CHIRAL SELECTION

IN

HYDROGEN ATOM TRANSFER REACTIONS

by

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A THESIS

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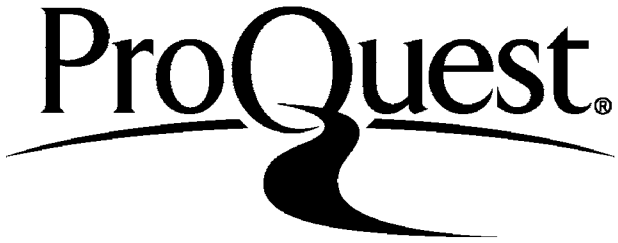

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To my family,

'The light at the end of the tunnel
is only the headlamps of the oncoming train.'

Anon.

ACKNOWLEDGEMENTS

I would like to thank Professor M.J. Perkins for his help, guidance and friendship during the course of this work. His kind and cheerful nature will be remembered. My thanks go also to Dr. A. Drake, Kings College, London, for providing facilities and assistance with the CD studies, and to Dr. L. Castle for his patient, but firm encouragement.

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ABSTRACT

This thesis describes an attempt to demonstrate enantioselectivity in free-radical hydrogen transfer reactions and was designed to test a novel extension of the Hammond Postulate.

It is proposed that the rates of two related reactions which are thermodynamically identical but kinetically distinct should differ most when the processes are thermoneutral since the transition state is remote from both reactant and product. By synthesis and subsequent oxidation of suitable chiral hydroxamic acids a series of persistent chiral acyl nitroxide radicals ArCON(R)O· has been made. By reacting such a series of nitroxide radicals with suitable chiral benzylic alcohols Ar'CHOHR it was hoped that by varying the nature of Ar', the α-CH bond strength of the alcohol would come within the compass of the O-H bond strengths of ArCON(R)OH. It was predicted that such an alcohol should show a maximum in a plot of enantioselectivity vs. O-H bond strength.

The target molecules for this work were optically active N-alkylbenzohydroxamic acids in which the alkyl substituent was both chiral and tertiary. Substitution of electron withdrawing and releasing groups, ranging from 3,5-$(NO_2)_2$ to 4-$N(Me)_2$, into the aroyl group of the hydroxamic acid and subsequent oxidation of the latter allowed the synthesis of

radicals with varying bond strengths. UV-visible, e.s.r. and CD spectra were determined for these radicals. O-H bond strengths of the hydroxamic acids were estimated using an e.s.r. technique which determined the equilibrium position for hydrogen atom transfer between the hydroxamic acid and a standard di-t-alkyl nitroxide radical which forms a bond of known strength to hydrogen. These estimated values range from 76 to 79 kcal mol^{-1}.

Enantioselectivity was searched for in two ways. The first employed UV spectroscopy to determine the second order rate constants for the four possible reaction pairs of chiral nitroxide enantiomers with benzylic alcohol enantiomers. The second method involved reaction of racemic alcohol with chiral radical and subsequent examination of enantiomeric excess by high performance liquid chromatography (HPLC); two approaches to this are described. In the majority of cases studied, however, enantioselectivity was immeasurably small. In the case of 2-methyl-1--phenylpropan-1-ol a small enantiomeric excess was observed but further work is needed to substantiate these results.

Small chiral discriminations were observed in the oxidation reactions of only one alcohol. These results were insufficient to investigate the extension of the Hammond Postulate as originally planned.

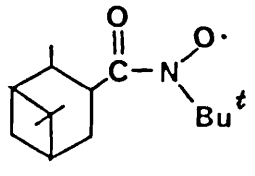
CONTENTS

CHAPTER 1

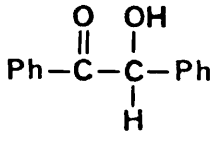
INTRODUCTION

A. Background

Berti and Perkins[1] have observed enantioselectivity using free-radical hydrogen atom transfer reactions. They have shown that the chiral nitroxide (aminyloxide) (1) will effect enantioselective oxidation of benzoin (2) leading to material enriched in one enantiomer. Thus, reaction of benzoin with approximately 1.5 molar equivalents of (1) in benzene gives benzil (3) (*ca.* 0.6 equivalents) together with unreacted benzoin (*ca.* 0.4 equivalents) which has $[\alpha]_D^{25}$ in chloroform of +14°. This corresponds to an enantiomeric excess of 7%.[2]



(1)



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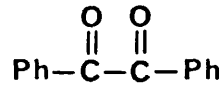


(3)

Free-radical hydrogen atom transfer has also been used by Hargis *et al*[3] to effect partial optical resolution of a hydrocarbon. In that work, two samples of 2-phenyl-2-butanol of differing optical purity were converted to the hypochlorites. Carbon tetrachloride solutions of these partially resolved hypochlorites and racemic 2-phenylbutane (10:1 molar ratio) were photolysed. The unreacted phenylbutanes

were recovered and checked for optical purity. Using 86.2% optically pure hypochlorite solution, Hargis achieved 15.4% resolution of the phenylbutane. He observed that although the degree of resolution achieved was low, there was a relatively large difference in the rate of reaction of the two enantiomers.

The work described in this thesis is the result of an analysis of factors which might influence selectivity in hydrogen atom transfer reactions of this kind, and is an extension of the work of Berti and Perkins.

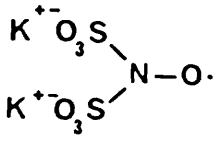
It is necessary to give first some relevant background to the Berti experiment. This introduction outlines the isolation and chemistry of members of the relatively reactive class of nitroxides in which there is an acyl group attached to nitrogen. It goes on to show how the Hammond Postulate might be modified to deal with selectivity in a class of reactions described as "equithermal"; hydrogen abstractions from enantiomeric substrates by the same chiral radical fall into this class.

B. Nitroxide Free Radicals

Organic free radicals are, by definition, compounds containing one or more unpaired electron(s) and their chemistry is almost entirely concerned with the direct involvement of those electrons. The

reactivity and hence the stability of this class of compounds depends on both the structure of the radical and the prevailing physical/chemical environment.

Radicals containing the N-O· group in which the unpaired electron is formally located on oxygen are known as nitroxides. Although the inorganic radical Fremy's salt[4] (4) has been known since 1845 it was not until 1901 that the first organic nitroxide was prepared when Piloty and Schwerin[5] isolated and characterized the heterocyclic free radical porphyrexide (5).



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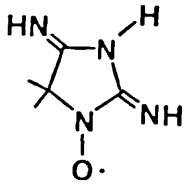
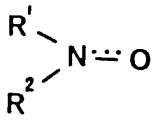


(5)

By analogy with the electronic structure of the related nitrogen oxides, the nitroxide group is sometimes represented as (6)[6,7] which emphasizes the 3π -electron arrangement. Since one of the π electrons is in an antibonding orbital the overall result is a two centered three-electron bond which can, for convenience, be shown by structure (7)



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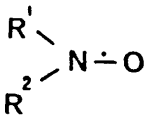
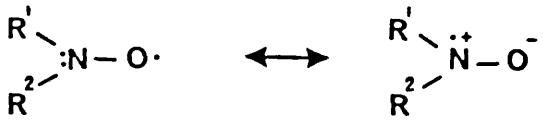


(7)

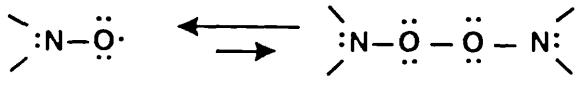
In an attempt to convey more information the nitroxide group can also be represented as a resonance hydrid receiving contributions from structures (8) and (9) below:



(8) (9)

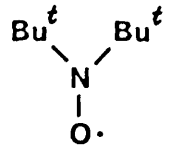
An alternative nitroxide model has been proposed by Linnett[8,9] using the double quartet hypothesis: this representation takes into account the mutual orientation of the electron spins.

Combination of two nitroxide radicals would lead to the formation of a dimer, equation 1:



Equation 1

However, nitroxides with no α-hydrogens are probably the stablest free radicals and show no tendency to dimerize or react with air. For example, di-t-butyl nitroxide **(10)** is easily obtained in the pure state by reaction of sodium with 2-methyl-2-nitropropane and is a red liquid stable[10,11] in air up to a temperature of 120°C.



(10)

For this radical the equilibrium in equation 1 lies well to the left-hand side. The stability of the free nitroxide can be explained in terms of the linear combination of the oxygen and nitrogen p_z orbitals. Combination of the two atomic p_z orbitals leads to a gain in energy resulting from delocalization of the three π electrons within the two molecular π-orbitals (Fig. 1).

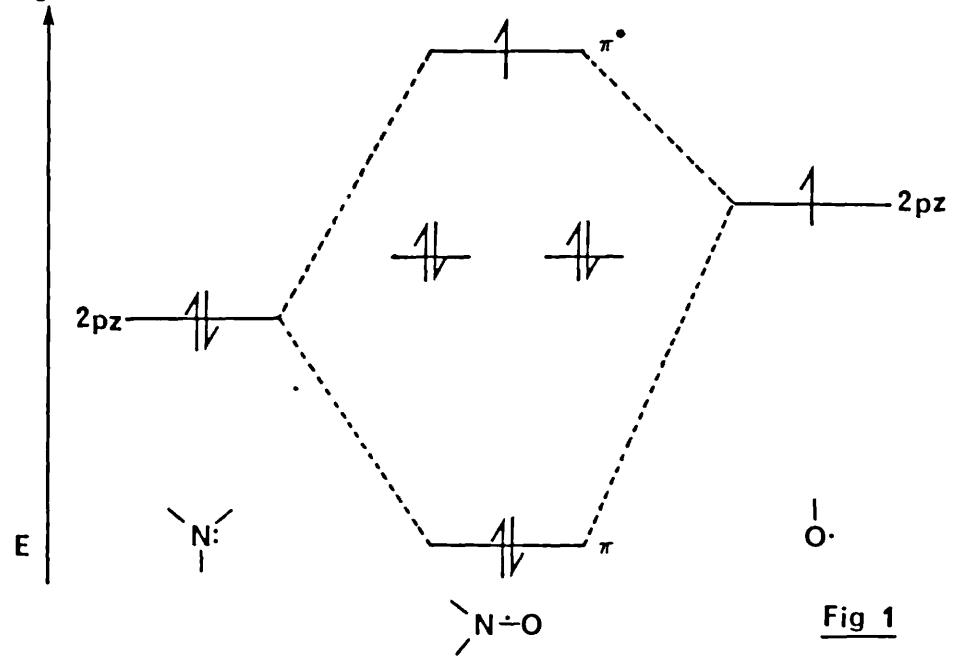
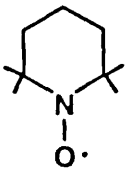


Fig 1

Two of the π electrons occupy the low lying bonding orbital, the third one is in the higher energy π^*-antibonding orbital, thus yielding the net π bonding of one electron depicted in **(7)**. The N-O bond order predicted for such a $\sigma^2\pi^2\pi^{*1}$ electronic configuration would then be 1.5 (*ie.* 1 + 1 - 0.5). In

2,2,6,6-tetramethylpiperidine-N-oxyl (11) the delocalization energy is of the order of 30 kcal/mol[12]



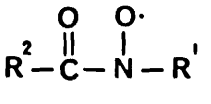
(11)

The formation of the dimer (i.e. creation of a new O-O bond) would achieve a gain in energy of 35 kcal/mole. This gain in energy cannot compensate for the loss of delocalization energy of the two nitroxide molecules. In short, the net π bonding of one electron will be lost. Such a high delocalization energy (30 kcal/mol) of the unpaired electron correlates with the mean thermochemical values of the energy of the N-O bond and is one of the reasons for the high stability of the free nitroxides.

Several reviews on the organic chemistry of nitroxide radicals have been compiled.[13,14,15]

C. Acyl Nitroxides

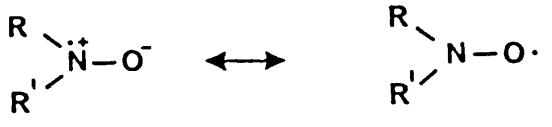
Nitroxides of the general formula (12) where there is an acyl group attached to nitroxide nitrogen are known as acyl nitroxides. The acyl group influences the structure, the reactivity and the pattern of reactions of these radicals.



(12)

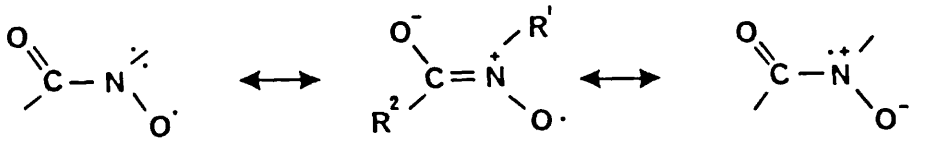
(i) Structure.

Dialkyl nitroxides are considered to have about 50% of the spin density on oxygen (13)



(13)

Acyl nitroxides exhibit a higher spin density at oxygen[16] and the estimated O-H bond strengths of the corresponding hydroxamic acids RCON(OH)R' are generally stronger than those in simple hydroxylamines. These observations lead to the conclusion that the principal effect of the acyl group is to delocalize the nitrogen lone pair. Perkins[17] and others before[16] have argued that lone pair delocalization from nitroxide nitrogen would tend to 'fix' the unpaired electron on oxygen producing a hybrid structure **(14)** with the radical centre 'destabilized' relative to the dialkyl nitroxides.



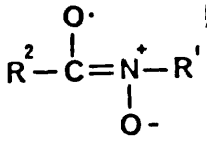
(14)

Supportive evidence for the concentration of spin density on nitroxide oxygen in acyl nitroxides is found in e.s.r. spectroscopy. The redistribution of

spin density within the N-O π system changes the nuclear hyperfine splitting constants, (a_N and a_O). The nitrogen hyperfine coupling constant (a_N) gives a useful guide to the degree of spin density at nitrogen, thus, the greater the spin density the greater the a_N value. The a_N values for dialkyl nitroxides are much larger (*ca.* 15 Gauss) than those of acyl nitroxides (*ca.* 7-8 Gauss) showing the lower spin density at nitrogen in the latter.

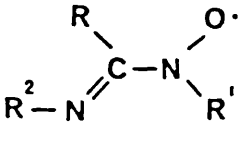
σ-π interaction parameters for ^{14}N and ^{17}O can be obtained by correlation of the isotropic hyperfine splitting, (hfs) and the electron-nuclear dipolar splitting (Ti, i = ^{14}N, ^{17}O) as determined from combined measurements of isotropic and anisotropic hfs.[18] Thus correlating a_N and a_O as directly proportional to ρ_N and ρ_O (the π electron spin densities on N and O), Aurich[16,19] found a very good correlation betwen a_N and a_O. In several respects this is an oversimplified picture of the acyl nitroxide structure. For $RCON(Bu^t)O\cdot$ where R = CH_3 a_N = 7.75 Gauss: a_O nitroxide = 20.3 Gauss) Jenkins *et al*[20] have shown that approximately 19% of the electron density must reside in the carbonyl group. Jenkins generated the carbonyl ^{17}O-labelled benzoyl *t*-butyl nitroxide R = Ph and found a_O = 4.49 (PhH, 293K). This corresponds to a ρ_O carbonyl of *ca.* 12%, and leads to the conclusion that there is a small but

appreciable contribution from (15)



(15)

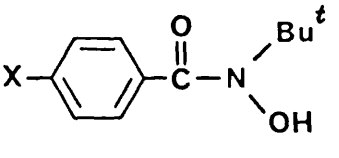
The interpretation of a_O (carbonyl) is complicated by the results of INDO calculations which suggest that ρ_O (carbonyl) maybe offset by a negative spin density on carbon and therefore ρ_O (carbonyl) might be even greater than 19%. The INDO calculations were made on coplanar HCONHO· with the oxygen atoms <u>anti</u> related[21]; similar spin polarization effects have been inferred from experimental hyperfine splitting found in α-iminioalkyl nitroxides (16)[16];



e.g $R' = Bu^t$

(16)

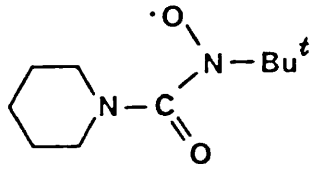
Nevertheless, the role of the lone pair delocalization seems to be supported by an excellent correlation between the O-H bond strengths of 17(a→d) and Brown's σ^+ constants.[22]



a: X= Ph
b: X= H
c: X= NO_2
d: X= OMe

(17)

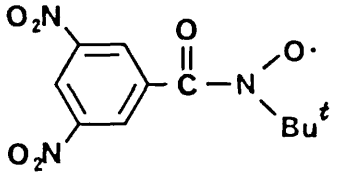
Although a_N for these nitroxides does not change very markedly with substituent there is a good correlation (0.99) between a_N and σ^+ over the range p-NO_2 - p-$N(Me)_2$ including eight p-substituted aroyl nitroxides.[17] The inference is that conjugation across the benzene ring competes with nitrogen lone pair delocalization. This effect is seen more dramatically in the tert-butyl dialkylaminocarbonyl nitroxide **(18)** for which an a_N value of ca. 12 Gauss accords with a nitroxide moiety intermediate between acyl and alkyl.



(18)

(ii) Geometry

Crystallographic studies on three acyl nitroxides (18), (19) and (20) have afforded a valuable insight into the structure of these acyl nitroxides.[23]



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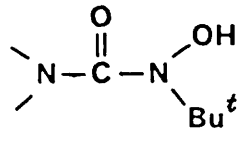

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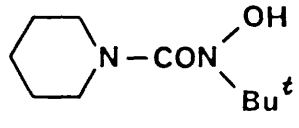
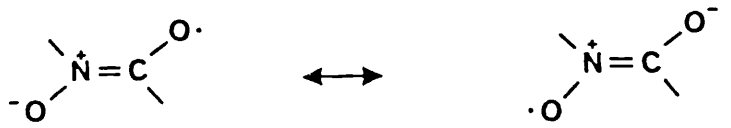


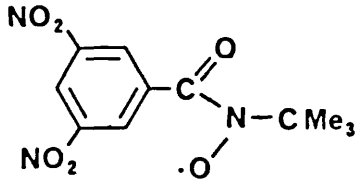
(18)

In the dinitrobenzoyl nitroxide crystal **(19)** the carbon and nitrogen centres are both essentially planar and there is a dihedral angle between these two planes of about 14°. The oxygen atoms are 'anti' related[24] **(21)** and the N-O bond lengths lie within the range found for other nitroxides.[25] The length of the carbonyl-N-bond is intermediate between that of a C-N single bond and a C-N amide bond, consistent with appreciable double-bond character required by contribution from structures (14) and (15), that is,



(15) (14)

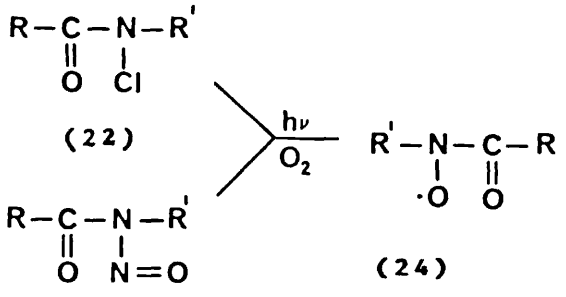
there is marked delocalization in the CON(O·)- system of **(21)**. In the case of the structure of the piperidinocarbonyl nitroxide **(18)** the carbonyl nitroxide bond length is much greater than for the dinitrobenzoyl nitroxide: the dihedral angle between the C and N centres is 56°, and whilst the piperidinocarbonyl amide unit is essentially planar, the nitroxide nitrogen is perceptibly bent (the N-O bond is ca. 12° out of the CNC plane). There is less delocalization in (18) compared to (19) because of competing interaction of the carbonyl group with the piperidine nitrogen.



(21)

(iii) Synthesis

Since the early observations by Aurich et al many different methods have been found to generate acyl nitroxides detected by e.s.r. spectroscopy. For example, low temperature photolyses of N-chloro- (22)[27] and N-nitroso-N-alkylamides (23)[28] gave the corresponding acyl nitroxide (24).

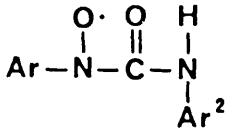


(22)

(23)

(24)

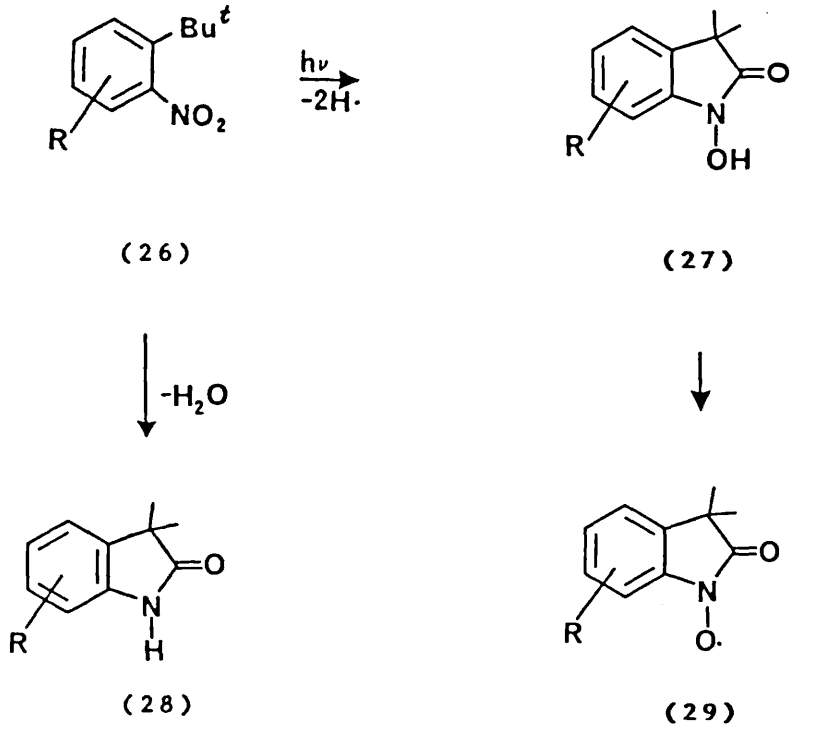
A number of acyl nitroxides (25) with differently substituted aryl groups were obtained upon oxidation of N-N'-diaryl-N-hydroxy urea[29]



(25)

Cyclic acyl nitroxides have also been reported by several groups.[24,30,31] Thus O-nitro-t-butylbenzenes (26) upon photolysis gave 1-hydroxy-3,3-dimethylindan-

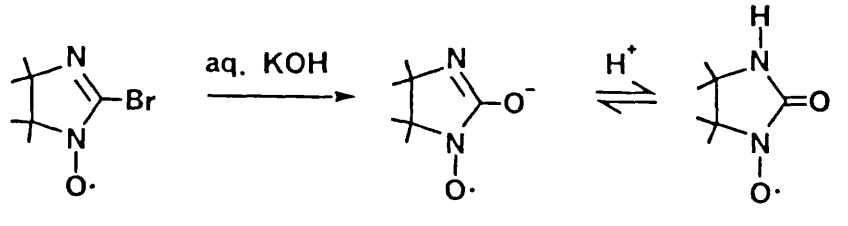
-2-ones **(27)** along with other products such as **(28)**. The cyclic hydroxamic acid **(27)** can be easily oxidised to highly persistent cyclic acyl nitroxides **(29)** with $Pb(OAC)_4$ or PbO_2:



(26) **(27)**

(28) **(29)**

Ullman's group[32] report the formation of an unisolated cyclic carbamoyl nitroxide upon hydrolysis of 2-bromo-4,4,5,5-tetramethyl-imidazolin-1-oxyl **(30)** with aqueous KOH:



(30)

All these experiments have generally been conducted in the e.s.r. cavity. Although there nitroxides have

been unambiguously observed by e.s.r. and low values for their nitrogen hyperfine coupling constants noted,[24] it was not until 1973 that Perkins and Ward isolated several t-alkyl acyl nitroxides.[33] The required starting material for the preparation of these radicals was the tertiary alkylhydroxylamine t-butylhydroxylamine **(31)**

(31)

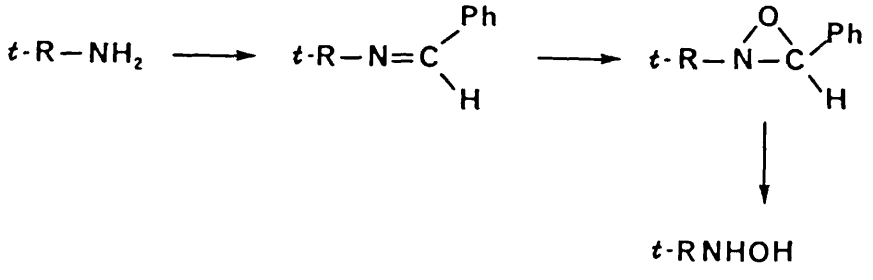
$$Bu^{t}-NHOH$$

Scheme's 1 and 2 show the general methods available for the synthesis of t-alkylhydroxylamines.

Scheme 1

$$t\text{-}R-NH_2 \longrightarrow t\text{-}R-NO_2 \longrightarrow t\text{-}RNHOH$$

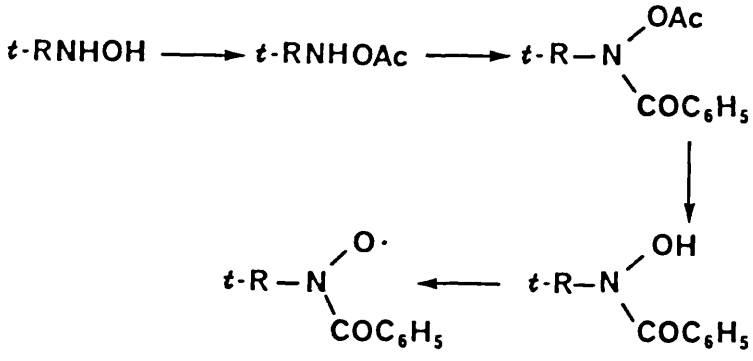
Scheme 2



t-Butylhydroxylamine on acylation gives a mixture of N and O mono-acyl derivatives, the proportions of which depend on the acylation procedure adopted. The predominant product, however, is always the O-acyl

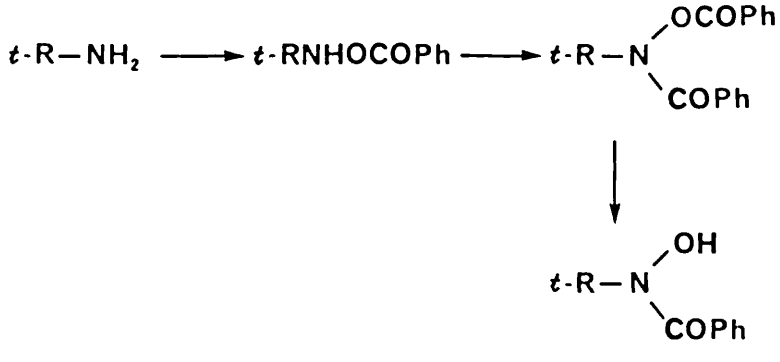
derivative. Use of acetic anhydride gives almost exclusive formation of O-acetyl-N-t-butylhydroxylamine which can be further acylated on nitrogen. The acetyl group may then be removed by hydrolysis to give N-t-butylhydroxamic acids in good yields, scheme 3:

Scheme 3



In 1963 Zinner[34] had proposed an alternative route to the hydroxamic acids which was later modified by Alewood.[35] In this case t-butylamine is converted directly to O-protected hydroxylamine, scheme 4:

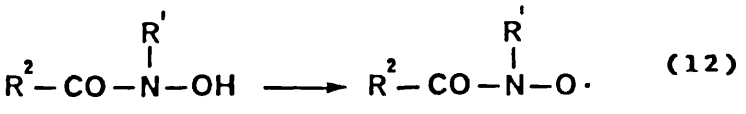
Scheme 4



Further discussion of these syntheses can be found in chapter (2).

(iv) Reactions

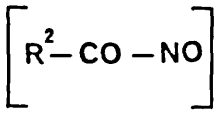
Acyl nitroxides were first detected[36] in an e.s.r. study of the fast flow oxidation of primary hydroxamic acids and N-hydroxycarbamates in aqueous media using one-electron oxidants.



(12)

The nature of the alkyl group R^1 dictates the persistance of acyl nitroxides.

When R^1 is hydrogen, oxidative cleavage of the hydroxamic acid leads to a transient nitroso-carbonyl compound (32) which can act as an acylating agent.[37]

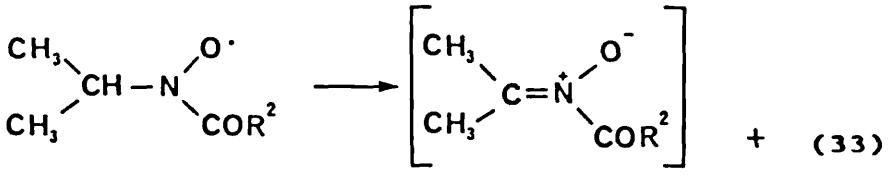


(32)

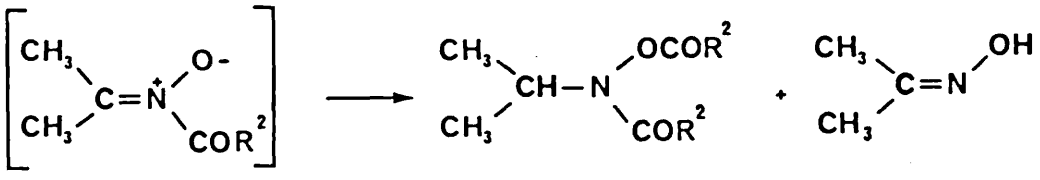
However, when R^1 is a primary or secondary alkyl group, for example, isopropyl, the alkyl acyl nitroxide **(34)** formed by one electron oxidation of the N-alkylhydroxamic acid **(33)** may disproportionate to give (35), an N-acyl nitrone.

The acyl nitrone **(35)** is highly susceptible to nucleophilic attack, and quickly reacts with **(33)** to give new products (36) and (37):

(33) (34)

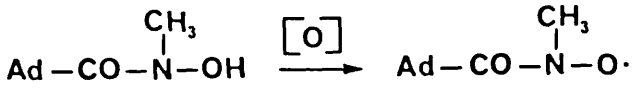


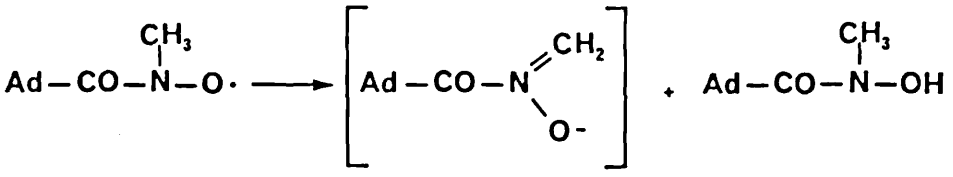
(34) (35)



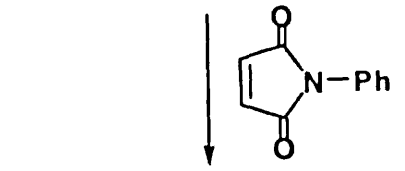
(35) (36) (37)

Hussain et al have shown that by structural modification of **(35)** it is possible to 'trap' the acyl nitrone.[38] Nucleophilic attack at carbonyl carbon can be hindered by a bulky tertiary alkyl group (R^2 = 1-Ad) and the reactivity of the 1,3-dipole enhanced by the removal of the methyl substituents (CH_3 = H). Thus, reaction of the acyl nitrone (38) with N-phenylmaleimide (39) gave the cycloaddition product (40) in 70% yield.

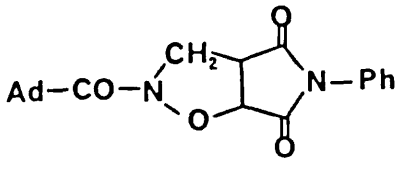




(38)

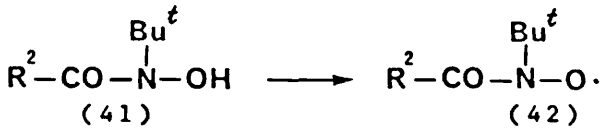


(39)



(40)

If R^1 in structure (12) is tertiary alkyl, that is, there are no α hydrogen atoms, then the acyl nitroxides are normally easily isolated. Perkins's group has investigated extensively the structure and chemistry of the radicals **(42)** produced by oxidation of N-tert-butylhydroxamic acids (41)



(41) (42)

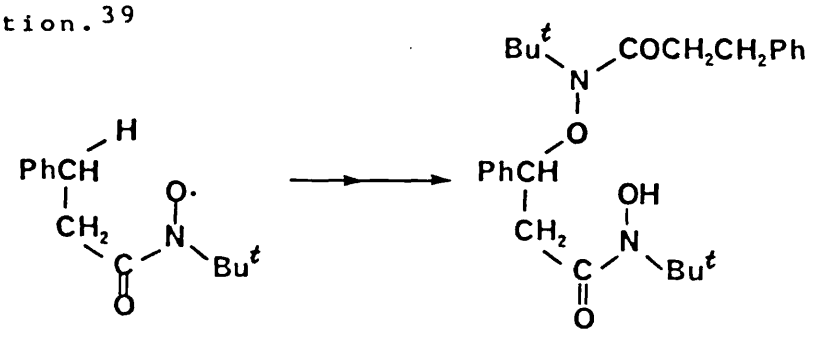
(42) R^2 = 3,5-dinitrophenyl; green solid

(42) R^2 = n-undecyl; blue oil

(42) R^2 = N-piperidinyl; red solid.

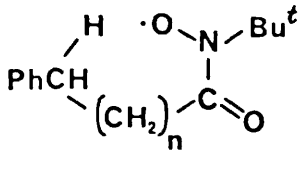
In the present work is was necessary to synthesize relatively reactive, isolable acyl nitroxides which could be handled with ease and in which disproportionation could not occur. The ideal system was therefore a tertiary alkyl acyl nitroxide.

Because of their ease of formation coupled with high reactivity the t-alkyl acyl nitroxides have already proved useful modes for investigating aspects of radical reactivity. For example, intramolecular hydrogen abstraction experiments involving acyl nitroxides have received much attention by Perkins's group.[38a] The hydrocinnamyl nitroxide **(43)** decays rapidly to give **(44)** by an initial intramolecular reaction.[39]



(43) **(44)**

Results obtained by Berti and Perkins[40] have shown that intramolecular benzylic hydrogen transfer to oxygen in a series of ω-phenyl-alkanoyl-t-butyl nitroxides **(45)** where n = 1→ 5, occurs most readily when n = 3 or 4.



n = 1→5

(45a)n = 3

(45b)n = 1

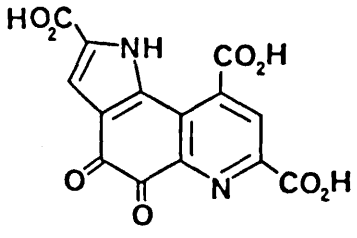
(45)

Indeed in **(45a)** where n = 3 the intramolecular hydrogen abstraction occurs faster than in **(45b)** where

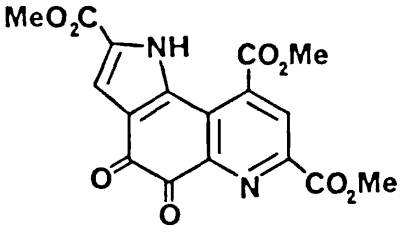
n = 1. This has been explained in terms of the relatively planar carbonyl nitroxide "template". The hydrogen is transferred to a p-orbital lobe on nitroxide oxygen in a direction roughly perpendicular to the plane of the -CON(O·)- unit. Molecular models show that such a relatively rigid π-electron system is easily spanned by the four methylene chain in (45a) but much less readily by the two methylene unit in (45b).

The strength of the O-H bond in the N-tertiary alkyl acyl hydroxamic acids is such that the nitroxides formed from them can be used in a variety of intermolecular free-radical hydrogen atom transfer reactions. With dialkyl nitroxides such reactions are observed only with particularly reactive substrates or following photoexcitation. Studies have shown that acyl nitroxides can be used to selectively oxidise benzylic and allylic alcohols to aldehydes and ketones; for example, hydrobenzoin can be cleanly oxidised to benzil: apparently unaccompanied by the usual cleavage of this molecule to benzoic acid. With the exception of Fremy's salt the use of stable radicals as reagents in preparative organic chemistry has found relatively few applications. However, recently MacKenzie et al have utilized benzoyl t-butyl nitroxide to effect oxidation of a monohydric phenol to a quinone.[41]

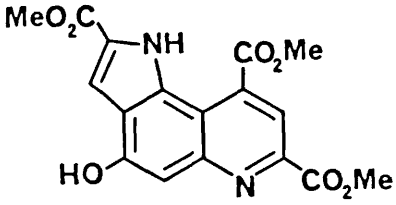
In total synthesis of the co-enzyme methoxation (46) the penultimate step involves oxidation of the phenol **(47)** to the quinone **(48)**.



(46)



(48)



(47)

Initial attempts to oxidize the phenol with Fremy's salt were unsatisfactory owing to the heterogeneous nature of the reaction mixture. However, using benzoyl t-butyl nitroxide in dichloromethane-methanol (9:1) the phenol **(47)** was efficiently oxidized to the orange quinone **(48)** in 93% yield.

D. Enantioselectivity and the Hammond Postulate

Berti and Perkins[1] have already demonstrated selective oxidation of racemic benzoin which led to material enriched in one enantiomer (section 1A). In an extension of this work we proposed to synthesize a series of closely related chiral tertiary alkyl acyl nitroxides which could be used to find maximum enantioselectivity in free-radical hydrogen atom transfer reactions. Berti and Perkins used compounds of the type $R-CO-N(O\cdot)(Bu^t)$ with chirality in the acyl group to show enantioselectivity. In the present work it was planned to incorporate chirality in the

tertiary alkyl group to allow a greater range of compounds to be synthesized.

It has been observed experimentally that the recombination reactions of atoms and free radicals do not involve activation energies of more than a few kilojoules[42] and that in solution rates of such reactions are frequently diffusion controlled.[43] By employing the principle of microscopic reversibility, the assumption that little excess activation energy is involved in such radical-radical associations constitutes the basis of the kinetic method for the determination of bond dissociation energies. On the basis of earlier work it seemed possible that the strength of the O–H bonds formed by members of a series of closely related hydrogen abstracting radicals XYNO·, where Y is an aroyl group, can be altered by at least 5 kcals mol^{-1} by structural variation in Y remote from the radical centre.[17]

The intention was to examine enantioselectivity in a series of reactions of the type:

$$\overset{*}{X}YNO\cdot + ArRCHOH \longrightarrow X^{*}YNOH + ArR\dot{C}OH$$

(49) **(50)**

where X is chiral and Y is one of a series of aroyl groups. The process is effectively irreversible since radical **(50)** once formed would be immediately scavenged by excess **(49)** to form ketone.

$$XYNO\cdot + ArR\dot{C}OH \longrightarrow XYNOH + ArRCO$$

The enantioselectivity could be established by quenching the reaction at varying degrees of conversion and examining the optical rotation of the recovered alcohol.

Attack of a chiral tertiary alkyl acyl nitroxide on a racemic benzylic alcohol leads to two diastereomeric transition states, which can differ in energy. This difference in energy means that one enantiomer could react faster than the other. This is the basis of kinetic enantioselectivity. Simplistically, the basis of this work was our proposal that <u>enantioselectivity should be greatest when the two diastereoisomeric transition states are remote from both reactants and products.</u> This is a novel extention of the Hammond Postulate.[44]

The Hammond Postulate states that for any single step of a reaction the geometry of the transition state for that step resembles more closely the side, reactants or products, to which it is closer in free energy. So, for a one step endothermic process leading to unstable intermediates (Fig. 2a) the activated complex will have a structure and geometry very similar to the product, that is, a "product-like" transition state.

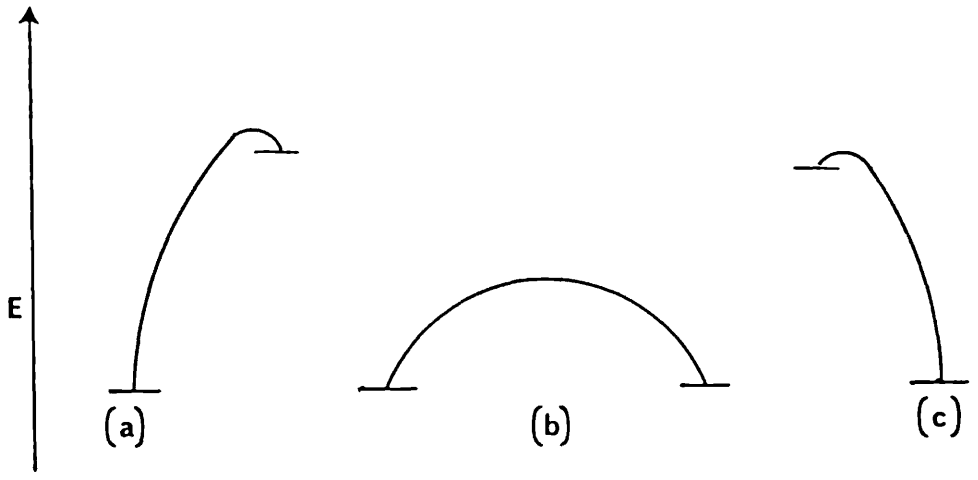


Fig 2

Fig. 2c shows the potential energy diagram for an exothermic reaction in which the transition state is "reactant-like". A thermoneutral reaction is one in which the reactants and products have the same energy (Fig. 2b).

It is proposed that the rates of two closely related reactions which are thermodynamically indistinguishable but kinetically distict should differ most when the processes are thermoneutral.

