last of which can be made and used immediately in solution, there are no examples of isolable compounds containing the IF_2 functionality being linked to an aliphatic hydrocarbon residue. It is for this reason that the synthesis of 4-(difluoroiodo)tricyclene (107) was undertaken.

The reasons for choosing 4-iodotricyclene (108) as the starting material are four: (a) it is considered unlikely that C(4)-I bond heterolysis will occur to give a positively charged iodine group in (108) or, more particularly in (107); (b) the reaction does not contain the ingredients for a C(4)-I bond cleavage to occur readily *via* an SET pathway; (c) Rüchardt *et al.*[224] have found the rate constant for the formation of the bridgehead radical from bicyclo[2.2.1]heptane-4-carboxylic acid, t-butyl per ester to be 6.8×10^{-7} s^{-1} at 80 °C in cumol, whilst the rate constant for the formation of the bridgehead carbocation from 4-bromobicyclo[2.2.1]heptane was found to be 7.0×10^{-16} s^{-1} at 25 °C in ethanol/water. Even allowing for the differences in solvent and temperature, this shows that the rate-determining formation of bridgehead radicals takes place with less reluctance than formation of

the corresponding carbocation, though there is a correlation between the two processes;[224] (d) since the loss of an ionic leaving group from the 4-tricyclyl position is the slowest known S_N1 reaction[64] it is conceivable that other groups will also leave with great difficulty from this position. Accordingly, it is envisaged that the 4-iodotricyclene moiety will be suitable for stabilising labile groups, and thus enable a series of unknown structures to be realised. The choice of 4-iodotricyclene (108) as the starting material is probably reinforced since recently the solvolysis of cubyl derivatives, previously thought to be the ultimate in inertia, have been shown[225] to be unexpectedly rapid.

The choice of XeF_2 as the fluorinating agent was necessitated by the fact that the more powerful fluorinating agents such as $C\ell F_3$, BrF_3 and F_2, employed in the synthesis of perfluoroalkyliodine (III and V) fluorides[222] would not be applicable in the synthesis of alkyliodine (III or V) fluorides owing to the destructive fluorination of alkyl groups.[227]

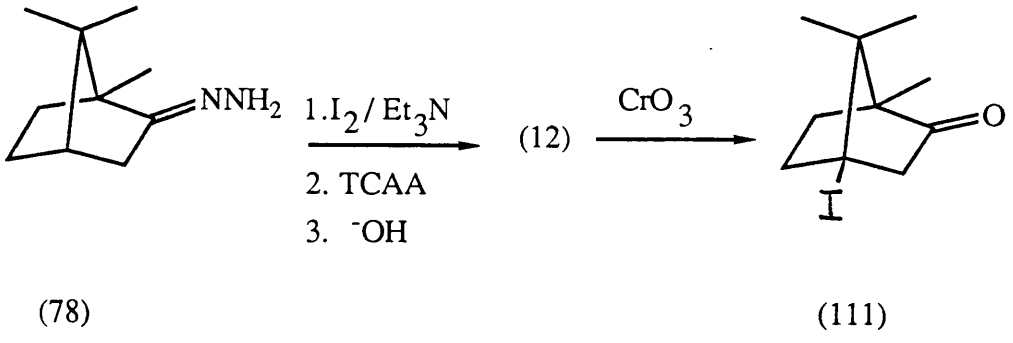
The success of XeF_2 as a mild and selective fluorinating agent is probably due to the formation of a thermodynamically favourable reaction product, *i.e.* Xe production being the driving force.

XeF_2 has also been shown to be a useful fluorinating agent which can be used to effect electrophilic aromatic substitution, in the presence of HF, in good yields.[228]

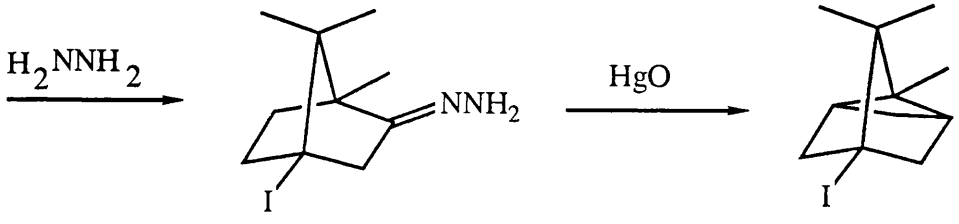
5.2 RESULTS AND DISCUSSION

In the synthesis of 4-iodotricyclene (108), outlined in Figure (58), one interesting point came to light. When camphor hydrazone (78) is treated with iodine and triethylamine, two major products are formed, *viz.* 1-iodocamphene (109) and 2-iodobornene (110). The mechanism for their formation was first proposed by Barton and co-workers,[229] Figure (59a), and later supported by Pross and Sternhell,[69] shown in Figure (59b).

Treatment of the hydrazone (113) with iodine gives the N-iodo derivative (114) which is converted to the aliphatic diazo compound (115) in the presence of triethylamine. Evidence for the diazo compound (115) as an intermediate is given by Neuman[230] who employed the treatment of aliphatic diazo compounds with iodine alone as a general method for the production of *gem*-diiodides. Iodine, then acting as an electrophile, converts the diazo-compound (115), *via* an intermediate iododiazonium compound (116) into an iodocarbonium ion (117). This iodocarbonium ion (117) can be related to the corresponding carbonium ion of the bornyl system (118), Figure (59b), employed in the synthesis of 4-iodotricyclene (108). (118) Can undergo either proton elimination to give 2-iodobornene (110) or a Wagner-Meerwein rearrangement, (118) to (119), followed by proton elimination to give 1-iodocamphene (109). On treatment with trichloroacetic acid (TCAA), the carbonium ions (118) and (120) obtained from (110) and (109), respectively, are linked by a Wagner-Meerwein rearrangement, (118) to (119) and as a result, both 1-iodocamphene (109) and 2-iodobornene (110) react with TCAA to give the same

