THERMAL REARRANGEMENTS OF SOME HYDROXAMIC ACID DERIVATIVES.

A Thesis submitted in part fulfilment
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by

W. B. Ankers B.Sc. (Hons.) A.R.C.S.

The Chemical Laboratory

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With Affection and Deepest Gratitude

To My Parents

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A B S T R A C T

An historical survey of the thermolyses of hydroxamic acids and O-acylated hydroxamic acids is presented, and thermal rearrangements which proceed by [1,3]-sigmatropic and free radical shifts are reviewed, together with the phenomenon of chemically induced dynamic nuclear polarisation (CIDNP).

N-Methyl hydroxamic acids are found to undergo, on distillation, a novel thermal rearrangement to the isomeric N-methyl-O-acylhydroxylamines, the thermodynamically less stable product. The rearrangement is shown to occur, at least in part, *via* an intermolecular mechanism involving formation of N-methylhydroxylamine and N-methyl-N,O-diacylhydroxylamine.

Various O-thiocarbamoylated N-methyl hydroxamic acids are found to undergo, in solution, a thermal [1,3] rearrangement to the isomeric hydrosulphamine derivatives. This rearrangement, which is accompanied by appreciable fragmentation to the corresponding N-methyl amide, is shown to proceed largely *via* a pathway involving caged free radical pairs.

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PART I

THE INTRODUCTION

CHAPTER I

THE HISTORICAL SURVEY

The present study is chiefly concerned with the thermal rearrangement of hydroxamic acids and certain of their derivatives. Accordingly, a brief outline of the history of the hydroxamic acids and of their chemistry is given below.

THE HYDROXAMIC ACIDS.

Hydroxamic acids are N-monoacyl hydroxylamines, $R-\overset{\overset{O}{\|}}{C}-NHOH$.

They first appeared in the literature in 1869, when H. Lossen reported that hydroxylamine reacted with diethyl oxalate to form an acidic compound which he named oxalohydroxamic acid.[1] Later, W. Lossen observed[2] that hydroxylamine reacted with benzoyl chloride to form a mixture of benzohydroxamic acid, O-benzoyl benzohydroxamate, and N,O-dibenzoylbenzohydroxamate. He discovered[2] the Lossen rearrangement (in which, in this case, the phenyl group undergoes a 1,2- shift to nitrogen), apparently by accident, when he heated O-benzoylbenzohydroxamate, (I), above its melting point and obtained a lachrymatory substance (phenyl isocyanate) (equation(I.I)).

$$\underset{\text{(I)}}{C_6H_5-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-O-\overset{\overset{O}{\|}}{C}-C_6H_5} \longrightarrow C_6H_5-N=C=O + C_6H_5COOH$$

$$\downarrow$$

$$(C_6H_5CO)_2O + C_6H_5NH_2 + CO_2$$

equation (I.I)

The structure of the hydroxamic acids was debated by Lossen,[3] Werner,[4] Tiemann[5] and others. It was finally shown[5] to possess the "hydroxyamide" structure (II):

$$R-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-OH \qquad \text{(II)}$$

The preparation[6] and the chemistry[6i,7] of the hydroxamic acids have been studied extensively and an excellent review of this field of chemistry provided by Smith.[8] Worthy of mention is that the hydroxamic acids are similar in acid strength to organic carboxylic acids[9] and that they are α-nucleophiles.[10,89,102]

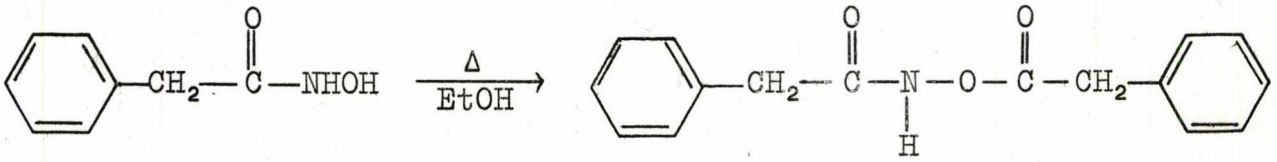
Furthermore, they are thermally unstable, and it is this aspect of the chemistry of hydroxamic acids which is of major importance in the present study. The modes of thermal decomposition of hydroxamic acids and of O-acylated hydroxamic acids are now reviewed.

A. THE THERMOLYSES OF HYDROXAMIC ACID DERIVATIVES

(i) **HYDROXAMIC ACIDS** are mostly stable to normal storage at room temperature, but decompose on strong heating:-

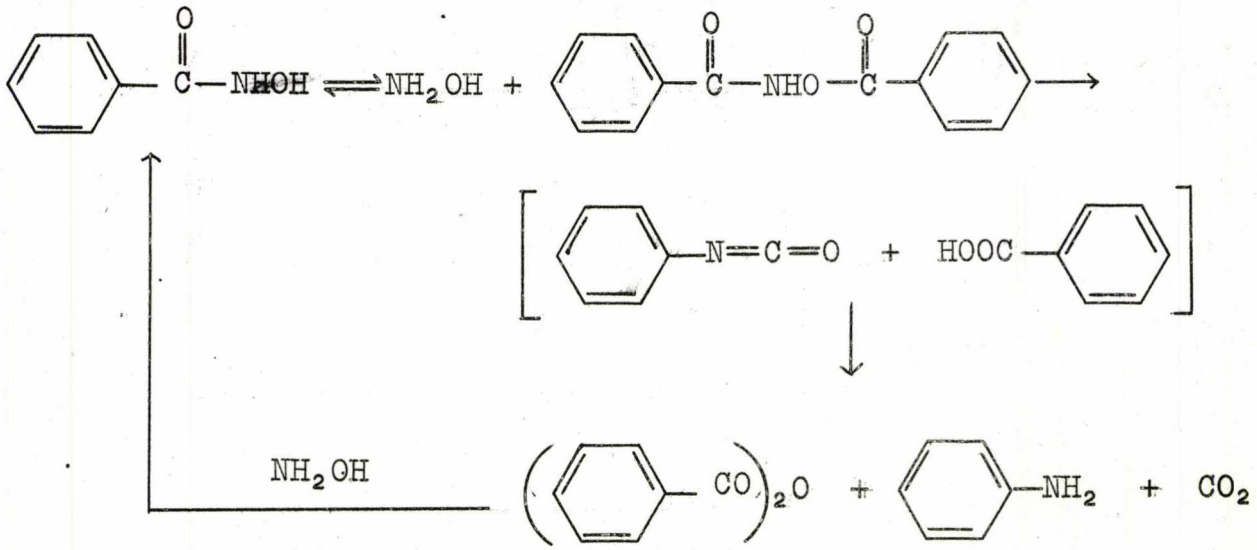
(a) Disproportionation.

Hydroxamic acids thermally disproportionate in solution to form N,O-diacylhydroxylamines[11] (equation (1.2)).



equation (1.2)

The reaction is catalysed by acid and also by potassium cyanide. On raising the temperature, the N,O-diacylhydroxylamines may undergo a Lossen rearrangement (see p.4) to form amines and carbon dioxide (equation (1.3)).

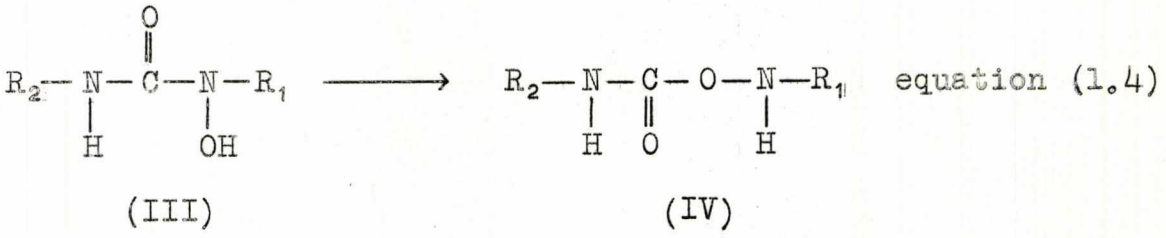


equation (1.3)

Similar behaviour is observed with hydroxamate salts, if damp.

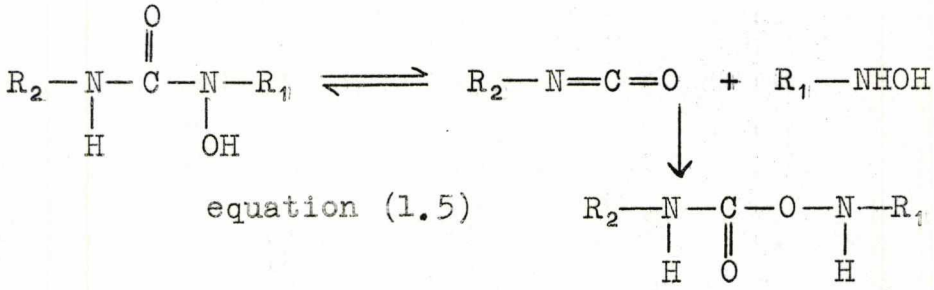
(b) Rearrangement via Fragmentation.

Aurich and co-workers[12] have shown that some N-hydroxy-ureas (III) on standing in solution at room temperature, rearrange to form O-carbamoyl-hydroxylamines (IV) (equation(1.4)).



(III) (IV) equation (1.4)

It was shown that the rearrangement (III) ⟶ (IV) is inter-molecular and that a dissociative equilibria between N-hydroxy-urea, isocyanate and hydroxylamine is involved (equation(1.5)).



equation (1.5)

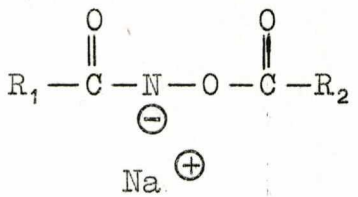
The presence of the t-butyl group in N-hydroxy-N-(t-butyl)-N'-phenyl-urea results in formation of the thermodynamically more stable and less sterically hindered N-(t-butyl)-O-phenylcarbamoyl-hydroxylamine in solution at room temperature. The dissociation of (III) is less as the bulk of R_1 decreases, so that rearrangement to (IV) requires a higher temperature or ceases altogether.

(ii) O-ACYLATED HYDROXAMIC ACIDS

(a) The Lossen Rearrangement.

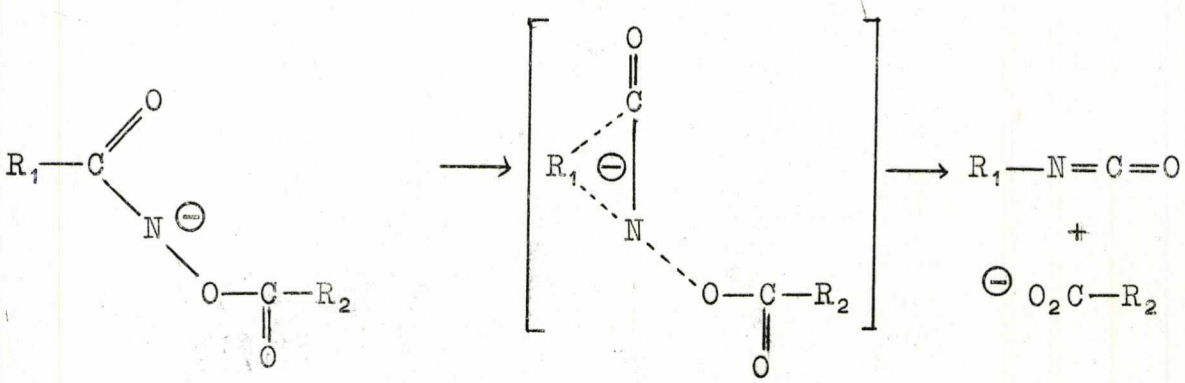
The Lossen rearrangement belongs to the group of 1,2 rearrangements to electron deficient nitrogen, represented by the Curtius rearrangement of acyl azides and the Hofmann rearrangement of N-haloamide salts, and related to the Beckmann rearrangement of oximes.[13]

The Lossen rearrangement of free hydroxamic acids takes place *via* both acid and base catalysed paths, and exceptionally *via* a thermal uncatalysed process.[14] More intensive study, however, has been devoted to N,O-diacylhydroxylamines, in which the sodium salts (V) fragment and rearrange much faster than the free acids, either spontaneously or on mild heating, and with first order kinetics.[15]



(V)

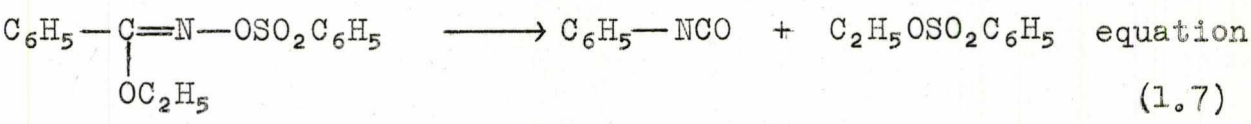
The rate of rearrangement of the salts is directly proportional to the strength of the acid from which the O-acyl group is derived.[15b] When the O-acyl group is sulfonyl or phosphoryl, rearrangement is very fast, and often occurs as fast as such O-acyl derivatives are formed.[16] Wallis showed that during the rearrangement, migration occurs with retention of optical and geometrical configuration, the migrating group never being free.[17] The mechanism of the rearrangement is accepted[14] to involve the departure of the carboxylate group as an anion, concerted with migration of the second group to nitrogen (equation(1.6)).



equation (1.6)

In the Lossen rearrangement of N,O-dibenzoylhydroxylamine at ~ 120°, about 1% of a concurrent side reaction involving radical decomposition of the N,O-dibenzoylhydroxylamine was detected.[18]

Interestingly, derivatives of the imido ester form of hydroxamic acids also rearrange. Thus ethyl O-benzenesulfonylbenzohydroximate spontaneously rearranges to phenyl isocyanate and ethyl benzenesulfonate (equation(1.7).[19]

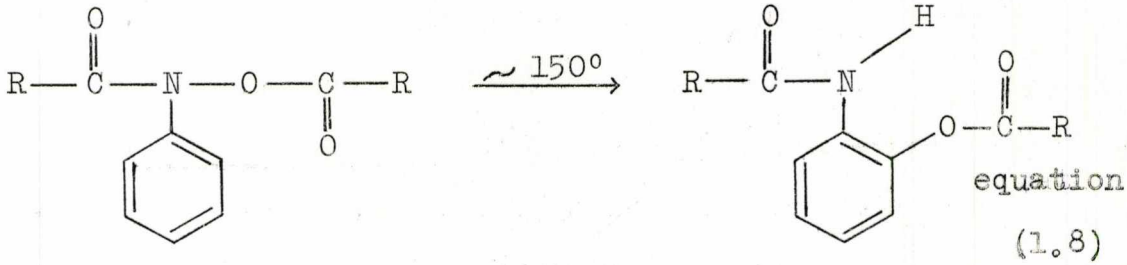


equation (1.7)

(b) Blocking of the Lossen rearrangement.

Occurrence of the Lossen rearrangement is almost invariably[20] blocked by the presence of an alkyl or aryl group on the nitrogen atom of N,O-diacylhydroxylamines and free hydroxamic acids.[21]

Thus strong heating may induce alternative thermal reactions. Horner and Steppan[21a] for example, have demonstrated that N-aryl-N, O-diacylhydroxylamines (VI) thermally rearrange at ~ 150° to ortho-acyloxyanilides (VII) (equation(1.8)).



equation (1.8)

(VI) (VII)

The mode of scission of the N-O bond is not clear in Horner's work, although free radicals have been shown to be involved by the characterisation of secondary products.

Walling and Naglieri,[18] in an attempt to demonstrate the extent of N-O bond homolysis in the thermal reactions of diacyl-

hydroxylamines, confirmed radical participation in the Horner-Steppan rearrangement, by showing that N-phenyl-N,O-dibenzoyl-hydroxylamine initiated some polymerization of methyl methacrylate at 80°. The rate constants for the radical decomposition of (I) at 80° and 100° were measured to be only about 1% of the rates of the competing Lossen rearrangement and only about 0.1% of the corresponding rates of thermal decomposition of benzoyl peroxide.

Anticipating, in the present work, the contribution of similar radical processes in the thermolytic 1,3 rearrangements of N-substituted hydroxamic acid derivatives, a comprehensive review of [1,3]-sigmatropic and free radical shifts will now be presented, followed by an outline of Chemically Induced Dynamic Nuclear Polarisation (CIDNP).

B. [1,3]-SIGMATROPIC AND FREE RADICAL THERMAL REARRANGEMENTS

The first part of this review is concerned exclusively with [1,3]-sigmatropic rearrangements where alternative homolytic stepwise processes are not believed to be involved, whilst the second part describes [1,3]-free radical rearrangements in which a competing [1,3]-sigmatropic rearrangement may or may not be present.

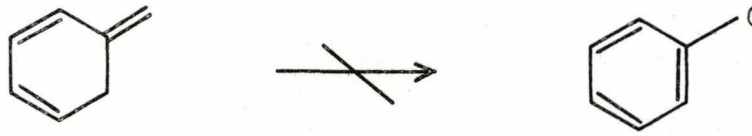
(i) [1,3]-SIGMATROPIC REARRANGEMENTS.

A [1,3]-sigmatropic rearrangement is one which involves the migration of a σ-bond, flanked by one or more π-electron systems, to a new position where terminus is two atoms removed from the original bonded locus, in an uncatalysed intramolecular process.

Hydrogen Migrations.

The selection rules of Woodward and Hoffmann[22] predict that antarafacial [1,3]-sigmatropic hydrogen shifts in neutral polyenes are thermally allowed. Antarafacial [1,3]-shifts, however, impose a geometrical barrier on the extent of orbital overlap; thus

concerted uncatalysed [1,3]-hydrogen shifts in dienes have not been established, the more facile [1,5]-shifts occurring.[23] The triene (VIII) is relatively stable[24] because the uncatalysed rearrangement to toluene requires a [1,3]-shift of a hydrogen atom antarafacially (equation(1.9))



equation (1.9)

(VIII)

[1-^{14}C]-propylene itself, does not rearrange to [3-^{14}C]-propylene.[25]

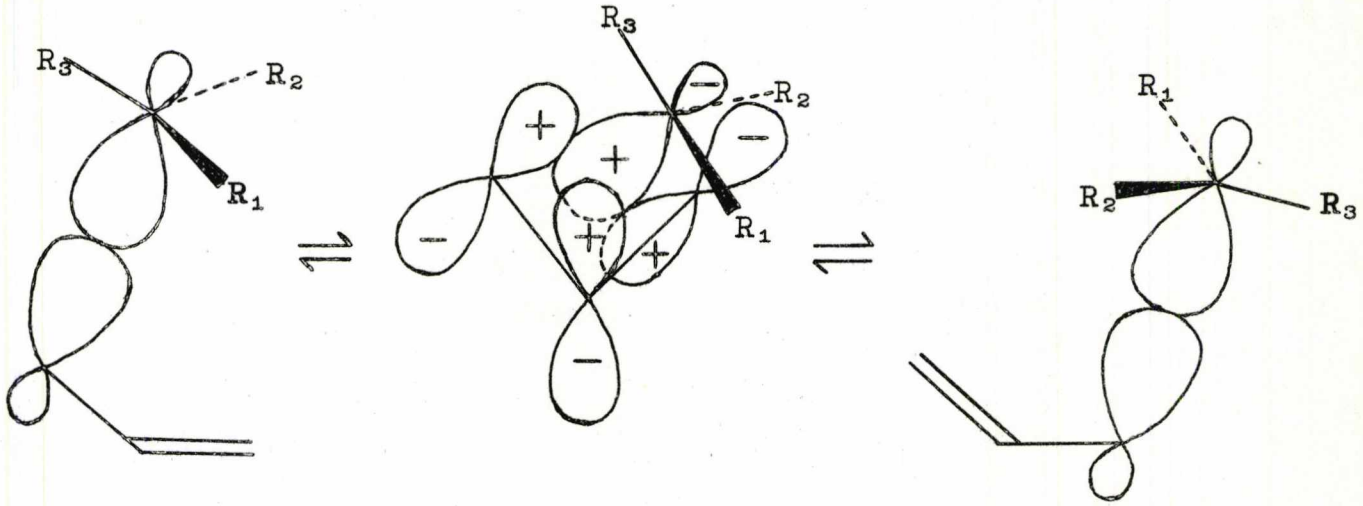
Migrations of atoms other than hydrogen.

All groups which, unlike hydrogen, can make use of a p- type orbital in the transition state have an alternative route of migration in undergoing a [1,3]-sigmatropic shift. The selection rules[22] predict that the thermally allowed migrations for [1,3]-sigmatropic shifts of such groups occur,

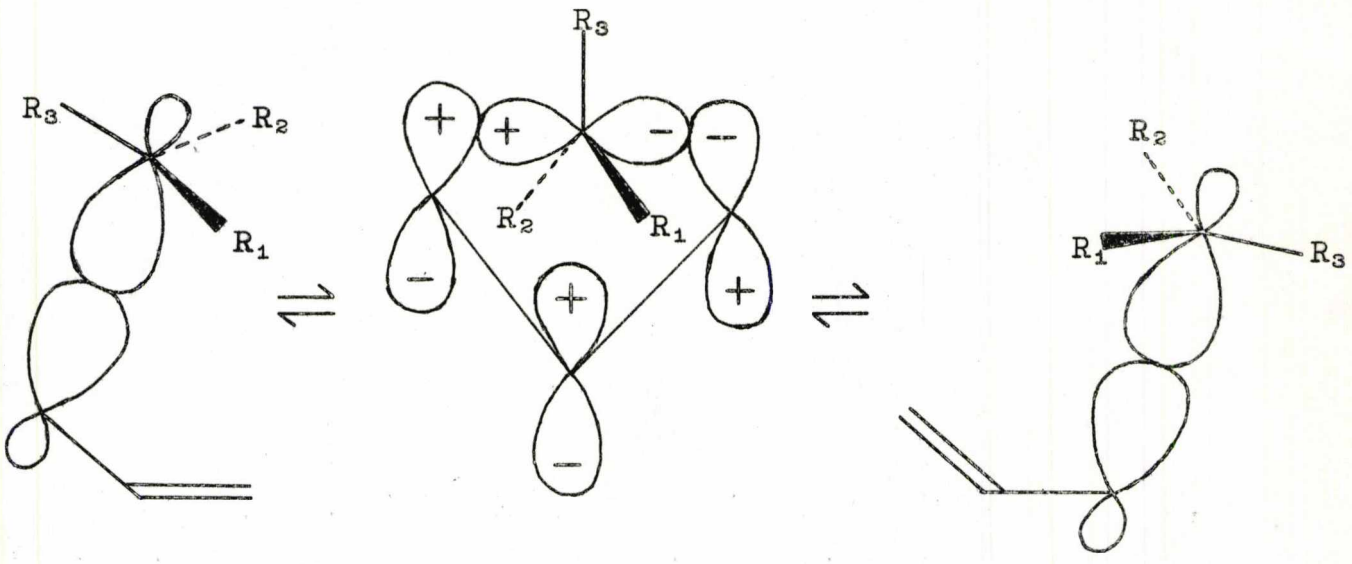
(a) antarafacially, with retention of configuration or

(b) suprafacially, with inversion of configuration.

Such modes of migration are demonstrated in Figure (1.1) for the hypothetical case of the [1,3]-migration of an alkyl group.



Antarafacial [1,3]-Alkyl migration - Retention of Configuration.



Suprafacial [1,3]-Alkyl migration - Inversion of Configuration.

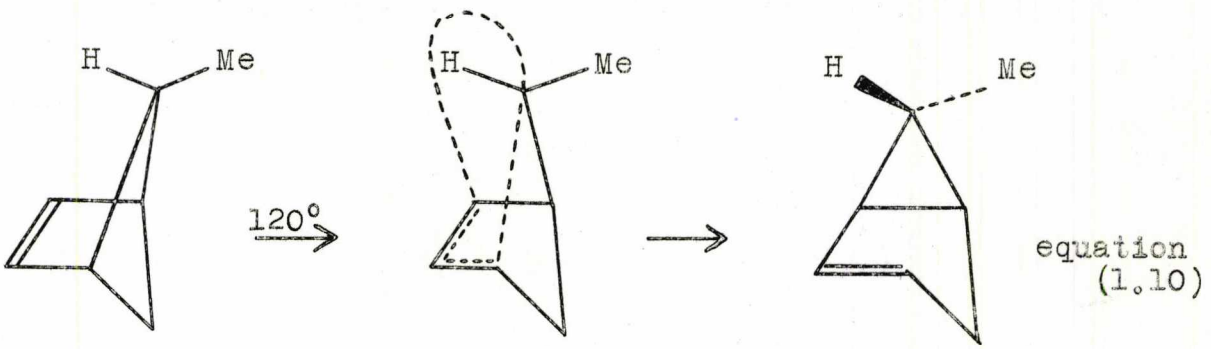
Figure(1.1)

The transition state for the antarafacial [1,3]-alkyl migration involves simultaneous bonding to the same lobe of the orbital of the alkyl group by the p- lobes on opposite sides of

the π system, whilst the transition state for the suprafacial [1,3]-alkyl migration utilises the back face of the alkyl bonding orbital to bond with the p- lobe on the same side of the π system.

Only a few thermal uncatalysed [1,3]-sigmatropic shifts have been observed and in view of the greater geometrical accessibility of the transition state, suprafacial migration with inversion of configuration is preferred to antarafacial migration with retention of configuration.

(a) The search for a thermal [1,3]-suprafacial shift of an alkyl group with inversion of configuration led to Berson's work on the rearrangement of bicyclo [3.2.0] hept-2-enes (discussed on page 14) and to Roth and Friedrich's work[26] on the thermal rearrangement of the bicyclohexene[27](IX) (equation(1.10)).



(IX)

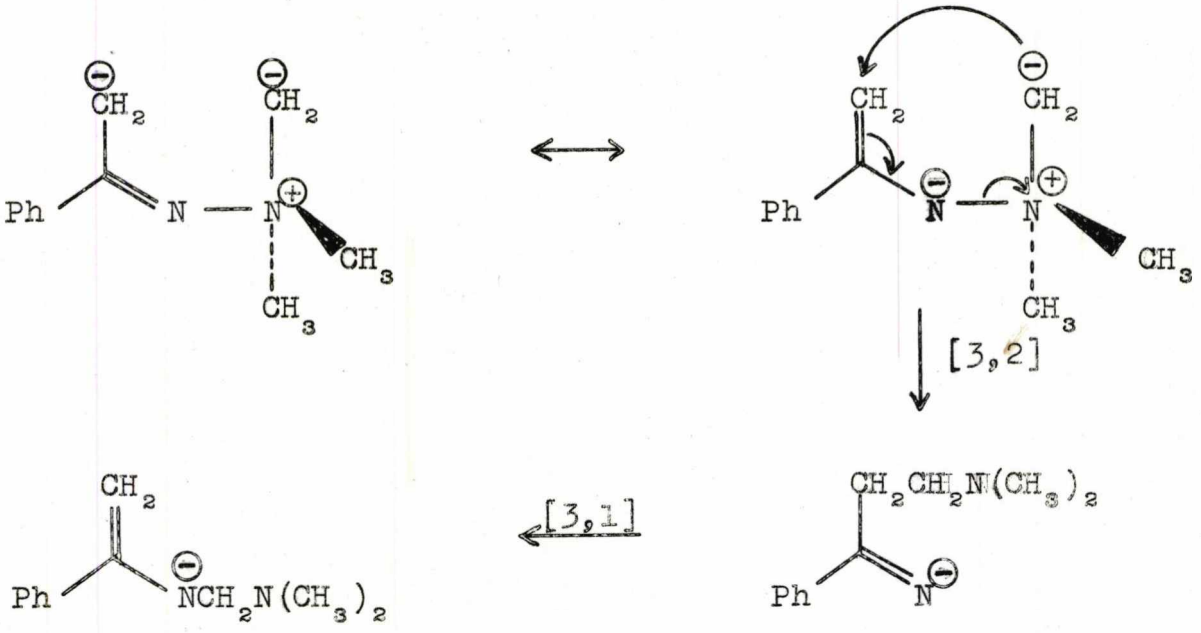
equation (1.10)

The methyl group is almost exclusively exo in the product, showing inversion of configuration in the migrating centre. These results were further confirmed by the observation of the analogous suprafacial [1,3]-sigmatropic rearrangement of exo-bicyclo [2.1.1] hex-2-en-5-yl acetate.[28]

(b) A [1,3]-allylic rearrangement by a sigmatropic process appears to have been established for triallylboron[29] at low temperatures although it has been suggested[30] that it may not

qualify as a concerted process.

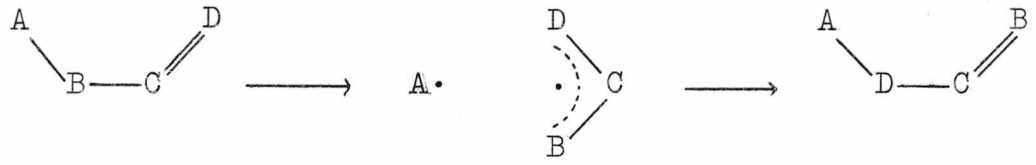
(c) The reaction of acetophenone N,N,N-trimethylhydrazonium iodide and n-butyl-lithium at room temperature to form n-hexyl phenyl ketone has been considered to involve either a [3,2]-sigmatropic rearrangement followed by a thermal [3,1]-sigmatropic rearrangement (Scheme(1.1)) or alternatively a heterolytic fragmentation-recombination mechanism.[31]



Scheme (1.1)

(ii) [1,3]-FREE RADICAL REARRANGEMENTS.

A [1,3]-free radical shift (Scheme(1.2))is a migration of an atom or group unchanged through a π system, the migration occurring by bond homolysis to form the migrating radical (A•) and a radical which can delocalise its electron through a π system and then recombine with the migrating radical at a position two atoms removed from the original position.

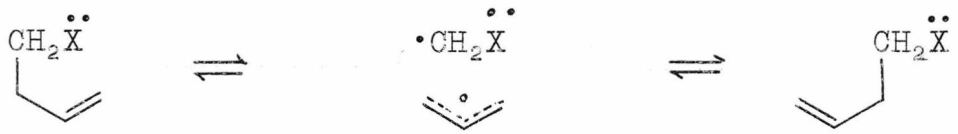


Scheme (1.2)

1,3 Free radical shifts have been discussed principally as a potentially competing pathway for [1,3]-sigmatropic processes.

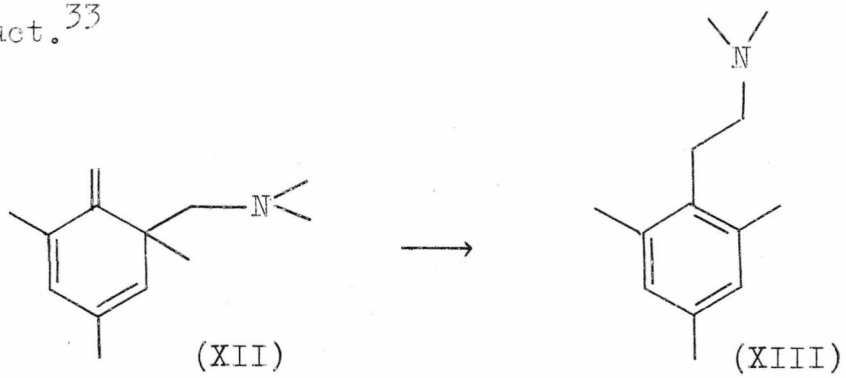
The known [1,3]-free radical rearrangements (in which a competing [1,3]-sigmatropic rearrangement may or may not be present) are reviewed below:

(a) The concerted [1,3]-shift from a carbon-carbon bond in an allyl system is not of any great generality.[26] The alternative stepwise pathway involving radical intermediates has been shown to operate in certain [1,3]-allylic rearrangements,[33,67i] e.g. (X) to (XI) where the radical intermediates are stabilised[32] by the lone pair on the substituent hetero-atom X and by allylic delocalisation,



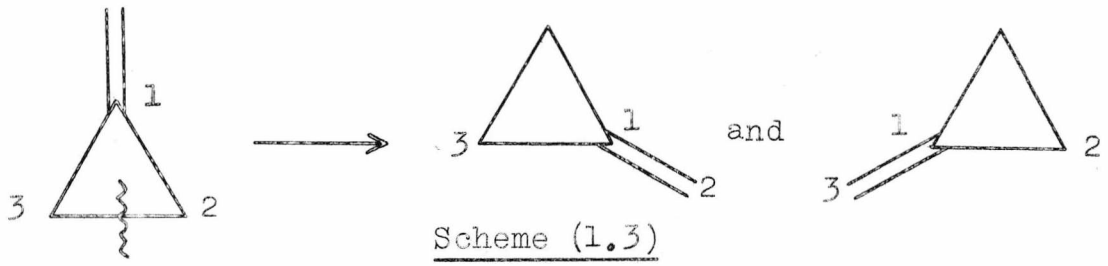
(X) (XI)

Such radical participation has been demonstrated to occur in the thermal conversion of the exo-methylenecyclohexadienamine (XII) to the aromatic isomer (XIII) by the observation of CIDNP phenomena in the product.[33]



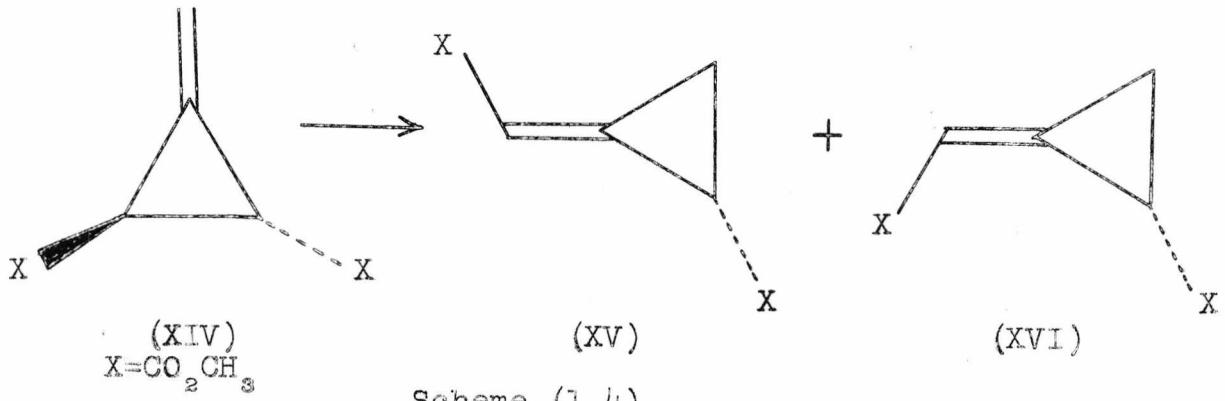
(XII) (XIII)

(b) Methylenecyclopropanes undergo thermal self-interconversions,[34] outlined in (Scheme(1.3)).



Scheme (1.3)

The optically active ester of Feist's acid (XIV) undergoes this rearrangement to form optically active products, (XV) and (XVI),[35] inversion of configuration occurring at the remaining chiral centre in (XV) and (XVI)[36] (Scheme(1.4)).



(XIV)
$X=CO_2CH_3$

(XV)

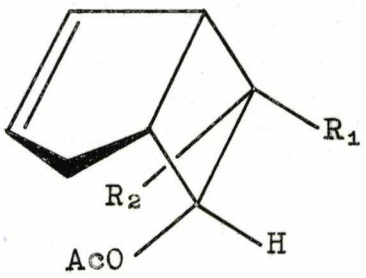
(XVI)

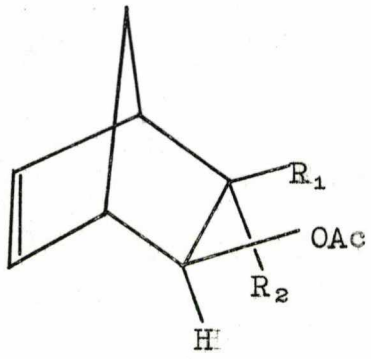
Scheme (1.4)

Woodward and Hoffmann[37] interpreted these results in terms of a [1,3]-suprafacial sigmatropic rearrangement, the [1,3]-antarafacial shift with retention at the migrating atom being blocked by the constraints imposed by the σ skeleton.

The sole intervention of such a concerted process has now been excluded, for both the rearrangement of Feist's ester and of dimethylmethylenecyclopropane, results consistent with a biradical pathway (involving [1,3]-radical shifts) having been advanced.[34] The concerted pathway may, however, be a parallel one. Theoretical calculations consistent with the biradical pathway have been made.[38]

(c) Berson observed[39,40] that inversion of configuration of the migrating group occurs in thermal suprafacial [1,3]-sigmatropic rearrangements of bicyclo [3.2.0] hept-2-enes when the exo substituent is deuterium (XVII) or methyl (XVIII). The products are (XIX) and (XX) respectively.

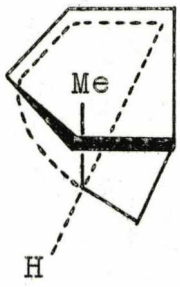




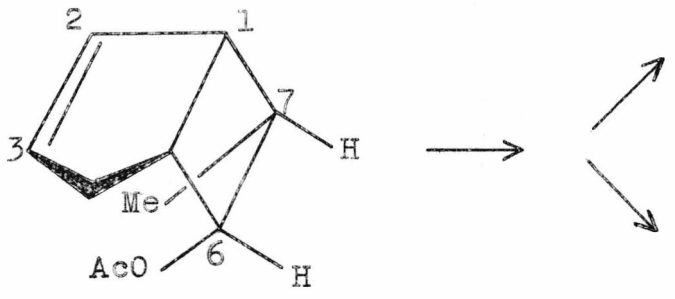
(XVII) $R_1 = D, R_2 = H$ (XIX) $R_1 = D, R_2 = H$

(XVIII) $R_1 = Me, R_2 = H$ (XX) $R_1 = Me, R_2 = H$

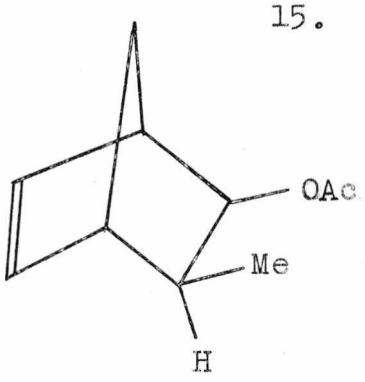
The endo-methyl isomer ((XXI); $R_1 = H, R_2 = Me$) however, isomerises with retention of configuration at the migrating carbon, ostensibly because the steric interaction between the methyl group and the ring, in the transition state (XXII) for a concerted reaction, would be too severe to allow bonding to be maintained. Consequently the endo-methyl isomer reacts by a diradical pathway. The intermediate, formed by C-7 - C-1 bond homolysis in (XXI), recyclises with <u>retention</u> of configuration at the migration terminus to give cis-exo product (XXIII) and recyclises after rotation about C-6 - C-7 to give the epimerisation product (XVIII).



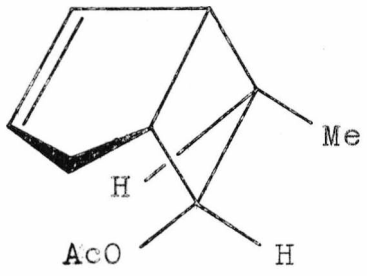
(XXII)



endo (XXI)

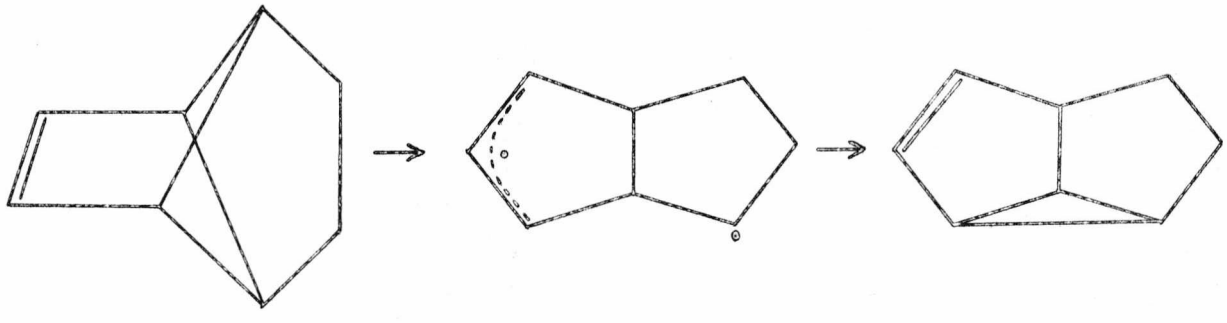


(XXIII)



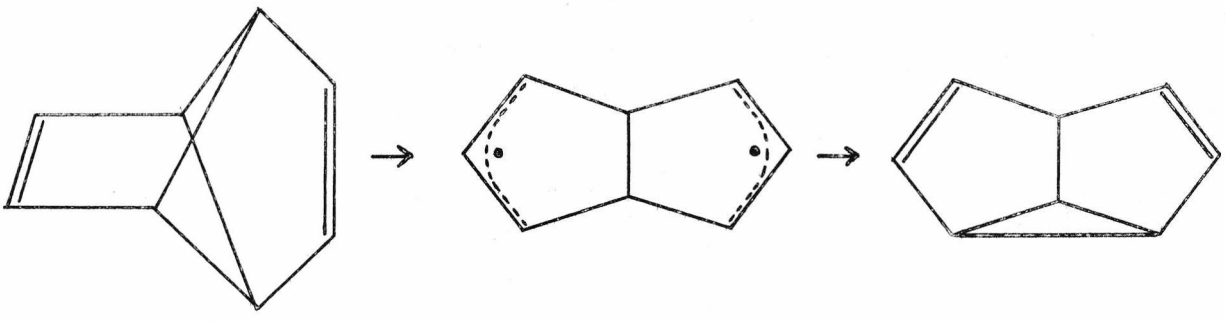
(XVIII)

(d) The thermal isomerisation of tricyclo [3.3.0.$0^{2,6}$]oct-3-ene (XXIV) to tricyclo [3.3.0.$0^{2,8}$]octa-3-ene (XXVI) cannot occur by a [1,3]-sigmatropic shift because of steric inhibition.[41] The bridging CH_2-CH_2 unit prevents rotation of the migrating C atom and so thermolytic rearrangement occurs by a [1,3]-radical shift involving a stabilised biradical (XXV).



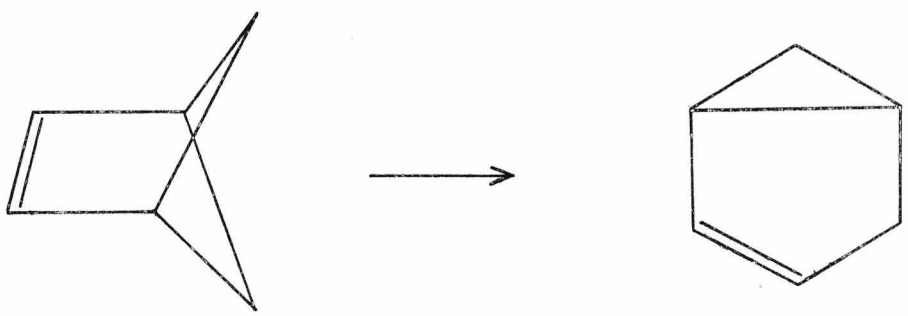
(XXIV) (XXV) (XXVI)

From these results the rate for the isomerisation of tricyclo [3.3.0.$0^{2,6}$]octa-3,7-diene (XXVII) to semibulvalene[42] (XXVIII), a [1,3]-radical shift, was estimated;[41]



(XXVII) (XXVIII)

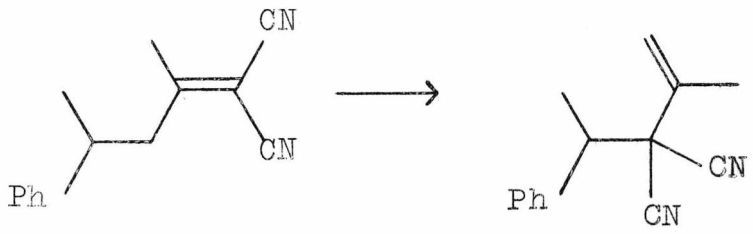
The rearrangement of the parent bicyclo [2.1.1]hex-2-ene (IX) to bicyclo [3.1.0]hex-2-ene (XXIX) is, however, concerted[41,26] (see p.10).



(IX)) (XXIX)

The determination of the concerted nature of this rearrangement (IX)⟶(XXIX) suggests that a similar concerted [1,3]-sigmatropic shift probably occurs in the related thermal isomerisation of bicyclo [2.2.1]heptadiene to cycloheptatriene[55] and of benzonorbornadiene to 1,2-benzocycloheptatriene[56] which have been considered as involving diradical mechanisms.

(e) Cookson and Kemp[43] have demonstrated that photoisomerisation of (+)-1,1-dicyano-2-methyl-4-phenylpent-1-ene (XXX) to 3,3-dicyano-2-methyl-4-phenylpent-1-ene (XXXI) occurs with ca. 85% retention of configuration at the migrating carbon atom and 15% inversion.



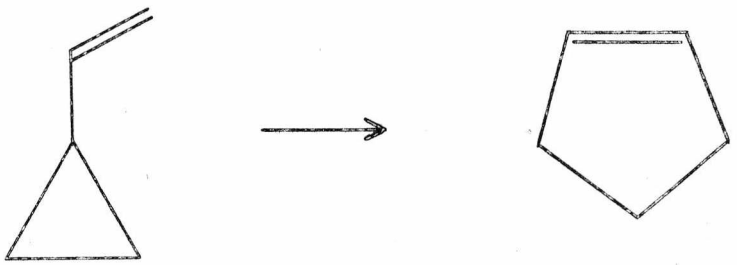
(XXX) (XXXI)

The predominant retention of configuration, in this photochemical process, is predicted by the Woodward-Hoffmann rules for sigmatropic reactions. The rearrangement can, however, be reversed thermally, and this also shows > 90% retention of configuration.

This apparent violation of the laws of orbital symmetry is attributed to the very unsymmetrical nature of the (dicyano) allyl group across which the α-phenylethyl group migrates. Despite Berson's classic work on endo-substituted bicyclo [3.2.0]

hept-2-enes (at ~ 300°, discussed on p. 14), Cookson and Kemp apparently thought a [1,3]- free radical shift mechanism involving recombination of unracemised singlet radical pairs to be unlikely in solution at 250°.

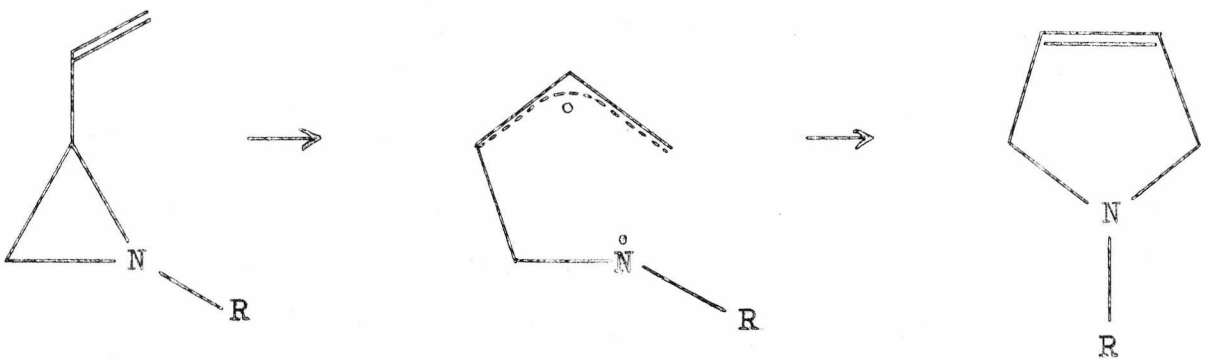
(f) Although concerted processes have been considered[44] for the rearrangement of vinylcyclopropane to cyclopentene (equation(1.11)), Woodward and Hoffmann, in view of the high activation energy of ca. 50 kcal. mole, considered[45] that the reaction quite possibly occurred via a two step, non-concerted path involving a diradical intermediate. Results consistent with such a [1,3]- radical shift mechanism have been observed.[46,47]



equation (1.11)

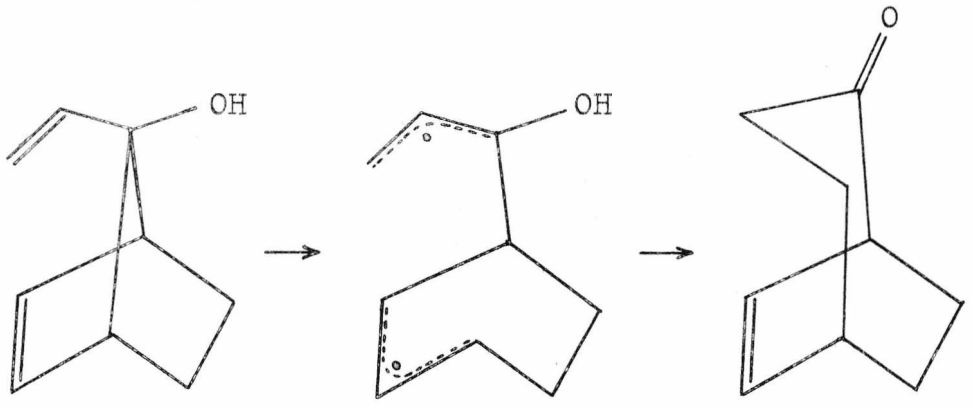
The pyrolysis of isopropenylcyclobutane to form 1-methylcyclohexene has been suggested[44] to proceed via a similar [1,3]-radical shift.

The analogous thermal rearrangement of the vinylaziridine (XXXII) to the Δ^3-pyrroline (XXXIV) was considered[48] to proceed via the diradical (XXXIII).