Fig 3a shows that for two closely related endothermic reactions $\Delta\Delta G^{\ddagger}$ will be quite large, whereas for a pair of exothermic reactions kinetic discrimination will be much smaller (Fig. 3b).

Typical examples would be hydrogen abstraction by Br. (endothermic) and Cl. (exothermic) from, for example, Me_3CH.

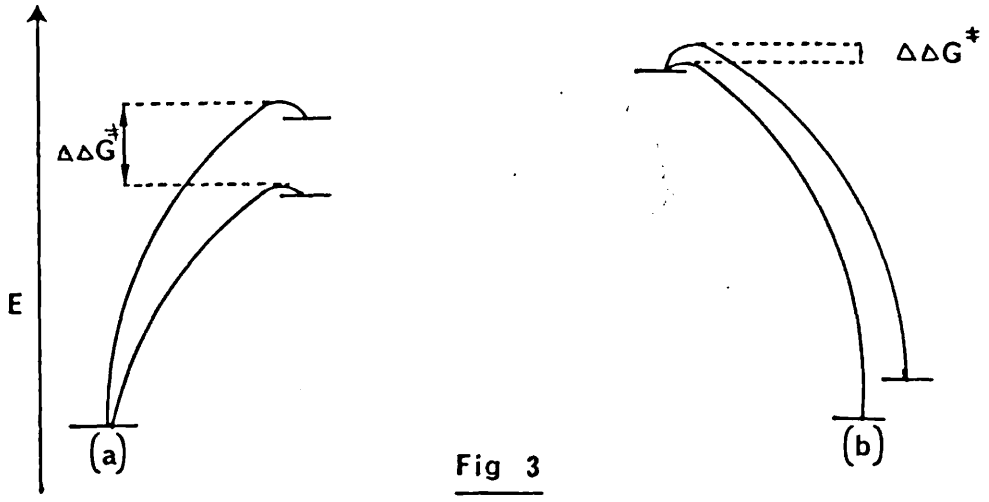


Fig 3

We define a pair of "equithermal" reactions in which on the one hand the reactants, and on the other the products, are thermodynamically indistinguishable but in which the activation barriers may differ. For example, Fig. 4a shows a pair of endothermic equithermal reactions.

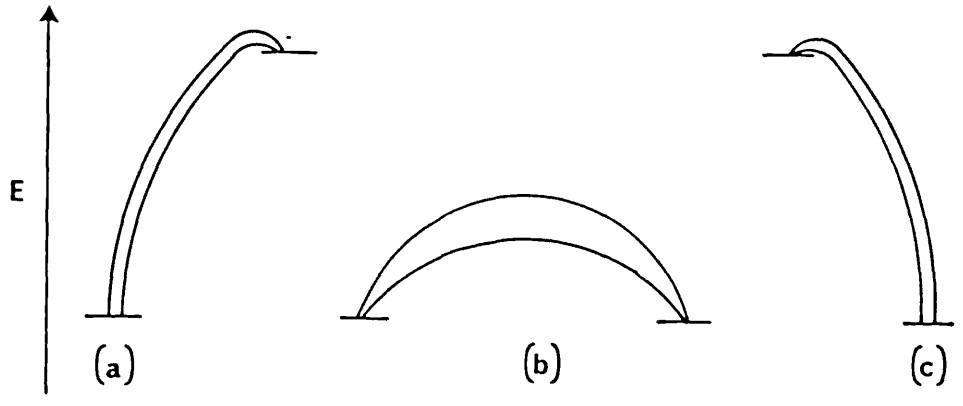


Fig 4

In equithermal reactions application of the Hammond Postulate to the two competing pathways leads to the conclusion that there is likely to be greater kinetic discrimination in the thermoneutral case (4b) than in either the exothermic (early transition state, Fig. 4c) or endothermic (late transition state, Fig 4a) alternatives, since differentiation will be greatest when the transition state is remote from both reactants and products.

To test this experimentally it was necessary to synthesize a series of closely related chiral acyl nitroxide radicals (XYNO•) whose precursors (XYNOH) had differing O-H bond strengths. These radicals once synthesized would be reacted with suitable secondary benzylic alcohols (ArRCHOH) for which by varying Ar one should be found in which D(αCH) should come within the compass of the O-H bond strengths of XYNOH. The initial aim of the project was to find an alcohol for which we could demonstrate the occurrence of a maximum in a plot of enantioselectivity vs. OH bond strengths of the hydroxamic acids XYNOH, although as our work progressed it was appreciated that other simpler tests of this new hypothesis would be equally valid.

CHAPTER 2

SYNTHESIS OF CHIRAL ACYL NITROXIDES

The target molecules for this work were of the type XYNO· where Y is acyl and X is chiral. To prevent disproportionation of the radical, X should also be tertiary alkyl. Substitution of electron withdrawing and donating groups into the acyl function Y, [$XN(O\cdot)COC_6H_3(NO_2)_2 \longrightarrow XN(O\cdot)COC_6H_4N(Me)_2$], allowed the synthesis of a series of closely related compounds of varying reactivity. For example, introduction of a 3,5-dinitro benzoyl group led to a hydroxamic acid with a strong NO-H bond. A high bond dissociation energy is indicative of a strong tendency for hydrogen abstraction by the nitroxide, that is, it has increased reactivity relative to the unsubstituted derivative $XN(O\cdot)COC_6H_5$.

The synthetic approach adopted in this work can be divided into two distinct sections.

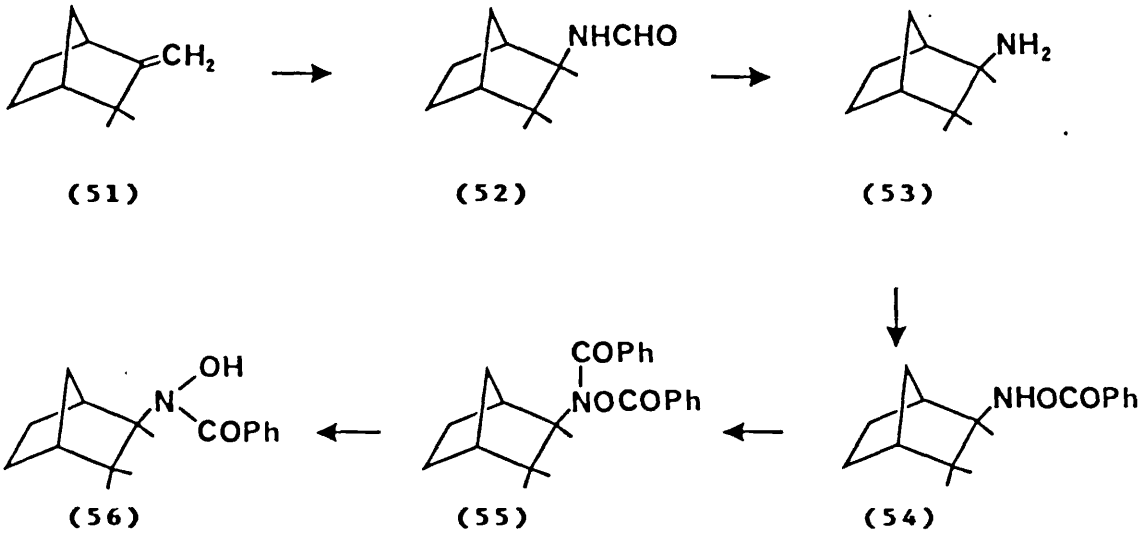
A) Preparation of a chiral tertiary alkyl primary amine X^*-NH_2

B) Conversion of X^*-NH_2 to the hydroxamic acid X^*YNOH.

A) PREPARATION OF X^*-NH_2

Some preliminary work on this synthesis had been carried out by Turner.[45] Using natures chirality he had attempted to synthesize N-(3-isocamphyl) benzohydroxamic acid **(56)** from naturally occurring

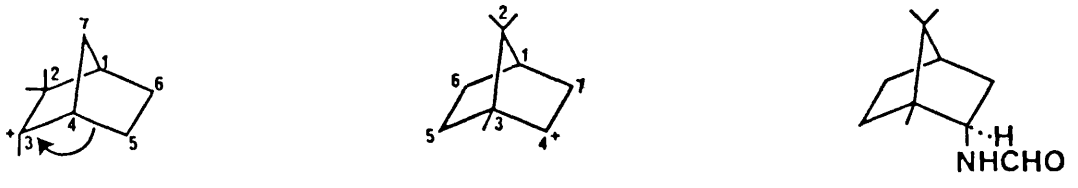
optically active camphene **(51)**, and his experiments have been repeated in this present work.



(51) **(52)** **(53)**

(56) **(55)** **(54)**

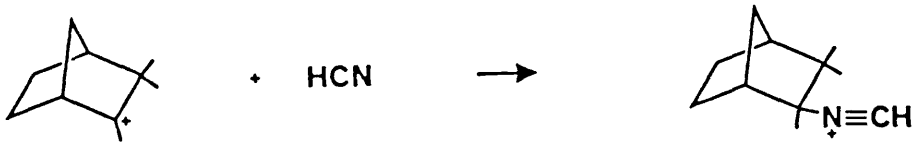
Conversion of **(51)** to **(52)** was achieved using the Ritter reaction.[46] Conflicting results have been reported on the products formed when camphene is subjected to Ritter conditions. Ritter and Minieri isolated the N-acylisobornylamines, a result of the Wagner rearrangement, when employing hydrogen cyanide or simple nitriles:[47]



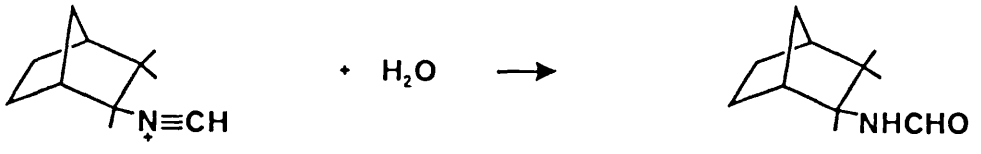
Other investigators also obtained N-acylisobornyl--amines from simple nitriles but found that hydrogen cyanide gave the unrearranged norcamphane derivative.[48] Stone *et al* showed that by treating racemic camphene with hydrogen cyanide at 0-3°C the

formation of the isobornyl derivative can be reduced to a minimum.[49] Using Stone's conditions, reaction of camphene with sodium cyanide gave 3-formamidoisocamphane **(52)** in 67% yield.

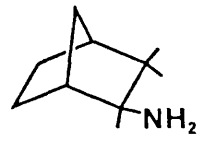
The Ritter reaction using hydrogen cyanide as the nitrile source involves protonation of the alkene by sulphuric acid to form a stable carbonium ion followed by nucleophilic addition of HCN:



Subsequent dilution with water yields the amide **(52)** which can be readily hydrolysed to give 3-aminoisocamphane **(53)**.



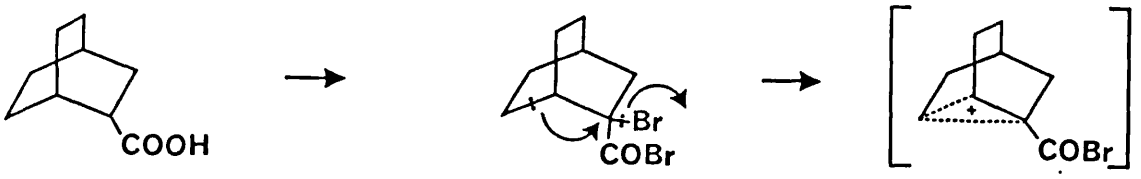
(52)



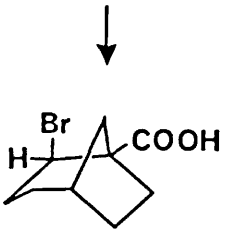
(53)

When the reaction was carried out using (-)-camphene racemization took place (for example, by methyl migration). The synthetic route to the required hydroxamic acid **(56)** was quite short, and so despite

the fact that optical activity had been lost, attempts were made to isolate the racemic product. Benzoyloxylation of the amine (53) with dibenzoyl peroxide gave O-benzoyl-N-(3-isocamphyl)--hydroxylamine (54). Introduction of the benzoyl group using benzoyl chloride and pyridine to give (55) proved impossible. Presumably steric hindrance prevents the entry of the relatively large benzoyl group. As a result of the difficulties encountered in Turner's synthesis, work began on preparing a tertiary alkyl amine, R^3-NH_2, from less hindered synthetic precursors which were racemic. It was assumed that at a suitable point in the synthesis optically active material could be obtained by resolution of the racemic mixture. The key synthetic target was bicyclo[3.2.1]octylamine **(60)** with the amine substituent on a bridgehead carbon. This was obtained *via* rearrangement of the readily available bicyclo[2.2.2]octane-2-carboxylic acid.[50] When bicyclo[2.2.2]octane-2-carboxylic acid (57) was subjected to Hell-Volhard-Zelinsky conditions[51,52] brominative rearrangement of the [2.2.2] acid gave 2-bromobicyclo[3.2.1]octane-1-carboxylic acid (58) in 65% yield. The rearrangement of (57) to (58) may be interpreted as 'Wagner-Meerwein' type involving the stereospecificity associated with a 'non-classical' carbonium ion or bridged transition state.

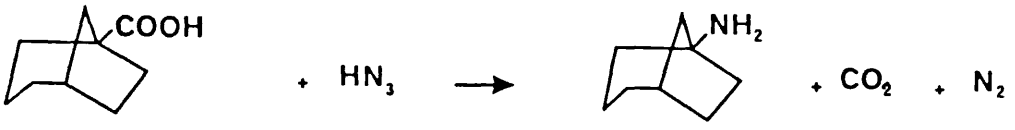


(57)



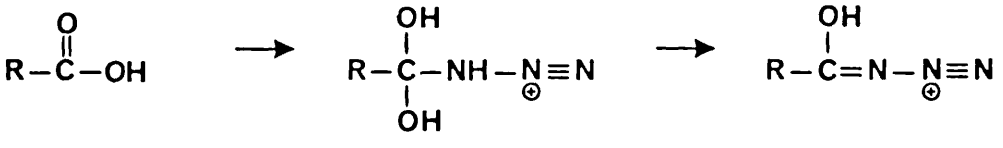
(58)

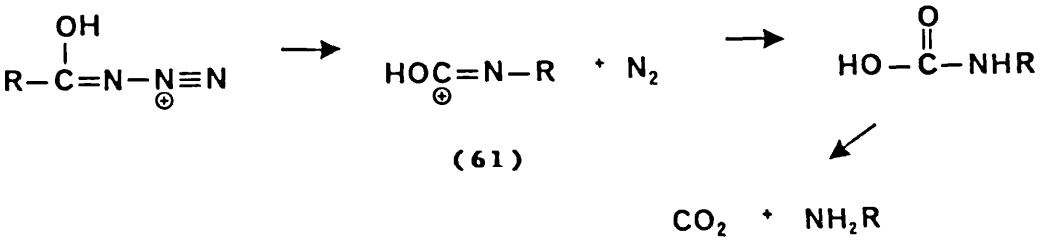
Hydrogenolysis of (58) with Pd/C under basic conditions[52,53] gave bicyclo[3.2.1]octane-1-carboxylic acid (59) in 88% yield. (59) was converted by the Schmidt reaction[54,55] to 1-bicyclo[3.2.1]octylamine (60).



(59) (60)

The Schmidt reaction is acid catalysed. The most common catalyst is sulphuric acid but Lewis acids have also been used. The reaction involves addition of HN_3 to the carbonyl group followed by dehydration:

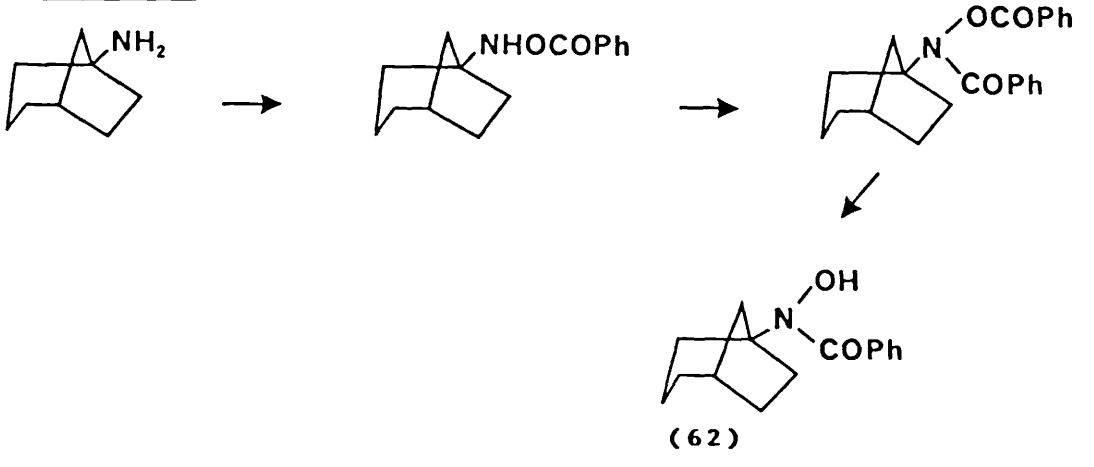




(61)

Although mechanisms can be formulated that do not involve dehydration and subsequent formation of the intermediate **(61)** there is strong evidence that these steps take place.[56] The intramolecularity of the migration step in the Schmidt rearrangements has been convincingly demonstrated by showing the retention of chirality of the migrating group.[57] To obtain optically active bicyclo[3.2.1]octylamine, optical resolution had to be carried out at a suitable point in the synthesis. However, before resolution was attempted, to ensure that the required product N-(1-bicyclo[3.2.1]octyl)benzohydroxamic acid (62) could be made, the complete synthesis according to scheme 5 (see section 2B) was carried through with racemic material.

Scheme 5.

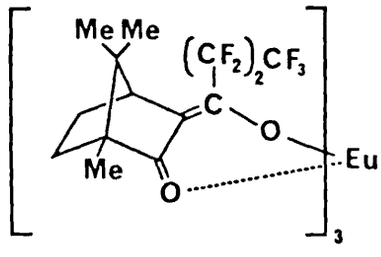


(62)

Bicyclo[2.2.2]octane-2-carboxylic acid was the stage at which resolution was first attempted because the yields of the five stages leading to the acid were all above 80% and so plenty of material was available.

The resolving agent, after unsuccessful attempts with brucine, strychnine and methylbenzylamine, was quinine. The solvent used was acetone. The specific rotation of the optically active quinine salt of bicyclo[2.2.2]octane-2-carboxylic acid was found to be low, the free acid having a rotation of $+5^{o}$ in $CHCl_3$. 2-Bromobicyclo[3.2.1]octane-1-carboxylic acid was then used in the hope that the large bromine atom would enhance the asymmetric nature of the molecule and therefore increase the rotation. Resolution of 98% was achieved, the free acid having $[\alpha]_D^{25} = +41^{o}$ in $CHCl_3$ (c = 0.1).

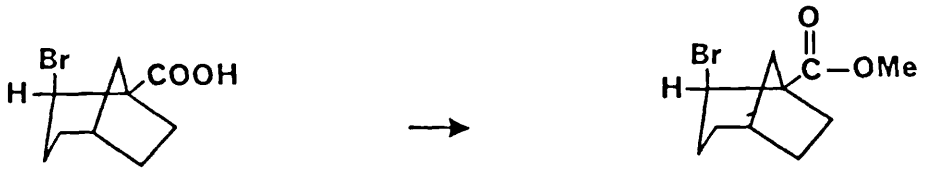
The percentage resolution was determined by ^{1}H-NMR spectroscopy using the lanthanide shift reagent europium (D-3-heptafluorobutyrylcamphorate)$_3$ (63).



(63)

The function of the lanthanide shift reagent, a hexacoordinate complex (which is a Lewis acid) is to complex with a lone pair (Lewis base) of the compound to be studied. The method cannot therefore be applied to saturated hydrocarbons. It works best with carbonyl compounds, alcohols and amines. To allow facile observation of the shift obtained, the resolved

bromoacid was converted to the methyl ester **(64)** using diazomethane. The methyl group showed as a strong singlet in the ^{1}H-NMR spectrum at 3.7ppm. Fig. 5a shows the ^{1}H-NMR 90Mz spectrum of **(64)**. Equimolar solutions of the methyl ester and Eu(hfbc)$_3$ were made in deuteriochloroform. Portions of the lanthanide shift reagent were added to the methyl ester and successive spectra recorded.



(64)

Fig. 5b shows the spectra of partially resolved (-)-methyl 2-bromobicyclo[3.2.1]octanecarboxylate in the presence of Eu(hfbc)$_3$. This clearly demonstrates the downfield shifts, the magnitude of which reflect the distance of each type of proton from the donor lone pair. Each downfield shift increases with the addition of more Eu(hfbc)$_3$ reaching a limit which is termed the bound shift. Fig. 6 shows the expanded (sweep range 100Mz) 90-MHz ^{1}H-NMR spectrum of the methyl proton absorptions of a 0.1M solution of (+)-**(64)** in $CDCl_3$ containing 1 equivalent of Eu(hfbc)$_3$. This figure shows that the (+)-bromoacid **(58)** has been successfully resolved to at least 98%.

Whitesides has proposed the recognition of two mechanisms by which the resolution of signals for the

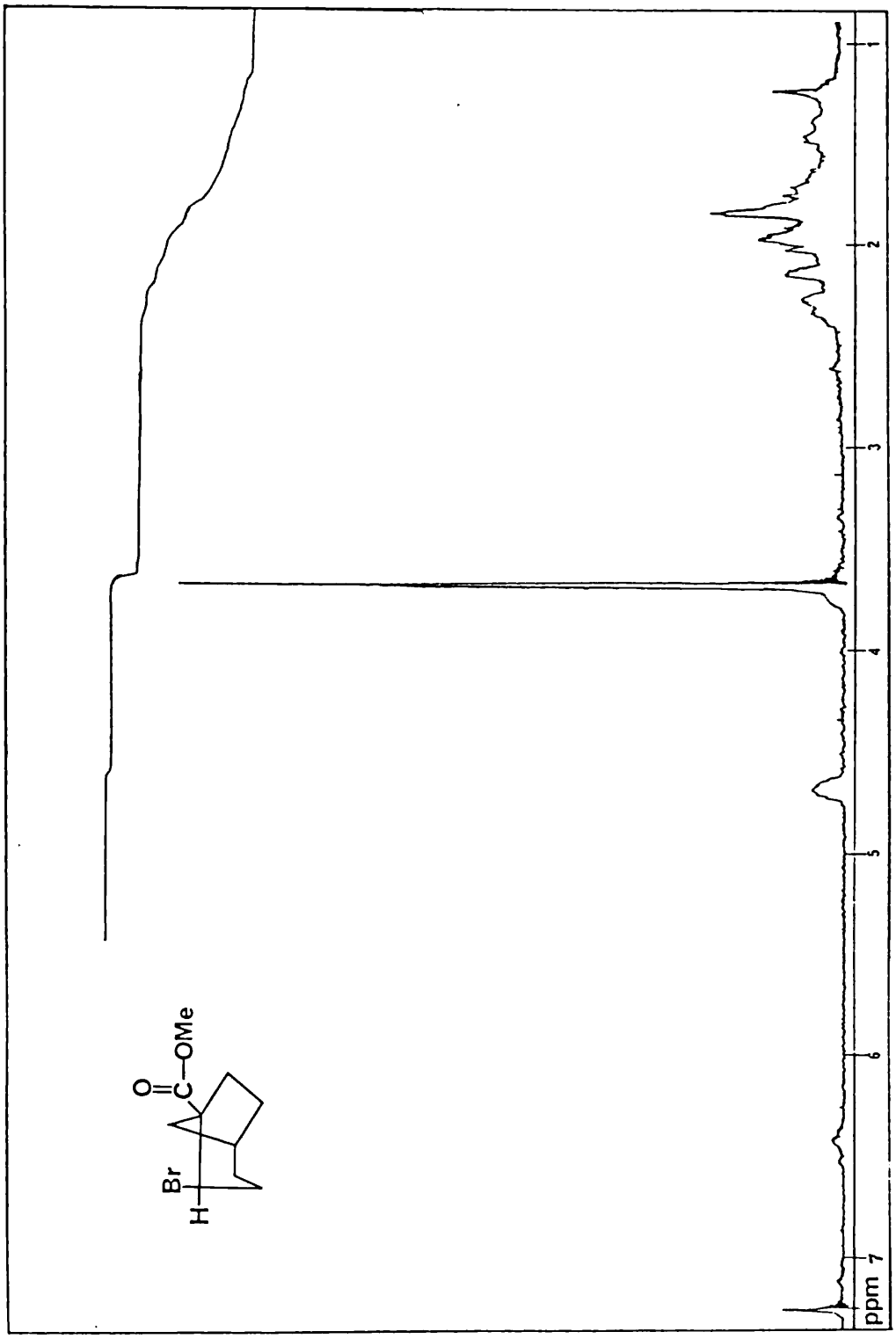


FIG. 5a

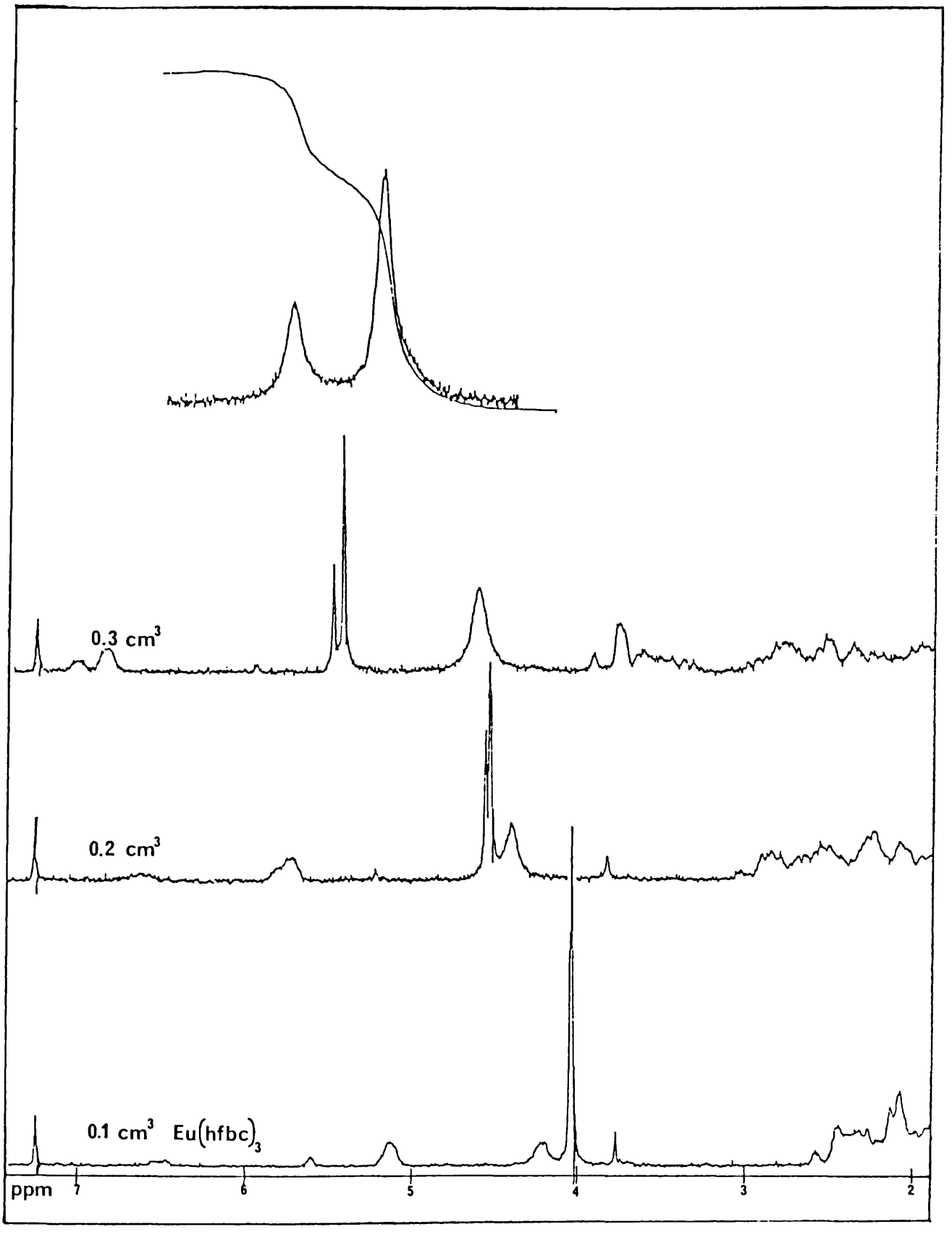


FIG. 5b

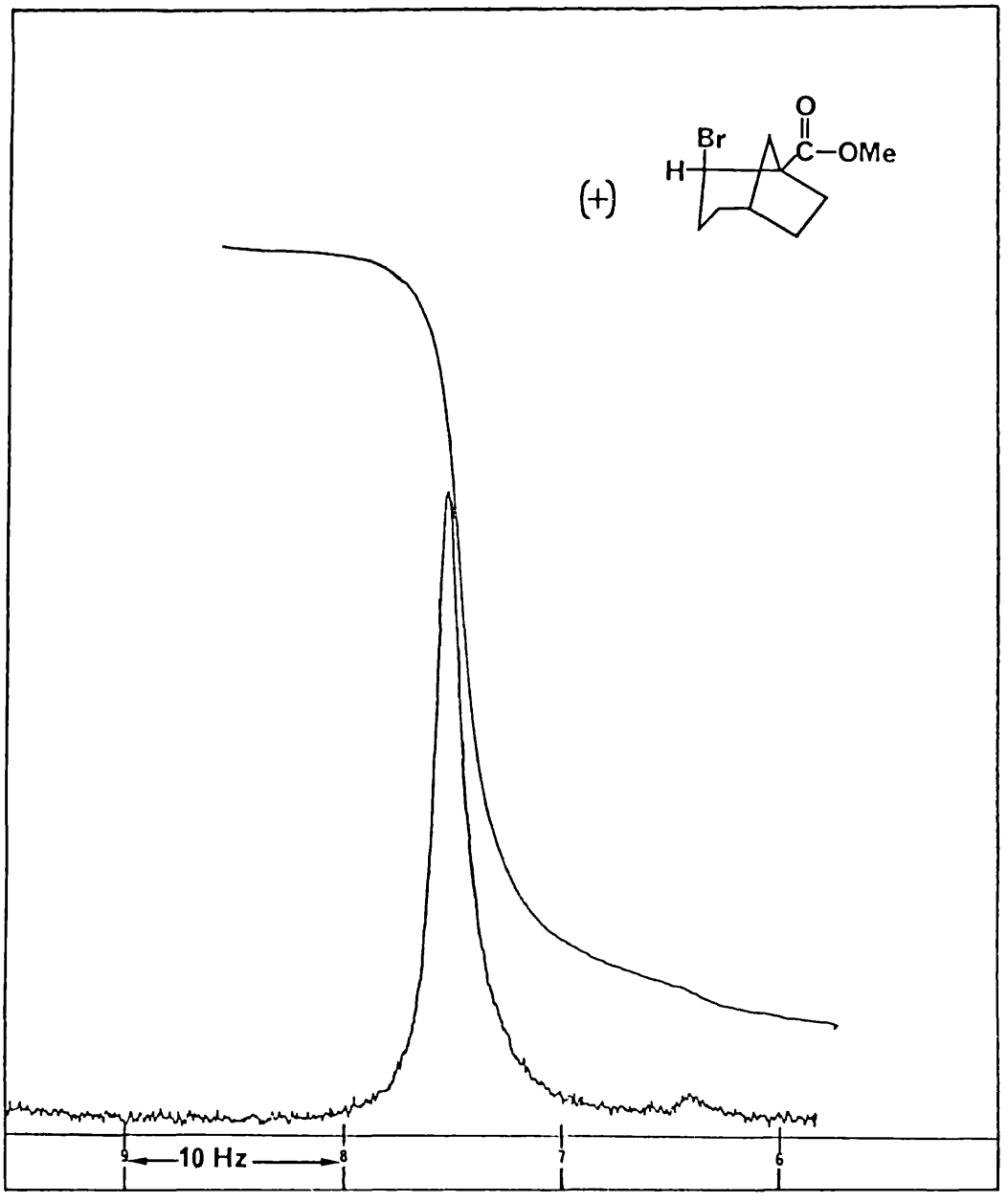


FIG. 6

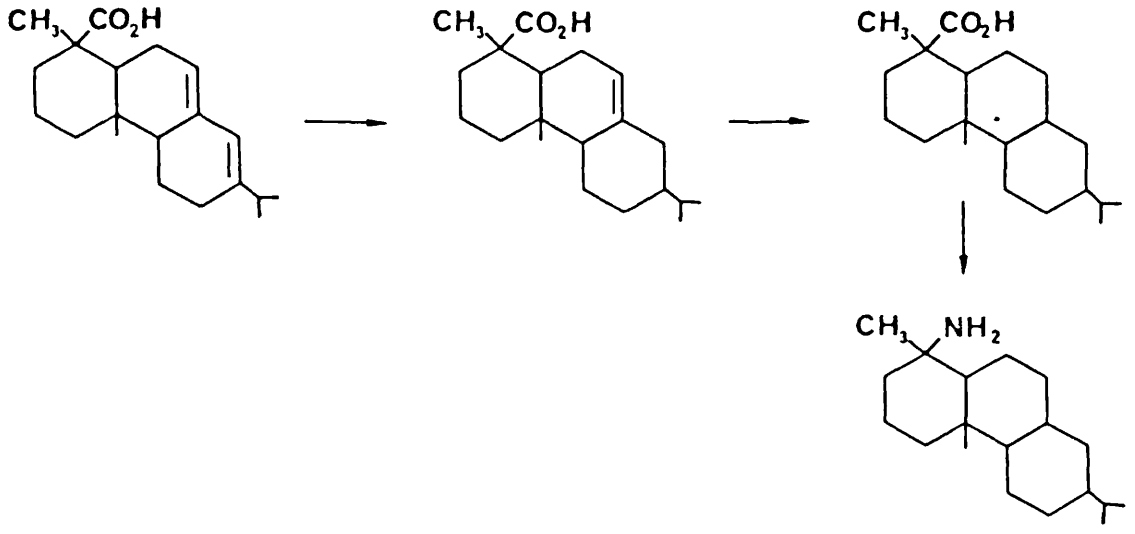
two enantiomers can be accomplished.[58]

a) A chiral shift reagent and a racemic mixture may form two diastereomeric complexes which will have different stabilities reflected in the values for their dissociation constants; as a result, all the signals for one diastereomer will be affected to a greater extent than those for the other, more weakly bound, isomer,

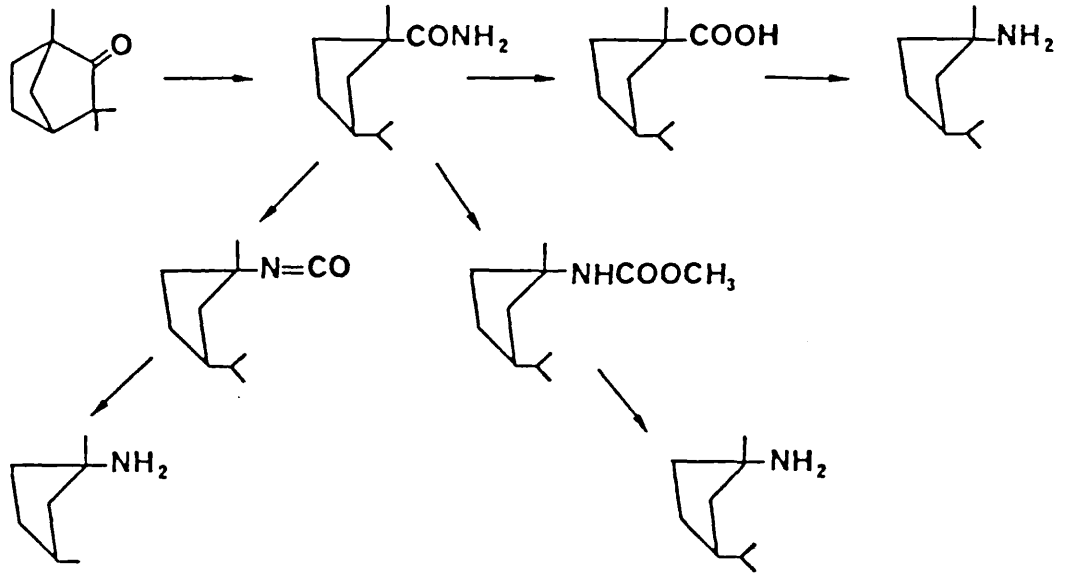
b) Each diastereomer will of necessity form complexes having different geometries; this will produce different induced shifts. A variety of evidence[58] indicates that both mechanisms may be operative, but the extent of the individual contributions cannot be evaluated.

Resolution by classical methods is time consuming, costly and extremely tedious since many recrystallizations are needed and yields of optically pure compounds are low. In this work 60.0g of racemic bromoacid was dissolved in 20 litres of acetone. After many recrystallizations of the quinine salt and subsequent hydrolysis to give the free acid the total yield of optically pure product was only 3g.

In view of these experimental difficulties the possibility of using naturally occurring optically active starting materials was reconsidered, and some of the possible chiral t-alkylamines which were examined are shown in scheme 6.

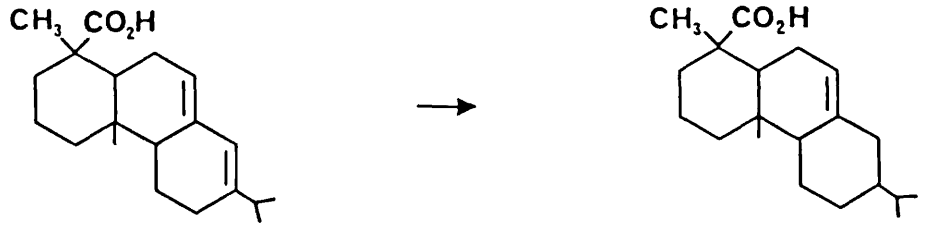

CH3
CO2H
CH3
CO2H
CH3
CO2H
CH3
NH2


CH3
OH
CH3
NH2


O
CONH2
COOH
NH2
N=CO
NHCOOCH3
NH2
NH2

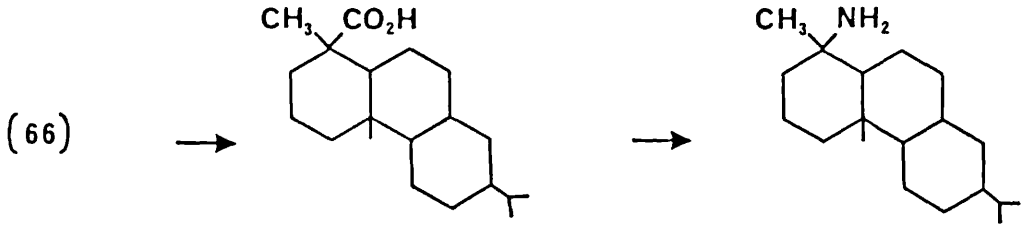
SCHEME 6

For example, abietic acid (65) was readily available from FLUKA. According to the method of E.E. Royals et al[59] reduction of the di-n-amylamine salt of abietic acid by treatment with lithium in liquid ammonia followed by addition of ethanol was carried out to obtain the 7,8-dihydroabietic acid (66). However, in our hands the yield of (66) by this method was very low. Reaction of abietic acid in dry ether with lithium in ammonia followed by addition of ethanol gave a dihydroabietic acid in 88% yield. Dry ether was used as a co-solvent to increase the solubility of abietic acid in liquid ammonia. To prevent separation of a bronze lithium ammonia layer a large volume of ammonia was required in relation to the co-solvent. Catalytic hydrogenation of the dihydroabietic acid over Pd/c led to absorption of



(65) (66)

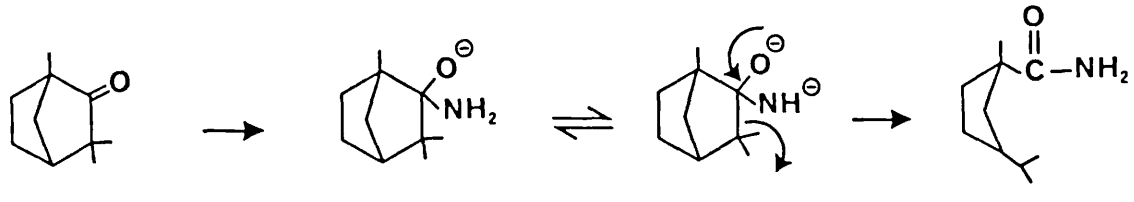
hydrogen and production of a tetrahydroabietic acid (67). When (67) was subjected to the Schmidt reaction the oily product obtained showed no NH_2 stretching in the infrared spectrum.



(67) (68)

After several attempts to obtain **(68)** by the Schmidt reaction had been carried out unsuccessfully, this route to the required chiral amine R^3-NH_2 was abandoned. Fenchone (69) was also commercially available from FLUKA. The Haller-Bauer reaction[60] is defined as the action of sodium amide on a non-enolizable ketone causing the cleavage of a carbon-carbon bond and resulting in the formation of an amide.