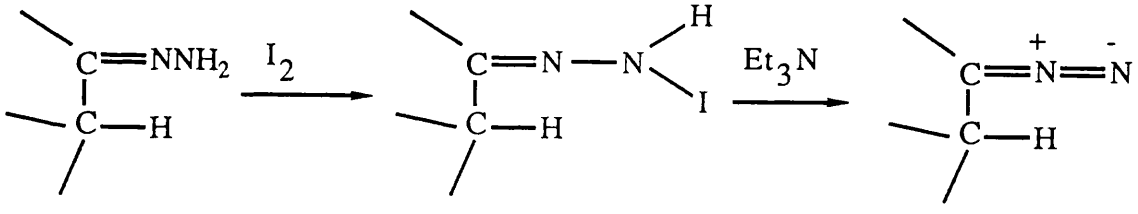


(78) (111)

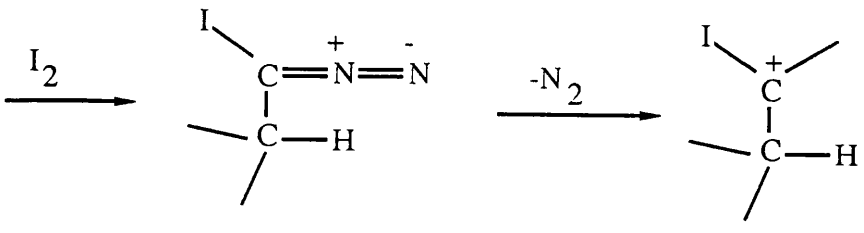


(112) (108)

Figure 58



(113) (114) (115)



(116) (117)

Figure 59a

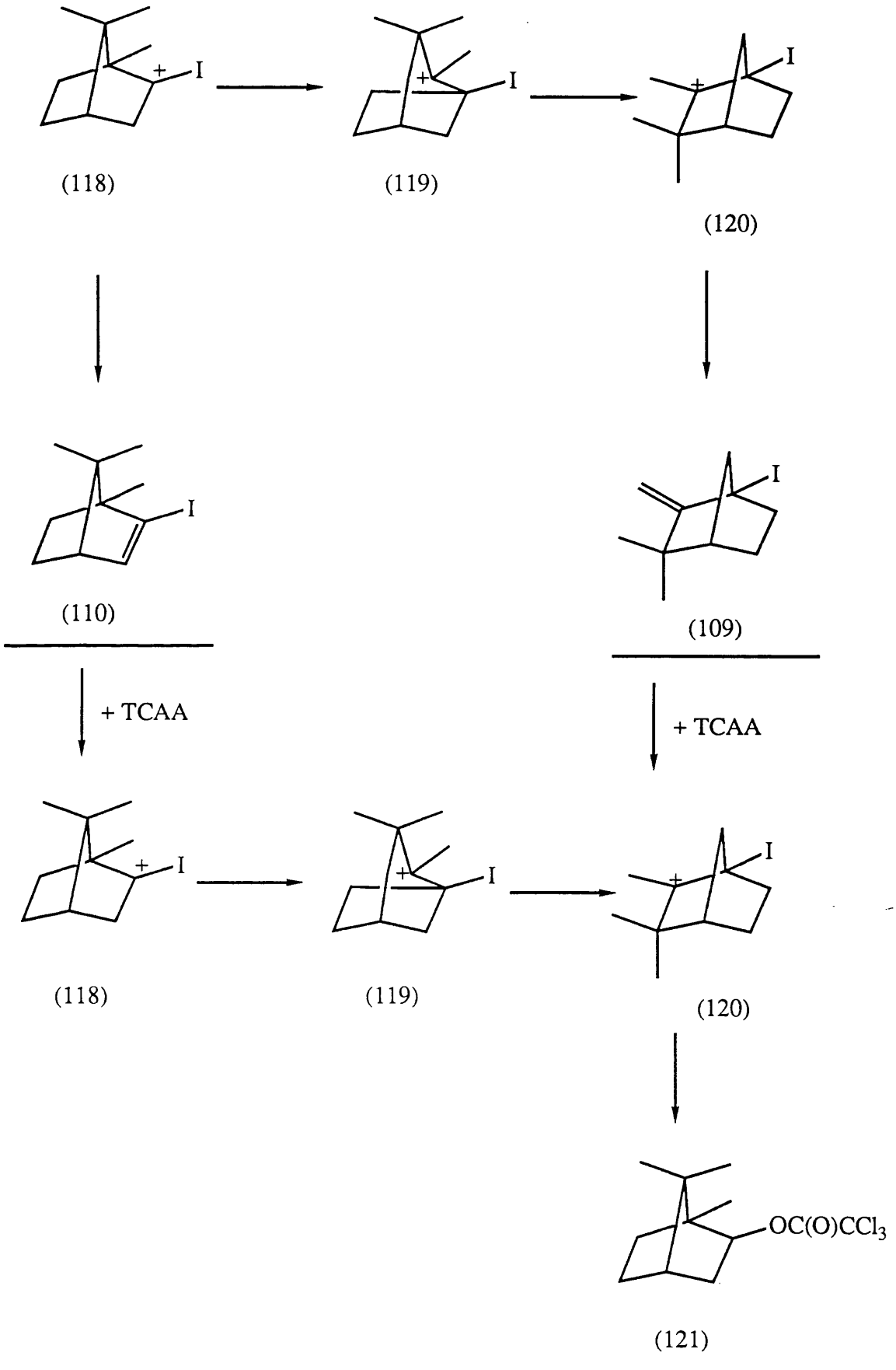


Figure 59b

trichloroacetate ester (121).

Previously, in the production of 4-iodo isoborneol (12) (Section 1.3.3.), 1-iodocamphene (109) and 2-iodobornene (110) were carefully and tediously separated, on an alumina column, and since both have similar R_f values an appreciable loss usually resulted.

Reaction of 4-iodocamphor hydrazone (112) with mercuric oxide was found to proceed more effectively in the presence of a small amount of methoxide ion.

When a solution of 4-iodotricyclene (108) in carbon tetrachloride was treated with a six-fold molar excess of XeF_2 at ambient temperature for 1 h, followed by removal of solvent and excess of XeF_2 by evacuation at 10^{-2} mm Hg at room temperature, a pale yellow solid product was obtained. Assignment of structure (107) to this product was made from NMR data. In 4-iodotricyclene (108) there exists a plane of symmetry and both ^1H and ^{13}C NMR spectra showed that this had been preserved in the product. In the ^1H NMR spectrum of (107) there is an AB pattern for protons H_{3a} and H_{3b} at 1.56 p.p.m. and 1.21 p.p.m. with a coupling of 11 Hz observed, indicating that the three-membered ring had been preserved. In such systems $J(H_{3a}H_2) = J(H_{3b}H_2) < 0.5$ Hz.