(XXXII) (XXXIII) (XXXIV)

The vinyl carbocyclic rearrangement has been extended to syn-7-vinyl-anti-7-hydroxynorbornene (XXXV) which thermolyses at 250° primarily to bicyclo [3,2,2] nonen-6-one-2 (XXXVI) by a [1,3]-radical shift[49] (equation(1.12)).



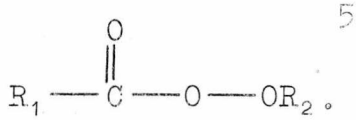
equation (1.12)

(XXXV) (XXXVI)

(g) There is some confusion regarding the oxygen scrambling of diacyl peroxides by [1,3]- and [3,3]-free radical shifts.

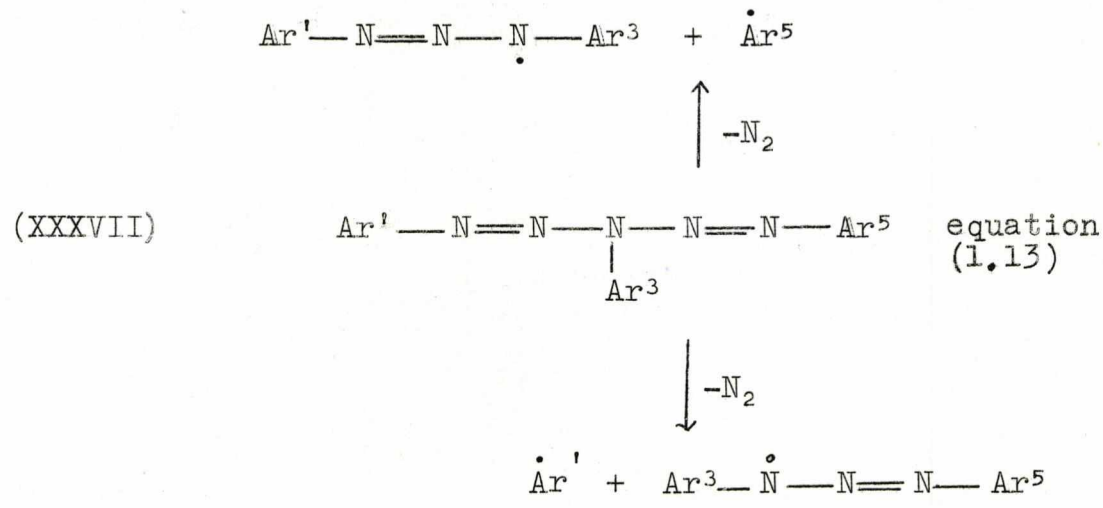
The early views that ester formation in the thermal decomposition of diacyl peroxides occurred by both heterolytic and homolytic paths simultaneously was endorsed in the main by a recent study.[50] However, Goldstein and Judson[51] maintain that oxygen scrambling of peroxidic substances can occur by [3,3]- and [1,3]- sigmatropic shifts, so that such scrambling is not a measure of the extent of radical pair recombination.

The [1,3]- sigmatropic shift was shown to play some role in the oxygen scrambling of peroxidic compounds by consideration of the oxygen scrambling in peresters,[51]



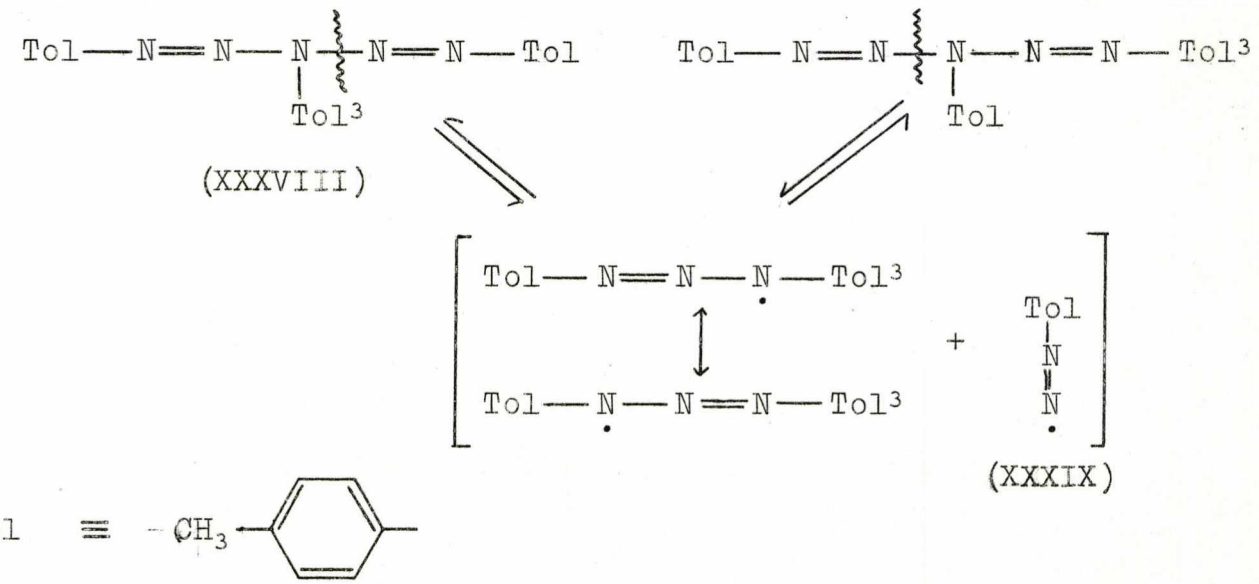
Walling and co-workers have conceived a different explanation[52] for the decomposition of diacyl peroxides, in which polar or radical products arise via the same transition state which passes to a transient "intimate radical-ion pair".

(h) 1,3,5-Triarylpentazadienes(XXXVII) spontaneously decompose at room temperature according to equation (1.13),



(XXXVII) equation (1.13)

A very rapid radical [1,3]- migration of arylazo groups has been found[53] also to occur. Thus,with (XXXVIII) an analysis of the observed CIDNP patterns shows that arylazo radicals (XXXIX) exist as reactive intermediates and can lead to radical pair recombination, with or without isomerisation, intramolecularly by way of a solvent cage.

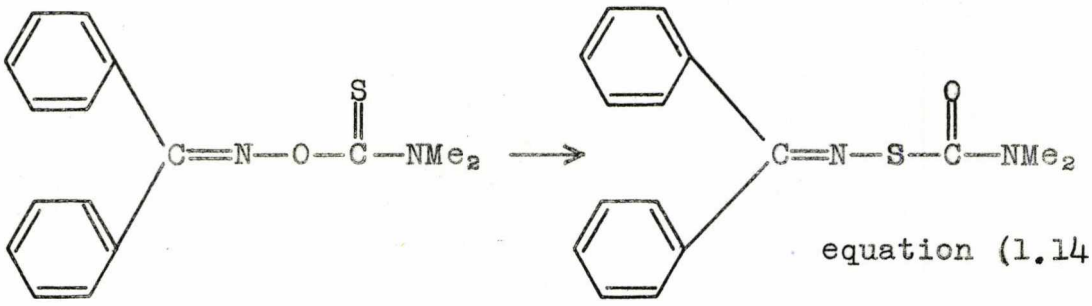


(XXXVIII) (XXXIX)

Tol ≡

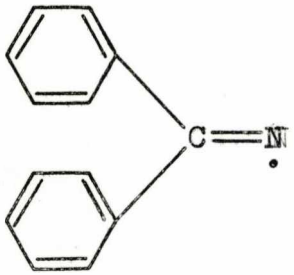
(i) Hudson, Lawson and Lucken have recently suggested[54] the mechanism of the thiono-thiolo rearrangement of oxime thiono-carbamates (equation(1.14))to be a [1,3]- radical shift reaction

occurring within a solvent cage. The rearrangement occurs in high yield on heating for a short while in carbon tetrachloride or benzene.



equation (1.14)

During rearrangement the imino radical (XXXX) was detected by ESR experiments and the radical trap DPPH was decolourised.



(XXXX)

Notably, however, the possibility remains in this case, that there is no radical pathway to products, the transient free-radical species detected being derived from oxime thionocarbamate, without necessarily leading to product, this being formed by an alternative route.

(j) The quantitative rearrangement of N-aryl-isoxazoline-3-ones to N-aryl-oxazoline-2-ones at ~150° has been proposed to involve a [1,3]-radical shift (see p. 93 and 110 for further details).

CONCLUSIONS

This review demonstrates that thermal uncatalysed [1,3]-shifts will occur only rarely by a concerted sigmatropic rearrangement. Stepwise processes increasingly compete as the transition state for a concerted sigmatropic process becomes more difficult to attain, total involvement of stepwise processes apparently occurring when the concerted rearrangement is "thermally forbidden". It is interesting that retention of configuration seems increasingly to indicate a transition state of "loosely bound free radicals".[57]

Although [1,3]- shifts by both sigmatropic and free radical processes have been demonstrated to take place, both types of reaction are rare in themselves. Aside from the observation of changes in migrating group geometry,[43,170] (and the conclusions from this are by no means certain,[57] and may even be mutually incompatible[43,170]), no reliable technique exists for estimating the relative contributions of the concerted and stepwise pathways in [1,3]- shifts.

One important tool, however, which has been recently applied to free radical shifts, is CIDNP. This has the unique advantage of displaying, in the products of reaction, the presence of a free radical precursor.

C. CHEMICALLY INDUCED DYNAMIC NUCLEAR POLARISATION

Chemically induced dynamic nuclear polarisation (CIDNP) describes the observation of enhanced absorption, or of emission spectra, when the products of a reaction involving radical intermediates are examined during or immediately after the course of the reaction, by high resolution nuclear magnetic resonance spectroscopy.

The phenomenon has provided considerable information[83] on radical reactions and on radical properties, since its discovery in 1967:[58]

(1) The observation of CIDNP effects is evidence for radical intermediates since the effects are considered a result of magnetic interactions in transient radical pairs which are involved in radical generation and consumption processes.

(2) Products of (a) geminate pair recombinations,
(b) encounters of independently formed radicals,
and (c) radical transfer reactions
can all be distinguished since the nature of the CIDNP effects is dependent upon the mode of product formation.

(3) The CIDNP phenomena is influenced by the mode of pair formation. The spin multiplicities of pair precursors can be determined by CIDNP since products from geminate radical pairs (and from the transfer of radicals escaping the pairs) exhibit different CIDNP patterns from reactions of singlet or triplet state precursors.

(4) Reactions involving radical intermediates where the products are chemically identical with the reactants may exhibit CIDNP effects, so demonstrating the occurrence of degenerate reaction and supplying information about the radical intermediates.

(5) Various magnetic properties of free radicals can be derived from CIDNP patterns, viz.: hyperfine coupling constants (magnitudes

and signs), g- factors and nuclear relaxation times.

Scope

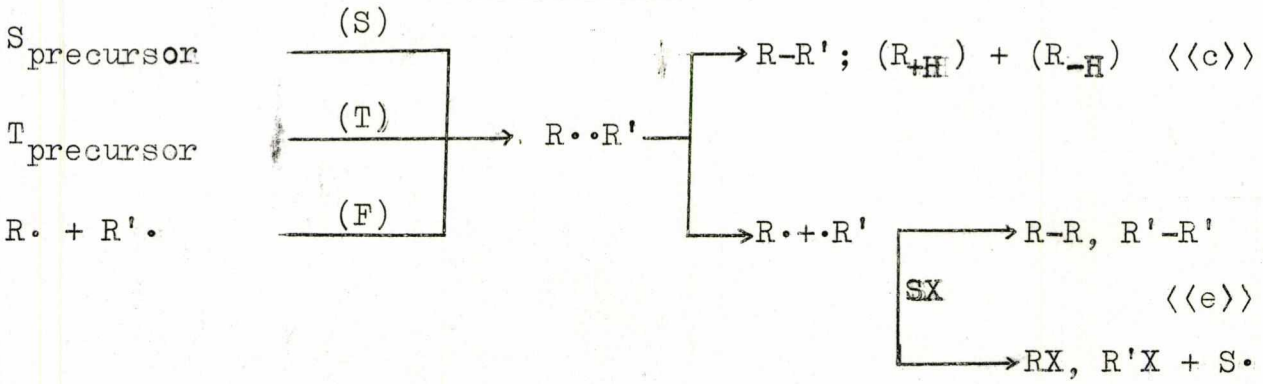
CIDNP effects have been reported for the following reaction types, all of which involve radical intermediates:

1. Thermal decompositions of acyl peroxides,[59] peresters[60], azo compounds[61] and N-nitrosohydroxylamine.[62]
2. Photolysis of acyl peroxides.[63]
3. Reactions of organometallic compounds with alkyl[64, 65] halides.
4. Reductions of diazonium salts.[66]
5. Molecular rearrangements involving [1,2]-[1,3][67][68]- and [1,4]-[69] shifts.
6. Insertion reactions of triplet[70] and singlet[71] carbenes.
7. Photoreductions of aromatic ketones and aldehydes.[72]
8. Photocleavage of aliphatic ketones[73].
9. Azo-coupling reactions.[74]
10. The formation of Grignard reagents.[75]
11. Biradical reactions.[76]
12. A few miscellaneous reactions.[77]

Most of the CIDNP effects have been observed with proton polarizations but recently the CIDNP phenomena has been extended to ^{13}C[59n,o], ^{15}N-[59o], ^{19}F-[59b,64k] and ^{31}P-[77e] resonances.

All the reactions that exhibit CIDNP phenomena can be expressed in terms of Scheme (1.5):

Scheme (1.5)



⟨⟨c⟩⟩ represents "cage" products i.e. for singlet and triplet state precursors the products formed by pair collapse of the geminate radicals

⟨⟨e⟩⟩ represents "escape" products i.e. the products of radicals escaping the pairs.

Intermediate radical pairs R··R' are formed by three possible pathways:

(a) Unimolecular decompositions or bimolecular reactions of precursor molecules $S_{precursor}$ from electronic singlet (S) states.

(b) Unimolecular decompositions or bimolecular reactions of precursor molecules $T_{precursor}$ from electronic triplet (T) states.

(c) Random encounters of freely diffusing radicals (F).

These radical pairs can collapse to form combination or disproportionation products ⟨⟨c⟩⟩ or separate into free radicals which may enter other pairs and form other radical-radical reaction products or may be scavenged by suitable agents (SX) ⟨⟨e⟩⟩.

Simultaneous CIDNP effects for the products of both types ⟨⟨c⟩⟩ and ⟨⟨e⟩⟩, have generally been observed.

The following two relationships have been established[59f,61c] for CIDNP phenomena:

(1) If a nucleus in the"cage" (⟨⟨c⟩⟩) product exhibits polarisation for a specific transition, then the corresponding transition of the same nucleus in the "escape" product (⟨⟨e⟩⟩) will exhibit the opposite polarisation.

(2) The polarisations of the products are dependent on the pathways of pair formation. T- and F- precursors lead to polarisations of the same sign whilst S- and T- (or F-) precursors lead to polarisations of opposite sign.

Kaptein[78] has proposed two rules by which qualitative predictions of the radical pair mechanism of CIDNP can be made, provided the reactions take place in a high magnetic field. Consider a pair of radicals α and β, with g-[79] factors g_α and g_β so that $\Delta g = g_\alpha - g_\beta$. Radical α contains a nucleus (or group of equivalent nuclei) i, (hyperfine coupling[79] constant A_i) whilst radical β contains a nucleus (or group of equivalent nuclei) j, (hyperfine coupling constants A_j).

The CIDNP spectrum of product nucleus i, which may be coupled to nucleus j in the product with nuclear spin coupling constant J_{ij}, can be described by the signs of two quantities: Γ_{ne} for net effects (net effects are CIDNP patterns which show enhanced absorptions (A) or emissions (E) for whole multiplets or single lines) and Γ_{me} for multiplet effects (multiplet effect polarisations in CIDNP patterns show either emission followed by enhanced absorption with increasing magnetic field (EA), or the reverse (AE)): for simplicity, we shall only consider net effects (Γ_{ne}) in the present review.

Thus

$$\Gamma_{ne} = \mu\epsilon\Delta g \mathbf{A}_i \qquad \text{equation (1.15)}$$

Positive Γ_{ne} corresponds to enhanced absorption, negative Γ_{ne} to emission.

The quantities μ and ϵ are reaction parameters and are defined below.

μ is positive when the radical pair is formed from a triplet (T) precursor or by encounter of free radicals (F), and negative when the pair is formed from a singlet (S) precursor.

ϵ is positive for nucleus i residing in a "cage" combination or disproportionation product, and negative for products of radicals escaped from the "cage".

With few exceptions,[63b,80] the published CIDNP patterns agree[81] with the predictions of Kaptein's Rules; it is important to remember, however, that caution should be exercised in the use of CIDNP in the determination of reaction mechanisms,[82] since although CIDNP effects are evidence for radical intermediates, alternative concurrent pathways may exist.[33,67]

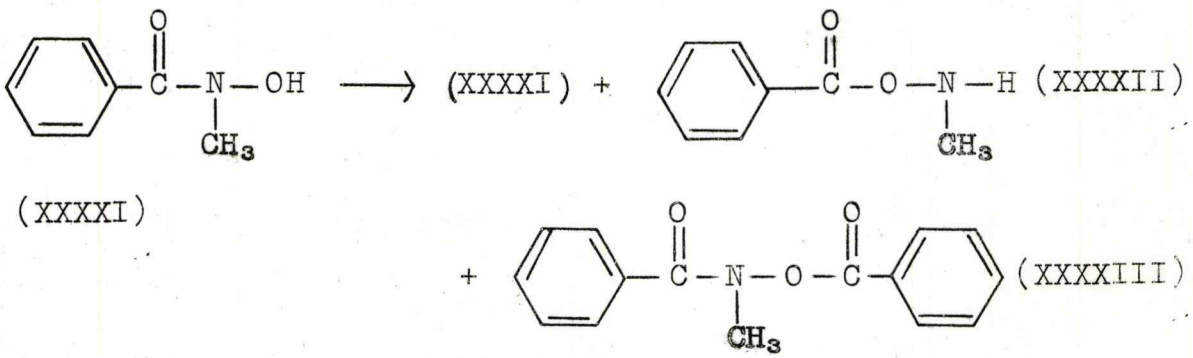
PART II

THE DISCUSSION

CHAPTER II

THE THERMAL REARRANGEMENT OF N-METHYL HYDROXAMIC ACIDS

(i) N-methyl benzhydroxamic acid (XXXXI) is thermally unstable and decomposes on distillation under reduced pressure. The distillate (b.p. 125-145° (oil bath temperature)/0.3 mm. pressure) is a mixture of unchanged acid and N-methyl-O-benzoylhydroxylamine (XXXXII). The residue contains N-methyl-N,O-dibenzoylhydroxylamine (XXXXIII), and variable amounts of (XXXXI) and (XXXXII), depending on the speed of distillation.



(XXXXI)

N-methyl-O-benzoylhydroxylamine (XXXXII) is unstable as a neat oil, samples in sealed ampoules slowly yielding over several days at room temperature N-methyl benzhydroxamic acid (XXXXI), but is quite stable in dilute solution. This behaviour is typical of O-acyl hydroxylamines.[84,85,86,87,104]

Thus, in the present work (XXXXII), prepared by an independent route (by reacting N-methylhydroxylamine with p-nitrophenyl benzoate in alcoholic solution[85]), also rearranges (in sealed ampoules) at room temperature over several days primarily to N-methyl benzhydroxamic acid. (XXXXI) with trace formation of N-methyl-N,O-dibenzoylhydroxylamine (XXXXIII).

The unexpected rearrangement of (XXXXI) → (XXXXII) on distillation of (XXXXI), therefore, is of interest, since uncatalysed non-degenerate molecular rearrangements are rarely reversible.

The technical difficulties of studying a reaction which takes place in a distillation pot are obvious; nevertheless the following observations have been made:-

(a) Rapid distillation under reduced pressure enables the N-methyl-O-benzoylhydroxylamine (XXXXII) to be distilled unchanged (95 - 99° (oil bath temperature)/ 0.8 mm. pressure).

(b) Pure N-methyl benzhydroxamic acid(XXXXI) sealed in ampoules indicates trace formation of N-methyl-N,O-dibenzoylhydroxylamine (XXXXIII) and N-methyl-O-benzoylhydroxylamine (XXXXII) after a period of several days at room temperature.‡

(c) N-methyl-N,O-dibenzoylhydroxylamine (XXXXIII) is thermally stable at the distillation temperatures used in the rearrangement of N-methyl benzhydroxamic acid.

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‡ <5% conversion occurs in five days.

(d) Distillation of N-methyl benzhydroxamic acid under reduced pressure (110 - 120° (oil bath temperature)/ 0.7 mm. pressure) and immediate re-distillation of the distillate (at 120° (oil bath temperature)/ 0.7 mm. pressure) showed the proportion of O-benzoyl/N-benzoyl isomer to be greater in the second distillation than in the first by a factor of 1.5.

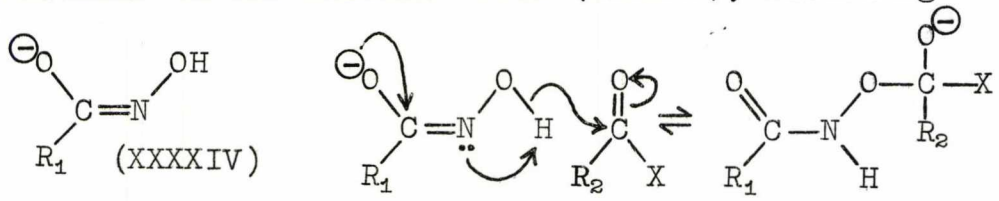
These observations suggest that N-methyl-O-benzoyl-hydroxylamine is thermodynamically unstable relative to N-methyl benzhydroxamic acid and that the two isomers are in equilibrium with one another, the equilibrium appearing to be in favour of the N-methyl benzhydroxamic acid. (XXXXII) (b.p., 95 - 99° (oil bath temperature)/ 0.8 mm.) is however more volatile than (XXXXI) (b.p., 115 - 137° (oil bath temperature)/ 0.7 - 1.1 mm.), resulting in preferential distillation of (XXXXII) with subsequent stabilisation of (XXXXII), so shifting any fast equilibria in the distillation pot.

The presence of (XXXXIII) in the residue may or may not be mechanistically significant.

To avoid unnecessary confusion, four possible mechanisms for the rearrangement of (XXXXI) → (XXXXII) will now be considered in the light of existing work on closely related systems, prior to a fuller presentation of experimental data.

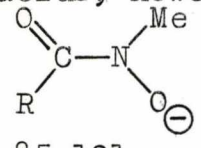
The lack of notable reactivity of N-methyl hydroxamic acids as nucleophiles in the neutral form, leads to consideration of reaction of the N-methyl benzhydroxamic acid, under distillation conditions, in the form of the zwitterion or of the hydroxamic hydroxamate conjugate acid/base pair (XXXXV).

Hydroxamic acids react as α-nucleophiles in acylation reactions in the oximino- form (XXXXIV), according to Scheme (2.1)[89]



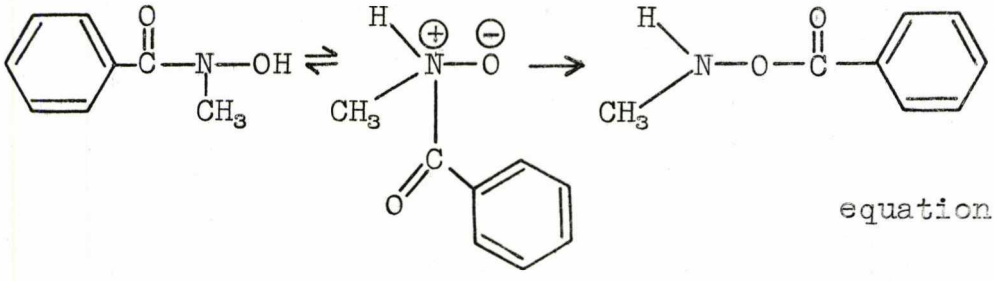
(XXXXIV)

Scheme (2.1)

The N-substituted hdroxamic acids, however, react in acylation studies as the anion,[89,90]  and generally act as α-nucleophiles.[89,102]

In view of the work of Jencks,[85,101] Aubert and Hudson[102] (see p.35), and Berndt and Fuller,[97] it seems possible that, in the present study, under distillation conditions, a small equilibrium concentration of the zwitterionic form of the N-methyl benzhydroxamic acid or of the hydroxamic hydroxamate conjugate acid/base pair (XXXXV)‡ is likely to be present, and may be involved in the rearrangement of (XXXXI)⟶(XXXXII). Such involvement of the zwitterion or of the hydroxamic hydroxamate conjugate acid/base pair (XXXXV) is now discussed.

(ii) INTRAMOLECULAR MECHANISMS: Rearrangement of the zwitterionic form of the N-methyl benzhydroxamic acid. (equation (2.1))



equation (2.1)

Such a zwitterion could undergo rearrangement to form N-methyl-O-benzoylhydroxylamine by two conceivable routes.

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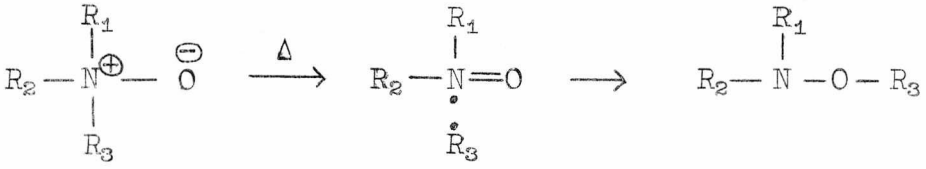
‡ See p. 34.

(a) A Meisenheimer-type rearrangement[91]

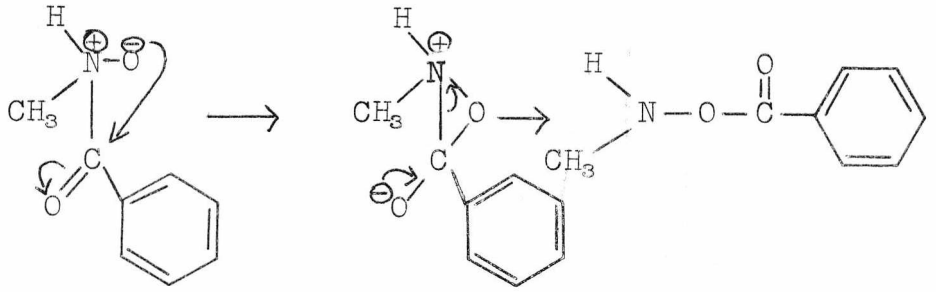
(cf. (XXXXVI) to (XXXXVII), involving a cleavage-recombination radical mechanism occurring within a solvent cage.



(XXXXVI) (XXXXVII)

(b) Rearrangement by an SNi reaction

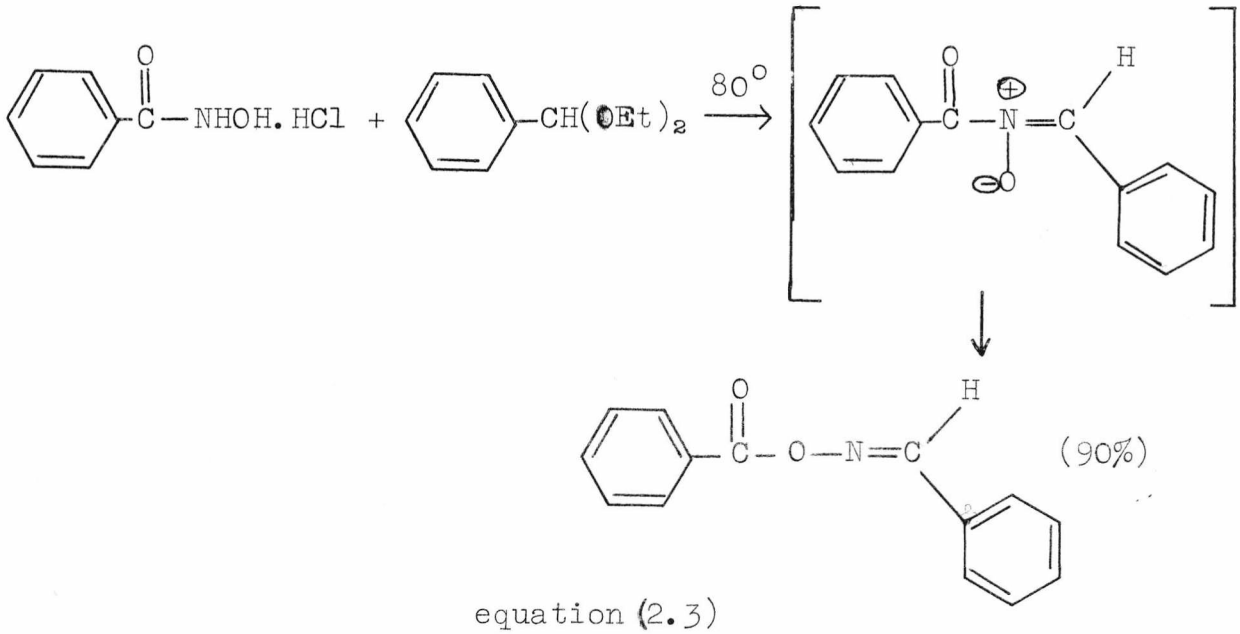
Alternatively, in the present case, internal nucleophilic attack (SNi) can conceivably also take place in the zwitterion. (equation (2.2))



equation (2.2)

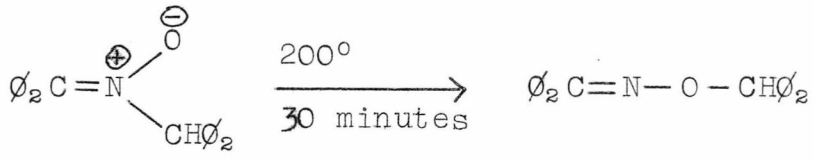
N-acyl amine oxides have proved difficult to prepare[92,93] and are of rare occurrence in the literature. Acetylphenylamine N-oxides have been obtained as intermediates in oxidation reactions but could not be isolated. There appears to be no indication that N-acyl amine oxides undergo the Meisenheimer rearrangement.[91]

A close analogue does exist, however, in the chemistry of nitrones. In the reaction of hydroxamic acids with acetals[95], N-acyl nitrones are presumed to be produced initially, but rearrange under the reaction conditions to the O-acyl oximes (equation (2.3)).



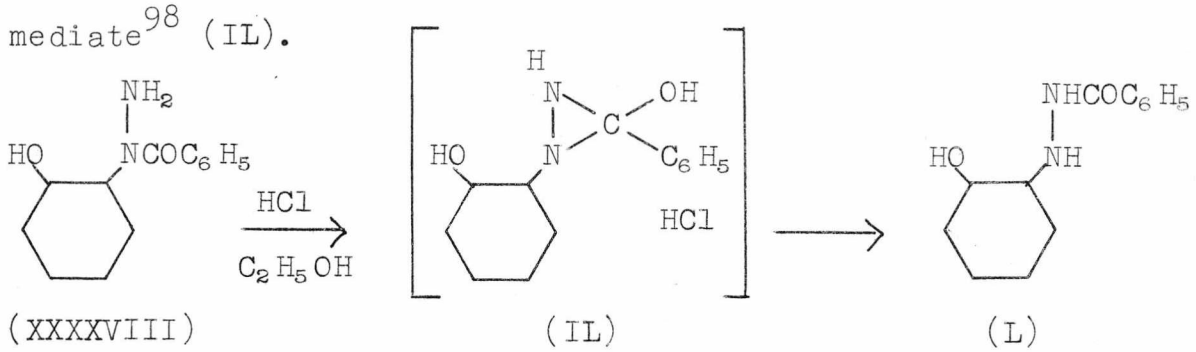
equation (2.3)

Nitrones, with a benzhydryl or triphenylmethyl group on nitrogen, also rearrange intramolecularly on heating to form the O-substituted isomers[96] (equation(2.4)) and this is a free radical process[67k], and is therefore strictly analogous to the Meisenheimer rearrangement.



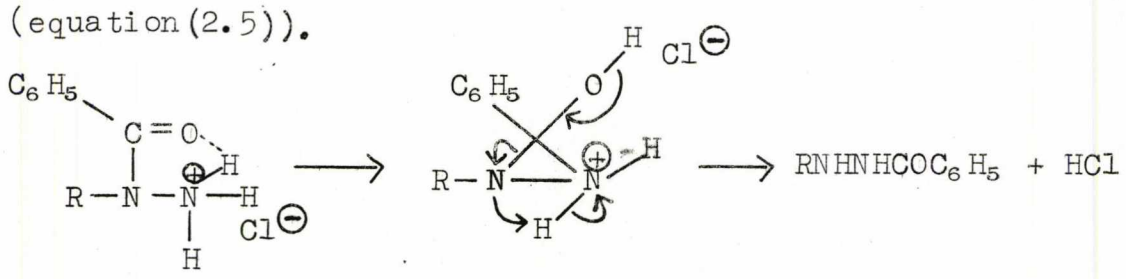
equation (2.4)

Support for the SNi pathway (eq. (2.2)), on the other hand, is found in the analogous interconversion of N-benzoyl-N-(2-hydroxycyclohexyl) hydrazine (XXXXVIII) which rearranges under acid catalysis into N-benzoyl-N'-(2-hydroxycyclohexyl) hydrazine (L), believed to occur via a diaziridine intermediate[98] (IL).



(XXXXVIII) (IL) (L)

Acyl migration was also observed on heating N-benzoyl-N-methyl-hydrazine hydrochloride (LI) or N-benzoyl-N-phenyl-hydrazine hydrochloride (LII) in a neat molten state at~200° and an intramolecular mechanism was considered likely[99] (equation(2.5)).



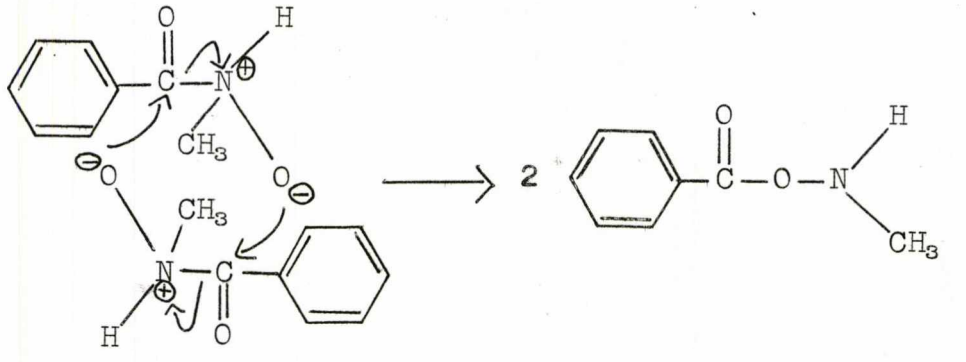
$$\left(\begin{array}{l} R = CH_3\ ;(LI) \\ R = C_6H_5;(LII) \end{array}\right) \qquad \text{equation(2.5)}$$

The free base of (LII) is thermally stable to 260°[99,100].

(iii) INTERMOLECULAR MECHANISMS

(a) Bimolecular concerted rearrangement.

Nucleophilic attack of one molecule of N-methyl benzhydroxamic acid upon another could give rise exclusively to two molecules of the O-benzoyl isomer. Such a reaction could be envisaged if an equilibrium concentration of (XXXXI) existed in the zwitterionic form (equation(2.6)).

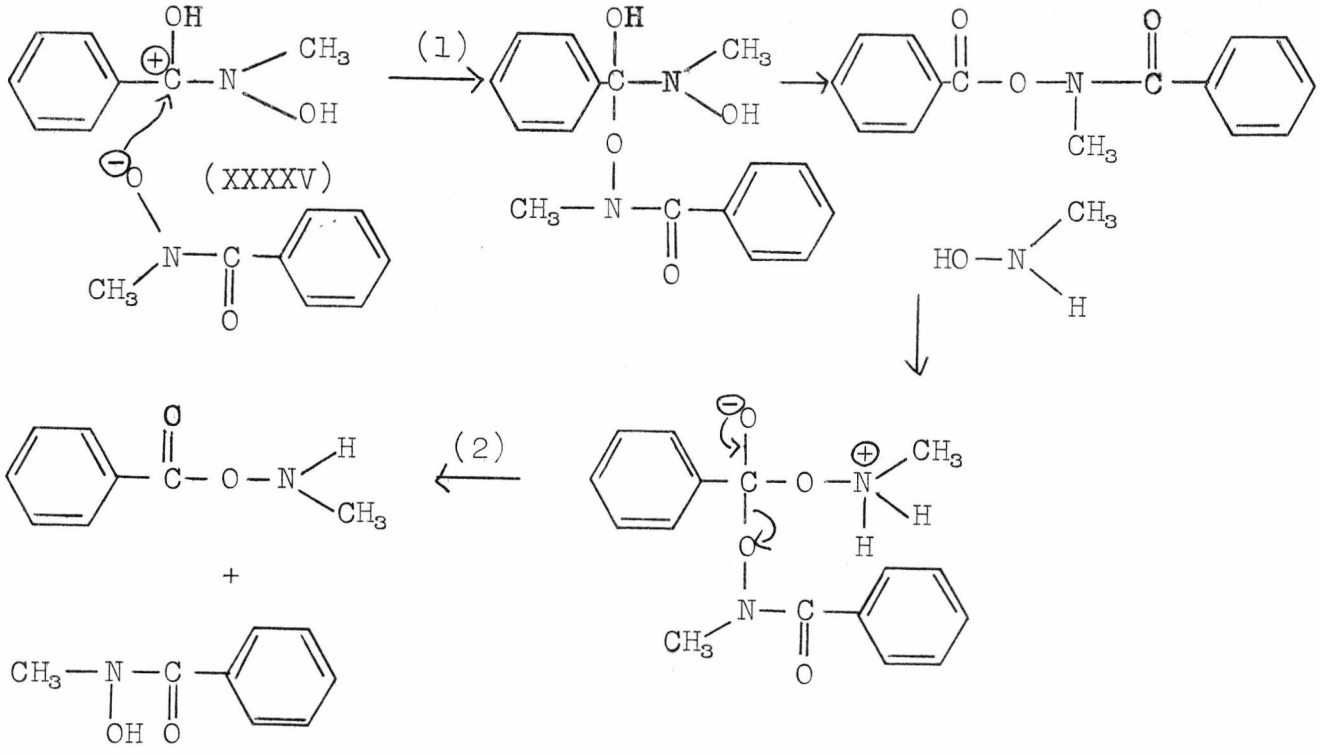


equation(2.6)

(b) Bimolecular non-concerted rearrangement.

Self-acylation of N-methyl benzhydroxamic acid by nucleophilic attack of one molecule upon another to form

(XXXXIII) and N-methylhydroxylamine is known to occur[11]. Subsequent reaction of these two products with one another could lead to the formation of both O-benzoyl and N-benzoyl N-methylhydroxylamines (Scheme(2.2)).

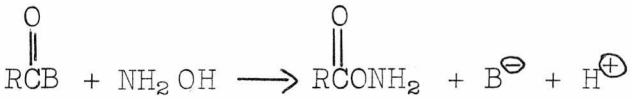


Scheme(2.2)

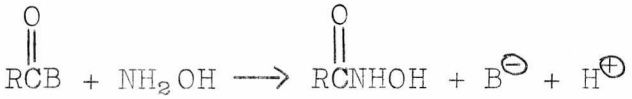
Each step of Scheme (2.2) can be deduced from known reactions. Thus, the self-acylation of hydroxamic acids is acid catalysed,[11] (step 1 of Scheme (2.2)).

The presence of the methyl group on nitrogen will prevent the N-methyl-N,O-dibenzoylhydroxylamine from undergoing decomposition by the Lossen rearrangement (see p. 6 of Chapter I). Consequent reaction with liberated N-methylhydroxylamine may then occur (step 2 of Scheme(2.2)), Jencks[85] having shown that hydroxylamine reacts with a number of acylating agents at neutral pH to form the unstable O-acylhydroxylamine and the

hydroxamic acid (equations(2.7)and(2.8)),the proportion of O-acylation varying considerably with the nature of the acylating agent.

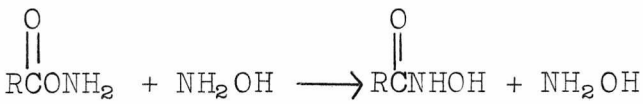


equation(2.7)



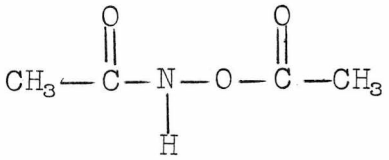
equation(2.8)

The O-acylhydroxylamine in turn will react more slowly with hydroxylamine to form hydroxamic acid[85] (equation(2.9)),



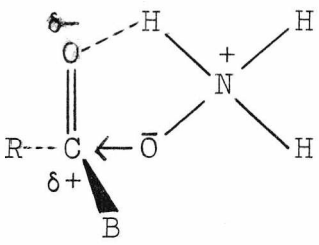
equation(2.9)

Hydroylamine underwent 92% O-acylation with diaceto-hydroxamic acid (LIII)[85].

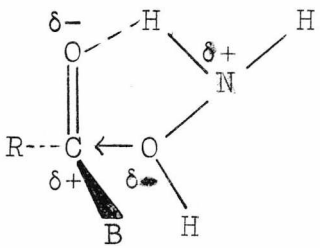


(LIII)

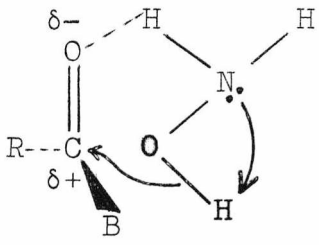
Jencks originally formulated three transition states (LIV), (LV) and (LVI) for the O-acylation of hydroxylamine, favouring (LIV) initially.



(LIV)



(LV)



(LVI)

Later, Jencks[101] and Aubort and Hudson[102] suggested that the probable mechanism which accounts for attack by the oxygen atom and the enhanced reactivity of hydroxylamine involves intramolecular base catalysis (formulation (LVI)), although formulations (LIV) and (LV) may contribute.

In order to determine, therefore, whether the O-acyl isomer, in the present study, was formed by an intra- or intermolecular process from the N-methyl hydroxamic acid, cross-over experiments were conducted.

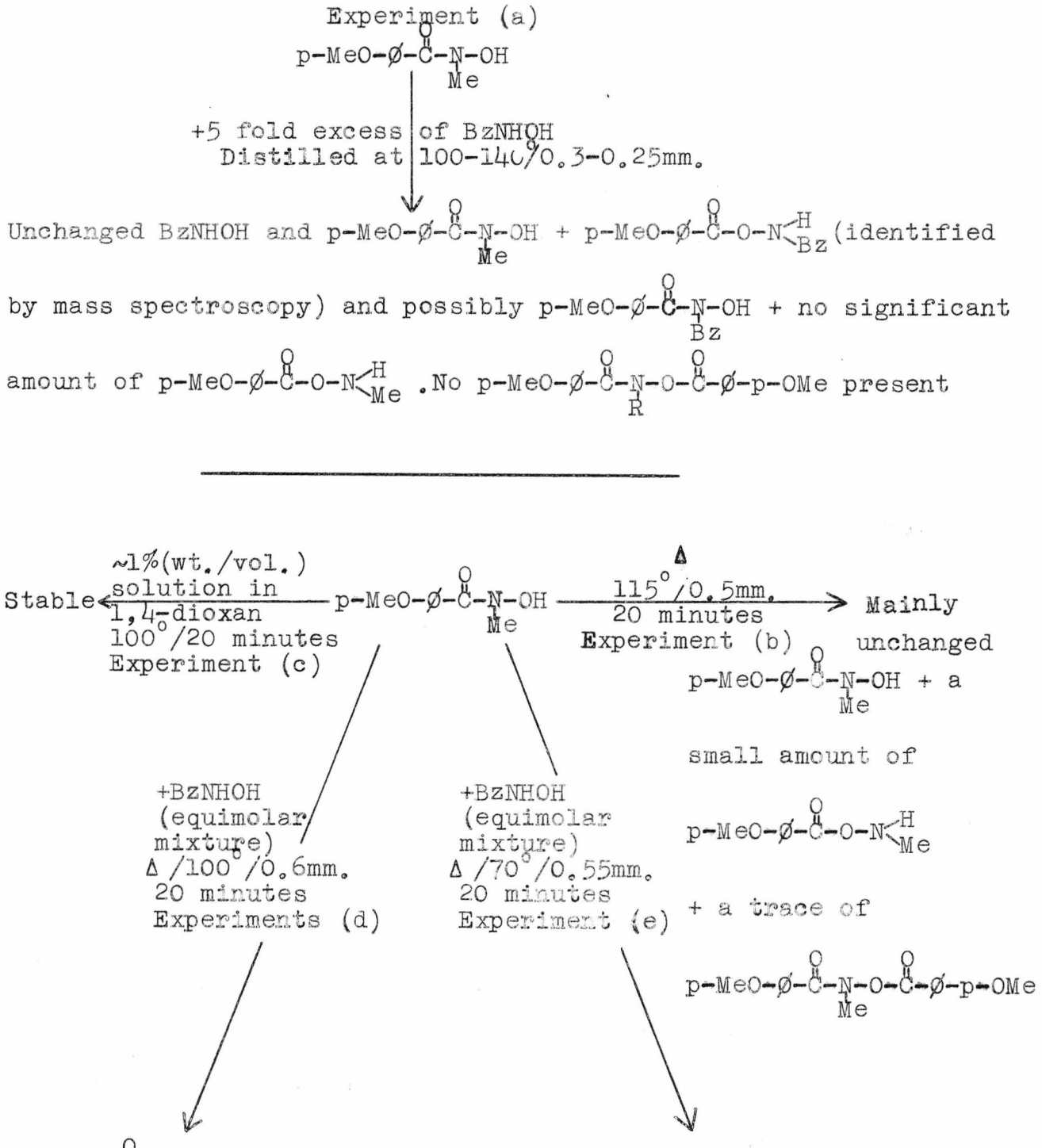
(iv) CROSS-OVER STUDIES

The principal cross-over experiment involved an analysis of the products resulting from the distillation of an N-methyl benzhydroxamic acid in the presence of N-benzylhydroxylamine [experiment (a)]. Such an experiment was found to necessitate several control experiments [experiments (b)-(i)], which are listed below, and to avoid confusion, in Scheme (2.3).

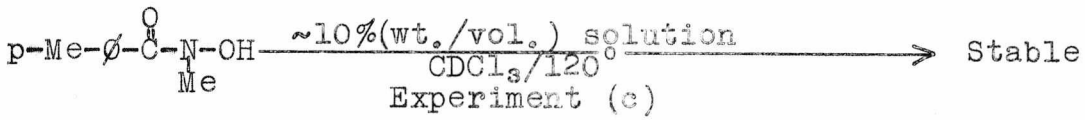
(a) N-methyl p-methoxy-benzhydroxamic acid (LVII) was distilled under reduced pressure in the presence of a five-fold excess of N-benzylhydroxylamine. Distillation of a white crystalline solid/colourless clear oil mixture occurred at 0.3 - 0.25 mm. pressure/100 - 140° (oil bath temperature). Infra-red analysis of the combined distillate and residue revealed it to be a mixture of O-aroyl and N-aroyl hydroxylamines and N-benzylhydroxylamine, whilst mass spectral analysis showed the presence of N- and/or O-(p-methoxy-benzoyl)-N-benzylhydroxylamine[‡] and of N-(p-methoxy-benzoyl)-N-methyl-hydroxylamine. No N-substituted N,O-di(p-methoxy-benzoyl)-hydroxylamines were detected.

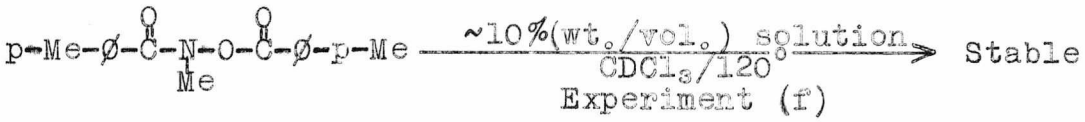
[‡] N- and/or O-(p-methoxy-benzoyl)-N-benzylhydroxylamine should be read as N-(p-methoxy-benzoyl)-N-benzylhydroxylamine and/or O-(p-methoxy-benzoyl)-N-benzylhydroxylamine.