Fenchone contains no α-hydrogen atom and sodium amide effects cleavage of fenchone to fencholamide (70) without causing rearrangement of the molecule.[61] It has been shown that the configuration of the optically active fenchone is retained[62] and that the NH_2 loses its proton before the ring is cleaved.[63]

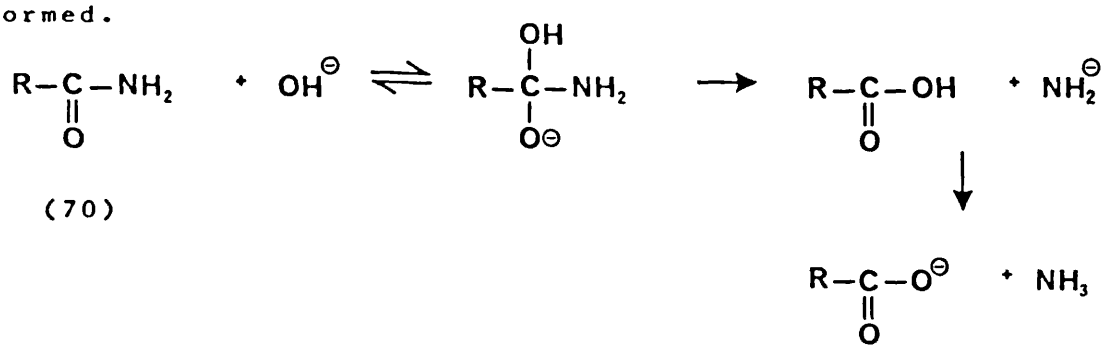


(69) (70)

Thus optically active fencholamide was obtained in good yield (93%).

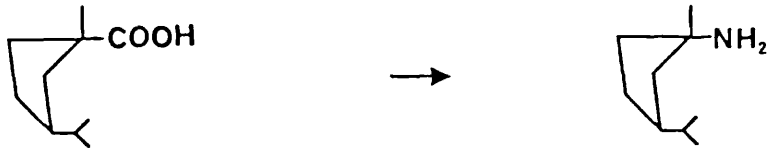
The base catalysed hydrolysis of fencholamide to fencholic acid (71) was achieved under extremely harsh

conditions by refluxing the amide with conc. NaOH in aqueous ethanol for 3 days. The hydrolysis of the amide is essentially irreversible since a salt is formed.



(70)

By using the Schmidt reaction [54,55] it was possible to convert fencholic acid to fenchelylamine (72).

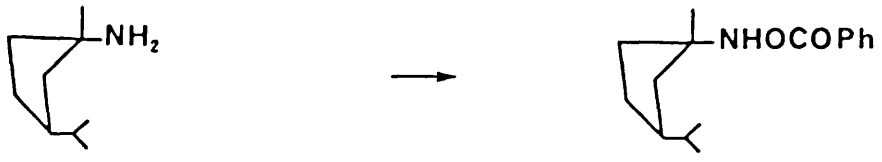


(71) (72)

However, it proved very difficult to obtain the pure amine. The reaction product always contained an impurity revealed by a sharp absorption in the infrared spectrum at 1670 cm^{-1}. On washing the reaction product with acid the peak shifted to 1750 cm^{-1}. A pure sample of fenchelylamine was obtained using fractional vacuum distillation of the crude reaction product but yields were very low.

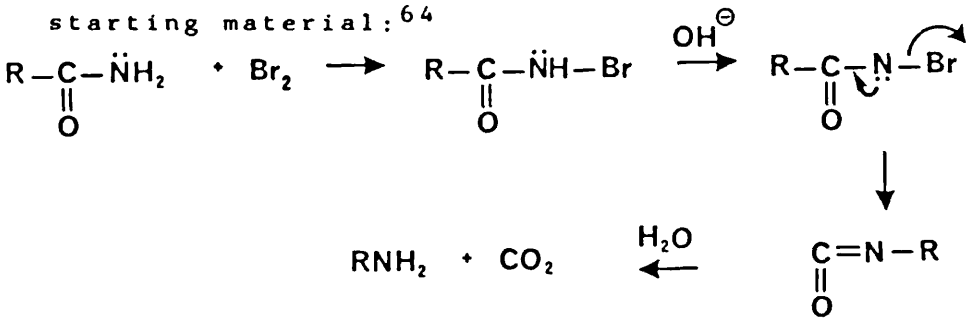
In the hope that the impurity could be removed at a later stage of the synthesis (for example, by recrystallization) the crude reaction product was reacted with dibenzoyl peroxide in dry benzene in an

attempt to obtain the hydroxylamine derivative:



Examination by infrared spectroscopy of the brown oil obtained from this reaction revealed that there was no -NH group present in the product.

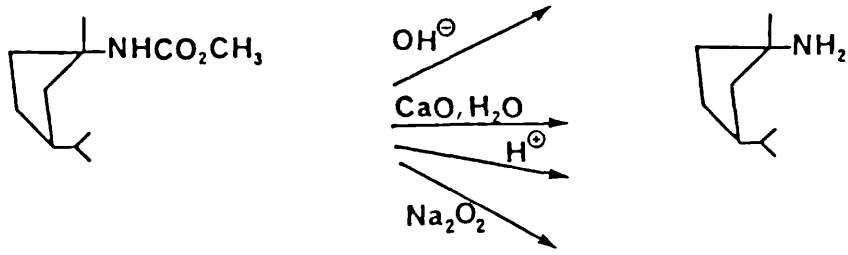
An alternative approach to the preparation of pure amine was to convert the amide to the amine via the isocyanate using the Hofmann rearrangement. In the Hofmann rearrangement an unsubstituted amide is treated with sodium hydroxide and bromine to give a primary amine which has one fewer carbons than the starting material:[64]



This reaction is intramolecular and occurs with retention of configuration under normal conditions. If the alkyl group (R) contains more than about six or seven carbons, low yields are often obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH. Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe, with

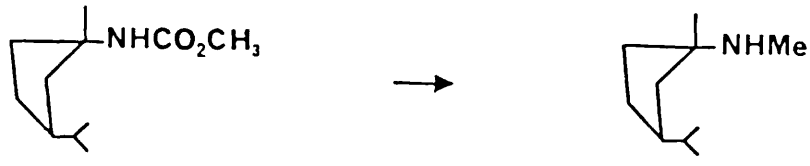
fencholamide the carbamate **(73)** was easily obtained in good yields but subsequent cleavage to give the primary amine proved extremely difficult. Scheme 7 outlines the methods of attempted hydrolysis:

Scheme 7



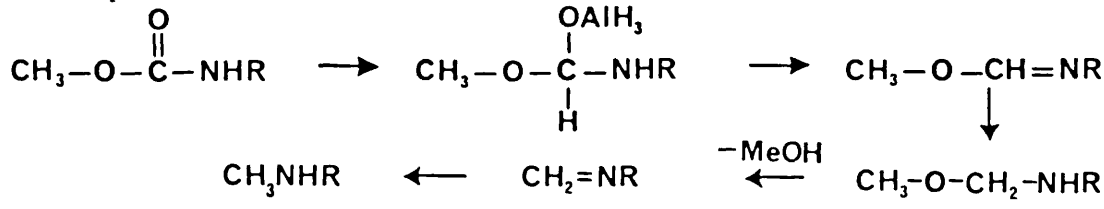
(73)

On reaction with lithium aluminium hydride spectroscopic evidence suggests that the carbamate was converted to N-methyl fenchelylamine (74):



(74)

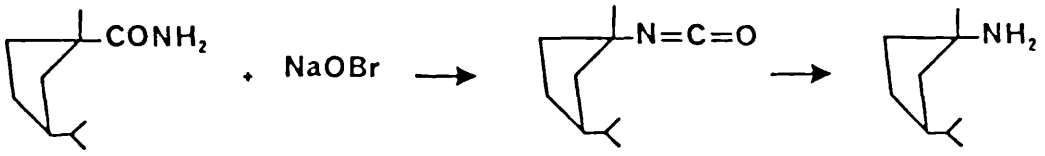
A possible mechanism for this reaction is as follows:



A side product of this reaction is thought, on the basis of spectroscopic evidence, to be N-fenchelylacetamide. The mechanism for the formation of this product is not clear.

Despite the fact the yields might be low a

straightforward Hofmann rearrangement (Br_2 and NaOH) was carried out on fencholamide:



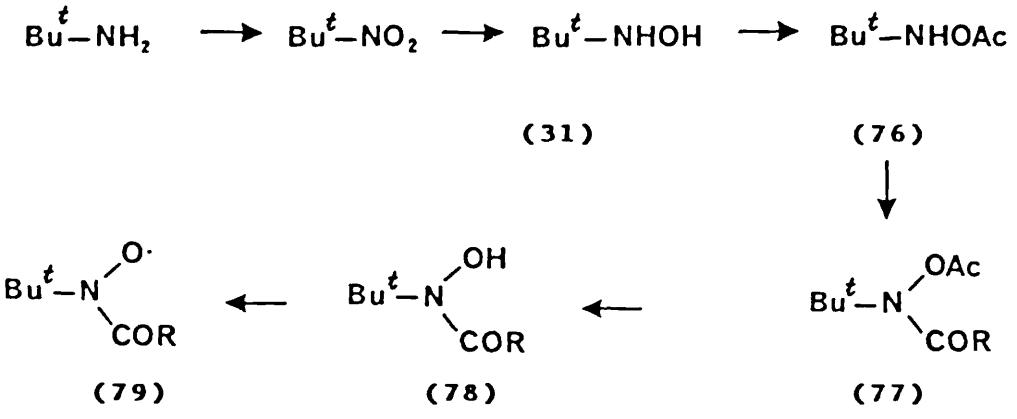
(70) (72)

The initial product of the reaction is the isocyanate, but this compound is seldom isolated since it is usually hydrolysed under the reaction conditions. However, in the case of fencholamide the corresponding isocyanate was isolable and easily handled. Facile hydrolysis of the isocyanate using hot dilute hydrochloric acid then gave the pure optically active fenchelylamine (X^*-NH_2) in good yield (93%).

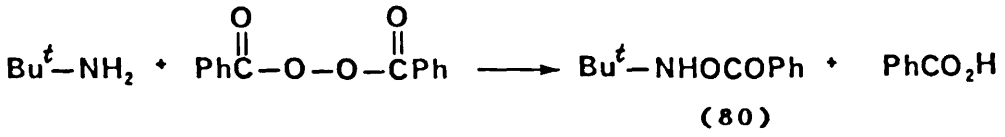
B. Conversion of X^*-NH_2 to X^*YNOH

Once obtained, the chiral fenchelylamine must be converted to the required N-fenchelylbenzohydroxamic acid. There are two main approaches to this synthesis. The first approach has as its precursor a t-alkylhydroxylamine. A typical example of such a system is t-butylhydroxylamine which will be used for the purposes of this discussion. The preparation of t-butylhydroxylamine (31) from t-butylamine via 2-methyl-2-nitropropane using aluminium and aqueous alkali to reduce the nitro-compound is well documented.[65,66,67]

Perkins *et al*[33] found that acylation of *N*-*t*-butylhydroxylamine with acetic anhydride gave essentially pure *O*-acetyl-*N*-*t*-butylhydroxylamine. This could be acylated at nitrogen, and the *O*-acetyl-group removed to give a variety of hydroxamic acids $RCON(Bu^t)OH$ **(78)** which could be oxidised to isolable acyl nitroxides $RCON(Bu^t)O^{\cdot}$ (79) (R = alkyl, aryl, alkoxy, or dialkylamino):

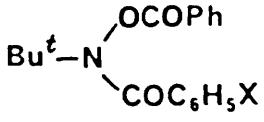


There are however several disadvantages in the above synthesis. The three-step preparation of *O*-acetyl-*N*-*t*-butylhydroxylamine **(76)** via *N*-*t*-butylhydroxylamine is difficult to achieve in good yield. This is due to the volatility of the hydroxylamine and its susceptibility to aerial oxidation. An improved procedure was reported by Alewood *et al*.[35] This approach was based on Zinner's[34] one-step preparation of *O*-benzoyl-*N*-*t*--butylhydroxylamine directly from the readily available t-butylamine.



(80)

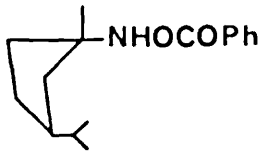
The key compound (80) is stable over prolonged periods and is easily handled. By reaction with a suitable acyl chloride the precursor (80) can be used to generate a series of substituted O-benzoyl-N-t--butylbenzohydroxamic acids (81).



(81)

For example, reaction of (80) with one equivalent of anisoyl chloride gives O-benzoyl-N-t-butyl-4--methoxybenzohydroxamic acid in 87% yield. Deprotection of the O-benzoyl- (81) or O-acetyl- (77) derivatives to give the hydroxamic acids (78) can be achieved by hydrolysis with ethanolic barium hydroxide followed by acidification with glacial acetic acid and ether extraction. However, this method requires an inert atmosphere and could only be achieved in approximately 60-90% yield. A major improvement in the deprotection of hydroxamic acylates was achieved by transamidation using hydrazine hydrate. Reaction of an ethanolic solution of (77) or (81) with a large excess of hydrazine hydrate at 40°C for 1½ hours gives the hydroxamic acid in high purity and greater than 95% yield.

Although the impure fenchelylamine obtained via the corresponding carboxylic acid gave no hydroxylamine derivative on reaction with benzoyl peroxide, the amine obtained via the Hofmann route reacted smoothly to give **(82)** in good yield.



(82)

Apparently the impurity in the Schmidt product interfered with this reaction in a manner which remains obscure. Both enantiomers of **(82)** were obtained from (+) and (-) - fenchone, and were tranformed to the hydroxamic acids **(83)** → **(87)** using Alewood's procedure.[35]

By reaction of **(82)** with optically pure (+) and (-)-pinanecarbonyl chloride followed by deprotection using ethanolic barium hydroxide, both enantiomers of the hydroxamic acid **(88)** were also synthesized. Finally, reaction of the fenchelyl analogue **(82)** with pinanecarbonyl chloride followed by deprotection using hydrazine hydrate gave the diastereomeric hydroxamic acids (89). All the above N-t-alkylhydroxamic acids are shown in table 1.

Although secondary alkyl acyl nitroxides disproportionate readily the commercially available chiral amine α-methylbenzylamine **(90)** was used to prepare both enantiomers of the hydroxamic acid (91)—

TABLE 1

Fenchelyl hydroxamic acids

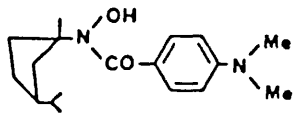
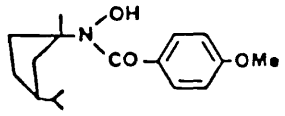
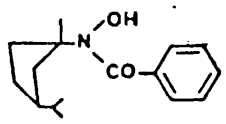
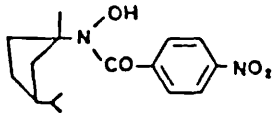
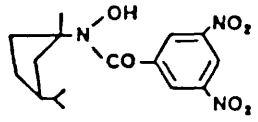
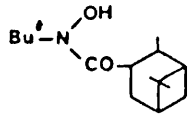
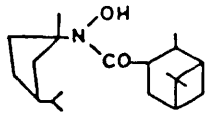
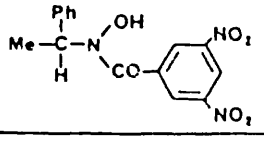
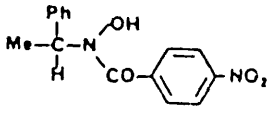
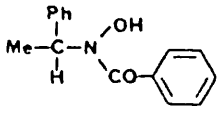
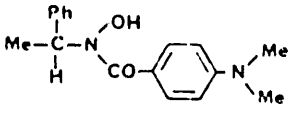
Hydroxamic acid	Number
	83
	84
	85
	86
	87
	88
	89

TABLE 2

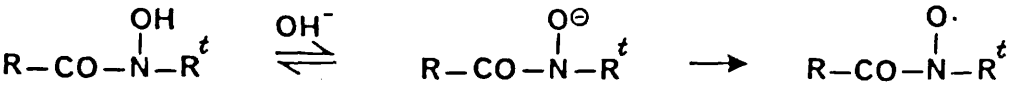
Methylbenzyl hydroxamic acids

Hydroxamic acid	Number
	91
	92
	93
	94

(94) according to the general method of Alewood *et al*[35] (Table 2).

All the hydroxamic acids shown in tables 1 and 2 were usually stable colourless crystalline solids. The compounds are very polar in nature and could be maintained indefinitely.

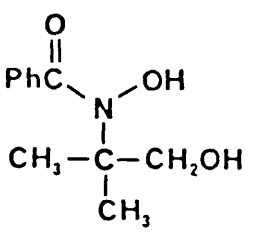
Rapid, quantitative conversion of the hydroxamic acids to nitroxide radicals by oxidation could be achieved simply by shaking an aqueous alkaline solution of potassium hexacyanoferrate(III) (ferricyanide) with a solution of the hydroxamic acid in an immisible organic solvent. All traces of acid are removed and the acyl nitroxide remains in the organic phase. By analogy with the formation of aroxyls from phenols using this oxidant[68] it is suggested that the hydroxamate anion of the acid undergoes one electron oxidation to the acyl nitroxide in alkaline media.



Organic solutions of the radicals were typically coloured, with the colour depending upon the nature of the acyl function. Thus, by spectroscopic observation the visible absorption characteristics of the radicals could be elucidated. (see section 3B). Evaporation of the organic layer at room temperature, after drying,

gave the neat acyl nitroxide as a liquid in all cases. Although the majority of the t-alkyl nitroxides examined were manipulated as normal organic compounds, the secondary alkyl nitroxides, even in dilute solution $\leqslant 10^{-4}$M, were prone to disproportionation. For this reason no radicals were stored, it being easier and more convenient to prepare the radicals from their more stable hydroxamic acid precursors immediately prior to use.

As a further extention of the use of hydrogen atom transfer reactions to observe enantioselectivity, a short piece of work was carried out in which the target molecule was **(95)**.

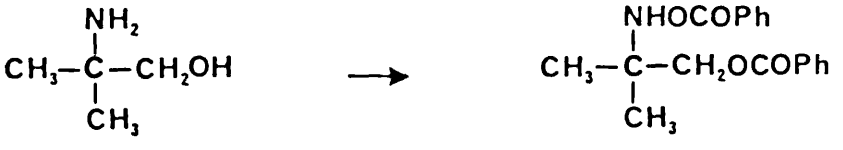


(95)

Reaction of e.g. racemic benzoin with (optically active) **(95)** should lead to a pair of diastereoisomeric transition states. If the hydroxyl group in **(95)** can be used to hold the transition state in a fixed orientation by hydrogen bonding to either the ketone or the hydroxyl group of the benzoin, then greater ordering, and hence enhanced enantiomeric selectivity should be observed in the hydrogen transfer process.

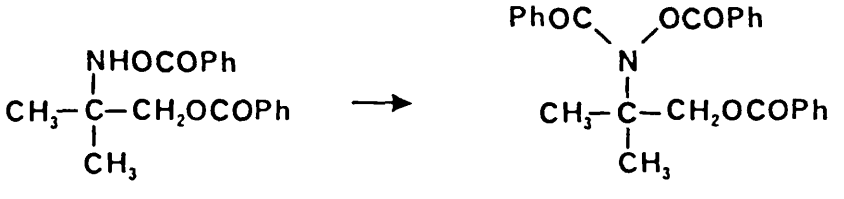
The synthesis of **(95)** by two alternative routes

was attempted using racemic starting materials. Our aim was to subsequently effect resolution at a suitable stage using traditional techniques. However, the synthesis of (95) was fraught with difficulty and neither route proved successful. Reaction of 2-amino-2-methylpropan-1-ol **(96)** with dibenzoyl peroxide according to Alewood's method[35] gave the doubly O- protected product **(97)**.



(96) (97)

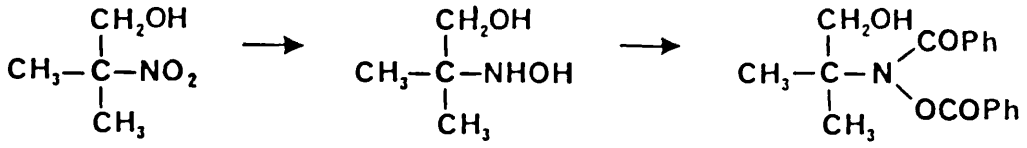
Reaction of (97) with one equivalent of benzoyl chloride and 1.1 equivalents of pyridine gave O-benzoyl-N-2(benzoyloxymethyl-2-propyl)benzohydroxamic acid) **(98)**.



(97) **(98)**

Hydrolysis of **(98)** using hydrazine hydrate gave an oil from which the required compound **(95)** could not be isolated.

In a further attempt to isolate a suitable precursor to (95),(101), 2-N-(hydroxyamino)-2-methyl propan-1-ol (100) was prepared from 2-methyl-2-nitropropanol (99):



(99) **(100)** **(101)**

Reaction of **(100)** with dry pyridine (2.2 equivalents) and benzoyl chloride (2 equivalents) gave a crude reaction product which was shown by t.l.c. to contain at least five compounds. The required compound **(101)** could not be isolated from this mixture.

CHAPTER 3

SPECTROSCOPIC STUDIES

A. Electron Spin Resonance (e.s.r.) Spectroscopy

ESR is a magnetic resonance technique which achieves a response only from those molecules with at least one unpaired electron. The method is in principle the same as nuclear magnetic resonance but relies on electron spin rather than nuclear spin. The spectrometer detects changes in energy states of the unpaired electron (a spin $\frac{1}{2}$ particle) in the presence of a magnetic field; because only unpaired electrons are detected, it is specific for radicals, and other paramagnetic particles such as transition metal ions. The technique was discovered in 1945[69] and has developed rapidly as a powerful tool in physics, biology and chemistry. The theory, instrumentation and applications of e.s.r. have been covered extensively in a large number of books[70,71] and reviews[72,73] and will not be discussed in this work.

The solution e.s.r. spectrum of a tertiary alkyl acyl nitroxide (e.g. **(104)**) appears as a 1:1:1 triplet as a direct result of unpaired electron-hyperfine interaction with the magnetic nitrogen (^{14}N, I=1) nucleus. A typical spectrum is shown in Fig. 7.

In the secondary alkyl acyl nitroxide (for example, **(109)**) each line of the 1:1:1 triplet is split by coupling to hydrogen into a doublet to give a

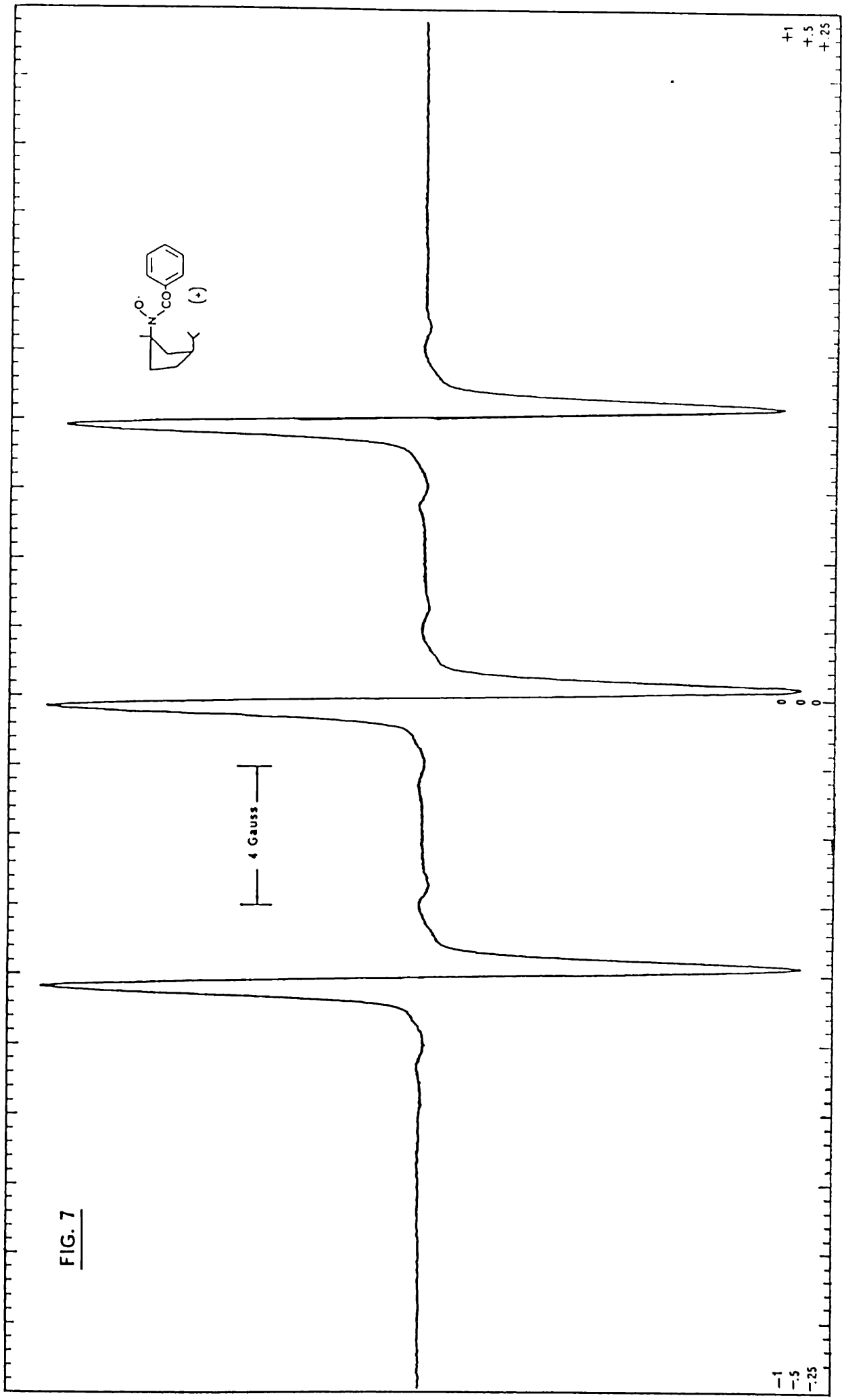
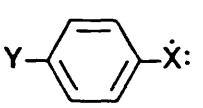


FIG. 7

total of 6 lines (Fig. 8).

Precise a_N values were determined for a number of acyl nitroxides (tables 3 and 4) after generating the radicals in dilute benzene solution by oxidizing the corresponding hydroxamic acid precursor with potassium hexacyanoferrate(III). The reduced magnitude of the nitrogen hyperfine splitting (a_N) in an acyl nitroxide relative to a di-t-alkyl nitroxide indicates a lower unpaired spin density at nitrogen for these radicals (see Chaper 1).

Reference to tables 3 and 4 reveals that the nature of a nuclear substituent has an effect on the magnitude of the nitrogen hyperfine splitting constant. Walter's theory of radical stabilization[74] suggests that the effect of polar substituents upon the radical chemistry facilitates division of the radical type into one of two catagories:



(111)

If the radical site X bears a lone pair of electrons, Walter predicts that delocalization of the electron pair into the aromatic nucleus will contribute more importantly to the resonance hydrid than will delocalisation of the unpaired electron, even when a suitable acceptor group Y is present (111) which makes

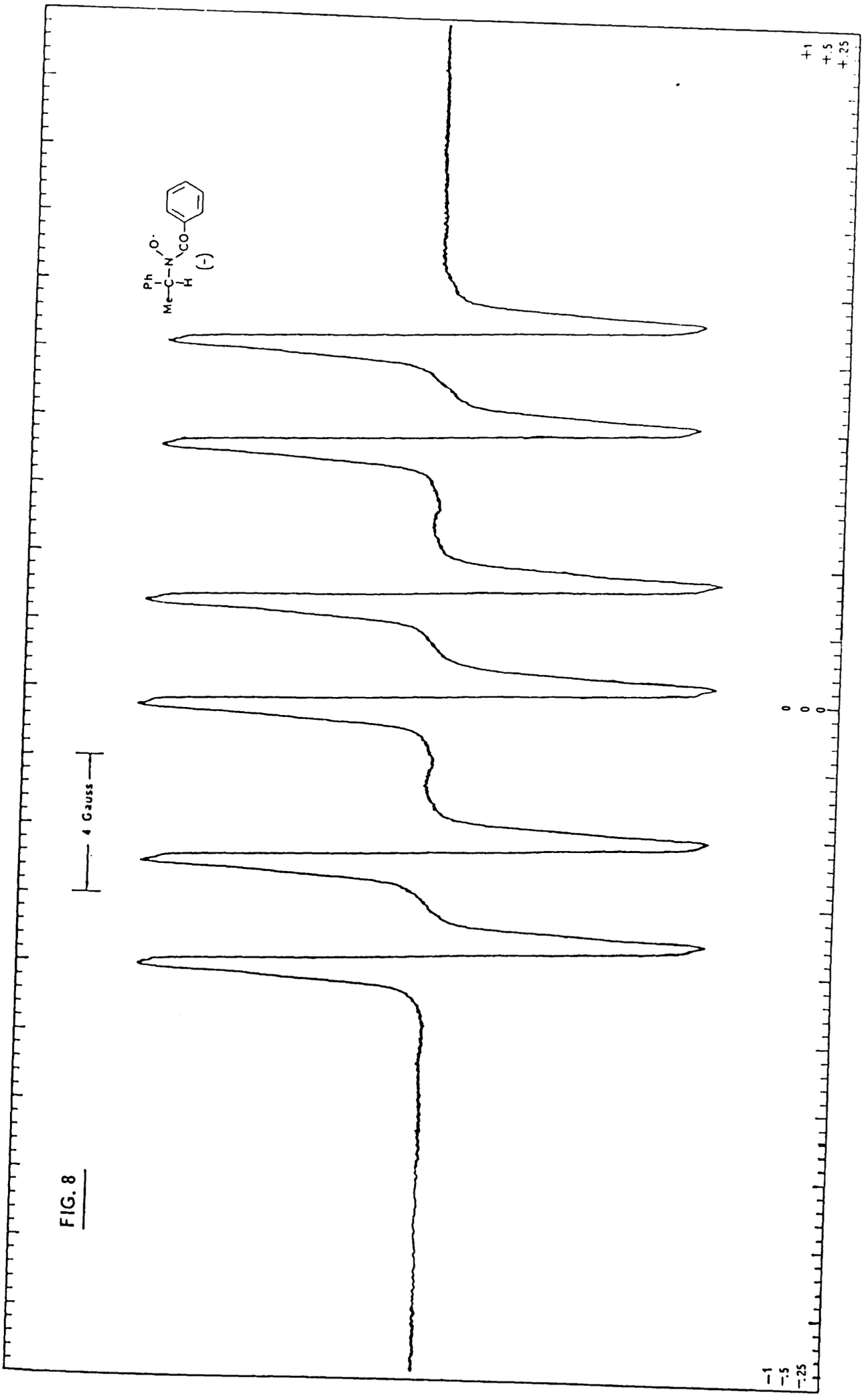


FIG. 8

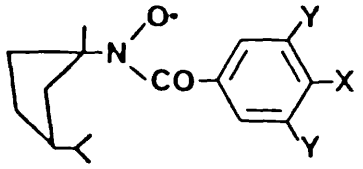


TABLE 3

a_N values for the fenchelyl nitroxides

Number	X	Y	a_N(gauss)
102	H	NO_2	7.23
103	NO_2	H	7.42
104	H	H	7.91
105	OMe	H	8.25
106	$(Me)_2$	H	8.74

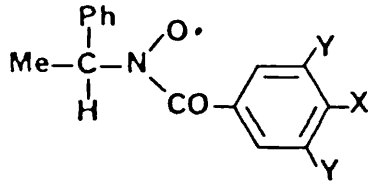


TABLE 4

a_N values for the α-methylbenzyl nitroxides

Number	X	Y	a_N(gauss)
107	H	NO_2	7.03
108	NO_2	H	7.23
109	H	H	7.42
110	$N(Me)_2$	H	8.20

both processes equally feasible.

In a series of radicals where it is possible to write both p-Y-C_6H_4-X· <u>and</u> p-Y-C_6H_4-$\ddot{X}$, donor and acceptor substituents (Y) shift the properties of the radicals in opposite directions (Walter's Class O). Nitroxides with an electron pair present fall into this class. Radicals devoid of a lone pair, i.e. where only p-Y-C_6H_4-X· can be written, show a shift in the same direction with both types of substituents (Walter's class S). Examples of the latter class are triarylmethyl radicals and triarylaminium radical cations (Ar_3C· and Ar_3N^{+}) both of which have no lone pair available for delocalization.

Numerous studies of substituent effects on the e.s.r. of nitroxides have been reported[14].

Class O radicals should exhibit behaviour consistant with the Hammett equation.[75] It has been shown that a_N's in diphenyl[76], <u>t</u>-butyl phenyl[77], <u>t</u>-alkenyl phenyl[78], phenyl hydro[79] and phenyl benzoyl nitroxides can all be correlated to the σ substituent constant, in the Hammett equation, using the expression:

$$a_N = (a_N)_o + \rho\sigma$$

where $(a_N)_o$ is the a_N value for the unsubstituted species and ρ is a proportionality constant. Janzen found that correlations were considerably improved by

using σ^- nucleophilic substituent constants.[14]

Jenkins has shown that for 4-substituted t-butyl benzoyl nitroxides there is only poor correlation between a_N and the σ constants. The correlation is greatly improved if Brown's σ^+ electrophilic substituent constants are used.[39] For the N-(fenchelyl) benzoyl nitroxides shown in table 3, least squares correlation analysis of the spectral data gives an expression for these radicals.

a_N(PhH, Gauss) = 7.86 - 0.521σ^+ with a correlation coefficient, r = 0.998 (Fig. 9). Interpretation of substituent effects in these radicals depends on whether the most important effect is the delocalization of either the π-bonding electron pair of the nitroxide or, of the unpaired electron in the π^* orbital. It has been argued that for the substituted aroyl nitroxides the former effect is dominant.

The Hammett obeying spectral dependence determined for the fenchelyl benzoyl nitroxides (Fig. 9) is consistant with a model in which lone pair (amide resonance) rather than unpaired electron delocalisation predominates. Introduction of an electron-pair donating group into the aromatic nucleus will lead to competing carbonyl involvement. This will effectively attenuate p-π 'amide resonance' with the :N-O fragment and hence facilitate an increased

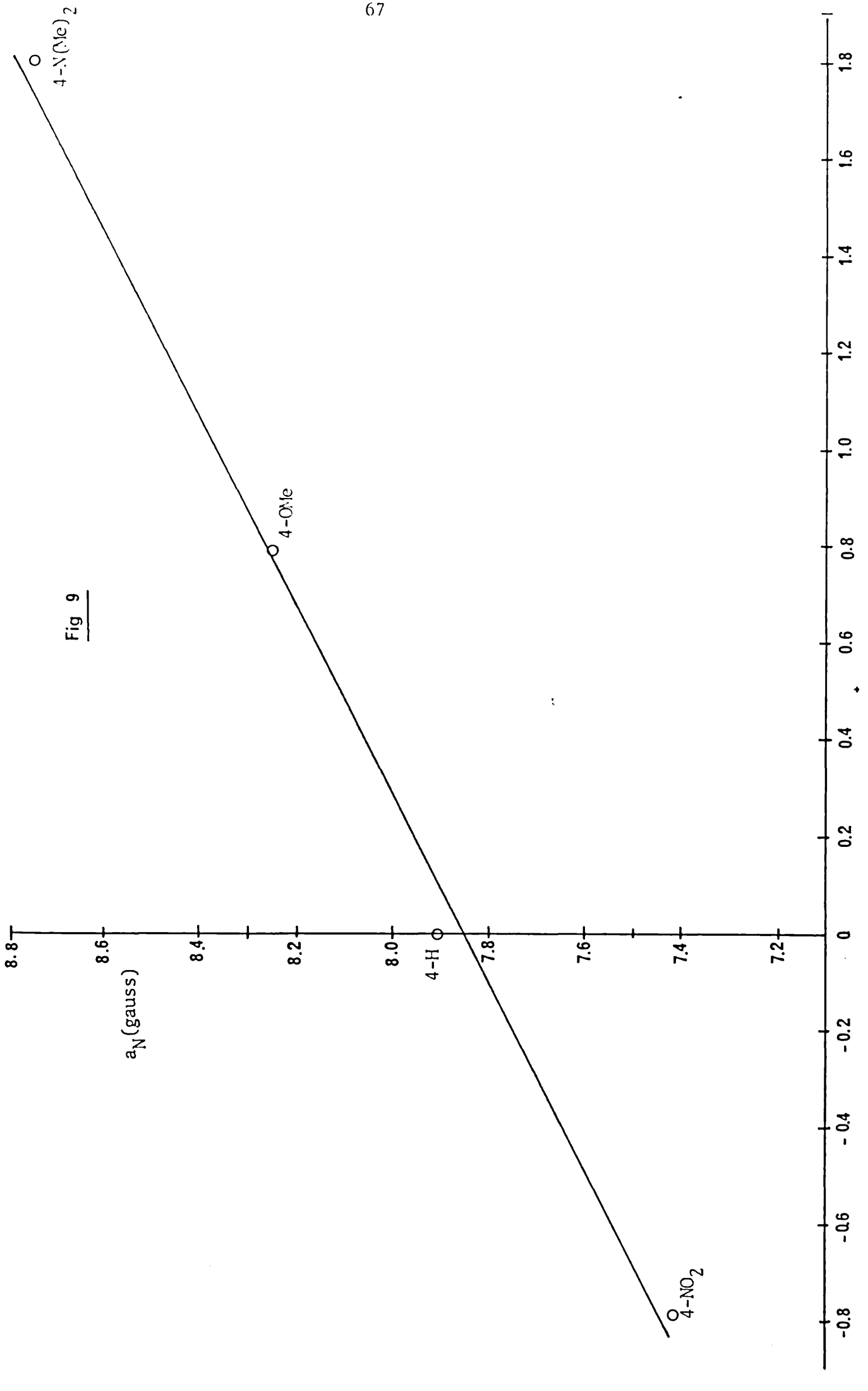
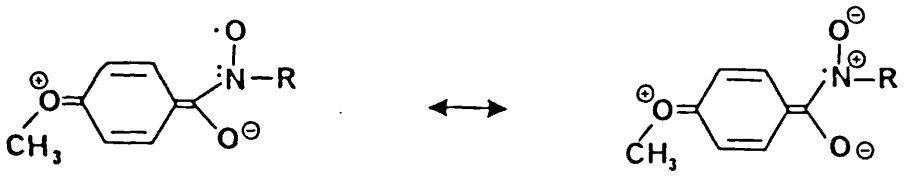

4-N(Me)2
4-OMe
4-H
4-NO2
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
aN(gauss)
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8

Fig 9

unpaired spin localization at nitrogen (112):



(112)

Increased unpaired spin localization at nitrogen should increase the observed a_N value for the 4-methoxy substituted nitroxide and indeed this is seen experimentally.

B. Ultraviolet and Visible Spectra

The electronic spectra of alkyl nitroxides are characterised by two absorptions associated with the N-O· fragment, one in the uv/vis, the other in the visible region. The position of λmax is dependent on the groups associated with a particular nitroxide. In di-t-alkyl nitroxides there is an intense band at about 230 nm with a molar extinction coefficient, ε - 3000 $M^{-1}cm^{-1}$. In acyl nitroxides this band appears at wavelengths considerably longer at about 330-370 nm, ε = 2000-3000 $M^{-1}cm^{-1}$. The visible absorption in dialkyl nitroxides occurs in the 410-450 nm region (ε- 5-10 $M^{-1}cm^{-1}$) whereas for acyl nitroxides λ max $\sim$ 640-660 nm (ε - 25-60 $M^{-1}cm^{-1}$).

Electronic (200-750 nm) absorption spectra were recorded for a number of N-(fenchelyl) acyl nitroxides

in benzene solvent of high purity. The observed uv/vis and vis maxima, the extinction coefficient and the characteristic colours of these nitroxides are shown in table 5.

Examination of table 5 reveals that the dimethylamino derivative (106) does not appear to behave as a 'normal' acyl nitroxide. This is reflected in λmax, ϵ and the colour of the nitroxide. For comparison the uv/vis λmax and colour were recorded for three other acyl nitroxides and this data is shown in table 6.

It is a useful approximation to consider the wavelength of an electronic transition to be determined by the energy difference between the molecular orbital originally occupied by the electron and the higher energy orbital to which it is excited. By considering the N-O· group in di-t-alkyl nitroxides to be analogous to a carbonyl group, Rassat[80] has assigned the intense 230 nm absorption to either a $\pi \rightarrow \pi^*$ or $n - \pi^*$ transition. Observation of the values for these two transitions, leads to the conclusion that in view of the orbital symmetries involved, these assignments are not unreasonable. $\pi \rightarrow \pi^*$ transitions will almost definitely be symmetry allowed and therefore large ϵ values can be expected whereas $n - \pi^*$ will necessarily be symmetry forbidden and will have much smaller ϵ values. If Rassat's

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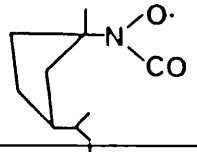
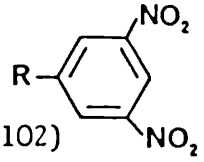
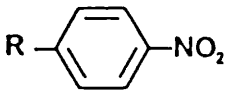
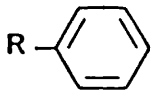
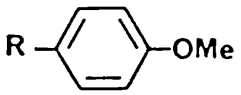
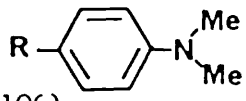
R = 

TABLE 5

Ultraviolet and visible spectrosconic data for the fenchelyl nitroxides.

Radical	uv/vis λmax (nm)	ε M^{-1} cm^{-1}	vis λmax (nm)	ε M^{-1} cm^{-1}	Colour
 (102)	344	1100	662	25.4	dark green
 (103)	346	1315	660	30.1	green
 (104)	335	1971	650	40.6	green
 (105)	343	2592	642	54.6	green/ yellow
 (106)	371	3437	518	43.5	mauve

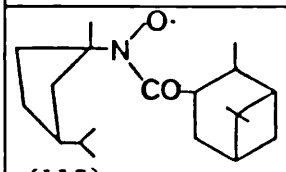
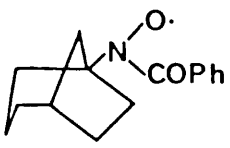
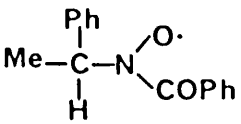
Radical	uv/vis λmax (nm)	Colour
 (113)	279	blue/ green
 (114)	336	green
 (109)	335	green

TABLE 6

Ultraviolet and visible spectroscopic data for some acyl nitroxides

orbital arrangement (Fig. 1, section 1) is assumed to apply equally to acyl nitroxides, then the longer wavelength absorption (λ = 620-650 nm) must be associated with n-π^* transitions involving the N-O· group. The oxygen lone pair (n) orbitals involved in such a transition are unlikely to be much affected by the introduction of a remote carbonyl moiety hence it is assumed that the π^* acceptor orbitals must be amenable to direct perturbation.

