A thesis entitled

"RING CLEAVAGE OF OXAZIRIDINES"

submitted by

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ABSTRACT

A general survey of the chemistry of oxaziridines is presented, previous studies on the mechanism of the acid and base catalysed hydrolysis are critically reviewed and the results discussed in relation with the hydrolysis of compounds with related structures.

Results of the acid hydrolysis of several oxaziridines are reported and agree with previous findings. These accord with a mechanism involving the breakdown of an O-conjugate acid intermediate to give either a carbonium ion or an immonium ion structure, which subsequently reacts with water. The importance of each pathway depends on the nature of the 3-substituent. The proton α to the ring nitrogen seems to be involved in the rate determining step for the reaction of 2-primary-alkyl 3-alkyl oxaziridines. For 2-secondary-alkyl 3-alkyl compounds extensive migration of an α group occurs and steric requirements and migratory aptitudes seem to be important. Investigations of the site of protonation suggest N as the most likely site, although hydrolysis probably proceeds via the O-conjugate acid: pK_A values for oxaziridines reflect the nature of the 3-substituent as well as the degree of branching at position 2 and lie in the range -1.9 to +0.30.

Results of basic hydrolysis of several oxaziridines are reported and are consistent with earlier findings. The hydrolytic mechanism which rationalisesall the data is a heterolytic bimolecular rate determining abstraction of an α proton to the ring nitrogen by the base.

Different catalysts, some powerful nucleophiles, some having

partial basic character, were studied in connection with 2,3,3-triethyloxaziridine. The mechanism for the attack is still unclear but a satisfactory fit to the Edward's oxi-base equation shows that nucleophilicity is more important than basicity in these reactions.

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my grateful thanks to my supervisor, Dr B.C. Challis, for his help and guidance given throughout this work. I am thankful to Professor D.H.R. Barton, F.R.S., for the privilege and opportunity of working in his Department and to Calouste Gulbenkian Foundation for providing me with a research grant for the past three years.

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Last, but not the least, thanks are due to Miss W. Coleman for typing the manuscript.

A.M.F.T. Lobo

"No single thing abides, but all things flow.
Fragment to fragment clings and thus they grow
Until we know and name them.
Then by degrees they change and are no more
The things we know."

LUCRETIUS

TO MY PARENTS

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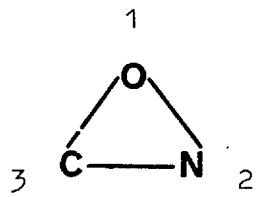
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PART I

GENERAL SURVEY OF OXAZIRIDINE CHEMISTRY

Introduction

Three-membered rings containing one heteroatom (oxiranes, thiiranes and aziridines) have been known for a very long time, and in spite of considerable ring strain, their synthesis requires only mild conditions. So it is not surprising that three-membered ring structures containing two heteroatoms were postulated in early investigations to solve structural problems, such as with nitrones,[1] hydrazones[2] and aliphatic diazo compounds[3]. However, further spectroscopical studies of these particular compounds showed that the postulated three-membered ring structure was incorrect and it was not until 1952, that Krimm and Hamann[4] synthesised unambigously the oxaziridine ring. This family of compounds soon acquired an



Oxaziridine Ring

extensive literature.

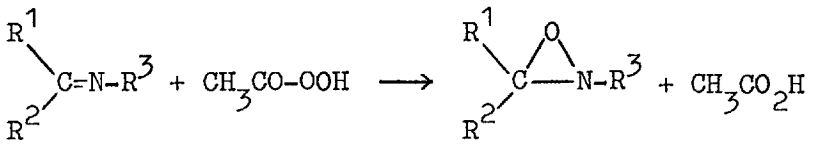
In the following sections of Part 1 their methods of preparation, physical properties and most important reactions will be briefly discussed. Particular emphasis will be given to the hydrolysis reactions and their analogy with those of other three-membered ring structures, since the experimental work described in Part 2 of this thesis is mainly connected with this topic. Part 3 is an account of the experimental details of the investigation.