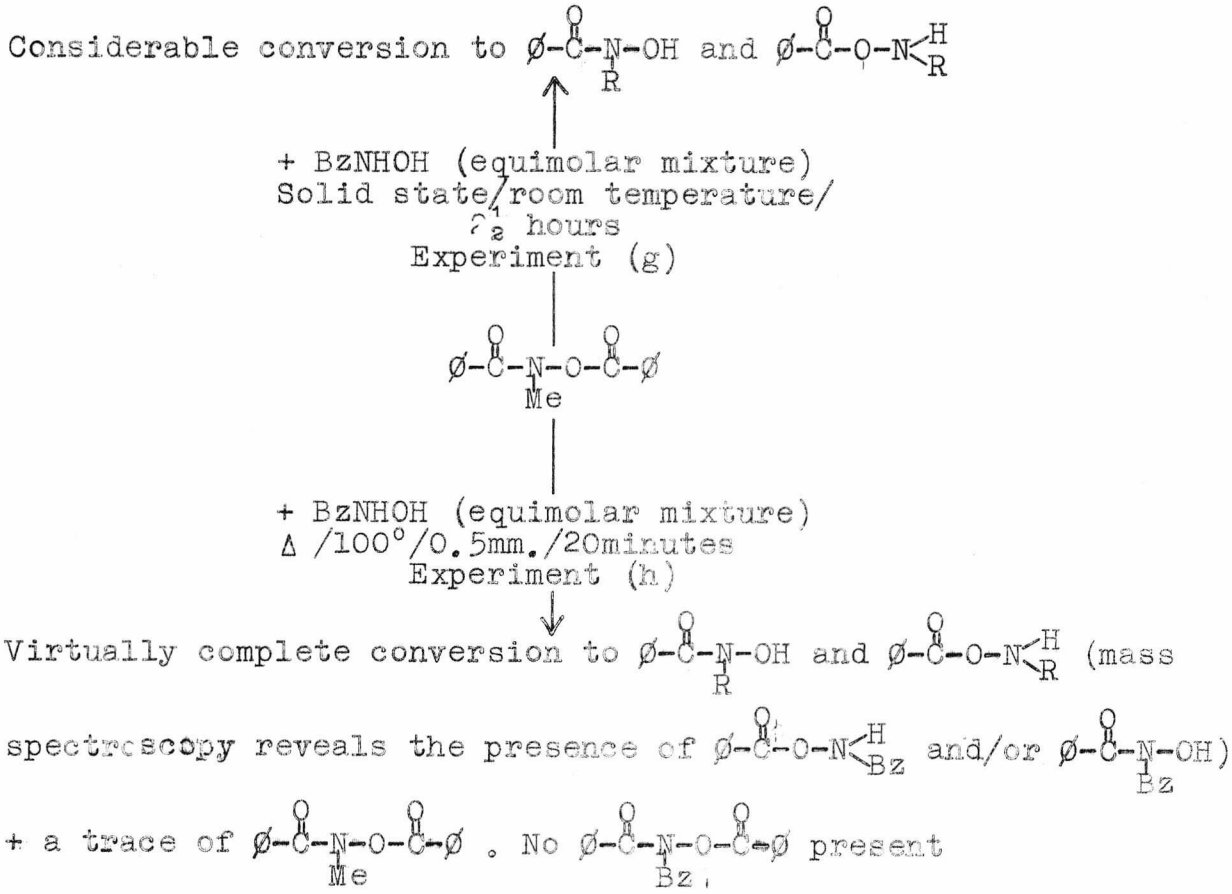
Scheme (2.3) -- Cross-over Experiments.

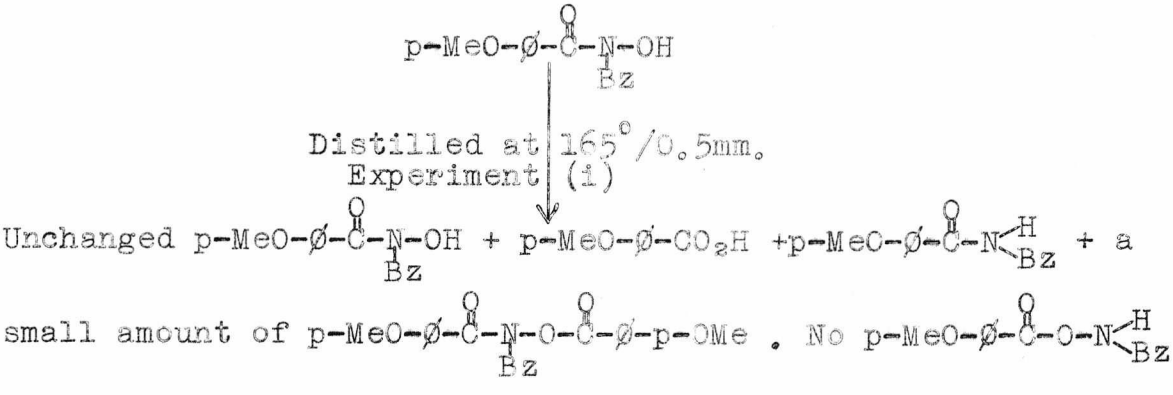


Scheme (2.3) continued,









To determine if any cross-over had occurred it was necessary to be able to detect O-(p-methoxy-benzoyl)-N-benzyl-hydroxylamine and O-(p-methoxy-benzoyl)-N-methylhydroxylamine, both unstable compounds. Rapid mass spectral assay‡ of the combined distillate and residue from this experiment resulted in a certain ambiguity between these two compounds and their respective N-(p-methoxy-benzoyl) isomers. The mass spectrum revealed peaks at m/e 257 and 181 corresponding to the parent ions of N- and/or O-(p-methoxy-benzoyl)-N-benzylhydroxylamine and N- and/or O-(p-methoxy-benzoyl)-N-methylhydroxylamine respectively and other ambiguous peaks were present. In view of this inevitable similarity of the mass spectra of the O-aroyl and N-aroyl N-substituted hydroxylamines, more detailed information concerning the products of the distillation was gleaned by analysis of the metastable pattern appearing in the mass spectrum, using the relationship[103], for a one-step decomposition process of ion a $\longrightarrow$ ion b,

$$m^* = \frac{b^2}{a}$$

where m^* is the position of the metastable peak.

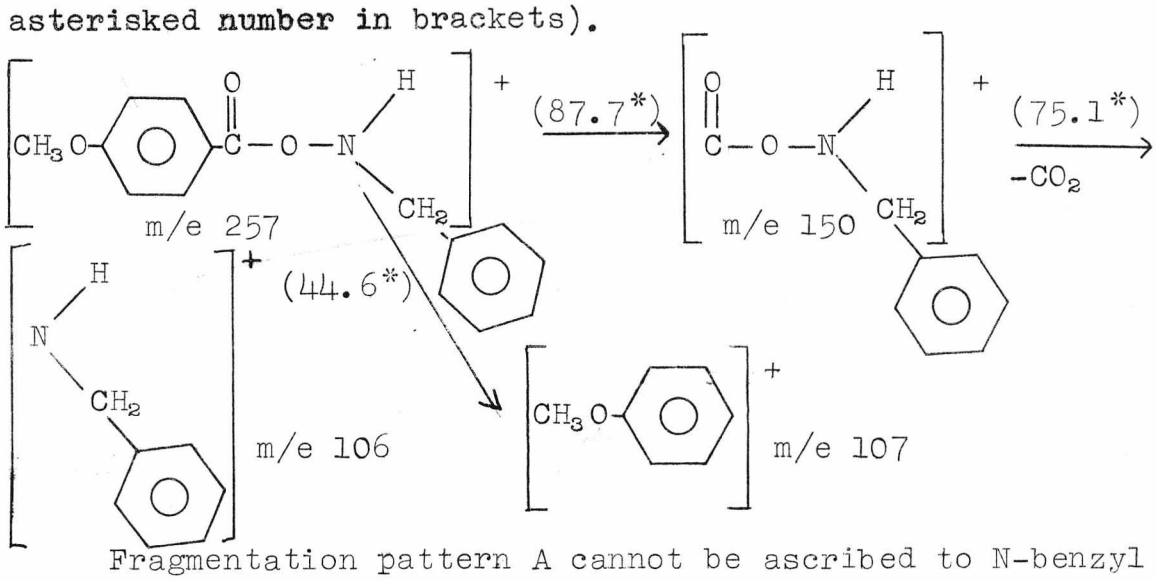
Such analysis revealed that:

(1) O-(p-methoxy-benzoyl)-N-benzylhydroxylamine is present since the observed fragmentation pattern A, giving rise to the observed metastable peaks can only be ascribed to this compound.

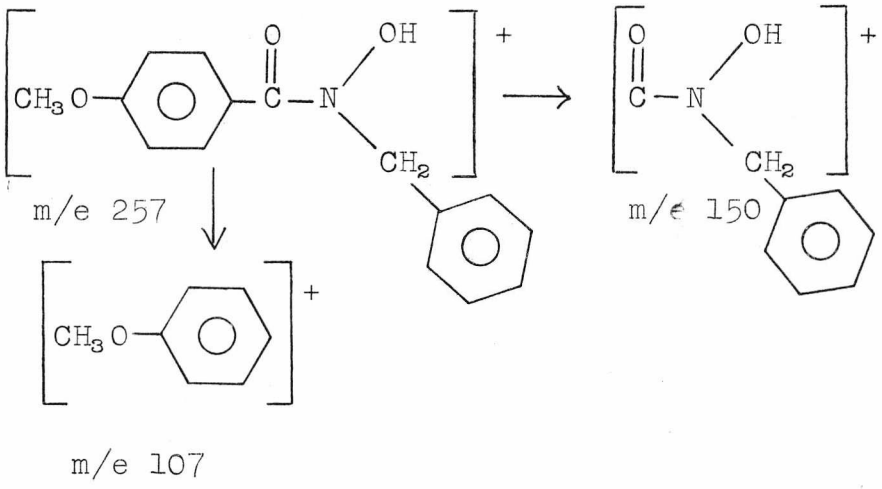
---

‡ Analysis by NMR was not employed because of the small proportion of products to starting material, whilst VPC analysis was excluded since N-methyl benzhydroxamic acids and the corresponding O-benzoyl-N-methylhydroxylamines generally underwent some rearrangement to one another on the VPC column.

FRAGMENTATION PATTERN A (metastable ions are indicated by an asterisked number in brackets).



Fragmentation pattern A cannot be ascribed to N-benzyl p-methoxy-benzhydroxamic acid (as outlined in Scheme (2.4)) as the mass spectrum of N-benzyl p-methoxy-benzhydroxamic acid alone shows no metastable peaks at m/e 87.7 and 44.6.



Scheme(2.4)

(2) Metastable peaks (at 30.3, 12.2, 63.3) expected to result from a breakdown of O-(p-methoxy-benzoyl)-N-methylhydroxylamine in a manner analogous to pattern A for O-(p-methoxy-benzoyl)-N-benzylhydroxylamine are, however, not present.

These results suggest that there has been a predominant formation of O-(p-methoxy-benzoyl)-N-benzylhydroxylamine over O-(p-methoxy-benzoyl)-N-methylhydroxylamine.

(b) N-methyl p-methoxy-benzhydroxamic acid (LVII) underwent rearrangement to a small extent to O-(p-methoxy-benzoyl)-N-methylhydroxylamine (LVIII) with trace formation of N-methyl-N,O-di (p-methoxy-benzoyl)-hydroxylamine (LIX) when heated in a molten state at 115° under a reduced pressure of 0.5mm. for 20 minutes.

(c) (LVII) was unchanged after heating an ~1% (wt./vol.) solution in 1,4-dioxan at 100° for 20 minutes.

An ~10% (wt./vol.) solution of N-methyl p-methyl-benzhydroxamic acid (LX) in deuterochloroform was stable at 120°.

(d) When an equimolar mixture of (LVII) and N-benzylhydroxylamine was heated at 100° under 0.6mm. pressure for 20 minutes some of the N-benzylhydroxylamine distilled out of the system to leave a clear very pale yellow oil residue. Infra-red analysis showed that some rearrangement to an N-substituted O-(p-methoxy-benzoyl)-hydroxylamine had occurred whilst mass spectral analysis revealed the presence of O- and/or N-(p-methoxy-benzoyl)-N-benzylhydroxylamine and of O- and/or N-(p-methoxy-benzoyl)-N-methylhydroxylamine. No N-substituted N,O-di(p-methoxy-benzoyl)-hydroxylamines were detected.

(e) Less rearrangement to an N-substituted O-(p-methoxy-benzoyl)-hydroxylamine occurred when experiment (d) was conducted at 70° under 0.55mm. pressure for 20 minutes. Mass spectral analysis gave a similar product analysis to experiment (d). No N-substituted N,O-di(p-methoxy-benzoyl)-hydroxylamines were detected.

(f) An ~10% (wt./vol.) solution of N-methyl-N,O-di (p-toluoyl)-hydroxylamine (LXI) in deuterochloroform was stable at 120°.

(g) Considerable conversion to O-benzoyl and N-benzoyl hydroxylamines occurred when an equimolar mixture of N-methyl-N,O-dibenzoylhydroxylamine (XXXXIII) and N-benzylhydroxylamine were left in the solid state at room temperature for $2\frac{1}{2}$ hours.

(h) When an equimolar mixture of (XXXXIII) and N-benzyl-hydroxylamine was heated at 100° for 20 minutes under 0.5mm. pressure, virtually complete conversion to O-benzoyl and N-benzoyl hydroxylamines occurred. No significant weight loss occurred during the thermolysis. Mass spectral and IR spectroscopic analysis revealed the presence of a trace of (XXXXIII), the absence of N-benzyl-N,O-dibenzoylhydroxyl-amine (LXII) and the presence of O- and/or N-benzoyl-N-benzylhydroxylamine.

(i) Distillation of N-benzyl p-methoxy-benzhydroxamine acid at 0.5mm./165° (oil bath temperature) resulted in formation of anisic acid and N-benzyl p-methoxy-benzamide. A small amount of N,O-di(p-methoxy-benzoyl)-N-benzylhydroxylamine remained in the residue, but no O-(p-methoxy-benzoyl)-N-benzylhydroxylamine was detected in the residue or distillate, the mass spectra of the residue and of the distillate not exhibiting the metastable peaks characteristic of the fragmentation (pattern A) of O-(p-methoxy-benzoyl)-N-benzyl-hydroxylamine. Some unchanged N-benzyl p-methoxy-benzhydroxamic acid remained.

The above results, will now be shown to support an intermolecular mechanism in which the N,O-diaroyl-N-methylhydroxylamine is involved (Scheme(2.2)),and not an intramolecular mechanism.

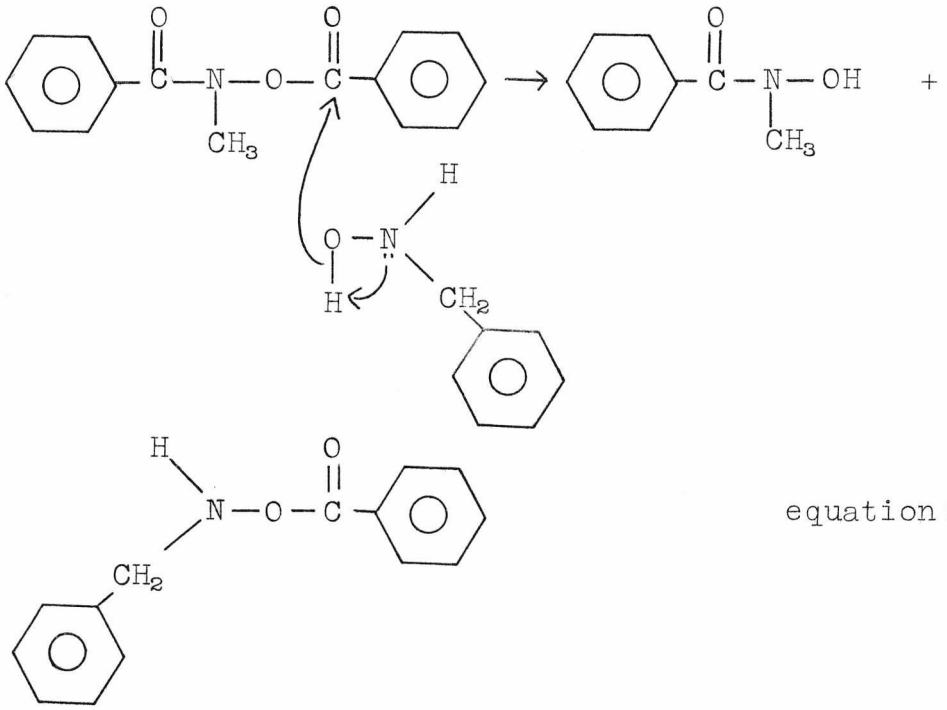
According to such an intermolecular mechanism, formation of the O-aroyl-N-methylhydroxylamine (LXIII) is a result of

reaction of liberated N-methylhydroxylamine with the N,O-diaroyl-N-methylhydroxylamine (LXIV), some of the N-methylhydroxylamine being distilled out of the system. Consequently, distillation of N-methyl p-methoxy-benzhydroxamic acid in the presence of an excess of the more involatile N-benzylhydroxylamine should result in the predominant formation of the O-(p-methoxy-benzoyl)-N-benzylhydroxylamine over the O-(p-methoxy-benzoyl) N-methylhydroxylamine.

Experiment (a) does indicate that cross-over occurs with predominant formation of O-(p-methoxy-benzoyl)-N-benzylhydroxylamine. The absence of N-substituted N,O-di(p-methoxy-benzoyl)-hydroxylamines supports reaction of N,O-di(p-methoxy-benzoyl)-N-methylhydroxylamine (LIX) with N-benzylhydroxylamine [(LIX) being formed in considerable amounts when (LVII) alone is distilled, see page 46].

The small loss in weight occurring during distillation in experiment (a) (see p.144) is due to the loss of N-methylhydroxylamine which can be trapped (see p.142) whilst the lack of a weight loss during the distillation of N-benzyl p-methoxy-benzhydroxamic acid is probably due to the presence of the more involatile N-benzylhydroxylamine.

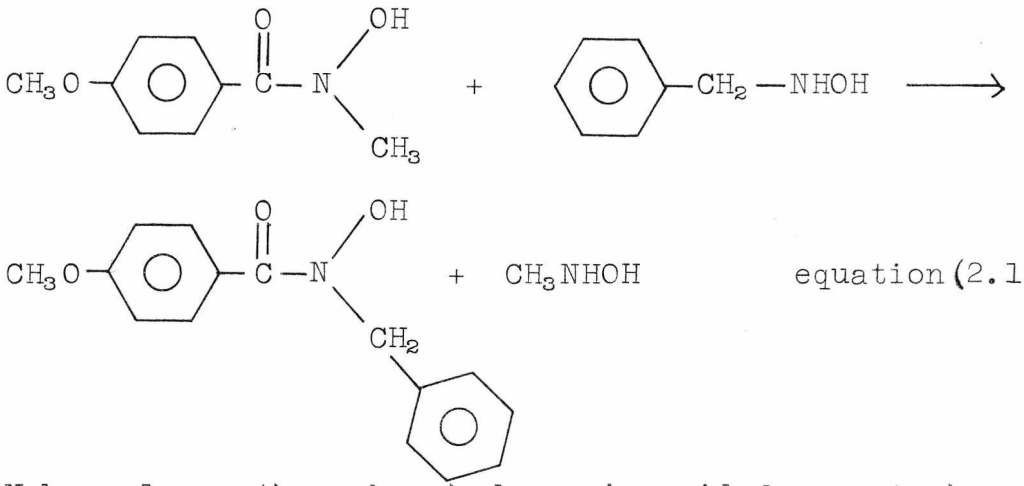
The facile reaction of N-benzylhydroxylamine with (XXXXIII) under distillation conditions is demonstrated by experiment (h) [and (g)] in which a complete loss of (XXXXIII) is observed. Such a reaction will involve predominant O-benzoylation (as opposed to N-benzoylation) of the N-benzylhydroxylamine (equation (2.10)).



equation (2.10)

The attempt [experiments (d) and (e)] to determine if N-benzylhydroxylamine reacted with (LVII) itself to form the N-benzyl hydroxamic acid was complicated by the observed rearrangement of (LVII) to a small extent to (LVIII) and (LIX) at such temperatures [experiment (b)].

Initial cross-over between (LVII) and N-benzylhydroxylamine (equation (2.11)) and subsequent rearrangement of the



equation (2.11)

N-benzyl p-methoxy-benzhydroxamic acid does not, however, explain the results of experiment (a) because, firstly, the distillation in experiment (a) occurs at a lower temperature

(for the same pressure) than the temperature of distillation of N-benzyl p-methoxy-benzhydroxamic acid [experiment (i)], and secondly, N-benzyl p-methoxy-benzhydroxamic acid distills to give products which are different from those of experiment (a) and significantly without formation of O-(p-methoxy-benzoyl)-N-benzylhydroxylamine.

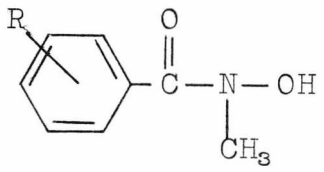
(v) PRODUCT DISTRIBUTION

The results of some typical bulb distillations under reduced pressure of some N-methyl benzhydroxamic acids (LXV) are shown in Table(2.1).

In view of the different temperatures and pressures which had to be employed for the various compounds, no firm conclusions can be drawn from this table on the influence of substituents on the extent of the rearrangement, except for the case of N-methyl-2,4,6-trimethylbenzhydroxamic acid, for which the virtually complete lack of rearrangement is probably due to steric blocking around the carbonyl group. Carpino[104] found O-mesitoylhydroxylamine to be more stable than O-benzoylhydroxylamine and furthermore, the steric effects exhibited by O-mesitoylhydroxylamine allow nucleophilic displacements on nitrogen to occur without complications due to attack of the nucleophile at the carbonyl group.

The relative proportions of (LXIII) and (LXV) were found to vary slightly with the length of distillation, but the amounts of rearranged product never exceeded the amount of unchanged acid on a single distillation. These observations disfavour a mechanism which would produce N-methyl-O-aroyl-hydroxylamine only, i.e. equation(2.6). Moreover, such a mechanism allows no role for the N-methyl-N,O-diaroylhydroxyl-amine which comprises a large part of the residue.

TABLE (2.1). THE THERMAL REARRANGEMENT OF N-METHYLBENZHYDROXAMIC ACIDS (100 mmoles)



R	CONDITIONS OF DISTILLATION	DISTILLATE (mmoles)		RESIDUE (mmoles)			WT. LOSS*
		(LXV)	(LXIII)	(LXV)	(LXIII)	(LXIV)	
p-NO_2	185-200°/15mm.	8	7	27	14	18	26
H	125-145°/0.3mm.	52	16	13	2	7	10
p-MeO	135-150°/0.5mm.	29	27	21	4	7	12
p-Me	140-150°/15mm.	27	19	20	-	11	23
o-Me	155-185°/15mm.	57	27	-	-	12	4
2,4,6-tri Me	170-185°/15mm.	99	1	-	-	-	very small 0

*calculated as mmoles of $NH(CH_3)OH$

In the present study, N-methylhydroxylamine has been shown to react with N-methyl-N,O-dibenzoylhydroxylamine under distillation conditions similar to those used in the re-arrangement of N-methyl benzhydroxamic acid to give both (XXXXI) and (XXXXII), as required by stage 2 of Scheme(2.2).

The first stage of Scheme(2.2)must be a relatively slow step and stage 2 of Scheme(2.2),the attack of N-methyl-hydroxylamine on the N-methyl-N,O-diaroylhydroxylamine, relatively fast or else the N-methylhydroxylamine would distill off under the high vacuum and temperature conditions used, before reaction occurred. N-methylhydroxylamine has a m.p. of 38.5° and a b.p. of 115° (760mm.)[105,106]; 62.5° at 15mm.[106,107]

According to such a mechanism, and indeed, to any formation of N-methyl-N,O-diaroylhydroxylamine from the self-acylation of an N-methyl benzhydroxamic acid, the weight loss during distillation, calculated on the basis of N-methyl-hydroxylamine, should be equivalent to the amount of N-methyl-N,O-diaroylhydroxylamine produced. The figures in Table(2.1)bear this out considering the small weight losses involved. Generally, the millimolar weight loss calculated in terms of N-methylhydroxylamine was slightly greater than the millimolar amount of N-methyl-N,O-diaroylhydroxylamine as determined by quantitative infra-red spectroscopy.

N-methylhydroxylamine lost from the distillation system on distilling N-methyl benzhydroxamic acid under reduced pressure was trapped in a liquid nitrogen cooled U-tube and characterised by its infra-red spectrum.

Pyrolysis of N-methyl benzhydroxamic acid in a sealed tube for 50 minutes at 75°,with subsequent quenching by rapid

cooling and infra-red analysis showed the reaction mixture to be mainly unchanged N-methyl benzhydroxamic acid (87 molar %) with very small amounts of the O-benzoyl isomer (XXXXII) (11 molar %) and N-methyl-N,O-dibenzoylhydroxylamine (2 molar %). Such low yields of (XXXXII) and (XXXXIII) when the N-methylhydroxylamine produced is confined to the reaction mixture, supports the bimolecular non-concerted mechanism of Scheme(2.2). The confined N-methylhydroxylamine would react with any N-methyl N,O-dibenzoylhydroxylamine formed, producing N-methyl benzhydroxamic acid and N-methyl-O-benzoylhydroxylamine . Such a confined pyrolysis would destroy the facility of selective distillation and hence stabilisation of (XXXXII) with consequent isomerisation of (XXXXII) to (XXXXI). Such quantities of (XXXXII) and (XXXXIII) as are obtained probably represent small equilibrium concentrations.

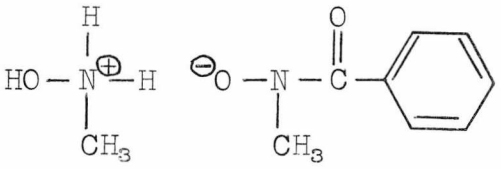
(vi) THE THERMAL STABILITY OF N-METHYLHYDROXYLAMINE

With N-methylhydroxylamine as a probable intermediate in the thermal rearrangement of N-methyl benzhydroxamic acids it is at first sight somewhat surprising that under the distillation conditions employed, owing to its volatility (b.p. 115°/760mm.[105]; 62.5°/15mm.[106,107]), it is not pumped out of the reaction mixture completely, before any reaction with N-methyl-N,O-diaroylhydroxylamine can occur.

The imperfect removal of the N-methylhydroxylamine indicates that reaction with N-methyl-N,O-diaroylhydroxylamine is extremely facile under the distillation conditions.

Considering the pKa values of N-methylhydroxylamine (6.24) and N-methyl benzhydroxamic acid (8.58) and the excess concentration of (XXXXI) over N-methylhydroxylamine in the distillation of (XXXXI), the N-methylhydroxylamine may well

exist to some extent as the hydroxamate salt (LXVI).



(LXVI)

Such a salt should be thermally stable under the employed distillation temperatures, hydroxylamines being stabilised[108], if there is no N-aryl substituent present[109], by protonation on nitrogen to form well-defined salts, and obviously becoming less volatile.

There are no direct observations in the literature regarding the thermal stability of N-methylhydroxylamine.

The thermal stability of hydroxylamines depends considerably on the degree as well as the nature of substitution. Hydroxylamine itself is an extremely unstable compound, decomposing above 15° to ammonia, water, and a mixture of nitrogen and nitrous oxide[108].

The disproportionation of some N-substituted hydroxylamines, giving the amine together with an azo or azoxy compound has been noted[110]. This occurs on heating N-phenylhydroxylamine[111], which even on standing undergoes slow conversion to azoxybenzene and aniline[109]. Disproportionation of o-[112] and p-hydroxylaminobiphenyl[110a], however, occurs at ~200-250° over long periods of time.

The O-methylation of free N-methylhydroxylamine in benzene solution at 90° with dimethyl sulphate[113] showed the N-methylhydroxylamine to be stable under these conditions. This observation, together with the observed reaction of N-methylhydroxylamine with N-methyl-N,O-dibenzoylhydroxylamine under distillation conditions (see page 47) and the N-aryl hydroxylamines disproportionating under considerably harsher

conditions (see previous page) than those employed in the distillation of the N-methyl hydroxamic acids, signify N-methylhydroxylamine to be thermally stable in itself, under the conditions of the distillations.

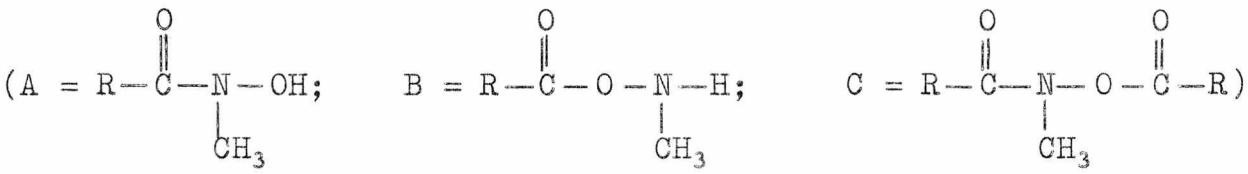
(vii) SUMMARY

The preceding results provide a strong weight of evidence indicating that the thermal rearrangement of N-methyl hydroxamic acids (LXV) $\longrightarrow$ (LXIII) proceeds, at least partly, by an intermolecular non-concerted mechanism outlined in Scheme(2.2). Simultaneous rearrangement by an intramolecular mechanism (equations(2.1)and(2.2))has not, however, been totally excluded, the metastable analysis of the mass spectrum of experiment (a), page39, suggesting that an intramolecular mechanism does not occur to any large extent.

(viii) THE THERMAL REARRANGEMENT OF N-METHYL-N-ACYLHYDROXYLAMINES

Several N-methyl-N-acylhydroxylamines (N-methyl aliphatic hydroxamic acids) (LXVII) were found to undergo a similar thermal rearrangement on distillation to that observed for the N-methyl benzhydroxamic acids, with formation of the correspond- N-methyl-O-acylhydroxylamine (LXVIII) and the N-methyl-N,O-diacyl- hydroxylamine (LXIX).

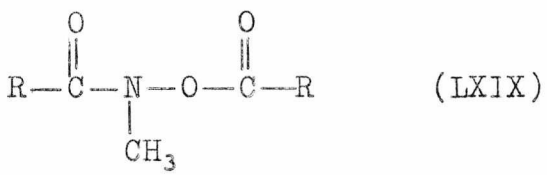
The results of some typical bulb distillations of these N-methyl aliphatic hydroxamic acids are shown in Table (2.2).



The increase of rearrangement with increasing temperature and pressure is probably due to (a) the higher temperature used and (b) at the higher pressure any difference between the b.ps. of (LXVIII) and (LXVII) will be greater than the difference at lower pressure, so facilitating more easily the selective distillation of (LXVIII).

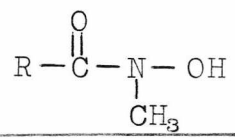
In order to obtain rearrangement of the N-methyl-N-acyl- hydroxylamines to N-methyl-O-acylhydroxylamines temperatures had to be employed which were generally higher than those employed in the distillation/rearrangement of N-methyl-N-aroylhydroxylamines.

Such distillations of the N-methyl-N-acylhydroxylamines produced considerable quantites of the corresponding N-methyl amides and carboxylic acids. It is likely that these products arise from cleavage of the N-O bond of the intermediate N-methyl- N,O-diacylhydroxylamine (LXIX).



(LXIX)

TABLE (2.2). THE THERMAL REARRANGEMENT OF SOME N-METHYL ALIPHATIC HYDROXAMIC ACIDS



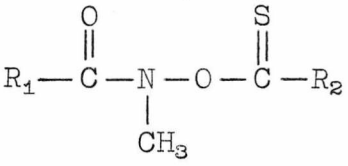
R	Conditions of Distillation (temperatures are oil bath temperatures)	Occurrence of Rearrangement to the N-methyl-O-acyl-hydroxylamine	RESULTS	
			Residue	Distillate
CH_3	105-120°/3.0 mm.	None	The N-methylacethydroxamic acid is unchanged	
CH_3	120-135°/18mm.	Very slight	Mainly A + trace C	Mainly A + trace B + trace C
CH_3	175-180°/Atmospheric pressure	Considerable	Only N-methylacetamide	A + B + N-methyl acetamide + acetic acid + trace C
$(CH_3)_3C$	120-135°/13.0-13.5mm.	Considerable	Mainly A + trace B + trace C	A + B
$(C_2H_5)_2CH$	130-140°/11.5mm.	Small amount	Mainly A + trace C + trace N-methyl 2-ethyl-n-butyramide + trace 2-ethyl n-butyric acid	Mainly A + small amount B
$(C_2H_5)_2CH$	155-170°/10.2-10.5mm.	Considerable	A + C + some N-methyl 2-ethyl-n-butyramide + some 2-ethyl n-butyric acid	A + B

/cont.

TABLE (2.2).(cont.)

R	Conditions of Distillation (temperatures are oil bath temperatures)	RESULTS		
		Occurrence of Rearrangement to the N-methyl-O-acyl-hydroxylamine	Residue	Distillate
$C_2H_5CH_2$	115-120°/15mm.	Small amount	A + trace C	A + very small amount B
$C_2H_5CH_2$	135-155°/6.4-7.1cm.	Considerable	Mainly N-methyl n-butyramide + trace C	Mainly B + some A + C + N-methyl n-butyramide + n-butyric acid

The cleavage of the N-O bond in (LXIX), however, need not <u>necessarily</u> lead to the fragmentation observed during distillation: some degenerate recombination of the fragments, ion or radical, would be expected. From this viewpoint, a study of the thermal reactions of thione esters of N-methyl hydroxamic acids (LXX) was undertaken, since the sulphur atom in the analogue removes the degeneracy of recombination, rendering this aspect of any N-O cleavage easily amenable to study.



(LXX)

CHAPTER III

THE THERMAL REACTIONS OF THIONE ESTERS OF N-METHYL HYDROXAMIC ACIDS

(i) The Thermal Rearrangement of N-Aroyl-O-(N',N'-Dimethylthiocarbamoyl)-N-Methylhydroxylamines.

It was convenient for the amide portion of the N-methyl hydroxamic acid thionocarbamate to contain a benzenoid system as these compounds are solids and easily purified by recrystallisation in the cold.

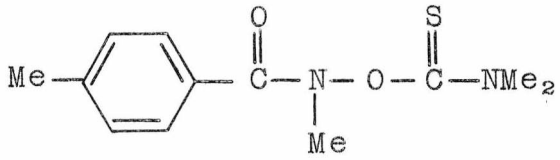
The compound first synthesised and examined was N-(p-toluoyl)-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine (LXXI). This compound was sufficiently stable to be prepared by reaction of N-methyl p-methyl-benzhydroxamic acid with N,N-dimethylthiocarbamoyl chloride in the presence of triethylamine in N,N-dimethylformamide solution at room temperature. The compound could be purified by recrystallisation from cold benzene/40-60° petroleum ether. It was stable in the solid state at room temperature for at least a year but was unstable in solution.

A 5% (wt./vol.) solution of (LXXI) in Analar grade chloroform underwent almost quantitative rearrangement to N-(p-toluoyl)-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine (LXXII) ($\sim$ 95%) with a small amount ($\sim$ 5%) of N-methyl p-toluamide (LXXIII) when left at room temperature for 5 days.

This rearrangement provides a novel synthetic route to the N-aroyl-S-acyl-N-methylhydrosulfamines (LXXIV); these compounds are unrecorded in the literature.

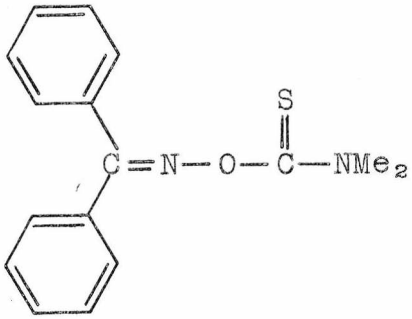
The spectral evidence for the structures of (LXXI) and (LXXII) is given below (Table(3.1)). Similar structural evidence for other compounds in the series along with analytical data will be found in the experimental section. The following

compounds (LXXV) ⟶ (LXXX) were used as models in making the structural assignments:

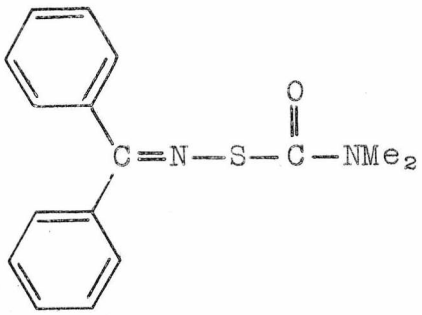


(LXXI)

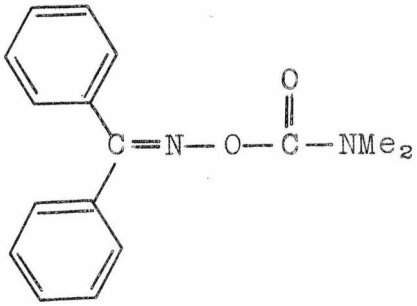
(LXXII)



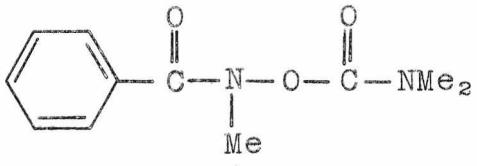
(LXXV)



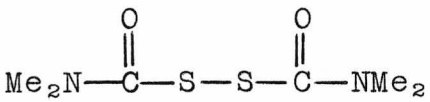
(LXXVI)



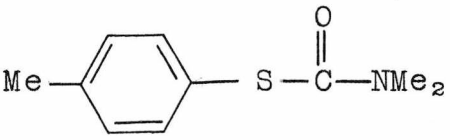
(LXXVII)



(LXXVIII)



(LXXIX)



(LXXX)

Only a small amount of data has been reported on the infra-red spectra of thiol esters.[114] Open-chain thiol esters, both saturated and α-amino-, are reported to exhibit carbonyl frequencies at 1675 cm^{-1}.[115]

Table (3.1). The Infra-red Spectra of Compounds (LXXI), (LXXII) and (LXXV) - (LXXX)

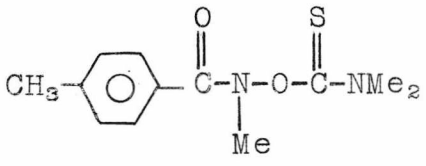
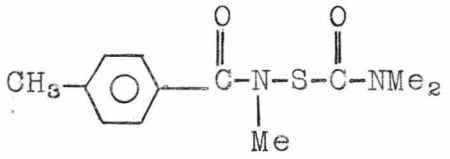
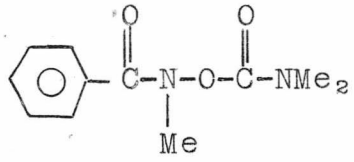
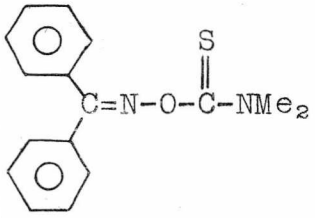
Compound	Absorptions ($cm.^{-1}$) in the infra-red spectra (all run in $CHCL_3$ A.R.); Range 4000-625 $cm.^{-1}$. Their relative intensities and assignments. s = strong, m = medium, w = weak.
	2978(m) C-H stretch of CH_3, 1656(s) C=O vibration, 1614(w), 1535(s), 1400(s), 1372(m), 1283(s), 1174(m), 1086(m) C=S stretching vibration, 1043(m), 974(w) N-O stretch, 940(w), 893(w), 826(m).
	2980(m) C-H stretch of CH_3, 1682(s)(1635-1700)C=O vibration, 1612(w), 1409(m), 1370(w), 1320(m), 1099(m), 1015(m), 827(w).
	2942(m) C-H stretch of CH_3, 1751(s) ester C=O vibration, 1662(s) amide C=O vibration, 1446(m), 1412(w), 1385(s), 1149(s), 993(m) N-O stretch, 904(w), 833(w).
	2944(s) C-H stretch of CH_3, 1874(m), 1720(s) C=N stretch, 1646(m), 1592(s), 1529(s), 1487(s), 1345(s), 1181(s), 1115(w), 1074(s) C=S stretching vibration.

Table (3.1) continued

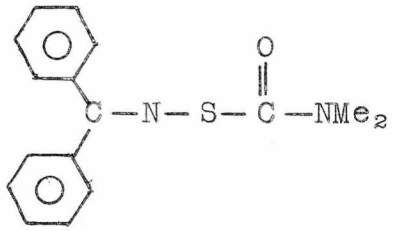
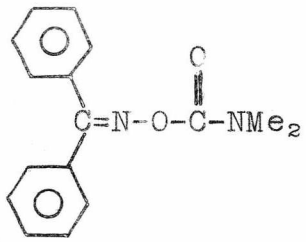
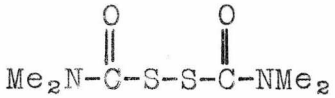
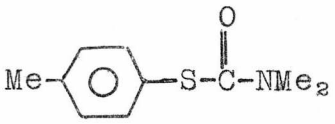
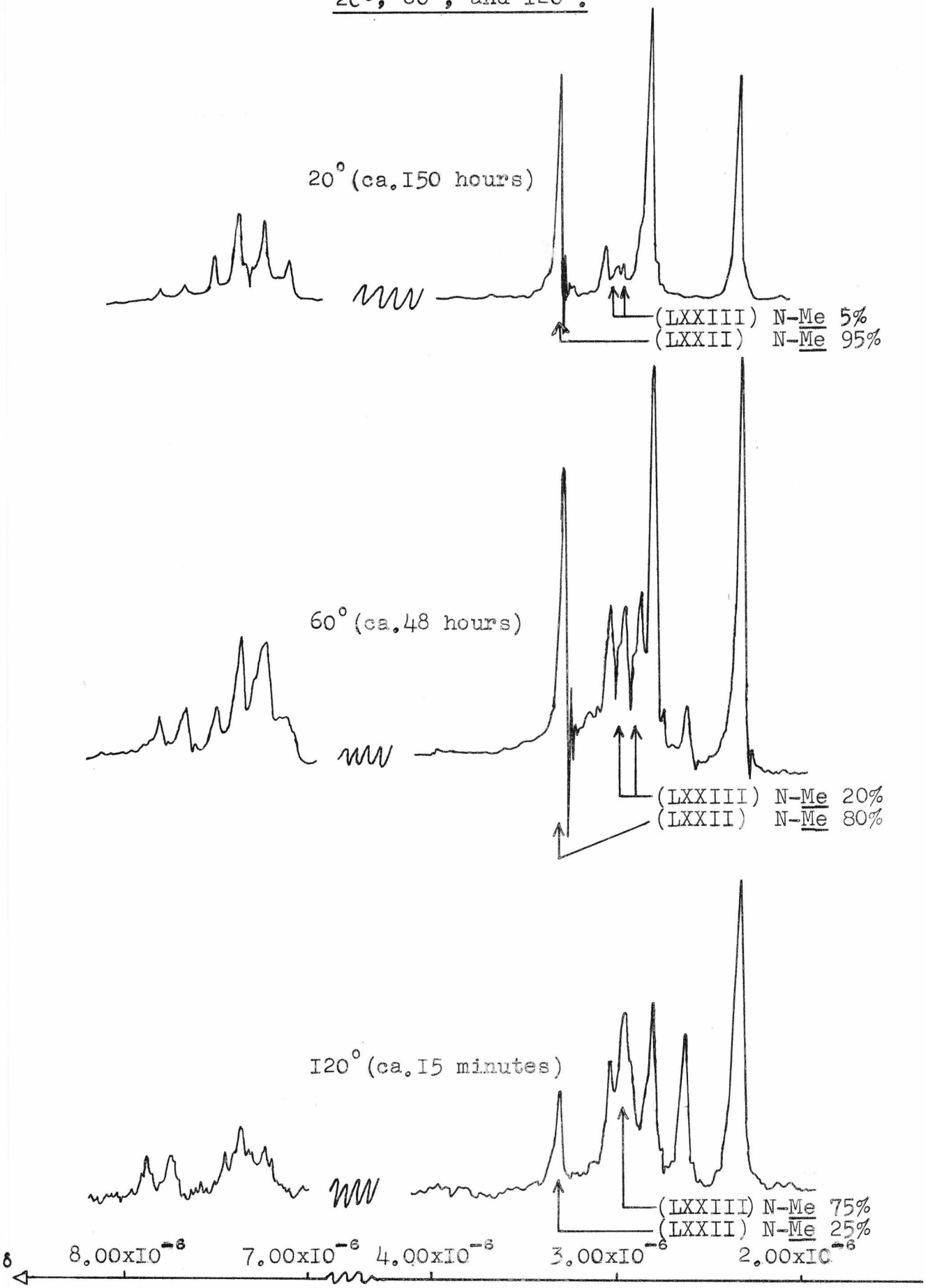
	2980(m) C-H stretch of CH_3, 1674(s) C=O vibration, 1445(m), 1408(w), 1370(s), 1316(w), 1296(w), 1260(w), 1100(s) 953(w), 911(m).
	~ 3000(w), C-H stretch of CH_3, 1727(s) C=O vibration, 1444(w), 1386(m), 1325(w), 1157(s), 986(m) N-O stretch, 901(m), 859(w).
	2992(m) C-H stretch of CH_3, 2926(m) C-H stretch of CH_3, 1678(s) C=O vibration, 1441(w), 1409(w), 1367(s), 1257(w), 1094(s), 901(m).
	2994(m) C-H stretch of CH_3, 2920(m) C-H stretch of CH_3, 1660(s) C=O vibration, 1600(w), 1492(m), 1441(w), 1404(m), 1368(s), 1260(m), 1108(s), 1093(s), 1019(w), 909(w).

Diagram (3.I). The NMR Spectra of the Products from the Thermal Rearrangement of (LXXI) in Deuterochloroform solution at 20°, 60°, and 120°.



The ratio of N- methyl p- toluamide (LXXIII) to N-(p-toluoyl)-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine (LXXII) increased with increasing temperature (Table(3.2)) in the thermal rearrangement of (LXXI) in solution in deutero-chloroform (Diagram(3.1)).

Table(3.2). The Thermal Rearrangement of (LXXI) in Deutero-chloroform

Temperature	LXXIII %	LXXII %
20°	5	95
60°	20	80
120°	75	25

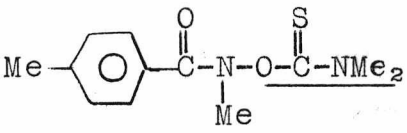
NMR analysis shows, rather surprisingly, that initially N-methyl p-toluamide is formed and not N-deutero N-methyl p-toluamide. This aspect of the NMR study will be discussed after consideration of the kinetics of the rearrangement.

(ii) Kinetics of the Rearrangement

(a) Over a wide range of concentrations (ca. 1.0×10^{-4}M - ca. 0.4M) and temperature (25°-83°) in a variety of organic solvents the rate of rearrangement of various N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines (LXXXI) to the corresponding N-aroyl-S-(N',N'-dimethylcarbamoyl-N-methyl-hydrosulfamine (LXXXII) was found to be first order (equation(3.1)).

$$\text{Rate} = k_1 \cdot [(\text{LXXXI})] \qquad \text{equation (3.1)}$$

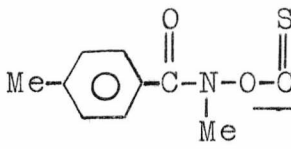
The first order dependence on the concentration of (LXXXI) is demonstrated by the data given in Tables (3.3) and (3.4), which list the percentage loss of N-(p-toluoyl)-O-(N',N'-dimethyl-thiocarbamoyl)-N-methylhydroxylamine (LXXI) versus time for kinetic runs followed by ultra-violet and infra-red spectroscopy.

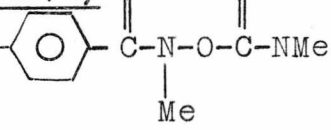
Table (3.3). The Rate of Rearrangement of  in Benzene at 59.0° - Monitored by Ultra-Violet Spectroscopy at 285 mμ. (Run 60)

$[Me\text{-}C_6H_4\text{-}C(=O)\text{-}N(Me)\text{-}O\text{-}C(=S)\text{-}NMe_2] = 2.113 \times 10^{-4}$ moles litre^{-1}

Time (minutes)	Concentration of (LXXI) (moles litre^{-1})	Percentage loss of (LXXI)
0	2.113×10^{-4}	0.0
60	1.819×10^{-4}	13.9
120	1.536×10^{-4}	27.3
180	1.289×10^{-4}	39.0
240	1.086×10^{-4}	48.6
300	0.909×10^{-4}	57.0
420	0.638×10^{-4}	69.8
540	0.435×10^{-4}	79.4
660	0.306×10^{-4}	85.5
780	0.224×10^{-4}	89.4
900	0.173×10^{-4}	91.8

$k = 0.294 \times 10^{-2} min.^{-1}$

Table (3.4). The Rate of Rearrangement of  in Benzene at 59.0° - Monitored by Infra-red Spectroscopy at 1286 cm^{-1}. (Run71)

Initial concentration of  = 0.1982 moles $litre^{-1}$.