Extensions of Rassat's nitroxide carbonyl analogy suggests that π-electron donor substituents attached to the nitroxide nitrogen would be expected to raise the π^* orbital energy and consequently shift the n - π^* absorption towards higher energies. On the other hand, attached groups which, like carbonyl, behave as acceptors should effectively lower the π^* energy level and shift the n - π^* absorption towards lower energies. The energy $\Delta E'$ between π^* and non-bonding (n_O) oxygen orbitals in the substituted radical is significantly smaller than the difference (ΔE) associated with the unsubstituted parent nitroxide. Jenkins[39] has shown that the absorption maxima for t-butyl acyl nitroxides represents ca. 34% reduction in (n, π^*) energy separation for these nitroxides relative to di-t-alkyl nitroxides and demonstrates the π- withdrawing nature of the carbonyl substituent, Fig. 10.

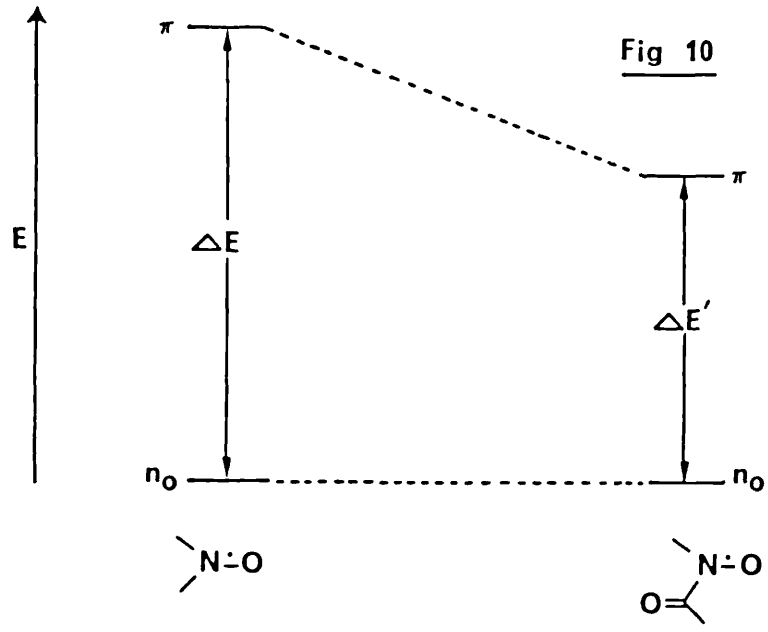


Fig 10

The uv/vis $\pi \rightarrow \pi^*$ absorptions do not, at first glance, appear to support Rassat's nitroxide carbonyl analogy. Upon closer examination it can be seen that spectroscopically the critical uv region involved is complicated by the intrusion of other bands associated with both the carbonyl and aromatic functions. In the case of 3,5-dinitro (102) and 4-nitro (103) this intrusion makes assignments of the uv/vis absorptions very difficult and λmax and ε cannot be determined with accuracy.

An important application of uv/vis spectroscopy is to define the nature, effect and extent of conjugation present in the system under study. For N-(fenchelyl) acyl nitroxides substitution into the aromatic nucleus modifies the carbonyl interaction with the nitroxide π-system and causes $n \rightarrow \pi^*$ shifts.

The direction of the shift is dependent upon the electronic nature of the substituent. Electron withdrawing substituents, for example 4-nitro- **(103)**, enhance electron pair removal from the nitroxide nitrogen and λ max ($n \rightarrow \pi^*$) moves to longer wavelengths. The dinitro value **(102)** (λ max = 662 nm) represents the most perturbed nitroxide studied in this work, and the unpaired electron distribution within the N–O fragment must therefore least resemble that of a dialkyl nitroxide.

Electron releasing substituents, for example, 4-methoxy **(105)** and 4-dimethylamino **(106)**, impede carbonyl involvement and induce λ max ($n \rightarrow \pi^*$) to return to shorter wavelengths. The 518 nm value for the mauve dimethylamino derivative is at very short wavelength for an acyl nitroxide.

For (102) to (105) there is a good correlation (r = 0.989) between λ max and the σ^+ substituent constants in an electrophilic form of the Hammett equation:

$$\lambda^{vis}_{max(nm)} = 650.6 + 11.4\sigma^+$$

However introduction of λ max for (106) into the above equation induces r to fall to 0.87.

The out-of-series behaviour of the dimethylamino derivative is also seen in the value of the extinction coefficient, ε, for acyl nitroxides which also appears to be sensitive to substituent effect. The more

electron-donating the substituent the greater the extinction coefficient. In the case of **(106)**, ε (435 $M^{-1}cm^{-1}$) is much greater than the value normally associated with acyl nitroxides (ε-25-60 $M^{-1}cm^{-1}$).

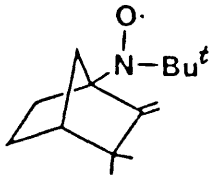
C. Circular Dichroism (CD)

Circular dichroism is the term used to describe the unequal absorption of left and right circularly polarized light by an optically active medium and was first observed in amethyst quartz by Haidinger[81] and Dove.[82]

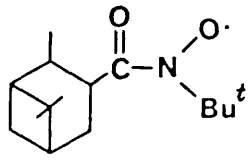
In this technique the molecular extinction coefficients of a compound are measured with both left and right circularly polarized light, and the difference between the values (called $\Delta\varepsilon$) is plotted against λ in the visible and uv regions of the spectrum.

The octant rule [83] has been used in the interpretation of the chiroptical properties of asymmetrically substituted ketones. The sign and amplitude of the observed curve (Cotton effect) associated with the $n \rightarrow \pi^*$ transition of the carbonyl chromophone yields valuable information concerning configurational and conformational assignments.[84] Rassat[80] has shown that there is a close similarity in symmetry and electronic configuration of the carbonyl group and the nitroxide function. For di-t-alkyl

nitroxides the low energy $n \rightarrow \pi^*$ transition (ca. 430 nm) is ideally suited for both ORD and CD studies. The camphenyl-1-t-butyl nitroxide (115) was the first optically active nitroxide radical to be examined by circular dichroism. However, because the -NO group



(115)

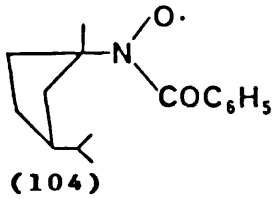


(116)

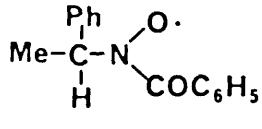
is not held in a fixed geometry the CD is difficult to interpret by the octant rule.

Attempts to apply the conditions of the octant rule to cyclic nitroxides have been made by several groups. [85,86]

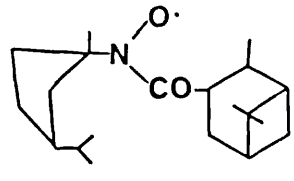
In the present work, the radicals **(104)**, **(109)**, (113) and (116) were generated in dichloromethane from their corresponding hydroxamic acid precursors using alkaline potassium hexacyanoferrate III solution.



(104)



(109)



(113)

The low temperatures required for this work presented difficulties in the choice of solvent. The following criteria were essential, the solvent should NOT:

(i) absorb in the spectral region of interest

(ii) be optically active

(iii) have the same density as water (to allow generation of the radical in a 2-phase system).

(iv) interact with the solute

(v) freeze above -70°C.

For these reasons dichloromethane was used in preference to benzene. To allow greater solubility of the radical at low temperature, methanol (1:3) was added. The CD curves for the above radicals were recorded at room temperature and -55 to -60°C.

At room temperature the CD curve of **(104)** was inconclusive. At -60°C there was some evidence of optical activity being developed. However, it was quite clear that even lower temperatures would be required in order to acquire reasonable data. In view of the inherent difficulties encountered with the solvent system, lower temperature (-120 to 150°C) CD work was not carried out.

The CD curve of (109) was first recorded at -60°C in an attempt to prevent decay of the radical by disproportionation. However, even at -60°C disproportionation occurred at such a rate that only a short observation of the true curve could be obtained and no reliable data was collected.

Radicals (-)-(113) and (+)-(116) showed strong CD curves at room temperature. The CD curves for (116)

at room temperature and at -55°C and -60°C are shown in fig. 11. The CD data of these compounds are collated in tables 7 and 8 respectively.

The bulky rigid pinanyl groups appear to be critical in these type of acyl nitroxides if CD curves are to be observed. All CD curves are Cotton effects (also termed ellipiticity bonds or Cotton bands). Radical (-)-**(113)** showed a positive Cotton effect whereas (+)-**(116)** showed a negative Cotton effect. The increased Cotton effect observed at lower temperatures suggests that a conformational equilibrium exists in the **(116)** system.

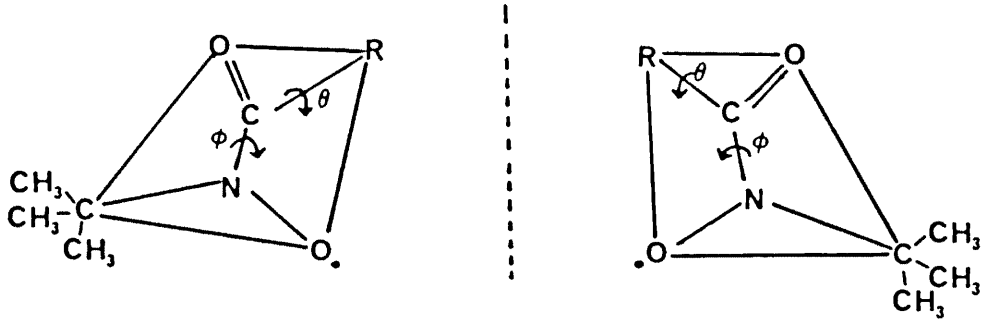


FIG 11a

In dinitrobenzoyl nitroxide (19), it has been shown[23] that the carbonyl carbon and the nitroxide nitrogen centres are both essentially planar and that there is a dihedral angle between these two planes of about 14°. Two enantiomeric conformations will be present (A and B Fig. 11a; R = 3,5-dinitrophenyl), but since there is no chiral substituent in the molecule, these will be of equal energy and hence equally populated.

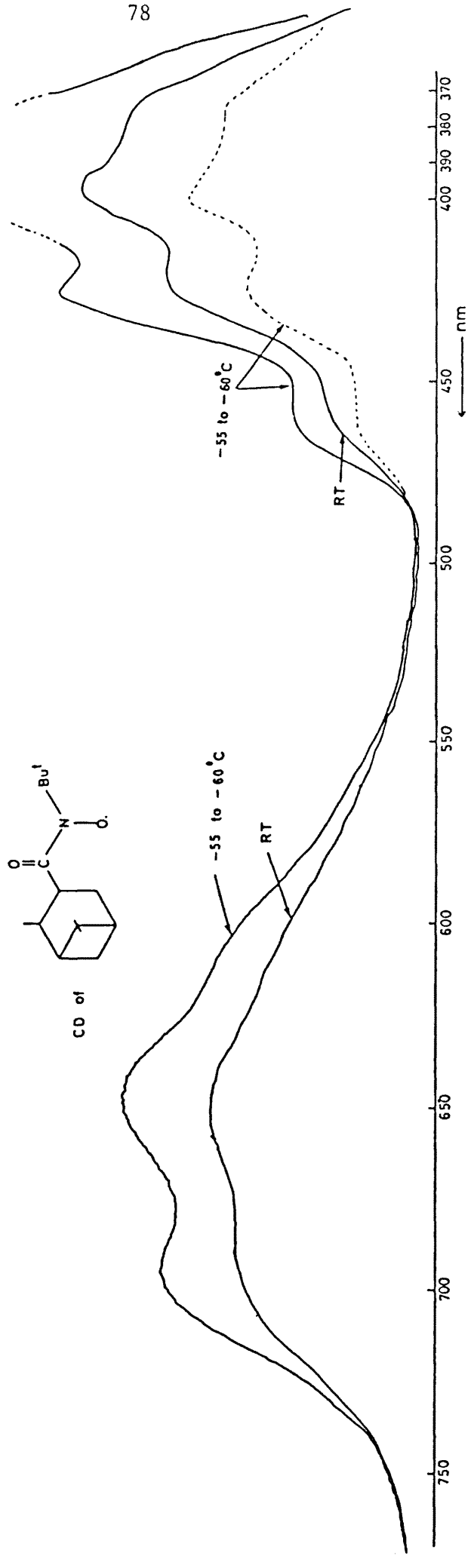
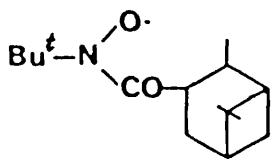

CD of
-55 to -60°C
RT
-55 to -60°C
RT
370
380
390
400
450
500
550
600
650
700
750
nm

FIG. 11

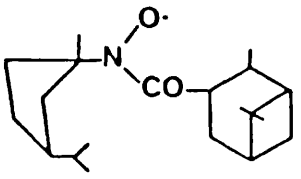


(+)-(116)

Room Temperature		
λmax (nm)	ΔE	$[\theta]$
695	0.070	230.6
647.5	0.081	269.0
447.5	0.033	110.2
426	0.099	325.4
397.5	0.137	450.9

−55 to −60 °C		
λmax (nm)	ΔE	$[\theta]$
695	0.103	340.8
647	0.119	392.0
447.5	0.043	143.5
426	0.134	440.7
398	0.184	609.8

TABLE 7 CD data for (+)-(116)



(-)-(113)

Room Temperature		
λmax (nm)	ΔE	[θ]
695	0.044	144.6
655	0.046	152.6
455	0.042	139.2
422.5	0.113	373.9
397	0.152	502.2

TABLE 8 CD data for -(113)

However, in **(116)** R (Fig. 11a) is the chiral bulky pinanyl group, so that the two conformations become diasteromeric with different energies and different populations. The excess of one of these, with its twisted CONO· chromophone (ϕ = 0) might be expected to result in CD effects. The magnitude of such effects will depend on the population difference between the two conformations. As the temperature is lowered it may be that one conformation is preferentially 'freezing out'. If time had allowed, a controlled variable temperature experiment could have been carried out to explore conformational population.

The two major CD bands observed for (113) are both of the same sign. The uv spectra of (113) and (116) show vibrational fine structure. Both radicals show maxima in the region 630-700 nm due to the $n \rightarrow \pi^*$ transition of the nitroxide function. The shape and appearance of the CD curve in this region closely resembles the absorption curve observed by uv spectroscopy. The curve showing maxima at $\sim$ 400 nm is probably due to a $\pi \rightarrow \pi^*$ transition.

In the absence of effects from overlapping electronic transitions the integrated area under the CD curve is proportional to the rotational strength R of the transition, according to equation 2:

$$R = \frac{3hc(10)^3 1n10}{32\pi^3 N} \int \frac{\Delta\varepsilon}{\nu} d\nu \qquad \text{Equation 2}$$

The rotational strength is a direct measurement of the intensity of the dichroism (i.e. of the magnitude of the optical rotatory power). The optical rotation of **(104)** is +6.6° (c = 0.05 in $CHCl_3$) and the molecule shows little CD activity. For **(116)** the optical rotation is +48.1° (c = 0.01 in $CHCl_3$) and much greater dichroism is observed.

A parallel could be made between the magnitude of the observed CD curves and enantioselectivity in hydrogen atom transfer reactions, since both are measures of how chirality is expressed in a molecule. If this comparison is valid then one might expect to see greater enantioselectivity in oxidations involving the diastereomeric nitroxide **(116)** than for the fenchelyl nitroxide (104).

CHAPTER 4

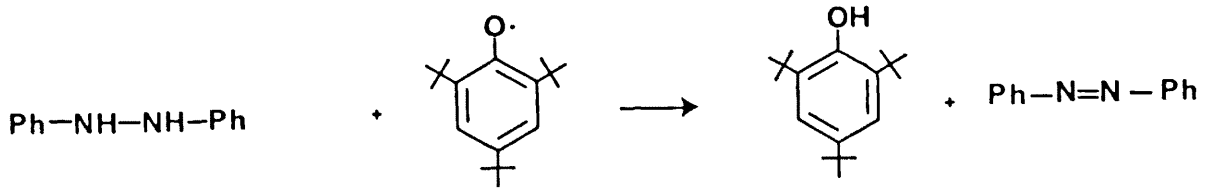
ESTIMATION OF O-H BOND STRENGTHS

The initial aim of this project was, by using hydrogen atom transfer reactions, to demonstrate the occurrence of a maximum in a plot of enantioselectivity vs. O-H bond strength for reactions of the type:

$$XYNO\cdot + ArCHOH \longrightarrow XYNOH + ArR\dot{C}OH$$

Once the synthesis of the required series of N-(alkyl)benzohydroxamic acids had been completed it was therefore necessary to estimate the O-H bond strengths for these compounds.

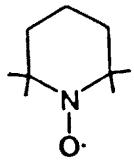
The first determination of the differences in the heat of formation in solution of a free radical and its hydrogenated precursor was carried out by Mahoney et al.[68] Using microcalorimetry, Mahoney's group determined the solution enthalpy for the reaction of hydrazobenzene **(117)** with 2,4,6,-tri-t-butylphenoxy radical **(118)** to give 2,4,6-tri-t-butylphenol **(119)** and trans-azobenzene **(120)**.



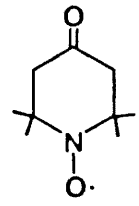
(117) **(118)** **(119)** **(120)**

Using available thermochemical data for hydrazobenzene and trans-azobenzene, the heat of formation difference between the phenoxyl and phenol in solution and hence an O-H bond dissociation energy could be estimated.

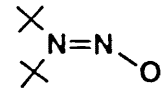
Ingold et al[87] have used e.s.r. spectroscopy to determine the equilibrium constant for the hydrogen transfer reaction of radicals **(11)**, **(121)** and **(122)**



(11)

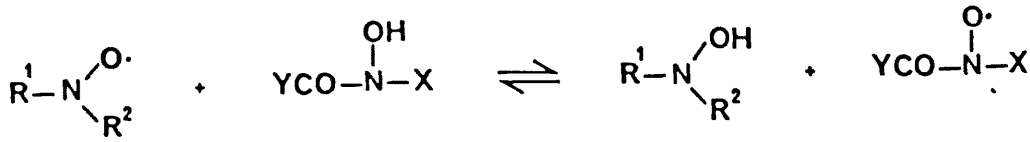


(121)



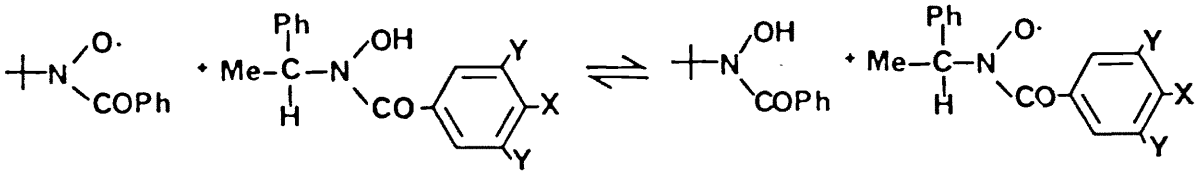
(122)

with certain hydroxylamines and oximes. Knowledge of the equilibrium constant gives an indirect method to estimate O-H bond energies for these radicals. Jenkins has extended Ingold's equilibrium method to calculate the O-H bond strengths of a series of substituted N-t-butylbenzohydroxamic acids (17a)→(d). The values obtained were 78.0, 77.5, 80.2 and 75.9 kcals mol^{-1} respectively, a range of 5 kcals mol^{-1}.[39] The accuracy of the results in the quantitative estimation of O-H bond strengths depends in part on the closeness of the O-H strength of the nitroxide acceptor **(123)** and the compound under study.



(123)

In the two series of substituted chiral N-(alkyl)benzohydroxamic acids studied in this work, two different nitroxide acceptors had to be used. The estimated bond strengths of the N-(α-methylbenzyl)--benzohydroxamic acids were expected to be ⩾ 78 kcals mol^{-1}. Jenkins has determined the O-H bond strength for N-t-butylbenzohydroxamic acid to be 78.0 kcals mol^{-1}. [39] Using **(124)** as the nitroxide acceptor it was possible to calculate the bond strengths of the secondary alkyl system.



(124)

The estimated bond strengths of the N-(fenchelyl)benzohydroxamic acids were ⩽ 78 kcals mol^{-1} and so **(121)** was used as a nitroxide acceptor. The hydrogen transfer from N-(fenchelyl)benzo-hydroxamic acid to 4-oxo-2,2,6,6-tetramethylpiperidin--1-oxyl can be readily detected by e.s.r. spectroscopy because the e.s.r. spectrum of the di-t-alkyl nitroxide (Fig. 12) is sufficiently different from that of the acyl nitroxide (Fig. 7)(Chapter 2A) to permit spectroscopic resolution of the individual radical components in an equilibrium mixture. This nitroxide acceptor was used because the O-H bond rupture energy estimated by Ingold (71.8 kcals mol^{-1})

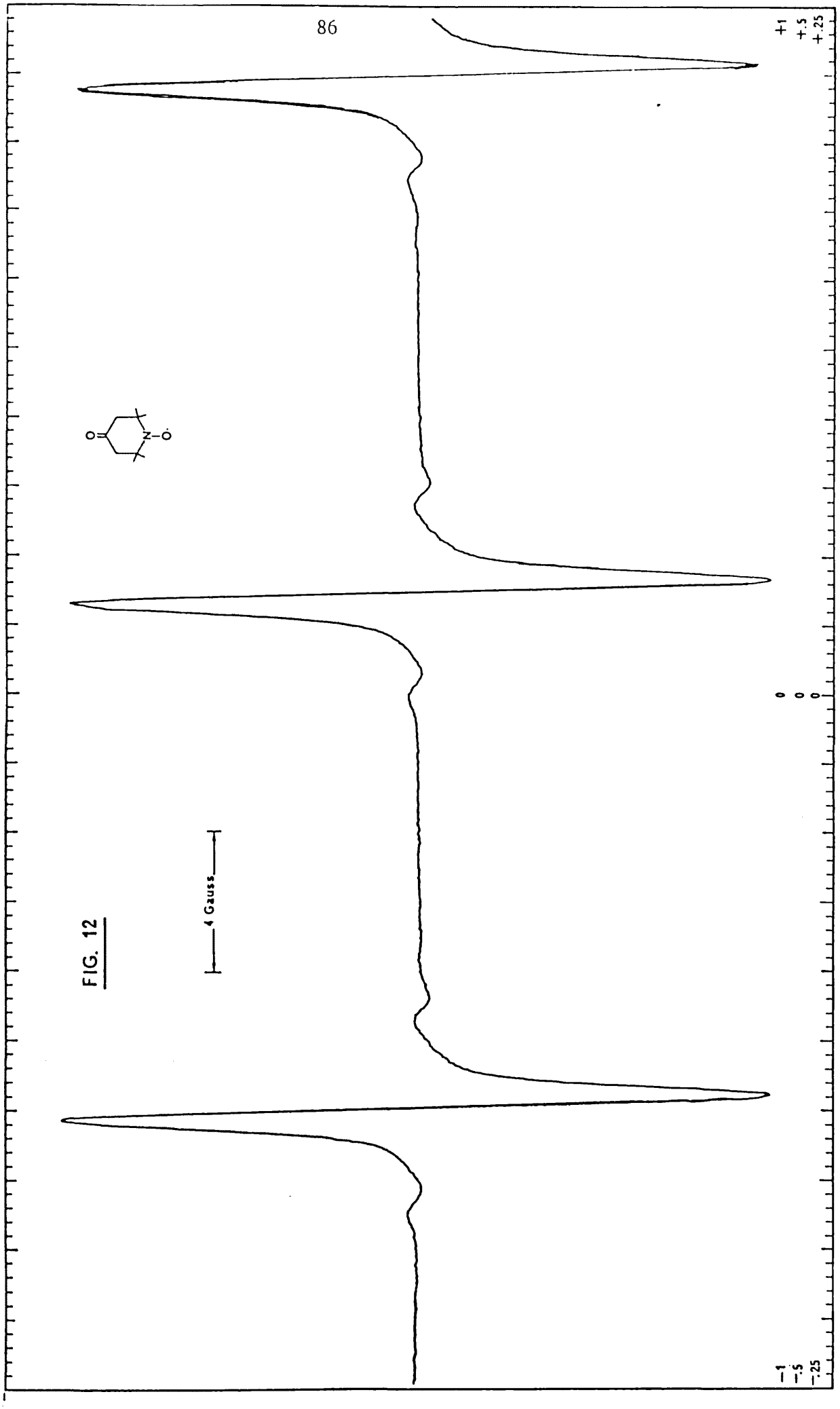
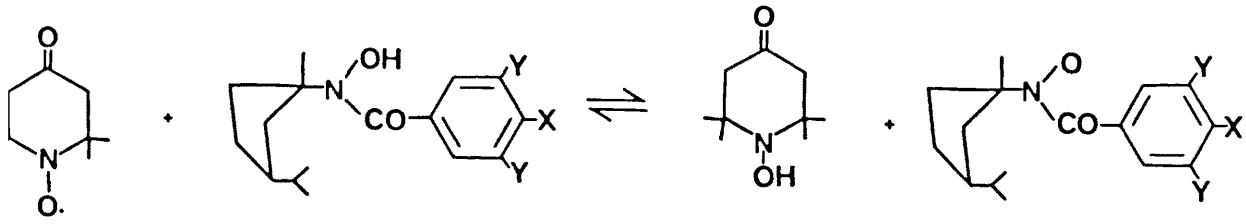


FIG. 12

for the hydroxylamine (121H) is in good agreement with the 71.9 ± 2.7 kcals mol^{-1} value estimated by Lebedev et al based from the heat of combustion and sublimation data.[12]

The practical procedure used for the estimation of the O-H bond strengths of both the secondary and tertiary alkyl substituted benzohydroxamic acids was identical except that in the former the nitroxide acceptor (124) had to be generated in known concentration from its hydroxamic acid precursor immediately prior to use, whereas in the latter the nitroxide acceptor **(121)** was commercially available.

The quantitative method for the estimation of O-H bond strengths is also the same and will only be described for the hydrogen transfer from the N-(fenchelyl)benzohydroxamic acids to **(121)**.



(121) A· BH (121H) AH B·

If A· + BH $\rightleftharpoons$ AH + B· is used to describe the reversible atom transfer between nitroxide (121) ≡ A· and the hydroxamic acid BH, then the equilibrium constant, K, for the process is given by the expression:

$$K = \frac{[AH][B\cdot]}{[A\cdot][BH]}$$

Provided known quantities of A· and BH are used in the experiment, evaluation of the constant can be effected by determination of the relative concentrations of the piperidin-1-oxyl and acyl nitroxide (A· and B· respectively) in an equilibriuim mixture. This should involve double integration of the e.s.r. spectrum. Electronic single integration[88] was employed in this work, and the necessary second integration achieved by measuring the areas of the absorption peaks recorded on an external chart recorder.

It is not necessary to measure absolute radical concentration in these experiments if it is assumed that no loss of total radical concentration occurs during equilibrium. Since only relative concentrations of the two radicals were required, spectrometer and sample tube calibration could be avoided. The maximum usable concentration of any radical was judged to be ca. 10^{-3}M as exchange broadening became apparent if this value was exceeded; no such effect could be detected at conc. $\leqslant 10^{-4}$M. Stock solutions of the pure hydroxamic acid (e.g. 104) and 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (Kodak) were separately prepared in purified 'AnalaR' benzene. ESR examination of the hydroxamic acid solutions at

this stage revealed the 'spontaneous' acyl nitroxide concentration to be below the detection limit of the spectrometer. Mixtures of the two reactants were prepared by careful transfer by microsyringe of known volumes of each stock solution to small sample tubes. A range of initial reactant [A·]:[BH] mixtures from 1:2 to 1:50 was prepared to permit observation of any concentration dependence of the estimated equilibrium constant. The resulting solutions were deoxygenated and allowed to stand for 10 minutes at room temperature before recording the derivative and integrated e.s.r. spectra. Long scan times (4 mins) and small modulation amplitude (0.8×10^{-1} Gauss) were used to optimize resolution. The integrator was adjusted for zero baseline drift throughout the field immediately prior to integration.

The first derivative spectrum of the equilibrium mixture obtained by mixing a solution of N-(fenchelyl)benzohydroxamic acid (104) (BH) with a solution of **(121)**(A·) is shown in Fig. 13. The individual peaks from the two nitroxides are well separated. Because of the slightly different a_N values for the two species, integration of peak d of the acyl nitroxide spectrum and peak a of the N-oxyl gave the most satifactory results. Because of the weakness of the acyl nitroxide lines compared to the N-oxyl lines the former had to be recorded at higher

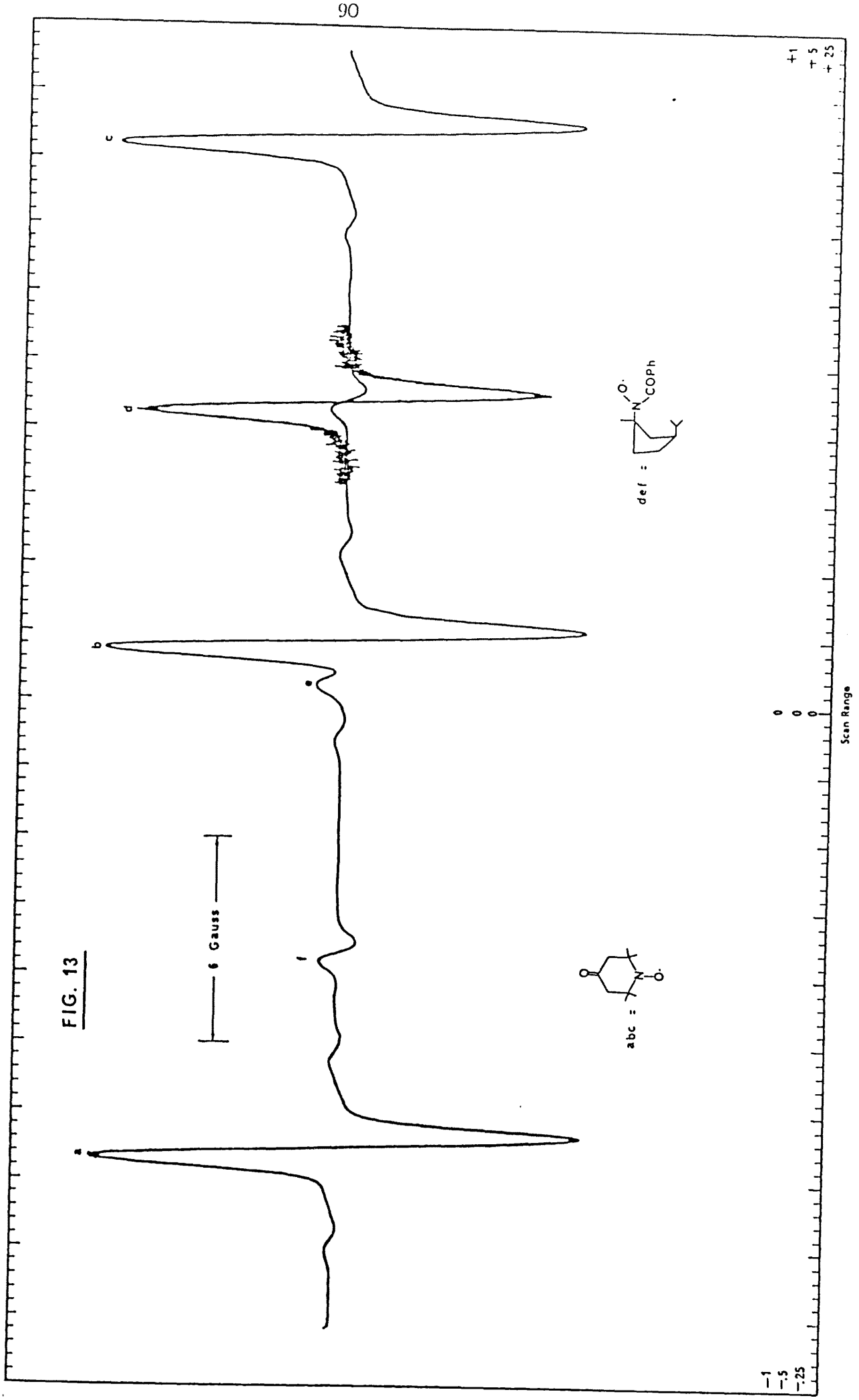


FIG. 13

gain. This 'weakness' is even more evident in the case of the dinitro- derivative (102), Fig. 14.

Fig. 15 shows a representative spectrum observed for the equilibrium reaction of N-(α-methylbenzyl)--benzohydroxamic acid with (109). The secondary alkyl group has an α-C-H group attached to the nitrogen. The nitrogen triplet observed in the secondary alkyl nitroxides is further split to give a six-line pattern because of the interaction with the α- hydrogen of the secondary alkyl group. The absorption spectrum shows marked overlap of peaks, though extraction of relative radical concentrations was fairly straightforward provided proper selection of peaks was made for integration. The integrated spectrum for the equilibrium mixture of N-(fenchelyl)benzohydroxamic acid (BH) and (121) A· (Fig. 13) is shown in Fig. 16.

$$A\cdot + BH \rightleftharpoons AH + B\cdot$$

If the initial concentrations of hydroxamic acid and piperidin-1-oxyl $[BH]_o$ and $[A\cdot]_o$ are denoted by x and y, then at equilibrium the concentrations of A·, BH, AH and B· will be (y-x), (x-α), α and α respectively, hence,

$$K = \frac{[AH][B\cdot]}{[A\cdot][BH]}$$

$$= \frac{\alpha^2}{(y-\alpha)(x-\alpha)}$$

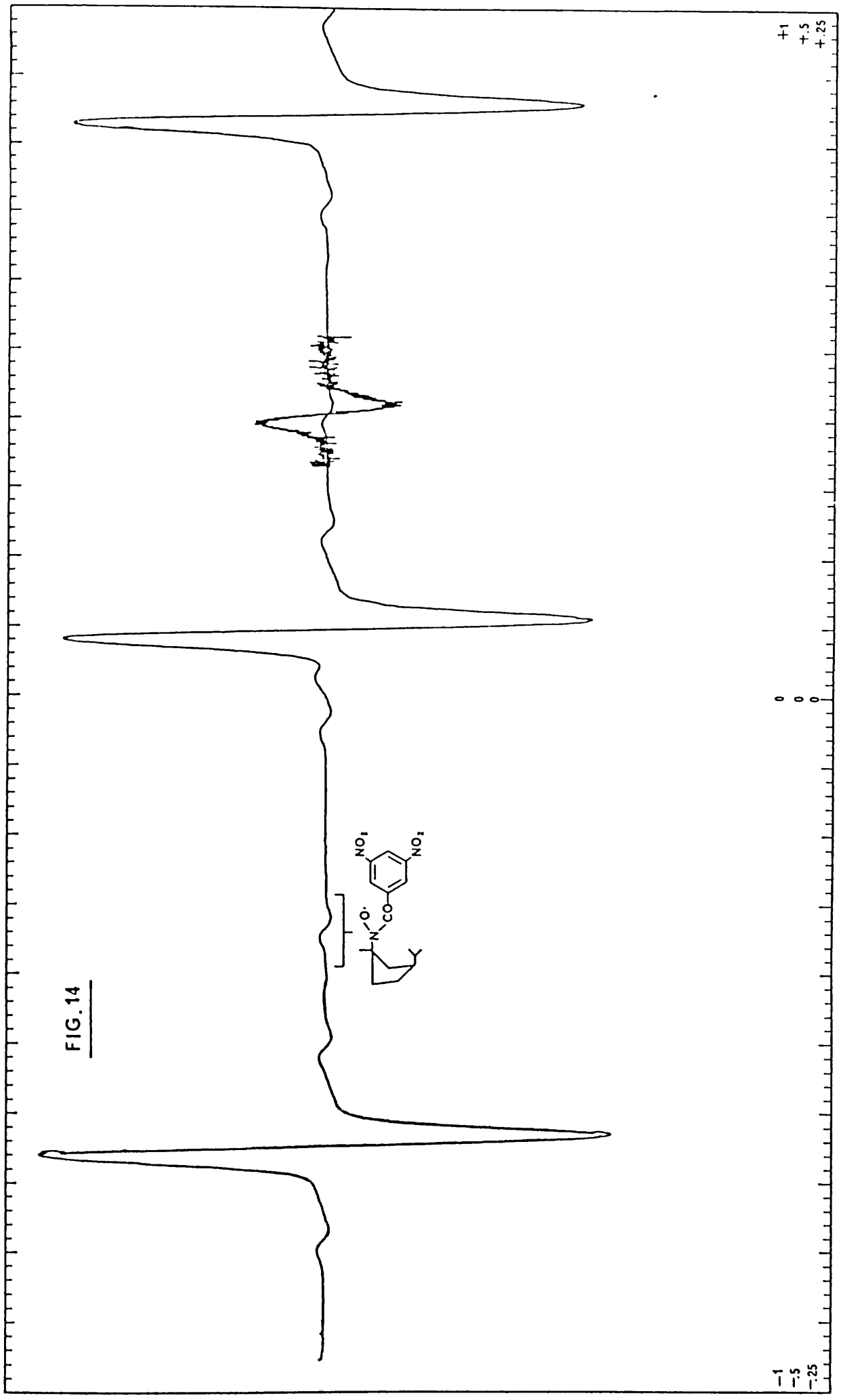
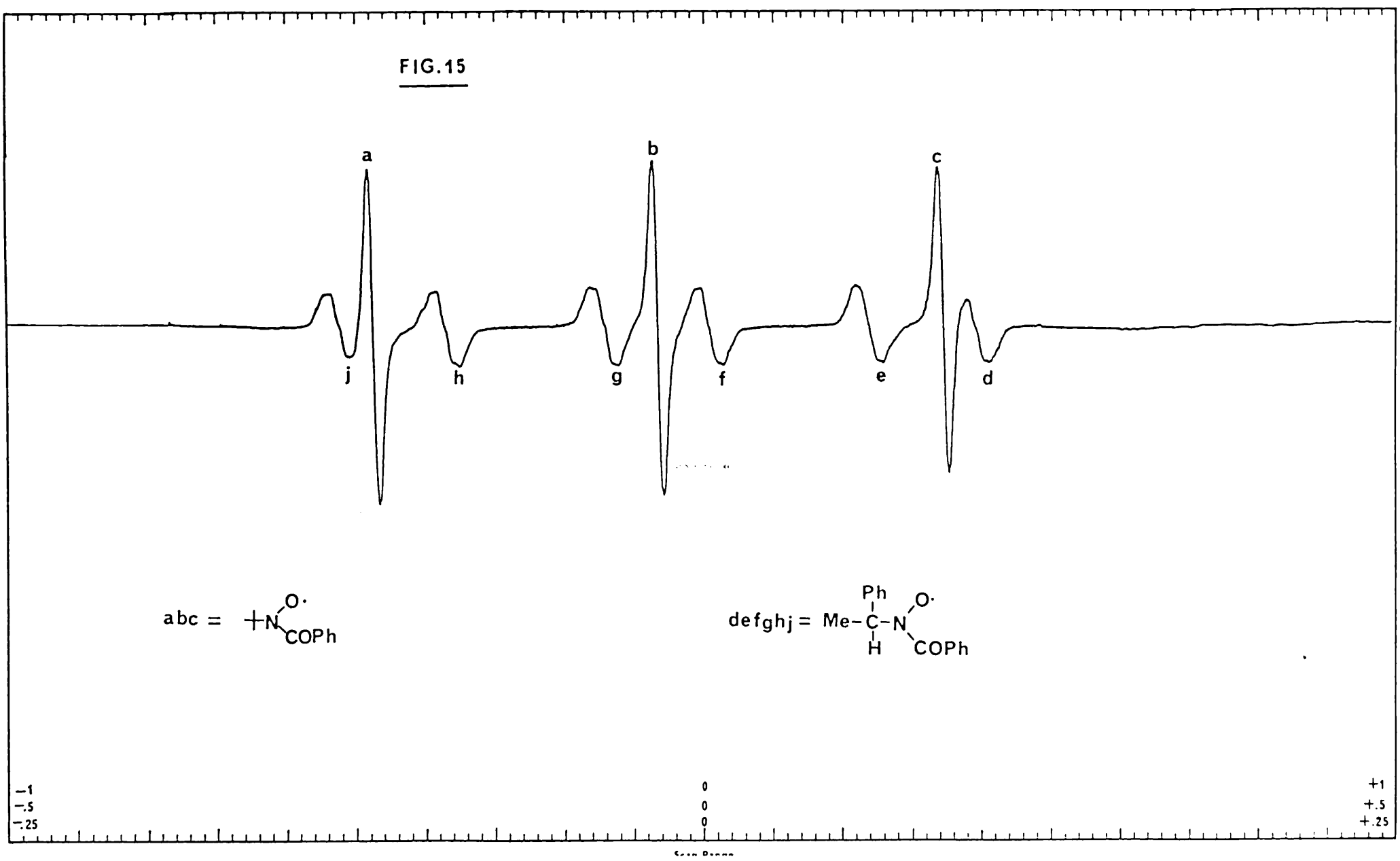


FIG. 14

FIG.15



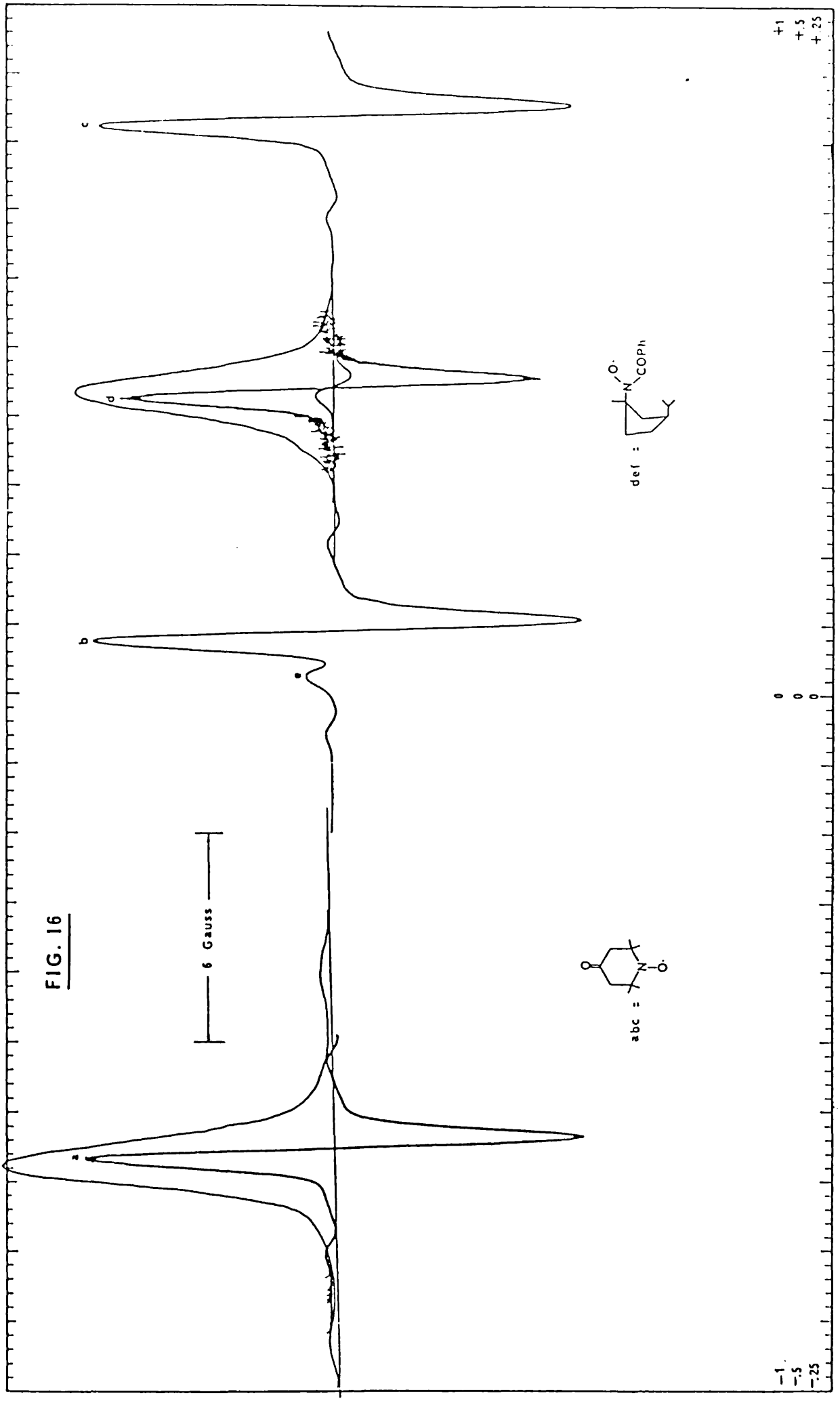


FIG. 16

If the ratio [B·] :[A·] determined by e.s.r. at equilibrium is denoted by m, then

$$m = \frac{\alpha}{y-\alpha} \quad \text{or} \quad \alpha = \frac{y}{1+1/m}$$

Thus K becomes:

$$K = \frac{m^2 y}{x(m+1)-my}$$

The potential reproducibility of this method for determination of K is shown in table 9.
Statistical analysis of these six independent results affords mean and standard deviation for the equilibrium constant at this temperature of:

$$4.08 \pm 0.21 \times 10^{-5}$$

The equilibrium constants determined for all five substituted N-(fenchelyl)benzohydroxamic acids by an identical procedure are collected in table 10.
Examination of table 10 shows that the electronic nature of the substituent has an effect upon the equilibrium position. The value for the dimethyl amino derivative is much higher than expected. Electron-releasing substituent would appear to facilitate hydrogen atom transfer to the di-t-alkyl nitroxide whereas a strongly electron withdrawing 4-nitro group clearly hinders such a process.