CHAPTER I

Methods of Preparation of Oxaziridines

I.1 Preparation of Oxaziridines from Schiff's Bases and Peracids

The oxaziridine ring (1) can be synthesised very easily by the action of a peracid on a Schiff's base (Scheme (I-1)). This reaction, which was first described by Krimm[4] in patents, and later, independently, by both Emmons[5,6] and Horner and Jürgens[7], is normally

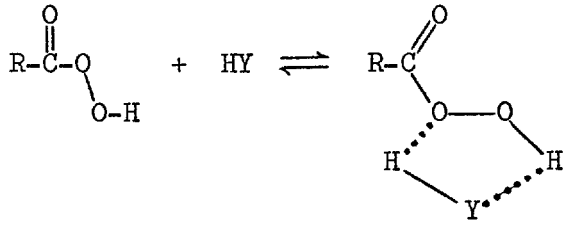


Scheme (I-1)

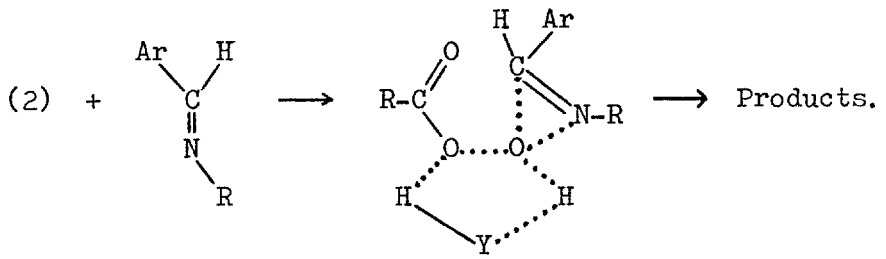
carried out by oxidation of the imine with peracetic acid, in a volatile solvent (dichloromethane) at $0^{o}C$.

The mechanism, however, was established only recently. Although Emmons[5,6] originally suggested a mechanism analogous with the oxidation of ketones in the Bayer-Villiger reaction, Bailey[8,9] described the ozonization of Schiff's bases as a nucleophilic attack of ozone on the C=N bond. Also Edwards[10] predicted that the C=N oxidation with peracids would be nucleophilic displacement on oxygen through a cyclic transition state. More recent work by Madan and Clapp[11,12] indicates complex (2) formation between the peroxy acid and another molecule (HY) of solvent, acid or any of the products formed. This complex, in turn, interacts with the Schiff's base and oxidation then proceeds through a five membered cyclic transition

state (3) (Scheme (I-2)).



(2)



(3)

Scheme (I-2)

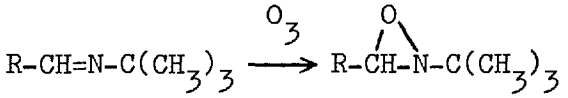
The oxidation of imines normally gives good yields of product (40-90%) and a wide variety of oxaziridines have been prepared in this way[6].

An important point concerns the amount of peracid used for oxidation. With an excess, further oxidation of the oxaziridine leads to appreciable quantities of nitroso-compounds (from the amine moiety) with a considerable reduction of product yield[6].

In some cases where the Schiff's bases are difficult to isolate, it is often sufficient to bring the carbonyl and the amine together

in an inert solvent and then to add the peracid to the mixture.[4,7]

Belew and Pearson[13] successfully prepared the oxaziridine (4), using ozone on isobutylidine-t-butylamine (Scheme (I-3)). Bailey[8] and co-workers obtained 2-t-butyl-3-phenyloxaziridine (5) by the same method.

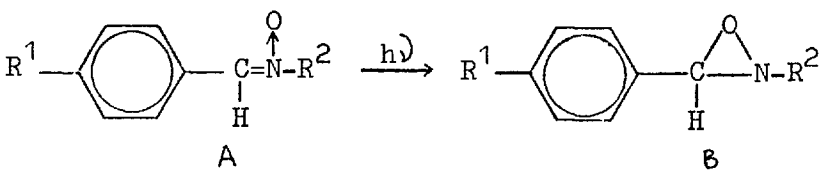


(4) R = isopropyl
(5) R = phenyl

Scheme (I-3)

I.2 Preparation of Oxaziridines via Nitrones Irradiation

Oxaziridines and nitrones are isomers and their possible interconversion had long been suspected. Kamlet and Kaplan[14] and Kröhnke[15] postulated oxaziridine formation to account for the light sensitivity of nitrones. Bonnett[16] and co-workers and Splitter and Calvin[17] managed to isolate and fully characterise oxaziridines (6), (7) and (8), as the first irradiation products of nitrones (Scheme (I-4)). With compound (6,A) the rearrangement proceeded in acetonitrile with a yield of 95%. Subsequently this reaction has also been widely employed[18,19,20] to synthesize other nitrones.