Time (minutes)	Absorbance at 1286 $cm.^{-1}$ of a solution diluted to 4 x its volume with benzene	Concentration of (LXXI) (moles $litre^{-1}$)	Percentage loss of (LXXI)
0	0.559	0.1870	0.0
31.5	0.526	0.1742	6.8
90	0.465	0.1522	18.6
168	0.385	0.1238	33.8
212	0.357	0.1134	39.4
251	0.325	0.1026	45.1
290	0.316	0.0994	46.8
320	0.267	0.0838	55.2

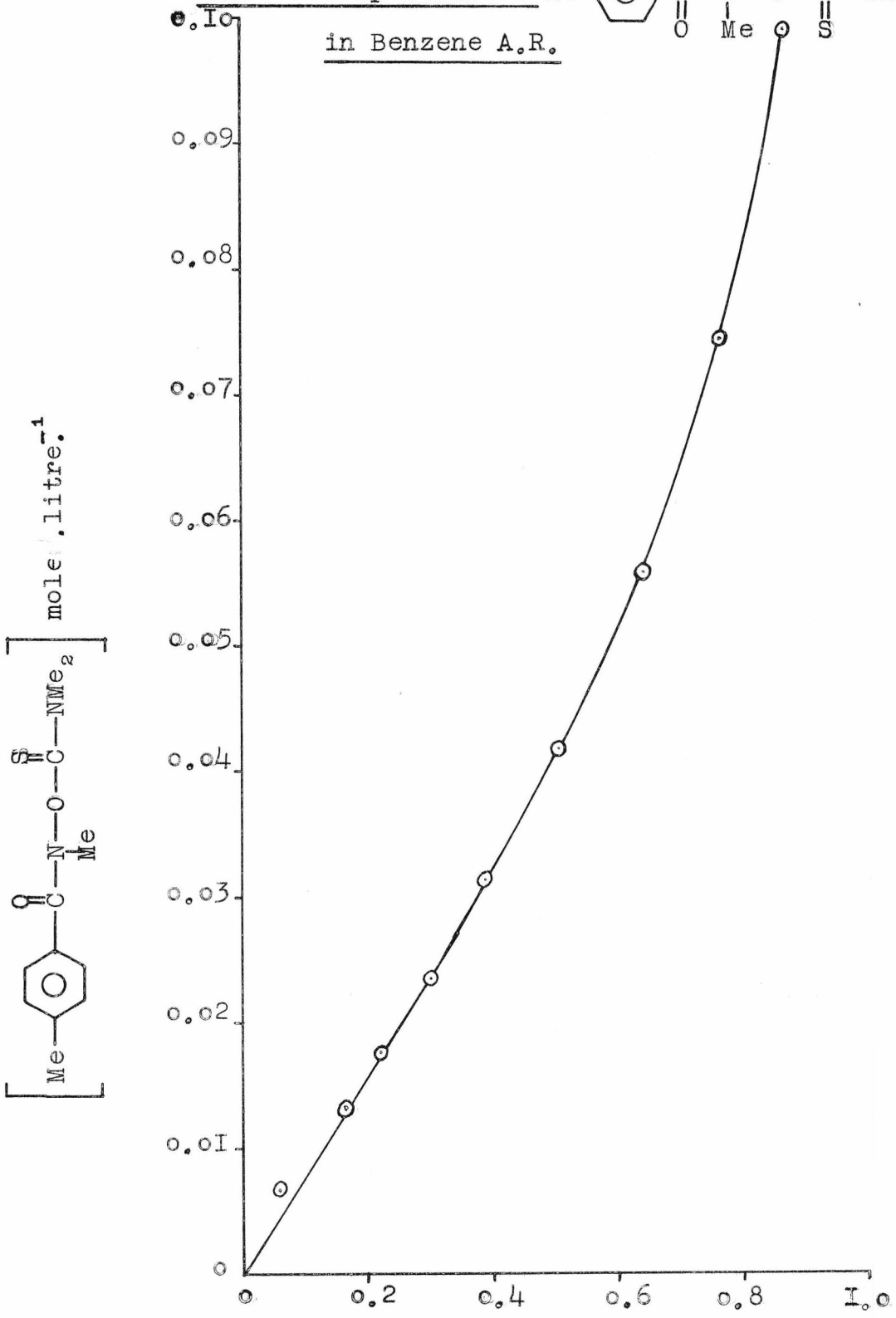
$k = 0.230 \times 10^{-2} min.^{-1}$

The relationship of concentration of (LXXI) to absorbance of the absorption at 1268 $cm.^{-1}$ in benzene solution is plotted in Graph(3.1).

In view of the facile photolytic decomposition of (LXXI)‡

‡A 0.1% wt./vol. solution of (LXXI) in Analar grade methanol undergoes photolysis, principally to N-methyl p-toluamide, on irradiation with a 100 watt mercury lamp contained in a quartz probe. The analogous photolytic cleavage of thiocarboxylic acid O- esters is known.[116,117] Horton and co-workers[116] have explained the photolysis of sugar dimethylthiocarbamates to deoxy-sugars by an initial thiono-thiolo rearrangement and subsequent C-S bond homolysis.

Graph (3.I). Calibration Curve (concentration versus absorbance) for the Absorption at I286 cm.$^{-1}$ in the Infra-red Spectrum of Me-C$_6$H$_4$-C(=O)-N(Me)-O-C(=S)-NMe$_2$ in Benzene A.R.



kinetic solutions of this compound were examined for any photolysis occurring whilst these solutions were being monitored in the beam of the ultra-violet spectrophotometer. It was observed that:-

(1) the rate of decomposition remained virtually unchanged when the slit width of the UV spectrophotometer was increased by a factor of 5 from 0.02 mm. to 0.10 mm. and the beam energy was simultaneously increased by a factor of 8.

(2) the rate of decomposition did not change significantly when a kinetic run was conducted outside the UV spectrophotometer cell block, samples from a sealed flask wrapped in aluminium foil being taken periodically for immediate assay by UV spectrophotometry.

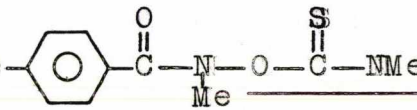
These factors are demonstrated in Table (3.5).

Table (3.5).

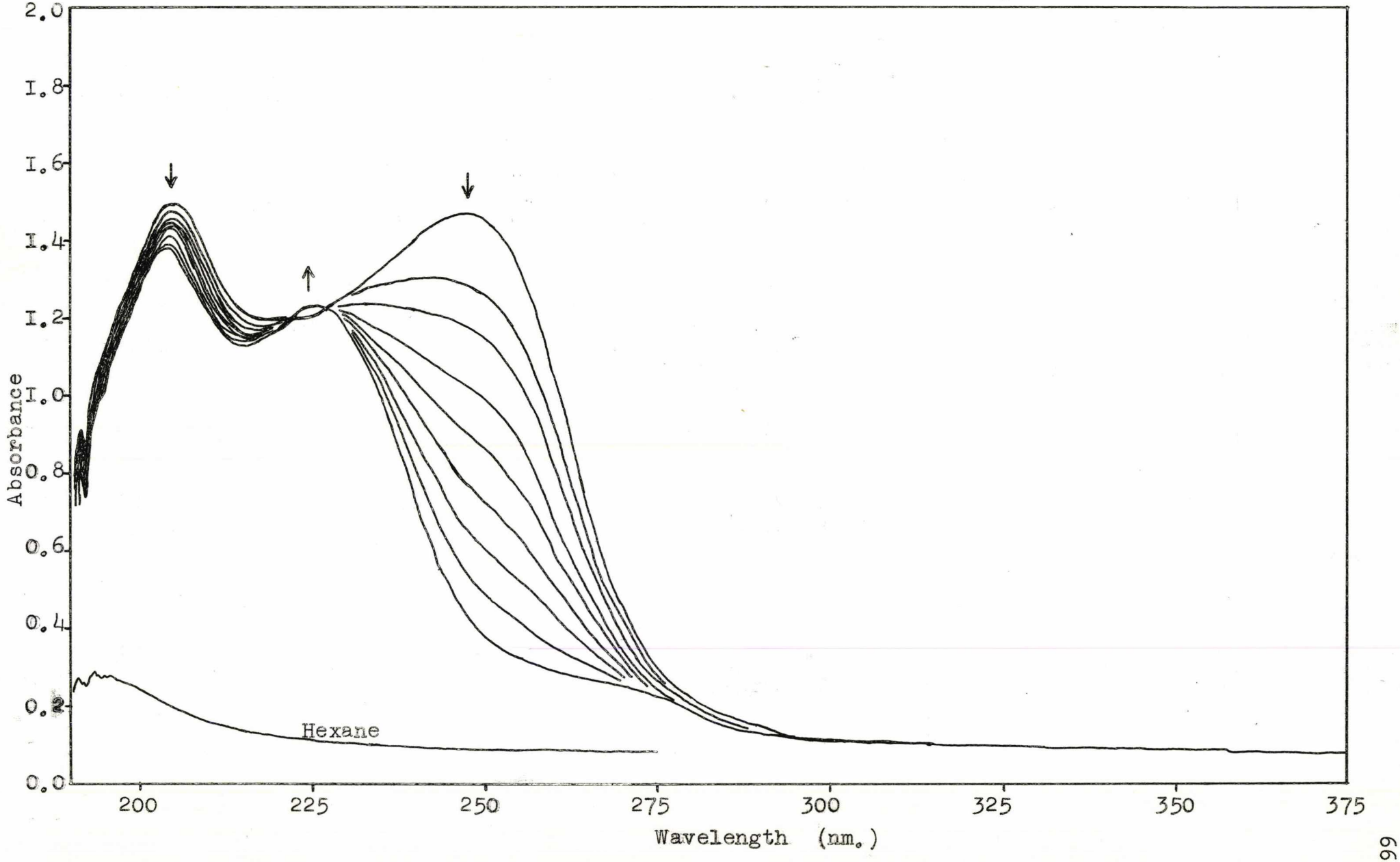
Conditions:- Solvent/ Temperature	Hexane; 60.8°	Hexane; 69.0° outside UV beam	Hexane; 69.0° within UV beam
Rate of Re-arrangement of (LXXI). Normal settings; slit width = 0.02mm. Beam energy = E	$k = 0.535 \times 10^{-2} min^{-1}$ (Interpolated from Arrhenius plot, Graph (3.6))	$k = 1.484 \times 10^{-2} min^{-1}$ (Run 61)	$k = 1.521 \times 10^{-2} min^{-1}$ (Interpolated from Arrhenius plot, Graph (3.6))
Rate of Re-arrangement of (LXXI). Slit width = 0.10mm. Beam energy = 8E	$k = 0.409 \times 10^{-2} min^{-1}$ (Run 17)	-	-

The rearrangement of (LXXXI) ⟶ (LXXXII) showed isosbestic points in the UV spectra in a variety of solvents (for example see diagram (3.2)) and the extinction coefficients of (LXXXI) and (LXXXII) correlated with the observed loss of absorbance at the wavelength monitored. The product UV spectra from the rearrangement of (LXXXI) corresponded closely to the UV spectra of pure (LXXXII). Both (LXXXI) and (LXXXII) obeyed Beer's law in the UV region.

In general, therefore, the kinetics of rearrangement were

Diagram (3.2). Ultra-violet spectrum of the Rearrangement of Me- 

in hexane at 60.0°

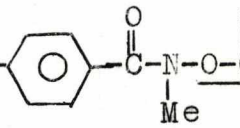


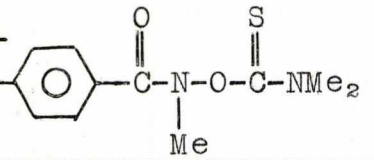
followed by observing the loss of the starting material by UV spectrophotometry.

Evidence is given in Table (3.6) that the rate of rearrangement of (LXXI) in hexane is not significantly altered when the hexane has been purged with oxygen for $1\frac{1}{2}$ hours.

Table (3.6).

Conditions:- Solvent/ Temperature	Hexane purged with oxygen for $1\frac{1}{2}$ hours. 66.0°.	Hexane unpurged 66.0°.
Rate of rearrangement of (LXXI).	$k = 1.122 \times 10^{-2} min^{-1}$. (Run 15)	$k = 1.057 \times 10^{-2} min^{-1}$ (Interpolated from Arrhenplot. Graph(3.6))

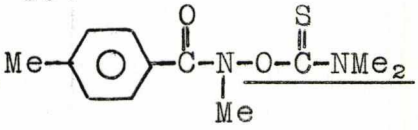
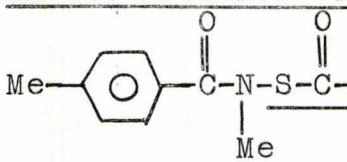
Table (3.7). The Rate of Rearrangement of Me-  -C-N-O-C-NMe$_2$ in Deuterochloroform at 65.4° - Monitored by NMR Spectroscopy at δ 3.48 (The N-Methyl Resonance of (LXXI)). (Run89)

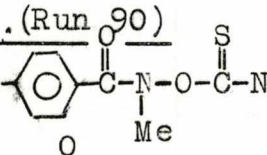
Initial concentration of Me-  -C-N-O-C-NMe$_2$ = 0.3998 moles litre^{-1}

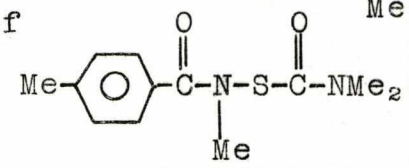
Time (minutes)	Corrected Integration for the N-methyl resonance at δ 3.48 for (LXXI)	Concentration of (LXXI) (moles litre^{-1})	Percentage loss of (LXXI)
0	100.0	0.3998	0.0
5	95.9	0.3834	4.1
39	84.2	0.3366	15.8
114	66.4	0.2655	33.6
186	56.8	0.2271	43.2
243	46.9	0.1875	53.1
298	39.4	0.1575	60.6
467	22.9	0.0916	77.1

$k = 0.304 \times 10^{-2} min^{-1}$

The absence of involvement of catalysis of the rearrangement by the product was shown by the similar rates obtained when (LXXI) underwent rearrangement by itself and in the presence of three equivalents of the product (LXXII). (Tables(3.7) and(3.8)). These rates were monitored by NMR spectroscopy.

Table (3.8). The Rate of Rearrangement of  in the Presence of 3 Equivalents of  in Deuterochloroform at 65.4° - Monitored by NMR Spectroscopy at δ3.48 (the N-Methyl Resonance of (LXXI)).(Run 90)

Initial concentration of  = 0.3998 moles litre^{-1}

Concentration of  = 1.2009 moles litre^{-1}

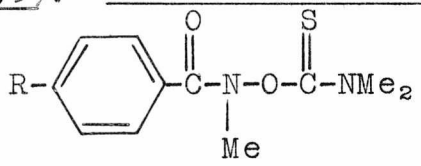
Time (minutes)	Corrected integration for the N-methyl resonance at δ3.48 for (LXXI)	Concentration of (LXXI) (moles litre^{-1})	Percentage loss of (LXXI)
0	100.0	0.3998	0.0
10	106.4	(0.4254)	-
78	83.9	0.3354	16.1
109	77.5	0.3098	22.5
177	76.3	0.3050	23.7
240	61.0	0.2439	39.0
306	36.4	0.1455	63.6

$k = 0.308 \times 10^{-2}$ min.$^{-1}$

By UV spectrophotometric monitoring the effect of structure, solvent changes and changes in temperature on the rate of the rearrangement was followed.

(b) Solvent Effects

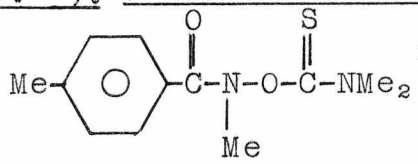
The rates or rearrangement of various N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines (LXXXI) to the corresponding N- aroyl-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine (LXXXII) in a range of solvents are given in Table (3.9).

Table (3.9). First-order Rate Coefficients for the Rearrangement of  in a Variety of Solvents.

Run/R	Temperature °C	10^2 x k($min.^{-1}$)	Solvent
(1)	60.5	0.510	Hexane
(47)	60.5	0.500	Ethanol
(16)	60.5	0.292	Acetonitrile
(60)	59.0	0.294	Benzene
(19)	60.5	1.407	Chloroform
(14)	60.5	1.895	Carbon tetrachloride
(12) CH_3	60.5	0.939	Deuterochloroform
Graph (3.6)	49.9	0.433	Hexane
(20)	49.9	1.126	Chloroform
Graph (3.6)	40.2	0.031	Hexane
46	40.2	0.051	Ethanol
(29) CH_3O	60.6	0.707	Hexane
(35) CH_3O	60.6	2.437	Chloroform
Graph (3.8) H	60.5	0.402	Hexane
(28) H	60.5	0.488	Chloroform
(36) O_2N	60.5	0.580	Hexane
(41) O_2N	60.5	0.384	Chloroform
(40) O_2N	60.5	0.153	Acetonitrile

Clearly the effect of solvent polarity on the reaction rate is negligible.

The rate coefficients for the rearrangement in chlorinated solvents, when R of (LXXXI) is CH_3O and CH_3, are thought to be anomalously high, the reaction rates at higher concentrations in these chlorinated solvents as determined by infrared (Table (3.10)) and NMR spectroscopy (Table (3.7)) and in benzene (by IR spectroscopy; Tables (3.4) and (3.10)) being comparable with the reaction rates of (LXXXI); R = CH_3O and CH_3 in the non-chlorinated solvents (Table (3.9)) and of (LXXXI); R = H and O_2N in chloroform (Table (3.9)) as determined by ultra-violet spectroscopy.

Table (3.10). First-order Rate Coefficients for the Rearrangement of  in a Variety of Solvents at Differing Concentrations

Solvent	Method of Monitoring	Concentration (moles litre^{-1})	Temperature °C.	10^2 x k (min.$^{-1}$)	Run
Benzene	IR at 1286cm.$^{-1}$	0.1982	59.0	0.230	(71)
Benzene	UV at 285 mμ	2.113×10^{-4}	59.0	0.294	(60)
Carbon tetrachloride	IR at 1288 cm.$^{-1}$	0.1982	60.7	0.717	(72)
Carbon tetrachloride	UV at 270 mμ	ca. 1.0×10^{-4}	60.5	1.895	(14)
Chloroform	IR at 1170 cm.$^{-1}$	0.1982	49.9	0.195	(75)
Chloroform	UV at 265 mμ	ca. 1.0×10^{-4}	49.9	1.126	(20)
Deuterochloroform	NMR at δ3.48	0.3998	65.4	0.304	(89)
Deuterochloroform	UV at 265 mμ	ca. 1.0×10^{-4}	60.5	0.939	(12)

Such anomalously high values for the reaction rate of (LXXXI); R = CH_3O and CH_3 in chlorinated solvents, as determined by ultra-violet spectroscopy, may well be due to the involvement of a photo-initiated radical chain process in the rearrangement of (LXXXI), photo-initiation occurring in the UV beam of the UV spectrophotometer. Such a photo-initiated radical chain process may well involve radicals from the photolytic decomposition of the chlorinated solvent.[118,167] A photo-initiated radical chain process is supported by (a) the decrease in the reaction rate of the rearrangement of (LXXI) in carbon tetrachloride when reaction was conducted under similar conditions outside the UV spectrophotometer in a flask covered in aluminium foil,

Outside UV Beam: $k_{60.7^\circ}$ = 1.407×10^{-2} $min.^{-1}$ (Run 62)

Within UV Beam: $k_{60.5^\circ}$ = 1.895×10^{-2} $min.^{-1}$ (Run 14)

(b) Extremely rapid reaction was observed when the rearrangement of (LXXI) was conducted in Analar grade chloroform which had been purified free from ethanol (~2% is added as a stabilizer).

Monitoring the reaction by UV spectroscopy at 265 mμ at 60.6° showed almost complete reaction to have occurred in less than two minutes. Such rapid reaction was quenched when a few drops of ethanol were added to the purified chloroform.

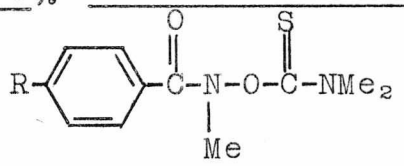
Thermolysis of a 10% wt./volume solution of (LXXI) in chloroform purified free from ethanol in a sealed tube at 120° for 20 minutes nevertheless resulted in the formation of the rearranged product (LXXII) and N-methyl p-toluamide in a proportion of 25% to 75%.

The rates of rearrangement of (LXXI) in chlorinated solvents measured at higher concentrations (Table (3.10)), however, apparently refer to a unimolecular process not involving any radical chain process, since the rates are comparable with reaction in non-chlorinated solvents.

(c) Substituent Effects

The variation with substitution in the benzene ring of the rates of rearrangement of various (LXXXI) to the corresponding (LXXXII) is given in Table (3.11).

Table (3.11). First-order Rate Coefficients for the Rearrangement of



R	Run	10^2 x k($min.^{-1}$)	Temperature °C.	Solvent
CH_3O	(29)	0.707	60.5	Hexane
CH_3	(1)	0.510	60.5	Hexane
H	Graph (3.8)	0.402	60.5	Hexane
O_2N	(36)	0.580	60.5	Hexane
CH_3O	(35)	2.437	60.6	Chloroform
CH_3	(19)	1.407	60.5	Chloroform
H	(28)	0.488	60.5	Chloroform
O_2N	(41)	0.384	60.5	Chloroform
CH_3	(16)	0.292	60.5	Acetonitrile
O_2N	(40)	0.153	60.5	Acetonitrile

The rate of rearrangement is therefore markedly insensitive to substitution in the benzene ring and indeed occurs at a

comparable rate with the aliphatic N-pivalyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine ($0.978 \times 10^{-2} min^{-1}$ at 60.7° in hexane ; Run 44).

Further information on the rearrangement may be derived from consideration of the decolourisation of free radical traps, and also from examination of the Arrhenius parameters for the reaction.

(d) The Decolourisation of DPPH

α,α-Diphenyl-β-picrylhydrazyl radical (DPPH) in boiling carbon tetrachloride solution was rapidly decolourised by the N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines (LXXXI), showing the presence of free radical species. The following compounds did not appreciably decolourise DPPH in boiling carbon tetrachloride indicating that these compounds were not a ready source of free radicals:-

(1) the N-aroyl-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamines, (LXXXII)

(2) N-aroyl-O-aroyl-N-methylhydroxylamines, (LXIV)

(3) Bis-(dimethylcarbamoyl) disulphide.

(4) Carbon oxysulphide.

Kinetics and Extent of DPPH Decolourisation

αα-Diphenyl-β-picrylhydrazyl (DPPH) can be used as a radical scavenger to measure the rate of generation of radicals in solution.[119]

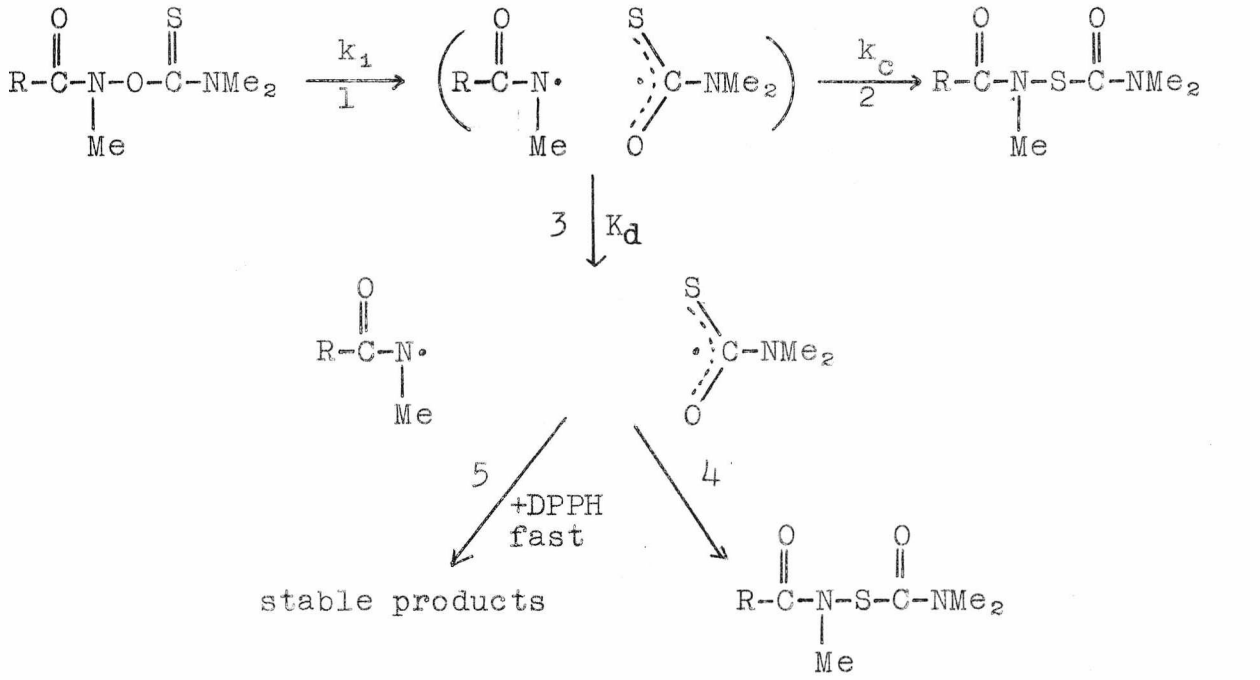
The kinetics and extent of DPPH decolourisation in the presence of N-(p-toluoyl)-O-(N'N'-dimethylthiocarbamoyl)-N-methylhydroxylamine were determined in benzene which had been purged of dissolved air (traces of oxygen interfere with the clean functioning of DPPH[120]).

Using equimolar quantities of N-(p-toluoyl)-O-(N',N'-dimethyl-

thiocarbamoyl)-N-methylhydroxylamine and DPPH, 100% of the DPPH was decolourised in the process of rearrangement of (LXXI) at 59.2° in benzene. When the initial concentration of DPPH was twice the initial concentration of (LXXI), 64.0% of the DPPH was decolourised. The decolourisation of DPPH under these conditions was monitored at 510 mμ in the visible spectrum. The percentage decolourisation of DPPH with time is given in Table (3.12). The decolourisation of DPPH alone under similar conditions is negligible, approximately 4% decolourisation occurring in 5 hours at 66° in carbon tetrachloride and benzene.

The infinity solution from this rearrangement kinetic study contained no ready source of free radicals as evidenced by its inability to decolourise DPPH further.

The decomposition of the N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines (LXXXI) may be represented by Scheme (3.1). Brackets are used to indicate pairs of radicals which have not been separated by diffusion, i.e. are within a solvent cage.



Scheme (3.1)

k_1 = the rate coefficient for decomposition of (LXXXI)

k_c = the rate coefficient for collapse of the radical pair within the solvent cage to the product (LXXXII)

k_d = the rate coefficient for escape of the radical pair from the solvent cage

It has always been found that DPPH completely inhibits vinyl polymerizations and disappears at a rate which is zero order with respect to its concentration,[120] so reaction (5) can be expected to occur with very high efficiency.

Assuming that reaction (4) becomes unimportant in the presence of DPPH then the rate of decolourisation of DPPH may be written as,

$$-\frac{d[DPPH]}{dt} = 2k_d\left[\left(R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}\cdot \quad \cdot\overset{\overset{S}{\|}}{C}-NMe_2\right)\right] \qquad \text{equation (3.2)}$$

i.e. DPPH only reacts with those radicals which have escaped from the solvent cage.

Applying the steady-state condition to Scheme (3.1) leads to,

$$k_1\left[R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2\right] = (k_c + k_d)\left[\left(R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}\cdot \quad \cdot\overset{\overset{S}{\|}}{C}-NMe_2\right)\right]$$

$$\text{so}\left[\left(R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}\cdot \quad \cdot\overset{\overset{S}{\|}}{C}-NMe_2\right)\right] = \frac{k_1}{(k_c + k_d)}\left[R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2\right] \qquad \text{equation (3.3)}$$

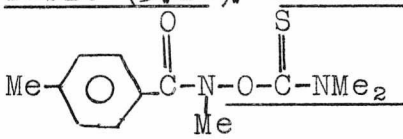
Substituting equation (3.3) in equation (3.2),

$$-\frac{d[DPPH]}{dt} = \frac{2k_dk_1}{(k_c + k_d)}\left[R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2\right] \qquad \text{equation (3.4)}^*$$

*An analogous kinetic expression has been derived for the decolourisation of DPPH by azo-bis-isobutyronitrile.[120]

Thus, a graph of $-\frac{d[DPPH]}{dt}$ versus $[R-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2]$ should give a straight line of slope $\frac{2k_dk_1}{(k_c + k_d)}$.

As k_1 is known, the ratio of k_d to k_c can be calculated.

Table (3.12). The decolourisation of DPPH at 510 mμ by  in benzene at 59.2°.(Run 97)

$[DPPH]_{t=o} \approx [Me-C_6H_4-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2]_{t=o}$

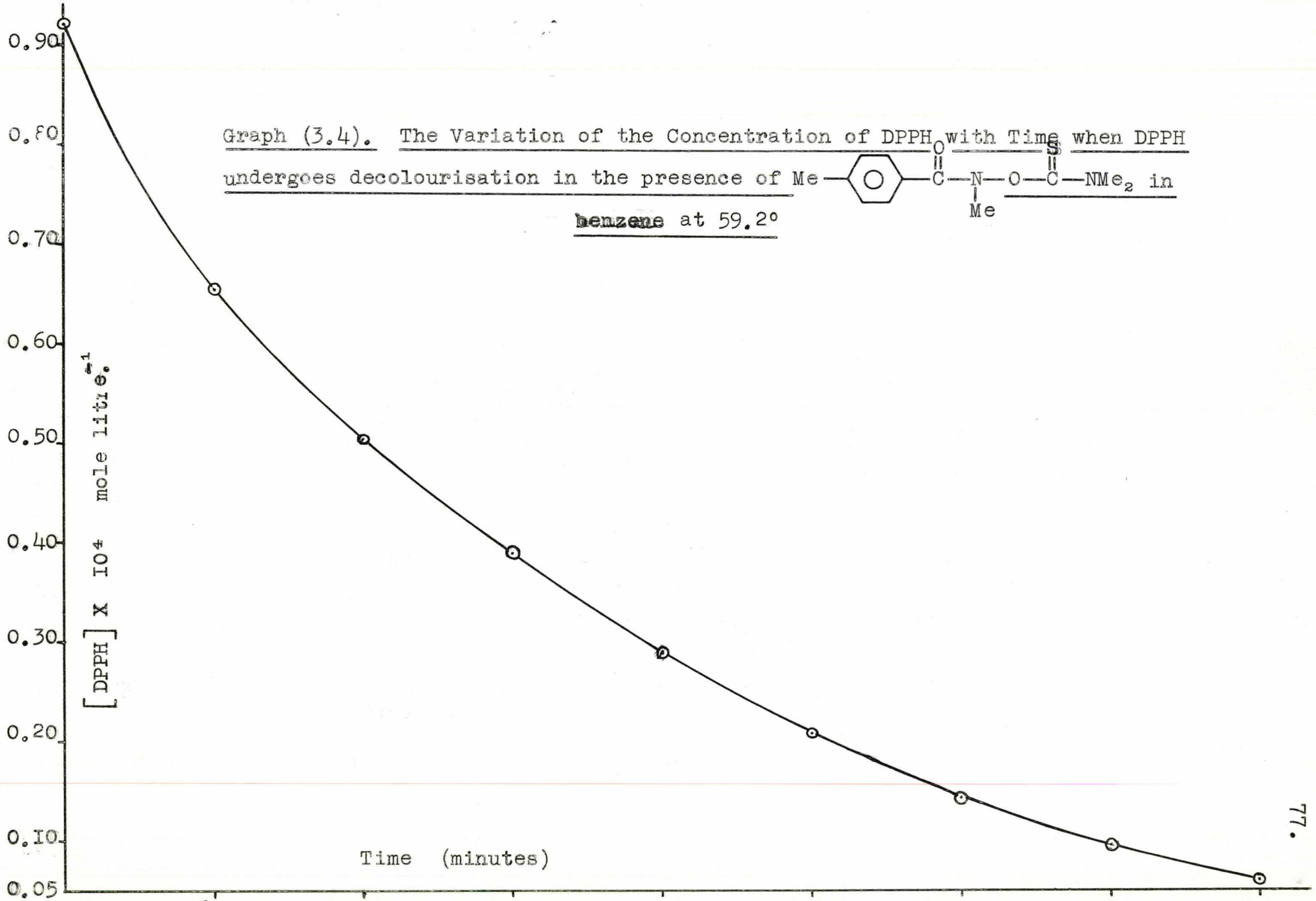
$[DPPH]_{t=o} = 0.91954 \times 10^{-4}$ moles litre^{-1}

$[Me-C_6H_4-\overset{\overset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-O-\overset{\overset{S}{\|}}{C}-NMe_2]_{t=o} = 0.95125 \times 10^{-4}$ moles litre^{-1}

Time (minutes)	Concentration of DPPH x 10^4 moles litre^{-1}	Percentage loss of DPPH
0	0.9195	0.00
60	0.6531	28.97
120	0.5035	45.24
180	0.3886	57.74
240	0.2889	68.58
300	0.2068	77.51
360	0.1423	84.52
420	0.0949	89.68
480	0.0596	93.52

$\frac{-d[DPPH]}{dt}$ represents the slopes of the tangents to the curve obtained from a plot of [DPPH] versus time, Graph (3.4).

Graph (3.4). The Variation of the Concentration of DPPH with Time when DPPH undergoes decolourisation in the presence of Me-C6H4-C(=O)-N(Me)-O-C(=S)-NMe2 in benzene at 59.2°



Such slopes of the tangents approximate to the slopes of the chords drawn between points 10 minutes either side of the points of contact of the tangents (Table (3.13)).

The rate equation for the decomposition of (LXXI) is,

$$-\frac{d[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]}{dt} = k_1[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2] \quad \text{equation (3.5)}$$

Integrating,

$$\ln\left[\frac{[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=o}}{[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=t}}\right] = k_1 t$$

$$\therefore \log_{10}[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=t} = \log_{10}[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=o} - \frac{k_1 t}{2.303} \quad \text{equation (3.6)}$$

Now $[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=o} = 0.95125 \times 10^{-4}$ moles litre^{-1}

and k_1 has been measured to be 0.294×10^{-2} min^{-1}, so equation (3.6) becomes,

$$\log_{10}[\text{Me-C}_6\text{H}_4\text{-C(=O)-N(Me)-O-C(=S)-NMe}_2]_{t=t} = \bar{5}.9783 - 0.001277 \times t \quad \text{equation (3.7)}$$

Application of equation (3.7) enables the concentrations of

Me-C$_6$H$_4$-C(=O)-N(Me)-O-C(=S)-NMe$_2$ to be determined during the reaction, Table (3.13).

Table (3.13). The Variation of -d[DPPH]/dt and [Me-C6H4-C(=O)-N(Me)-O-C(=S)-NMe2] with Time during the Decolourisation of DPPH by Me-C6H4-C(=O)-N(Me)-O-C(=S)-NMe2 in Benzene at 59.2°. (Run 97)

Time (minutes)	$\frac{-d[DPPH]}{dt} \times 10^{7}$ (mole litre^{-1} min.$^{-1}$)	Concentration of Me-C6H4-C(=O)-N(Me)-O-C(=S)-NMe2 (mole litre^{-1})
0	-	0.9513×10^{-4}
60	3.132	0.7975×10^{-4}
120	2.096	0.6685×10^{-4}
180	1.789	0.5603×10^{-4}
240	1.490	0.4697×10^{-4}
300	1.213	0.3938×10^{-4}
360	0.897	0.3301×10^{-4}
420	0.642	0.2767×10^{-4}
480	0.528	0.2319×10^{-4}

A graph of $\frac{-d[DPPH]}{dt}$ versus [Me-C6H4-C(=O)-N(Me)-O-C(=S)-NMe2] gives a straight line of slope = 0.379×10^{-2} min.$^{-1}$. (Graph (3.5)).

$$\therefore \quad 0.379 \times 10^{-2} = \frac{2k_d k_1}{(k_c + k_d)}$$

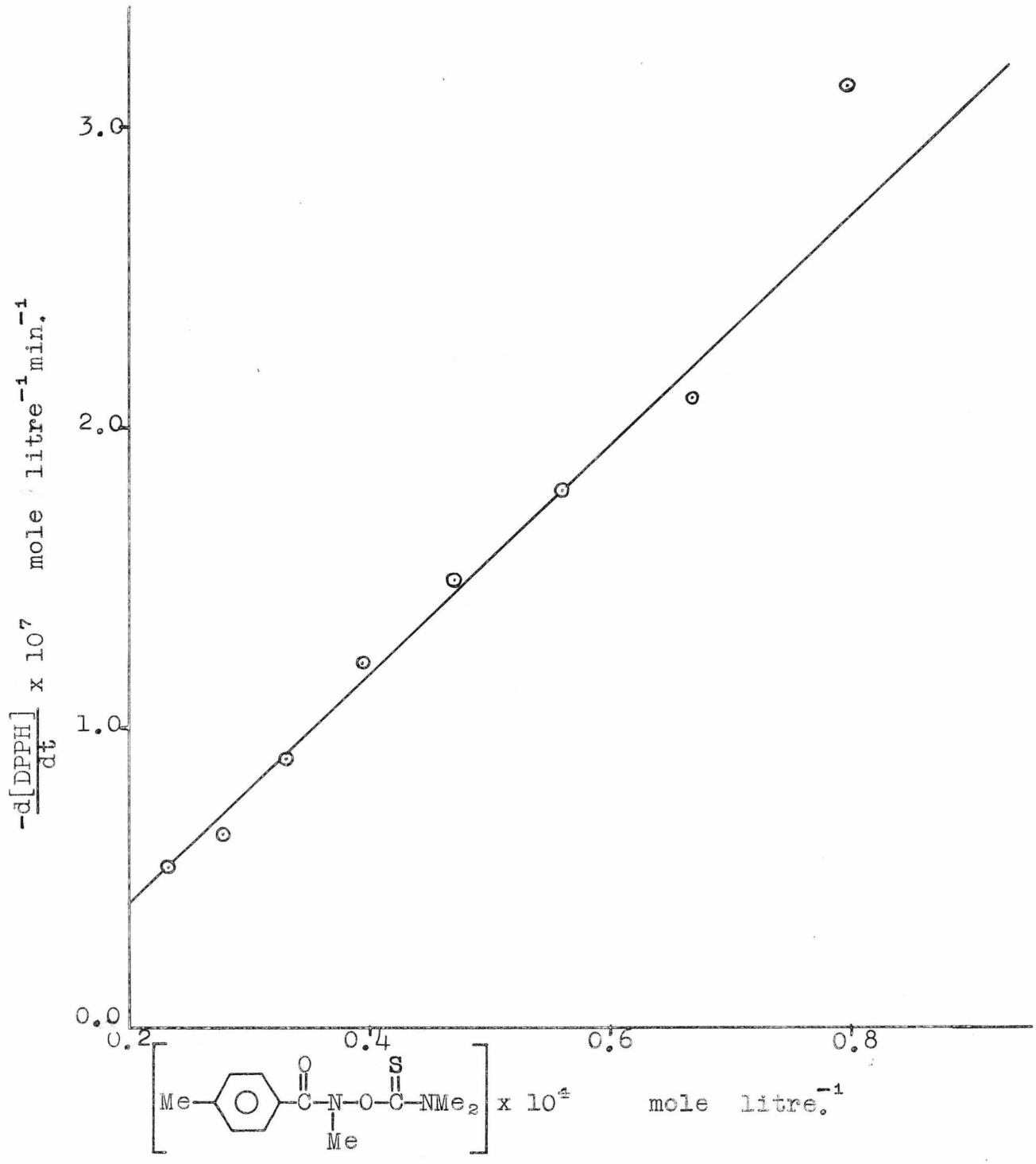
$$k_1 = 0.294 \times 10^{-2} \text{min.}^{-1}$$

$$0.379 = \frac{0.588 \times k_d}{(k_c + k_d)}$$

$$\underline{\underline{k_d = 1.81 \times k_c}}$$

In this run 100% decolourisation of the DPPH occurred showing that $k_d/k_c \gg 1$.

Graph (3.5). Plot of $-\frac{d[DPPH]}{dt}$ versus $\left[Me\text{-}C_6H_4\text{-}C(=O)\text{-}N(Me)\text{-}O\text{-}C(=S)\text{-}NMe_2\right]$ for the decolourisation of DPPH in the presence of $Me\text{-}C_6H_4\text{-}C(=O)\text{-}N(Me)\text{-}O\text{-}C(=S)\text{-}NMe_2$ in benzene at 59.2°



PERCENTAGE DECOLOURISATION OF DPPH (at 510 mμ)

When (LXXI) is heated in the presence of twice its own concentration of DPPH in benzene at 59.2°, 64.0% of the DPPH is decolourised so as stage (3) of Scheme (3.1) involves the escape from the solvent cage of two radicals then 64.0% decolourisation of DPPH corresponds to 64.0% of (LXXI) having decomposed to N-methyl p-toluamide and the remaining 36.0% having rearranged to the hydrosulfamine compound (LXXII). Such a product ratio entails,

$$\frac{k_d}{k_c} = \frac{64.0}{36.0} = 1.78$$

$$\underline{\underline{k_d = 1.78 \times k_c}}$$

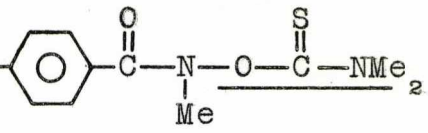
PRODUCT ANALYSIS BY NMR

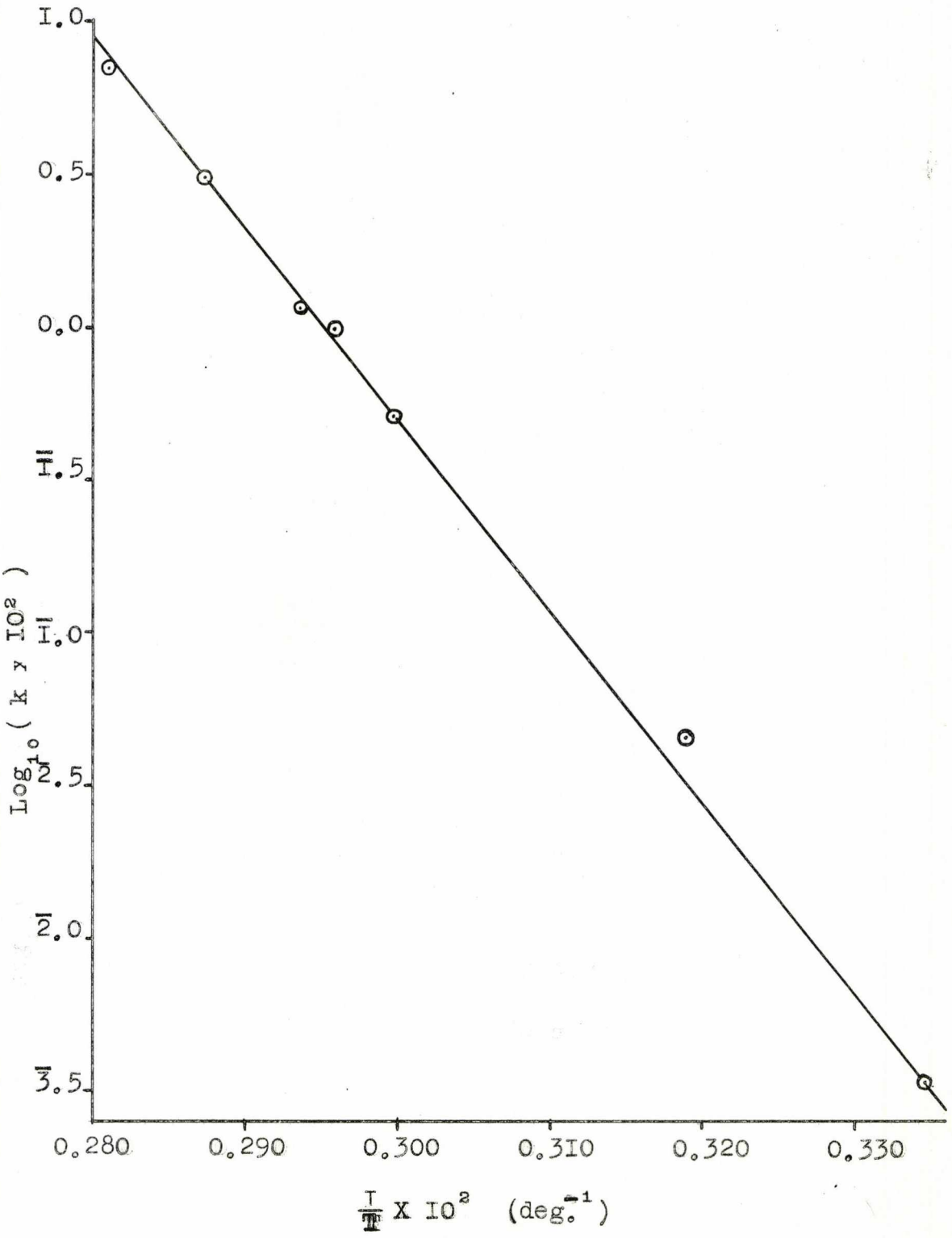
Integration of the N-methyl signals of the hydrosulfamine compound (LXXII) and N-methyl p-toluamide formed when a 10% wt./volume solution of (LXXI) in deuterobenzene was heated in a sealed tube for 48 hours at 60° showed that 59.1% conversion to N-methyl p-toluamide and 40.9% conversion to the rearranged compound (LXXII) had occurred.

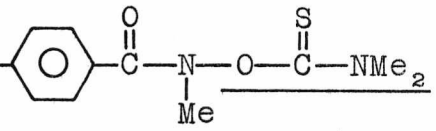
Thus $$\frac{k_d}{k_c} = \frac{59.1}{40.9} = 1.44$$

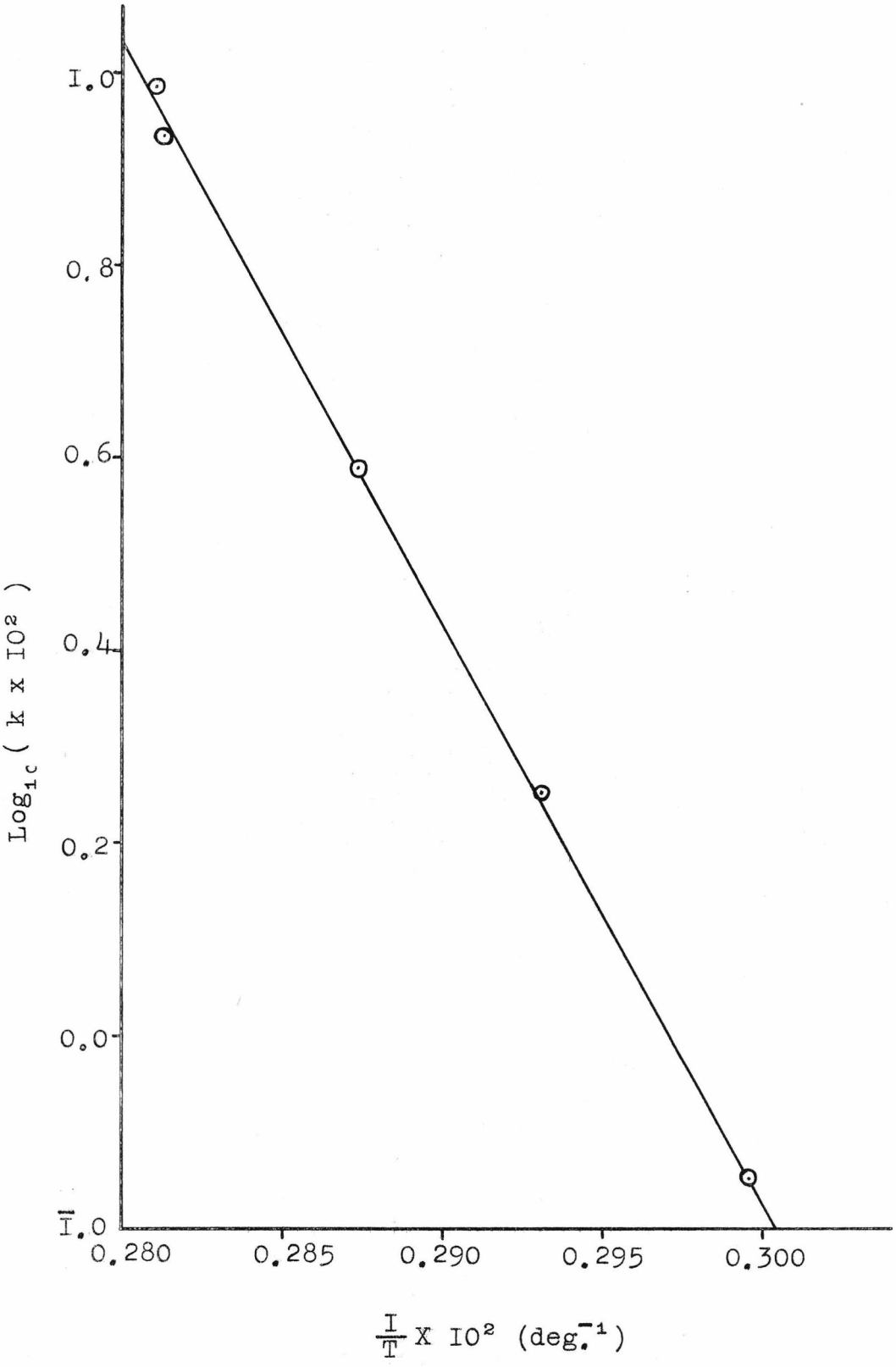
$$\underline{\underline{k_d = 1.44 \times k_c}}$$

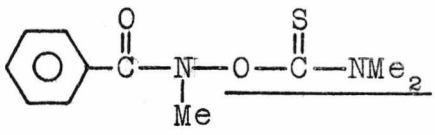
The approximate correspondence of the values obtained for k_{d/k_c} whether by a kinetic method, by percentage decolourisation of DPPH or by NMR product analysis strongly supports Scheme (3.1) as the mode of breakdown of the N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines (LXXXI).