Approx. initial concentration ratio $BH_o : A_o$	Calculated K 10^5 (PhH, 21°C)
1 : 1	4.03 4.42 4.13
2 : 1	4.16 3.80 3.95

TABLE 9.

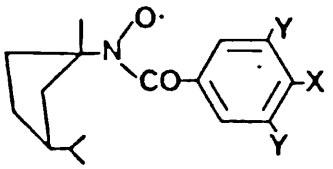


TABLE 10

Calculated K values for the fenchelyl nitroxides

Number	X	Y	Calculated K (10^5, PhH, 21°C)	No. of Results
102	H	NO_2	1.20 ± 0.43	3
103	NO_2	H	1.46 ± 0.25	4
104	H	H	4.08 ± 0.21	3
105	OMe	H	1.62 ± 0.22	4
106	$N(Me)_2$	H	4.9 ± 1.5	5

Knowledge of the equilibrium constant K enables the change in Gibbs free energy associated with a system at thermodynamic equilibrium to be calculated:

$$\Delta G = -RT\ln K$$

Table 11 shows the ΔG values (in kcals mol^{-1}) calculated for (102)→(106) in benzene at 21°C.

TABLE 11 Calculated ΔG values for the fenchelyl nitroxides.

Number	Substit-uent	ΔG(Kcals mol^{-1})
102	3,5-$(NO_2)_2$	6.56 ± 0.17
103	4-NO_2	6.45 ± 0.11
104	4-H	5.85 ± 0.01
105	4-OMe	5.05 ± 0.07
106	4-N(Me)	5.77 ± 0.20

If the entropy change ΔS for the hydrogen atom transfer equilibrium is assumed to be negligible then the enthalpy change ΔH may be equated with ΔG and will represent the difference between the summed solution enthalpies of formation (ΔH_f) of the products and reactants: i.e.

$$\Delta H^{PhH} = \left[(\Delta H_f)^{PhH}_{B\cdot} - (\Delta H_f)^{PhH}_{BH}\right] - \left[(\Delta H_f)^{PhH}_{A\cdot} - (\Delta H_f)^{PhH}_{AH}\right]$$

where AH ≡ 132H and BH represents the tertiary alkyl

hydroxamic acid.

Ingold *et al* estimated a calorimetric value for $\left[(\Delta H_f)_{A\cdot} - (\Delta H_f)_{AH}\right]$ in carbon tetrachloride solution at 25°C as 19.7 ± 0.43 kcals mol^{-1}, and argued that the specific solvent effects involved in a transfer from CCl_4 to benzene (at infinite dilution) contributes only negligibly (1 kcal mol^{-1}). Although benzene was used as the solvent in the equilibrations, Ingold's CCl_4 value will be used in the following treatment,

hence $\left[(\Delta H_f)_{B\cdot}^{PhH} - (\Delta H_f)_{BH}^{PhH}\right] = \Delta H^{PhH} + 19.7 \pm 0.43$ kcals mol^{-1}

The differences in enthalpy of formation calculated for the fenchelyl aroyl nitroxides and their corresponding hydroxamic acids are given in table 12.

In the secondary alkyl system where AH ≡ 135H Jenkins[39] estimated a value of $\left[(\Delta H_f)_{A\cdot} - (\Delta H_f)_{AH}\right]$ in benzene solution at 15°C of 25.93 ± 0.44 kcals mol^{-1}, hence for the (α-methylbenzyl) benzoyl nitroxides and their corresponding hydroxamic acids the differences in enthalpy of formation becomes:

$$\left[(\Delta H_f)_{B\cdot}^{PhH} - (\Delta H_f)_{BH}^{PhH}\right] = \Delta H^{PhH} + 25.93 \pm 0.44 \text{ kcals mol}^{-1}$$

and these values are shown in table 13.

Bond dissociation energies (D(O-H)) for the hydroxamic acids in solution may be estimated only if a reliable value is available for the solution phase enthalpy of formation of a hydrogen atom:

$$BH \longrightarrow B\cdot + H\cdot$$

$$\therefore \quad D(O\text{-}H) = \left[(\Delta H_f)_{B\cdot}^{PhH} - (\Delta H_f)_{BH}^{PhH}\right] + (\Delta H_f)_{H\cdot}$$

As a $(\Delta H_f)_{H\cdot}^{sol}$ value of 52.1 kcals mol^{-1} has been used in previous bond energy work, this value is assumed in the present treatment. Estimated D(O-H) values for the tertiary alkyl and secondary alkyl benzohydroxamic acids are shown in tables 12 and 13 respectively.

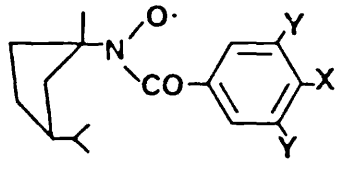
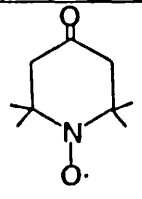


TABLE 12

Estimated O-H bond strengths for the fenchelyl nitroxides.

Number	X	Y	$(\Delta Hf)_{B\cdot}^{PhH} - (\Delta Hf)_{BH}^{PhH}$	D(O-H) Kcals mol^{-1}
102	H	NO_2	26.26	78.4
103	NO_2	H	26.15	78.25
104	H	H	25.55	77.65
105	OMe	H	24.75	76.85
106	$N(Me)_2$	H	25.47 ?	77.6 ?

A·≡ 

$$\left[(\Delta Hf)_{A\cdot} - (\Delta Hf)_{AH}\right] = 19.7 \text{ kcals } mol^{-1}.$$ [12]

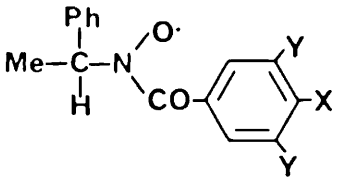


TABLE 13

Estimated O-H bond strengths for the α-methylbenzyl nitroxides.

Number	X	Y	$(\Delta Hf)^{PhH}_{B} - (\Delta Hf)^{PhH}_{BH}$	D(O-H) Kcals mol^{-1}
107	H	NO_2	27.72	79.82
108	NO_2	H	27.58	79.68
109	H	H	27.19	79.29
110	$N(Me)_2$	H	25.79	77.89

$$A^{\cdot} \equiv +N^{O^{\cdot}}_{COPh} \left[(\Delta Hf)_{A^{\cdot}} - (\Delta Hf)_{AH}\right] = 25.93 \text{ kcals mol}^{-1}.^{39}$$

The above treatment of experimental data assumes that specific solvent interations with the hydroxamic acids and/or acyl nitroxides are unimportant and thus contribute negligibly to the ΔH.

Thus: $\left[(\Delta H_f)^{gas}_{B^{\cdot}} - (\Delta H_f)^{sol}_{B^{\cdot}}\right] = \left[(\Delta H_f)^{gas}_{BH} - (\Delta H_f)^{sol}_{BH}\right]$

Jenkins has carried out the equilibration of **(17a)** with (132) using benzene, n-hexane and carbon tetrachloride. The ΔH values, (in kcals mol^{-1}) obtained were 5.06 ± 0.17, 5.40 ± 0.08 and 6.23 ± 0.07 respectively. Jenkins concluded that the increase in ΔH observed in benzene solution is probably due to

additive solvent interation with all the participating species and that specific interations with one particular solute are unimportant.

The 1 kcal mol^{-1} increase in the calculated ΔH solvent value for benzene could not explain the 5 kcal mol^{-1} gradation of D(O-H) estimated for the 4-substituted t-butylbenzohydroxamic acids.

In its initial concept, this work required a wide range of O-H bond strengths and extrapolation of Jenkins data suggested that the 4-dimethylamino through to the 3,5-dinitro derivative should embrace a variation of at least 10 kcals mol^{-1}. Our results are clearly inconsistant with this ideal. The first measurements were in fact made on the secondary alkylhydroxamic acids (table 13), and it seemed possible that a steric component played an important role in the wide spread of D(O-H) reported for the t-butyl system. However, the results with the fenchelyl derivatives (table 12) were very similar to those for the secondary alkyl system and so several of Jenkins's compounds were re-examined.

Jenkins suggested a correlation between the a_N hyperfine coupling constants of acyl nitroxides and the O-H bond energies estimated for their respective precursors. Figures 17, 18 and 19 show the plots of a_N versus D(O-H) for the t-butyl, N(fenchelyl) and N-(α-methylbenzyl)benzohydroxamic acids respectively.

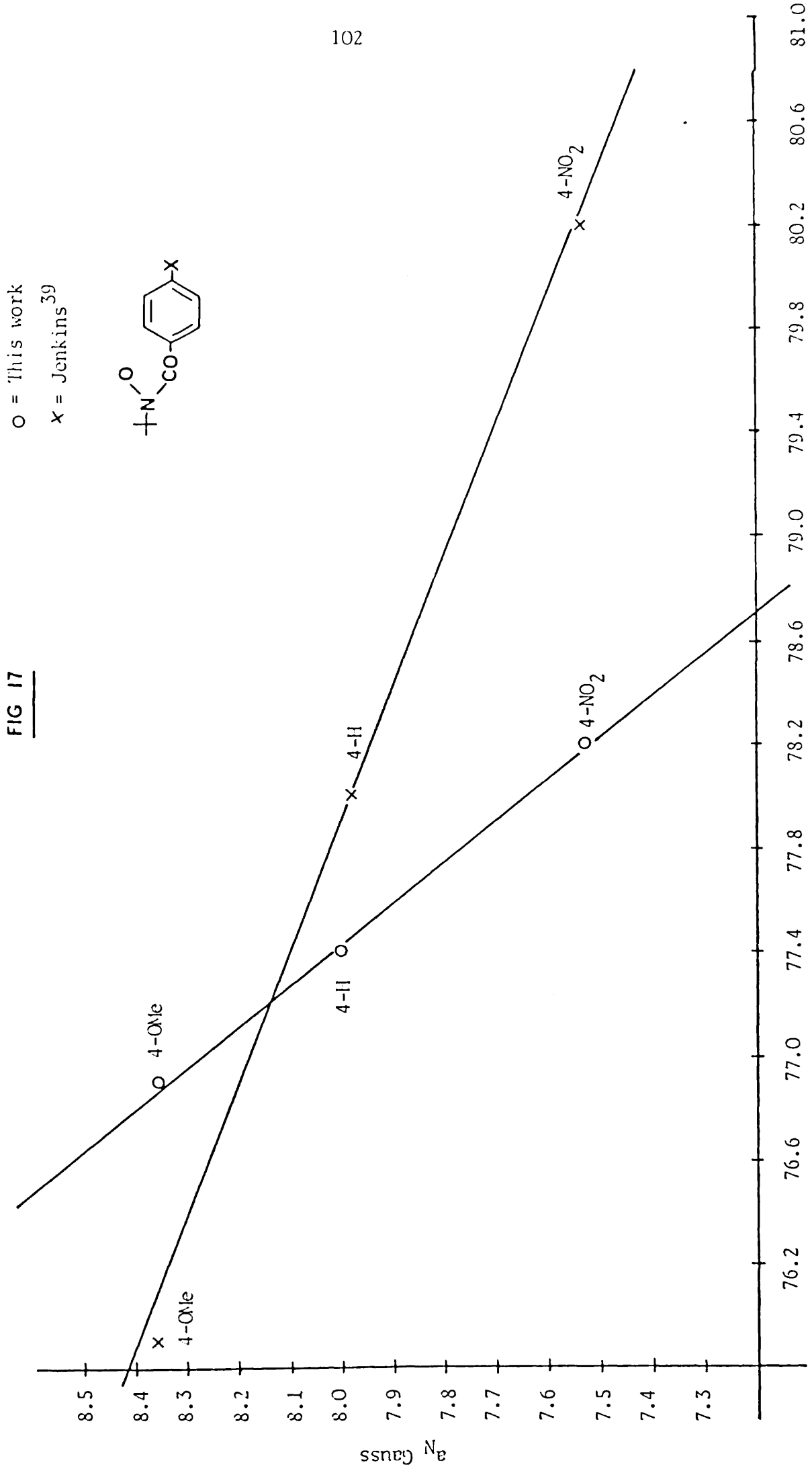

o = This work
x = Jenkins[39]
4-OMe
4-H
4-NO2
4-OMe
4-H
4-NO2
a_N Gauss
D(O-H) kcals mol^{-1}

FIG 17

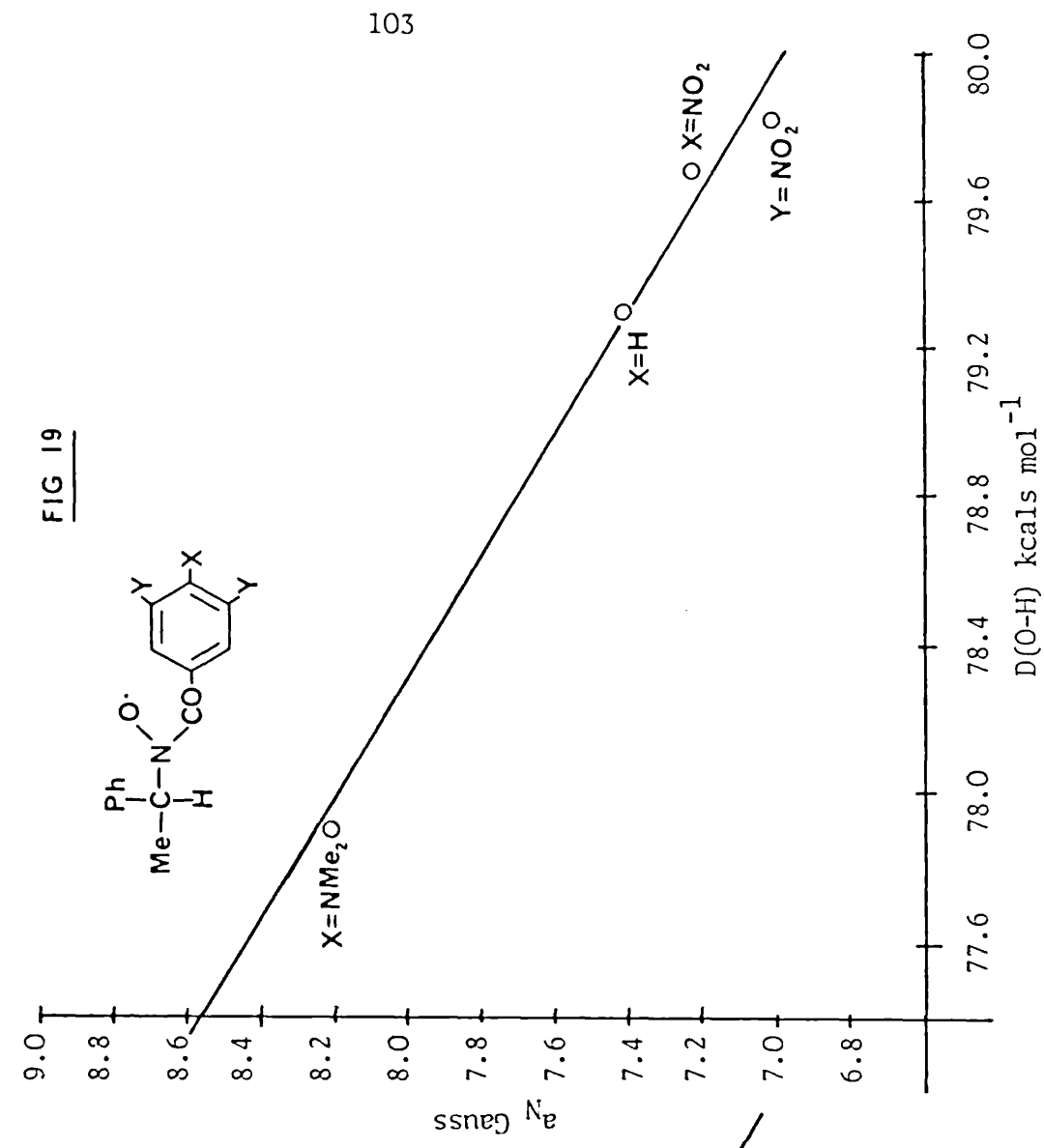


FIG 19
X=NMe2
X=H
X=NO2
Y=NO2
aN Gauss
D(O-H) kcals mol-1
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
77.6
78.0
78.4
78.8
79.2
79.6
80.0

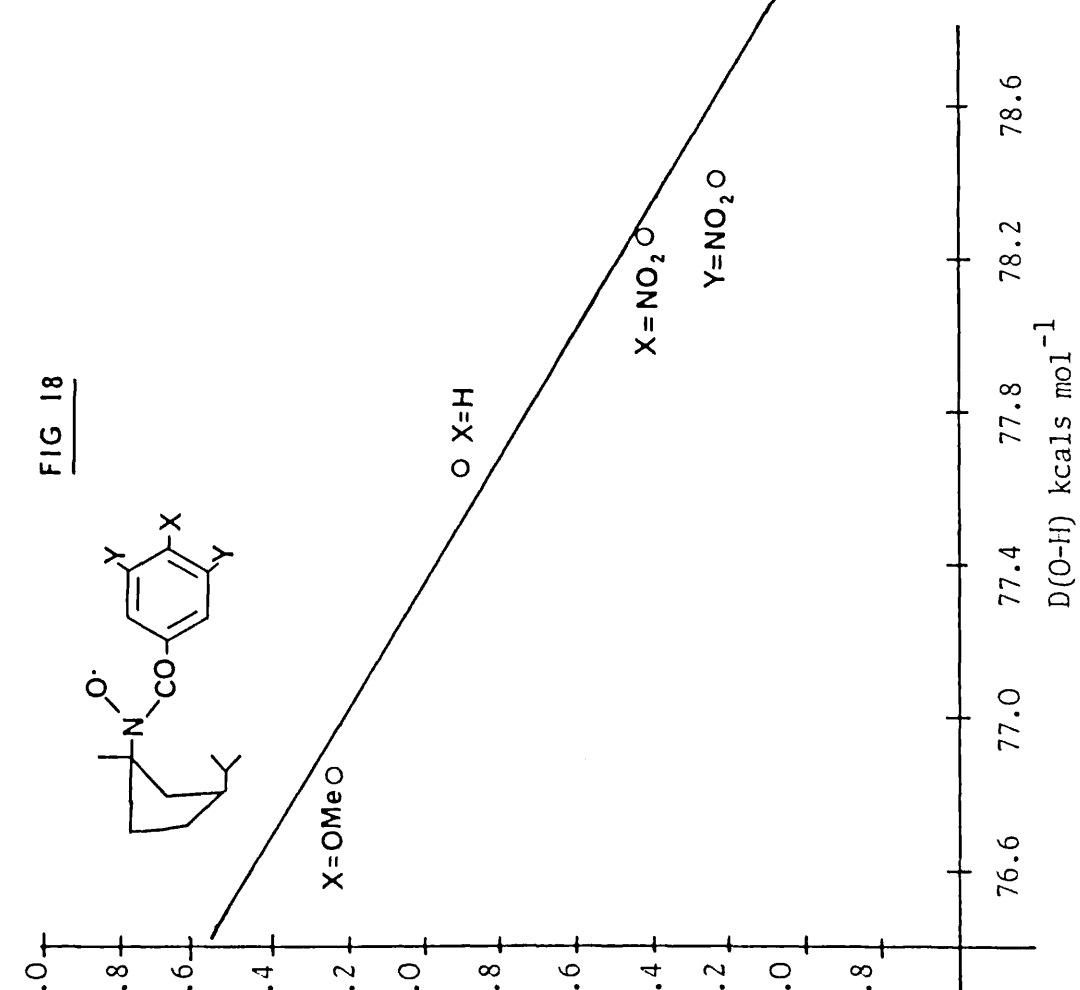


FIG 18
X=OMe
X=H
X=NO2
Y=NO2
D(O-H) kcals mol-1
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
76.6
77.0
77.4
77.8
78.2
78.6

Despite the excellent correlation found by Jenkins for the t-butyl system, his results could not be reproduced (table 14).

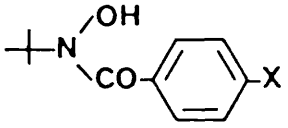


TABLE 14

Comparison of the estimated D(O-H) values of the t-butyl acyl nitroxides.

X	D(O-H) Jenkins[39]	D(O-H) This Work	K Jenkins[39]	K This Work
OMe	75.9	76.9	7.39×10^{-4}	2.2×10^{-4}
H	78.0	77.4	1.89×10^{-5}	1.05×10^{-4}
NO_2	80.2	73.2	5.4×10^{-7}	1.95×10^{-5}

Table 14 shows the large discrepancies between the calculated K values obtained by Jenkins compared to those obtained in this work.

The closest accord with Jenkin's results is found for the unsubstituted N-t-butylbenzohydroxamic acid. One possible source of error lies in a key procedural difference whereby the equilibration time used by Jenkins was several hours. In the present work it appeared that, as might be expected, equilibrium was established rapidly, but there was then, in some cases, at least, a gradual change not only in nitroxide ratio, but also in total radical

concentration, consistant with chemical change. This was expected for the secondary alkyl nitroxide but not for the fenchelyl system. The present results are therefore based on radical concentrations measured ca. 5 minutes after mixing. Results at different initial hydroxamic acid nitroxide acceptor ratio's were reasonably consistant, but the plots of D(O-H) versus a_N show that the D(O-H) value for the dimethyl--aminobenzoyl nitroxides do not fall on the a_N correlation plots. Neglecting these points the slopes of the plots a_N vs. D(O-H) for the fenchelyl and α-methylbenzyl systems are both ca. -0.6. This is significantly different from Jenkins -0.2 for the t-butyl system.

CHAPTER 5

EXAMINATION OF ENANTIOSELECTIVITY

The reaction which is of most importance for this piece of work is hydrogen atom transfer from a suitable benzylic alcohol to a chiral acyl nitroxide:

$$X^{*}YNO\cdot \quad + \quad ArCHOHR \longrightarrow X^{*}YNOH \quad + \quad Ar\dot{C}OHR$$

(19) **(50)**

$$R\cdot \quad + \quad BH \longrightarrow RH \quad + \quad B\cdot$$

The process is effectively irreversible since radical (50) once formed would be immediately scavenged by excess **(49)** to form ketone:

$$X^{*}YNO\cdot \quad + \quad Ar\dot{C}OHR \longrightarrow X^{*}YNOH \quad + \quad ArRCO$$

Enantioselectivity in hydrogen atom transfer reactions of this type was searched for using two different techniques. The first employed UV spectroscopy to determine the second order rate constants for the reaction between chiral radicals and chiral benzylic alcohols. The second method involved reaction of racemic alcohol and chiral acyl nitroxide and subsequent examination for enantiomeric excess by HPLC using a covalently bound chiral column. These two different techniques will be dealt with independently.

A. UV Kinetics.

Attack of a chiral nitroxide (+)R· on a chiral alcohol (+)BH leads to a diastereoisomeric transition state, the energy of which will be different to that obtained by reaction of (+)R· and (-)BH. The transition state with the lowest energy will proceed to products fastest. If this is the case, one enantiomer of the radical will react preferentially with the alcohol (i.e. there is enantioselectivity) and the second order rate constants for the two reactions will be different.

Kinetic ESR techniques[89] provide a valuable method for monitoring radical-substrate reactions but for reasons which will be discussed later, this technique was not chosen for the present study.

Reaction of the highly coloured acyl nitroxide (see chapter 3B) with the chiral alcohol leads to colourless products and so the kinetics of this reaction can be monitored by UV spectroscopy. A measurement of the optical density as a function of time permits the rate of the reaction to be calculated. UV spectroscopy was used in preference to ESR for three main reasons,

i) A 1^{o} rise in temperature is roughly equivalent to a 10% rise in reaction rate. The maximum difference in second order rate constants we had estimated might be observed was approximately 10%. It was therefore

critical that all the kinetic runs were carried out at constant temperature (± 0.2°C). The thermostated cell holder of the UV spectrometer could hold 4 cuvettes (allowed multiple runs) within a temperature range of ±0.1°C for at least 24 hours. It is difficult to ensure a constant uniform temperature in the ESR cavity of ±0.5°C for long periods of time.

ii) Accurate alcohol concentrations could be calculated by careful weighing of the cuvette and its contents.

iii) The technique is quick, easy and reproducible. Once the reaction had been set up, the spectrometer could be left to automatically record absorptions at x minute intervals until reaction was complete, i.e. there was no detectable change in optical density.

The optically active benzylic alcohols phenylethanol and methyl mandelate were commercially available (Aldrich and Fluka chemical companies respectively).

The bond strengths of the aroyl substituted N-(fenchelyl)benzohydroxamic acids depend on the nature of the substituent (see Chapter 4). A high bond dissociation energy is indicative of a strong tendency for hydrogen atom abstraction in the nitroxide. Thus, the dinitro derivative (102) (D(O-H) = 78.4 kcals mol^{-1}) will abstract the benzylic hydrogen from the alcohol faster than the more weakly

bonded methoxy derivative **(105)** (D(O-H) = 76.85 kcals mol^{-1}). In order to obtain reasonable reaction rates for the concentration of radicals which were most convenient for the UV studies, a 100-fold excess of alcohol was necessary. This ratio of substrate to radical ensured that the kinetics were truly pseudo-first order.

The procedure for a typical kinetic run is outlined below:

The silica cuvette was weighed both empty and containing a solution of the freshly prepared (+)-acyl nitroxide in purified 'AnalaR' benzene. 50 µl of (+)-phenylethanol was introduced to the cuvette by microsyringe and the total mass recorded. The cuvette was placed in the thermostated cell holder of the UV spectrometer at 40°C. The optical density of the reaction mixture was recorded at five minute intervals for several half-lives and then scans were made every 10 minutes until reaction was complete. Although in practice it was possible to use the visible band to follow the reaction of radical with alcohol, it proved more convenient to use the more intense UV band at 335nm where there appeared to be no interference from, for example, the products formed. Fig. 20 shows a typical scan recorded at 40°C, λ = 335nm.

For reactions involving methyl mandelate the solid alcohol was added to the preweighed empty

Reaction of (+) 104 with (±) phenylethanol

Time interval = 10 minutes.

λ = 335nm.

T = 40°C

FIG 20

cuvette and this mass recorded prior to introduction of the benzene radical solution. The radical concentration at time, t, is taken to be directly proportional to the height of the recorded UV absorption at time t,

$$R^{\cdot} + BH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RH + B^{\cdot}$$

$$B^{\cdot} + R^{\cdot} \xrightarrow[k_2]{} RH + C$$

In a given abstraction experiment, the rate expression for acyl nitroxide depletion will be given by:

$$\frac{-d[R^{\cdot}]}{dt} = k_1[R^{\cdot}][BH] + k_2[B^{\cdot}][R^{\cdot}]$$

where $[R^{\cdot}]$ and $[BH]$ represent the instantaneous concentration of the nitroxide $R^{\cdot}$ and the benzylic alcohol BH. The back reaction (k_{-1}) is assumed to contribute negligibly to this expression since the radical $B^{\cdot}$ will be very rapidly scavenged by further acyl nitroxide. Since $k_2 >> k_1$ application of the steady state approximation to radical $B^{\cdot}$ gives,

$$\frac{d[B^{\cdot}]}{dt} = k_1[R^{\cdot}][BH] - k_2[R^{\cdot}][B^{\cdot}] = 0$$

i.e. $k_2[R^{\cdot}][B^{\cdot}] = k_1[R^{\cdot}][BH]$

and hence:

$$\frac{-d[R^{\cdot}]}{dt} = 2k_1[R^{\cdot}][BH]$$

where $2k_1 = k_3$ for the overall process of:

$$2R^{\cdot} + BH \longrightarrow 2RH + C \qquad \text{equation 3.}$$

The concentration of the benzylic alcohol BH is much greater than the initial nitroxide concentration (i.e. $[R^{\cdot}]_o \ll [BH]$) and so [BH] will be virtually unaffected by reaction progess. Equation 3 reduces to a pseudo-first-order dependence upon $[R^{\cdot}]$ alone:

$$\frac{-d[R^{\cdot}]}{dt} = k_{obs}[R^{\cdot}] \text{ where } k_{obs} = k_3[BH]$$

$$\ln R^{\cdot} = k_{obs}t + \text{constant}$$

when $R^{\cdot} = R^{\cdot}_o$ at $t = 0$, $\ln R^{\cdot} = \text{constant}$.

Therefore:

$$\ln R^{\cdot} = -k_{obs}t + \ln R^{\cdot}_o$$

A plot of ln(peak height)($[R^{\cdot}]$) versus time (t) should give a straight line plot with a slope = $-k_{obs}$. This is indeed the case and a typical plot is shown in Fig. 21.

The second order rate constant (k_3) can be calculated from k_{obs} by using the expression:

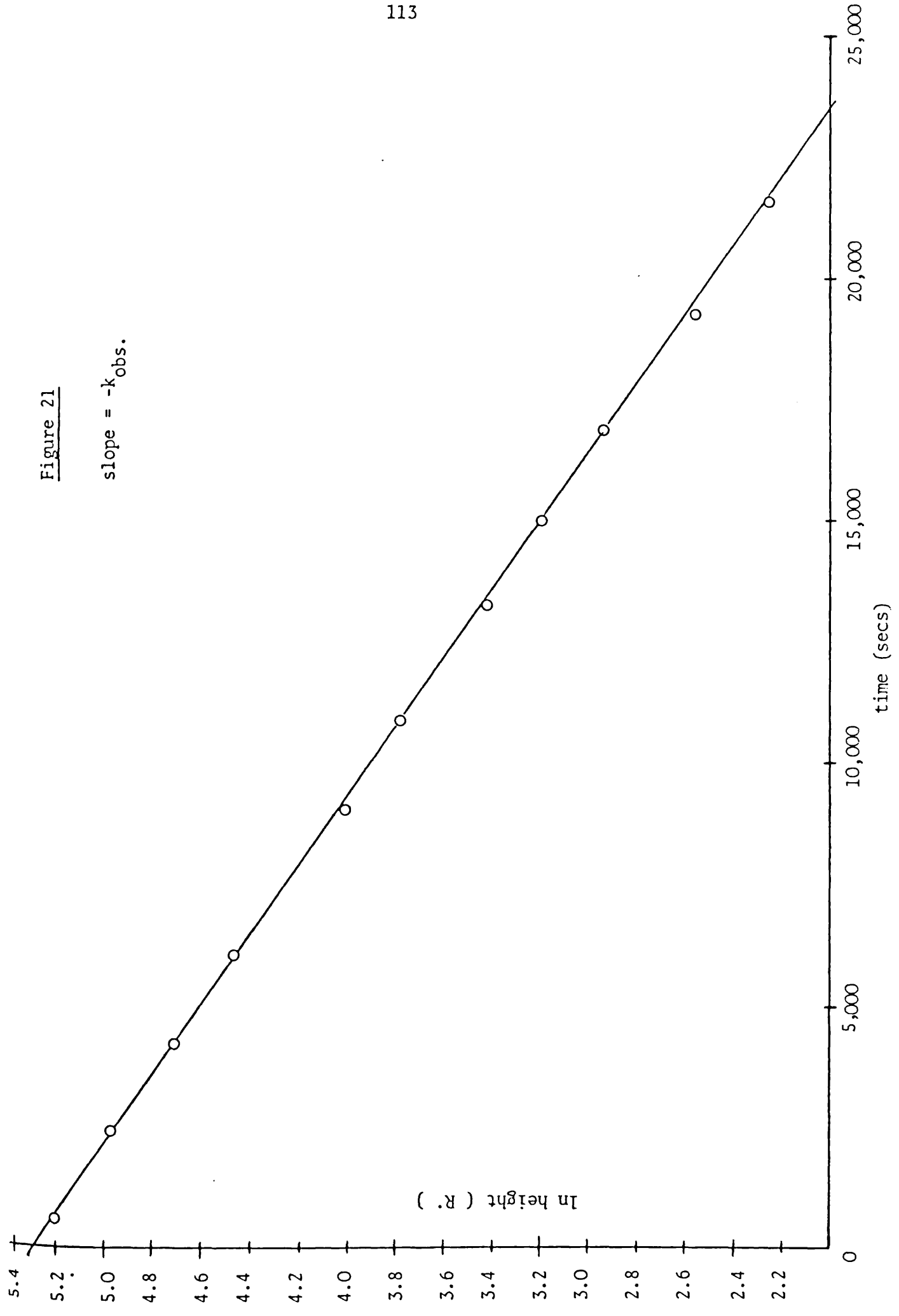


Figure 21

slope = $-k_{obs.}$

$$k_3 = \frac{k_{obs}}{[BH]}$$

Tables 15 and 16 show the second-order rate constants k_3 calculated for the reactions of racemic alcohol and chiral acyl nitroxides. Each calculated value is the mean of at least two independent kinetic runs. Usually the kinetics runs were carried out in duplicate. If the numerical results of these runs differed by more than 4% than the experiments were repeated. The mean values of the rate constants are recorded in the tables. Tables 15 and 16 show the dramatic effect that the substitution of electron donating and withdrawing groups into the acyl function has on the reactivity of these nitroxide radicals. The 3,5-dinitro derivative (102) reacts approximately 40 times faster with phenylethanol than does the 4-dimethylamino derivative (106).

The estimated bond strength for (106) was 77.6 kcals mol^{-1} (see chapter 4). This D(O-H) value did not fall on the a_N correlation plot constructed for radicals (102)→(106). The higher than expected bond strength value implies a reactivity comparable to that of the parent nitroxide (104). Kinetically however, the observed reactivity was five times less than (104). This suggests that the estimated D-(O-H) is indeed too high and in view of the low reactivity

TABLE 16. Rate constants for the reaction of the fenchelyl nitroxides with phenylethanol.

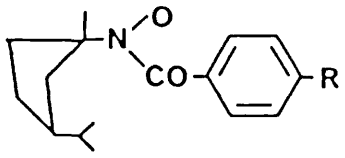
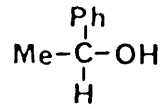
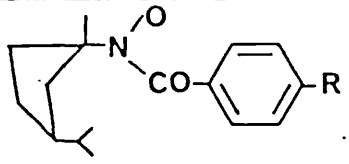
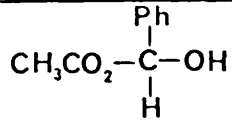
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
R = 3,5-NO_2 (102)	(±)	9.99×10^{-3}
R = 4-NO_2 (103)	(±)	3.44×10^{-3}
R = 4-H (104)	(±)	1.09×10^{-3}
R = 4-OMe (105)	(±)	5.31×10^{-4}
R = 4-$N(Me)_2$ (106)	(±)	2.26×10^{-4}

TABLE 15. Rate constants for the reaction of some fenchelyl nitroxides with methyl mandelate.

		$k_3 M^{-1} sec^{-1}$
R = 3,5-NO_2	(±)	7.70×10^{-2}
R = 4-H	(±)	6.56×10^{-3}
R = 4-$N(Me)_2$	(±)	1.61×10^{-3}

D(O-H) for (106) should be $\leq$ 76.85 kcals mol^{-1}. A lower value of this nature would permit much better correlation between a_N (8.74 Gauss) and D(O-H).

Tables 16-21 show the second order rate constants determined at 40°C for the reaction of phenylethanol and optically active fenchelyl benzoyl nitroxides.

Tables 15,22-24 show the second order rate constants determined at 40°C for the reaction of methyl mandelate and the optically active fenchelyl benzoyl nitroxides. Examination of the data in these tables reveals no kinetic indication for enantioselectivity in the reactions of the alcohols studied with these acyl nitroxides.