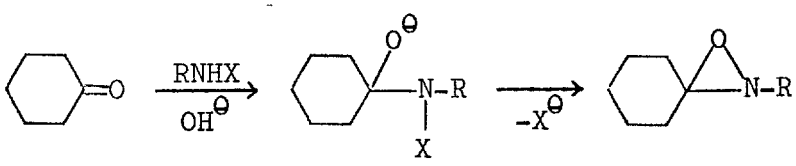
A B

(6) $R^1 = NO_2$; $R^2 = C_2H_5$
(7) $R^1 = NO_2$; $R^2 = t\text{-}C_4H_9$
(8) $R^1 = H$; $R^2 = t\text{-}C_4H_9$

Scheme (I-4)

I.3 Preparation of Oxaziridines by Reaction between Carbonyl Compounds and Derivatives of Hydroxylamine and Chloramine

When an aldehyde or a ketone is mixed with N-methylchloramine or N-methyl-hydroxylamine-O-sulphonic acid and dilute sodium hydroxide, oxaziridines are formed in good yields[21-24] (Scheme (I-5)). The mechanism probably involves an intramolecular nucleophilic attack of the alkoxide oxygen on the nitrogen bearing the



X = Cl, $OSO_3^{\ominus}$

Scheme (I-5)

leaving group X. This is substantiated by the fact that when R is a t-butylgroup, or an equivalent bulky substituent, no closure of the ring is observed due to steric hindrance at the nitrogen atom. Yields of oxaziridine formation are often low, however, because there is considerable base catalysed hydrolysis competing with ring closure.

CHAPTER II

Properties and Proof of the Structure of Oxaziridines

Oxaziridines are usually distillable liquids with boiling points higher than the corresponding imines.

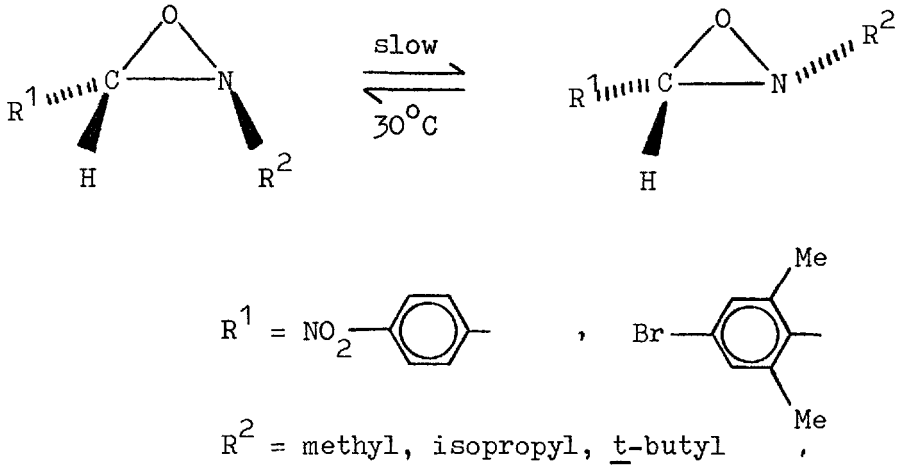
They are colourless compounds with no appreciable characteristic absorption in the u.v. spectral region and, in this respect, are quite different from the isomeric nitrones which have strong u.v. absorption.

Their infrared spectra show no C=N absorption, but a band in the region 1400 to 1450 cm^{-1} has been attributed to the oxaziridine ring[25]. Since the C-H bending vibrations of methyl groups appear in the same region, this band is not of great diagnostic value. The work of Shinkawa and Tanaka[26] with 2,3-diphenyloxaziridine gives evidence that bands characteristic of the oxaziridine ring are at 1250 and 734 cm^{-1}. The corresponding nitrone absorbs at different frequencies (1547 and 1067 cm^{-1}).

The n.m.r. spectra of oxaziridines are consistent with a three-membered ring structure[5,6], and more detailed studies show that "umbrella" inversion around the nitrogen in the ring occurs slowly by comparison with the n.m.r. time scale[27,28] (Scheme (II-1)).