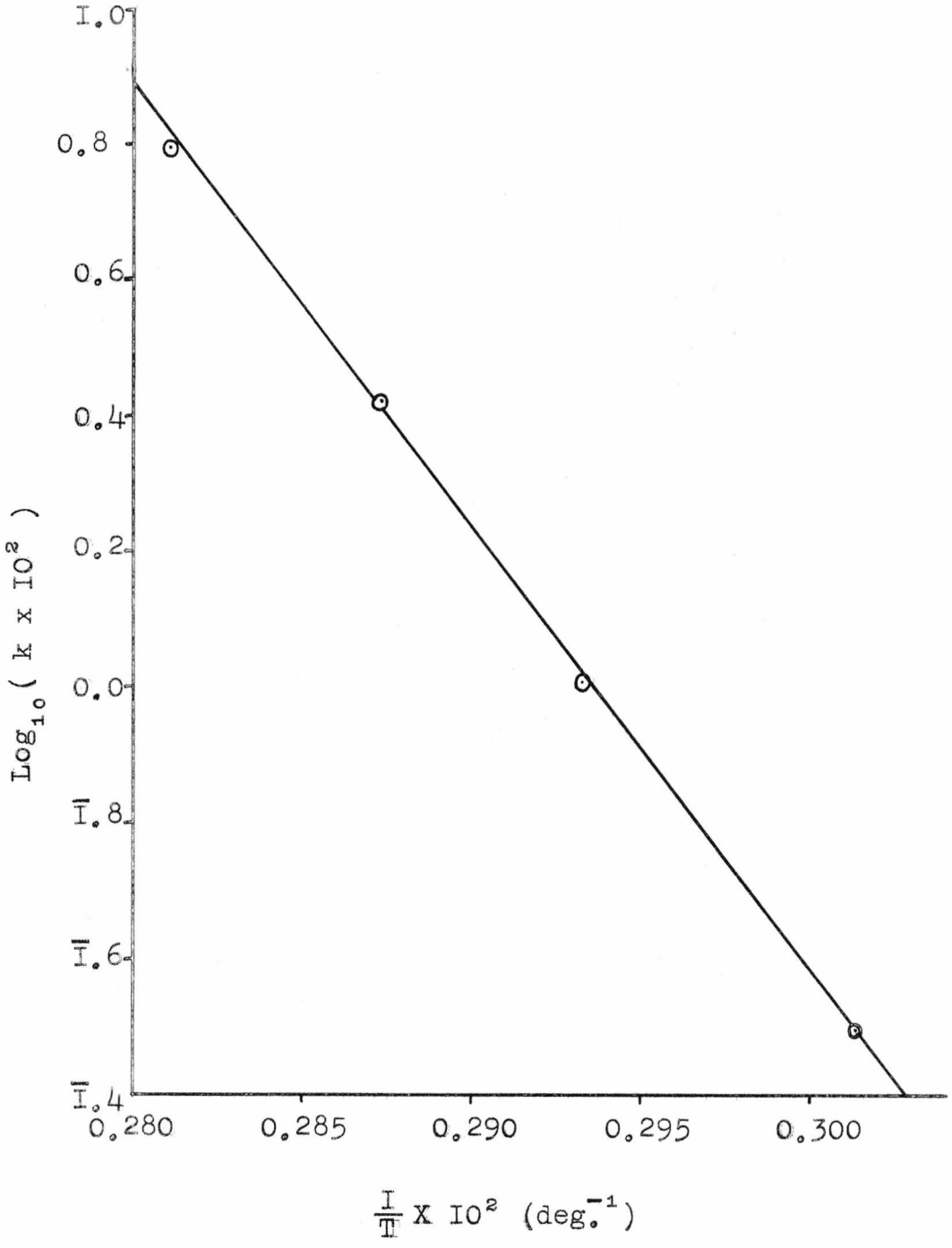
Graph (3.6). Arrhenius Plot for  in Hexane.

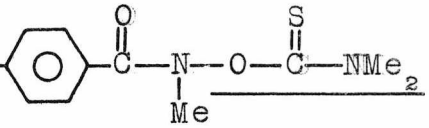


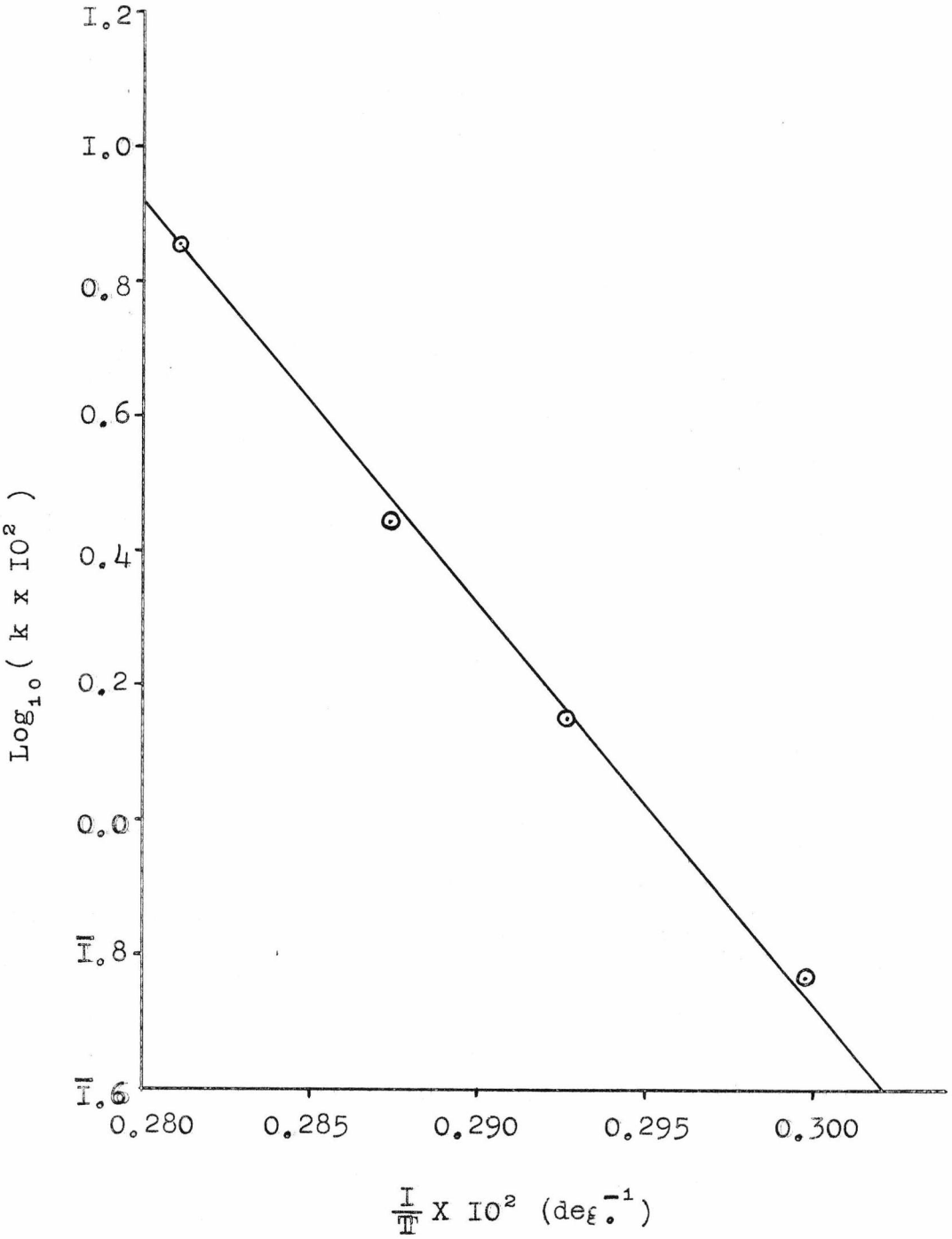
Graph (3.7). Arrhenius Plot for  in Hexane.



Graph (3.8). Arrhenius Plot for  in Hexane.



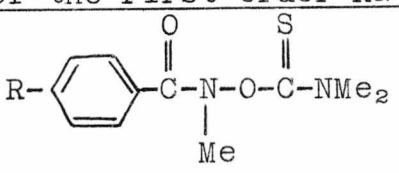
Graph (3.9). Arrhenius Plot for  in Hexane.



(e) The Activation Parameters

The effect of temperature on the rate of rearrangement of the four N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines in hexane was studied. Hexane was selected as solvent by reason of its weakly-solvating properties. Good linear Arrhenius plots were obtained, Graphs (3.6 - 3.9). Results are collected in Table (3.14), together with the corresponding enthalpies and entropies of activation.

Table (3.14). Temperature Dependence of the First-order Rate Coefficients for the Rearrangement of



in Hexane

R	Run	Temperature °C.	10^2 x k(min^{-1})
	(5)	82.6	6.925
	(4)	74.8	3.102
	(3)	67.4	1.150
	(2)	64.8	0.975
CH_3	(1)	60.5	0.510
	(6)	40.3	0.045
	(7)	25.6	0.3315×10^{-2} (a)
		$\Delta H^{\ddagger}$ 27.2 ± 0.6 kcal.$mole^{-1}$	
		$\Delta S^{\ddagger}$ 4.3 ± 1.9 e.u.	
	(33)	82.6	9.640
	(32)	82.2	8.573
	(31)	74.8	3.872
	(30)	68.0	1.782
CH_3C	(24)	60.6	0.707
		$\Delta H^{\ddagger}$ 26.9 ± 0.4 kcal.$mole^{-1}$	
		$\Delta S^{\ddagger}$ 3.8 ± 1.1 e.u.	

Table (3.14) continued

	(25)	82.6	6.255
	(24)	74.8	2.635
	(23)	67.8	1.021
H	(22)	58.6	0.312
		$\Delta H^{\ddagger}$	28.8 ± 0.5 kcal.mole^{-1}
		$\Delta S^{\ddagger}$	8.6 ± 1.6 e.u.
	(39)	82.6	7.148
	(38)	74.8	2.764
	(37)	68.5	1.410
O_2N	(36)	60.4	0.580
		$\Delta H^{\ddagger}$	25.8 ± 0.9 kcal.mole^{-1}
		$\Delta S^{\ddagger}$	0.3 ± 2.6 e.u.

(a) Determined by the method of initial rates.[121]

(iii) Summary of the Kinetic Results

The rearrangement of (LXXXI) to (LXXXII) thus displays the following features:-

(1) The absence of an appreciable solvent effect (except in chlorinated solvents).

(2) The absence of a significant substituent effect.

(3) A significant amount of DPPH decolourisation.

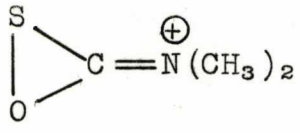
(4) A small positive entropy of activation and an enthalpy of activation which is less than the N-O bond energy.

The material (LXXXI) bears a close structural resemblance to each of three known compounds which undergo reactions involving charge separation in the transition state, which are believed to follow discretely different pathways. These will now be examined in turn in an attempt to deduce the pathway(s)

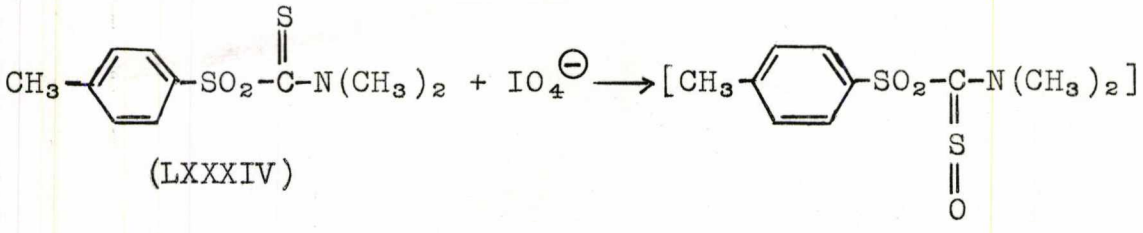
followed in the present study.

(1) Via the N,N-dimethylthiocarbamate cation.

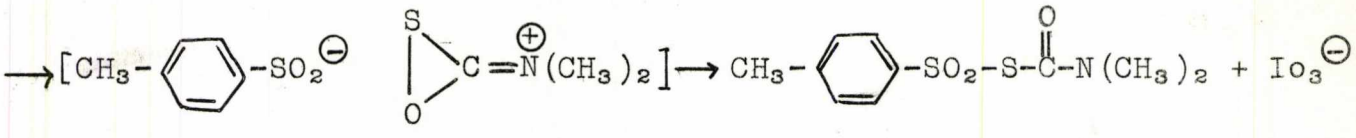
The N,N -dimethylthiocarbamate cation (LXXXIII) has been invoked to explain the oxidation/rearrangement of C-sulfonylthioformamides (LXXXIV) to S-sulfonylthiourethanes (LXXXV) outlined in Scheme (3.2).[122]



(LXXXIII)



(LXXXIV)



(LXXXV)

Scheme (3.2)

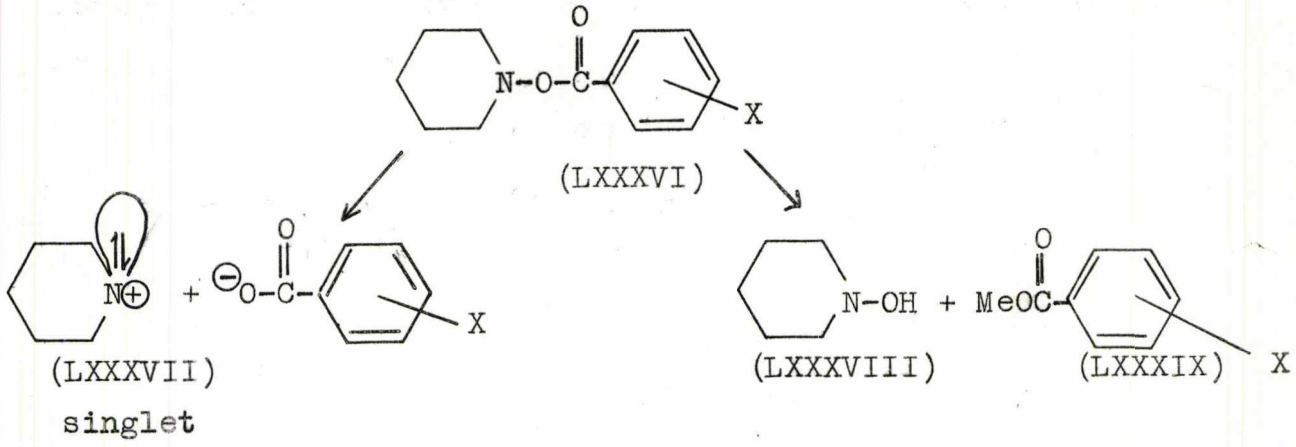
An analogous rearrangement has been reported to occur in the oxidation of thiuram sulphides.[123]

(2) Nitrenium ion formation.

Gassman and Hartman[124] have shown that two competing reactions occur during the methanolysis of piperidin-1-yl benzoates (LXXXVI). One reaction, a transesterification, produced N-hydroxypiperidine (LXXXVIII) and the appropriate methyl benzoate (LXXXIX), whilst the other gave a nitrenium ion (LXXXVII) and a benzoate anion, Scheme (3.3).

Such a heterolytic cleavage of the N-O bond in (LXXXVI) was

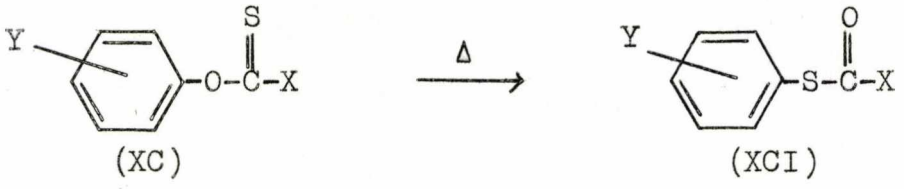
strongly supported by a ρ- value of + 0.68 for the methanolysis of (LXXXVI) to form (LXXXVIII) and (LXXXIX).

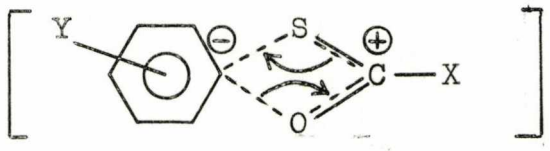


Scheme (3.3)

(3) Nucleophilic attack.

Various investigators[125-128] have regarded the thermal rearrangement of aryl thiono-esters (XC) to the corresponding aryl thiol-esters (XCI) as a nucleophilic displacement of the oxygen on the aromatic ring by sulphur, involving a four-membered cyclic intermediate and transition state (XCII).





(XCII)

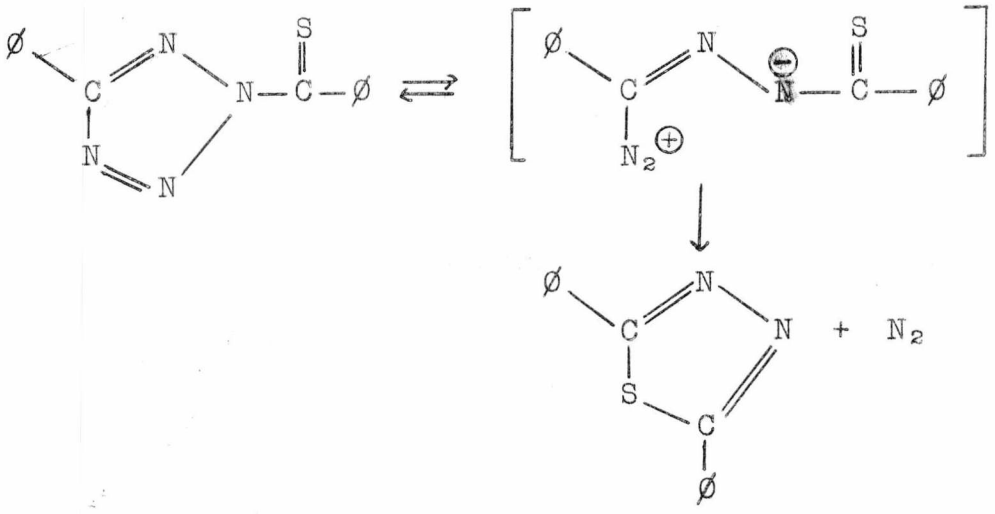
Miyazaki[126,127] supported this mechanism in his studies on the thermal rearrangement of thionocarbamates ((XC); X = NMe_2) to thiolcarbamates ((XCI); X = NMe_2). The reaction was shown

to be intramolecular, to exhibit first order kinetics and have a ρ value of 1.83 in diphenyl ether at 200.5°.

The negative entropies of activation for the rearrangement of aryl thionobenzoates ((XC); X = Ph) to aryl thiolbenzoates[128] ((XCI); X = Ph) and facilitation of the rearrangement by substitution with an electron-withdrawing group in the migrating aromatic ring further supports such a cyclic mechanism.[128]

That these three analogues merit consideration, despite the observed lack of solvent effect on the reaction (LXXXI)⟶(LXXXII), is readily seen from a consideration of some dipolar reactions.

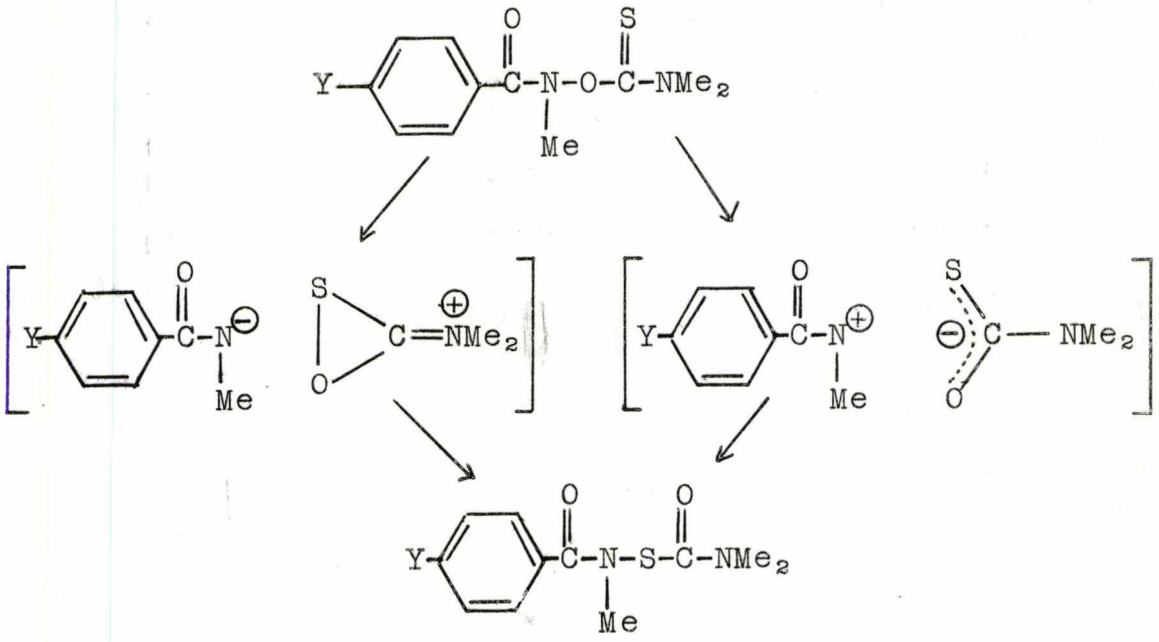
Huisgen[129] has studied the reaction shown in Scheme (3.4):



Scheme (3.4)

and considers the dipolar intermediate to be well established. An examination[130] of the rates of reaction in various solvents however shows $k_{acetonitrile} \approx k_{hexane}$. Although it is not clear if this similarity to the solvent effect of the present study is a result of an inaccurate assignment of mechanism in the reactions of tetrazoles, the pathways (1)⟶(3) clearly cannot be disregarded on the strengths of a kinetic solvent effect alone.

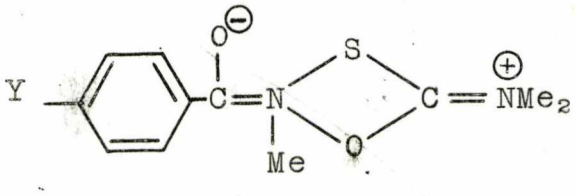
It is more difficult, however, to accommodate the virtually complete insensitivity observed of the rate on the nature of the substituent Y in either of the pathways (below in Scheme (3.5)) analogous to routes (1) or (2) above.



Scheme (3.5)

Since these systems might be expected to be excellent models for the Hammett sigma function, a ρ-value of only +0.03 (Graph (3.10)) can only be reasonably interpreted in terms of a transition state involving negligible charge separation.

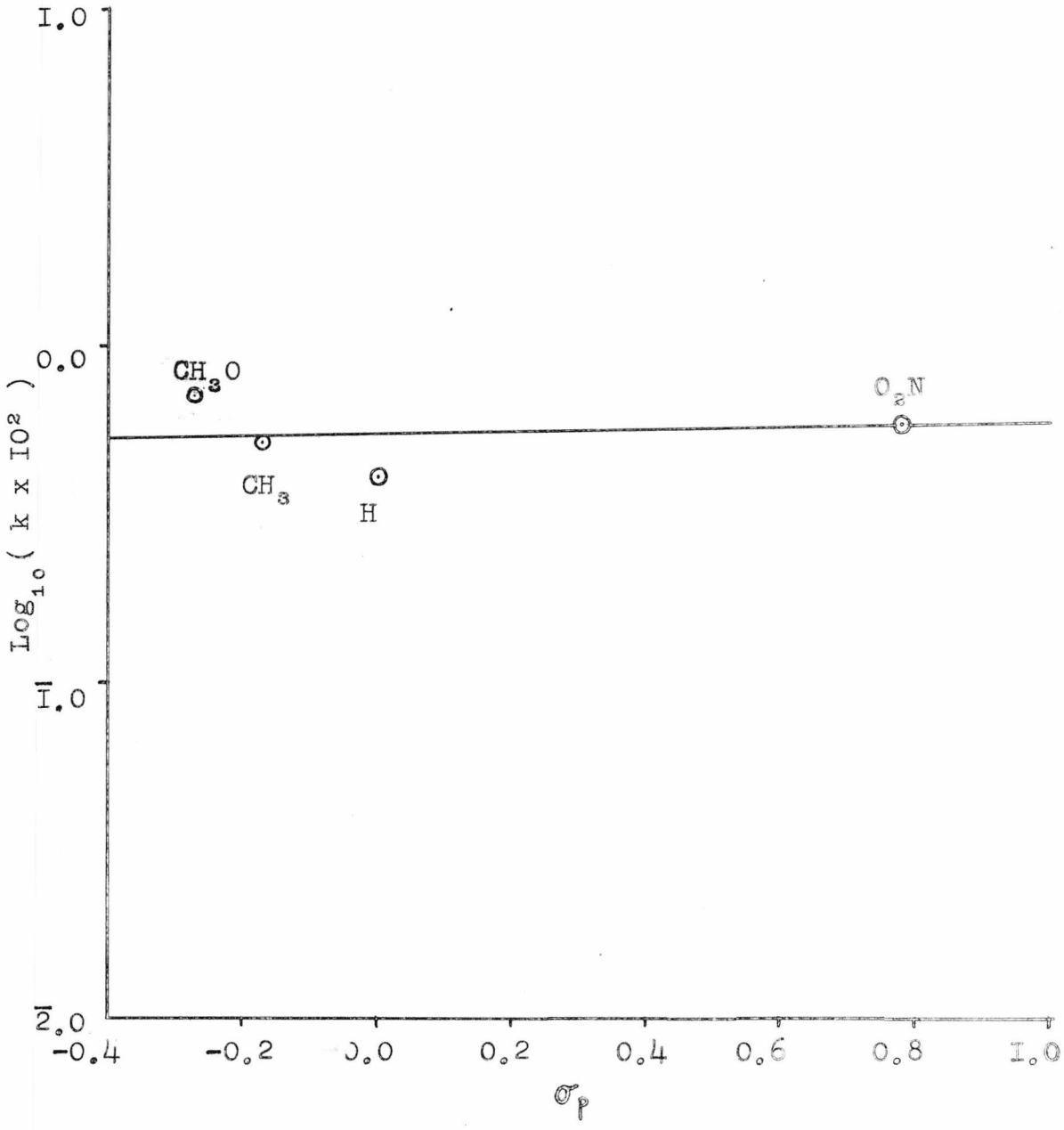
The third possibility, (3), which would involve nucleophilic attack on amide nitrogen,



can likewise be discounted on the grounds of the small observed ρ- value and the positive value of the reaction entropy.

It is reasonable, therefore, to consider only transition states involving negligible charge separation, in view of the

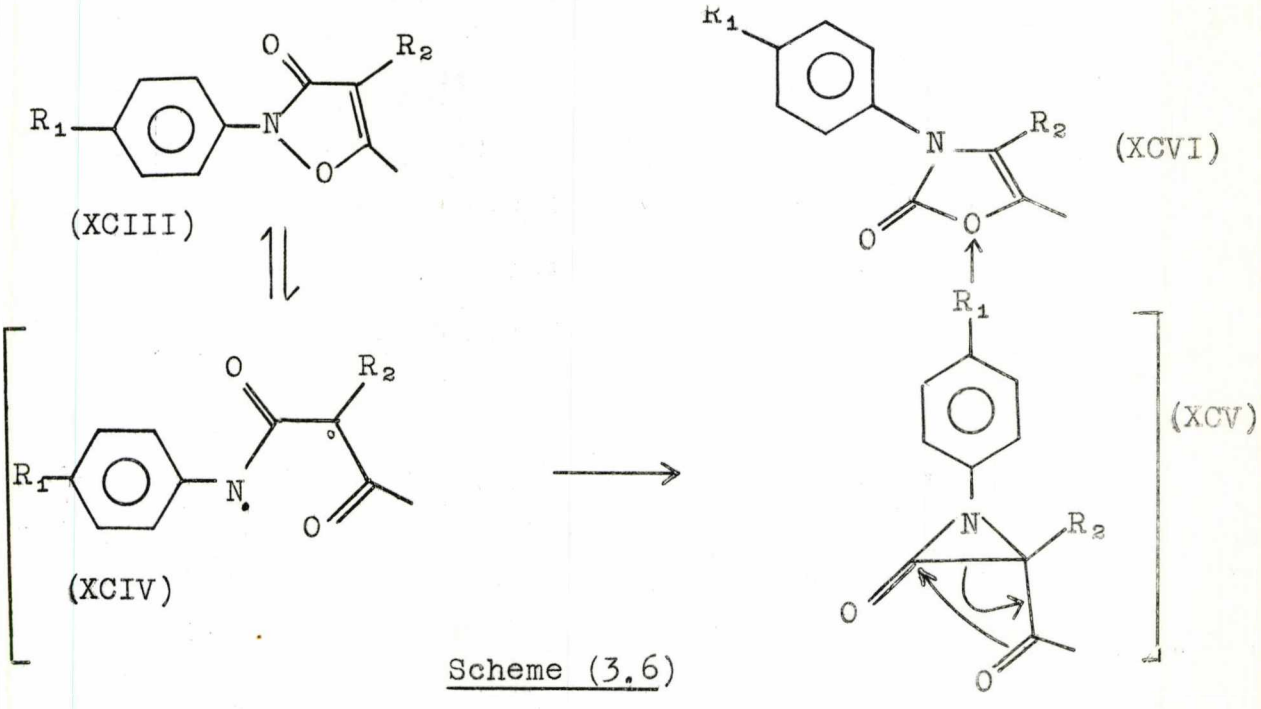
Graph (3.10). Hammett Plot for the Rate of Rearrangement of R—C(=O)—N(Me)—O—C(=S)—NMe$_2$ at 60.5° in Hexane.



effect of both solvent and substitution patterns, on the rate of rearrangement of (LXXXI) ⟶ (LXXXII).

This leads to a consideration of the two outstanding possibilities for reaction, via (a) free radical and (b) concerted pathways.

A comparable analogue to the thiono-thiolo rearrangement considered here is found in the quantitative rearrangement of N-aryl-isoxazoline-3-ones (XCIII) to N-aryl-oxazoline-2-ones (XCVI) at ~ 150°.[131] A homolytic cleavage of the N-O bond and recoupling of the biradical (XCIV) to the α-lactam (XCV), a [1,3]-radical shift, was proposed, Scheme (3.6).



Scheme (3.6)

Such a scheme, proposing homolytic cleavage of the N-O bond as the rate-determining step, was supported by the insensitivity of the rate of rearrangement, the enthalpy of activation and the entropy of activation towards polar and steric alterations (R_1 = H, R_2 = H; R_1 = F, R_2 = H; R_1 = H, R_2 = $(CH_3)_2CH$).

A discussion of the similarity of the values of $\Delta H^{\ddagger}$ and

$\Delta S^{\ddagger}$ for the rearrangement of (XCIII) ⟶ (XCVI) in comparison to the values for the rearrangement of (LXXXI) ⟶ (LXXXII) is reserved until later (p. 110).

The decolourisation of DPPH (reported above) suggests that free radicals are present during the thiono-thiolo rearrangement, (LXXXI) ⟶ (LXXXII), but this alone does not in any way show that radicals lie on the path to products. CIDNP effects, however, if observed, necessitate paramagnetic intermediates.

(iv) Chemically Induced Dynamic Nuclear Polarisation Effects.

(a) The Rearrangement (LXXXI) ⟶ (LXXXII). CIDNP Effects.

Solutions of (LXXI) in deuterochloroform were placed in the preheated (120°) probe of a 14092 gauss NMR spectrometer. Pronounced CIDNP effects in the NMR spectra of both the rearrangement product, N-(p-toluoyl)-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine (LXXII) and N-methyl p-toluamide (the latter CIDNP effects are discussed later) were observed. The N-methyl resonance of (LXXII) at δ 3.30 appears in absorption, enhanced by a factor of ~15, (V_{expt} = 15),[132] being at its maximum 1 - 1½ minutes after insertion of the sample into the preheated NMR probe and decaying rapidly over 5 minutes (Diagram(3.3)).

Similar results (Table (3.15)) were obtained for the other N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines, (LXXXI). These results indicate, without equivocation, the intervention of radical species in the formation of both the rearranged product (LXXXII) and the substituted N-methyl benzamide.

A number of further important conclusions can be drawn from consideration of these effects.

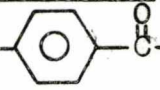
Diagram (3.3). CIDNP Effects in the Products from the Thermolysis of Me-  -C(=O)-N(Me)-O-C(=S)-NMe_2 in Deuterochloroform at I20°.

Diagram (3.3).contd.

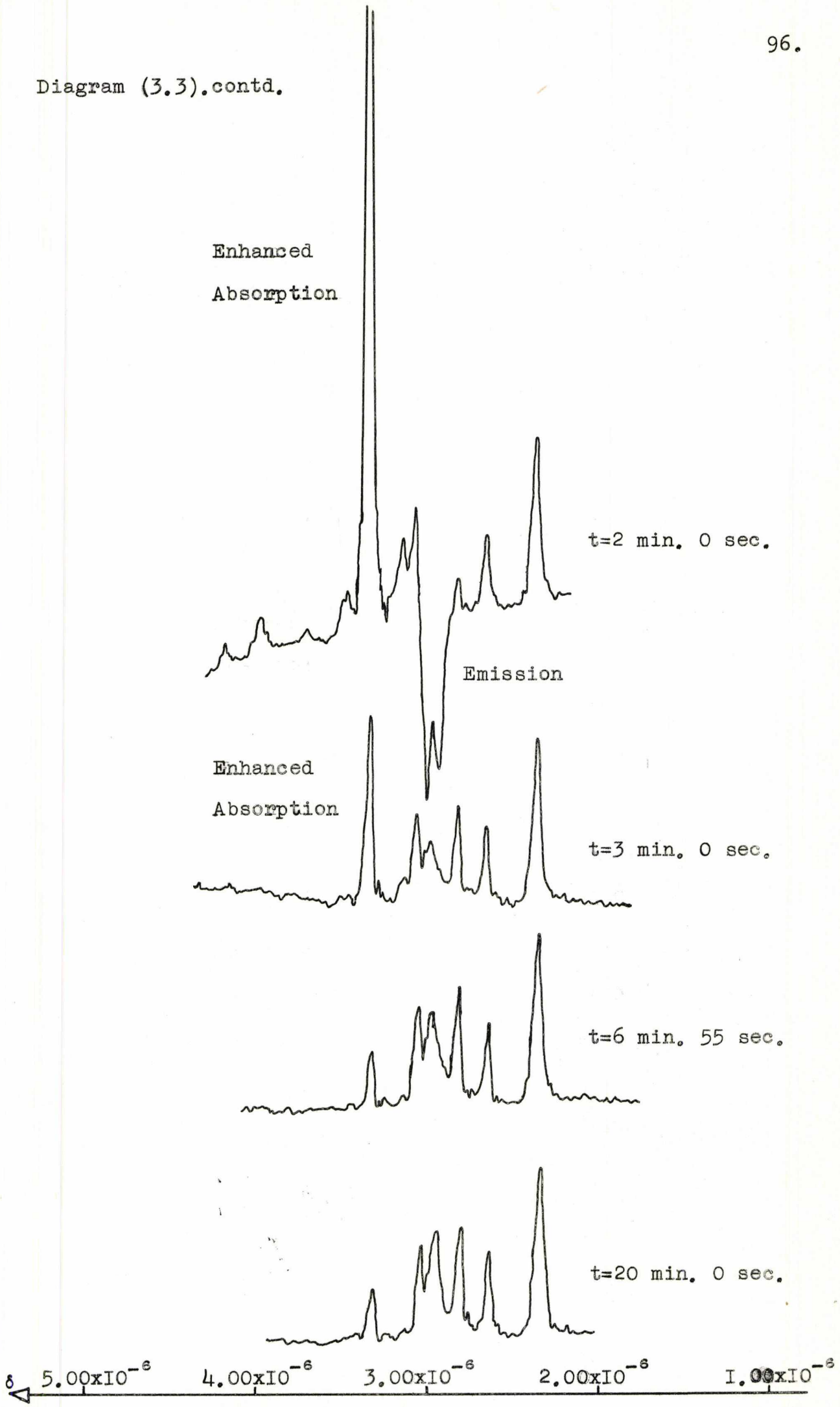
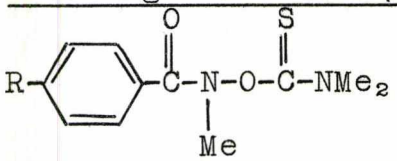


Table (3.15). Spin Polarised NMR Resonances of the Rearranged Product (LXXXII) from the Thermolysis of

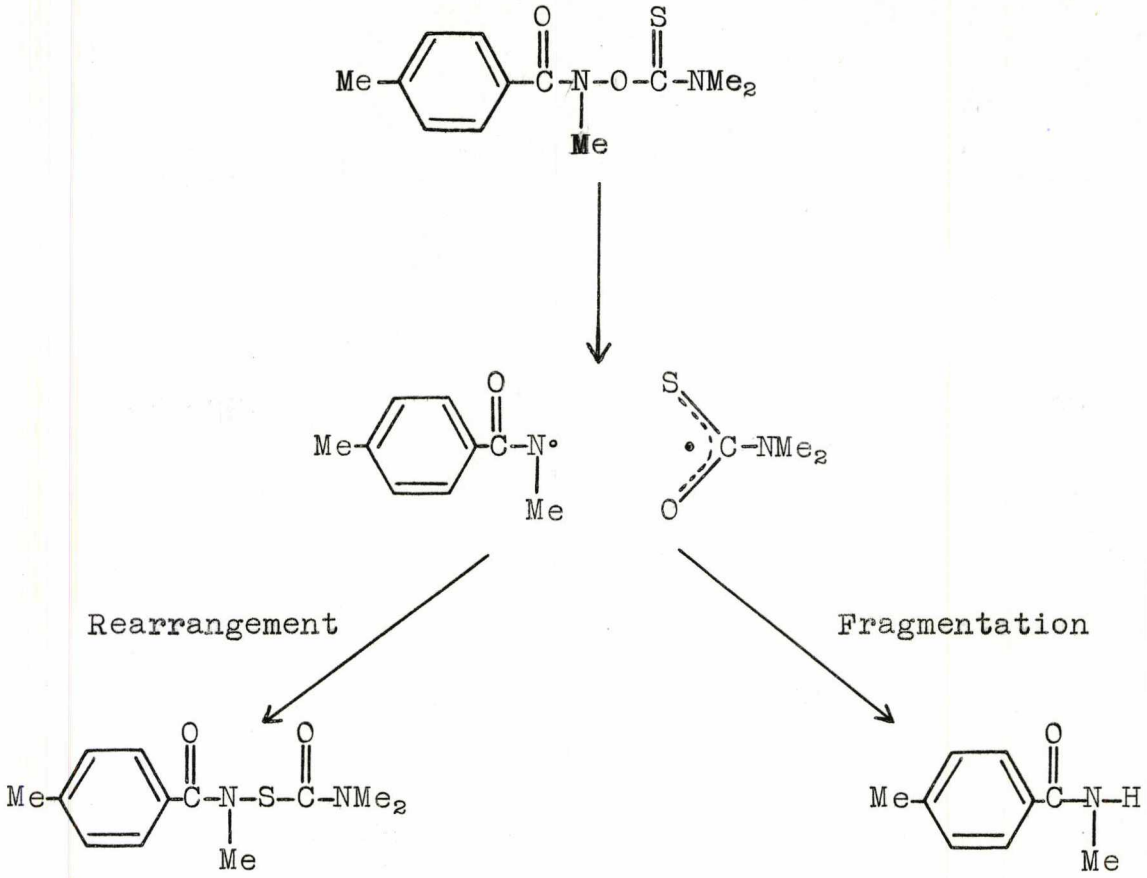


in Deuterochloroform at 120°.

R	N-Me Resonance of (LXXXII) δ	Sign of Signal	$V_{expt.}$ [132]
H	3.36	Enhanced absorption	5
CH_3O	3.35	Enhanced absorption	19
O_2N	3.35	Enhanced absorption	16

(b) Mechanistic Implications of the CIDNP Effects.

The polarisations observed in the present study are net effect polarisations so employment of Kaptein's rule, equation (1.15), enables the signs of the polarisations to be predicted correctly from a knowledge of the signs of the parameters μ, ε, Δg and A_i (defined on p. 26). Alternatively, any one of the four factors in equation (1.15) can be deduced from a knowledge of the other three. For the decomposition and rearrangement paths of (LXXI), we may reasonably assume the radicals formed to be those generated from simple homolysis of the N-O bond, as shown in Scheme (3.7).



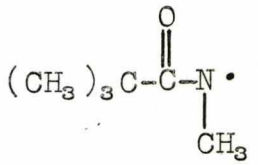
Scheme (3.7)

REARRANGEMENT

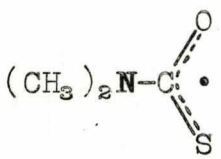
According to such a scheme, for the rearrangement to (LXXXII):-

(1) The reaction is thermal, the radical pairs being formed from singlet precursors, so μ is negative.

(2) From ESR studies, the g factor of the N-methyl amide radicals[133] (XCVII) are ca. 2.005 whilst that of the N,N-dimethylthiocarbamate radical[134] (XCVIII) is 2.05.



(XCVII)



(XCVIII)

Thus $\Delta g = g_{(\text{N-methyl benzamido radical})} - g_{(\text{XCVIII})}$ is negative.

(3) The hyperfine coupling constant $A^{H}_{CH_3}$ of the N-methyl protons

of (XCIX) is positive.[133]

(4) The N-methyl resonance of the product (LXXXII) exhibits enhanced absorption, so Γ_{ne} is positive.

Thus the factor ϵ is the only unknown in the equation (1.15), and enables the mode of formation of (LXXXII) to be deduced.

$$\Gamma_{ne} = \mu \epsilon \Delta g A_i$$

$$+ = - \epsilon - +$$

so ϵ is positive, i.e. formation of (LXXXII) occurs from collapse of the radical pair (XCIX) and (XCVIII) within a solvent cage.

(v) The Fragmentation Pathway.

(a) The Occurrence of Thermal Fragmentation of (LXXXI).

In addition to the thermal rearrangement to (LXXXII), compounds of type (LXXXI) decompose by a fragmentation pathway leading to the p-substituted N-methyl benzamide, (C). Quantitative conversion into (C) and (LXXXII) is observed and as noted in Table (3.2) the ratio of (C) to (LXXXII) increases with temperature. Fragmentation to (C) is the major pathway at 110-120°, the temperature necessary for the satisfactory observation of CIDNP effects.

(b) CIDNP Effects.

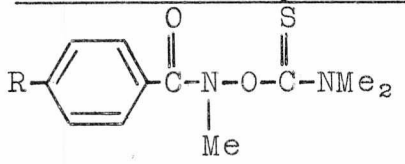
As noted earlier, during the thermal rearrangement of (LXXI) at 120°, the resonances at δ 2.92 and δ 3.00 exhibit a CIDNP effect, appearing in emission as a doublet (see diagram 3.3) and correspond to authentic N-methyl p-toluamide resonances. The emission was very large after $\sim 1\frac{1}{2}$ minutes and decays over several minutes, eventually becoming a positive absorption signal but collapsed as a singlet at δ 2.97.

These results indicate that the amido radical formed by

N-O bond homolysis, rather surprisingly, abstracts a hydrogen radical and not a deuterium radical from the deuterochloroform solvent, since the N-methyl resonance of N-methyl p-toluamide initially appears as a doublet. The eventual collapse of the doublet to a singlet is of course due to exchange with the deuterochloroform to yield N-deutero N-methyl p-toluamide.

Similar CIDNP results (Table (3.16)) were obtained for the other N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methyl-hydroxylamines (LXXXI).

Table (3.16). Spin Polarised NMR Resonances of the p-Substituted N-Methyl Benzamide (C) From the Thermolysis of



in Deuterochloroform at 120°.

R	N-Me Resonances of (C) δ	Sign of Signal	$V_{expt.}$[132]
H	2.97 3.03	Emission	-4
CH_3	2.92 3.00	Emission	-9
CH_3O	2.91 2.98	Emission	-2
O_2N	3.00 3.07	Emission	-2

(c) Mechanistic Implications of the CIDNP Effects.

FRAGMENTATION

Further analysis of these net effect polarisations may be carried out by application of Kaptein's rule, equation (1.15), to Scheme (3.7), for the fragmentation pathway leading to p-substituted N-methyl benzamide:-

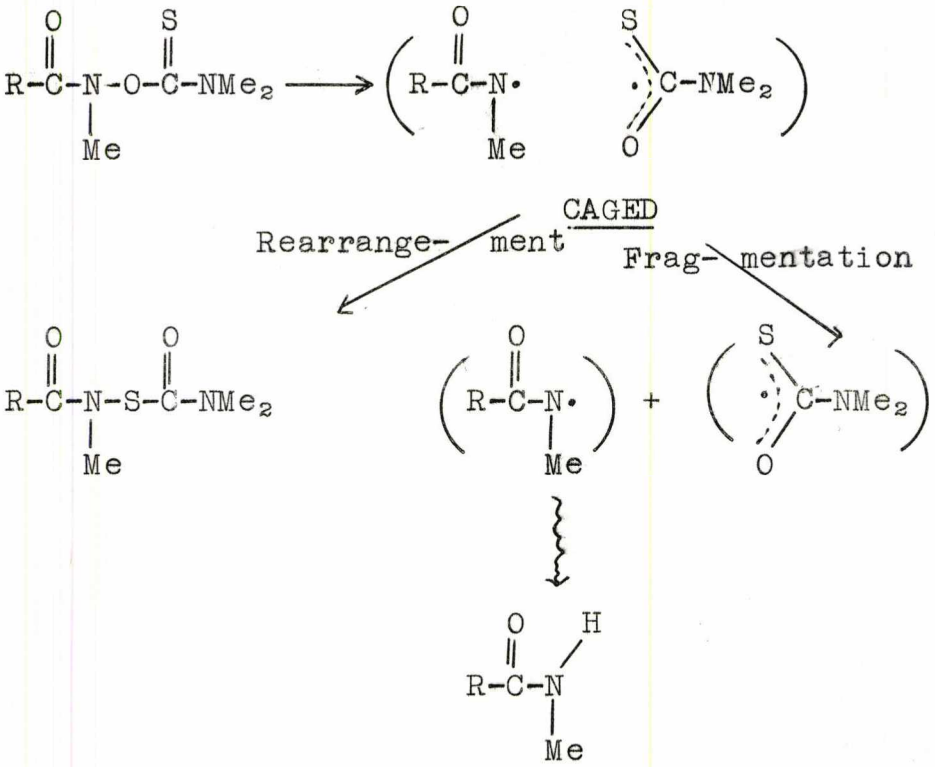
$$\Gamma_{ne} = \mu \epsilon \Delta g A_i$$

(μ, Δg and A_i are identical to those values already considered)

i.e. $\quad - \quad = \quad - \epsilon - +$

so ϵ is negative, i.e. the p-substituted N-methyl benzamide (C) is a product of the amido radical which has escaped from the solvent cage.

Such a conclusion is entirely consistent with the earlier conclusion (p.99) that the thiono-thiolo rearrangement (LXXXI) $\longrightarrow$ (LXXXII) involves a [1,3] radical shift within a solvent cage. It is the escape of the radicals from this cage that provides the observed fragmentation decomposition to (C). This is outlined in Scheme (3.8):-



Scheme (3.8)

The observed CIDNP effects are unequivocal evidence for radical participation and in view of this an analysis of the side products resulting from the fragmentation pathway will now be presented.

(d) Product Analysis of the Thermal Fragmentation of (LXXXI)

In addition to the resonances due to N-methyl p-toluamide and N-(p-tolucyl)-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine, the NMR spectra of the final solution from the thermal rearrangement of (LXXI) in deuterochloroform solution showed two small unassigned peaks at δ3.02 and δ2.60. These resonances are apparently due to a brown tarry intractable side product of reaction, which could not be further purified by chromatography or crystallisation, (refer Diagram (3.1)). These two peaks were sometimes obscured by other resonances in the NMR spectra of the products of thermolysis of the other O-thiocarbamoylated hydroxamic

acids studied (Table(6.8)).

When the rearrangement of (LXXI) was conducted in deuterochloroform solution at 60°, peaks at δ3.02 and δ2.60 were observed in the NMR, the relative intensity of both of these peaks increasing when the rearrangement was conducted at 120°.

Vapour phase chromatographic analysis confirmed fragmentation to N-methyl p-methoxy-benzamide to predominate over rearrangement to (LXXXII; R = CH_3O) when (LXXXI; R = CH_3O) was thermolysed at 120°, and revealed the presence of small amounts of unidentified volatiles.

The fate of the amido radical on the fragmentation pathway is interesting. The NMR evidence demonstrates clearly that such an amido radical abstracts a hydrogen radical and not a chlorine or a deuterium radical from the solvent (refer p.100).

Rapid evaporation of the solvent and the volatiles from the products from the thermolysis of (LXXI) in deuterochloroform for 15 minutes at 120°, by placing under high vacuum via a liquid nitrogen cooled trap enabled chloroform‡ and carbon oxysulphide to be detected in the deuterochloroform.

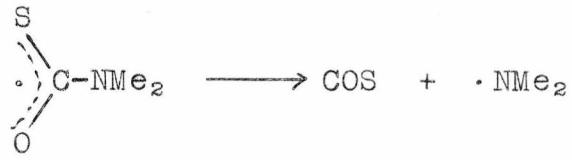
NMR analysis of the products from the thermolysis of (LXXI) in deuterochloroform solution for 15 minutes at 120° revealed an absence of starting material, and also of N,N'-di(p-toluoyl)-N,N'-dimethylhydrazine and bis-(dimethylcarbamoyl) disulphide (both appreciably stable at this temperature) showing that no radical dimerisation of this sort occurred. Such an absence of

---

‡Chloroform clearly results from the secondary hydrogen exchange (page 100) of the benzamide with the deuterated solvent.

secondary recombination and the preferential abstraction of hydrogen to deuterium by the amido radical suggests, in one possible scheme, a very rapid decomposition of the N,N-dimethylthiocarbamate radical (XCVIII) to provide a ready source of hydrogen radicals.

Infra-red spectroscopic assays of the reaction solution during and after rearrangement reveal the presence of carbon oxysulphide, supporting the proposal that the N,N-dimethylthiocarbamate radical could escape from the solvent cage with subsequent loss of carbon oxysulphide to form the dimethylamino radical (equation (3.8)).

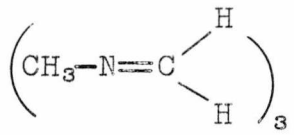


equation (3.8)

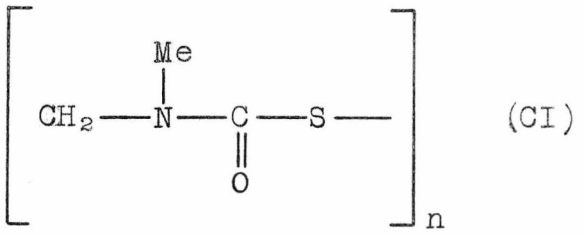
That the dimethylamino radical was not lost by dimerisation or by combination with amido radicals was shown by comparison of the NMR spectrum with that of N,N-dimethylhydrazine, N,N,N',N'-tetramethyl-diaminomethane and N,N'-di(p-toluoyl)-N,N'-dimethylhydrazine. Such a dimethylamino radical if formed, will disproportionate to form N-methylazomethine[135] and a hydrogen radical (equation(3.9)), which can then combine with an amido radical to yield amide.

equation (3.9)

The ultimate fate of the reactive N-methylazomethine and carbon oxysulphide is not known with certainty, although by comparison with authentic material, it is certain that no trimer[136]

 results.