The ^{13}C NMR spectrum of (107) shows that the heavy atom effect, by which carbon atoms bonded to monovalent iodine absorb at abnormally high fields,[231] is not present. In the ^{13}C NMR spectrum of (107), a C(4)-F coupling of 9 Hz is observed. Table (6) shows the ^{13}C chemical shift data for (107) and (108) and a previously made related compound (122).[232] The absence of a heavy atom effect for carbons

bonded to trivalent iodine[233] can be satisfactorily rationalised in terms of the increased electronegativity of $-IF_2$ over -I.

One resonance was observed in the ^{19}F NMR spectrum, a sharp singlet at -193.3 p.p.m. (ext. std. $CC\ell_3F$) in the region associated with RIF_2.[222,223]

There was no evidence to suggest the presence of 4-(tetrafluoroiodo)tricyclene (123) either from fluorination of (108) by excess XeF_2 or by disproportionation of the observed RIF_2 (107). This is probably due to the fact that a species of the type RIF_4 would be fairly hindered, even allowing for the 'tied back' nature of the 4-tricyclyl system employed.

This idea is supported by two pieces of available NMR evidence. Firstly, the ^{13}C NMR spectra of some pentavalent iodine compounds[234] indicate that C(4) of (128) would absorb at significantly higher field than the observed value of (107). Secondly, the four equivalent, coplanar fluorines of (123) would show a ^{19}F resonance in a very different region of the spectrum[234] than (107). Perfluoroalkyliodine (V) tetrafluoride shows a ^{19}F absorption at ~ -30 p.p.m. for $-IF_4$.

Allied to the NMR evidence for the assignment of structure (107) to the product, mass spectral analysis showed a parent ion for (107) at $m/z = 300$ (70 eV, electron impact) with no evidence for a tetrafluoroiodo product. However in the absence of a mass spectrum of (107) determined by a 'soft ionisation' method *e.g.* Chemical Ionisation, the determination by electron impact is confirmatory rather than definitive.

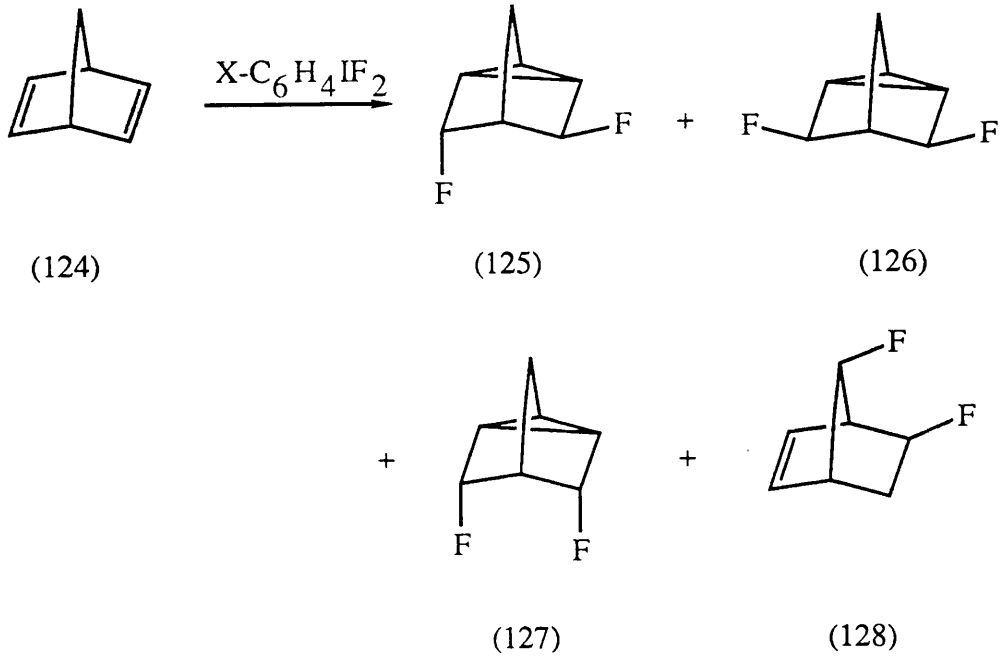
4-(Difluoroiodo)tricyclene (107) is a pale yellow waxy solid which is stable in

air for up to 4 h and in carbon tetrachloride solution under an inert atmosphere, indefinitely. It is thought that (107) is probably an optimum structure for conferring longevity on aliphatic compounds of the type RIF_2 and very likely places an upper limit on the lifetime of such compounds.

Also of interest, is the reactivity of (107) as a fluorinating agent, as has been observed for $ArIF_2$.[235] Treatment of norbornadiene (124) with $ArIF_2$ yields four difluorinated products, *viz.* 3-*endo*, 5-*exo*-difluorotricyclo[2.2.1.$0^{2,6}$]heptane (125), 3-*exo*, 5-*exo*-difluorotricyclo[2.2.1.$0^{2,6}$]heptane (126), 3-*endo*, 5-*endo*-difluorotricyclo-[2.2.1.$0^{2,6}$]heptane (127) and 5-*exo*, 7-*syn*-difluoronorborn-2-ene (128).

Preliminary studies by ^1H NMR analysis, carried out by Paul Watson at the University of Leicester, have shown that treatment of norbornadiene (124) with (107) results in the same products as shown in Figure (60).

Finally, as an extension of this work, reaction of CI_4 with XeF_2 under the same conditions was found to lead to extensive decomposition with copious evolution of brown and white fumes rather than tetra(difluoroiodo)-methane, as had been hoped.