In this respect oxaziridines behave very much like aziridines[29], which also show slow inversion about the nitrogen, dependent on the nitrogen substituent.

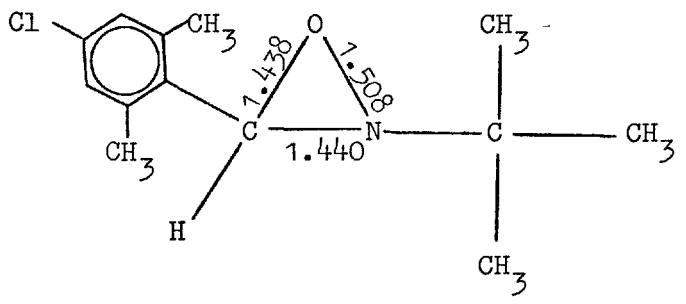
Concerning their optical properties, Emmons[6] succeeded in partially resolving 2-n-propyl-3-methyl-3-isobutyl-oxaziridine using brucine base, and this is powerful additional proof of the



Scheme (II-1)

3-membered ring structure with its asymmetric carbon atom. More recently, Boyd and co-workers[30,31] have shown asymmetry in oxaziridines due solely to the nitrogen atom.

In 1967, Jerslev[32] produced the first X-ray analysis of compound (A). The measured ring dimensions (in Ångstroms) are written along the appropriate bonds.



(A)

CHAPTER III

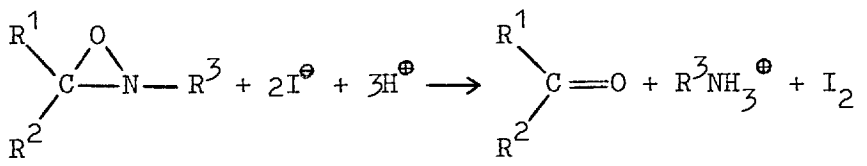
Reactions of Oxaziridines

Oxaziridines are high energy compounds and, consequently, it is not surprising that they undergo attack by a wide range of reducing and oxidising agents, acids, bases and radical reagents. Without exception the oxaziridine ring opens in every reaction, showing that relief of ring strain provides a powerful driving force for bond cleavage as in other three-membered ring systems such as diaziridines[33], aziridines[34], oxiranes[35] and cyclopropanes[36].

The discovery of these reactions was mainly by Emmons[5,6], who classified the reactions, analysed the products and postulated mechanisms.

III.1 Redox Reactions of Oxaziridines

One of the most interesting properties of oxaziridines is their oxidising character, which is of the same order as hydrogen peroxide. Thus oxaziridines react with iodide solutions under acid conditions liberating two equivalents of iodine, according to (Scheme (III-1)), together with a carbonyl product and an amine[6]. This



Scheme (III-1)

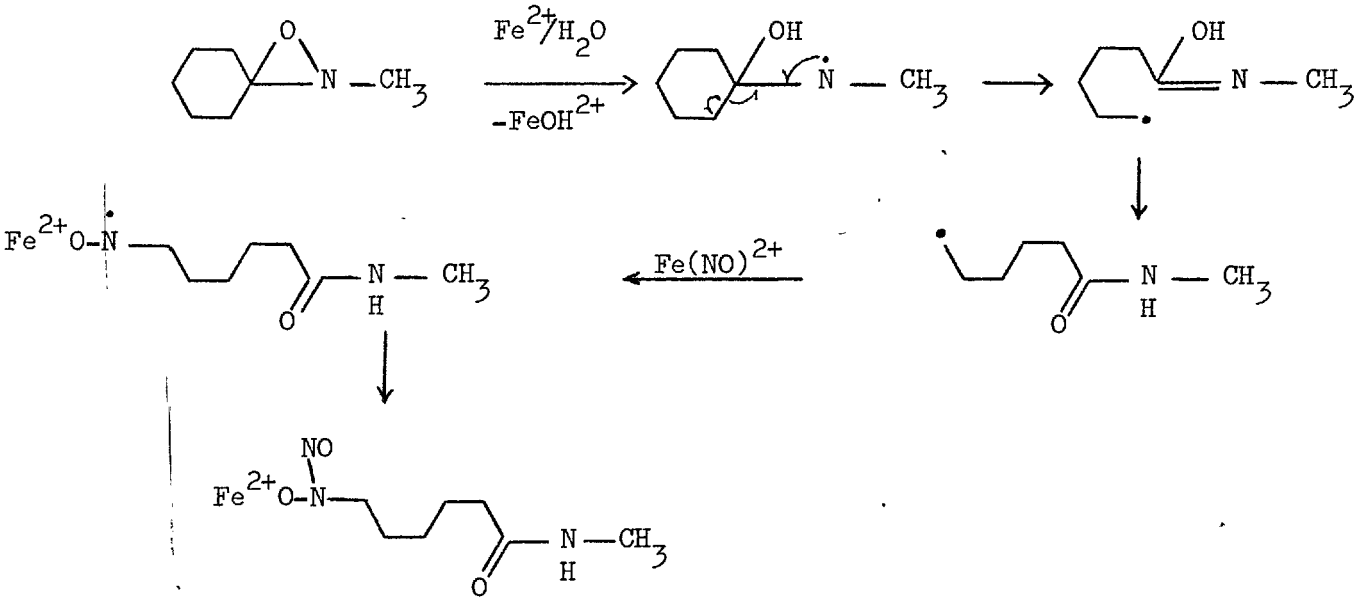
reaction has been used extensively to determine the purity of oxaziridines and has become almost diagnostic of oxaziridine