B. Examination of enantioselectivity using high-performance liquid chromatography (HPLC).

The kinetic studies described in section 5A necessitated the use of optically pure substrates. Only a limited number of such optically pure alcohols are commercially available and these are very expensive. An alternative approach, and one used in the original Berti experiments[1], is to react an excess of racemic alcohol with an optically active nitroxide and determine enantioselectivity by examining the enantiomeric composition of the unreacted alcohol. In this competitive technique the ratio of unreacted materials is related to the ratio of their individual

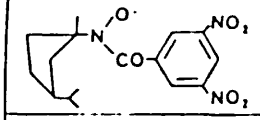
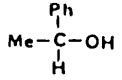
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	9.99×10^{-3}
(+)	(+)	1.16×10^{-2}
(-)	(-)	1.25×10^{-2}
(+)	(-)	1.24×10^{-2}
(-)	(+)	1.16×10^{-2}

TABLE 17. Rate constants for the reaction of (102) with phenylethanol

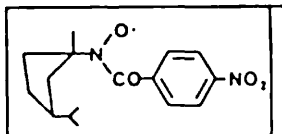
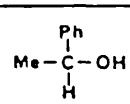
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	3.44×10^{-3}
(-)	(±)	3.37×10^{-3}
(+)	(+)	3.46×10^{-3}
(-)	(-)	3.87×10^{-3}
(+)	(-)	3.89×10^{-3}
(-)	(+)	3.53×10^{-3}

TABLE 18. Rate constants for the reaction of (103) with phenylethanol

TABLE 19. Rate constants for the reaction of (104) with phenylethanol

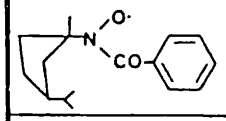
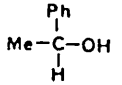
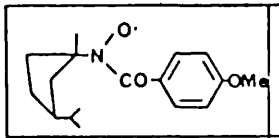
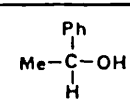
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(-)	(±)	1.08×10^{-3}
(+)	(±)	1.09×10^{-3}
(+)	(+)	1.12×10^{-3}
(-)	(-)	1.11×10^{-3}
(-)	(+)	1.14×10^{-3}
(+)	(-)	1.14×10^{-3}

TABLE 20. Rate constants for the reaction of (105) with phenylethanol

		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	5.31×10^{-4}
(-)	(±)	5.45×10^{-4}
(+)	(+)	5.38×10^{-4}
(-)	(-)	5.55×10^{-4}
(+)	(-)	5.71×10^{-4}
(-)	(+)	5.53×10^{-4}

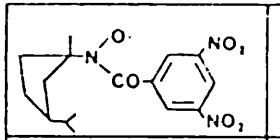
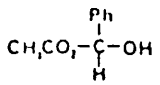
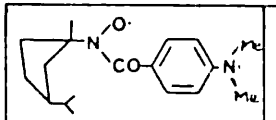
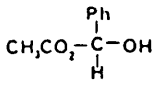
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	7.70×10^{-2}
(-)	(±)	7.48×10^{-2}
(+)	(+)	7.21×10^{-2}
(-)	(-)	7.67×10^{-2}
(+)	(-)	7.79×10^{-2}
(-)	(+)	7.81×10^{-2}

TABLE 22. Rate constants for the reaction of (102) with methylmandelate.

TABLE 24. Rate constants for the reaction of (106) with methylmandelate.

		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	1.61×10^{-3}
(-)	(±)	1.63×10^{-3}
(+)	(+)	1.66×10^{-3}
(-)	(-)	1.58×10^{-3}
(+)	(-)	1.62×10^{-3}

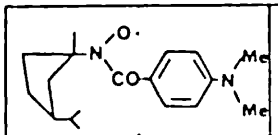
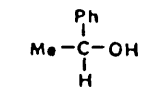
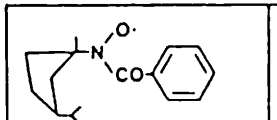
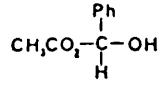
		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(-)	(±)	2.29×10^{-4}
(+)	(±)	2.26×10^{-4}
(+)	(+)	2.35×10^{-4}

TABLE 21. Rate constants for the reaction of (106) with phenylethanol.

TABLE 23. Rate constants for the reaction of (104) with methylmandelate.

		$k_3 M^{-1} sec^{-1}$ (PhH, 40°C)
(+)	(±)	6.56×10^{-3}
(+)	(+)	6.68×10^{-3}
(-)	(-)	6.62×10^{-3}
(+)	(-)	6.63×10^{-3}
(-)	(+)	6.77×10^{-3}

rate constants for the reaction according to equation 4:

$$\frac{k_R}{k_S} = \frac{\log \frac{R}{R_o}}{\log \frac{S}{S_o}}$$ Equation 4.

For our purposes k_R and k_S are the second order rate constants for the reaction of each enantiomer (R and S) of the racemic alcohol with the chiral nitroxide. R_o and S_o are the initial concentrations of the alcohol and R and S are their concentrations at time t. The general aim of such competitive experiments is to react a two fold excess of racemic alcohol (1 molar equivalent) with chiral nitroxide and subsequently to determine the enantiomeric excess of unreacted alcohol. Knowledge of the enantiomeric excess allows evaluation of $\frac{k_R}{k_S}$.

Several experimental techniques can be used to determine the enantiomeric composition of the unreacted alcohol. As previously mentioned, the specific rotation of the recovered alcohol can be measured. Isolation of the chemically pure alcohol from the reaction mixture is difficult and usually involves the use of column chromatography or preparative t.l.c. If any chiral radical is present in the final alcohol sample, this will give rise to a misleading specific rotation and thus calculation of

the enantiomeric excess (e.e.) will be incorrect.

^{1}H-NMR can also be used. Using a chiral shift reagent it should be possible to separate the (+) and (-) enantiomers of the alcohol (see Chapter 2). Integration of the separated enantiomers leads to the determination of the enantiomeric excess. However, in the Berti experiment[1], the observed e.e. was 7% and it is doubtful whether such a small e.e. would be detectable by ^{1}H-NMR integration.

An alternative method involved the use of HPLC, and enantiomeric resolution by this technique can be achieved in two ways:

(i) A chiral stationary phase can be used to separate the enantiomers of the unreacted alcohol. Integration of the individual peak areas gives the ratio of the (+) and (-) enantiomers.

(ii) Reaction of the unreacted alcohol with an optically pure isocyanate leads to the synthesis of a pair of diastereomeric carbamates. The diastereomers can be separated by HPLC using a silica stationary phase.

These two HPLC techniques will be dealt with independently.

(i) <u>Separation of enantiomers using a chiral stationary phase (CSP).</u>

Pirkle and his co-workers were the first to prepare a series of chiral phases bonded ionically to

a silanized silica column that could separate a racemate without the necessity of converting the latter to a mixture of diasteromers.[90,91,92]
Later, Kasai et al investigated the elution order and absolute stereochemistry of a number of alkylarylcarbinols using a Pirkle column.[93] The method of employing a chiral stationary phase to effect direct enantiomeric resolution in HPLC uses the formation of temporary diasteromeric complexes between the solute enantiomers and the CSP. The difference in stability between the diastereomeric complexes leads to a difference in retention times of the two enantiomers, that is, the solute enantiomer that forms the less stable diastereomeric complex with the CSP will elute first.

The CSP used in this work was designed by Pirkle et al[92] and was purchased from J.T. Baker Chemicals B.V. The column is composed of (R)-N-(3,5-dinitro--benzoyl)phenylglycine (DNBPG) bonded covalently to 5 μm particle size α-aminopropyl silica. The CSP has five possible sites for interaction with a solute and is depicted in Fig. 22. These available sites are:
(i) the dipole formed by the amide linkage between the 3,5-dinitrobenzoyl (DNB) moiety and the phenylglycine,
(ii) the amide hydrogen, (hydrogen bonding),
(iii) the amide carbonyl, (hydrogen bonding),

(iv) the 3,5-dinitrobenzoyl ring (electron-poor and available for π- bonding with other aromatic rings),

(v) the carbonyl and phenyl groups on the phenylglycine (can interact with the solute either attractively or repulsively).

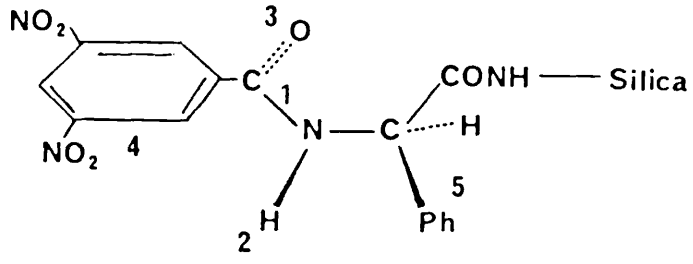


Fig. 22

The degree of chromatographic separation achieved is denoted by α, and is defined as the retention volume of the second peak less the dead volume divided by the retention volume of the first peak less the dead volume. In studying the chromatographic behaviours of a series of substituted benzylic alcohols and their corresponding acetates, Kasai et al have shown that larger separations of the enantiomers occur for polycyclic aromatics.[93] For phenylethanol, 1-(2-naphthyl)ethanol and 2,2,2-trifluoro-1--(9-anthryl)ethanol, α = 1.03, 1.08 and 1.33 respectively. So, although it proved possible to separate racemic 2,2,2-trifluoro-1-(9-anthryl)ethanol directly on the CSP, in the case of phenylethanol and 1-(2-naphthyl)ethanol, to achieve chromatographic separation it was necessary to generate their corresponding acetates (α = 1.11 and 1.30 resp.)

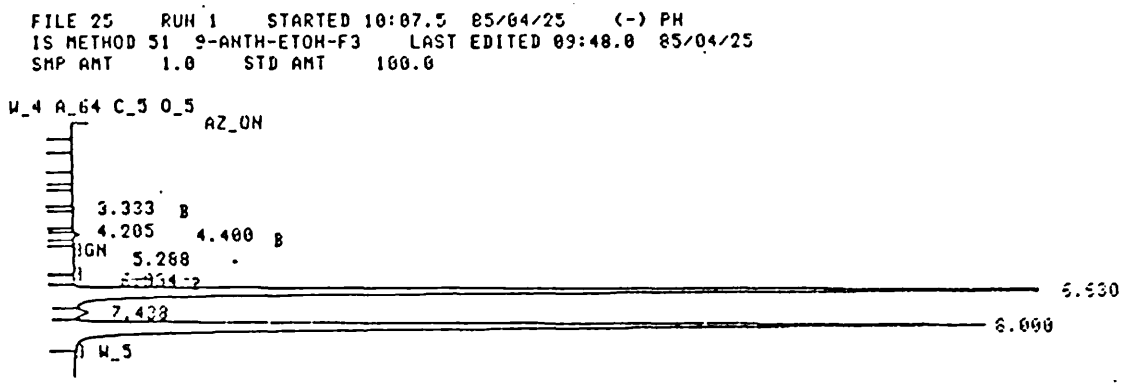
A general procedure for the reaction of a chiral

nitroxide with a racemic alcohol and the subsequent formation of the acetate is outlined below:

1.52mg (4.3μmoles) N-(fenchelyl)-3,5-dinitrobenzoyl hydroxamic acid was dissolved in 10 cm^3 of pure benzene. Once the radical had been generated using alkaline potassium ferricyanide, the organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The neat nitroxide was redissolved in 250 μl benzene and added to 5.5mg (2.7 μmoles) 1-(2-naphthyl)ethanol in the screw cap septum vials. The reaction mixture was placed in an oven at 40°C for 24 hours. After this time 25 μl acetic anhydride and 10 μl pyridine were added and the resulting solution shaken for 6 hours. The crude reaction mixture was then passed through a short silica column (to remove unreacted acetic anhydride) and the column eluted with 10 cm^3 of 10% ethyl acetate:hexane.

Two sets of (+) and (-)-(102) to (106) were generated in the manner described above. One set was reacted with 2,2,2-trifluoro-1-(9-anthryl)ethanol, the other with 1-(2-naphthyl)ethanol. After reaction was complete the latter set were derivatized to their corresponding acetates.

Fig. 23 shows a typical HPLC trace for the alcohol obtained from the reaction of (104) with 2,2,2-trifluoro-1-(9-anthryl)ethanol.



FILE 25 RUN 1 STARTED 10:07.5 85/04/25 (-) PH
IS METHOD 51 9-ANTH-ETOH-F3 LAST EDITED 09:48.0 85/04/25
SMP AMT 1.0 STD AMT 100.0

RT	AREA	BC	RT/10	RF	REL.AMOUNT	NAME
6.630	8642284	T	0.663	1.000000e+00	100.0000	(R)-ALCOHOL
8.000	8645535		0.800	1.000000e+00	100.0377	(S)-ALCOHOL

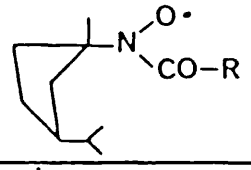
2 MATCHED COMPONENTS 99.25% OF TOTAL AREA
1 UNKNOWN PEAK > UNRET PK 0.75% OF TOTAL AREA
3 PEAKS > AREA REJECT 17418054 TOTAL AREA

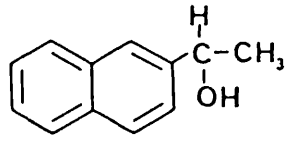
FIG. 23

After three days the colour of the nitroxide in these reactions had not been bleached and the ratio of the enantiomers present was 1:1. It was suspected that no reaction had taken place. Inspection of these samples using an ODS column (methanol/water, 85:15) to analyse for product formation (ketone) revealed that indeed this was the case and virtually no product had been formed.

In the 1-(2-naphthyl)ethanol reactions the colour was readily bleached and the experimental data obtained from these reactions is collated in table 25. Examination of table 25 shows that no enantioselectivity could be detected in these reactions. That this was not due to a racemization of

TABLE 25. HPLC data[a,b,c] for the reaction of the N-fenchelyl nitroxides with racemic 1-(2-naphthyl)ethanol.[d]





NO.	Radical R	PEAK AREAS[e]		
		R	S	R/S
102	(+) C_6H_3-$(NO_2)_2$	10.63	10.49	1.01
	(-) C_6H_3-$(NO_2)_2$	8.12	8.05	1.01
103	(+) C_6H_4-NO_2	6.85	6.72	1.02
	(-) C_6H_4-NO_2	8.57	8.47	1.01
104	(+) C_6H_5	10.45	10.50	0.997
	(-) C_6H_5	9.49	9.51	0.998
105	(+) C_6H_4-OMe	4.40	4.45	0.988
	(-) C_6H_4-OMe	6.46	6.38	1.01
106	(+) C_6H_4-$N(Me)_2$	25.14	24.41	1.02
	(-) C_6H_4-$N(Me)_2$	19.05	19.07	0.998

a. Solvent, 0.5% isopropanol:hexane
b. Flow rate 1 ml min^{-1}
c. Column, CSP
d. Analysed as acetates
e. Acetates (% of total at 280nm).

unreacted substrate at the acetylation step was shown by the acetylation of standard phenylethanols for which we had the individual optical isomers. Each isomer, upon acetylation gave only its corresponding acetate with no formation of the other hand. This was in contrast to acetylation using acetic anhydride with sulphuric acid as a catalyst, where complete racemization was observed.

(ii) Separation of diastereomers using an alumina or silica stationary phase.

Using HPLC Pirkle et al[94] have separated the diastereomers derived from the reaction of alkylarylcarbinols with chiral 1-(1-naphthyl)ethyl isocyanate. The values obtained for the resulting diastereomeric carbamates are generally adequate for facile separation on silica or alumina columns. Nitroxide radicals were prepared from their corresponding hydroxamic acid precursors and then reacted with excess alcohol as described in (i). After reaction, the unreacted alcohol was derivatized to diastereomeric carbamate as follows:

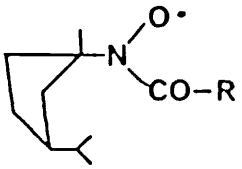
R-1-(1-naphthyl)ethyl isocyanate (1.2 equivalents) and N,N-dimethylethanolamine (1 wt%) in benzene (25 µl) were added to the reaction mixture in screw cap septum vials and the resulting solutions heated to 80°C for 24-36 hours.

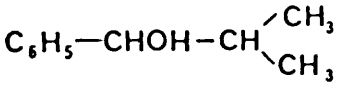
The fenchelyl nitroxides (+) and (-)-**(102)** to **(106)**

were reacted with racemic phenylethanol in the manner described above. Chromatographic examination of the subsequent diastereomeric carbamates obtained from these reactions (silica, ethyl acetate:hexane, 8:92) showed, once again, a 1:1 ratio for this alcohol indicating that no enantioselectivity had taken place. This agrees with the lack of enantioselectivity suggested by our measurements of absolute rate constants (chapter 5A).

In a further set of experiments using racemic 2-methyl-1-phenylpropan-1-ol, the results were more promising. The data for the reaction of the fenchelyl nitroxides with this substrate are shown in table 26. In the case of (+) and (-)-(105), the ratio R/S shows that enantioselectivity, though small, has taken place. Since the results of this experiment seemed promising, duplicate injections were made and the same ratio's were observed (within 1.5%). Comparison of the data for **(104)** and **(105)** indicate that in each case, R/+ and S/- pairs react fastest suggesting that enantioselectivity has taken place. Pirkle has given the experimental procedure to obtain optically pure alcohols from preparative HPLC by acid hydrolysis of the separated carbamates.[94,95] If pure (+) and (-) 2-methyl-1-phenylpropan-1-ol's could be obtained in this manner then absolute rate constants could be determined using u.v spectroscopy, (chapter 5A). If

TABLE 26. HPLC data[a,b,c] for the reaction of the N-fenchelyl nitroxides with racemic 2-methyl-1-phenylpropan - 1-ol.





No.	R Radical (μ moles)	alcohol[d] (μ moles)	Intended Conversion	PEAK AREAS[e]		
				R	S	R/S
(103)	(+) C_6H_4-NO_2 8.46	8.66	49%	1.18	1.15	1.02
	(-) C_6H_4-NO_2 7.57	8.13	47%	2.32	2.28	1.02
(104)	(+) C_6H_5 8.30	6.86	60%	5.07	5.30	0.96
	(-) C_6H_5 8.80	6.60	67%	4.35	4.23	1.03
(105)	(+) C_6H_4-OMe 8.03	6.66	60%	13.31	14.95	0.89
	(-) C_6H_4-OMe 8.48	6.46	65%	3.49	2.94	1.19

a. Solvent, 8:92, ethyl acetate:hexane
b. Flow rate, 2 ml min^{-1}
c. Column, silica
d. Analysed as carbamates
e. Carbamates (% of total, at 280nm).

the second order rate constants obtained for the reaction of (+) alcohol and (+) radical were different from those obtained for (+) alcohol and (-) radical and vice versa then enantioselectivity would be more rigorously established.

It is particularly significant that the selectivity seems pronounced with the methoxy nitroxides **(105)**, small but detectable with the unsubstituted benzoyl derivatives (104), and undetectable when the substituent was 4-nitro. However, these must be regarded as preliminary findings meriting further study, furthermore extension to the more hindered 2,2-dimethyl-1-phenylpropanol should now be investigated.

If, as suggested in chapter 3C, a parallel can be made between the magnitude of the observed CD curves and enantioselectivity then, in the light of the large CD curves observed for (-)-(113) and (+)-(116), it was hoped that reaction of these radicals with a series of alkylarylcabinols would lead to the observation of greater enantioselectivity.

(-)-**(113)** and (+)-**(116)** were reacted with racemic phenylethanol, 2,2,2-trifluoro-1-(9-anthryl)ethanol, 2-methyl-1-phenylpropan-1-ol, phenylbutanol and 1-phenylpropanol and the unreacted alcohols converted to their corresponding carbamates in the manner described above. Disappointingly the results obtained

from HPLC analysis indicated that the ratio of the (+) and (-) diastereomers were all 1:1 within 0.8% and so enantioselectivity was not observed.

CHAPTER 6

CONCLUSION

The original aim of this work was to test an extension of the Hammond Postulate by using chiral selection in hydrogen atom transfer reacitons. It was hoped that in the oxidation of optically active benzylic alcohols by a series of closely related chiral t-alkyl acyl nitroxides enantioselectivity should be greatest when the bond dissociation energy of the hydrogen donor and the hydrogen acceptor are most closely matched.

Unfortunately, our results suggest that either;
a) the series of nitroxides and alcohols that were available do not have comparible bond dissociation energies (BDE),
b) the enantioselectivity exhibited is so small as to be below the threshold of our analytical methods, or
c) this novel approach to the Hammond Postulate is inappropriate.

After considerable synthetic effort, the goal of an optically pure t-alkyl acyl nitroxide in which chirality resides in the alkyl substituent has been achieved. In its initial concept this work required the series of nitroxides to have as wide a range of O-H bond strengths as possible. We expected a range of 10 kcal mol^{-1} based on a similar series of hydroxamic acids (R = t-butyl) studied by Jenkins.[39]

We were disappointed to find that although the BDE of the unsubstituted member is very close to that reported by Jenkins, the range from 4-methoxy to 4-nitro was much smaller (1.5 kcals mol^{-1}). Since the BDE should be rather insensitive to the nature of the alkyl group (t-butyl vs. fenchelyl) we are forced to conclude that Jenkins's data is suspect and this conclusion seems to be supported by the cursory reexamination of the acyl t-butyl nitroxides reported in chapter 4. Investigation of enantioselectivity in the reaction of nitroxides derived from this series of N-fenchelylbenzohydroxamic acids with benzylic alcohols proved relatively disappointing. Some success was achieved in the reaction of the unsubstituted (104) and 4-methoxy (105) derivatives with 2-methyl-1-phenylpropan-1-ol. To substantiate these results, further work needs to be undertaken. This could be achieved by the determination of the absolute rate constants for the reaction of optically active alcohol with optically active nitroxides using u.v spectroscopy (see chapter 5A). The racemic alcohol can be resolved by isolation of the individual diastereomeric carbamates by HPLC. Hydrolysis of the latter gives the optically pure alcohols. It was unfortunate that time did not allow this final confirmatory piece of work to be carried out. It is suspected that the asymmetry of the alkyl substituent

is too small to induce observable enantioselectivity in the oxidation reactions studied. In accord with this, no circular dichroism could be detected in the case of (104) obtained from the optically active hydroxamic acid precursor.

Although the readily accessible chiral secondary alkyl acyl nitroxides do reveal weak CD effects, they have given no evidence for chiral selection when used, in trial, as oxidants. It should be emphasized that this line of work was not pursued because the kinetic studies were very complicated. Relatively low radical and high alcohol concentrations had to be used in order that competing radical disproportionations were minimized, this led to very weak initial absorbancies and introduced experimental error.

It was hoped that the large pinanyl groups in the nitroxides (113) and (116) would induce large asymmetry in these molecules. In turn, this asymmetry should lead to more marked differences in the relative energies in the diastereomeric transition states and hence lead to greater enantioselectivity. Perhaps the most disappointing result was that although strong CD curves were seen for these nitroxides no enantioselectivity in these reactions could be detected by the HPLC technique. The original chiral selection in oxidation of benzoin by (116) remains the only successful example detected with this nitroxide.

CHAPTER 7

EXPERIMENTAL

General

(i) Infrared (IR) spectra

Infrared spectra were recorded on either a Perkin-Elmer SP.257 or Perkin-Elmer 197 Grating Infrared Spectrophotometer. Samples were examined between sodium chloride plates either as Nujol-mulls (solids) or neat films (liquids).

(ii) Ultraviolet-visible (UV) spectra

Absorption spectra were recorded on either a Perkin-Elmer 551S or Pye Unicam SP8-100 Ultraviolet-Visible spectrophotometer.

(iii) Proton magnetic resonance (^{1}H-NMR) spectra

The ^{1}H-NMR spectra for most samples were recorded on a Perkin-Elmer R-32 (90MHz) NMR spectrometer. Deuteriochloroform ($CDCl_3$) solutions were doped with tetramethylsilane (TMS) to provide an internal reference and the chemical shifts are expressed as δ-parts per million from this standard.

(iv) Carbon nuclear magnetic resonance (^{13}C-NMR) spectra

The ^{13}C-NMR spectra were recorded on a Jeol fx 90Q (90 MHz) NMR spectrometer. $CDCl_3$ and TMS were used as a solvent and standard as detailed above (iii). Off-resonance techniques were used to assign carbon multiplicities.

(v) Electron spin resonance (ESR) spectra

Electron spin resonance spectra were recorded on a Varian E4 e.s.r. spectrometer operating at a frequency of approximately 9.1 GHz (X-band): resonance absorptions were thus centered at magnetic field strengths of *ca.* 3300 Gauss. Modulation amplitudes 0.05-0.189 Gauss were used to maximize spectral resolution.

The spectrometer was fitted with an electronic integrator capable of single integration of the spectrometer output, the details of the integrator have been published.[88]

Integrated e.s.r. absorption spectra were recorded on a servoscribe RE-541 potentiometric recorder. Solution spectra were recorded using cylindrical quartz tubes of 3mm diameter. Solutions were carefully deoxygenated by bubbling with a capillary flow of oxygen-free nitrogen for *ca.* 3 minutes immediately prior to e.s.r. examination.

Hyperfine coupling constants were determined from the recorded derivative spectra and are quoted in units of Gauss. The values given represent an average from at least two separate measurements and are corrected by a factor of 0.977 for a field scan error on the particular spectrometer used.

(vi) Melting-points

Melting points (m.p) were determined in open capillary tubes using an Electrothermal Melting-Point Apparatus with range selection guide for coarse and fine control. All values are uncorrected.

(vii) Purification of benzene

Commercial 'AnalaR' grade benzene was purified by repeated extraction with conc. H_2SO_4 until the extracts were colourless (sulphuric acid removes thiophene and olefinic impurities). The benzene was washed with saturated aqueous sodium bicarbonate solution and then repeatedly with water until the washings were neutral. It was dried ($CaCl_2$) and distilled, collecting the fraction with b.p 80-80.5°C/750 mmHg.

(viii) Cleaning of glassware

All glassware for e.s.r. spectroscopy, uv kinetic and HPLC experiments was cleaned with chromic acid as

follows:

The glassware was immersed in chromic acid and allowed to soak over-night. After removal of chromic acid and washing with distilled water, the glassware was soaked over-night in 2M H_2SO_4. The glassware was then thoroughly washed with distilled water and allowed to air dry.

(ix) Elemental analyses

Early elemental analyses were generally carried out by the Butterworth Micro-analytical consultancy Ltd. (Teddington, Middlesex). After the move to Royal Holloway and Bedford New College later elemental analyses were carried out by Mrs. L. Whitaker in the Chemistry Department. All analytical samples were dried in the presence of P_2O_5 *in vacuo*.

(x) Chromatography

Thin-layer chromatography plates were prepared using Merck silica gel GF_{254} (type 60). The thickness of the ordinary t.l.c. plats was 0.25mm. Unless otherwise stated, air dried plates were developed with ethyl acetate/petrol (b.p. 60-80°C, 20:80) and visualized beneath a uv lamp and/or by iodine staining. Kieselger 60 (35-70 mesh ASTM) was used for column chromatography.

EXPERIMENTS

1. Preparation of O-benzoyl-N-t-butylhydroxylamine

$$Bu^t-NH_2 \longrightarrow Bu^t-NHOCOPh$$

O-Benzoyl-N-t-butylhydroxylamine was prepared from commercial tert-butylamine by reaction with dry dibenzoyl peroxide according to a modification[35] of Zinner's method.[34]

a. Dibenzoyl peroxide.

Commercial dibenzoyl peroxide (paste with water) (25.0g. 0.01 mole) in chloroform (150 cm^3) was added slowly and with stirring to an excess of methanol (200 cm^3). The precipitate, dibenzoyl peroxide freed from water, was filtered and dried in air (16.5g. 95%).

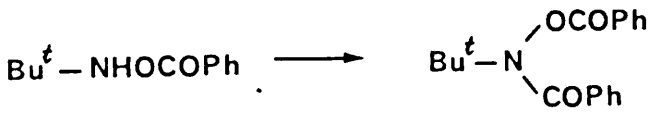
b. Freshly distilled tert-butylamine (6.0,g, 8.3 mmole) was added dropwise with stirring to a solution of freshly crystallized dibenzoyl peroxide (10.0g, 41.3 mmole) in sodium dried benzene (100 cm^3). The reaction was then stirred for one hour at 40°C. Additional tert-butylamine (3.0g, 41.0 mmole) was then added and stirring continued for 48 hours at 40°C. Diethyl ether (100 cm^3) was added to the cooled reaction mixture and the precipitated amine salt was filtered and washed with diethyl ether (2 x 50 cm^3). The filtrate was washed with acidic iron (II) sulphate solution (60.0g $FeSO_4$, 110 cm^3 H_2O, 6 cm^3 H_2SO_4). The organic layer was dried (Na_2SO_4), filtered, and

evaporated to give an amber oil (5.5g, 69% based on dibenzoyl peroxide).

IR (ν cm^{-1}, neat): 3240 (N-H str.), 1740 (C = O str.), 1600 (C = C str.).

H—NMR (δ ppm, $CDCl_3$): 1.21 (s, 9H, Bu^t), 7.3-8.2 (m, 5H, Ar-H).

2. Preparation of O-benzoyl-N-t-butylbenzo--hydroxamic acid



To a stirred solution of crude O-benzoyl-N-t-butylhydroxylamine (4.5g, 23.3 mmole) (from exp. 1) in sodium dried benzene (50 cm^3) was added molecular sieve-dried pyridine (1.9g, 25.0 mmole) and benzoyl chloride (3.25g, 23.1 mmole). A slight precipitate of pyridinium chloride was evident at this stage. The mixture was refluxed for 6 hours, cooled and poured into 2M HCl (150 cm^3). The solution was extracted with diethyl ether (250 cm^3). The organic phase was washed with 2M HCl (2 x 50 cm^3), water (2 x 50 cm^3), dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a white crystalline product. Recrystallization from hexane/CH_2Cl_2 gave the title compound as colourless crystals (5.2g, 75%), m.p. 99-100°C. (Lit.,[39] 98-99°; Lit.,[96] 98-99°C).

IR (ν cm^{-1}, Nujol): 1760 (OCO C = O str.), 1650 (NCO

C = O str.), 1605 and 1580 (C = C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.6 (s, 9H, Bu^t), 7.2-7.9 (m, 10H, Ar-H (2)).

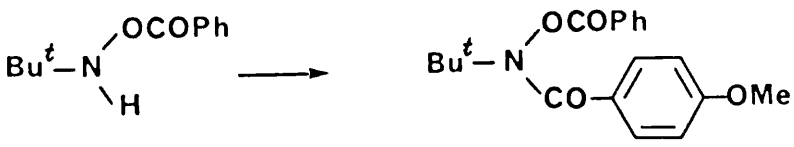
3. Preparation of N-t-butylbenzohydroxamic acid

Hydrazine hydrate (6.3g, 0.13 mole) was added to a stirred solution of O-benzoyl-N-t-butylbenzohydroxamic acid (5.0g, 0.16 mole) in absolute ethanol (50 cm^3). The reaction mixture was stirred at 40° for 1½ hours, cooled and poured onto ice (200 cm^3). The resulting solid was filtered off and dried in a desiccator over NaOH pellets. Recrystallization from hexane/CH_2Cl_2 gave the title compound as colourless prisms (3.2g, 97%), m.p. 113-114°C (Lit.,[96] 109°; lit.,[97] 113°C).

IR (ν cm^{-1}, Nujol): 3540-2540 br. (3140 max. O-H str.), 1605 (max. C = O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.32 (s, 9H, Bu^t), 7.29 (s, 5H, Ar-H), 8.45 br. (s, 1H, exchanged with D_2O,-OH).

4. Preparation of O-benzoyl-N-t-butyl-4-methoxy--benzohydroxamic acid

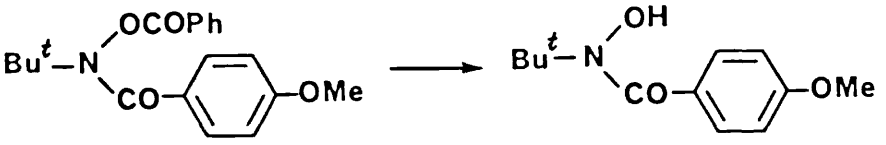


To a stirred solution of O-benzoyl-N-t-

-butylbenzohydroxamic acid (2.0g, 0.01 mole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.9g, 0.011 mole) and anisoyl chloride (1.7g, 0.01 mole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t-butylbenzohydroxamic acid (exp 2) to give a pale yellow oil. Column chromatography (silica/$CHCl_3$) gave a liquid product that showed a single spot on t.l.c. (2.9g, 87%).

IR ($\nu\ cm^{-1}$, neat): 1760 (max. OCO C = O str.), 1640 (max. NCO C = O str.).

5. Preparation of N-t-butyl-4-methoxy--benzohydroxamic acid.



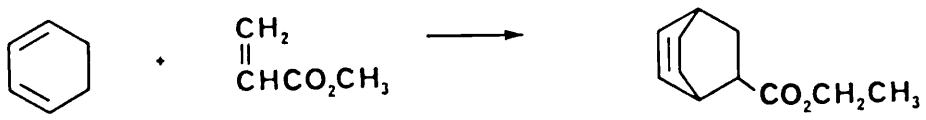
Using a procedure similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3), the title compound was prepared in 83% yield. Crystallization from hexane/methanol furnished the hydroxamic acid as fine colourless needles m.p. 113-114°C (Lit.,[39] 113-114°C).

IR ($\nu\ cm^{-1}$, Nujol): 3400-2800 (3120 max. O—H str.), 1600 (C = O str.).

^{1}H-NMR (δppm, $CDCl_3$): 1.34 (s, 9H, Bu^t), 3.78 (s, 3H, $-OCH_3$), 6.77 and 7.41 (AA'BB' J = 8Hz, 4H, XC_6H_4Y),

8.0 br. (s, 1H, -OH).

6. Preparation of ethyl bicyclo[2.2.2]oct--5-ene-2-carboxylate



Ethyl bicyclo[2.2.2]oct-5-ene-2-carboxylate was prepared by the method of Seka and Tromposch.[50] 1,3——Cyclohexadiene (5.0g, 62.5 mmole) and ethyl acrylate (8.0g, 80.0 mmole) were placed in a glass tube which was sealed, and heated for 12 hours in a Carius furnace at 160-170°C. The reaction mixture was distilled at atmospheric pressure to remove excess ethyl acrylate and the residue was vacuum distilled to give a colourless oil with a pungent odour (8.8g, 78%) b.p.$_{6.0}$ 89-90°C (Lit.,[50] b.p.$_{12.0}$ 98-100°C)

IR (ν cm^{-1}, neat): 1730 (C = O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.0-1.8 (m,. 9H, CH_3 of ethyl group and CH_2 groups H-3, H-7, H-8), 2.6 (m, 2H, H-1 and H-4), 2.9 (m, 1H, H-2), 4.1 (q, 2H, CH_2 of ethyl group), 6.3 (m, 2H, olefinic protons H-5 and H-6).

Mass Spectrum (m/z, 70 eV): 180 (M^+, 8.9%), 151 (29, M-C_2H_5), 107 (73, M-$CO_2C_2H_5$).

7. Preparation of ethyl bicyclo[2.2.2]octane--2-carboxylate

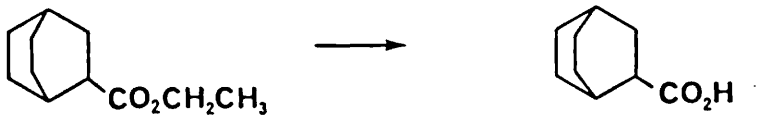
10% Pd/C catalyst (200 mg) in ethanol (2 cm^3) was added to ethyl bicyclo[2.2.2]oct-5-ene-2-carboxylate (7.0g, 38.8 mmole) in 15 cm^3 absolute ethanol. The reaction mixture was shaken with hydrogen at room temperature and atmospheric pressure for 3 hours, and then filtered through celite. Evaporation of solvent yielded the title compound (6.96g, 98%) $b.p_{15}$ 111-112°C (Lit.,[50] $b.p._{12}$ 102-103°C).

IR (νcm^{-1}, neat): 1730 (C = O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.3 (t, 3H, CH_3), 1.5-2.0 (m, 10H, CH_2 groups (5)), 2.5 (m, 1H, H-2), 4.0-4.3 (q, 2H, CH_2 of ethyl group).

Mass Spectrum (m/z, 70 eV): 182(M^+, 8.6%), 136 (46, $M-OC_2H_5$), 73 (109, $CO_2CH_2CH_3$).

8. Preparation of bicyclo[2.2.2]octane-2-carboxylic acid



Ethyl bicyclo[2.2.2]octane-2-carboxylate (5.5g, 30.2 mmole) was dissolved in absolute ethanol (30 cm^3) and refluxed for 1½ hours with NaOH solution (1.6g, 39.0 mmole) in 15 cm^3 H_2O.

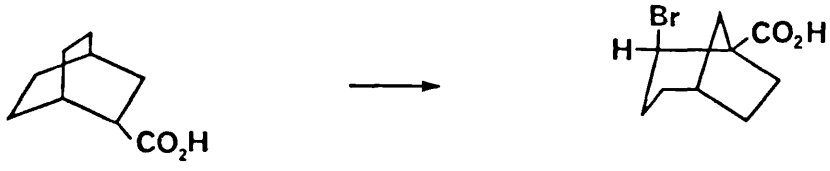
After removal of the ethanol by distillation the cooled reaction mixture was poured into water (100 cm^3). Conc. HCl was added until the solution was

slightly acidic, at which point a white solid precipitated. The solid was extracted with methylene chloride and the organic phase was separated and dried (Na_2SO_4). Evaporation of solvent yielded the title compound as a white solid (4.8g, 98%) m.p. 83-84°C (Lit.,[50] 84-85°C).

IR (ν cm^{-1}, Nujol): 3300-2300 br. (-OH str.), 1700 (C = O str.).

Mass spectrum (m/z, 70 eV): 154(M^+, 7.5%), 136(18), 108 (46).

9. Preparation of 2-bromobicyclo[3.2.1]octane--1-carboxylic acid.



The title compound was prepared by Hell-Volhard-Zelinsky bromination.[51,52] Bicyclo--[2.2.2]octane-2-carboxylic acid (13.7g, 0.089 mole), bromine (8.14 g, 0.1 mole) and phosphorus trichloride (0.5 cm^3) were heated on a steam bath at 80-90°C for 12 hours. After cooling, the mixture was dissolved in diethyl ether and the resulting solution was washed with sodium metabisulphite solution (3 x 250 cm^3) and water (3 x 250 cm^3). The ethereal phase was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded

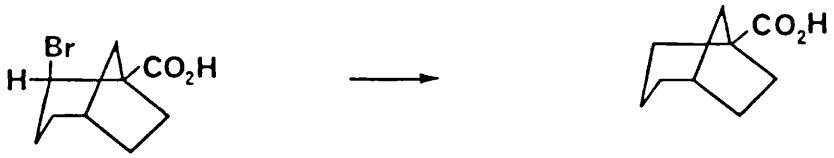
a yellow solid which was washed with hexane. Recrystallization from benzene yielded a cream solid (13.5g, 65%) m.p. 151-152°C (Lit.,[52] 152-153°C).

IR (ν cm^{-1}, Nujol): 3200-2500 br. (OH str.), 1700 (C = O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.0-2.5 (m, 11H, H-1 to H-8, bar H_2), 4.7 (s, 1H, H-2), 11.05 (s, 1H, $-CO_2H$).

Mass spectrum (m/z, 70eV): 189/187 (45, $M-CO_2H$), 153(79/81, M-Br), 140/138 (94, M-Br, CO_2H, CH_2, base peak).

10. Preparation of bicyclo[3.2.1]octane-1-carboxylic acid.



Bicyclo]3.2.1]octane-1-carboxylic acid was prepared by hydrogenolysis of the bromoacid under basic conditions according to the method of Vaughan et al.[53]

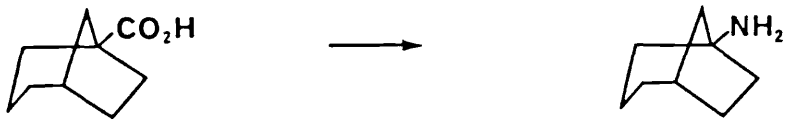
A solution of 2-bromobicyclo[3.2.1]octane-1--carboxylic acid (8.0g, 0.034 mole) and potassium hydroxide (5.3g, 0.15 mole) in 120 cm^3 of 70% aqueous ethanol was hydrogenated at atmospheric pressure over 0.5g of 10% palladium on carbon. After filtration, the solution was diluted with water and then concentrated to approximately 1/3 volume by rotary

evaporation. Acidification with conc. HCl afforded the title compound (4.6g, 88%) m.p. 67-68°C (Lit.,[53] 69.5-70.5°C)

^{1}H-NMR (δ ppm, $CDCl_3$): 1.4-2.5 (m, 13H, hydrocarbon protons), 10.2-10.5 br. (s, 1H, $-CO_2$ H).

Mass spectrum (m/z, 70eV): 154 (M^+, 100%), 109 (45, $M-CO_2H$).

11. Preparation of 1-bicyclo[3.2.1]octylamine



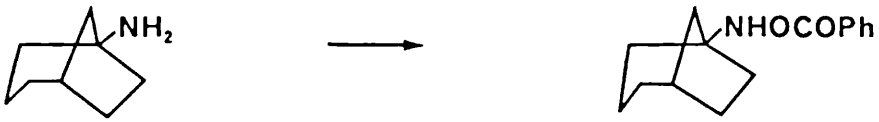
1-Bicyclo[3.2.1]octylamine was prepared by the Schmidt reaction[55] on bicyclo[3.2.1]-octane-1--carboxylic acid according to Wolff[54] with slight modifications as follows: Conc. H_2SO_4 was added to a cooled (0-5°C) stirred solution of bicyclo[3.2.1]-octane-1-carboxylic acid (4.0g, 0.026 mole) in chloroform (30 cm^3). Sodium azide (3.4g, 0.052 mole) was added portionwise to the vigorously stirred solution maintained at 40-45°C. Once addition was complete the reaction was allowed to stir at 40-45°C for a further 4 hours until evolution of nitrogen had ceased. The reaction mixture was then cautiously made strongly basic with sodium hydroxide solution (50% w/v). The amine (which is extremely air sensitive) was extracted with chloroform under nitrogen and the organic phase dried (Na_2SO_4). The

chloroform was removed by distillation under a nitrogen atmosphere to give crude amine as a pale brown mobile oil (2.1g, 65%).

IR (νcm^{-1}, neat): 3325 and 3280 (NH_2 str.), 1600 (N-H def.).

Mass spectrum (m/z, 70 eV): 125 (M^+, 8.8%).

12. Preparation of O-benzoyl-N-(1-bicyclo[3.2.1]-octyl)hydroxylamine.



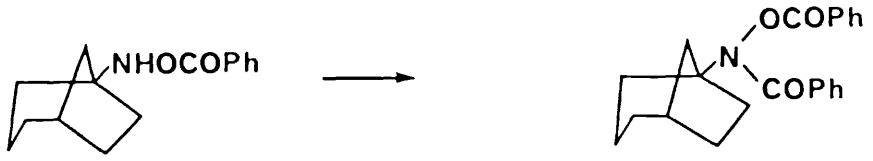
The title compound was prepared using a procedure similar to the preparation of O-benzoyl-N-t-butylhydroxylamine (exp. 1). The crude reaction product was further purified by column chromatography (SiO_2;ethyl acetate : petrol 60-80°; 20:80) to give a colourless oil which showed a single spot on t.l.c. (2.9g, 50% based on dibenzoyl peroxide).