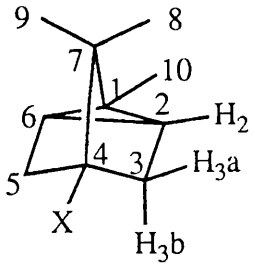


(124) (125) (126)

(127) (128)

X = H, p- OMe, m- Cl, m-NO_2

Figure 60



(107) X = IF_2

(108) X = I

(123) X = IF_4

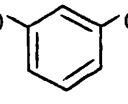
(122) X = I (OCO  $C\ell)_2$

Table 6. ^{13}C NMR data for compounds (107), (108) and (122) in $CDC\ell_3$

	(107)	(108)	(122)
C(1)	24.77	23.74	23.85
C(2)	20.66	20.55	20.00
C(3)	37.26	43.40	38.26
C(4)	80.99	43.90	80.26
C(7)	49.27	47.34	49.27
C(8)	20.23	19.52	20.23
C(10)	12.23	11.77	12.23

5.3 EXPERIMENTAL

For general experimental details, see Section 1.3.1.

5.3.1 PREPARATION OF COMPOUNDS

4-Iodotricyclene (108)

Jones oxidation of 4-iodoisoborneol (12) gave 4-iodocamphor (111) which was recrystallised from ethanol; m.p. 157-159 °C (sealed tube); ν_{max} (KBr) 1745 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.87 (3 H, s), 0.96 (3 H, s), 1.08 (3 H, s), 1.20-3.10 (6 H, m).

A mixture of 4-iodocamphor (111) (1.5 g, 5.40 x 10^{-3} mol), hydrazine hydrate (0.67 g, 1.34 x 10^{-2} mol) and acetic acid (0.15 g) in ethanol (25 ml) was refluxed at 60 °C for 48 h. On cooling, the ethanol was evaporated off and the original volume made up with ether. After washing successively with 10% aqueous sodium hydroxide and saturated brine, the ethereal solution was dried. On removal of the ether, a clear yellow oil was left, identified as 4-iodocamphor hydrazone (112) (0.96 g, 61%); ν_{max} (film) 3350, 3250 and 1665 cm^{-1}.

4-Iodocamphor hydrazone (112) (0.96 g, 3.29 x 10^{-3} mol) was dissolved in ethanol (5 ml) at room temperature. After a few minutes, mercuric oxide (1.10 g, 5 x 10^{-3} mol) and a few drops of a concentrated solution of sodium methoxide in methanol were added. The resultant mixture was heated at 70 °C for 10 h. On cooling, the ethanol was removed leaving a yellow solid (0.76 g). The crude product was purified on an alumina column (eluted with petroleum ether (40-60 °)) to give

pure 4-iodotricyclene (108) (0.35 g, 41%) as a white solid; m.p. 90-91 °C; ν_{max} (nujol) 3050 cm^{-1}; δ_H ($CDC\ell_3$) 90 MHz, 0.8 (6 H, s), 0.89 (2 H, s), 1.14 (3 H, s), 1.60 (2 H, d, J_{AB} 11), 2.15 (2 H, d, J_{AB} 11).

4-(Difluoroiodo)tricyclene (107)

To a stirred, degassed solution of 4-iodotricyclene (108) (30 mg, 0.12 mmol), in a standard Schenk apparatus under an atmosphere of nitrogen, was added a sample of XeF_2 (120 mg, 0.7 mmol), pre-weighed into a sample bottle in a dry-box. After 1 h, the colourless solution had turned pale yellow and was subjected to high vacuum for 15 min to remove solvent and excess of XeF_2. The resulting yellow solid was then dissolved in $CDC\ell_3$ and transferred to a NMR tube by a Pasteur pipette; δ_H ($CDC\ell_3$) 200 MHz, 0.28 (6 H, s), 0.41 (3 H, s), 0.57 (2 H, s), 1.21 (2 H, d, J_{AB} 10.7), 1.56 (2 H, d, J_{AB} 10.7); δ_C ($CDC\ell_3$) 50 MHz, 12.23 (C-10), 20.23 (C-8, C-9), 20.66 (C-2, C_6), 37.26 (C-3, C-5), 49.27 (C-7), 80.99 (C-4, t, J_{CF} 9); ^{19}F ($CDC\ell_3$) 188 MHz, -193.3 (2 F, s).

REFERENCES

1. M. Berthelot, C. Laurence, J.Y. Le Questel, G.W. Bradley and D.G. Morris, *Spectrochim. Acta*, 1991 **47A**, 1649.
2. L.J. Bellamy, "The Infrared Spectra of Complex Molecules", Volume 3, Chapman and Hall, London, 1980.
3. L.J. Bellamy, "Advances in Infrared Group Frequencies", Chapman and Hall, London, 1975.
4. N.B. Colthup, L.H. Daly and S.E. Wiberly, "Introduction to Raman and Infrared Spectroscopy", Academic Press, New York, 1975.
5 I.I. Rabi, S. Millman, P. Kusch and J.R. Zacharias, *Phys. Rev.*, 1939, **55**, 507.
6. P.R. Griffiths, "Chemical Infrared Fourier Transform Spectroscopy", John Wiley and Sons, New York, 1975.
7. K. Nakamoto, "Infrared and Raman Spectra of Inorganic and Coordination Compounds", John Wiley and Sons, New York, 1986.
8. S. Pinchas and I. Laulicht, "Infrared Spectra of Labelled Compounds", Academic Press, London, 1971.
9. A. Finch, P.N. Gates, K. Radcliffe, F.N. Dickson and F.F. Beatley, "Chemical Applications of Far Infrared Spectroscopy", Academic Press, London, 1970.
10. H.J. Bernstein, *Spectrochim. Acta*, 1962, **18**, 161.
11. E.R. Lippincott and R. Schroeder, *J. Am. Chem. Soc.*, 1956, **78**, 5171.
12. H. Aschkinass, *Wied. Ann.*, 1895, **55**, 41.