formation.

The action of HCl on oxaziridines results in the slow liberation of chlorine which is partially consumed in secondary reactions[6,25].

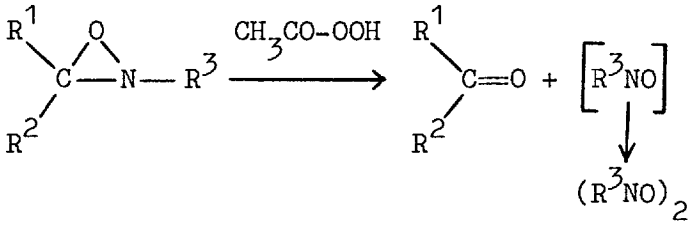
Other evidence of their oxidising properties is manifold. For example, they readily convert triphenylphosphine and tertiary amines to their corresponding oxides.[6,37] Reduction by lithium aluminium hydride allows further differentiation between oxaziridines which yield an imine and the nitrones which yield a hydroxylamine[6]. Other catalytic reductions have a similar effect.[7]

Also of considerable interest is the reaction between oxaziridines and ferrous[6] or titanous salts[38]. The alkyl radical obtained from 2-methyl-3,3-penta-methylene-oxaziridine undergoes reduction or oxidation depending on the redox potential of the ionic metal couple. The intermediate formation of an alkyl radical, previously postulated by Emmons[6], was identified by capture with nitric oxide to give a nitrosohydroxylamine derivative[38] (Scheme (III-2)).



Scheme (III-2)

Oxaziridines may undergo oxidative fission by peracids yielding nitroso compounds as dimers and carbonyl products, thereby providing an easy route to the nitroso group[4,6] (Scheme (III-3)).

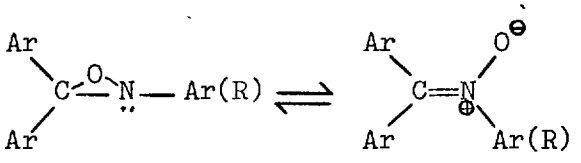


Scheme (III-3)

III-2 Isomerisation of Oxaziridines

Oxaziridines may isomerise to nitrones or to amides on either heating[6] or irradiation[17]. These reactions have been extensively reviewed[39] and again emphasize the relationship between oxaziridines and nitrones or amides.

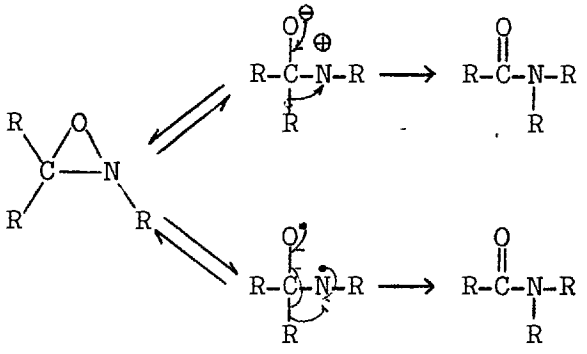
Several mechanisms have been postulated for the isomerizations, some of them involving homolysis and radical intermediates, some of them involving heterolytic fission[17] as shown in (Scheme (III-4)) and (Scheme (III-5)).