IR (νcm^{-1}, neat): 3210 (N-H str.), 1720 (C = O str.), 1600 (C = C str.)

^{1}H-NMR (δ ppm, $CDCl_3$): 1.0-2.0 (m, 13H, hydrocarbon protons), 7.3-8.2 (m, 6H, Ar-H and N-H).

Mass Spectrum (m/z, 70eV): 122 (PhOCOH), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$, base peak).

13. Preparation of O-benzoyl-N-(1-bicyclo[3.2.1]-octyl)benzohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of O-benzoyl-N-t-butylbenzohydroxamic acid (exp. 2). Recrystallization from methanol gave O-benzoyl-N-(1-bicyclo[3.2.1]-octyl)-benzohydroxamic acid as a colourless solid (1.8g, 60%) m.p. 100-101°C.

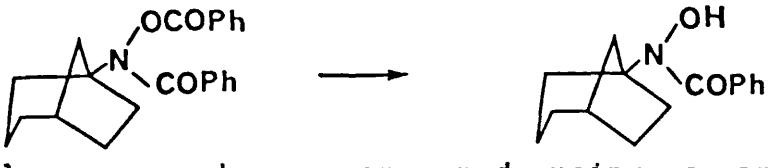
IR (νcm^{-1}, Nujol): 1765 (OCO C = O str.), 165 (max. NCO C = O str.), 1600 (C = C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.2-2.5 (m, 13H, hydrocarbon protons), 7.15-7.9 (m, 10H, Ar-H (2)).

Mass Spectrum (m/z, 18eV): 349 (M^+, 1.5%), 229 (121, M-$PhCOO^+$), 105 ($C_6H_5CO^+$, base peak), 77 (Ph^+).

(Found: C, 75.5; H, 6.65; N, 4.3. $C_{22}H_{23}NO_3$ required C, 75.6; H, 6.6; N. 4.0%).

14. Preparation of N-(1-bicyclo[3.2.1]octyl)-benzohydroxamic acid



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3) Recrystallization from hexane gave the

hydroxamic acid as a colourless solid m.p. 158-159°C.
IR (ν cm^{-1}, Nujol): 3310-3050 br. (3190 max. -OH str.), 1605 (C = O str.).
^{1}H-NMR (δ ppm, $CDCl_3$): 1.1-2.3 (m, 13H, hydrocarbon protons), 7.4 (s, 5H, Ar-H), 8.3-8.5 br. (s, 1H, -OH).
Mass Spectrum (m/z, 18eV): 245 (M^+, 13.%), 122 (PhOCOH), 105 ($PhCO^+$, base peak), 77 (Ph^+)
(Found: C,73.2; H, 7.8; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.75; N, 5.7%).

15. Resolution of 2-bromobicyclo[3.2.1]octane--1-carboxylic acid.

A mixture of the acid (10.0g, 0.043 mole) and quinine (13.90g, 0.043 mole) in 3 litres of acetone was warmed until solution was complete. The warm solution was filtered and reduced in volume to 2 litres. After prolonged standing at room temperature 11.1g of a white solid, m.p. 171-173°C was filtered off. The filtrate was reduced in volume to 1 litre and, after standing at room temperature for 24 hours 3.1g of a solid m.p. 168-169°C was filtered off. The two crops of solids were combined and after three recrystallizations from acetone showed constant melting-point 174-175°C and unchanged optical rotation $[\alpha]_D^{25}$ - 106.7° (c = 0.1 in $CHCl_3$).

The solid salt was dissolved in 100 cm^3 $CHCl_3$ and 100 cm^3 of 5% HCl added with vigorous shaking. The

layers were separated and the chloroform solution dried with magnesium sulphate. The dried solution was evaporated at room temperature to give a white solid, m.p. 130-131°C.

After two recrystallizations from chloroform/hexane this solid gave colourless cubic crystals m.p. 131-132°C, $[\alpha]_D^{24}$ + 40.9 ± 2° (c = 0.1 in $CHCl_3$). Further recrystallisations did not change either the melting point or the optical rotation.

16. Preparation of (+)-ethyl 2-bromobicyclo[3.2.1]-octanecarboxylate.

a. Generation of diazomethane.

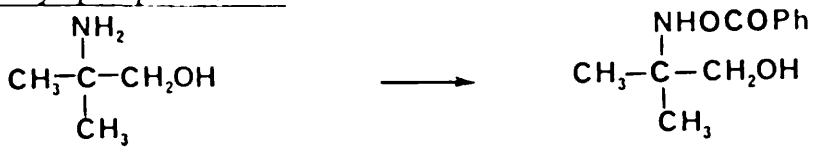
Potassium hydroxide in ethanol (10 cm^3, 0.4g, 0.01 mole) was added dropwise to a cooled solution of N-methyl-N-nitroso-toluene-p-sulphonamide (Diazald) (2.14g, 0.01 mole) in diethyl ether (30 cm^3). After 5 minutes the ethereal diazomethane solution was distilled using a water bath. This solution contained 0.32-0.35g of diazomethane.

b. The diazomethane solution was added dropwise to a cooled solution of (+)-2-bromobicyclo-[3.2.1]octane-1--carboxylic acid (0.05g, 0.21 mmole) in sodium dried ether (5 cm^3), until the reaction mixture retained a persistant yellow colour. The organic phase was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded the title compound as a colourless liquid (0.048g,

98%).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.1-2.5 (m, 12H, hydrocarbon protons), 3.7 (s, 3H, CH_3) 4.7 br (s, 1H, H-2).

17. Attempted preparation of N-benzoyloxy-2-amino--2-methylpropan-1-ol



Freshly distilled 2-amino-2-methylpropan-1-ol (14.0g, 0.15 mole) was added dropwise with stirring to a solution of freshly crystallized dibenzoyl peroxide (17.3g, 0.07 mole). The reaction was carried out as per O-benzoyl-N-t-butylhydroxylamine (exp. 1).

Column chromatography (SiO_2, ethyl acetate: petrol 60-80°, 20:80) of the crude reaction product yielded a white solid m.p. 49.5-50.5°C. Spectral data revealed that the product obtained was O-benzoyl-N-benzoyloxy--2-amino-2-methylpropan-1-ol and not N-benzoyloxy-2--amino-2-methylpropan-1-ol.

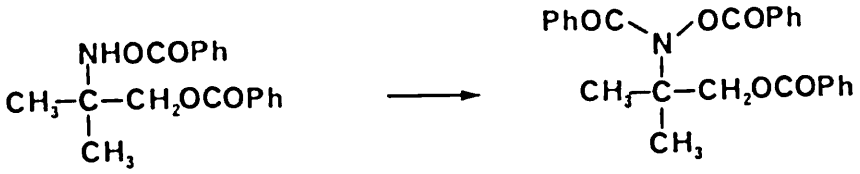
IR (ν cm^{-1}, Nujol): 3240 (NH str.), 1740 max. (OCO str.), 1600 (C = C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.3 (s, 6H, CH_3(2)), 4.3 (s, 2H, CH_2), 7.3-8.2 (m, 10H, Ar-H(2)).

Mass Spectrum (m/z, 35eV): 178 (125, M-CH_2OCOPh), 122 (PhOCOH, base peak), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$).

(Found: C, 68.8; H, 6.24; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.7; N, 4.5%).

18. Preparation of O-benzoyl-N-(2-benzoyloxymethyl--2-propyl)benzohydroxamic acid.



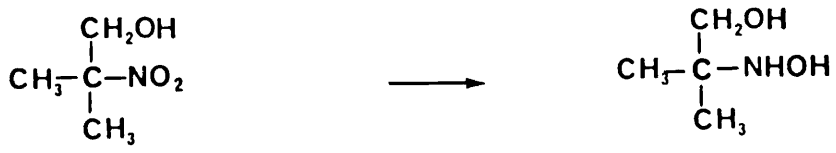
To a stirred solution of O-benzoyl-N-benzoyloxy-2--amino-2-methylpropan-1-ol (15.g, 4.7 mmole) in sodium dried benzene (40 cm^3) was added dry pyridine (0.39 g, 5.0 mmole) and benzoyl chloride (0.66g, 4.7 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t-butylhydroxamic acid (exp. 2) to give a pale yellow oil which solidified on cooling. Recrystallization from methanol yielded the title compound as a colourless solid (0.42g, 21%) m.p. 74-76°C.

IR (νcm^{-1}, Nujol): 1760 (OCO str.), 1720 (OCO str.), 1655 (NCO str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.7 (s, 6H, CH_3 (2)), 4.75 (s, 2H, CH_2), 7.1-8.2 (m, 15H, Ar-H (3)).

(Found: C, 71.7; H, 5.6; N, 3.3. $C_{24}H_{21}NO_5$ required C, 71.9; H, 5.5; N, 3.35%).

19. Preparation of 2-(N-hydroxyamino)-2-methyl--propan-1-ol



The title compound was prepared according to the method of Alewood *et al*.[98]

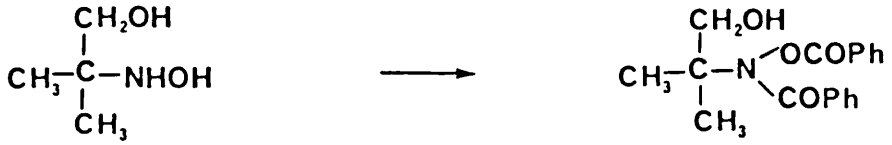
A stirred solution of 2-methyl-2-nitro-propanol (5.95g, 0.05 mole) in aqueous ethanolic NH_4Cl (2.5g in 50 cm^3 50%) was treated with acid-washed zinc dust (10g) during 3 hours, the temperature being kept below 15°C. The mixture was stirred for 3 hours at room temperature and then filtered; the solids were washed with water (4 x 20 cm^3). The combined filtrate and washings were acidified to pH 2 with conc. HCl and most of the solvent was then removed under reduced pressure to give a syrup to which was added K_2CO_3 (20g). The resulting mixture was extracted by $CHCl_3$ in a soxhlet apparatus for 4 hours. Removal of chloroform from the extract left a viscous oil which was mixed with an equal volume of fresh chloroform. Crystals slowly separated (2.98g) and after recrystallization from hexane/$CHCl_3$ pure 2-(N-hydroxyamino)-2-methylpropan-1-ol was obtained as colourless hygroscopic crystals, m.p. 63-64°C (Lit.,[98] 62-64°C)

IR (ν cm^{-1}, Nujol): 3500-2400 br., 3200 max (OH, and -NH str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.0 (s, 6H, CH_3 (2)), 3.4 (s, 2H, CH_2), 4.6-6.1 br. (s, 3H, -OH (2) and -NH).

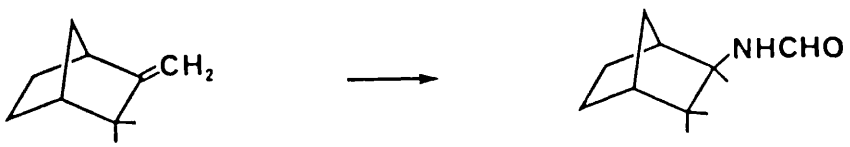
Mass Spectrum (m/z, 18eV): 74 (31, M-CH_2OH_2 base peak).

20. Attempted preparation of O-benzoyl-N--(2-hydroxymethyl-2-propyl)benzohydroxamic acid



To a stirred solution of 2-(N-hydroxyamino)-2--methylpropanol (2.1g, 0.02 mole) in sodium dried benzene (50 cm^3) was added molecular sieve dried pyridine (3.3g, 0.042 mole) and benzoyl chloride (6.16g, 0.044 mole). The mixture was heated to reflux at which stage a brown oil appeared at the bottom of the reaction vessel. After refluxing for 2 hours the cooled solution was poured into 1M HCl (150 cm^3) and shaken. The solution was extracted with diethyl ether (2 x 50 cm^3). The organic phase was washed with 1M HCl (2 x 50 cm^3) and water (2 x 50 cm^3), dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a viscous yellow oil which partially solidified on cooling. T.l.c. (SiO_2, ethyl acetate: petrol 60-80°, 20:80) showed at least five components in the crude reaction product. Column chromatography was carried out but the title compound could not be isolated.

21. Preparation of 3-formamidoisocamphane

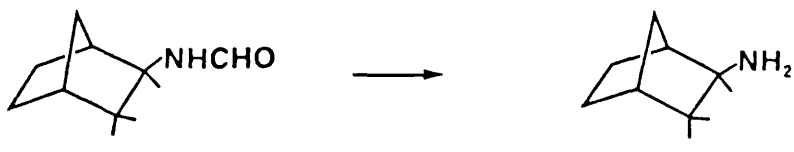


The title compound was prepared by slight modification of Stone's method[49] as follows:

To a solution of camphene (10.0g, 0.07 mole) in glacial acetic acid (25 cm^3) at 0°C was added sodium cyanide (10.8 g, 0.22 mole). Conc. H_2SO_4 (5 cm^3) was added dropwise with stirring at 0-3°C over a period of one hour. When addition was complete the reaction was stirred for one hour at 0°C and then allowed to warm to room temperature. After 48 hours the reaction mixture was cautiously poured onto ice (200g). The aqueous solution was neutralized with sodium hydroxide solution (20% w/v) keeping the temperature below 20°C. The solution was extracted with chloroform (2 x 250 cm^3), washed with water and dried over dry $MgSO_4$. Filtration and evaporation of solvent yielded a brown oil. Column chromatography (SiO_2, ethyl acetate: petrol 60-80°, 20:80) yielded the title compound as a white crystalline solid (8.4g, 67%) m.p 170-172°C (Lit.,[49] 170-174°C).

IR (νcm^{-1}, Nujol): 3200 br. (NH str.), 1660 max (C=O str.).

22. Preparation of 3-aminoisocamphane

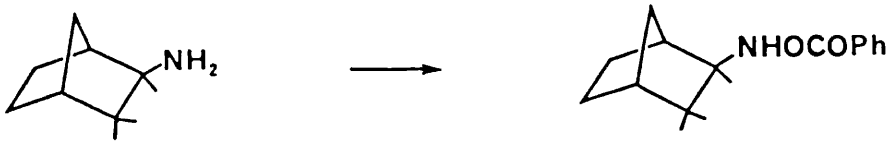


The above formamide (10.0g, 0.55 mole) in methanol (50

cm^3) was hydrolysed by adding, with stirring, 4.4g of sodium hydroxide in 40 cm^3 water. The mixture was refluxed for 48 hours and the methanol distilled in vacuo until two phases separated. The residue was diluted with 50 cm^3 of water and then extracted with 2 x 50 cm^3 of ether. The ether extracts were dried over magnesium sulphate, filtered, and concentrated to dryness. The concentrate was practically pure 3-aminoisocamphane (7.5g, 88%).

IR ($\nu\ cm^{-1}$, neat): 3400-3200 br. (NH_2 str.), 1600 (N-H def.).

23. Preparation of O-benzoyl-N-(3-isocamphyl)--hydroxylamine.



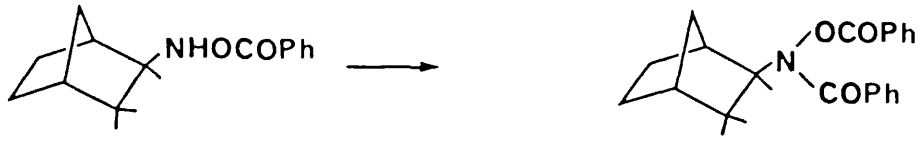
The title compound was prepared using a procedure similar to the preparation of O-benzoyl-N-t--butylhydroxylamine (exp. 1). The crude reaction product was further purified by column chromatography (SiO_2; ethyl acetate: petrol 60-80°; 20:80) to yield a pale yellow oil which showed a single spot on t.l.c. (0.62g, 70% based on dibenzoyl peroxide).

IR ($\nu\ cm^{-1}$, neat): 3220 (N-H str.), 1710 (C = O str.), 1600 (C = C str.).

^{1}H-NMR (δ ppm, $CDCl_3$) : 0.9-2.8 (m, 18H, hydrocarbon

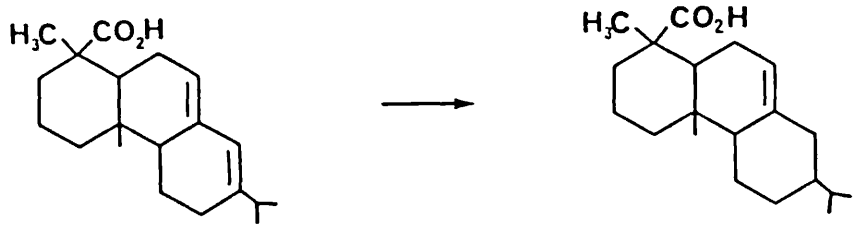
protons and N-H), 7.3-8.0 (m, 5H, Ar-H).

24. Attempted preparation of O-benzoyl-N-(3-iso--camphyl)benzohydroxamic acid.



The above synthesis was attempted using a procedure similar to the preparation of O-benzoyl-N-t--butylbenzohydroxamic acid (exp. 2). The crude reaction mixture showed no NCO C=O stretch in the infrared spectrum. Column chromatography of the crude product (SiO_2,$CHCl_3$) gave only starting material.

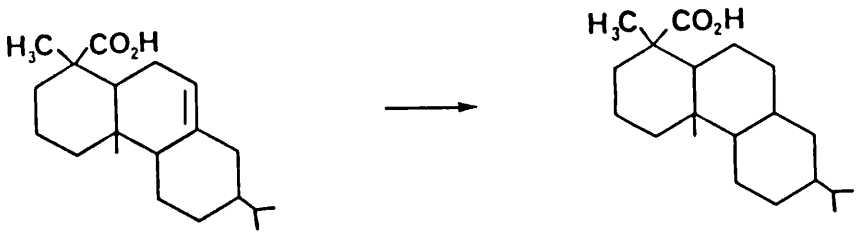
25. Preparation of dihydroabietic acid.



Recrystallized abietic acid (FLUKA) (3g, 9.9 mmole) was dissolved in sodium dried ether (50 cm^3) and the solution cooled to -40°C using a cardice/acetone bath. Dry liquid ammonia was added (100 cm^3) with rapid stirring. Fresh lithium (cut under toluene) was added slowly in small pieces (addition of larger pieces caused frothing to occur) until a large excess had been added. After stirring for a further 15 minutes

at -40°C, absolute alcohol (50 cm^3) was added dropwise over a period of half an hour. The reaction mixture was allowed to warm to room temperature and when the ammonia had evaporated, diethyl ether (250 cm^3) and 50% HCl/water (250 cm^3) were added. The ethereal phase was separated and washed with 50% HCl/water (2 x 200 cm^3) and then dried ($MgSO_4$). Evaporation of solvent yielded a colourless oil which solidified on cooling. Recrystallization from acetone yielded cubic crystals (2.65g, 88%) m.p 185-187°C (Lit.,[59] 197-197-°C). ^{1}H-NMR spectroscopy showed complete reduction of the double bond at 5.7 ppm but suggested the presence of more than one isomer of dihydroabietic acid (broad singlet at δ 5.27ppm and a smaller singlet at δ 5.03 ppm (4:1)), since the next stage involved catalytic hydrogenation to tetrahydroabietic acid and since actual configuration was not important further purification was not carried out.

26. Preparation of tetrahydroabietic acid



10% Pd/C catalyst (500 mg) in ethanol (2 cm^3) was added to dihydroabietic acid (0.2g, 0.65 mmole) in absolute ethanol (25 cm^3). The reaction mixture was

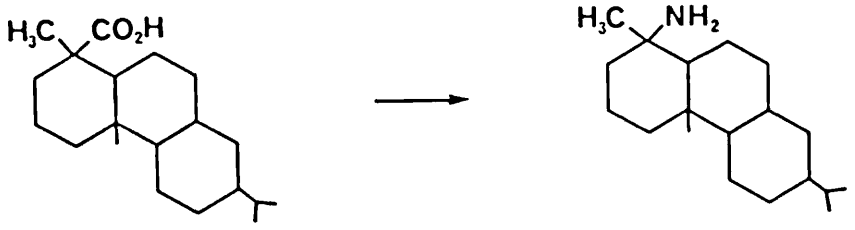
hydrogenated at room temperature and atmospheric pressure for 2 hours and then filtered through celite. Evaporation of solvent and recrystallization from acetone yielded a colourless crystalline solid (0.18g, 96%) m.p 181-182°C.

IR (ν cm^{-1}, Nujol): 3250-2500br. (O-H str.), 1690 (max C=O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): showed no olefinic protons.

Mass Spectrum (m/z, 35eV): 306 (M^+, 9.6%), 289 (17, M^+-OH), 261 (45, M^+-CO_2H).

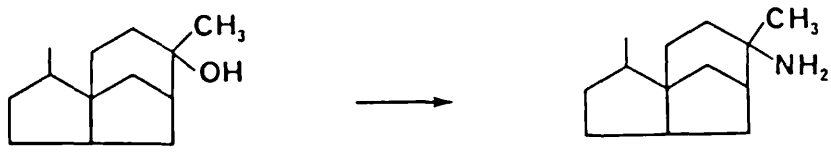
27. Attempted preparation of 4-aminoabietane.



Conc. H_2SO_4 (3 cm^3) was added to a cooled stirred solution (0-5°C) of tetrahydroabietic acid (1.0g, 3.3 mmole) in chloroform (10 cm^3) sodium azide (0.42g, 6.5 mmole) was added portionwise to the vigorously stirred solution maintained at 0°C. When addition was complete the reaction mixture was warmed to 40-45°C and allowed to stir for a further 2 hours. After this time, the reaction mixture was made strongly basic with 50% w/v NaOH solution. The resulting solution was extracted with diethyl ether and the organic phase

dried ($MgSO_4$). Filtration and evaporation of solvent yielded a yellow oil. T.l.c. of the crude reaction mixture (SiO_2; $CHCl_3$) showed at least five components to be present. Infrared spectroscopy showed none of the required bands (-NH str. and -NH def.).

28. Attempted preparation of 8-aminocedrane.

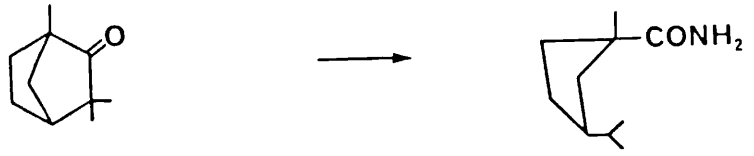


Sodium cyanide (0.66g, 13.5 mmole) was added portionwise to glacial acetic acid (1 cm^3). Cedrol (1g, 4.5 mmole) was added slowly, keeping the temperature below 20°C. The reaction mixture was allowed to warm to room temperature and then heated at 60°-70°C for 3½ hours. The cooled mixture was poured onto ice (200 cm^3), made alkaline (30% NaOH solution) and the resulting solution was extracted with diethyl ether. The organic extract was washed with water, dried (Na_2SO_4) and filtered. Evaporation of solvent yielded only starting material (0.92g, 93%).

N.B. For convenience of terminology only, the intermediates in the synthesis of optically active hydroxamic acids have been designated with the sign of the rotation of their optically active precursors. The optical rotation of these intermediates was not

routinely recorded and only the rotations of the final hydroxamic acids have been measured.

29. Preparation of (+)-fencholamide



(+)-Fencholamide was prepared using the method of Semmler.[61]

(+)-Fenchone (FLUKA) (40.0g, 0.26 mole) in sodium dried benzene (80 cm^3) was added in one portion to sodamide powder (May and Baker)(12.3g, 0.32 mole) and the reaction mixture was stirred vigorously on a steam bath for 6 hours. After cooling, ice was cautiously added followed by diethyl ether (500 cm^3). The ethereal phase was washed with water (3 x 250 cm^3) and dried (Na_2SO_4). Filtration and evaporation of solvent yielded a white solid (41.2g, 93%) m.p 94-95°C (Lit.,[61] 94°C).

IR (ν cm^{-1}, Nujol): 3400 and 3200 (NH_2 str.) , 1700 (C=O str.).

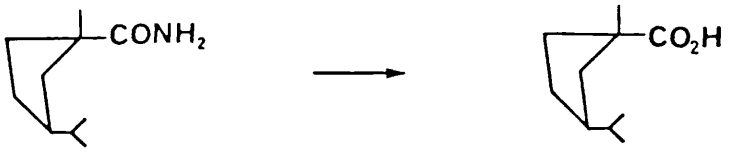
^{1}H-NMR (δ ppm, $CDCl_3$): 0.5-2.10 (m, 17H, fenchelyl protons), 0.8 and 0.9 (dd, 6H, isopropyl), 1.15 (s, 3H, CH_3), 5.2-5.8 br. (s, 2H, NH_2).

Mass Spectrum (m/z, 70eV): 169 (M^+, 8.9%), 154 (15, $M-CH_3^+$), 126 (43, $M-C_3H_2^+$), 125 (44, M- $O=C=NH_2^+$).

$[\alpha]_D^{25}$ + 1.65° (c=0.1 in $CHCl_3$).

(Found C, 71.5; H, 11.1; N, 8.8 calc. for $C_{10}H_{19}NO$. C, 71.0; H, 11.2; N, 8.3%).

30. Preparation of (+)-fencholic acid



To a concentrated solution of sodium hydroxide (40.0g in 200 cm^3 water) contained in a stainless steel vessel was added fencholamide (30.0g, 0.17 mole) in ethanol (200 cm^3). The reaction mixture was refluxed for 3 days. After removal of the ethanol by distillation, water was added and the reaction mixture was washed with diethyl ether (3 x 100 cm^3) to remove any basic components. The aqueous phase was then made strongly acidic with conc. HCl and extracted with diethyl ether (3 x 500 cm^3). The organic phase was dried (Na_2SO_4), and filtered. Evaporation of solvent yielded a yellow oil. Vacuum distillation of the crude reaction product gave the title compound as a colourless oil (28.8g, 96%) $b.p_{12}$ 143-144°C (Lit.,[99] $b.p_{10}$ 140-141°C).

IR (ν cm^{-1}, neat): 3500-2250 br. (-OH str.), 1700 (C=O str.).

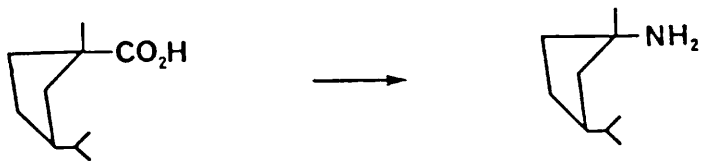
Mass Spectrum (m/z, 70eV): 170 (M^+, 1.1%), 127 (43, $M-C_3H_7^+$) 125 (45, $M-CO_2H$).

$[\alpha]_D^{25}$ + 3.2° (c=0.1 in $CHCl_3$).

31. Alternative preparation of fencholic acid

An alternative synthesis of fencholic acid was attempted using the method Vaughan and Robbins.[100] Fencholamide (2g, 0.012 mole) was suspended in water (40 cm^3) and the mixture heated to 50°C on a steam bath. Sodium peroxide (0.92g, 0.12 mole) was cautiously added. No evolution of ammonia was detected. After stirring for | hour the reaction mixture was cooled to 0°C and carefully acidified. The aqueous phase was extracted with diethyl ether (2 x 50 cm^3). After drying (Na_2SO_4), filtration and evaporation of solvent no acidic products could be found. The acidic aqueous phase was made basic (50% NaOH solution) and extracted with diethyl ether. Fencholamide (1.95g) was found in the organic phase. It was concluded that no reaction had taken place.

32. Preparation of (+)-fenchelylamine -(a)-



Fenchelylamine was prepared from fencholic acid by the Schmidt reaction as per bicyclo[3.2.1]octylamine (exp. 11). The crude reaction product was further purified by vacuum distillation $b.p_{15}$ 64-66°C (Lit.,[101] 173°C). Infrared spectroscopy showed an unknown absorption at 1680 cm^{-1}. Vacuum fractional distillation did remove

this impurity but the yield of the uncontaminated amine was small. Experiments using the contaminated amine (for example reaction with dibenzoyl peroxide to form the N-benzoyloxy derivative) were unsuccessful.

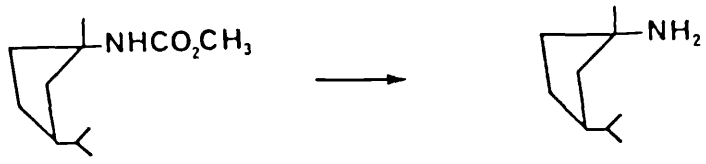
33. Preparation of methyl N-fenchelylcarbamate.

Methyl N-fenchelylcarbamate was prepared by the Hofmann rearrangment[64] according to Bouveault and Lavallois.[102]

Fencholamide (10.0g, 0.059 mole) in methanol (50 cm^3) was added to a solution of sodium (2.7g, 0.12 mole) in methanol (80 cm^3). Bromine (9.44g, 0.059 mole) was added with rapid stirring. The resulting reaction mixture was heated on a steam bath for 10 minutes. The methanol was removed by distillation and the reaction mixture was rendered acidic using glacial acetic acid. The product was washed with water (to removed sodium bromide) and light petroleum (b.p 60-80°C) was added. The organic phase was washed with water (2 x 100 cm^3), dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a pale yellow oil. Vacuum distillation then gave the title compound as a colourless oil (9.5g, 81%) $b.p_{18}$ 140-141°C.

IR (νcm^{-1}, neat): 3340 br. (N-H str.), 1720 (max C=O str.).

34. Attempted hydrolysis of methyl N-fenchelyl--carbamate



a. Acid hydrolysis

Concentrated hydrochloric acid (0.5 cm^3) was added to a solution of methyl N-fenchelylcarbamate (0.5g) in methanol (10 cm^3). Water was added until the solution became turbid (1 cm^3). After refluxing for 24 hours the reaction mixture was cooled and made basic with 50% sodium hydroxide solution (w/v), and then extracted with diethyl ether. The ethereal layer was dried ($MgSO_4$) and filtered. Evaporation of solvent yielded a pale yellow oil (0.48g). Infrared spectroscopy showed the product to be starting material. Acid hydrolysis was unsuccessful.

b. Base hydrolysis

Methyl N-fenchelylcarbamate (3.0g, 0.15 mole) was refluxed with ethanolic alkali (1.8g, 0.045 mole NaOH in H_2O: ethanol, 50:50) for 24 hours. The ethanol was removed and the reaction mixture was extracted with diethyl ether. The ethereal phase was dried (Na_2SO_4)

and filtered. Evaporation of solvent yielded a pale yellow oil (2.9g, 98%). Infrared spectroscopy showed the product to be starting material. Base hydrolysis was unsuccessful.

c. Calcium oxide, water.

Methyl N-fenchelylcarbamate (7.0g, 0.05 mole) was thoroughly mixed with calcium oxide (27.5g, 0.7 mole) to which 30 cm^3 of water had been added. The mixture was steam distilled into ligroin. The ligroin layer was separated, dried ($MgSO_4$) and filtered. Evaporation of solvent yielded a colourless oil. Infrared spectroscopy showed the product to be starting material.

d. Wet DMSO, NaI

Methyl N-fenchelylcarbamate (2.0g, 0.01 mole), sodium iodide (4.5g, 0.03 mole), DMSO (10 cm^3) and water (1 cm^3) were heated to 150°C for 8 hours. After cooling the reaction mixture was poured into water. The resulting solution was extracted with diethyl ether (2 x 50 cm^3) and the organic phase was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a colourless oil. Infrared spectroscopy showed the product to be starting material.

e. Sodium peroxide, water.

Methyl N-fenchelylcarbamate (2.0g, 0.01 mole) was suspended in water (40 cm^3) and the mixture heated to 50°C on a steam bath. Sodium peroxide (0.77g, 0.01 mole) was cautiously added. After heating at 50°C for one hour the solution was cooled and made basic. Extraction with diethyl ether, revealed only starting material (1.9g, 95%).

f. $LiAlH_4$

Lithium aluminium hydride (0.25g, 6.6 mmole) was added in small portions to the carbamate (0.5g, 2.5 mmole) in sodium dried ether (10 cm^3). The reaction mixture was refluxed for 45 minutes, cooled and then quenched with ethyl acetate (5 cm^3). 2M H_2SO_4 was added (20 cm^3) and the solution was extracted with diethyl ether. The aqueous phase was then made basic with NaOH pellets and further extracted with diethyl ether. This basic extract was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded 0.17g of liquid product (48% based on carbamate).

GC-MS (m/z, 70eV): OV101 capillary glass column, 50-230°C at 15°C min^{-1}).

GC-MS showed the product to comprise of 2 components:

a) N-methyl fenchelylamine

155(M^+, 2.55%), 140 (15, $M-CH_3$), 112 (43, $M-C_3H_7^+$).

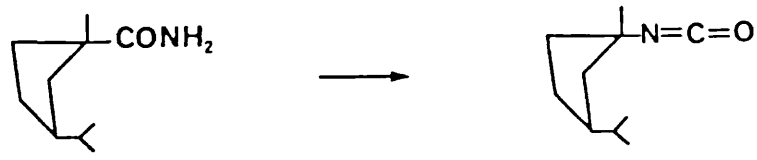
b) N-fenchelylacetamide

183 (M^+, 6.3%), 168 (15, M-CH_3, base peak), 140 (43, M-$C_3H_7^+$).

^{1}H-NMR (δ ppm, $CDCl_3$): NMR spectroscopy confirmed the presence of the secondary amine with the appearance of a singlet at 2.30. A second singlet at 2.13 showed the presence of N-fenchelylacetamide.

IR (ν cm^{-1}, neat): Infrared spectroscopy showed the presence of N-methyl fenchelylamine. 3275 (N-H str.), 2790 (N-CH_3 str.).

35. Preparation of (+)-fenchelyl isocyanate

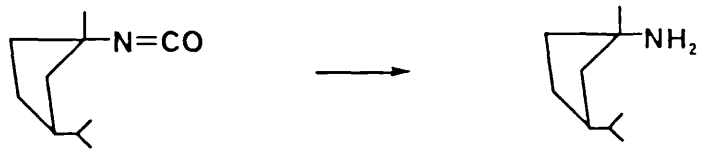


(+)-fenchelyl isocyanate was prepared according to the method of Wallach.[101]

Bromine (7.1g, 0.044 mole) was added dropwise with shaking to finely powdered fencholamide (7.5g, 0.044 mole). The resulting dark-red solution was cooled in ice and cold NaOH solution (25 cm^3, 10% w/v) was added portionwise. When addition was complete the reaction mixture was heated on a steam bath for 10 minutes, cooled and then extracted with diethyl ether (2 x 50 cm^3). The ethereal layer was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded the title compound as a pale yellow oil (7.25g, 98%).

IR (νcm^{-1}, neat): 2250 (-N=C=O str.).

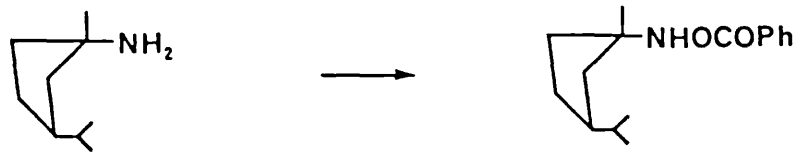
36. Preparation of (+)-fenchelylamine -(b)-



Hydrochloric acid solution (conc. HCl:water, 40:60) was added to neat (+)-fenchelyl isocyanate (6.5g, 0.036 mole) and the reaction mixture was stirred vigorously at 100°C for 4 hours. On cooling the solution was extracted with diethyl ether (2 x 100 cm^3). The aqueous phase was made strongly basic with sodium hydroxide pellets and then extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and filtered. Evaporation of solvent yielded the title compound as a pale amber oil (5.12g, 93%).

IR (νcm^{-1}, neat): 3250 and 3350 br. (NH_2 str.), 1600 br. (N-H def.).

37. Preparation of (+)-O-benzoyl-N-fenchelyl--hydroxylamine



The title compound was prepared by a modification of Alewoods[35] method as follows: fenchelylamine (6.8g, 0.048 mole) was added dropwise with stirring to a solution of freshly crystallized dibenzoyl peroxide (5.83g, 0.024 mole) in sodium dried benzene (100 cm^3).

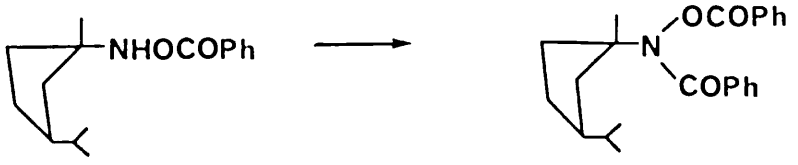
The reaction mixture was stirred for 3 days at room temperature. Diethyl ether was added (100 cm^3) and the precipitated amine salt was filtered and washed with diethyl ether (2 x 50 cm^3). The filtrate was washed with water (2 x 100 cm^3), saturated sodium bicarbonate solution (2 x 100 cm^3) and finally with water (2 x 100 cm^3). The organic layer was dried (Na_2SO_4), filtered and evaporated to yield a pale brown oil which partially solidified on cooling. The product was washed with hexane.

Unreacted dibenzoyl peroxide was removed by filtration and the filtrate concentrated by rotary evaporation. Column chromatography (silica, ethyl acetate : petrol 60-80°, 20:80) of the crude reaction product gave O-benzoyl-N-fenchelylhydroxylamine as a colourless oil (5.0g, 82% based on dibenzoyl peroxide).

IR (ν cm^{-1}, neat): 3200 (N-H str.), 1700 (C=O str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.6-2.0 (m, 17H, fenchelyl protons), 0.8-0.9 (d, 6H, isopropyl CH_3(2)), 7.5 and 8.0 (m, 5H, Ar-H).

38. Preparation of (+)-O-benzoyl-N-fenchelylbenzo--hydroxamic acid



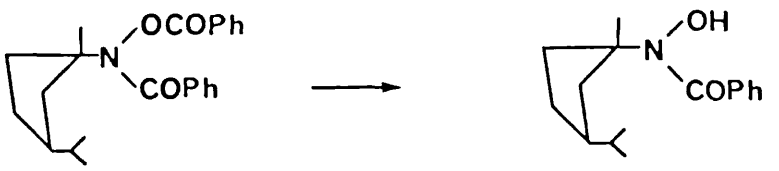
To a stirred solution of (+)-O-benzoyl-N-fenchelyl--hydroxylamine (1.60g, 6.13 mole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.5g, 6.3 mmole) and benzoyl chloride (0.9g, 6.4 mmole). After refluxing for 24 hours the reaction mixture was poured into 2M. HCl (3 x 50 cm^3). The solution was extracted with diethyl ether (2 x 50 cm^3). The organic phase was washed with water (2 x 50 cm^3), dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a pale yellow oil. Column chromatography (SiO_2, $CHCl_3$) of the crude reaction product removed any unreacted acid chloride and gave the title compound as a liquid which showed a single spot on t.l.c. (1.9g, 85%).

IR (νcm^{-1}, neat): 1760 (max OCO C=O str.), 1640 (max NCO C=O str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.5-2.4 (m, 17H, fenchelyl protons), 0.8 and 0.9 (2 doublets, 6H isopropyl), 1.15 (s, 3H, CH_3), 7.0-8.0 (m, 10, Ar-H (2)).

Mass Spectrum (m/z, 70eV): 122 (C_6H_5OCOH), 105 ($PhCO^+$, 77 (Ph^+).

39. Preparation of (+)-N-fenchelylbenzohydroxamic acid



The title compound was prepared using a procedure

similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3). Recrystallization from hexane/MeOH gave the hydroxamic acid in 92% yield as colourless needles m.p 116-117°C.

IR (ν cm^{-1}, Nujol): 3400 (O-H str.), 1620 (max. C=O str.).

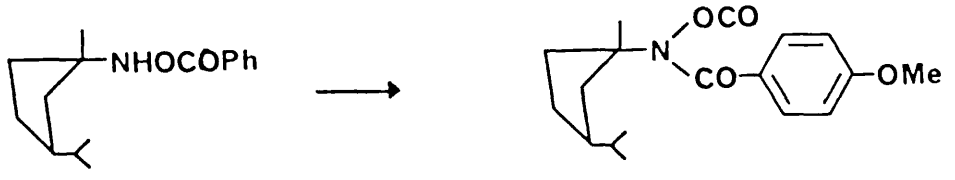
^{1}H-NMR (δ ppm, $CDCl_3$): 0.5-2.10 (m, 17H, fenchelyl protons), 0.6-0.8 (dd, J = 5HZ, 6H, isopropyl CH_3(2)), 1.25 (s, 3H, CH_3), 7.1-7.4 (m, 5H, Ar-H), 8.25-8.4 br. (s, 1H, O-H).

^{13}C-NMR (δ ppm. $CDCl_3$): 21.7 (q, isopropyl CH_3 (2)), 24.3 (q, CH_3), 28.2 (t, CH_2) 34.4 (d, CH of isopropyl), 38.8 (t, CH_2), 44.8 and 45.2 (d,t, CH and CH_2), 70.2 (s, C-N), 127.8 (d, o and m aryl carbons), 130.0 (d, p- aryl carbon), 135.9 (s, Co-C, ipso), 169.6 (s, C=O)

$[\alpha]_D^{25}$ + 6.61° (c=0.05 in $CHCl_3$).

(Found C, 73.7; H, 8.9; N, 5.2. $C_{16}H_{23}NO_2$ required C, 73.5; H, 8.8; N, 5.3%).