13. A.V. Stuart and G.B.B.M. Sutherland, *J. Chem. Phys.*, 1956, **24**, 559.

14. A.R. Katritzky and R.D. Topsom, *Chem. Rev.*, 1977, **77**, 639.

15. R.M. Badger and S.H. Bauer, *J. Chem. Phys.*, 1937, **5**, 839.

16. M.L. Huggins, *J. Org. Chem.*, 1936, **1**, 407.

17. T.A. Kletz and W.C. Price, *J. Chem. Soc.*, 1947, 644.

18. R.E. Richards and H.W. Thompson, *J. Chem. Soc.*, 1947, 1260.

19. E.G. Hoffman, *Z. physikal Chem.*, 1943, **B53**, 179.

20. W. Lüttke and R. Mecke, *Z. Electrochem.*, 1949, **53**, 241.

21. O. Exner, "Advances in Linear Free Energy Relationships", Plenum Publishing Company, London, 1978.

22. J. Shorter, "Correlation Analysis in Chemistry", Plenum Publishing Company, London, 1978.

23. C. Laurence and M. Berthelot, *Spectrochim. Acta*, 1978 **34A**, 1127.

24. T.L. Brown, *J. Phys. Chem.*, 1957, **61**, 820.

25. K.U. Ingold, *Can. J. Chem.*, 1960, **38**, 1092.

26. C.J.W. Brooks, G. Eglinton and J.F. Morman, *J. Chem. Soc.*, 1961, 106.

27. M.L. Josien, D. Peltier and A. Pichevin, *C.R. Acad. Sci. Paris*, 1960, **250**, 1643.

28. L.J. Bellamy and D.W. Mayo, *J. Phys. Chem.*, 1976, **80**, 1217.

29. C.K. Ingold, "Structure and Mechanism in Organic Chemistry", G. Bell and Sons Ltd., London, 1969.

30. R. Piccolini and S. Winstein, *Tetrahedron Lett.*, 1959, **13**, 4.

31. M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, 1959, **32**, 950.

32. A.R.H. Cole, P.R. Jeffries and G.T.A. Miller, *J. Chem. Soc.*, 1959, 1222.

33. A.R.H. Cole, G.T.A. Miller, D.W. Thornton and R.L.S. Willix, *J. Chem. Soc.*, 1959, 1221.

34. H.S. Aaron and C.P. Rader, *J. Am. Chem. Soc.*, 1963, **85**, 3046.

35. F. Dalton, G.D. Meakins, J.H. Robinson and W. Zahavia, *J. Chem. Soc.*, 1962, 1566.

36. P.J. Kreuger, J. Jan and H. Weiser, *J. Mol. Structure*, 1970, **5**, 375.

37. E.T.G. Lutz and J.H. Van der Maas, *Spectrochim. Acta*, 1978, **34A**, 915.

38. R.W. Taft and R.D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 1.

39. R.D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 125.

40. C. Laurence, M. Berthelot, M. Lucan, M. Herbert, D.G. Morris and J.-F. Gal, *J. Chem. Soc., Perkin Trans. 2*, 1984, 705.

41. M. Taagepara, W.J. Hehre, R.D. Topsom and R.W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 7438.

42. S. Marriott and R.D. Topsom, *J. Am. Chem. Soc.*, 1984, **106**, 7.

43. W.F. Reynolds and R.D. Topsom, *J. Org. Chem.*, 1984, **49**, 1989.

44. S. Marriott, W.F. Reynolds and R.D. Topsom, *J. Org. Chem.*, 1985, **50**, 741.

45. C. Laurence, M. Berthelot and D.G. Morris, *Spectrochim. Acta*, 1983, **39A**, 699.

46. C. Altona and M. Sundaralingham, *J. Am. Chem. Soc.*, 1970, **92**, 1955.

47. C.D. Ritchie and E.S. Lewis, *J. Am. Chem. Soc.*, 1962, **84**, 591.

48. J. Cantacuzene, *J. Chim. Phys.*, 1962, 186.

49. O. Exner, "Dipole Moments in Organic Chemistry", G. Thieme, Stuttgart, 1975.

50. M. Tichy, *Adv. Org. Chem.*, 1965, **5**, 115.

51. P.J. Kreuger and H.D. Mettee, *Can. J. Chem.*, 1965, **43**, 2970.

52. P.J. Kreuger and H.D. Mettee, *Can. J. Chem.*, 1965, **43**, 2888.

53. H. Mollendal, *J. Molec. Struct.*, 1983, **97**, 303.

54. L. Sobczyk, H. Engelhardt and K. Banzyl, "The Hydrogen Bond", (Edited by P. Schuster, G. Zundel and C. Sandorfy), Amsterdam, North Holland, 1976.

55. D.G. Morris and A.M. Murray, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1579.

56. O.A. Gansow, D.A. Schexnyder and B.Y. Kimura, *J. Am. Chem. Soc.*, 1972, **94**, 3406.

57. P. Metzger, E. Casadevall, A. Casadevall and M.J. Pouet, *Can. J. Chem.*, 1980, **58**, 1503.

58. W.Z. Antkowiak, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, 1966, **14**, 437.

59. H. Toivonen, *Tetrahedron Lett.*, 1968, 3041.

60. N.C. Deno, J.J. Jaruzelski and A. Schrieshien, *J. Am. Chem. Soc.*, 1955, **77**, 3044.

61. S.S. Nametkin, A.A. Kichkina and D.N. Kursanov, *J. Prakt. Chem.*, 1930, **124**, 144.

62. D.G. Morris, A.G. Shepherd, M.F. Walker and R.W. Jemison, *Aust. J. Chem.*, 1982, **35**, 1061.

63. M. Kagawa, *Chem. Pharm. Bull.*, 1959, **7**, 306.

64. S.A. Sherrod, R.G. Bergman, G.J. Gleicher and D.G. Morris, *J. Am. Chem. Soc.*, 1972, **94**, 4615.

65. J. Houben and E. Pfankuch, *Justus Liebigs Ann. Chem.*, 1930, **483**, 271.

66. A. Nickon, T. Nishida, J. Frank and R. Muneyuki, *J. Org. Chem.*, 1971, **36**, 1075.

67. *Organic Synthesis*, Coll. Vol. 5, 351.