Scheme (III-4)

Cleavage of the C-O bond leads to nitrone formation, whereas N-O bond fission gives an amide. In general, ionic C-O bond cleavage leading to a nitrone occurs when there is an alkyl group on the

nitrogen atom and aryl groups on the carbon atom[5,6,7,40] capable of stabilising the developing carbonium ion relative to the developing nitrogen cation. The N-O bond cleavage, which can be heterolytic or homolytic, depending on conditions and substituents[5,6], is the preferred route whenever the substituents on both carbon and nitrogen atoms are alkyl groups.[5,25]



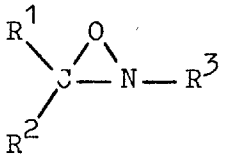
Scheme (III-5)

III.3 Hydrolysis of Oxaziridines

III.3.1 Acid-Catalysed Fission of the Oxaziridine Ring

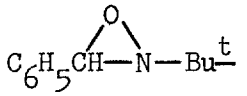
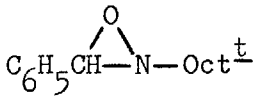
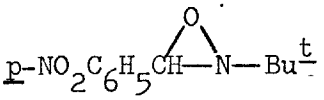
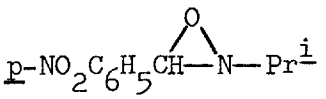
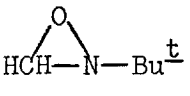
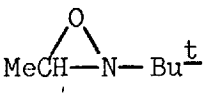
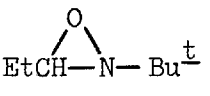
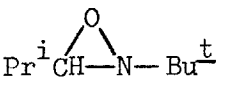
The behaviour of oxaziridines towards acidic reagents is not readily predicted from experiences with other classes of compounds. They show, for example, a remarkable resistance towards strong acids unlike N,O-acetals or compounds containing an O-C-N group in a larger ring[33]. However, they do show a striking resemblance to diaziridines, another group of compounds having a three-membered ring with two hetero-atoms[41].

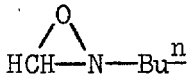
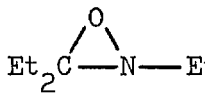
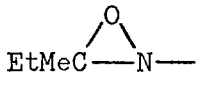
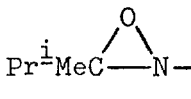
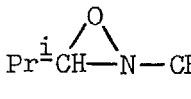
Emmons[6] studied the behaviour of several oxaziridines in methanolic sulphuric acid and reported ring opening in all cases. He found, however, that the subsequent course of the reaction was strongly dependent on the nature of the substituents R^1, R^2 and R^3, as can be seen by the different types of product listed in Table (III-1). When either R^1 or R^2 was an aryl group, and R^3 was an



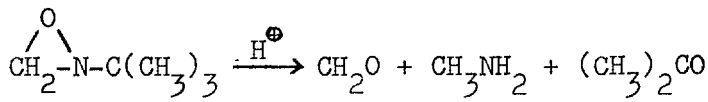
alkyl group, hydrolysis yielded a carbonyl product (R^1R^2CO) and a hydroxylamine (R^3NHOH). For example, with 2-t-butyl-3-phenyloxaziridine the acid hydrolysis gave a 93% yield of benzaldehyde and an 82% yield of β-t-butylhydroxylamine[6]. When R^1 and R^2 were not aromatic, and R^3 was a primary alkyl group, he reported the formation of two carbonyl products (R^1R^2CO, R^4CHO) and ammonia (Table (III-1)). Thus with 2-n-butyloxaziridine, the products

Table (III-1)

Oxaziridine	Medium	Products	Yields	Ref.
	H_2SO_4/MeOH	C_6H_5CHO t-Bu-NHOH	93% 82%	6,42
	H_2SO_4/MeOH	C_6H_5CHO t-Oct-NHOH	91% 86%	6
	$HClO_4/H_2O$	p-$NO_2C_6H_5CHO$	-	42
	$HClO_4/H_2O$	p-$NO_2C_6H_5CHO$	-	43
	H_2SO_4/MeOH	$MeNH_2$ HCHO Me_2CO	60% 91%	6
	$HClO_4/H_2O$	MeCHO Me_2CO	- -	42
	$HClO_4/H_2O$	EtCHO Me_2CO	- -	42
	$HClO_4/H_2O$	i-PrCHO Me_2CO	- -	42