The NMR resonances of the principal unidentified side product, (δ 3.02, 2.60) are consistent with a polymeric material (CI)



(CI)

which is one possible structure which can be speculatively assigned at this stage to the tarry side products which have so far defied adequate purification.

CHAPTER IV

SUMMARY OF RESULTS

(i) THE THERMAL REARRANGEMENT OF N-METHYL HYDROXAMIC ACIDS.

(a) The thermal rearrangement of N-methyl hydroxamic acids to the isomeric N-methyl-O-acylhydroxylamines has been shown to occur, at least in part, by an intermolecular mechanism (Scheme(2.2))involving formation of N-methylhydroxylamine and N-methyl-N,O-diacylhydroxylamine. By virtue of the presence of the methyl group on nitrogen in the latter compound, a Lossen rearrangement cannot occur, reaction takes place instead with N-methylhydroxylamine with consequent formation of the N-methyl-O-acylhydroxylamine. Simultaneous formation of the N-methyl-O-acylhydroxylamine by an intramolecular mechanism (equations(2.1)and(2.2))has not however been totally excluded, although indications are that such a mechanism does not occur to any large extent.

(b) At higher temperatures, carboxylic acids and N-methyl amides appear as products from the distillation of N-methyl hydroxamic acids. By analogy to the thiono-thiolo rearrangement of (LXXXI) it seems likely that the intermediate N-methyl-N,O-diacylhydroxylamine fragments to the carboxylic acid and the N-methyl amide, in part at least, by a radical pathway.

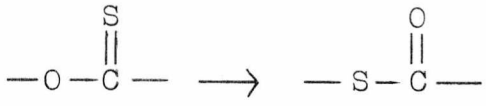
(ii) THE THERMAL REARRANGEMENT OF O-THIOCARBAMOYLATED N-METHYL HYDROXAMIC ACIDS.

The thiono-thiolo rearrangement of (LXXXI) → (LXXXII) occurs, at least partly, by a pathway involving free radical

intermediates, since the CIDNP effects discussed in Chapter III are unequivocal.

The test for nuclear polarisation, however, was not available to Hudson, Lawson and Lucken[54] in the analogous rearrangement of oxime thionocarbamates. Their proposal of a [1,3] free radical shift was founded on a large weight of circumstantial evidence, which has however, been supported by the present work.

Although thiono → thiolo rearrangements (Scheme(4.1)) are well known[137], the [1,3] rearrangements of both O-thiocarbamoylated N-methyl hydroxamic acids and oxime thionocarbamates are the first examples of a thiono → thiolo rearrangement occurring by a free radical shift.

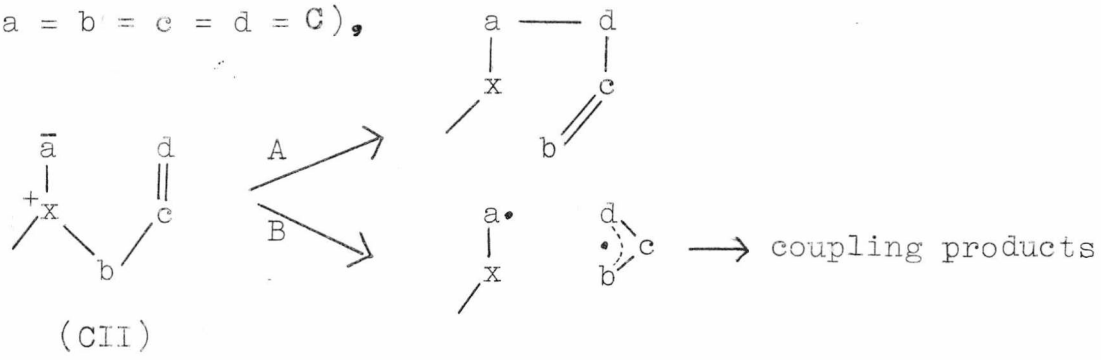


Scheme(4.1)

What is not clear, however, is whether these [1,3] rearrangements of both (LXXXI) and oxime thionocarbamates proceed via a free radical shift alone.

Consideration will therefore be given to a possible duality of mechanism in these reactions: a [1,3] sigmatropic rearrangement competing with a free radical shift.

Such a duality of mechanism between concerted (A) and non-concerted (B) pathways has been observed by Baldwin[138,139] in the rearrangements of sulphonium ylides [(CII); X = S, a = b = c = d = C),



(CII)

and considered to extend to systems where X = N, O, P etc. Baldwin showed [138] that path A had a lower activation energy than path B and was consequently favoured at low temperatures. The temperature dependence of the Stevens-Sommelet-Hauser reaction[140] and of the Wittig rearrangement[141] was also suggested to originate from a similar duality of mechanism.

The thermally allowed migrations for a [1,3] sigmatropic rearrangement of N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine involve antarafacial migration, with retention of configuration at the migrating nitrogen atom (Diagram(4.1))or suprafacial migration, with inversion of configuration at the migrating nitrogen atom (Diagram(4.2)). Since the transition state for antarafacial migration would be very strained and difficult to attain, concerted rearrangement would only occur by suprafacial migration in which the transition state is geometrically more accessible. (Diagrams(4.1)and(4.2)).

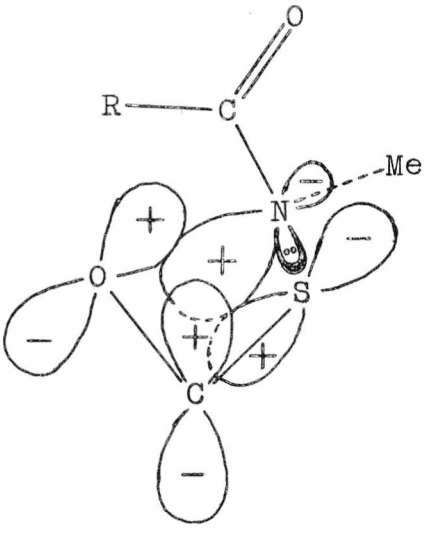


Diagram (4.1)

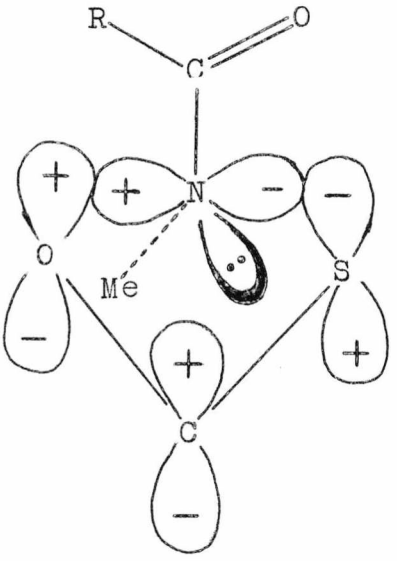


Diagram (4.2)

The determination of stereospecificity in the rearrangement by attempting to observe inversion of configuration at the migrating nitrogen atom for a suprafacial [1,3] shift cannot be used as evidence for a concerted mechanism in this case, however, because of the low nitrogen inversion barriers observed in hydroxylamine derivatives[142].

Thus a close study of the kinetic data is the only viable method of determining the predominant mode of rearrangement.

The absence of both a kinetic solvent effect and a regular substituent effect on the rate of rearrangement of N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine also supports a concerted [1,3] shift mechanism as well as a radical mechanism.

THE ACTIVATION PARAMETERS.

An analysis of the activation parameters, $_{\Delta}H^{\ddagger}$ and $_{\Delta}S^{\ddagger}$, will reflect the mechanism of the rearrangement of N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine.

The entropy of activation, $_{\Delta}S^{\ddagger}$, reflects the difference in ordering between reactants and transition state (includes the solvent molecules) in the rate determining step of a reaction. Generally, concerted rearrangements possess large negative entropies of activation because these rearrangements require a specific orientation of atoms. Such specific alignment is not required by stepwise (e.g. radical) rearrangements, which consequently generally show small, positive, entropies of activation.

Concerted processes usually have a small enthalpy of activation, $_{\Delta}H^{\ddagger}$, relative to the bond dissociation energy of the broken bond.

The absolute value of $\Delta H^{\ddagger}$ (25.8-28.8 kcal.mole^{-1}) for the rearrangement of (LXXXI)⟶(LXXXII) does not differentiate between the sigmatropic and radical processes, since both processes should result in a value of $\Delta H^{\ddagger}$ considerably less than the bonding energy of the N-O bond (48 kcal. mole^{-1})[143] due to:

(a) partial bond formation in the sigmatropic process.

(b) allylic stabilisation of $Me_2N-C\begin{smallmatrix}O\\ \bullet\\ S\end{smallmatrix}$ in the radical process.

The consistently positive value of the reaction entropy (0.3-8.6e.u.), however, (measured in the poorly solvating solvent hexane) is inconsistent with a large proportion of the reaction occurring via a[1,3] sigmatropic process, which must of necessity demand a tight four-membered cyclic transition state, and thus a strongly negative $\Delta S^{\ddagger}$.

Thus the [1,3] shift involved in the rearrangement of (LXXXI)⟶(LXXXII) is likely to proceed largely by a homolysis mechanism, justifying Hudson, Lawson and Lucken's earlier hypothesis in the rearrangement of oxime thionocarbamates[54] .

This conclusion is supported by a comparison of the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the thermal rearrangement of N-aryl-isoxazoline-3-ones (XCIII) to N-aryl-oxazoline-2-ones (XCVI) (Scheme (3.6)).[131] Kinetic data supporting a homolytic cleavage of the N-O bond of (XCIII) has been obtained (see page 93), and indeed, the values of $\Delta H^{\ddagger}$ (33.4 ± 0.3 kcal. mole^{-1}; $R_1 = R_2 = H$) and $\Delta S^{\ddagger}$ (+3.0 e.u.; $R_1 = R_2 = H$) are very close to those recorded in the present work for the thiono → thiolo rearrangement of (LXXXI)⟶(LXXXII), ($\Delta H^{\ddagger}$, 25.8-28.8 kcal. mole^{-1}; $\Delta S^{\ddagger}$, 0.3-8.6 e.u.).

Thus the conclusions of this study suggest that, for this example of a thiono ⟶ thiolo rearrangement, the radical pair stepwise mechanism contributes to a considerably greater extent than the concerted process.

PART III

THE EXPERIMENTAL

INSTRUMENTATION

Infra-red spectra (range, 4000-625 $cm.^{-1}$) were recorded on a Perkin Elmer 257 (and occasionally a 237 model) grating infra-red spectrophotometer and were calibrated against polystyrene.

Ultra-violet spectra were recorded on a Unicam SP800 UV/Visible spectrophotometer fitted with a repeat scan unit.

Nuclear magnetic resonance spectra were recorded by Mr. David O. Smith on a Perkin Elmer R10 NMR spectrometer operating at 60 MHz.

All mass spectra were measured by Mr. R. Turner on an A.E.I./M.S.9 mass spectrometer. The mass spectra are quoted by giving the significant m/e values followed by the corresponding peak intensity in parentheses as a percentage of the base peak. Peaks less than 1% or below m/e 25 are generally not included, unless they are of particular significance.

Vapour phase chromatographic analyses were conducted using a Pye Series 104 chromatograph fitted with a flame ionisation detector and coupled to a Speedomax W recorder.

Elemental micro-analyses (C, H and N) were conducted by Mr. G. Powell using a Hewlett-Packard Model 185 Analyser.

Melting points were recorded on a Kofler block melting point apparatus using a thermometer calibrated against standard compounds.

Refractive indices were recorded using an Abbé refractometer operated in daylight conditions.

Thin layer chromatography and preparative thin layer chromatography were conducted on Merck pre-coated chromatography plates Silica Gel F_{254}.

CHAPTER V

THE THERMAL REARRANGEMENT OF N-METHYL HYDROXAMIC ACIDS

(i) Preparative Methods

(a) Materials

Carboxylic Acids

p-Toluic acid, σ-toluic acid and 2,4,6- trimethyl-benzoic acid were supplied by Koch-Light Laboratories.

n-Butyric acid, 2-ethyl n-butyric acid and pivalic acid were of Laboratory Reagent grade supplied by the British Drug Houses Ltd.

Acid Chlorides

Anisoyl chloride, benzoyl chloride and acetyl chloride were of Laboratory Reagent grade supplied by the British Drug Houses Ltd.

p-Nitrobenzoyl chloride of Laboratory Reagent grade supplied by the British Drug Houses Ltd. often contained considerable quantities of p- nitrobenzoic acid so it was refluxed with an excess of thionyl chloride for one hour, the excess thionyl chloride then distilled off to leave the p-nitrobenzoyl chloride as a yellow crystalline solid of m.p. 72-73°, (lit.[144] 75°).

p-Methyl benzoyl chloride, σ-methyl benzoyl chloride, mesitoyl chloride, n-butyryl chloride, 2-ethyl n-butyryl chloride, and pivaloyl chloride were prepared from the corresponding carboxylic acid by refluxing with a 75% excess of thionyl chloride.

The excess of thionyl chloride was distilled off through a vacuum-jacketed Vigreux column and the acid chloride then fractionally distilled. The thionyl chloride was of Laboratory Reagent grade supplied by the British Drug Houses Ltd.

(b) Preparation of Hydroxylamines

N-Methylhydroxylamine Hydrochloride

N-Methylhydroxylamine hydrochloride was prepared by reduction of nitromethane (Fisons Ltd., Laboratory Reagent grade) with zinc dust (Fisons Ltd., Analar grade) /ammonium chloride (Laboratory Reagent grade) as described by Beckmann.[6] Recrystallised from ethanol/diethyl ether to yield white needles of m.p. 82-83.5° (lit.[145] 87°). The extremely hygroscopic material was stored under vacuum in a vacuum desiccator over concentrated sulphuric acid and sodium hydroxide pellets. Yield = 43%.

N-Benzylhydroxylamine

N-Benzylhydroxylamine was prepared by oxidation of N,N-dibenzylhydroxylamine and hydrolysis of the resulting nitrone by the method of Jones and Sneed.[146] Recrystallised as white long needles from 80-100° petroleum ether,m.p. 56-57° (lit.[146] 57°). Yield = 10%.

Found: C, 68.0; H, 7.1; N, 11.3.

Calculated for C_7H_9NO: C, 68.3; H, 7.4; N, 11.4.

IR spectrum ($CHCl_3$): 3580 (m) free O-H stretch, 3400-2800 (s) O-H and N-H stretch and C-H stretch, 1951 (w), 1881 (w), 1813 (w), 1605 (w) and 1589 (w) and 1499 (s) C=C skeletal in-plane vibrations,1458 (s), 1411 (s), 1333 (s), 1223 (s), 1099 (s), 1021 (s), 952 (s), 890 (s), 842 (s).

(c) Preparation of N-Methyl Hydroxamic Acids

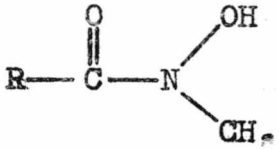
The N-methyl hydroxamic acids were prepared by a modification of the second method of Jones and Hurd.[147]

The acid chloride (in the neat state or in ethereal solution) was slowly added to a vigorously stirred suspension of N-methylhydroxylamine hydrochloride and anhydrous sodium

carbonate (which had both been ground together as a paste before suspension in ether) in diethyl ether containing approximately 1% of water. All three compounds were present in equimolar quantities.

The reaction mixture was stirred for 3-4 hours and then filtered. The ethereal filtrate was extracted with 0.2M potassium hydroxide solution and the base soluble extract acidified and ether extracted. The ether extract was dried over anhydrous magnesium sulphate, filtered and rotary evaporated below 30° to leave the hydroxamic acid, which was purified by recrystallisation.

Table (5.I). Analytical Data for the N-Methyl Hydroxamic Acids



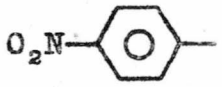
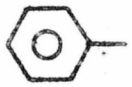
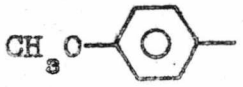
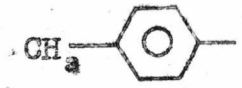
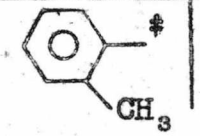
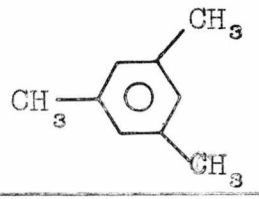
R	Analysis Calculated C	H	N	Found C	H	N	M.p./b.p.	Solvent used in recrystallisation and crystalline state	Yield in preparation
	49.0	4.1	14.3	49.2	4.2	14.3	180-182° Lit., 180°; 148 185 - 187°[88d]	Methanol White needles	76
	Not obtained in a state of analytical purity						Cannot be distilled without rearrangement occurring. Lit., 42° crystallised with difficulty[88a,88d,149]	Colourless oil	70
	59.7	6.1	7.7	59.9	6.2	8.0	109-110.5° Lit., 108°[150]	Benzene White prisms	76
	65.4	6.7	8.5	65.7	6.9	8.4	121-122° Lit., 122°[88d]	Benzene White microcrystalline solid	89
	65.4	6.7	8.5	65.5	6.9	8.6	121.5-122.5°	Benzene White prisms	44

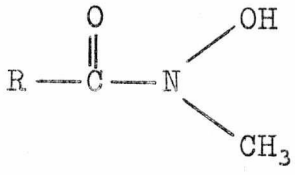
Table (5.I) contd.

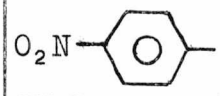
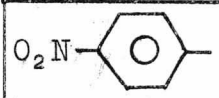
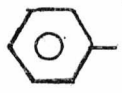
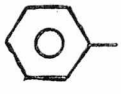
 ‡	68.4	7.8	7.25	68.6	7.65	7.3	I38-I39°	Cyclohexane White platelets	80
CH_3—	40.4	7.9	I5.7	40.35	7.9	I5.0	b.p. 60°/ 0.3mm. n = I.4499 Lit., b.p.74-76°/ 0.8mm.,[I5I] 80°/2mm.[I52] n_D^{23} I.45I2[I5I]; n_D^{20} I.4523[I52]	Colourless mobile oil	89
$C_2H_5CH_2$— ‡	5I.3	9.5	I2.0	5I.2	9.4	II.85	Distills unchanged at I20-I30° (oil bath temp.)/0.6mm.	Colourless mobile oil	87
$(C_2H_5)_2CH$— ‡	57.9	I0.4	9.65	58.I	I0.6	9.8	b.p.70-75°/0.24-0.45 mm.	Colourless mobile oil	72
$(CH_3)_3C$— ‡	54.9	I0.0	I0.7	55.I5	9.8	I0.9	70.5-7I.5°	60-80° pet. ether White platelets	72

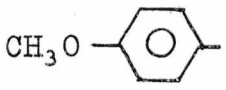
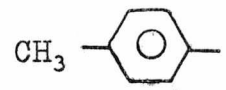
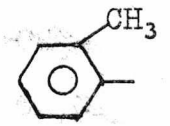
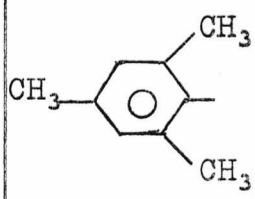
‡ Compounds previously unrecorded in the literature.

In view of the extensive use of IR spectroscopy in the analysis of the products resulting from the distillation of the N-methyl hydroxamic acids the IR spectra of the components of the distillations are reported.

Table (5.2). The Infra-Red Spectra of the N-Methyl Hydroxamic Acids,



R and solvent	Absorptions ($cm.^{-1}$) in the infra-red spectra; range 4000-625 $cm.^{-1}$. Their relative intensities and assignments. s = strong, m = medium, w = weak.
 CH_2Br_2	3300-3000 (w) O-H stretch, 1623 (s) C=O vibration, 1595 (s) C=C skeletal In-plane vibration, 1525 (s), 1352 (s), 864 (s), 852 (s), 719 (s).
 KCl disc	3280-3020 (m) O-H stretch, 2878 (m) C-H stretch of CH_3, 1945 (w), 1634 (s) C=O vibration, 1612 (s), 1595 (s) C=C skeletal In-plane vibration, 1514 (s), 1467 (s), 1393 (s), 1360 (s), 1221 (s), 869 (s), 857 (s), 771 (s), 724 (s).
 CH_2Cl_2	3350-3100 (m) O-H stretch, 2930 (w) C-H stretch of CH_3, 1622 (s) C=O vibration, 1601 (m) C=C skeletal In-plane vibration, 1578 (m), 1511 (w), 1371 (s).
 Neat-thin film	3660-3000 (s) O-H stretch, 2900(m) C-H stretch of CH_3, 1680-1590 (s) C=O vibration, 1573 (s), 1450-1425 (s), 1390 (s), 1219 (s), 711 (s).

 CH_2Br_2	3300-3150 (w) O-H stretch, 2958 (w) and 2932 (w) and 2836 (w) C-H stretch of CH_3, 1610 (s) C=O vibration, 1572 (w), 1511 (m), 1365 (s), 1258 (s), 844 (s).
 CH_2Cl_2	3300-3150 (w) O-H stretch, 2922 (w) C-H stretch of CH_3, 1618 (s) C=O vibration, 1571 (w), 1526 (w), 1370 (s).
 CH_2Cl_2	3300-3150 (w) O-H stretch, 2924 (w) C-H stretch of CH_3, 1619 (s) C=O vibration, 1599 (w) C=C skeletal in-plane vibration, 1526 (w), 1373 (s) 1199 and 1191 (s), 931 (s).
 CH_2Br_2	3300-3150 (w) O-H stretch, 2920 (w) C-H stretch of CH_3, 1617 (s) C=O vibration, 1604 (s) C=C skeletal in-plane vibration, 1529 (w), 1460-1430 (m) C-H deformation of $C-CH_3$ (asym.) and $-CH_2-$, 1369(s) C-H deformation (sym.) of $C-CH_3$.
CH_3- CH_2Cl_2	3496 (w) and 3300-3050 (m) O-H stretch, 2932 (m) C-H stretch, 1629 (s) C=O vibration, 1388 (s).
$C_2H_5\ CH_2-$ CH_2Cl_2	3498 (w) and 3300-3100 (m) O-H stretch, 2962 (s) and 2936 (w) and 2878 (m) C-H stretch, 1623 (s) C=O vibration, 1388 (s).
$(C_2H_5)_2CH-$ CH_2Cl_2	3496 (w) and 3300-3100 (m) O-H stretch, 2964 (s) and 2934 (m) and 2878 (m) C-H stretch, 1616 (s) C=O vibration, 1519 (w), 1460 (s), 1399 (s).
$(CH_3)_3C-$ CH_2Cl_2	3496 (w) and 3300-3100 (m) O-H stretch, 2965 (s) C-H stretch, 1598 (s) C=O vibration, 1510 (w), 1480 (s), 1402 (s), 1349 (s).

The NMR spectra of the above N-methyl hydroxamic acids were in accord with the assigned structures.

(d) Preparation of N-Benzyl p-Methoxy-Benzhydroxamic Acid

N-Benzyl p-methoxy-benzyhydroxamic acid was prepared according to the method described for the N-methyl hydroxamic acids. The base soluble extract was recrystallised from carbon tetrachloride/60-80° petroleum ether to give the required product as cream-coloured micro-prisms. M.p. 105-108°. Yield = 70%.

Analysis: Found: C, 69.9; H, 6.0; N, 5.4.

$C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4.

IR spectrum ($CHCl_3$): 3600-3020 (m) O-H stretch, 3005 (w) possibly =C-H stretch, 2944 (w) and 2920 (w) and 2846 (w) C-H stretch of CH_3 and CH_2, 1612 (s) C=O vibration, 1576 (w), 1514 (m), 1384 (s), 1256 (s), 1177 (s), 846 (s).

(e) Preparation of p-Nitrophenyl Esters

The following p-nitrophenyl esters were prepared from p-nitropherol (the British Drug Houses Ltd., Laboratory Reagent) dissolved in pyridine and the appropriate acid chloride.* The pyridine was of Analar grade (British Drug Houses Ltd.) dried by refluxing over and then distilling from potassium hydroxide pellets.

p-Nitrophenyl Benzoate

Recrystallised from 95% ethanol. M.p. 142-143° (Lit. 145°[85a]) Yield = 91%.

p-Nitrophenyl p-Nitrobenzoate

Recrystallised from 95% ethanol. M.p. 159-161°. (Lit. 158-159°[153]). Yield = 77%.

p-Nitrophenyl p-Methoxybenzoate

Recrystallised from 95% ethanol. M.p. 165-166°. (Lit. 166°[154]). Yield = 87%.

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* In the case of esters which separated as oils on pouring the bulked reaction mixture into water, the oil was obtained by extraction with diethyl ether and purified by distillation.

p-Nitrophenyl p-Methylbenzoate

Recrystallised from 95% ethanol. M.p. 119-120°. (Lit. 120.3-121.3°[155]). Yield = 93%.

p-Nitrophenyl σ-Methylbenzoate

Recrystallised from 95% ethanol. M.p. 109-110°. Yield = 90%. (This compound is unrecorded in the literature).

Analysis: Found: C, 65.3; H, 4.3; N, 5.3.

$C_{14}H_{11}NO_4$ requires C, 65.4; H, 4.3; N, 5.4.

p-Nitrophenyl Mesitoate

Recrystallised from 95% ethanol. M.p. 96-98°. Yield = 96%. (This compound is unrecorded in the literature).

Analysis: Found: C, 67.6; H, 5.3; N, 4.8.

$C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9.

p-Nitrophenyl Acetate

p-Nitrophenyl acetate was prepared by reacting p-nitrophenol with acetic anhydride in pyridine at 100° for three hours. Recrystallised from benzene/40-60° petroleum ether. M.p. 78-79°. (Lit. 81-82°[154]). Yield = 94%.

p-Nitrophenyl n-Butyrate

Purified by distillation under reduced pressure. B.p. 125-126°/0.12 mm. (Lit. 162-164°/7 mm.[156]) A pale amber liquid. Yield = 80%.

p-Nitrophenyl 2-Ethyl n-Butyrate

Purified by distillation under reduced pressure. B.p. 126-129°/0.6 mm. A pale yellow mobile oil. Yield = 95%. (This compound is unrecorded in the literature).

Analysis: Found: C, 60.8; H, 6.5; N, 5.9.

$C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.4; N, 5.9.

p-Nitrophenyl Pivalate

Recrstallised from 60-80° petroleum ether. M.p. 96-96.5°. (Lit. 94-95°[157]). Yield = 94%.

(f) Preparation of N-Methyl-O-Aroyl/Acylhydroxylamines

N-methyl-O-aroyl/acylhydroxylamines were prepared by slight modification of the method described by Jencks.[85]

15 ml of an aqueous mixture of equal parts of 4N. N-methyl hydroxylamine hydrochloride and 3.5N. sodium hydroxide were added all at once with stirring to 20mmoles of the appropriate p-nitrophenyl ester in ~ 500 ml of 95% ethanol (in some cases methanol was used instead as it can be removed by rotary evaporation at a lower temperature) at 65-20° , (depending on the particular N-methyl-O-acylhydroxylamine with regard to its thermal stability in solution) and the mixture was stirred for 3/4 - 30 hours (again depending upon the particular preparation). The development of a yellow colour within 1 minute of making the addition indicated the liberation of p-nitrophenol. The reaction mixture was partially rotary evaporated to approximately a quarter bulk at as low a temperature as possible to minimise rearrangement of the N-methyl-O-acylhydroxylamine. The reaction mixture was then dissolved in diethyl ether and extracted several times with 0.2 M aqueous sodium carbonate solution. The base insoluble ethereal solution was washed once with a small volume of water, dried over anhydrous magnesium sulphate, filtered and the solvent removed by rotary evaporation at as low a temperature as possible. The material was stored at 4° to reduce the rate of decomposition but when storage for a considerable time was necessary the material was stored in dilute ethereal solution at 4° . The N-methyl-O-acylhydroxylamine was purified immediately before use by recrystallisation at or near room temperature if it was a solid or by rapid bulb distillation under high vacuum if it was a liquid or oil.

(1) The N-Methyl-O-Aroylhydroxylamines

N-Methyl-O-p-Nitrobenzoylhydroxylamine

Yield = 37% as a pale yellow crystalline solid. Recrystallised in the cold from acetone/40-60° petroleum ether m.p. 104-106° .

Analysis: Found: C.49.1; H, 4.0; N, 14.0.

Calculated for $C_8H_8N_2O_4$: C, 49.0; H, 4.1; N, 14.3.

N-Methyl-O-Benzoylhydroxlyamine

Yield = 57% as a yellow oil. Purified by rapid bulb distillation, b.p. 95-99° (oil bath temperature)/ ~0.8 mm. At room temperature, this compound (in the neat state) has a half-life of ~20 hours.

Analysis: Found: C, 63.4; H, 5.9; N, 9.1.

$C_8H_9NO_2$ requires C, 63.5; H, 6.0; N, 9.3.

N-Methyl-O-p-Methoxybenzoylhydroxylamine

Yield = 50% as a white crystalline solid. Recrystallised in the cold from 40-60° petroleum ether, m.p. 49-50° .

Analysis: Found: C, 59.4; H, 6.0; N, 7.8.

$C_9H_{11}NO_3$ requires C, 59.7; H, 6.1; N, 7.7.

N-Methyl-O-p-Methylbenzoylhydroxylamine

Yield = 62% as a very mobile clear amber oil. Not purified further.

N-Methyl-O-o-Methylbenzoylhydroxylamine

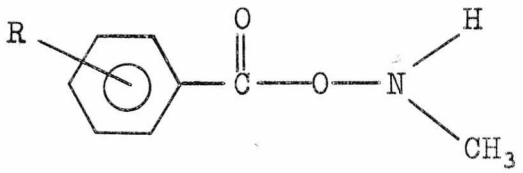
Yield = 82% as a very mobile clear amber oil. Not purified further.

N-Methyl-O-Mesitoylhydroxylamine

Attempts to prepare N-methyl-O-mesitoylhydroxylamine from reaction of N-methylhydroxylamine hydrochloride with p-nitrophenyl mesitoate failed, the p-nitrophenyl ester being recovered unchanged.

The above N-methyl-O-aroylhydroxylamines are novel compounds.

Table (5.3). The Infra-Red Spectra of the N-Methyl-O-Aroylhydroxylamines



R and Solvent	Absorptions ($cm.^{-1}$) in the infra-red spectra; range 4000-625 cm^{-1}. Their relative intensities and assignments. s = strong, m = medium, w = weak.
p-O_2N Et_2O	3232 (w) N-H stretch, 1729 (s) C = O vibration, 1604 (m) C = C skeletal in-plane vibration, 1530 (s), 718 (s).
p-O_2N KCl disc	3226 (w) N-H stretch, 3102 (w), 2994 (w) and 2972 (w) and 2902 (w) C-H stretch of CH_3, 1727 (s) C=O vibration, 1607 (m), 1597 (m), 1529 (s), 1522 (s), 1350 (s), 1283 (s), 1104 (s), 716 (s).
H Et_2O	3242 (w) N-H stretch, 1726 (s) C = O vibration, 1600 (w) C=C skeletal in-plane vibration, 1582 (w), 1261 (s), 711 (s).
p-CH_3O CH_2Br_2	3238 (w) N-H stretch, 2960 (w) and 2932 (w) and 2900 (w) and 2838 (w) C-H stretch of CH_3, 1712 (s) C=O vibration, 1608 (s) C=C skeletal in-plane vibration, 1579 (w), 1511 (s), 1260 (s).
p-CH_3O KCl disc	3244 (w) N-H stretch, 2972-2900 (w) and 2842 (w) C-H stretch of CH_3, 1716 (s) C = O vibration, 1607 (s) C=C skeletal in-plane vibration, 1580 (w), 1511 (m), 1281 (s), 1261 (s).

Table (5.3) continued.

p-CH_3 CH_2Cl_2	3244 (w) N-H stretch, 3030 (w) = C-H stretch, 2966 (w) and 2926 (w) C-H stretch of CH_3, 1719 (s) C=O vibration, 1612 (s) C=C skeletal in-plane vibration, 1575 (w), 1519 (w), 1501 (w), 1181 (s).
o-CH_3 CH_2Cl_2	3248 (w) N-H stretch, 3050 (w) = C-H stretch, 2966 (w) and 2934 (w) and 2902 (w) C-H stretch of CH_3, 1721 (s) C=O vibration, 1597 (m) C=C skeletal in-plane vibration, 1519 (m), 1501 (m), 1342 (s), 1294 (s), 1243 (s), 1056 (s).

The NMR spectra of the above N-methyl-O-aroylhydroxylamines were in accord with the assigned structures.

(2) The N-Methyl-O-Acylhydroxylamines

The N-methyl-O-acylhydroxylamines proved more difficult to obtain in a pure state than the N-methyl-O-aroylhydroxylamines. N-methyl - O-n-butyrylhydroxylamine, N-methyl-O-(2-ethyl-n-butyryl) hydroxylamine and N-methyl-O-pivalylhydroxylamine were prepared by the general method described on p.122. The preparation of N-methyl-O-acetylhydroxylamine is given below.

N-Methyl-O-Acetylhydroxylamine

Difficulty was experienced in attempting to prepare N-methyl-O-acetylhydroxylamine in that it was found to be water soluble and very unstable.

25 ml of an aqueous mixture of equal parts of 4N. N-methyl-hydroxylamine hydrochloride and 3.5N. sodium hydroxide were added rapidly with shaking to p-nitrophenyl acetate (9.1 g, 50 mmoles) in 150 ml of methanol at room temperature. The solution immediately turned bright yellow due to the liberation of p-nitrophenolate ion. After 5 hours the reaction mixture was dissolved in diethyl

ether and extracted with water (8 x 120 ml). The ethereal solution was dried over anhydrous magnesium sulphate, filtered and rotary evaporated at as low a temperature as possible to leave a yellow solid. Yield = 7.0 g. IR analysis showed this to be mainly p-nitrophenol with some unchanged p-nitrophenyl acetate.

The aqueous washings (pH 6) were acidified with 2N. hydrochloric acid to pH 1 and ether extracted to yield 1.4 g of a yellow-brown oily solid. The IR spectrum showed this to be a mixture of p-nitrophenol and N-methyl-O-acetylhydroxylamine (exhibiting a strong peak at 1747 $cm.^{-1}$) with a trace of N-methyl-N,O-diacetylhydroxylamine .‡ In an attempt to isolate N-methyl-

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‡The appearance of N-methyl-O-acetylhydroxylamine and N-methyl-N, O-diacetylhydroxylamine in this extract as opposed to the ether solution initially washed with water is due to the solubility of these compounds in aqueous methanol. Removal of the majority of the methanol (only methanol is removed) by rotary evaporation at $< 25°/1$ mm. prior to dissolution in diethyl ether and extraction with water resulted in a similar partition of products and did not improve on recovered yields.

O-acetylhydroxylamine some of this product (0.45 g) was rapidly bulb distilled under reduced pressure. Distillation of a yellow oil occurred at 90° (oil bath temperature)/0.55 mm. which consisted of N-methyl-N,O-diacetylhydroxylamine containing a trace of N-methyl-O-acetylhydroxylamine. The residue was a mixture of p-nitrophenol and N-methyl-N,O-diacetylhydroxylamine.

On leaving a neat sample of the yellow-brown oily solid sealed in a sample tube at room temperature complete disappearance of the peak at 1747 $cm.^{-1}$ in the IR spectrum had occurred in 72 hours with appearance of N-methyl acethydroxamic acid. After 96 hours at room temperature the material was bulb distilled under reduced pressure. The pale yellow oil (0.05 g) distilling over at 145-180° (oil bath temperature)/13 mm. consisted (by IR spectroscopic analysis) principally of p-nitrophenol and N-methyl-N,O-diacetylhydroxylamine with some N-methyl acethydroxamic acid. The very dark brown solid residue (0.17 g) was primarily p-nitrophenol.

The yellow-brown oily solid obtained as the ether extract of the acidified aqueous washings was re-dissolved in diethyl ether to give an ~1% wt./vol. solution.

(a) 5.0 ml of this solution was divided into ten 0.5 ml portions in glass phials, the ether removed by rotary evaporation at as low a temperature as possible at 15 mm.pressure, the phials sealed and left at room temperature. The phials were opened periodically, 0.5 ml of diethyl ether added and the solutions assayed by infra-red spectroscopy. This showed continued disappearance of N-methyl-O-acetylhydroxylamine (loss of $\nu_{C=O}$ at 1747 $cm.^{-1}$) with appearance of N-methyl acethydroxamic acid ($\nu_{C=O}$ at 1640$cm.^{-1}$, and 1671 $cm.^{-1}$ - broad band), the concentration

of N-methyl-N,O-diacetylhydroxylamine remaining unchanged. The decomposition of the N-methyl-O-acetylhydroxylamine showed a half-life of ~2 hours.

(b) 2.4 ml of this solution were left at room temperature in a sealed 10 ml flask and periodically assayed by infra-red spectroscopy. After 13 days a noticeable loss of N-methyl-O-acetylhydroxylamine with concomitant formation of N-methyl acethydroxamic acid had occurred.

An ~1%wt./vol. solution of the yellow-brown oily solid product in carbon tetrachloride was sealed in a stoppered flask and maintained at 45° in a water bath. The solution was periodically assayed by infra-red spectroscopy. Continued loss of N-methyl-O-acetylhydroxylamine ($\nu_{c=o}$ at 1746 $cm.^{-1}$) with concomitant formation of N-methyl acethydroxamic acid ($\nu_{c=o}$ at 1630 $cm.^{-1}$) was observed, the concentration of N-methyl-N,O-diacetylhydroxylamine ($\nu_{c=o}$ at 1714 and 1804 $cm.^{-1}$) remaining unchanged. Complete loss of N-methyl-O-acetylhydroxylamine was observed in 48 hours.

Such lability of the N-methyl-O-acetylhydroxylamine did not permit it to be obtained in a pure state (see ref. 151).

N-Methyl-O-n-Butyrylhydroxylamine, N-Methyl-O-(2-Ethyl-n-Butyryl)-Hydroxylamine and N-Methyl-O-Pivalylhydroxylamine

The title compounds were purified by rapid distillation under high vacuum, the colourless clear liquid distillates being collected in a cooled (0°) receiving flask.

The compounds were unstable in a neat state but could be stored unchanged for several weeks as a 1% wt./vol. solution in diethyl ether at 4°.

The NMR spectra were in accord with the assigned structures.

N-Methyl-O-n-Butyrylhydroxylamine

Distills at 40-52° (oil bath temperature)/0.04 mm. Yield

= 16%. At room temperature, this compound (in the neat state) has a half-life of ~12 hours.

Analysis: Found: C, 51.2; H, 9.3; N, 11.8.

$C_5H_{11}NO_2$ requires: C, 51.3; H, 9.5; N, 12.0.

N-Methyl-O-(2-ethyl-n-butyryl)-hydroxylamine

Distills at 30-34° (distillation temperature)/0.20 mm. Yield = 40%. This compound is considerable more stable (in the neat state) than N-methyl-O-n-butyrylhydroxylamine.

Analysis: Found: C, 57.7; H, 10.5; N, 9.9.

$C_7H_{15}NO_2$ requires: C, 57.9; H, 10.4; N, 9.65.

N-Methyl-O-pivalylhydroxylamine

Distills at 21° (water bath temperature)/1.4 mm. Yield = 32%. This compound is considerably more stable (in the neat state) than N-methyl-O-n-butyrylhydroxylamine.

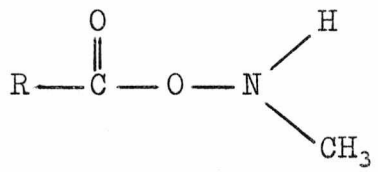
Analysis: Found: C, 54.6; H, 9.7; N, 10.55.

$C_6H_{13}NO_2$ requires: C, 54.9; H, 10.0; N, 10.7.

Toxicological and Physiological Activity.

Extreme care was taken in handling the aliphatic N-methyl-O-acylhydroxylamines as exposure to them resulted in sternutation and prolonged congestion of the lungs.

Table (5.4). The Infra-Red Spectra of the N-Methyl-O-Acylhydroxylamines



R and Solvent	Absorptions ($cm.^{-1}$) in the infra-red spectra; range 4000-625 $cm.^{-1}$. Their relative intensities and assignments. s = strong, m = medium, w = weak.
CH_3	In Et_2O solution the carbonyl vibration frequency appears at 1747 $cm.^{-1}$ (s) and the N-H stretching frequency at 3230 $cm.^{-1}$ (m).
$C_2H_5CH_2$ CCl_4	3250 (w) N-H stretch, 2968 (s) and 2938 (m) and 2878 (m) C-H stretch of CH_3, CH_2, 1741 (s) C=O vibration, 1470 (m) and 1436 (m) C-H deformation of $-CH_2-$ and $C-CH_3$ (asym.) respectively, 1382 (w) C-H deformation (sym.) of $C-CH_3$, 1177 (s).
$(C_2H_5)_2CH$ Neat-thin film	3254 (w) N-H stretch, 2970 (s) and 2940 (s) and 2880 (m) C-H stretch of CH_3, CH_2 and CH respectively, 1734 (s) C=O vibration, 1462 (m) and 1439 (w) C-H deformation of $C-CH_3$ (asym.), $-CH_2-$, 1385 (w) C-H deformation (sym.) of $C-CH_3$, 1350 (w) C-H deformation of -CH-, 1176 (s).
$(C_2H_5)_2CH$ CH_2Cl_2	3250 (w) N-H stretch, 2966 (s) and 2938 (m) and 2880 (m) C-H stretch of CH_3, CH_2 and CH respectively, 1730 (s) C=O vibration, 1461(m) and 1436 (w) C-H deformation of $C-CH_3$ (asym.), $-CH_2-$, 1385 (w) C-H deformation (sym.) of $-C-CH_3$.
$(CH_3)_3C$ CH_2Cl_2	3248 (w) N-H stretch, 2966 (m) and 2939 (w) and 2908 (w) and 2874 (w) C-H stretch of CH_3, 1728 (s) C=O vibration, 1481 (m), 1436 (w) C-H deformation of $C-CH_3$ (asym.), 1399 (w) and 1369 (m) C-H deformation of $-C-(CH_3)_3$, 1161 (s), 1123 (s).

$(CH_3)_3C$ Neat-thin film	3255 (w) N-H stretch, 2976 (s) and 2940 (w) and 2910 (w) and 2876 (w) C-H stretch of CH_3, 1731 (s) C=O vibration, 1482 (m), 1439 (m) C-H deformation of $C-CH_3$ (asym.), 1399 (w) and 1369 (m) C-H deformation of $-C-(CH_3)_3$, 1162 (s), 1124 (s).

The infra-red spectra of the N-methyl-O-aroylhydroxylamines (Table(5.3.)) and of the N-methyl-O-acylhydroxylamines (Table (5.4.)) were in accord with the published infra-red spectra of O-acylhydroxylamines.[85, 87, 104, 151]

(g) Preparation of N-Methyl-N,O-Diaroyl-Hydroxylamines.

N-Methyl-N,O-Dibenzoylhydroxylamine

N-methyl-N,O-dibenzoylhydroxylamine was obtained by recrystallisation from 40-60° petroleum ether of the base insoluble extract obtained from the preparation of N-methyl benzhydroxamic acid. A white micro-crystalline solid, m.p. 55-56° (Lit. 58°[21a]).

Analysis: Found: C, 70.8; H, 5.0; N, 5.6.

Calculated for $C_{15}H_{13}NO_3$: C, 70.6; H, 5.1; N, 5.5

IR spectrum (CH_2Cl_2): 3050 (w) =C-H stretch, 2982 (w) C-H stretch of CH_3, 1763 (s) C = O (ester) vibration, 1665 (s) C = O (amide) vibration, 1600 (m), C = C skeletal in-plane vibration, 1580 (w), 1013 (s), 1004 (s).

N-Methyl-N,O-Di-(p-Methyl-Benzoyl)-Hydroxylamine

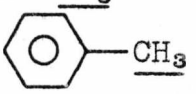
N-Methyl-N,O-di-(p-methyl-benzoyl)-hydroxylamine was similarly obtainedby recrystallisation from 80 - 100° petroleum ether of the base insoluble extract of the product from the preparation of N-methyl p-methyl-benzhydroxamic acid. A white micro-crystalline solid, m.p. 80-84°.

Analysis: Found: C, 72.3; H, 6.1; N, 5.1.

$C_{17}H_{17}NO_3$ requires: C, 72.1; H, 6.05; N, 4.9.

IR spectrum ($CHCl_3$): 2925 (w) C-H stretch of CH_3, 1762 (s) C = O (ester) vibration, 1660 (s) C = O (amide) vibration, 1614 (s) C = C skeletal in-plane vibration, 1574 (w), 1007 (s).

NMR Spectrum (deuterochloroform):

δ 7.93, 7.80, 7.31, 7.18 and 7.68, 7.53, 7.22, 7.09	Two quartets	Aromatic protons
δ 3.49	Singlet	N—CH_3
δ 2.38 and2.30	Singlets	

N-Methyl - N,O-Di-(p-Nitro-Benzoyl)-Hydroxylamine

The title compound was similarly obtained by dissolution in methanol of the base insoluble extract of the reaction products from the preparation of N-methyl p-nitro-benzhydroxamic acid, boiling with decolourising charcoal, filtering and allowing to crystallise.

Pale lemon prisms. M.p. 122-126°.

Analysis: Found: C, 52.3; H, 3.3; N, 12.4.

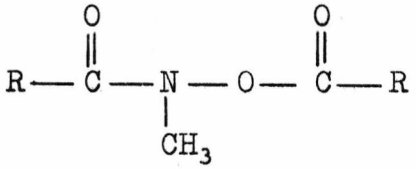
$C_{15}H_{11}N_3O_7$ requires: C, 52.2; H, 3.2; N, 12.2.

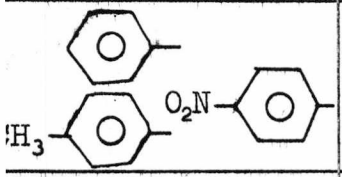
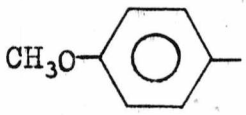
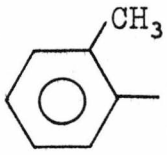
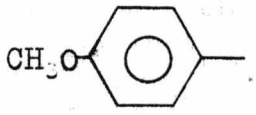
IR spectrum (KBr disc): 3112 (w) and 3078 (w) and 3056 (w) C-H stretch, 1779 (s) C = O (ester) vibration, 1680 (s) C = O (amide) vibration, 1606 (s) C = C skeletal in-plane vibration, 1523 (s), 1348 (s), 1252 (s), 1239 (s), 1031 (s), 1010 (s), 874 (s), 858 (s), 716 (s).

NMR spectrum (deuterochloroform):

δ 8.44, 8.36, 8.30, 8.23, 8.09, 7.93, 7.77	Two quartets.	Aromatic protons
δ 3.58	Singlet	N—CH_3

Table (5.5). The Infra-Red Spectra of the N-Methyl-N,O-Di(Aroyl/Acyl)-Hydroxylamines



R and Solvent	Absorptions ($cm.^{-1}$) in the Infra-red spectra; range 4000-625 $cm.^{-1}$ Their relative intensities and assignments. s = strong, m = medium, w = weak.
	Recorded above
 KCl disc	1752 (s) C=O (ester) vibration, 1652 (s) C=O (amide) vibration, 1605 (s) C=C skeletal In-plane vibration, 1577 (w), 1511 (s), 1257 (s), 1170 (s), 1031 (s), 1022 (s), 1002 (s).
 Et_2O	1764 (s) C=O (ester) vibration, 1674 (s) C=O (amide) vibration, 1601 (m) C=C skeletal in-plane vibration, 1576 (w), 1230 (s), 988 (s), 773 (s), 737 (s).
	In CH_2Br_2 solution the carbonyl vibration frequencies appear at 1754 $cm.^{-1}$ (s) (ester) and 1656 $cm.^{-1}$ (s) (amide).
CH_3-	In Et_2O solution the carbonyl vibration frequencies appear at 1800 $cm.^{-1}$ (s) (ester) and 1692 $cm.^{-1}$ (s) (amide).
$C_2H_5CH_2$- CH_2Cl_2	2966 (s) and 2938 (m) and 2878 (m) C-H of CH_3, CH_2, 1787 (s) C=O (ester) vibration, 1674 (s) C=O (amide) vibration, 1122 (s), 1062 (s).

$(C_2H_5)_2CH-$ CH_2Cl_2	2966 (s) and 2940 (s) and 2882 (s) C-H stretch of CH_3, CH_2 and CH, 1779 (s) C=O (ester) vibration, 1667 (s) C=O (amide) vibration, 1463 (s), 1386 (s), 1063 (s).
$(CH_3)_3C-$ $CHCl_3$	2935 (m) and 2874 (w) C-H stretch of CH_3, 1777 (s) C=O (ester) vibration, 1651 (s) C=O (amide) vibration, 1479 (s), 1366 (s), 1096 (s), 1062 (s), 1016 (s).

Samples of the compounds in Table (5.5) were obtained by crystallisation/purification of the base insoluble extract obtained from the preparation of the corresponding N-methyl hydroxamic acid

(h) N-Methyl Amides

N-Methyl Acetamide

N-Methyl acetamide of Laboratory Reagent grade was supplied by British Drug Houses Ltd.