68. W. Reusch, W.M. DiCarlo and L. Traynor, *J. Org. Chem.*, 1961, **26**, 1711.

69. A Pross and S. Sternhell, *Aust. J. Chem.*, 1970, **23**, 989.

70. G.C. Joshi and E.W. Warnhoff, *J. Org. Chem.*, 1972, **37**, 2383.

71. J. Houben and E. Pfankuch, *Ann.*, 1931, **489**, 216.

72. D.G. Morris, A.G. Shepherd, G. Lamaty, B. Boyer and C. Moreau, *New J. Chem.*, 1988, **12**, 277.

73. Y. Brunel, H. Lemaire and A. Rassat, *Bull. Soc. Chim., France*, 1964, 1895.

74. M.C.R. Symons, W.R. Bowman, G.W. Bradley and D.G. Morris, *J. Chem. Soc., Perkin Trans. 2*, 1992, 545.

75. N.M. Atherton, "Electron Spin Resonance: Theory and Applications", John Wiley and Sons Inc., New York, 1973.

76. P.W. Atkins and M.C.R. Symons, "The Structure of Inorganic Radicals", Elsevier Publishing Company, Amsterdam, 1967.

77. W. Weltner, "Magnetic Atoms and Molecules", Scientific and Academic Editions, New York, 1983.

78. Y.K. Zavoisky, *J. Phys. U.S.S.R.*, 1945, **9**, 245.

79. B. Bleaney and K.W.H. Stevens, *Rept. Prog. Phys.*, 1953, **16**, 108.

80. M.C.R. Symons, *Advan. Phys. Org. Chem.*, 1963, **1**, 284.

81. A.M. Bass and H.P. Broida, "Formation and Trapping of Free Radicals", Academic Press, New York, 1961.

82. J.E. Wertz and J.R. Bolton, "Electron Spin Resonance: Elementary Theory and Practical Applications", McGraw-Hill Book Company, New York, 1972.

83. A. Abragham, "The Principles of Nuclear Magnetism", Oxford University Press, London, 1961.

84. J.R. Morton, J.R. Rowlands and D.H. Whiffen, *Natl. Phys. Lab.*, Circ. No. BPR 13.

85. J.A. Pople, D.L. Beveridge and P.A. Dobosh, *J. Am. Chem. Soc.*, 1968, **90**, 4201.

86. J.R. Morton and K.F. Preston, *J. Magn. Reson.*, 1978, **30**, 577.

87. J.H. Mackey and D.E. Wood, *J. Chem. Phys.*, 1970, **52**, 4914.

88. D. Lipkin, *Science*, 1953, **117**, 534.

89. H.M. McConnell, *J. Chem. Phys.*, 1956, **24**, 762.

90. H.M. McConnell, C. Heller, T. Cole and R.W. Fessenden, *J. Am. Chem. Soc.*, 1960, **82**, 766.

91. M.S. Matheson and B. Smaller, *J. Chem. Phys.*, 1958, **28**, 1169.

92. S.I. Weissman, T.R. Tuttle and E.J. de Boer, *J. Phys. Chem.*, 1957, **61**, 28.

93. A.D. McLachlan, H.H. Dearman and R. Lefebvre, *J. Chem. Phys.*, 1960, **33**, 65.

94. M.C.R. Symons, *J. Chem. Soc.*, 1959, 277.

95. J.R. Morton, *Chem. Rev.*, 1964, **64**, 453.

96. C. Heller and H.M. McConnell, *J. Chem. Phys.*, 1960, **32**, 1535.

97. E.W. Stone and A.H. Maki, *J. Chem. Phys.*, 1962, **37**, 1326.

98. M.C.R. Symons, *Pure Appl. Chem.*, 1981, **53**, 223.

99. N. Kornblum, footnote 11 in Y. Kai, P. Knockel, S. Kwiatkowski, J.D. Dunitz, J.F.M. Oth, D. Seebach and H.-O. Kalinowski, *Helv. Chim. Acta*, 1982, **65**, 137.

100. A. Berndt, "Landolt-Bornstein Numerical Data and Functional Relationships in Science and Technology", vol. 9, part d1, Springer-Verlag, Berlin, 1980.

101. M.C.R. Symons and W.R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1988, 583.

102. A. Berndt, *Agnew. Chem. Int. Ed. Engl.*, 1967, **6**, 251.

103. M.C.R. Symons and W.R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1983, 25; *J. Chem. Res. (S)*, 1984, 162.

104. M.C.R. Symons and W.R. Bowman, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1077.

105. D.I. Edwards, *Biochem. Pharmacol.*, 1986, **35**, 53.

106. E. Perez-Reyes, B. Kalyanaraman and R.P. Mason, *Mol. Pharmacol.*, 1980, **17**, 239.

107. H.B. Hass and L.W. Siegle, *J. Org. Chem.*, 1940, **5**, 100.

108. G.A. Russell and W.C. Dannen, *J. Am. Chem. Soc.*, 1966, **88**, 5663.

109. J.F. Bunnett, *Accounts Chem. Res.*, 1978, **11**, 413.

110. J.K. Kim and J.F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 7463.

111. A.T.O.M. Adebayo, W.R. Bowman and W.G. Salt, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2819.

112. W.R. Bowman, *Chem. Soc. Rev.*, 1988, 283.

113. L. Horner, L. Hockenberger and W. Kirmse, *Chem. Ber.*, 1961, **94**, 290.

114. J.W. Suggitt, G.S. Myers and G.F. Wright, *J. Org. Chem.*, 1947, **12**, 373.

115. O. Manasse and L. Claisen, *Justus Liebigs Ann. Chem.*, 1893, **274**, 71.

116. S. Adamopolous, A.J. Boulton, R.T. Tadayani and G.A. Webb, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2073.

117. A. Angeli and E. Rimini, *Gazz. Chim. Ital.*, 1895, **251**, 406.

118. O. Angelucci, *Justus Liebigs Ann. Chem.*, 1905, **341**, 172.

119. T.S. Cameron, R.E. Cordes, D.G. Morris and A.M. Murray, *J. Chem. Soc., Perkin Trans. 2*, 1979, 300.

120. J.J. Freeman, *J. Org. Chem.*, 1961, **26**, 4190.

121. R. Scholl, *Justus Liebigs Ann. Chem.*, 1906, **338**, 1.

122. J.F. Brown, *J. Am. Chem. Soc.*, 1955, **77**, 6341.

123. R.N. Haszeldine and J. Jander, *J. Chem. Soc.*, 1954, 691,

124. H.E. Zimmerman and D.H. Paskovich, *J. Am. Chem. Soc.*, 1964, **86**, 2149.

125. M. Hanack and E. Eggensperger, *Ann.*, 1961, **648**, 10.

126. V.S. Dalavoy, V.B. Deodhar and U.R. Nayak, *Ind. J. Chem.*, 1982, **21B**, 396.

127. S.P. Mishra and M.C.R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 1973, 394.

128. Dictionary of Organic Compounds, Eyre and Spottiswode, London, 1973.

129. S.G. Brooks, R.M. Evans, G.F.H. Green, J.S. Hunt, A.G. Long, B. Mooney and L.J. Wayman, *J. Chem. Soc.*, 1958, 4614.