40. Preparation of (+)-O-benzoyl-N-fenchelyl-4--methoxybenzohydroxamic acid

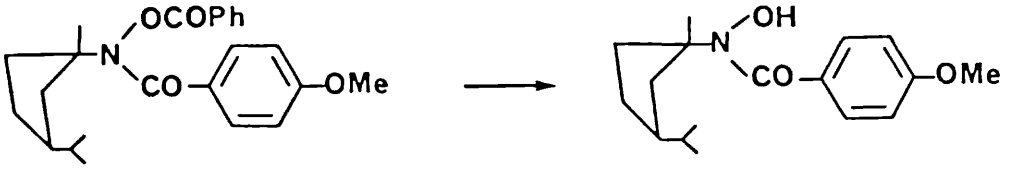


The title compound was prepared using a procedure similar to the preparation of O-benzoyl N-t-butyl-4-

-methoxybenzoyhydroxamic acid (exp. 4). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave O-benzoyl-N-fenchelyl-4--methoxybenzohydroxamic acid as a colourless oil in 93% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1760 (max OCO C=O str.), 1640 (max NCO C=O str.), 1600 (C=C str.).

41. Preparation of (+)-N-fenchelyl-4-methoxy--benzohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of N-t-butyl-4--methoxybenzohydroxamic acid (exp. 5). Recrystallization from hexane gave the hydroxamic acid in 93% yield as colourless needles m.p 114-115°C.

IR (ν cm^{-1}, Nujol): 3200 (O-H str.), 1610 (max. C=O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.3-0.2 (m,. 17H, fenchelyl protons), 0.4-0.5 (dd, J = 1.3HZ, 6H, isopropyl CH_3(2)), 0.6 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 6.7 + 7.3 (AA'BB', J = 8.5 HZ, 4H, XC_6H_4Y).

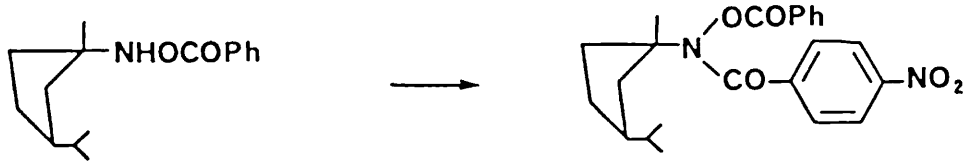
^{13}C-NMR (δ ppm, $CDCl_3$: 21.9, 24.0, 28.4, 34.6, 38.8, 45.0, 45.1, (fenchelyl carbons), 56.0 (O-CH_3), 71.0 (C-N), 113.9 and 130.7 (o and m aryl carbons), 128.6

(CO-C), 161.8 (C-OMe), 170.9 (C=O).

$[\alpha]_D^{25}$ + 9.1 (c=0.05 in $CHCl_3$).

(Found: C, 70.3; H, 8.8; N, 4.8. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.6; N, 4.8%).

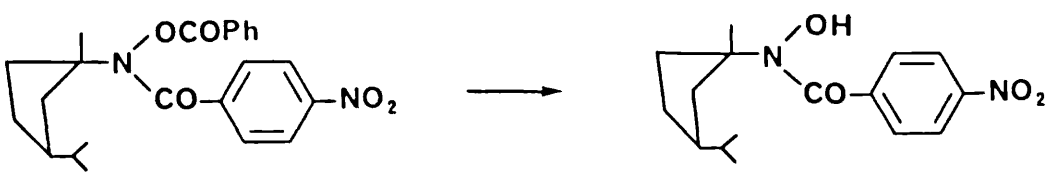
42. Preparation of (+)-O-benzoyl-N-fenchelyl-4--nitrobenzohydroxamic acid.



To a stirred solution of (+)-O-benzoyl-N--fenchelylhydroxylamine (2.0g, 7.6 mmole) in sodium dried benzene (30 cm^3) was added pyridine (0.6g, 7.7 mmole) and 4-nitrobenzoyl chloride (1.4g, 7.6 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-fenchelylbenzohydroxamic acid (exp. 38). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O-benzoyl-N--fenchelyl-4-nitrobenzohydroxamic acid (liquid) in 93% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1760 (max. OCO C=O str.), 1640 (max. NCO C=O str.), 1600 (C=C str.).

43. Preparation of (+)-N-fenchelyl-4-nitrobenzo--hydroxamic acid



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzo--hydroxamic acid (exp. 3). Recrystallization from benzene gave the hydroxamic acid in 90% yield as colourless crystals m.p 129.5-131°C.

IR (ν cm^{-1}, Nujol): 3100 (O-H str.), 1610 (max. C=O str.).

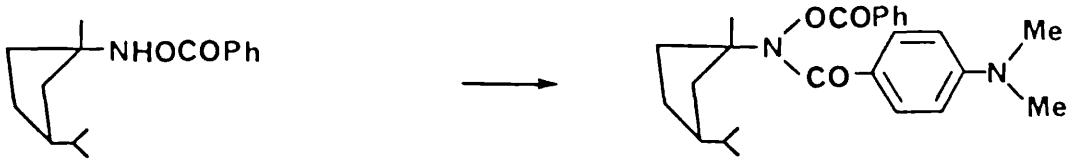
^{1}H-NMR (δ ppm, $CDCl_3$): 0.7-2.0 (m, 17H, fenchelyl protons), 0.8 (dd, J = 3HZ, 6H, isopropyl CH_3(2)), 1.38 (s, 3H, CH_3), 7.5 + 8.1 (AA'BB', J_{AB} = 8.3HZ, 4H, XC_6H_4Y).

^{13}C-NMR (δ ppm,$CDCl_3$): 21.7 23.9, 28.2, 34.5, 38.6, 44.6, 45.1 (fenchelyl carbons), 71.1 (C-N), 123.8 and 129.4 (o and m aryl carbons), 142.7 (s, p-aryl carbon), 149.1 (s,C-NO_2), 168.6 (C=O).

$[\alpha]_D^{25}$ + 12.2° (c=0.05 in $CHCl_3$).

(Found: C, 62.25; H, 7.1; N, 8.9. $C_{16}H_{22}NO_4$ requires C, 62.7; H, 7.2; N, 9.15%).

44. Preparation of (+)-O-benzoyl-N-fenchelyl-4--dimethylaminobenzohydroxamic acid

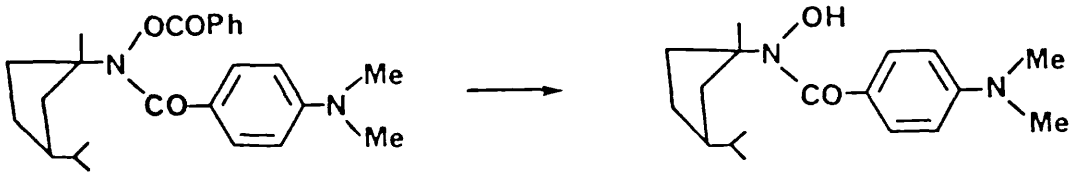


To a stirred solution of (+)-O-benzoyl-N-fenchelyl--hydroxylamine (2.0g, 7.6 mmole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.6g, 7.7

mmole) and 4-dimethylaminobenzoyl chloride (.14g, 7.6 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N--fenchelylbenzohydroxamic acid (exp. 38). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$), gave (+)-O-benzoyl-N-fenchelyl-4--dimethylaminobenzohydroxamic acid (liquid) in 84% yield which showed a single spot on t.l.c..

IR (ν cm^{-1}, neat): 1760 (max. OCO C=O str.), 1640 (max. NCO C=O str.), 1600 (C=O str.).

45. Preparation of N-fenchelyl-4-dimethylaminobenzo--hydroxamic acid



The title compound was prepared using a procedure similar to the preparation of N-t-butyl benzohydroxamic acid (exp. 3). Recrystallization from hexane gave the hydroxamic acid in 90% yield as colourless crystals m.p 121-122°C.

IR (ν cm^{-1}, Nujol): 3140 (O-H str.), 1620 (max. C=O str.).

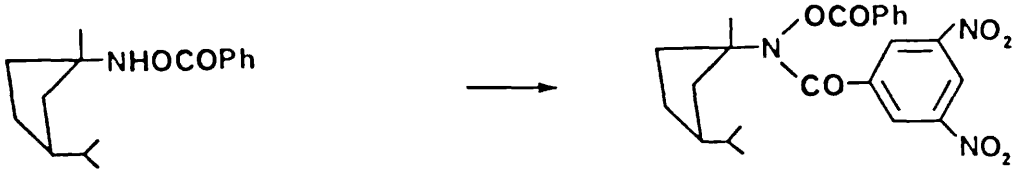
^{1}H-NMR (δ ppm, $CDCl_3$): 0.8-1.5 (m, 17H, fenchelyl protons), 0.86 (m, 6H, isopropyl CH_3 (2)), 1.35 (s, 3H,CH_3), 2.95 (s, 6H, N-$(CH_3)_2$), 6.6 + 7.5 (AA'BB', J = 10 HZ, 4H, X(C_6H_4Y).

^{13}C-NMR (δ ppm, $CDCl_3$): 21.5, 23.5 28.0, 34.2, 38.6 40.5 (fenchelyl carbons), 44.7 (N-$(CH_3)_2$), 70.7 (C-N), 111.1 (m-aryl), 122.8 (CO-C), 130.3 (o-aryl), 152.1 (C-N-$(Me)_2$), 171.8 (C=O).

$[\alpha]_D^{25}$ + 10.1° (c=0.05 in $CHCl_3$).

(Found: C, 71.1; H, 9.3; N, 9.1. $C_{18}H_{28}N_2O_2$ requires C, 71.05; H,9.2; N, 9.2%).

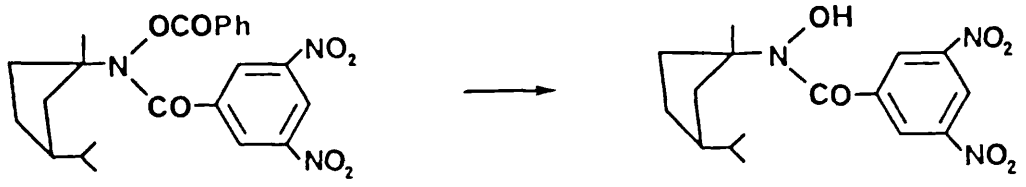
46. Preparation of (+)-O-benzoyl-N-fenchelyl-3,5--dinitrobenzohydroxamic acid



To a stirred solution of (+)-O-benzoyl-N-fenchelyl--hydroxylamine (2.0g, 7.6 mmole) in sodium dried benzene (30 cm^3) was added pyridine (0.6g, 7.7 mmole) and 3,5-dinitrobenzoyl chloride (1.4g, 7.6 mmole). After refluxing for 24 hours the reaction mixture was worked up as per (+)-O-benzoyl-N-fenchelylbenzo--hydroxamic acid (exp. 38). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O-N--fenchelyl-3,5-dinitrobenzohydroxamic acid (liquid) in 94% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1760 (max. OCO C=O str.), 1640 (max. NCO C=O str.) 1600 (C=C str.).

47. Preparation of (+)-N-fenchelyl-3,5-dinitrobenzo--hydroxamic acid



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzo--hydroxamic acid (exp. 3). Recrystallization from benzene gave the hydroxamic acid in 91% yield as colourless crystals m.p 141-142°C.

IR (νcm^{-1}, Nujol): 3380 (O-H str.), 1620 (C=O str.),

^{1}H-NMR (δ ppm, $CDCl_3$): 0.8-2.1 (m, 17H, fenchelyl protons), 0.9 (dd, J=1HZ, 6H, isopropyl CH_3 (2)), 1.46 (s, 3H, CH_3), 8.7 (d, 2H, o-aryl protons), 9.0 (t, 1H, p-aryl protons).

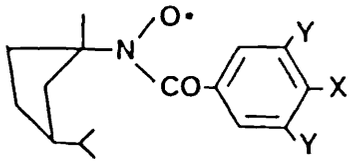
$[\alpha]_D^{25}$ + 14.6° (c=0.05 in $CHCl_3$).

(Found: C, 54.9; H, 6.0; N, 11.9. $C_{16}H_{21}N_3O_6$ requires C, 54.7; H, 6.0; N, 12.0%).

The optically active (-)-N-fenchelylbenzohydroxamic acids were prepared in exactly the same manner as the (+) enantiomers. Table 27 shows the physical data for these compounds.

48. Preparation of (+)-3-pinanecarbonyl chloride

TABLE 27. Physical data for the (-)-N-fenchelylbenzohydroxamic acids.



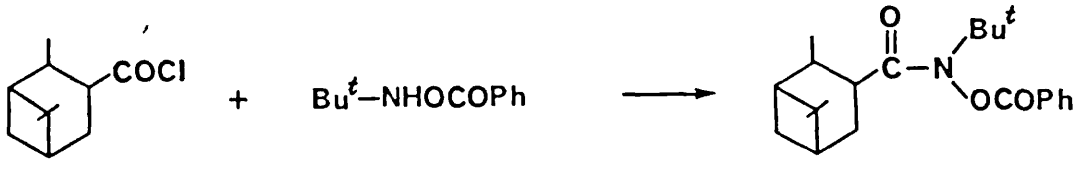
No.	X	Y	Mpt. (°C)	$[\alpha]^{25}$ (c = 0.05 in $CHCl_3$)	Found% (Required) C	H	N
(102)	H	NO_2	143-144	-15.5°	54.4 (54.7)	6.1 (6.0)	11.9 (12.0)
(103)	NO_2	H	126.5-128	-12.7°	62.4 (62.7)	7.2 (7.2)	9.0 (9.1)
(104)	H	H	116-117	-6.6°	73.7 (73.5)	8.9 (8.8)	5.2 (5.3)
(105)	OMe	H	114-115	-10.4°	69.8 (70.1)	8.7 (8.6)	4.7 (4.8)
(106)	$N(Me)_2$	H	121-122	-9.3°	70.7 (71.0)	9.3 (9.2)	9.1 (9.2)

Oxalyl chloride (9.5g, 0.075 mole) in sodium dried toluene (20 cm^3) was added dropwise to a stirred solution of (+)-pinanecarboxylic acid (5.0g, 0.027 mole) in toluene (20 cm^3). When the initial violent reaction had subsided the mixture was refluxed for 3 hours. After cooling, the solvent and excess oxalyl chloride were removed under reduced pressure to give a yellow oil. Vacuum distillation furnished the title compound as a colourless oil (4.5g, 81%) b.$p_{0.2}$ 75-76°C.

IR (νcm^{-1}, neat): 1800 (max. C=0 str.).

Mass Spectrum (m/z, 35eV): 165 (35/37, M-Cl), 149 (51/53, M-OCl), 137 (63/65, M-COCl).

49. Preparation of (+)-O-benzoyl-N-t-butylpinane--carbohydroxamic acid



To a stirred solution of O-benzoyl-N-t-butylhydroxy--lamine (3.7g, 0.02 mole) in sodium dried benzene (30 cm^3) was added molecular sieve dried pyridine (1.7g, 0.02 mole) and (+)-3-pinanecarbonyl chloride (4.0g, 0.02 mole). The mixture was refluxed for 6 hours, cooled and poured into 2M HCl (3 x 50 cm^3) and the resulting solution was extracted with diethyl ether (2 x 50 cm^3). The organic phase was washed with water (2

x 50cm^3), dried (Na_2SO_4) and filtered. Evaporation of solvent yielded a white solid. Recrystallization from methanol gave the title desired compound as colourless crystals (6.1g, 88%) m.p 79-80.5°C.

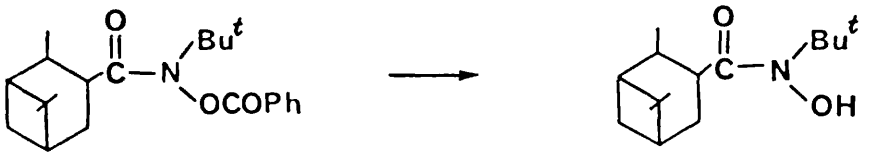
IR (νcm^{-1}, Nujol): 1760 (OCO C=O str.), 1655 (NCO C=O str.), 1600 (C=C str.).

^1H NMR (δ ppm, $CDCl_3$): 0.5-3.0 (m, 26H, all hydrocarbon protons), 1.5 (s, 9H, Bu^t), 7.4-8.2 (m, 5H, Ar-H).

Mass Spectrum (m/z, 35eV): 166 (137, M-$C_{10}H_{17}^+$), 137 ($C_{10}H_{17}^+$), 105 ($PhCO^+$), 77 (Ph^+).

$[\alpha]_D^{25}$ + 32.7° (c=0.01 in $CHCl_3$).

50. Preparation of (+)-N-t-butylpinanecarbo--hydroxamic acid



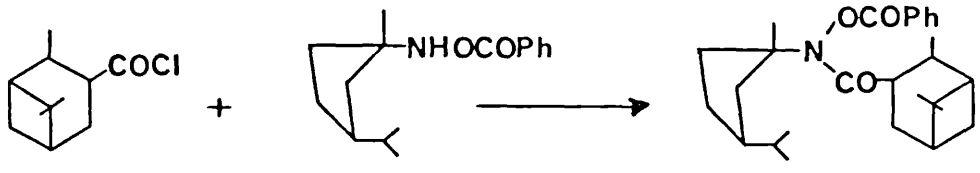
Hydrated barium hydroxide (17.2g, 0.05 mole) was added to a solution of (+)-O-benzoyl-N-t-butylpinane--carbohydroxamic acid (3.0g, 0.012 mole) in ethanol (60 cm^3). The mixture was then mechanically shaken for 40 minutes, after which, three evaporations to dryness with ethanol were performed to ensure complete hydrolysis. Water (30 cm^3) was added to the mixture which was then acidified to pH 1 with 12M. HCl. This mixture was extracted with diethyl ether (3 x 100 cm^3)

and the combined extracts were washed with 10% aqueous sodium bicarbonate (100 cm^3) and water (2 x 100 cm^3), and then dried (Na_2SO_4). Evaporation of solvent yielded a white solid. One crystallization from hexane (CH_2Cl_2)(5:1) gave the hydroxamic acid as colourless needles (2.8g, 97%) m.p 154-155°C (Lit.,[1] 156-157°C).

IR ($\nu\ cm^{-1}$, Nujol): 3120 (O-H str.), 1605 br. (c=O str.).

$[\alpha]_D^{25}$ + 48.1° (c=0.01 in $CHCl_3$). (Lit.,[1] for the (-)-enantiomer a rotation of -49.0° (c=0.01 in $CHCl_3$) has been reported.)

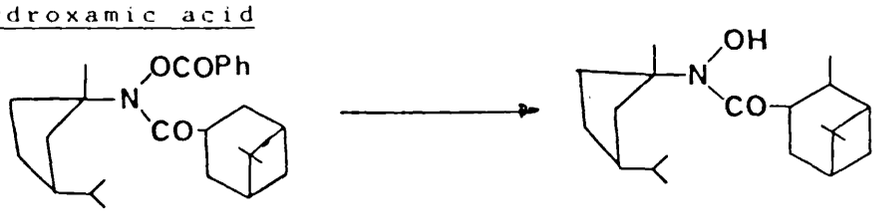
51. Preparation of (+)-O-benzoyl-N-fenchelylpinane--carbohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of O-benzoyl-N-t-butyl--pinanecarbohydroxamic acid (exp. 49). Column chromatography (SiO_2, $CHCl_3$) gave a liquid product in 86% yield which showed a single spot on t.l.c.

IR (νcm^{-1}, neat): 1760 (max. OCO c=0 str.), 1680 (max. NCO C=0 str.), 1600 (C=C str.).

52. Preparation of (+)-N-fenchelylpinanecarbo--hydroxamic acid



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3). Recrystallization from aq. ethanol gave the hydroxamic acid in 71% yield as colourless crystals m.p 133-135°C.

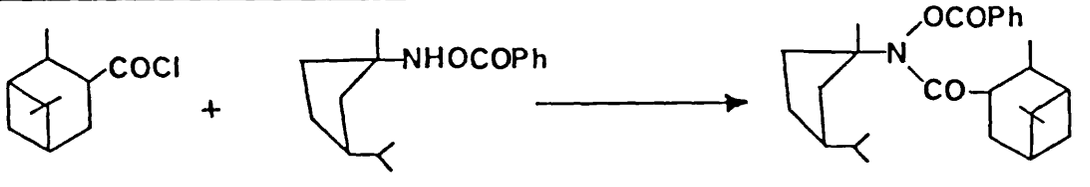
IR (ν cm^{-1}, Nujol): 3200 br. (O-H str), 1610 (C=O str.).

Mass Spectrum (m/z, 35eV): 305 (17, M-OH), 165 ($C_{10}H_{17}CO^+$), 137 ($C_{10}H_{17}^+$), 125 ($C_{10}H_{17}^+$).

$[\alpha]_D^{25}$ + 34.1° (c=0.05 in $CHCl_3$).

(Found: C, 74.5; H, 11.1; N, 4.6. $C_{20}H_{35}NO_2$ required C, 74.7; H, 10.9; N, 4.4%).

53. Preparation of (-)-O-benzoyl-N-fenchelylpinane--carbohydroxamic acid.



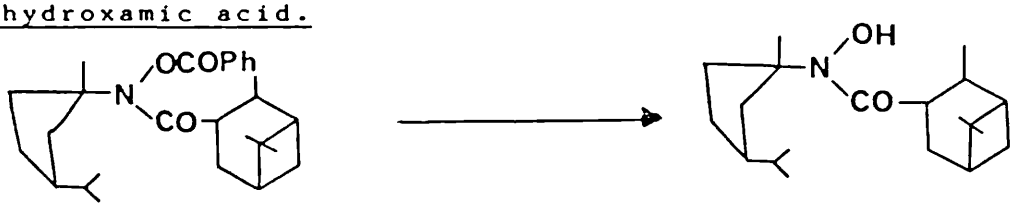
The title compound was prepared using a procedure similar to the preparation of (+)-O-benzoyl-N--fenchelylpinanecarbohydroxamic acid (exp. 51). Column chromatography (SiO_2, $CHCl_3$) of the crude

reaction product gave the title compound as a colourless oil in 89% yield. The product showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1760 (OCO C=O str.), 1660 (NCO C=O str.), 1600 (C=C str.).

Mass Spectrum (m/z, 35eV): 165 ($C_{10}H_{17}CO^+$), 137 ($C_{10}H_{17}^+$), 105 (Ph^+, base peak), 77 (Ph^+).

54. Preparation of (-)-N-fenchelylpinanecarbo--hydroxamic acid.



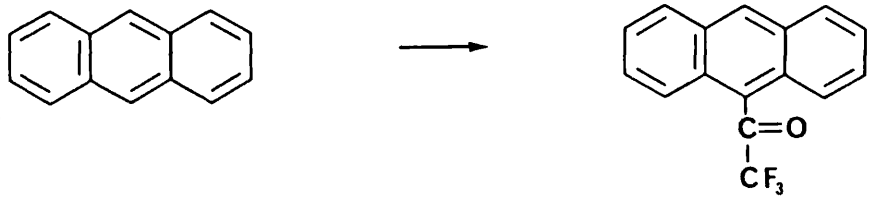
The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzo--hydroxamic acid (exp. 3). Recrystallization from aq. ethanol furnished the hydroxamic acid in 73% yield as colourless crystals m.p 154.5-156°C.

IR (ν cm^{-1}, Nujol): 3200 br. (O-H str.), 1610 (C=O str.).

$[\alpha]_D^{25}$ - 29.1° (c=0.01 in $CHCl_3$).

(Found C, 74.6; H, 11.0; N, 4.9. $C_{20}H_{35}NO_2$ requires C, 74.7; H, 10.9; N, 4.4%).

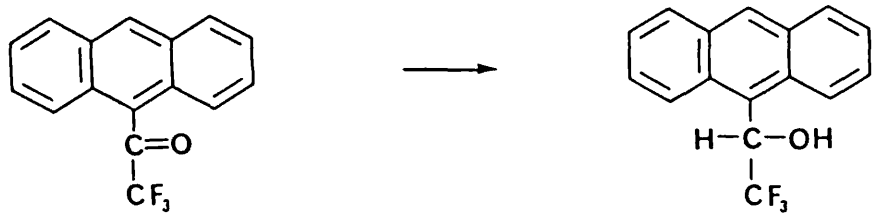
55. Preparation of 9-anthryl trifluoromethyl ketone



The title compound was prepared according to the method of Pirkle *et al.*[103] A thick-walled glass tube was charged with anthracene (5.9g, 0.033 mole), trifluoroacetic anhydride (7.3g, 0.035 mole) and benzene (25 cm^3), sealed and heated at 200°C for 15 hours. The tube was then cooled to room temperature, and cautiously opened. The dark reaction mixture was poured onto a column of silica gel (30g) and eluted with pentane (500 cm^3). The reddish-orange eluate was concentrated and rechromatographed on silica gel (100g). Elution with n-pentane gave a long yellow band of ketone. Crystallization from methanol gave bright yellow crystals (6.1g, 68%) m.p 81-82.5°C (Lit.,[103] 81-84°C).

IR (νcm^{-1}, Nujol): 1750 (C=O str.), 1200 and 1150 CCF_3 str.).

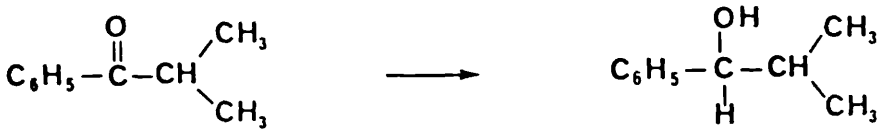
56. Preparation of 2,2,2-trifluoro-1-(9-anthryl)--ethanol.



Sodium borohydride (0.33g, 8.75 mmole) was added in portions to a stirred solution of 9-anthryl trifluoromethyl ketone (2.0g, 7.3 mmole) in methanol (50 cm^3). After stirring for 2 hours, water (50 cm^3) was cautiously added. The aqueous solution was

extracted with methylene chloride (2 x 50 cm^3). Evaporation of the dried (Na_2SO_4) combined organic extracts gave the desired alcohol which after crystallization from MeOH/water (3:1) was obtained as colourless needles (1.95g, 98%) m.p 140-141°C (Lit.,[103] 140-142°C).

57. Preparation of phenylisobutanol (2-methyl-1--phenylpropan-1-ol).



Sodium borohydride (15gg, 0.04 mole) was added in portions to a stirred solution of isobutyrophenone (5g, 0.033 mole) in ethanol (75 cm^3). After stirring for 2 hours, water (100 cm^3) was cautiously added. The aqueous solution was extracted with methylene chloride (2 x 75 cm^3). Evaporation of the dried (Na_2SO_4) combined organic extracts and distillation under reduced pressure gave the title compound as a colourless liquid $b.p_{15}$ 112-113 (Lit.[104] b.p 224°C) (4.95g, 98%).

IR ($\nu\ cm^{-1}$, neat): 3400 br. (max. O-H str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.75 and 0.95 (dd. J=6Hz, 6H, isopropyl CH_3 (2)), 1.7 - 2.0 (m, 1H, CH of isopropyl), 2.1 br. (s, 1H, O-H), 4.3 br. (d, J=5Hz,

CH), 7.3 (s, 5H, Ar-H).

Mass Spectrum (m/z, 35eV): 150 (M^+, 5.2%). 107 (43, $M-C_3H_7^+$, base peak), 77 (Ph^+).

58. Preparation of 1-phenylbutanol

The title compound was prepared using a procedure similar to the preparation of phenylisobutanol (exp. 57). Vacuum distillation of the crude reaction product furnished the alcohol in 98% yield $b.p_{15}$ 113-115°C (Lit.,[104] b.p 232°C).

IR (νcm^{-1}, neat): 3350 br. (max O-H str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.8-1.9 (m, 7H, $CH_2CH_2CH_3$), 2.4 (s, 1H, OH), 4.6 (t, 1H, CH), 7.3 (s, 5H, Ar-H).

Mass Spectrum (m/z, 35eV): 150 (M^+, 6.1%), 132 ($M-H_2O^+$), 107 ($M-CH_3CH_2CH_2^+$, base peak), 77 (Ph^+).

59. Preparation of 1-phenylpropanol

The title compound was prepared using a procedure similar to the preparation of phenylisobutanol (exp. 57). Vacuum distillation of the crude reaction

product furnished the alcohol in 98% yield b.p_{15} 105-106°C (Lit.,[104] 213-215°C).

IR (ν cm^{-1}, neat): 3350 br. (max. O-H str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 0.6-1.0 (t, 3H, CH_3), 1.6-1.9 (m, 2H, CH_2), 2.4 (s, 1H, OH), 4.5 (t, 1H, CH).

Mass Spectrum (m/z, 34eV): 136 (M^+, 10.2%), 118 ($M-H_2O^+$), 107 ($M-C_2H_5^+$), 77 (Ph^+).

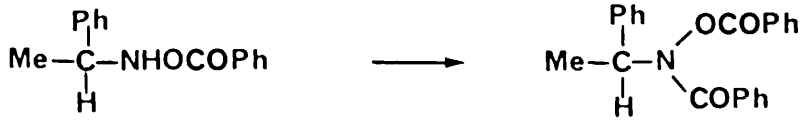
60. Preparation of (+)-O-benzoyl-N-(α-methylbenzyl)-hydroxylamine.

Using a procedure similar to the preparation of (+)-O-benzoyl-N-(fenchelyl)hydroxylamine (exp. 37) the title hydroxylamine was prepared as a colourless oil in 70% yield (based on dibenzoyl peroxide).

IR (ν cm^{-1}, neat): 3220 (N-H str.), 1720 (C=O str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.4-1.5 (d, 3H, CH_3), 4.25-4.5 (q, 1H, CH), 7.2-8.0 (m, 10H, Ar-H(2)).

61. Preparation of (+)-O-benzoyl-N-(α-methylbenzyl)--benzohydroxamic acid.

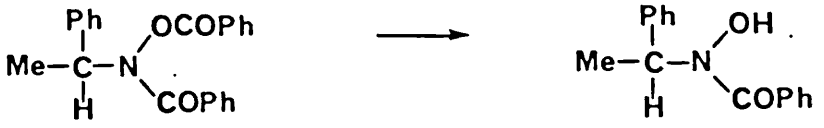


To a stirred solution of (+)-O-benzoyl-N-(α--methylbenzyl)hydroxylamine (2.0g, 8.3 mmole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.65g, 8.3 mmole) and benzoyl chloride (1.2g, 8.4 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t--butylbenzohydroxamic acid (exp. 2). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O-benzoyl-N-(α-methylbenzyl)benzo--hydroxamic acid (liquid) in 65% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1740 (OCO C=O str.), 1660 (max. NCO str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 5.6-5.9 (q, 1H, CH), 7.2-7.9 (m, 15H, Ar-H(3)).

62. Preparation of (+)-N-(α-methylbenzyl)benzo--hydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzo--hydroxamic acid (exp. 3). Recrystallization from hexane/MeOH gave the hydroxamic acid in 92% yield as colourless crystals m.p 100-101°C.

IR (ν cm^{-1}, Nujol): 3380-3180 br. (-OH str.), 1610

(C=O str.), 1600 (C=C str.).

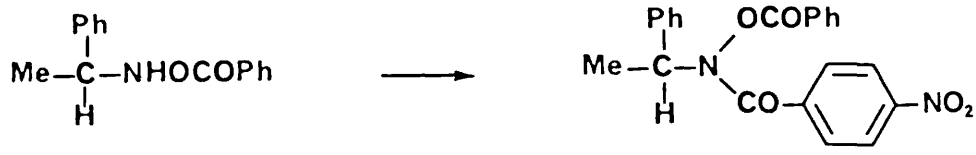
^{1}H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 5.1-5.3 (q, 1H, CH), 7.2-7.6 (m, 10H, Ar-H(2)).

Mass Spectrum (m/z, 35eV): 225 (15, M-CH_3), 105 ($PhCO^+$), 77 (Ph^+).

$[\alpha]_D^{25}$ + 125.1° (c=0.01 in $CHCl_3$).

(Found C, 74.2; H, 6.2; N, 5.9. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.2: N, 5.8).

63. Preparation of (+)-O-benzoyl-N-(α-methylbenzyl)--4-nitrobenzohydroxamic acid.



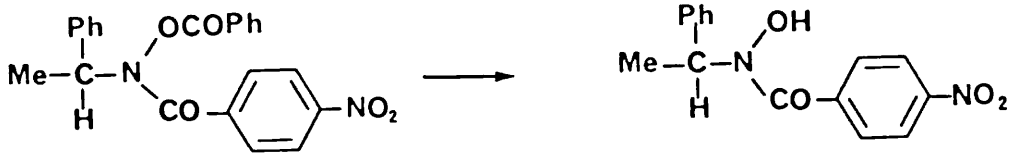
To a stirred solution of (+)-O-benzoyl-N-(α-methyl--benzyl)hydrozylamine (2.0g, 8.3 mmole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.66g, 8.35 mmole) and 4-nitrobenzoyl chloride (1.5g, 8.2 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t-butylbenzo--hydroxamic acid (exp. 2). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O-benzoyl-N-(α-methylbenzyl)-4-nitrobenzo--hydroxamic acid (liquid) in 60% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1770 (OCO C=O str.), 1660 (max. NCO str.), 1600 (C=C str.), 1540 (C-NO_2 satr.), 1350

($C-NO_2$ str.).

^1H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 5.7-6.0 (q, 1H, CH), 7.2-8.2 (m, 15H, Ar-H (3)).

64. Preparation of (+)-N-(α-methylbenzyl)-4-nitro--benzohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of N-t-butyl--benzohydroxamic acid (exp. 3). Recrystallization from hexane: ethyl acetate gave the hydroxamic acid as a colourless solid m.p 130-131°C.

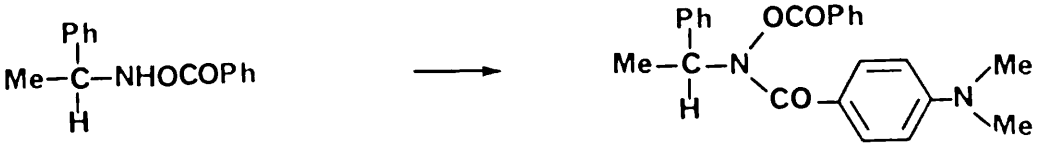
IR (ν cm^{-1}), Nujol): 3300-3100 br. (O-H str.), 1610 (C=O str.), 1600 (C=C str.).

^1H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 5.2 br. (d, 1H, CH), 7.3 (s, 5H, Ar-H), 7.6 + 8.2 (AA'BB', J = 8 Hz, 4H, XC_6H_4Y).

$[\alpha]_D^{25}$ + 118.9° (c=0.01 in $CHCl_3$).

(Found: C, 62.8; H, 4.8; N, 9.7. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%).

65. Preparation of (+)-O-benzoyl-N-(α-methylbenzyl)--4-dimethylaminobenzohydroxamic acid.

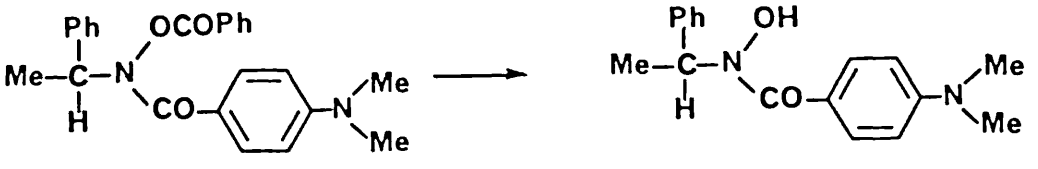


To a stirred solution of (+)-O-benzoyl-N-(α-methyl--benzyl)hydroxylamine (2.0g, 8.3 mmole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.66g, 8.35 mmole) and 4-dimethylaminobenzoyl chloride (1.5g, 8.2 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t-butylbenzo--hydroxamic acid (exp. 2). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O--benzoyl-N-(α -methylbenzyl)-4-dimethylaminobenzo--hydroxamic acid (liquid) in 72% yield which showed a single spot on t.l.c.

IR ($\nu\ cm^{-1}$, neat): 1760 (OCO C=O str.), 1650 (NCO C=O str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 2.9 (s, 6H, N-Me_2), 5.7-5.9 (q, 1H, CH), 6.5-8.0 (m, 14H, Ar-H and XC_6H_4Y).

66. Preparation of (+)-N-(α -methylbenzyl)-4--dimethylaminobenzohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3). Recrystallization from benzene gave the hydroxamic acid in 75% yield as a crystalline solid m.p. 151-152°C.

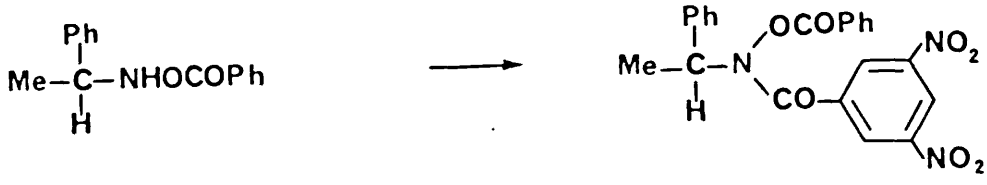
IR (ν cm^{-1}, Nujol): 3100 br. (O-H str.), 1615 (C=O str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.75-1.85 (d, 3H, CH_3), 3.0 (s, 6H, N-Me_2), 5.3-5.5 (q, 1H, CH), 6.6-7.6 (m, 9H, Ar-H and XC_6H_4Y), 8.0-8.4 br. (s, 1H, OH, D_2O removed OH).

$[\alpha]_D^{25}$ + 259.0° (c=0.01 in $CHCl_3$).

(Found: C, 71.6; H, 7.0; N, 11.4. $C_{17}H_{20}N_2O_2$ requires C, 71.8; H, 7.0; N, 11.3%).

67. Preparation of (+)-O-benzoyl-N-(α-methylbenzyl)--3,5-dinitrobenzohydroxamic acid.

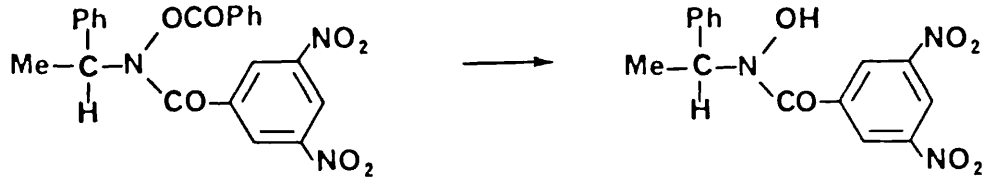


To a stirred solution of (+)-O-benzoyl-N-(α-methyl--benzyl)hydroxylamine (2.0g, 8.3 mmole) in sodium dried benzene (50 cm^3) was added dry pyridine (0.66g, 8.35 mmole) and 3,5-dinitrobenzoyl chloride (1.9g, 8.2 mmole). After refluxing for 24 hours the reaction mixture was worked up as per O-benzoyl-N-t-butylbenzo hydroxamic acid (exp. 2). Column chromatography of the crude reaction product (SiO_2, $CHCl_3$) gave (+)-O--benzoyl-N-(α-methylbenzyl)-3,5-dinitrobenzo--hydroxamic acid (liquid) in 77% yield which showed a single spot on t.l.c.

IR (ν cm^{-1}, neat): 1760 (OCO C=O str.), 1660 (NCO C=O str.), 1600 (C=C str.).

^{1}H-NMR (δ ppm, $CDCl_3$): 1.7-1.8 (d, 3H, CH_3), 5.9-6.0 (q, 1H, CH), 7.2-7.8 (m, 5H, Ar-H), 8.7 (d, 2H, o-aryl protons), 8.9 (t, 1H, p-aryl proton).

68. Preparation of (+)-N-(α-methylbenzyl)-3,5--dinitrobenzohydroxamic acid.



The title compound was prepared using a procedure similar to the preparation of N-t-butylbenzohydroxamic acid (exp. 3). Recrystallization from hexane/ethyl acetate gave the hydroxamic acid in 78% yield as a crystalline solid m.p 160-161°C.

IR (ν cm^{-1}, Nujol): 3210 br. (O-H str.), 1610 (C=O str.), 1540 (C-NO_2 str.), 1350 (C-NO_2 str.).

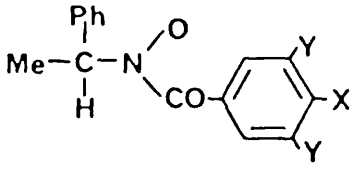
^{1}H-NMR (δ ppm, $CDCl_3$): 1.6-1.7 (d, 3H, CH_3), 5.7-5.9 (q, 1H, CH), 7.3-7.6 (m, 5H, Ar-H), 8.8 (d, 2H, o-aryl protons), 8.9 (t, 1H, p-aryl proton).

$[\alpha]_D^{25}$ + 48.23° (c=0.01 in $CHCl_3$).

(Found: C,54.9; H, 6.0; N, 11.9. $C_{16}H_{21}N_3O_6$ requires C, 54.7; H, 6.0; N, 12.0%).

The optically active (-)-N-(α-methylbenzyl)benzo--hydroxamic acids were prepared in exactly the same manner as the (+)-enantiomers. Table 28 shows the physical data for these compounds.

TABLE 28. Physical data for the (-)-N-(α-methylbenzyl)hydroxamic acids.



No.	X	Y	Mpt. (°C)	α_o^{25} (c = 0.01 in $CHCl_3$)	Found% (Required) C	H	N
(107)	H	NO_2	160-161	-53.0°	54.2 (54.4)	3.9 (3.9)	12.9 (12.7)
(108)	NO_2	H	130-131	-115.4°	62.4 (62.9)	4.9 (4.9)	9.6 (9.8)
(109)	H	H	100-101	-130.4°	74.2 (74.7)	6.2 (6.2)	5.7 (5.8)
(110)	OMe	H	151-152	-249.6°	71.5 (71.8)	6.9 (7.0)	11.4 (11.3)

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