IR spectrum (CH_2Cl_2): 3465 (s) N-H stretch, 2940 (w) C-H stretch of CH_3, 1676 (s) C = O vibration, 1525 (s) amide II band-combination band of NH deformation and C-N stretching vibrations.

N-Methyl Pivalamide

N-Methyl pivalamide was prepared by reaction of methylamine gas with pivaloyl chloride in sodium dried benzene. Recrystallised at room temperature from carbon tetrachloride/40-60° petroleum ether as white needles. M.p. 91-92°.

Analysis: Found: C, 62.5; H, 11.3; N, 12.1.

$C_6H_{13}NO$ requires C, 62.6; H, 11.4; N, 12.2.

IR spectrum ($CHCl_3$): 3485 (m) N-H stretch, 2950 (m) and 2914 (w) and 2874 (w) C-H stretch of CH_3, 1659 (s) C=O vibration, 1518 (s).

(ii) Distillation/Rearrangement of the N-Methyl Hydroxamic Acids

(a) General Distillation Procedure

Distillations of the N-methyl benzhydroxamic acids in order to induce rearrangement were conducted under reduced pressure in a bulb distillation apparatus constructed out of 8 mm. external diameter glass tubing according to the specification of diagram (5.1).

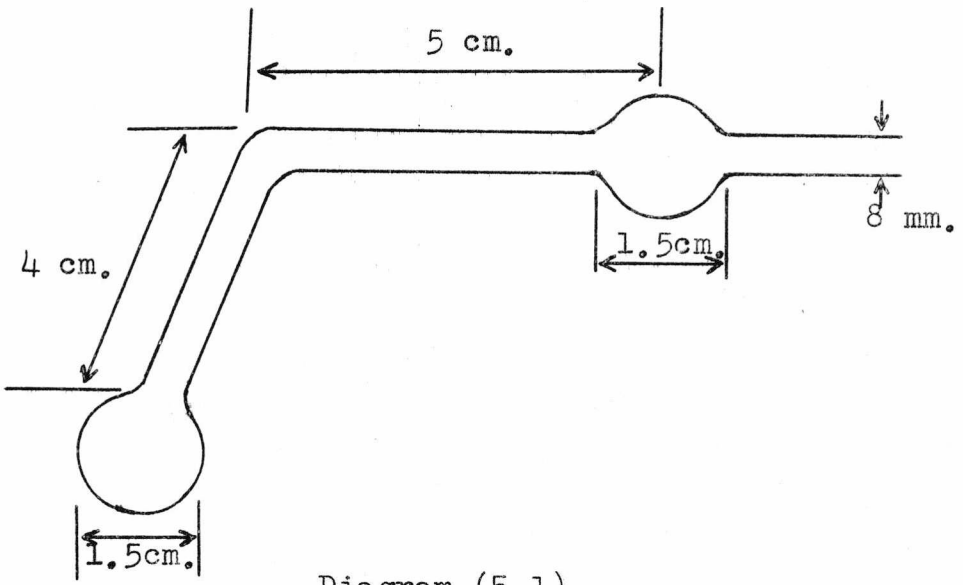


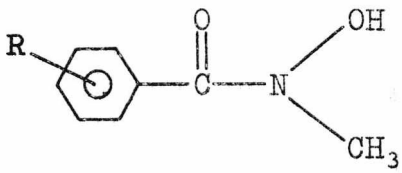
Diagram (5.1)

The N-methyl hydroxamic acid (0.5-1.0 g) was added to the bulb distillation apparatus as a finely divided solid by means of a long stemmed micro-funnel inserted into the receiving tube to reach the head of the distillation neck of the apparatus (or if an oil, pipetted into the distillation bulb). A few anti-bumping granules were added, the apparatus placed under high vacuum and the distillation bulb immersed in a stirred oil bath which was slowly heated until distillation occurred. The receiving bulb was cooled with a current of air. When distillation was complete the distillation apparatus was removed from the oil bath, allowed to cool and the vacuum released. The apparatus was cut in two and the residue and distillate subjected to infra-red spectroscopic analysis.

The distillate was found to be a mixture of the N-methyl-O-aroylhydroxylamine and the N-methyl hydroxamic acid, whilst the residue contained the N-methyl-N,O-diaroylhydroxyl amine and variable amounts of the O-aroyl and N-aroyl N-methyl-hydroxylamines, depending on the speed of distillation.

Rapid base extraction of the distillate and of the residue by dissolution in diethyl ether and extraction with 0.2M. aqueous potassium hydroxide followed by recrystallisation/distillation and infra-red spectral analysis enabled separation and identification (by comparison with authentic samples) of the N-methyl-O-aroylhydroxylamine and the N-methyl-N,O-diaroylhydroxylamine from the N-methyl hydroxamic acid.

The following N-methyl substituted-benzhydroxamic acids were distilled according to the above procedure and found to undergo rearrangement to the N-methyl-O-aroylhydroxylamine and the N-methyl-N,O-diaroylhydroxylamine:

N-Methyl Benzhydroxamic Acids	Distillation Conditions (temperatures are oil bath temperatures)
	
R = p-NO_2	185-200°/15 mm.
R = H	125-145°/0.3 mm.
R = p-CH_3O	135-150°/0.5 mm.
R = p-CH_3	140-150°/15 mm.
R = o-CH_3	155-185°/15 mm.

(b) Distillation of N-Methyl 2,4,6-Trimethyl-Benzhydroxamic Acid

Attempts to distill N-methyl 2,4,6-trimethyl-benzhydroxamic acid at 0.16 mm.pressure by using the above procedure resulted in virtually all of the hydroxamic acid subliming over into the

receiving bulb unchanged (by infra-red spectroscopic analysis) at 115-146° (oil bath temperature). The small amount of residue was N-methyl 2,4,6-trimethyl-benzhydroxamic acid (by IR analysis) containing a trace of a compound with a carbonyl frequency at 1721 $cm.^{-1}$ (possibly N-methyl-O-mesitoyl-hydroxylamine - mesitoic acid exhibits carbonyl frequencies at 1733 (m) and 1694 $cm.^{-1}$ (s), (CH_2Br_2)).

N-Methyl 2,4,6-trimethyl-benzhydroxamic acid does, however, undergo distillation at 15 mm. pressure. A small amount of sublimation occurs at 120°, followed by melting to a clear yellow liquid at 140-145° and distillation at 170-185° (oil bath temperatures) of a colourless liquid which solidifies to a white solid on cooling. The distillate was principally unchanged hydroxamic acid but contained a trace of a compound with a carbonyl frequency at 1721 $cm.^{-1}$ (in CH_2Br_2) (possibly N-methyl-O-mesitoylhydroxylamine). The trace of residue remaining in the distillation pot gave a similar infra-red spectroscopic analysis.

The distillate and residue were subjected to VPC analysis using a column packed with 20% Methyl Silicone Gum SE30 on 60-80 DCMS acid washed Chromosorb W. This indicated the distillate to be N-methyl 2,4,6-trimethyl-benzhydroxamic acid‡ containing approximately 0.01% N-methyl-O-(2,4,6-trimethylbenzoyl)-hydroxylamine and a trace of mesitoic acid (the latter compound was not evident by IR spectroscopic analysis), whilst the residue consisted of ~ 95% N-methyl 2,4,6-trimethyl-benzhydroxamic acid, ~3% N-methyl-N,O-di(2,4,6-trimethyl-benzoyl)-hydroxylamine and ~2% N-methyl-O-(2,4,6-trimethyl-benzoyl)-hydroxylamine, i.e. overall much less than 1% of the O-(2,4,6-trimethyl-benzoyl)-isomer or of the N-methyl-N,O-di-(2,4,6-trimethyl-benzoyl)-hydroxylamine was formed.

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‡ N-methyl 2,4,6-trimethyl-benzhydroxamic acid was stable to VPC analysis the other N-methyl benzhydroxamic acids generally undergoing some rearrangement to the O-benzoyl isomer on the VPC column.

(c) Distillation of the N-Methyl Aliphatic Hydroxamic Acids

N-Methyl acethydroxamic, N-methyl pivalhydroxamic, N-methyl 2-ethyl-n-butyrhydroxamic and N-methyl n-butyrhydroxamic acid were bulb distilled according to the procedure outlined on p.135.

The results of such distillations are summarised in Table(2.2). The product analyses involved infra-red spectroscopic analysis of the residue and distillate both before and after separation into base soluble and insoluble components resulting from extraction with 0.2M aqueous potassium hydroxide.

(d) Double distillation of N-Methyl Benzhydroxamic Acid

N-methyl benzhydroxamic acid (~ 1.0 g) was carefully distilled under reduced pressure in the usual manner (p.135). The colourless clear oil distilling at 135-146° (oil bath temperature)/ 0.7 mm.was shown by infra-red spectroscopic analysis to contain N-methyl benzhydroxamic acid and N-methyl-O-benzoylhydroxylamine whilst the residue contained N-methyl benzhydroxamic acid and N-methyl-N,O-dibenzoylhydroxylamine with some N-methyl-O-benzoyl-hydroxylamine.

The distillate was distilled again and the colourless clear oil distilling at 118-122° (oil bath temperature)/0.8 mm.collected in the air cooled receiving bulb.

Infra-red spectroscopic analysis of the distillate revealed it to be principally N-methyl-O-benzoylhydroxylamine with some N-methyl benzhydroxamic acid, whilst the residue contained N-methyl-N,O-dibenzoylhydroxylamine and N-methyl benzhydroxamic acid with a small amount of N-methyl-O-benzoylhydroxylamine.

The distillate and residue from this second distillation were then combined and an infra-red spectrum of this bulked material run. Comparison of this infra-red spectrum with that of a

similarly bulked residue and distillate from a distillation of N-methyl benzhydroxamic acid under similar conditions of temperature, pressure and distillation time in a bulb distillation apparatus of similar specification showed that the ratio of N-methyl-O-benzoylhydroxylamine to N-methyl benzhydroxamic acid had increased during the second distillation by a factor of 1.5.

(e) Stability of N-Methyl Benzhydroxamic Acid at Room Temperature

Samples of N-methyl benzhydroxamic acid (~ 0.025 g) were sealed in glass ampoules in the neat state and left to stand at room temperature. Periodically the ampoules were opened and assayed by infra-red spectroscopy (diethyl ether as solvent). Over five days trace formation (< 5% conversion) of N-methyl-N,O-dibenzoylhydroxylamine and of N-methyl-O-benzoylhydroxylamine occurred.

(f) Thermolysis of N-Methyl Benzhydroxamic Acid in a Sealed Tube

A sample of N-methyl benzhydroxamic acid (~ 1.0 g) in the neat state was sealed in a glass ampoule and placed in an oven thermostatted at 75.0-75.4° for 50 minutes. The ampoule was rapidly cooled and the contents analysed by infra-red spectroscopy. The reaction mixture was largely N-methyl benzhydroxamic acid (87 molar %) with very small amounts of the N-methyl-O-benzoylhydroxylamine (11 molar %) and of N-methyl-N,O-dibenzoylhydroxylamine (2 molar %).

(g) Stability of N-Methyl-O-Benzoylhydroxylamine

Samples of N-methyl-O-benzoylhydroxylamine (~ 0.025 g), obtained (a) from the distillate from the distillation of N-methyl benzhydroxamic acid (see p.135) and (b) by preparation from p-nitrophenyl benzoate and N-methylhydroxylamine were sealed in glass

ampoules in the neat state and left to stand at room temperature. Periodically, over the next few days, the ampoules were opened and assayed by infra-red spectroscopy, (diethyl ether as solvent).

Isomerisation of the N-methyl-O-benzoylhydroxylamine to N-methyl benzhydroxamic acid occurred with a half-life of approximately 20 hours, the carbonyl absorption at ~ 1640 $cm.^{-1}$ (due to(XXXXI)) increasing in intensity as the carbonyl absorption at 1725 $cm.^{-1}$ (due to (XXXXII)) decreased in intensity. At completion of isomerisation, the product was N-methyl benzhydroxamic acid containing a trace of N-methyl-N,O-dibenzoylhydroxylamine.

The N-methyl-O-benzoylhydroxylamine was stable in dilute solution, ~ 1% (wt./vol.) solutions of the compound in 40-60° petroleum ether, diethyl ether and carbon tetrachloride showing no change in the infra-red spectra over 100 hours at room temperature.

(h) Distillation of N-Methyl-O-Benzoylhydroxylamine

N-methyl-O-benzoylhydroxylamine was obtained as a colourless clear mobile oil by base extraction (0.2 M aqueous potassium hydroxide) of the distillate from the vacuum distillation of N-methyl benzhydroxamic acid. This product was bulb distilled under high vacuum in the usual way. Distillation of a colourless clear mobile oil occurred at 95-110° (oil bath temperature)/0.8 mm. pressure.

Infra-red spectral analysis showed this distillate to contain only N-methyl-O-benzoylhydroxylamine whilst the small amount of residue consisted mainly of N-methyl-N,O-dibenzoylhydroxylamine together with a little N-methyl-O-benzoylhydroxylamine.

(i) Thermal Stability of N-methyl-N,O-di-(p-methyl-benzoyl)-hydroxylamine

An ~ 10% wt./vol. solution of N-methyl-N,O-di-(p-methyl-

benzoyl)-hydroxylamine in deuterochloroform was stable at 120.5°, the NMR spectrum remaining unchanged over 20 minutes.

(j) Reaction of N-Methylhydroxylamine with N-Methyl-N,O-Dibenzoylhydroxylamine

1. Reaction at Atmospheric Pressure

Finely ground N-methyl-N,O-dibenzoylhydroxylamine (0.2378 g, 0.0009 mole) was placed in a long narrow glass ampoule with equimolar amounts of anhydrous sodium carbonate (0.0991 g, 0.0009 mole) and N-methylhydroxylamine hydrochloride (0.0783 g, 0.0009 mole) ground together as a paste. The reactants were thoroughly mixed by vibro-shaking, the end of the ampoule plugged with cotton wool, and the contents rapidly heated in an oil bath to and maintained at ~ 100-108° (oil bath temperature) at atmospheric pressure for 20 minutes. The reaction mixture melted to a yellow liquid. After thermolysis the reaction mixture was partially dissolved in diethyl ether, filtered from insoluble inorganic salts and the infra-red spectrum recorded. This revealed the presence of principally N-methyl benzhydroxamic acid with smaller amounts of N-methyl-O-benzoylhydroxylamine and of N-methyl-N,O-dibenzoylhydroxylamine.

2. Reaction at Reduced Pressure Under Distillation Conditions

N-methyl-N,O-dibenzoylhydroxylamine was mixed with equimolar quantities of N-methylhydroxylamine hydrochloride and anhydrous sodium carbonate and distilled under reduced pressure in a bulb distillation apparatus.

N-Methylhydroxylamine hydrochloride (0.0445 g, 0.0005 mole) was added to finely ground N-methyl-N,O-dibenzoylhydroxylamine (0.1359 g, 0.0005 mole) in a bulb distillation apparatus and put under vacuum to remove any adsorbed water. Anhydrous sodium carbonate (0.0564 g, 0.0005 mole) and a few anti-bumping granules

were added, the contents thoroughly mixed by vibro-shaking, and the distillation bulb rapidly immersed in an oil bath at 140°. The organic components rapidly melted and after one minute the apparatus was put under vacuum. A clear colourless oil rapidly distilled at 145° (oil bath temperature)/1.0 mm. pressure and was collected in an air cooled receiving bulb.

The residue and distillate were separated and their infra-red spectra recorded. The residue (a light yellow-brown solid, 0.1502 g) was principally N-methyl-N,O-dibenzoyl-hydroxylamine with a small amount of N-methyl benzhydroxamic acid, whilst the distillate (0.1044 g) was a mixture of N-methyl-O-benzoylhydroxylamine and N-methyl benzhydroxamic acid.

(k) Trapping of Free N-Methylhydroxylamine in the Distillation of N-Methyl Benzhydroxamic acid

In an attempt to trap and identify any gaseous products being lost during the vacuum distillation of N-methyl benz-hydroxamic acid a distillation was conducted in a bulb distillation apparatus which was connected to a vacuum line via a liquid nitrogen cooled U-tube.

N-Methyl benzhydroxamic acid (0.88 g) and a few anti-bumping granules contained in a standard size bulb distillation apparatus were placed under high vacuum to ensure complete removal of solvent, the apparatus connected to a U-tube trap and re-evacuated.

The N-methyl benzhydroxamic acid was carefully distilled using a stirred heated oil bath, the receiving bulb cooled in a current of air and the U-tube cooled in a dewar of liquid nitrogen. A colourless clear oil distilled at 125-136° (oil bath temperature)/ 0.9 mm. The residue and distillate were separated and their IR spectra recorded. The distillate (0.59 g) was a mixture of N-methyl-O-benzoylhydroxylamine and N-methyl benzhydroxamic acid

whilst the residue was principally N-methyl-N,O-dibenzoyl-hydroxylamine with some N-methyl-O-benzoylhydroxylamine and N-methyl benzhydroxamic acid. Approximately 0.5 ml of a colourless clear liquid containing traces of a white solid were trapped in the liquid nitrogen cooled U-tube.

This liquid was identified as N-methylhydroxylamine by comparison of its infra-red spectrum with that of[106] an authentic sample.

(1) Quantitative Distillations of Some N-Methyl Hydroxamic Acids

The components of distillate and residue from the quantitative bulb distillation under reduced pressure of several N-methyl hydroxamic acids were estimated by quantitative infra-red analysis.

A weighed amount (0.5 - 1.0 g) of the N-methyl hydroxamic acid was distilled according to the procedure outlined on p.135. The weight loss occurring during distillation was measured and calculated in terms of mmoles of free N-methylhydroxylamine for 100 mmoles of starting acid (Table (2.1)). The residue and distillate were separated, weighed and subjected to quantitative infra-red analysis, each component exhibiting a distinct carbonyl absorption (the ester carbonyl frequency was employed in the analysis of the N-methyl-N,O-diaroylhydroxylamines).

(iii) Cross-over Studies

Experiment (a)

An intimate mixture of N-methyl p-methoxy-benzhydroxamic acid (LVII) (0.0543 g, 3.0 x 10^{-4} moles) and N-benzylhydroxylamine (0.2239 g, 18 x 10^{-4} moles) was distilled under 0.3 - 0.25 mm. pressure in a bulb distillation apparatus (see p.135for procedure). The mixture became completely molten at 85° and distillation occurred at 100-140° (oil bath temperatures). The small amount of residue was a pale amber oil and the distillate a white crystalline solid/colourless clear oil mixture. The residue and distillate were combined by dissolution in chloroform and the IR spectrum recorded. After removal of the solvent under reduced pressure at room temperature the mass spectrum was recorded. A loss in weight of 0.0079 g occurred during distillation. IR spectrum of combined residue and distillate ($CHCl_3$):

3582 (m) O-H stretch of BzNHOH, 3500-3130 (s), 2950-2850 (w), 1953 (w), 1900-1870 (w), 1810 (w), 1716 (m) and 1609 (s) C=O vibrations, 1497 (m), 1456 (w), 1309 (w), 1171 (w), 1016 (m), 950 (m), 889 (m), 841 (w).

Mass spectrum of combined residue and distillate:

46(2), 74 (1), 91 (100), 106 (3), 107 (2), 122 (1), 123 (33), 135 (12), 150 (0.1), 151 (0.2), 181 (0.9), 257 (0.1).

No ions of m/e > 257 were observed.

Experiment (b)

N-methyl p-methoxy-benzhydroxamic acid(0.0510 g, 2.8 x 10^{-4} moles) in a glass tube sealed at one end was weighed, placed under vacuum (0.5 mm) and immersed in an oil bath at 115° for 20 minutes. Melting to a clear liquid occurred. After thermolysis the tube and contents were reweighed and the contents analysed by IR spectroscopy and mass spectrometry which showed a small amount of rearrangement to (LVIII) and trace formation of (LIX). A weight loss of

0.0009 g occurred during the experiment.

IR spectrum ($CHCl_3$): 3400-3000 (m) O-H stretch, 3000 (w), 2970 (w), 2942 (w), 2845 (w), 1757 (w) and 1715 (m) and 1662 (w) and 1611 (s) C=O vibrations, 1578 (w), 1512 (m), 1463 (m), 1416 (m), 1308 (m), 1259 (s), 1173 (s), 1120-1085 (m), 1031 (m), 931 (m), 845 (m).

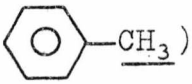
Mass spectrum: 46 (1), 74 (1), 107 (7), 135 (100), 181 (3), 315 (< 0.2).

Experiment (c)

An ~1% (wt./vol.) solution of (LVII) in 1,4-dioxan was assayed by IR spectroscopy and sealed in a glass ampoule. The dioxan (Fisons Analytical Reagent) had been freed from peroxides by percolation through a column of neutral aluminium oxide, "CAMAG" M.F.C, 100-240 mesh) immediately prior to use.

The ampoule was immersed in an oil bath at 100° for 20 minutes, then cooled to room temperature. The IR spectrum of the contents was unchanged.

IR spectrum (1,4-dioxan): 3400-3100 (m) O-H stretch, 1634 (s) and 1611 (s) C=O vibrations, 1578 (w), 1513 (m), 1407 (m), 1351 (w), 1212 (w), 930 (m), 836 (m), 800 (w), 761 (s), 720 (w), 698 (w).

An ~10% (wt./vol.) solution of N-methyl p-methyl-benzhydroxamic acid in deuterochloroform in a sealed NMR tube showed no change in its NMR spectrum (δ7.55, 7.41, 7.30, 7.16 quartet, aromatic protons; δ3.37 singlet, N-$\underline{CH_3}$; δ2.37 singlet, ) over 20 minutes at 120°.

Experiment (d)

An equimolar mixture of N-methyl p-methoxy-benzhydroxamic acid (0.0544 g, 3.0×10^{-4} moles) and N-benzylhydroxylamine (0.0370 g, 3.0×10^{-4} moles) was placed in a glass ampoule and vibro-shaken to homogenise the mixture. After evacuating to 0.6 mm.pressure, the

ampoule was immersed in an oil bath at 100° for 20 minutes. The N-methyl p-methoxy-benzhydroxamic acid dissolved completely in the molten N-benzylhydroxylamine and during the thermolysis white needles condensed on the cool part of the ampoule outside of the oil bath. These white needles (0.0237 g) of m.p. 55.5-57° were N-benzylhydroxylamine (lit. m.p. 57° [147]) which had distilled out of the system (also identified by IR analysis). The residue (0.0641 g), a clear very pale yellow oil was subjected to IR and mass spectrometric analysis. A weight loss of 0.0047 g occurred during the thermolysis.

IR spectrum of residue ($CHCl_3$); 3400-3000 (m), 3000 (w), 2841 (w), 1714 (m) and 1611 (s) C=O vibrations, 1580 (w), 1512 (m), 1461 (w), 1414 (m), 1372 (m), 1308 (w), 1259 (s), 1173 (s), 1120-1085 (m), 1031 (m), 930 (w), 844 (m).

Mass spectrum of residue: 46 (4), 74 (1), 106 (1), 107 (9), 122 (1), 123 (1), 135 (100), 150 (0.25) 151 (0.25), 181 (5), 257 ($<$ 0.05). No ions of m/e $>$ 257 were observed.

Experiment (e)

Experiment (d) was repeated using the same equimolar quantities but conducting the thermolysis at 70° under 0.55 mm. pressure for 20 minutes. At this lower temperature only a small amount (0.0092 g) of the N-benzylhydroxylamine distilled out to condense on the cool walls of the ampoule as white needles. The residue (0.0793 g) was subjected to IR and mass spectrometric analysis. The weight loss occurring during the experiment was 0.0027 g.

IR spectrum of residue ($CHCl_3$): 3574 (w) O-H stretch of BzNHOH, 3400-3000 (m), 3000 (w), 2841 (w), 1714 (m) and 1611 (s) C=O vibrations, 1577 (w), 1512 (m), 1458 (m), 1414 (m), 1373 (m), 1308 (m), 1259 (s), 1173 (s), 1120-1085 (m), 1031 (m), 930 (w), 843 (m).

Mass spectrum of residue: 46 (2), 74 (2), 106 (7), 107 (11), 122 (2), 123 (4), 135 (100), 150 (1), 151 (1), 181 (8), 257 (< 0.5).

No ions of m/e > 257 were observed.

Experiment (f)

An ~10% (wt./vol.) solution of N-methyl-N,O-di (p-toluoyl)-hydroxylamine in deuterochloroform sealed in an NMR tube showed no change in the NMR spectrum for 20 minutes at 120°.

Experiment (g)

An equimolar mixture of N-methyl-N,O-dibenzoylhydroxylamine (0.0756 g, 3.0×10^{-4} moles) and N-benzylhydroxylamine (0.0369 g, 3.0×10^{-4} moles) was left in the solid state in a glass ampoule sealed by a rubber stopper, at room temperature. After 2½ hours the mixture was examined by IR spectroscopy which revealed the presence of considerable amounts of O-benzoyl and N-benzoyl hydroxylamines together with unreacted N-methyl-N,O-dibenzoyl-hydroxylamine.

IR spectrum after 2½ hours ($CHCl_3$): 3578 (w) O-H stretch of BzNHOH, 3400-3000 (m), 3002 (w), 1764 (s) and 1721 (m) and 1664 (s) and 1622 (m) C=O vibrations, 1605 (w), 1580 (w), 1497 (w), 1454 (m), 1411 (m), 1373 (m), 1320 (w), 1270-1200 (s), 1180 (w), 1120-1085 (m), 1067 (w), 1010 (s), 938 (w).

Experiment (h)

An equimolar mixture of N-methyl-N,O-dibenzoylhydroxylamine (0.0781 g, 3.06×10^{-4} moles) and N-benzylhydroxylamine (0.0370 g, 3.0×10^{-4} moles) in a glass ampoule was vibro-shaken to mix the compounds thoroughly. On immersion in an oil bath at 100°, whilst under 0.5 mm. pressure, immediate melting to a clear colourless liquid occurred. After 20 minutes the ampoule was removed. A small amount (0.0027 g) of N-benzylhydroxylamine had distilled and

condensed on the cool part of the ampoule as white needles of m.p. 57° (lit. 57° [147]). The residue (0.1118 g) was subjected to IR and mass spectrometric analysis. No significant weight loss (0.0006 g) occurred during the thermolysis.

IR spectrum of residue ($CHCl_3$): 3500-3000 (m), 3240 (w) N-H stretch, 3002 (w), 1762 (w) and 1721 (s) and 1664 (w) and 1622 (s) C=O vibrations, 1604 (w), 1578 (w), 1497 (w), 1454 (m), 1413 (m), 1376 (m), 1320 (m), 1271 (s), 1180 (w), 1106 (m), 1093 (m), 1069 (m), 1029 (w), 940 (w).

Mass spectrum of residue: 30 (0.25), 46 (0.25), 74 (1), 77 (40), 105 (100), 106 (8), 121 (0.5), 122 (8), 123 (0.75), 134 (0.3), 150 (0.05), 151 (7), 210 (0.5), 227 (1), 255 (< 0.025).

No ions of m/e $>$ 255 were observed.

Experiment (i)

N-benzyl p-methoxy-benzhydroxamic acid (0.0397 g, 1.54×10^{-4} moles) was distilled at 0.5 mm. pressure in a micro bulb distillation apparatus using a procedure similar to that described on p.135. Melting of the hydroxamic acid occurred when the oil bath temperature reached 107-110°, and distillation occurred at 165°. The residue (0.0110 g) was a dark brown-orange oil and the distillate (0.0257 g) was a white solid and clear colourless oil. A weight loss of 0.0005 g occurred during the distillation.

The residue and distillate were examined by IR and mass spectrometric analysis.

IR spectrum of residue ($CHCl_3$): 3454 (w), 3440-3000 (m), 3005 (w), 2845 (w), 1756 (m) and 1690-1630 (s) and 1611 (s) C=O vibrations, 1581 (w), 1512 (s), 1500 (s), 1458 (w), 1443 (w), 1408 (w), 1352 (w), 1310 (m), 1258 (s), 1173 (s), 1116 (m), 1031 (m), 1009 (w), 978 (w), 846 (m).

Mass spectrum of residue: 106 (4), 107 (16), 122 (9), 123 (2), 134 (1), 135 (100), 150 (2), 151 (9), 152 (60), 240 (0.1), 241 (0.5), 257 (0.1), 391 (0.5).

IR spectrum of distillate ($CHCl_3$): 3440-3000 (m), 2842 (w), 1690 (m) and 1610 (s) C=O vibrations, 1582 (w), 1512 (m), 1456 (w), 1407 (m), 1318 (w), 1304 (w), 1258 (s), 1171 (s), 1111 (m), 1031 (w), 951 (w), 930 (w), 870 (w), 848 (w).

Mass spectrum of distillate: 106 (20), 107 (18), 122 (4), 134 (0.5), 135 (96), 150 (0.25), 151 (5), 152 (100), 241 (0.5), 257 (0.5). No ions of m/e $>$ 257 were observed.

(iv) The Determination of Ionisation Constants

The pKa values of N-methyl benzhydroxamic acid, N-methyl p-methoxy-benzhydroxamic acid, N-methyl p-nitro-benzhydroxamic acid and N-methylhydroxylamine hydrochloride were determined at a constant ionic strength of 0.1 M by measuring the pH of a solution of the compound near the point of half neutralisation and applying the Henderson-Hasselbach equation.

All volumetric solutions were made up using carbon dioxide free distilled water. This was obtained by boiling distilled water for 10-15 minutes, allowing to cool and using immediately. Standard aqueous solutions of sodium hydroxide were prepared by diluting British Drug Houses CVS concentrated volumetric solution with this water.

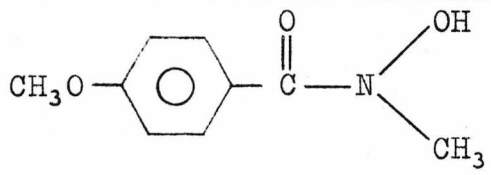
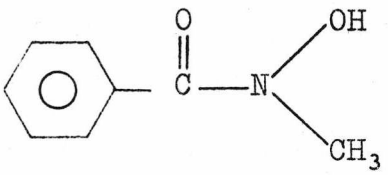
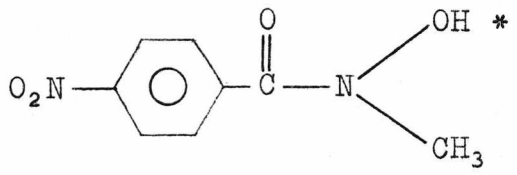
pH measurements were conducted using a Radiometer pH meter type PHM 25b fitted with a glass electrode and a calomel electrode, the meter being standardised with standard Radiometer buffer at $25.0 \pm 0.1^{\circ}$.

A known weight of the compound (0.0001 ± 0.00001 mole) was dissolved in 8 ml of a 0.10625 molar aqueous solution of potassium chloride in the electrode cell of the pH meter which was thermostatted at $25.0 \pm 0.1^{\circ}$. After allowing the solution 15 minutes to equilibrate thermally, 0.500 ml of a 0.1 N aqueous solution of sodium hydroxide (5×10^{-5} mole) was added from a micrometer operated syringe and the solution allowed to equilibrate to 25.0°. Throughout the determination a slow stream of nitrogen was passed over the surface of the solution in the electrode cell. The pH was then measured.

The mean values of three determinations of the pKa of N-methylhydroxylamine hydrochloride, N-methyl benzhydroxamic acid, N-methyl p-methoxy-benzhydroxamic acid and N-methyl p-nitro-

benzhydroxamic acid are given in Table (5.6). The pKa of the latter two hydroxamic acids was determined for comparison with the pKa of N-methyl benzhydroxamic acid as these two compounds were readily purified to analytical purity by recrystallisation, the N-methyl benzhydroxamic acid, being an oil, not being so easy to purify.

Table (5.6). pKa values (I = 0.1 M, 25°) of Various N-Methyl Benzhydroxamic Acids and of N-Methylhydroxylamine Hydrochloride.

Compound	pKa
	8.62
	8.58
	8.13
$NH(CH_3)OH.HCl$	6.24 (Lit. 6.002[105])

*Owing to its insolubility in water, 0.02×10^{-3} mole of this compound were employed per determination of pKa.

CHAPTER VI

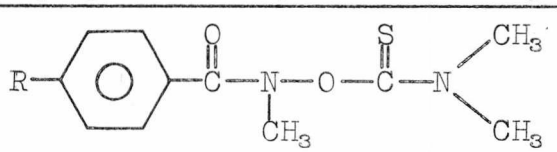
THE THERMAL REARRANGEMENT OF O-THIOCARBAMOYLATED N-METHYL HYDROXAMIC ACIDS.

(i) Preparative Methods

(a) Materials

The hydroxamic acids were prepared as outlined on p.114. N,N-dimethylthiocarbamoyl chloride was supplied by the Aldrich Chemical Co., Inc. and N,N-dimethylcarbamoyl chloride by Koch-Light Laboratories, Ltd. The latter compound was purified by distillation under reduced pressure and the fraction boiling at 22-23°/0.06mm. (85-88°/55-60mm.)[158] employed. The acid chlorides have been described (p. 113). Triethylamine was supplied by Hopkin and Williams Ltd. (General Purpose Reagent), and methylamine and carbon oxysulphide by the British Drug Houses Laboratory Gas Service. N,N-dimethylformamide (Fisons Laboratory Reagent grade) was dried over molecular sieves, decanted and partially distilled under reduced pressure, the first 10-20% discarded and the residue stored. The 36% wt./vol. formaldehyde (Analar) solution and the resublimed iodine were B.D.H. reagents. Fisons Ltd. supplied methylamine as a 25% wt./vol. aqueous solution (Laboratory Reagent) and Ralph N. Emanuel, Ltd. supplied p-thiocresol and sym-dimethylhydrazine dihydrochloride.

(b) Preparation of the N-Aroyl O-(N',N'-Dimethylthiocarbamoyl)-N-Methylhydroxylamines, (LXXXI),



(R = CH_3O, CH_3, H, O_2N).

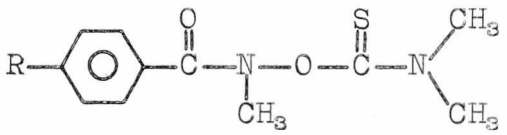
A solution of the respective N-methyl benzhydroxamic acid

(0.045 mole) in triethylamine (4.55g., 0.045 mole) and N,N-dimethylformamide (30ml) was added to a stirred solution of N,N-dimethylthiocarbamoyl chloride (8.34g, 0.0675 mole) in N,N-dimethylformamide (60ml) at room temperature. On making the addition the very pale yellow colour of the N,N-dimethylthiocarbamoyl chloride immediately intensified. After stirring for 1½ hours at room temperature the reaction mixture containing a suspension of fine white particles of triethylamine hydrochloride was poured into an ice/water mixture (~800ml) and the resulting solid precipitate filtered off, washed several times with water and sucked dry.

This solid was recrystallised in the cold by dissolution in the minimum volume of benzene, clouding with 40-60° petroleum ether and cooling in ice. Recrystallised to constant m.p. Each compound gave one spot on TLC.

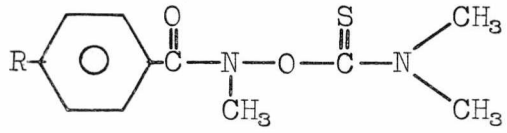
These compounds were stable in the solid state at room temperature for at least a year.

Total yields of <u>N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamines</u>,



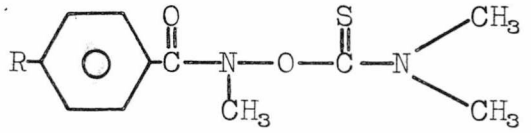
R = CH_3O, 5.1g, 43% ; R = CH_3, 4.1g, 37% ; R = H, 5.0g, 46% ; R = O_2N, 9.1g, 71% .

TABLE (6.1). ANALYTICAL DATA FOR THE N-AROYL-O-(N',N'-DIMETHYLTHIOCARBAMOYL)-N-METHYLHYDROXYLAMINES, (LXXXI).



R	ANALYSIS Calculated C	H	N	Found C	H	N	M.p.	Crystalline state
CH_3O	53.7	6.0	10.4	54.0	6.1	10.45	86.5-87.5°	White needles
CH_3	57.1	6.4	11.1	57.9	6.6	11.15	99-101°	White needles
H	55.5	5.9	11.8	55.3	5.9	11.6	55-56°	White needles
O_2N	46.65	4.6	14.8	46.2	4.7	14.8	131-134°, dec.	Cream coloured micro-crystalline solid

TABLE (6.2). THE INFRA-RED SPECTRA OF (LXXXI).

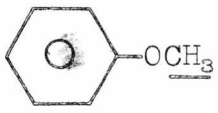
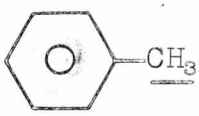


R	Absorptions ($cm.^{-1}$) in the infra-red spectra (A.R. $CHCl_3$); Range 4000 -625 $cm.^{-1}$, Their relative intensities and assignments. s = strong, m = medium, w = weak.
CH_3O	2978 (m) C-H stretch of CH_3, 1653 (s) C=O vibration, 1403 (s), 1286 (s), 1176 (s), 1089 (s) C=S stretching vibration, 977 (w) N-O stretch.
CH_3	Recorded in Table (3.1).
H	2986 (m) C-H stretch of CH_3, 1661 (s) C=O vibration, 1402 (s), 1286 (s), 1174 (m), 1092 (s) C=S stretching vibration, 977 (w) N-O stretch.
O_2N	2988 (m) C-H stretch of CH_3, 1665 (s) C=O vibration, 1404 (s), 1284 (s), 1176 (m), 1079 (m) C=S stretching vibration, 977 (w) N-O stretch.

UV DATA FOR (LXXXI) IN HEXANE SOLUTION

R = CH_3O:	λmax 214mμ	(ε 9,900)	ascribed to the amide carbonyl group
	λmax 254mμ	(ε16,000)	ascribed to the -O-C(=S)- moiety
R = CH_3:	λmax 214mμ	(ε 9,200)	ascribed to the amide carbonyl group
	λmax 251mμ	(ε14,400)	ascribed to the -O-C(=S)- moiety
R = H:	λmax 212mμ	(ε 9,300)	ascribed to the amide carbonyl group
	λmax 253mμ	(ε12,700)	ascribed to the -O-C(=S)- moiety
R = O_2N:	λmax 207mμ	(ε10,600)	ascribed to the amide carbonyl group
	λmax 253mμ	(ε18,200)	ascribed to the -O-C(=S)- moiety

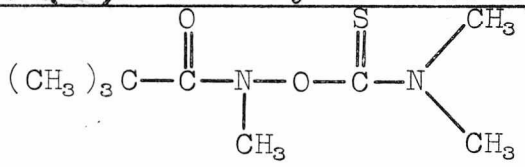
NMR DATA FOR (LXXXI) IN DEUTEROCHLOROFORM

R = CH_3O:	δ 7.76, 7.61, 7.00, 6.86 Quartet	Aromatic protons
	δ 3.86 Singlet	
	δ 3.50 Singlet	N-CH_3
	δ 3.34 and 3.09 Doublet	N-$(CH_3)_2$
R = CH_3 :	δ 7.63, 7.50, 7.26, 7.12 Quartet	Aromatic protons
	δ 3.48 Singlet	N-CH_3
	δ 3.29 and 3.01 Doublet	N-$(CH_3)_2$
	δ 2.35 Singlet	
R = H :	δ 7.80 - 7.20	Aromatic protons
	δ 3.50 Singlet	N-CH_3
	δ 3.38 and 3.14 Doublet	N-$(CH_3)_2$
R = O_2N :	δ 8.38, 8.23, 7.92, 7.77 Quartet	Aromatic protons
	δ 3.50 Singlet	N-CH_3
	δ 3.29 and 3.05 Doublet	N-$(CH_3)_2$

Note that in (LXXXI) the N-$(CH_3)_2$ methyl groups are non-equivalent whilst they become equivalent in the rearranged isomer, (LXXXII).

THE MASS SPECTRA were in accord with the structures assigned to (LXXXI), giving appropriate values of the molecular ion.

(c) **N-Pivalyl-O-(N',N'-Dimethylthiocarbamoyl)-N-Methyl-hydroxylamine,**



In view of the solubility of the title compound in water, diethyl ether was employed as the reaction solvent.

A solution of N-methyl pivalohydroxamic acid (11.81g, 0.09 mole) in triethylamine (9.11g, 0.09 mole) and sodium dried diethyl ether (50ml) was added to a stirred solution of N,N-dimethylthiocarbamoyl chloride (12.36g, 0.10 mole) in sodium dried diethyl ether (50ml) at room temperature. On making the addition a small amount of white solid precipitated out of solution. After 1⅝ hours the ether solution was washed with a small quantity of water (2 x 10ml), dried over anhydrous magnesium sulphate, filtered, rotary evaporated at room temperature and put under high vacuum to yield an orange oily solid.

The material was partially dissolved in benzene at room temperature. The insoluble triethylamine hydrochloride was filtered off, washed with benzene and the filtrate clouded with 40-60° petroleum ether and left to stand at room temperature. A small amount of white needles crystallised out. The mother liquor was decanted off, 40-60° petroleum ether added and the solution cooled in ice when crystallisation occurred. The liquid was decanted off from the small amount of yellow crystalline solid.

This mother liquor was rotary evaporated at room temperature and then put under high vacuum to leave a clear mobile yellow oil which contained the required N-pivalyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine.
Yield = 11.0g (56%).

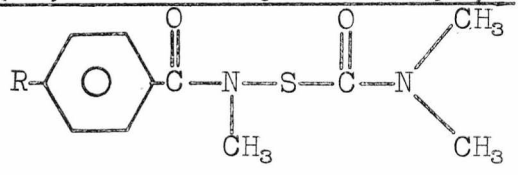
A solution of this oil in Analar grade chloroform immediately decolourised DPPH at room temperature. In view of the instability of this material it was not purified further.

IR spectrum ($CHCl_3$ A.R.): 2938 (s) C-H stretch of CH_3, 1680-1640 (s) C=O vibration, 1099 (s) C=S stretching vibration.

UV spectrum (hexane): λmax 224mμ (ε not measured as sample impure)
λmax 275mμ

The mass specttum was in accord with the assigned structure, giving a molecular ion of m/e 218.

(d) **Preparation of the N-Aroyl-S-(N',N' -Dimethylcarbamoyl)-N-Methylhydrosulfamines, (LXXXII),**



(R = CH_3O, CH_3, H).

The title compounds (LXXXII),(R = CH_3O, CH_3, H) were prepared by allowing a solution of 2.0g of the respective N-aroyl-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine (LXXXI) in 40ml Analar grade chloroform (a 5% wt./vol. solution) in a stoppered flask, to stand at room temperature. The spontaneous rearrangement of (LXXXI) to (LXXXII) was followed by infra-red spectroscopy. After 240 hours TLC showed a complete loss of starting material to have occurred. NMR showed there to be ca. 95% (LXXXII) and ca. 5% N-methyl p-substituted benzamide present.

The solution was evaporated at room temperature to leave a colourless oil (golden yellow when R=H). On storage under high vacuum, partial or total crystallisation occurred. The product was fractionally recrystallised to constant m.p. from benzene/40-60° petroleum ether at room temperature. Yields of (LXXXII): R = CH_3O, 0.51g, 26%; R = CH_3, 0.26g, 13%; R = H, 0.66g, 33%.

(e) N-(p-Nitro-benzoyl)-S-(N',N' -Dimethylcarbamoyl)-N-Methylhydrosulfamines, (LXXXII); R = O_2N.

Difficulty was experienced in obtaining the p-nitro substituted compound (LXXXII); R = O_2N, on a preparative scale by rearrangement of (LXXXI); R = O_2N in solution.

(1) A solution of 5.0g of (LXXXI); R = O_2N in 100ml Analar chloroform was left in a stoppered flask at room temperature. After 23 days infra-red analysis showed no conversion to (LXXXII); R = O_2N but some carbon oxysulphide was present (ν 2045 $cm.^{-1}$).

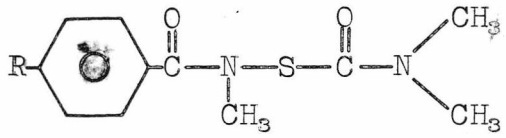
(2) A solution of 0.2g of (LXXXI); R = O_2N in 4ml Analar chloroform was refluxed for 10½ hours. Infra-red spectroscopic analysis (in $CHCl_3$ A.R.) indicated nearly complete loss of starting material with principally formation of N-methyl p-nitro benzamide and possibly some formation of the rearranged isomer.

(3) In view of the results of experiments (1) and (2) above, the solution of 5.0g of (LXXXI); R = O_2N in 100ml Analar chloroform which had been used in experiment (1) was maintained at 45° and periodically sampled and assayed by infra-red spectroscopy. After 75 hours the IR spectrum indicated considerable loss of starting material and formation of N-methyl p-nitro benzamide.

After 120 hours the IR spectrum indicated an increase in the amount of carbon oxysulphide present (2045 $cm.^{-1}$). Despite this inability to obtain the p-nitro substituted compound (LXXXII); R = O_2N on a preparative scale, CIDNP resonances (p.94 and 97) are observed totally consistent with product being formed in small quantities (<25%) in deutero-chloroform at 120°. Attempted chromatographic separation of

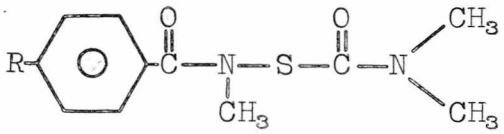
this compound from the product mixture was unsuccessful. No explanation is apparent for the slow rearrangement/decomposition of (LXXXI); R = O_2N in chloroform, although nitro compounds can inhibit free radical chain reactions[159] which have been postulated as a contributing mechanism (p.71) in chlorinated solvents.

TABLE (6.3). ANALYTICAL DATA FOR THE N-AROYL-S-(N',N'-DIMETHYLCARBAMOYL)-N-METHYLHYDROSULFAMINES, (LXXXII).



R	ANALYSIS Calculated C	H	N	Found C	H	N	M.p.	Crystalline state
CH_3O	53.7	6.0	10.4	53.9	6.1	10.5	103.5-106°	White prisms
CH_3	57.1	6.4	11.1	57.4	6.4	10.8	99-103°	White prisms
H	55.5	5.9	11.8	56.05	5.9	11.8	78.5-80°	White platelets
O_2N	Not obtained in pure state.							

TABLE (6.4). THE INFRA-RED SPECTRA OF (LXXXII).

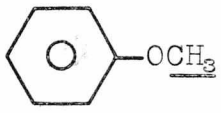
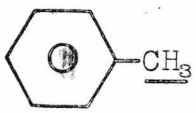


R	Absorptions ($cm.^{-1}$) in the infra-red spectra (A.R. $CHCl_3$); Range 4000-625 $cm.^{-1}$, Their relative intensities and assignments. s = strong, m = medium, w = weak.
CH_3O	2998 (m) C-H stretch of CH_3, 1685 (s) (1645-1700) C=O vibration, 1612 (s), 1513 (m), 1462 (w), 1442 (w), 1412 (m), 1373 (m), 1322 (s), 1308 (w), 1251 (s), 1176 (s), 1101 (s), 1023 (m), 1009 (m), 908 (w), 842 (m).
CH_3	Recorded in Table (3.1).
H	2990 (m) C-H stretch of CH_3, 1682 (s) (1635-1705) C=O vibration, 1443 (w), 1411 (m), 1372 (m), 1325 (s), 1259 (m), 1100 (s), 1034 (w), 1018 (s), 905 (w).
O_2N	Not obtained in a pure state.

UV DATA FOR (LXXXII) IN HEXANE SOLUTION

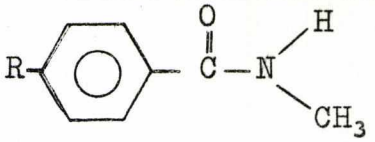
R = CH_3O:	Small shoulder at	221mμ	(ϵ 6,500)	ascribed to the amide carbonyl group
	λmax	236mμ	(ϵ 7,900)	ascribed to the -S-C(=O)- moiety
R=CH_3 :	λmax	212mμ	(ϵ11,200)	ascribed to the amide carbonyl group
	Shoulder at	223mμ	(ϵ11,200)	ascribed to the -S-C(=O)- moiety
R=H :	λmax	230mμ	(ϵ 4,200)	ascribed to the -S-C(=O)- moiety
	No other λmax (shoulder or peak)			
R=O_2N :	Not obtained in a pure state			

NMR DATA FOR (LXXXII) IN DEUTEROCHLOROFORM

R = CH_3O:	δ 7.85, 7.70, 6.97, 6.82 Quartet	Aromatic protons
	δ 3.81 Singlet	
	δ 3.35 Singlet	$N-CH_3$
	δ 2.82 Singlet	$N-(CH_3)_2$
R = CH_3:	δ 7.45, 7.32, 7.16, 7.02 Quartet	Aromatic protons
	δ 3.30 Singlet	$N-CH_3$
	δ 2.80 Singlet	$N-(CH_3)_2$
	δ 2.33 Singlet	
R = H:	δ 8.0-7.2	Aromatic protons
	δ 3.36 Singlet	$N-CH_3$
	δ 2.84 Singlet	$N-(CH_3)_2$
R = O_2N:	δ 8.05 - 7.51	Aromatic protons
	δ 3.35 Singlet	$N-CH_3$
	δ 2.83 Singlet	$N-(CH_3)_2$

THE MASS SPECTRA were in accord with the structures assigned to (LXXXII), giving appropriate values of the molecular ion.