130. A. Angeli and E. Rimini, *Ber.*, 1895, **28**, 1078.

131. J.A. Berson, J.S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff and D. Willner, *J. Am. Chem. Soc.*, 1961, **83**, 3986.

132. R.W. Cottingham, *J. Org. Chem.*, 1960, **25**, 1473.

133. F. Tieman and F. Mahla, *Ber.*, 1896, **29**, 2807.

134. S. Ranganathan, B.B. Singh and C.S. Panda, *Tetrahedron*, 1977, **33**, 2415.

135. J. Melton and J.E. McMurray, *J. Org. Chem.*, 1975, **40**, 2138.

136. E.J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, 1978, **100**, 6294.

137. P. Dampawan and W.W. Zajac, *Tetrahedron Lett.*, 1982, **23**, 135.

138. K. Schofield, "Aromatic Nitration", Cambridge University Press, 1980.

139. A.T. Nielsen, A.P. Chaffin and S.L. Chrishan, *J. Org. Chem.*, 1984, **49**, 4576.

140. R.A. Marcus and J.M. Frescoe, *J. Chem. Phys.*, 1957, **27**, 564.

141. M. Liler, "Reaction Mechanisms in Sulphonic Acid and other Strong Acid Solutions", Academic Press, London, 1971.

142. P.B.D. De La Mare and J.H. Ridd, "Aromatic Substitution: Nitration and Halogenation", Butterworth Scientific Publications, London, 1959.

143. D.J. Millen, *J. Chem. Soc.*, 1950, 2589.

144. H. Wolff, *Org. React.*, 1946, **3**, 307.

145. A.J. McNamara and J.B. Strothers, *Can. J. Chem.*, 1964, **42**, 2354.

146. C.D. Hurd, "Organic Chemistry", I, 699, 1st ed., John Wiley and Sons, New York, 1938.

147. R.N. Keller and P.A.S. Smith, *J. Am. Chem. Soc.*, 1944, **66**, 1122.

148. J.F. Bunnett and R.E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

149. R. Meldola and F.G.C. Stephens, *J. Chem. Soc.*, 1905, **87**, 1199.

150. C.H. De Puy, G.M. Dappen, K.L. Eilers and R.A. Klein, *J. Org. Chem.*, 1964, **29**, 2813.

151. C.H. Hassall, *Org. React.*, 1957, **9**, 73.

152. J.E. Leffler, *Chem. Rev.*, 1949, **45**, 385.

153. H. Gilman and P.R. Van Ess, *J. Am. Chem. Soc.*, 1933, **55**, 1258.

154. A.P.G. Kieboom, *Synthesis*, 1975, 327.

155. G.S. Hammond and F.J. Modic, *J. Am. Chem. Soc.*, 1953, **75**, 1385.

156. J.W. Emsley, L. Phillips and V. Wray, "Fluorine Coupling Constants", Pergamon Press, Oxford, 1977.

157. G.C. Levy, R.L. Lichter and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy", 2nd ed., John Wiley and Sons, New York,

158. R. DuVernat and V. Boekelheide, *Proc. Nat. Acad. Sci. (USA)*, 1974, **71**, 296.

159. J.O. Edwards and R.G. Pearson, *J. Am. Chem. Soc.*, 1962, **84**, 16.

160. M.L. Bender, *Chem. Rev.*, 1960, **60**, 62.

161. A.F. Ferris, *J. Org. Chem.*, 1960, **25**, 12.

162. W.P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1960, **82**, 1778.

163. L.P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., New York, 1940.

164. J. Hine, "Physical Organic Chemistry", McGraw-Hill Book Co., New York, 1956.

165. P.T. Scott, D.E. Pearson and L.T. Bircher, *J. Org. Chem.*, 1954, **19**, 1817.

166. C.A. Grob, *Agnew. Chem. Int. Ed. Engl.*, 1968, **8**, 535.

167. R.E. Clewley, G.C. Cross, A. Fischer and G.N. Henderson, *Tetrahedron*, 1989, **45**, 1299.

168. M.D. Stephens, J.D. Reinheimer and A.H. Kappelman, *Can. J. Chem.*, 1971, **49**, 3759.

169. B.H. Lipshutz and J.J. Pegram, *Tetrahedron Lett.*, 1980, **21**, 3343.

170. E.J. Corey and B.B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.

171. E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.

172. J. Donogues, A. Ekovya, R. Calas and N. Duffant, *J. Organomet. Chem.*, 1975, **87**, 160.

173. H. Goldstein and A. Giddey, *Helv. Chim. Acta*, 1954, **37**, 2083.

174. J.J. Kane, N. Akmal, C. Janivala and M. Sinsky, *Mat. Res. Soc. Symp. Proc.*, 1989, **134**, 133.

175. C. Clemm, *J. Prakt. Chem.*, 1870, **1**, 145.

176. J.W. Powell and M.C. Whiting, *Tetrahedron*, 1959, **7**, 305.

177. F.C. Brown, Ph.D. Thesis, University of Glasgow, 1977.

178. N. Rabjohn, *Org. React.*, 1976, **24**, 261.

179. E.J. Corey and J.P. Schaefer, *J. Am. Chem. Soc.*, 1960, **82**, 918.

180. P.A. Best, J.S. Littler and W.A. Waters, *J. Chem. Soc.*, 1962, 822.

181. D. Arigoni, A. Vasella, K.B. Sharpless and H.P. Jensen, *J. Am. Chem. Soc.*, 1973, **95**, 7917.

182. K.B. Sharpless and K.M. Gordon, *J. Am. Chem. Soc.*, 1976, **98**, 300.

183. W.C. Evans, J.M. Ridgeon and J.L. Simonsen, *J. Chem. Soc.*, 1934, 137.

184. M.P. Cava, R.L. Litle and D.R. Napier, *J. Am. Chem. Soc.*, 1958, **80**, 2263.

185. R.L. Hinman, *J. Org. Chem.*, 1960, **25**, 1775.

186. J.M. Muchorski, *Tetrahedron Lett.*, 1966, 1773.

187. D.M. Lemal and A.J. Fry, *J. Org. Chem.*, 1964, **29**, 1673.

188. A.R. Chamberlain and F.T. Bond, *J. Org. Chem.*, 1978, **43**, 154.

189. B. Shive, W.W. Crouch and H.L. Lochte, *J. Am. Chem. Soc.*, 1941, **63**, 2979.

190. J. Katsuhura, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 2593.

191. W.M. Dadson, J.M. Hutchinson and T. Money, *Can. J. Chem.*, 1990, **68**, 1821.

192. M. Nishikawa, *Chem. Abstr.*, 1953, **47**, 6379h.

193. J.H. Hutchinson, T. Money and S.E. Piper, *Can. J. Chem.*, 1986, **64**, 854.

194. J.A. Clase and T. Money, *J. Chem. Soc., Chem. Commun.*, 1990, 1508.

195. J. Meinwald, C.B. Jensen, A. Lewis and C. Swithenbank, *J. Org. Chem.*, 1964, **29**, 3469.

196. G.A. Russell, G.W. Holland and K.-Y. Chang, *J. Am. Chem. Soc.*, 1967, **89**, 6629.

197. H.D. Scharf and W. Kusters, *Chem. Ber.*, 1972, **105**, 564.

198. R.L. Blankespoor and D. Gollehon, *J. Org. Chem.*, 1977, **42**, 63.

199. P.C. Cherry, W.R.T. Cottrell, G.D. Meakins and E.E. Richards, *J. Chem. Soc.*, 1968, **C**, 459.

200. N.N. Shapetto, D.N. Shigrorin, A.P. Skoldinov, T.S. Ryabchikova and L.N. Reshetova, *Optics and Spectroscopy* 1964, **17**, 247.

201. C.H. De Puy and B.W. Ponder, *J. Am. Chem. Soc.*, 1959, **81**, 4629.

202. E.H. Cordes and W.P. Jencks, *J. Am. Chem. Soc.*, 1963, **85**, 2843.

203. G.H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 1971, 195.

204. E.J. Corey and J.E. Richman, *J. Am. Chem. Soc.*, 1970, **92**, 5277.

205. S.H. Pines, J.M. Chemedra and M.A. Kozlowski, *J. Org. Chem.*, 1966, **31**, 3446.

206. H. von Pechman, *Ber.*, 1887, **20**, 2539.

207. H.H. Sisler and L.F. Audrieth, *J. Am. Chem. Soc.*, 1939, **61**, 3389.

208. P. Duden and W. Pritzkow, *Ber.*, 1899, **32**, 1539.

209. W.A. Noyes and G. Meitzner, *J. Am. Chem. Soc.*, 1932, **54**, 3768.

210. A. McKillop, J.D. Hunt, R.D. Naylor and E.C. Taylor, *J. Am. Chem. Soc.*, 1971, **93**, 4918.

211. H. Alper and J.I. Edward, *J. Org. Chem.*, 1967, **32**, 2938.

212. D.H.R. Barton, D.J. Lester and S.V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1212.

213. C.R. Narayan, P.S. Ramaswany and M.S. Wadia, *Chem. Ind.*, 1977, 454.

214. C.G. Rao, A.S. Radhakrishna, B.S. Singh and S.P. Bhatanger, *Synthesis*, 1983, 808.

215. Y. Yukawa, M. Sakai and S. Suzuki, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 2266.

216. J.K. Sugden, *Chem. Ind.*, 1972, 680.

217. J.W. Bird and D.G.M. Diaper, *Can. J. Chem.*, 1969, **47**, 145.

218. B.S. Furniss, A.J. Hannaford, P.W.G. Smith and A.R. Tatchell, "Vogels Textbook or Practical Organic Chemistry", 4th ed., John Wylie and Sons Inc., New York, 1989, 409.

219. A. Hassner, W.A. Wentworth and I.H. Pomerantz, *J. Org. Chem.*, 1963, **28**, 304.

220. M.O. Forster, *J. Chem. Soc.*, 1903, **83**, 535.

221. G.W. Bradley, J.H. Holloway, H.J. Koh, D.G. Morris and P.G. Watson, *J. Chem. Soc., Perkin Trans. 1*, 1992, in press.

222. D.F. Shelhammer, R.J. Conner, R.E. Richardson, V.L. Heasley and G.E. Heasley, *J. Org. Chem.*, 1984, **49**, 5015.

223. J.A. Gibson, R.K. Marat and A.F. Janzen, *Can. J. Chem.*, 1975, **53**, 3044.

224. C. Rüchardt, V. Golzke and G. Range, *Chem. Ber.*, 1981, **114**, 2767.

225. D.N. Kevill, M.J. D'Souza, R.M. Moriarty, S.M. Tuladhar, R. Penmasta and A.K. Awasthi, *J. Chem. Soc., Chem. Commun.*, 1990, 623.

226. J.A. Berry, G. Oates and J.M. Winfield, *J. Chem. Soc., Dalton Trans.*, 1974, 509.

227. J.A. Gibson and A.F. Janzen, *J. Chem. Soc., Chem. Commun.*, 1973, 739.

228. M.J. Shaw, H.H. Hyman and R. Filler, *J. Am. Chem. Soc.*, 1970, **92**, 6498.

229. D.H.R. Barton, R.E. O'Brien and S. Sternhell, *J. Chem. Soc.*, 1962, 470.

230. R.E. Neuman, *Tetrahedron Lett.*, 1964, 2541.

231. F.W. Wehrli, A.P. Marchand and S. Wehrli, "Interpretation of Carbon-13 NMR Spectra", 2nd ed., Wiley, Chichester, 1983.

232. D.G. Morris and A.G. Shepperd, *J. Chem. Soc., Chem. Commun.*, 1981, 1250.

233. T.M. Balthazar, D.E. Godar and B.R. Strults, *J. Org. Chem.*, 1979, **44**, 1447.

234. G. Oates and J.M. Winfield, *J. Chem. Soc., Dalton Trans.*, 1974, 119.

235. A. Gregorcic and M. Zupan, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1446.

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