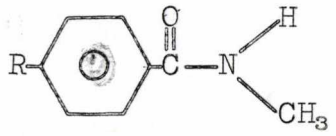
(f) The N-Methyl p-substituted Benzamides, (C̄),



(R = CH_3O, CH_3, H, O_2N).

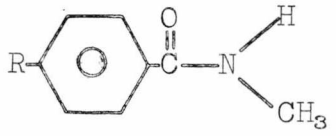
The title compounds were prepared by reaction of methylamine with the aroyl chloride dissolved in sodium dried benzene. Recrystallised from hot water.

TABLE (6.5). ANALYTICAL DATA FOR THE N-METHYL p-SUBSTITUTED BENZAMIDES, (C).



R	ANALYSIS Calculated C	H	N	Found C	H	N	M.p.	Crystalline state
CH_3O	65.4	6.7	8.5	65.7	6.9	8.4	121-122° Lit.[160] 117-119°	White prisms
CH_3	72.5	7.4	9.4	72.3	7.7	9.3	147-148° Lit.[161] 145°-145.5	White needles
H	71.1	6.7	10.4	71.1	7.0	10.1	85-87° Lit.[162] 79°	White platelets
O_2N	53.3	4.5	15.55	53.0	4.5	15.5	220-222° Lit.[163] 217°	White fine needles

TABLE (6.6). THE INFRA-RED SPECTRA OF ($\overline{C}$).

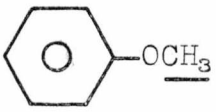


R	Absorptions (cm^{-1}) in the infra-red spectra (run in $CHCl_3$ A.R.); Range 4000-625 cm^{-1}, Their relative intensities and assignments. s = strong, m = medium, w = weak.
CH_3O	3462 (m) N-H (free) stretch, 2990 (m) C-H stretch of CH_3, 1658 (s) C=O vibration, 1533 (m) and 1501 (s) Amide II Band, 1284 (w) Amide III Band.
CH_3	3476 (m) N-H (free) stretch, 3002 (m) C-H stretch of CH_3, 1662 (s) C=O vibration, 1537 (s) and 1507 (s) Amide II Band, 1284 (s) Amide III Band.
H	3460 (m) N-H (free) stretch, 2990 (m) C-H stretch of CH_3, 1661 (s) C=O vibration, 1527 (s) Amide II Band, 1284 (m) Amide III Band.
O_2N (in $CHCl_3$ A.R.)	3448 (m) N-H (free) stretch, 2998 (m) C-H stretch of CH_3, 1671 (s) C=O vibration, 1526 (s) Amide II Band, 1284 (m) Amide III Band.
O_2N (KBr Disc)	3328 (s) N-H stretch, 3100 (w) and 3070 (w) C-H stretch of CH_3, 1650 (s) C=O vibration, 1553 (s) and 1513 (s) Amide II Band.

NMR DATA FOR (C) IN DEUTEROCHLOROFORM

R = CH_3O: δ 7.90, 7.75, 6.95, 6.80 Quartet Aromatic protons

N-H proton hidden under aromatic protons

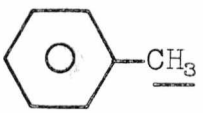
δ 3.81 Singlet 

δ 2.98 and 2.91 Doublet $N-CH_3$

R = CH_3 : δ 7.76, 7.62, 7.27, 7.13 Quartet Aromatic protons

δ 6.72 Broad singlet N-H

δ 3.00 and 2.92 Doublet $N-CH_3$

δ 2.36 Singlet 

R = H: δ 7.93 - 7.28 Aromatic protons

δ 3.03, 2.97 Doublet $N-CH_3$

R = O_2N : δ 8.38, 8.23, 8.01, 7.87 Quartet Aromatic protons

δ 3.07, 3.00 Doublet $N-CH_3$

(g) Benzophenone Oxime N,N-Dimethylthionocarbamate (LXXV), Benzophenone Thioxime N,N-Dimethylcarbamate (LXXVI) and Benzophenone Oxime N,N-Dimethylcarbamate (LXXVII).

The title compounds were kindly supplied by Dr. A.J.Lawson, (IR data collected in Table (3.1)).

(h) N-Benzoyl-O-(N',N'-Dimethylcarbamoyl)-N-Methylhydroxylamine. (LXXVIII).

A solution of N-methyl benzhydroxamic acid (6.05 g, 0.04 mole) and triethylamine (4.0 g, 0.04 mole) in diethyl ether (100 ml, sodium dried) was added to a stirred solution of N,N-dimethylcarbamoyl chloride (4.28 g, 0.04 mole) in ether (25 ml, sodium dried). After five hours the pale yellow solution was washed with water, dried over anhydrous magnesium sulphate, filtered and rotary evaporated to yield impure (LXXVIII) as a pale yellow oil/solid mixture. Yield = 4.4 g. (50%).

Purified by partial dissolution in benzene, the insoluble pale yellow crystalline solid being filtered off (3.4 g) and the filtrate rotary evaporated to leave (LXXVIII) as a clear pale yellow mobile oil. Yield = 0.9 g.

Analysis. Found: C, 59.7; H, 6.4; N, 12.8.

$C_{11}H_{14}N_2O_3$ requires C 59.45; H, 6.35; N, 12.6.

IR spectrum: reported in Table (3.1).

(i) Bis-(dimethylcarbamoyl) Disulphide. (LXXIX).

Bis-(dimethylcarbamoyl) disulphide was prepared by the method described by Gregg.[164] M.p. 87-91° (Lit.[164] 90-91° (uncor.)). Yield = 19%.

The disulphide was stored at -25°, at which temperature it could be kept pure indefinitely.

IR spectrum: reported in Table (3.1).

NMR (deuterochloroform): δ 3.11 Singlet $N-(CH_3)_2$

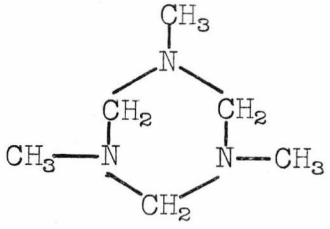
(j) p-Methyl-Phenyl N,N-Dimethylthiolcarbamate,(LXXX).

p-Methyl-phenyl N,N-dimethylthiolcarbamate was prepared according to the method outlined by Miyazaki.[126]

A white micro-crystalline solid. M.p. 35.5-37.5°. (Lit.[126] 36-37°). Yield = 18%).

IR spectrum: reported in Table (3.1).

(k) N-Methylazomethine



N-methylazomethine was prepared as its trimer by the following method.

30ml of a 25% w./v. aqueous solution of methylamine (0.24 mole) and 20ml of a 36% w./v. formaldehyde solution (0.24 mole) were stirred together for one and three quarter hours, the reaction mixture being cooled for the first quarter of an hour in an ice/water bath. The solution was then stirred with 1N. sodium hydroxide aqueous solution (100ml) for four hours and extracted with chloroform (5 x120ml), the combined chloroform extracts washed once with water, dried over anhydrous magnesium sulphate, filtered and rotary evaporated at <35°C /15mm. mercury pressure to yield a clear colourless liquid.

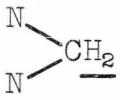
The product was fractionally distilled under reduced pressure to give pure N-methylazomethine as its trimer. A colourless clear liquid with a pungent odour. Yield = 8.8g (85%).

B.p., 66-68° /27mm, (Lit.[165] 68.3°/26mm).

IR spectrum ($CHCl_3$): 2940 (s) and 2794 (s) C-H stretch, 2728(w), 2666(w), 2638 (w), 2602 (w), 2576 (w), 2500 (w), 1466 (s) C-H deformation,

1445 (s) C-H deformation, 1429 (w), 1387 (s), 1377 (s), 1349 (w), 1257 (s), 1154 (s), 1110 (s), 1045 (m), 1021 (s), 1000 (s), 981 (w), 939 (w), 913 (s), 855 (s), 655 (w), 619(w).

NMR (deuterochloroform):

δ 3.13 Singlet 

δ 2.21 Singlet $N-\underline{CH_3}$

(1) N,N'-Di(p-Toluoyl)-N,N'-Dimethylhydrazine.

Sym-dimethylhydrazine dihydrochloride (2.66g, 0.02 mole) and anhydrous sodium carbonate (4.24g, 0.04 mole) were ground together as a paste and suspended in 50ml benzene in a round-bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser. On running p-toluoyl chloride (6.18g, 0.04 mole) into the vigorously stirred suspension the mixture became warm and bubbled vigorously. After stirring for 19 hours at room temperature the solution was filtered, the solid filtered off, washed with chloroform, and the combined filtrate and washings rotary evaporated to leave the title compound as a white solid. Yield = 5.80g. (98%). Re-crystallised from hot cyclohexane to yield a white micro-crystalline solid. M.p. 102-105^{c} .

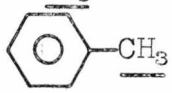
Analysis: Found: C, 73.05; H, 6.8; N, 9.4.

$C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.8; N, 9.45.

IR spectrum ($CHCl_3$): 2998 (m) C-H stretch of CH_3, 1661 (s) C=O vibration, 1614 (m), 1510 (w), 1473 (m), 1422 (m), 1366 (s), 1180 (m), 1122 (w), 1032 (w), 1013 (m), 829 (m).

NMR (deuterochloroform): δ 7.27 Singlet(broad)Aromatic protons

δ 3.21 Singlet $N-\underline{CH_3}$

δ 2.37 Singlet 

(ii) Kinetics of the Rearrangement of (LXXXI)

(a) Materials

All samples were freshly recrystallised to constant m.p.

Solvents

Hexane was "Spectrograde" quality supplied by Fisons, Ltd., and distilled before use.

Absolute Ethanol was supplied by British Drug Houses Ltd. and was distilled before use.

Acetonitrile of Laboratory Reagent grade was supplied by Fisons, Ltd. and was dried and purified by distillation twice from phosphorus pentoxide and storage over calcium hydride.

Benzene of Analar grade supplied by Fisons, Ltd. was dried over sodium wire and distilled.

Chloroform of Analar grade was supplied by Fisons, Ltd. This contained ~ 2% ethanol as a stabilizer.

Chloroform free from ethanol was obtained by shaking Analar grade chloroform (Fisons, Ltd.) several times with concentrated sulphuric acid, washing several times with water, drying over anhydrous calcium chloride and filtering. The liquid was distilled through a 12 inch vacuum-jacketed Vigreux column, the first 10% of the distillate discarded and the chloroform distilling at 61°/760 mm. (literature b.p.[166]) collected. To avoid the photochemical formation of phosgene[167] this chloroform was kept in a stoppered flask wrapped in aluminium foil and stored in a dark cupboard.

Deuterochloroform was supplied by Prochem, The British Oxygen Company, Ltd.

Carbon Tetrachloride of Analar grade was supplied by Fisons, Ltd. and distilled before use.

(b) The Kinetic Methods

The rates of rearrangement of (LXXXI) ⟶ (LXXXII) were principally determined spectrophotometrically by observing the loss of (LXXXI) by ultra-violet and infra-red spectroscopy.

(i) UV Spectrophotometric Assay

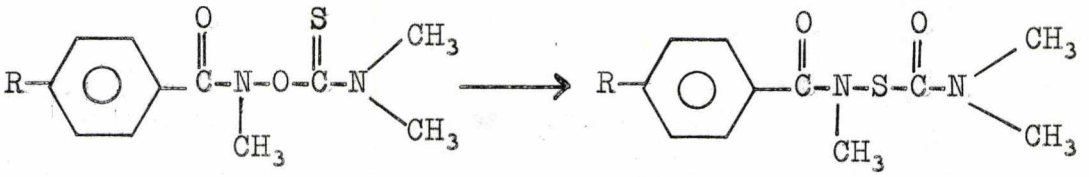
Rates of rearrangement of (LXXXI) ⟶ (LXXXII) in a variety of organic solvents over a range of temperature (40° - 83°) at concentrations of ~ 1.0×10^{-4}M were determined directly by continuous monitoring by UV spectrophotometry. The respective wavelengths monitored according to the solvent are collected in Table (6.7).

A 10 mm.silica cell was filled with ~ 3 ml of the solution of(LXXXI) of concentration ≈ 1.0×10^{-4} M, sealed with a well-fitting teflon stopper to prevent evaporation and thermostatted in a brass block in the cell compartment of a Unicam SP800 UV/Visible spectrophotometer, through which water from a constant temperature bath was circulated. The temperature of the bath was controlled to within ± 0.1° by a thermostat and pump unit.

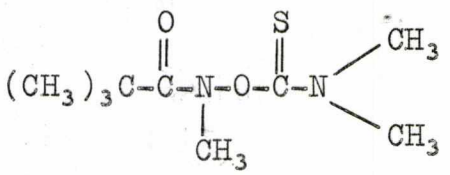
The decrease in absorbance of the solution was recorded continuously on a flat-bed Servoscribe external recorder. Reaction was followed to > 95% completion.

The temperature of the solution in the UV cell in the cell block of the spectrophotometer was recorded using a thermometer graduated in 0.1°.

Table (6.7.). Wavelengths Monitored in the UV Spectrophotometric Assay of the Rearrangement of (LXXXI) ⟶ (LXXXII)



R	CH_3O	CH_3	H	O_2N
Solvent	λ mμ	λ mμ	λ mμ	λ mμ
Hexane	250	250	250	250
Ethanol		250		
Acetonitrile		250		250
Benzene		285		
Chloroform	265	265	265	265
Chloroform free from ethanol		265		
Deuterochloroform		265		
Carbon Tetrachloride		270		



was monitored in hexane at 250 mμ.

(2) Kinetics by the Method of Initial Rates

In view of the slow rate of rearrangement of (LXXI) in hexane at 25.6° the rate coefficient at this temperature was determined by continuous UV spectrophotometric monitoring at 250 mμ by the method of initial rates.[121]

The loss of absorbance at 250 mμ of a solution in hexane ~ 1.0×10^{-4} molar in (LXXI) was monitored at 25.6° for 100 hours and at 64.8° until complete reaction had occurred (for the same solution), by the method described previously on p.174.

(3) IR Spectrophotometric Assay.

The kinetics of the rearrangement of (LXXI) ⟶ (LXXII) at concentrations of 5% wt./vol., 0.1982 mole litre^{-1} in carbon tetrachloride (at 60.7°), chloroform (at 49.9°) and benzene (at 59.0°) were determined by infra-red spectrophotometric assay.

10 ml of a 5% wt./vol. solution of (LXXI) in the respective solvent in a tightly stoppered flask were immersed in a water bath thermostatted at the required temperature to within 0.1°.

At noted periods, 0.30 ml samples (0.25 ml in the case of benzene as solvent) were rapidly pipetted from the flask and diluted to 1.00 ml with the same solvent, and the infra-red spectrum recorded in 0.5 mm. sodium chloride IR cells.

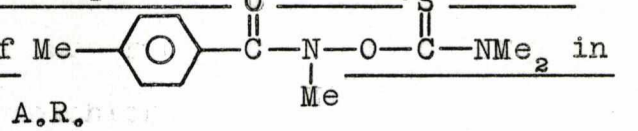
The rearrangement was monitored to completion.

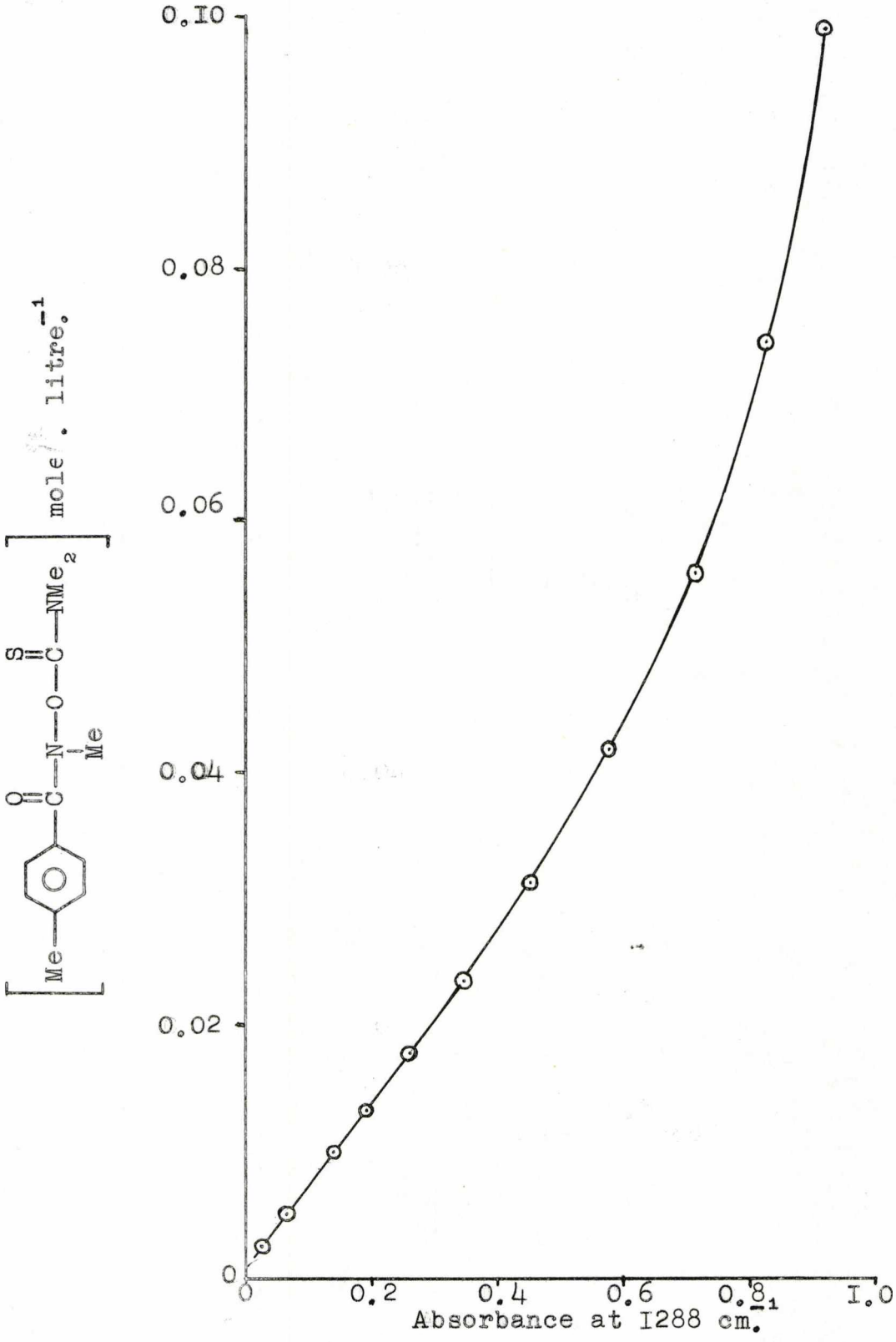
The first-order rate coefficients were calculated using the absorbance of the peak at 1288 cm.$^{-1}$ in carbon tetrachloride, at 1286 cm.$^{-1}$ in benzene and 1170 cm.$^{-1}$ in chloroform and a calibration curve relating the absorbance at these wavelengths to concentration for each solvent (Graphs (3.2), (3.1), (3,3)). These plots were constructed by recording the IR spectra of solutions obtained by successive dilution of a solution of (LXXI) of known suitable concentration in each of the solvents.

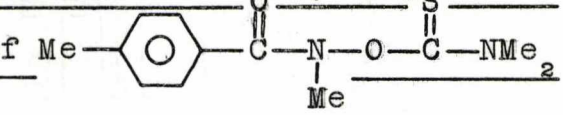
(4) Calculation of Rate Coefficients.

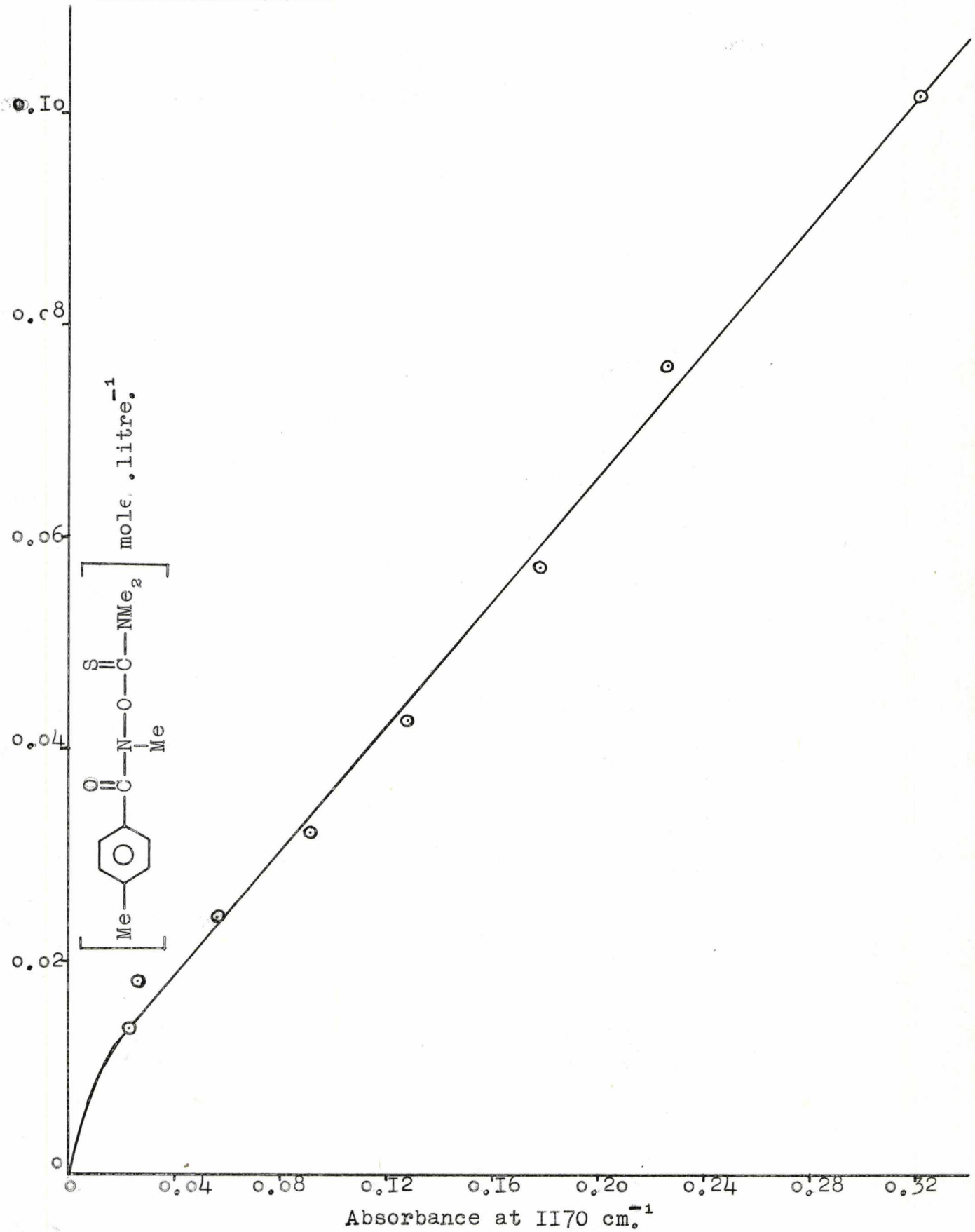
First-order rate coefficients were obtained by plotting the logarithm of the extent of rearrangement, $\log_{10}(x_\infty - x_t)$ against time and calculating the first-order rate coefficient from the equation, slope $= \frac{k}{2.303}$.

The infinity value employed was a measured one or one calculated using the Guggenheim method.[168]

Graph (3.2). Calibration Curve (concentration versus absorbance) for the Absorption at I288 $cm.^{-1}$ in the Infra-red Spectrum of  in Carbon tetrachloride A.R.



Graph (3.3). Calibration Plot (concentration versus absorbance) for the Absorption at 1170 $cm.^{-1}$ in the Infra-red Spectrum of  in Chloroform A.R.



(5) Calculation of the Activation Parameters.

Good linear Arrhenius plots were obtained for the rearrangement of (LXXXI) in hexane, (Graphs(3.6)-(3.9)). Theoretical analysis of the experimental data to yield $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ was conducted on an Elliott 4130 computer using a "Dartmouth Basic Language" computer programme.

(6) Examination for Photolysis of (LXXI) during Kinetic Measurement.

1. The rate of rearrangement of (LXXI) in hexane at 60.8° at a concentration of $\sim 1.0 \times 10^{-4}$M was determined by UV spectrophotometric monitoring within the UV spectrophotometer at a slit width of 0.02 mm.and a beam energy of E (Unicam SP800 model) and at a slit width of 0.10 mm.,and a beam energy of 8E.

2. The rates of rearrangement of (LXXI) in hexane at 69.0° and in carbon tetrachloride at 60.7° at concentrations of $\sim 1.0 \times 10^{-4}$M were determined by conducting the kinetic runs outside of the UV spectrophotometer cell block, the solutions being held in tightly stoppered flasks wrapped in aluminium foil and immersed in a water bath which was thermostatted to within 0.1°. Samples of the solution were periodically taken for immediate (undiluted) assay by UV spectrophotometry. For comparison the rate coefficients for the rearrangement of (LXXI) in hexane and carbon tetrachloride at the same temperatures and concentrations were determined by continuous UV spectrophotometric monitoring of the sample in a UV cell kept within the UV beam in the cell block (as described on p.174).

(7) Kinetic Measurement in the Presence of Oxygen.

The rate of rearrangement of (LXXI) at 66.0° at a concentration of $\sim 1.0 \times 10^{-4}$M in hexane, which had been purged with oxygen for 1½ hours was determined by continuous monitoring by UV spectrophotometry.

(8) Kinetic Measurement in Chloroform Free from Ethanol.

Attempts to determine the rate of rearrangement of (LXXI) in chloroform free from ethanol at a concentration of $\sim 1.0 \times 10^{-4}$M at 60.6° by continuous monitoring at 265 mμ showed almost complete reaction to have occurred in less than two minutes. This rapid reaction was quenched by the addition of a few drops of ethanol to the purified chloroform.

A solution of 2.0007 g of (LXXI) in 20.0 ml of chloroform free from ethanol (10% wt./vol.) was sealed in a thick-walled Carius tube ampoule and immersed in an oil bath at 120° for 20 minutes. The solution, initially very pale yellow in colour, became amber-brown. After cooling to room temperature, the tube was shaken and cut open. NMR analysis showed the presence of the hydrosulfamine (LXXII) and N-methyl p-toluamide in the ratio of 25% to 75%.

Infra-red spectral analysis confirmed these two products and the presence of carbon oxysulphide (2040 $cm.^{-1}$).

(9) Examination for Catalysis of the Rearrangement (LXXI) ⟶ (LXXII) by the Product (LXXII).

(LXXI) (0.10087 g) was made up to 1.0 ml of solution with deuterochloroform (a 10% wt./vol. solution) and 0.5 ml of this solution pipetted into a flask containing 0.15157 g (3 equivalents) of (LXXII). This solution and the remaining one were then sealed in NMR tubes containing tetramethylsilane sealed in capillary tubes. Both tubes were immersed in a water-bath thermostatted at 65.4° and periodically removed at noted intervals and the NMR spectra recorded together with the integrations, the NMR probe of the Perkin Elmer R10 NMR spectrometer (60 MHz) being preheated to 65.4°. Both kinetic runs were monitered at δ3.48, the N-methyl

resonance of (LXXI), see Tables (3.7) and (3.8).

For the kinetic run involving (LXXI) values of the integral of the N-methyl resonance at δ3.48 of (LXXI) were obtained, and corrected by comparison with the "internal standard" of the p--methyl resonance at δ2.35.

For the kinetic run involving (LXXI) in the presence of 3 equivalents of (LXXII) it was necessary (for reasons of relative concentration) to correct the integral of the N-methyl resonance at δ3.48 using a mean value of the integrals of the aromatic resonances at δ7.90 - 7.00 as a standard.

Graphs of $\log_{10}$ [corrected integral of the N-methyl resonance at δ3.48 of (LXXI)] against time gave good first-order linear plots of slope = $\frac{k}{2.303}$ (Tables (3.7) and (3.8)).

(iii) The Decolourisation of DPPH.

(a) Materials

α,α-Diphenyl-β-Picrylhydrazyl Radical was supplied by Koch-Light Laboratories,Ltd.

Carbon Oxysulphide was supplied by British Drug Houses Laboratory Gas Service.

(b) Kinetics and Extent of DPPH Decolourisation.

The kinetics of DPPH decolourisation in the presence of N-(p-toluoyl)O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine (LXXI) were determined in benzene (Fisons Analar grade) which had been dried over sodium wire and purged of dissolved air by boiling for 10-15 minutes and rapidly cooling to room temperature immediately prior to use.

A benzene solution, equimolar in (LXXI) and DPPH ($\sim 0.92 \times 10^{-4}$M) was prepared by directly weighing 0.00091 g of DPPH into a 25 ml volumetric flask, which was then made up to volume with a solution of 0.00120 g of (LXXI) per 50.0 ml of air-free benzene. 3.0 ml of this solution was pipetted into a 10 mm. silica cell fitted with a well-fitting teflon stopper and thermostatted at 59.2° in a brass block in the cell compartment of a Unicam SP800 UV/Visible spectrophotometer.

The visible spectrum (300 - 700 mμ) was immediately recorded (Diagram (6.1)) and the decolourisation of DPPH monitored at 510 mμ according to the procedure described on p. 174.

To determine the extent of decolourisation of DPPH, 2.5 ml of the infinity solution were pipetted into a 4 ml volumetric flask containing an approximately three-fold excess of (LXXI) (0.00021 g), the flask stoppered and heated at 61.5° for ten half-lives. The visible spectrum of the solution was then recorded (Diagram(6.1)). This showed no further decolourisation

of the DPPH to have occurred indicating that total decolourisation had occurred during the kinetic run. In view of this, the extent of decolourisation of DPPH (0.7628×10^{-4}M) in the presence of half quantities of (LXXI)(0.3805×10^{-4}M)(Diagram (6.2)) was determined in a similar manner. The DPPH underwent 64.0% decolourisation under these conditions,(the DPPH obeyed Beer's law at 510 mμ).

The extremely slow decolourisation of DPPH alone in A.R. grade carbon tetrachloride and benzene at 66.4° was followed by monitoring a solution of DPPH of suitable concentration in a stoppered 10 mm. silica cell at 510 mμ. Approximately 4% decolourisation occurred in 5 hours.

(c) Product Analysis by NMR.

A 10% wt./vol. solution of (LXXI) in d_6-benzene was sealed in an NMR tube using an oxygen blow-torch, TMS being present in a sealed capillary. After 48 hours immersion in an oil bath at 60°, the NMR spectrum was recorded. Intergration of the N-methyl signals of the hydrosulfamine compound (LXXII) and of the N-methyl p-toluamide revealed 40.9% conversion to (LXXII) and 59.1% conversion to N-methyl p-toluamide.

Diagram (6.I). The Decolourisation of DPPH in the presence of an equimolar amount of (LXXI) in benzene at 59.2°

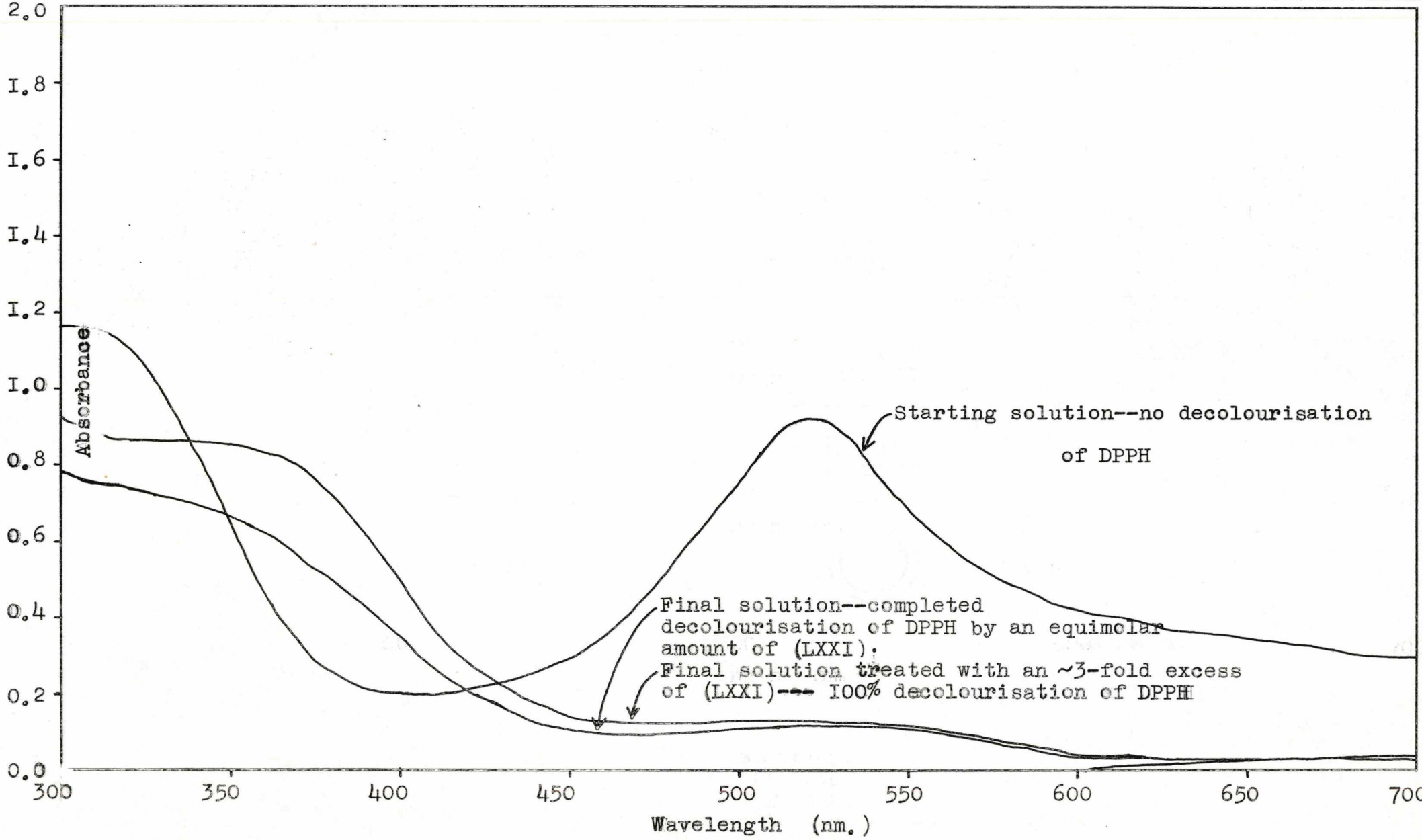
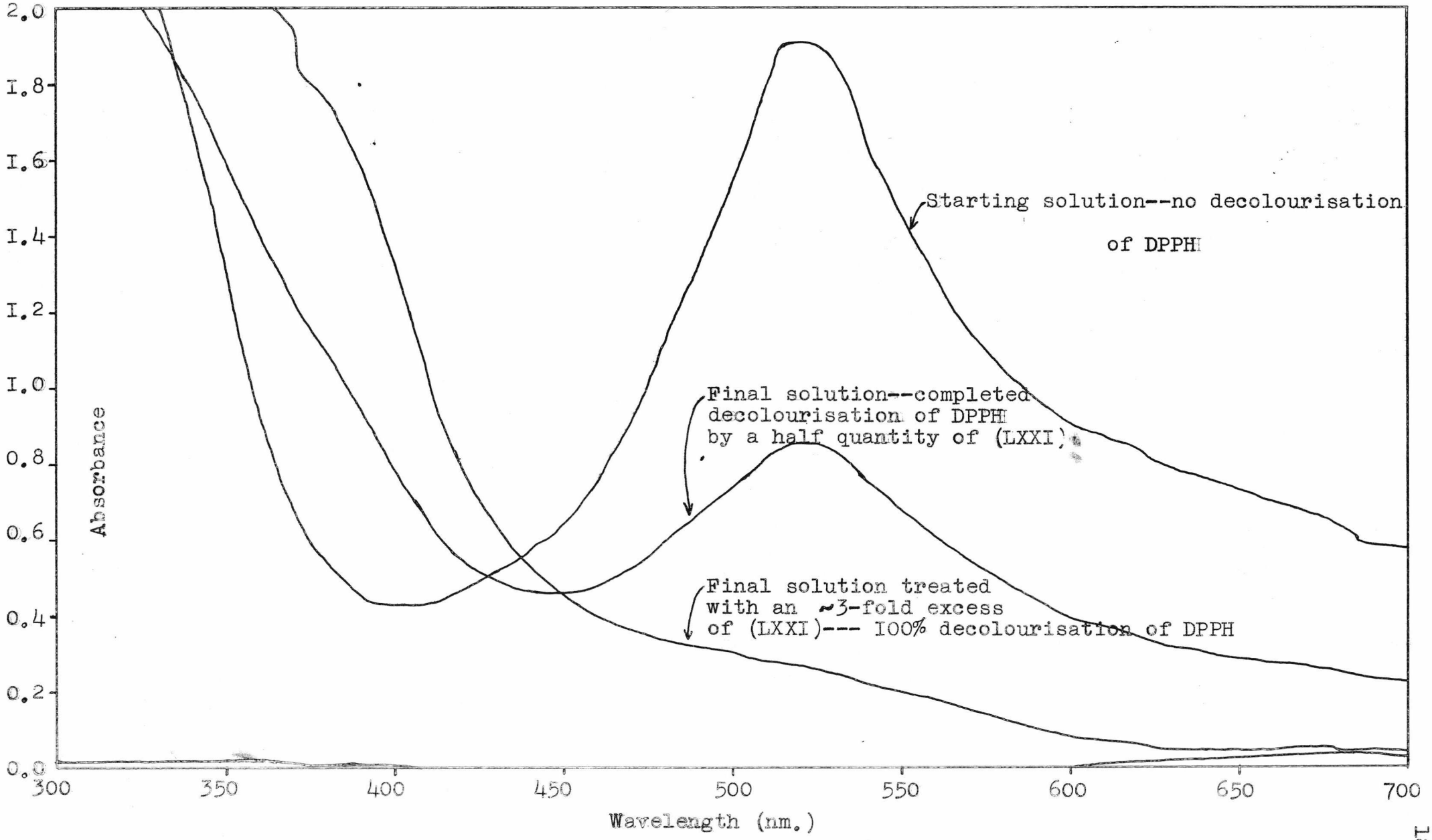


Diagram (6.2). The Decolourisation of DPPH in the presence of half quantities of (LXXI) in benzene at 59.2°



(iv) General Procedure for the Recording of CIDNP Spectra in the Thermolysis of N-Aroyl-O-(N',N'-Dimethylthiocarbamoyl)-N-Methylhydroxylamines (LXXXI).

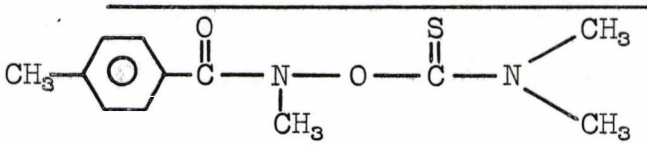
An nmr tube containing ~10% wt./vol. solution of (LXXXI) in deuterochloroform and tetramethylsilane as an internal standard, was sealed using a blow torch flame and placed in the preheated probe of a Perkin Elmer R10 NMR spectrometer operating at 60 MHz. The spectral region of interest was scanned repeatedly. After an initial period of time for the sample to warm up (about 1 minute), the base line of the scan was sufficiently stable for polarisation to be observed for periods of several minutes. Spectra were recorded until an unchanging absorption pattern was obtained for the product mixture. The complete spectrum from δ10 - 0 was then recorded and integrated. The times of recording the spectra were noted using the position of emission of the amide N-methyl resonance as a marker.

(v) Product Analysis of the Thermal Fragmentation of (LXXXI).

(a) Materials

The preparations of (LXXXI), the N-methyl p-substituted benzamides, (LXXXII), N,N'-di(p-toluoyl)-N,N'-dimethyl-hydrazine, bis-(dimethylcarbamoyl) disulphide and N-methyl-azomethine have already been described (p.152,166,159,172,170,171). N-chloro-N-methyl-p-toluamide and N,N,N',N'-tetramethyl-diaminomethane were kindly supplied by Dr. C. Brown. Hexachloroethane was supplied by British Drug Houses, Ltd. N,N-dimethylhydrazine was supplied by Ralph N. Emanuel, Ltd.

(b) Product analysis of the thermolysis of (LXXI),



in deuterochloroform at 120°.

Five sealed NMR tubes containing an ~10% wt./vol. solution of (LXXI) in deuterochloroform (tetramethylsilane as an internal standard) which had spent 20 minutes in the preheated (120°) probe of a Perkin Elmer R10 NMR spectrometer in CIDNP experiments were allowed to cool to room temperature, vigorously shaken, cut open, bulked, and the infra-red spectrum (in $CDCl_3$) quickly recorded. The infra-red spectrum revealed the product to contain principally N-methyl p-toluamide with some of the hydrosulfamine compound (LXXII). Some carbon oxysulphide was also present. During thermolysis the clear colourless solution became a clear amber in colour.

The solvent was removed from this bulked solution under high vacuum to leave a yellow-brown solid/oil residue (0.28g). The residue was dissolved in Analar chloroform (~1.5ml), applied to three 20 x 20cm. preparative TLC plates and eluted with chloroform.

The chromatogram contained two major bands (visible by UV) which were removed, eluted with methanol and acetone and filtered. The filtrate was evaporated under reduced pressure. The upper band yielded 0.09g of a light yellow clear oil containing a small amount of light yellow solid. IR and TLC analysis showed this to be the hydrosulfamine compound (LXXII) containing a trace of N-methyl p-toluamide.

The lower band yielded 0.09g of white long prisms, m.p. 133 - 145° , and identified as N-methyl p-toluamide (by IR and TLC analysis).

Systematic recrystallisation (benzene/40-60° petroleum ether) and TLC of the products from the thermolysis of (LXXI) in deuterochloroform (a 10% wt./vol. solution) at 120° enabled N-methyl p-toluamide to be separated in a pure state. The other products could not be extracted in a pure state.

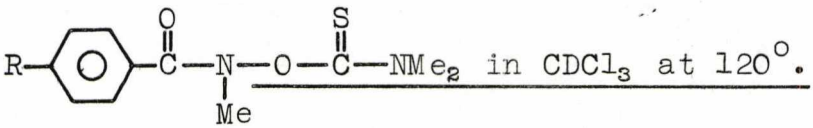
(c) NMR Product Analysis.

Analysis by NMR of the products resulting from the thermolysis of (LXXI) in deuterochloroform at 20°, 60° and 120° involved leaving a sealed NMR tube containing an ~10% wt./vol. solution of (LXXI) in deuterochloroform and TMS as an internal standard, at room temperature (20°), in an oil bath at 60° and in the preheated probe of the NMR spectrometer (120° - i.e. a sample used for a CIDNP experiment) until no further changes took place. The NMR spectra were then recorded (Diagram (3.1)), assignments being made against authentic samples and product ratios (Table (3.2)) determined from the integration.

In this way, (LXXI) was shown to undergo thermolysis principally to two products, N-methyl p-toluamide and the hydrosulfamine compound (LXXII). Two small peaks at δ3.02 and

δ 2.60 (Diagram (3.1)) were present, in addition to those due to the two main products, but were sometimes obscured by other resonances when the thermolysis products from the other O-thiocarbamoylated hydroxamic acids were examined (Table (6.8)).

Table (6.8). Visibility of NMR Resonances at δ 3.02 and δ 2.60 in the Thermolysis of (LXXXI).

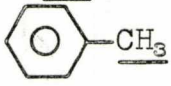


in $CDCl_3$ at 120°.

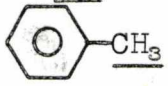
R	δ 3.02	δ 2.60
H	Obscured	Obscured
CH_3O	Visible and present	Visible and present
NO_2	Obscured	Not obscured - very small peak; principally fragmentation to (C; R = O_2N); very small amount of rearrangement to (LXXXII; R = O_2N)

NMR analysis (all NMRs recorded in deuterochloroform solvent) showed that none of the following compounds were formed as products in the thermolysis of the O-thiocarbamoylated hydroxamic acids:

N-chloro-N-methyl-p-toluamide:

δ 7.52, 7.39, 7.24, 7.11	Quartet	Aromatic protons
δ 3.34	Singlet	$N-CH_3$
δ 2.30	Singlet	

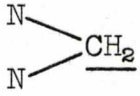
N,N'-di(p-toluoyl)-N,N'-dimethylhydrazine:

δ 7.27	Singlet	Aromatic protons
δ 3.21	Singlet	$N-CH_3$
δ 2.37	Singlet	

bis-(dimethylcarbamoyl) disulphide:

δ 3.11	Singlet	$N(\underline{CH_3})_2$

and N-methylazomethine:

δ 3.13	Singlet	
δ 2.21	Singlet	$N-\underline{CH_3}$

There was an absence of resonances comparable to those due to N,N-dimethylhydrazine:

δ 3.13	Singlet	$-\underline{NH_2}$
δ 2.42	Singlet	$-N(\underline{CH_3})_2$

and N,N,N',N'-tetramethyl-diaminomethane:

δ 2.74	Singlet	$-\underline{CH_2}$
δ 2.23	Singlet	$-N(\underline{CH_3})_2$

(d) VPC Product Analysis.

The final solution from the thermolysis of N-(p-anisoyl)-O-(N',N'-dimethylthiocarbamoyl)-N-methylhydroxylamine in deuterochloroform at 120° for 15 minutes was subjected to VPC analysis using a column packed with 20% Methyl Silicone Gum SE30 on 60 - 80 DCMS acid washed Chromosorb W. By comparison with chromatograms of authentic samples the chromatogram demonstrated the presence of a large amount of the N-methyl p-methoxy-benzamide and a small amount of N-(p-anisoyl)-S-(N',N'-dimethylcarbamoyl)-N-methylhydrosulfamine. Small amounts of unidentified volatiles were present, whilst N-methylazomethine and hexachloroethane were absent.

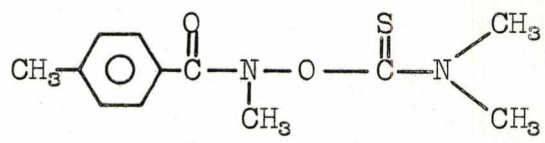
(e) Detection of Carbon Oxysulphide.

Infra-red spectrophotometric assays of solutions of (LXXXI) in chloroform and deuterochloroform, taken both during and after completion of rearrangement of (LXXXI) at temperatures of 20° - 120°, revealed the presence of an intense peak at

2044cm^{-1}., characteristic of carbon oxysulphide[169]. In addition, the infra-red spectra were consistent with the progressive loss of (LXXXI) and formation of the corresponding hydrosulfamine compound (LXXXII) and N-methyl p-substituted benzamide (Tables (6.2),(6.4),(6.6)).

Immediate examination by infra-red spectroscopy (in $CDCl_3$) of the final solution from the thermolysis in a sealed NMR tube of (LXXI) in deuterochloroform at 120° for 15 minutes (i.e. after a CIDNP experiment), revealed the presence of carbon oxysulphide (2044cm^{-1}).

Bulking of the solutions from five such thermolyses in NMR tubes and subsequent removal of the solvent at room temperature under a reduced pressure of ~2.5 - 3.0mm. pressure via a liquid nitrogen cooled trap, resulted in the trapping of a colourless clear liquid (at room temperature). Infra-red spectroscopic analysis of this liquid(recorded with deuterochloroform as the reference) revealed the presence of chloroform and of carbon oxysulphide (2044cm^{-1}). No N-methylazomethine was present.

(vi) Photolysis of (LXXI), 

600ml of a 0.1% wt./vol. solution of (LXXI) in Analar grade methanol was photolysed in a photolysis cell fitted with a water-cooled quartz probe containing a 100 watt mercury lamp. Prior to photolysis the solution was purged with a nitrogen stream for 45 minutes. The gas outlet from the photolysis cell was connected to a Dreschel bottle containing concentrated sodium hydroxide aqueous solution and the outlet from this passed into a fume hood. Prior to photolysis the solution was colourless. During photolysis

the temperature of the solution was 23°. After 135 minutes a 10ml sample of the photolysis solution had a faint yellow colouration and possessed the characteristic odour of carbon oxysulphide. Evaporation of this sample at room temperature, under high vacuum gave a white crystalline solid containing traces of a very pale yellow solid. IR spectrophotometric analysis showed this material to be principally N-methyl p-toluamide.

The photolysis was stopped after 210 minutes and the very pale yellow solution, which possessed the characteristic odour of carbon oxysulphide, evaporated at room temperature, under reduced pressure to give a yellow crystalline solid (0.42g).

IR and NMR spectral analysis showed the material to be principally N-methyl p-toluamide.

Appendix

N-(p-Nitro-benzoyl)-S-(N',N''-dimethylcarbamoyl)-N-methylhydrosulfamine, (LXXXII); R = O_2N which defied adequate purification as discussed earlier in the text (p.160)has recently been prepared by allowing a 5% wt./vol. solution of (LXXXI); R = O_2N in Analar chloroform to stand at room temperature for 60 days. The solvent was removed under high vacuum at low temperature and the product repeatedly recrystallised from benzene/ 40-60° petroleum ether.

The p-nitro substituted hydrosulfamine compound, (LXXXII); R = O_2N was obtained as very pale lemon prisms, m.p. 140-142°.

Analysis: Found: C, 46.6; H, 4.6; N, 14.5.

$C_{11}H_{13}N_3O_4S$ requires C, 46.65; H, 4.6; N, 14.8.

UV spectrum in hexane solution:

λ_{max} 200 mμ

λ_{max} 273 mμ

NMR spectrum: Recorded on p. 165.

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