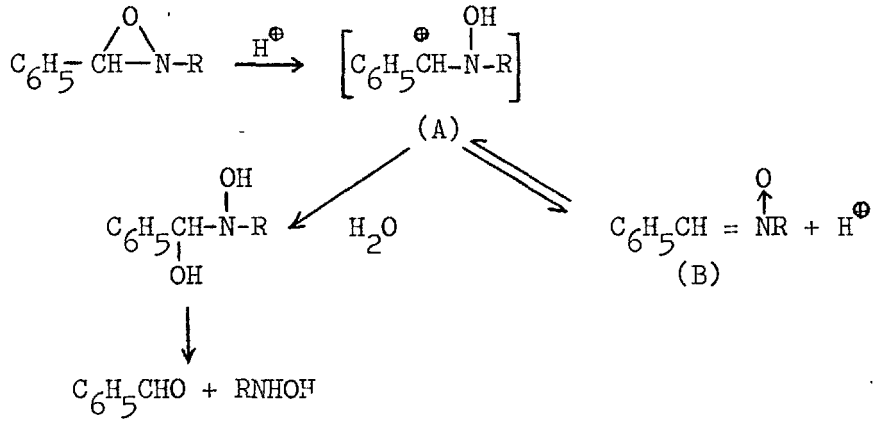
Oxaziridine	Medium	Products	Yields	Ref.
	H_2SO_4/MeOH	NH_3 HCHO n-PrCHO	79% 95%	6
	$HClO_4/H_2O$	Et_2CO MeCHO	- -	43
	$HClO_4/H_2O$	EtMeCO n-PrCO	- -	43
	$HClO_4/H_2O$	i-PrMeCO EtCHO	- -	43
	H_2SO_4/MeOH	$PhNH_2$ i-PrCHO MeCHO	86% 100%	6

obtained were formaldehyde, butyraldehyde and ammonia[6]. With either a secondary or a tertiary alkyl group for R^3, extensive rearrangement accompanied hydrolysis, apparently due to migration of an alkyl fragment to the adjacent nitrogen atom. In the case of 2-t-butyloxaziridines, methylamine, rather than ammonia, was formed, together with two carbonyl compounds (Scheme (III-6)).



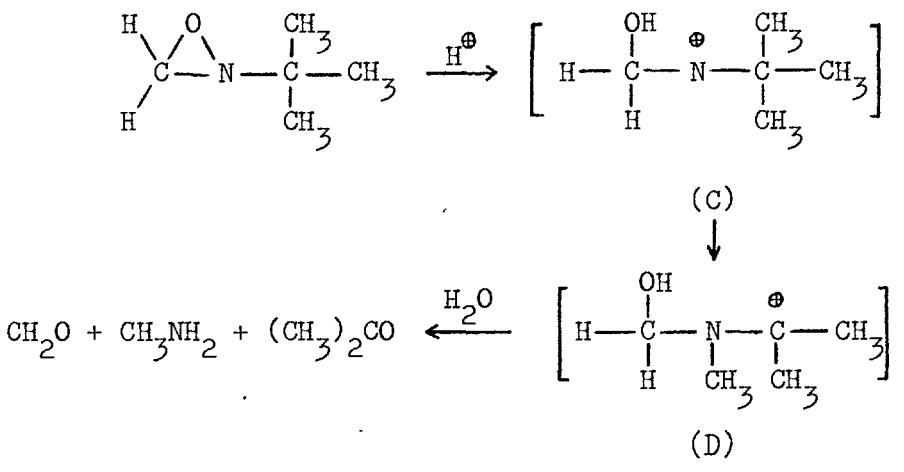
Scheme (III-6)

On the basis of the product analysis, Emmons[6] postulated that the acid catalysed hydrolysis involved the O-conjugate acid which subsequently undergoes ring opening through either C-O or N-O bond breakage. With a 2-aryl substituent to stabilize the incipient carbonium ion, C-O bond fission was favoured and the unstable intermediate (A) was converted either to the isomeric nitrone (B), by loss of a proton, or by reaction with water to the aldehyde and the hydroxylamine[6](Scheme (III-7)). Without a 2-aryl group

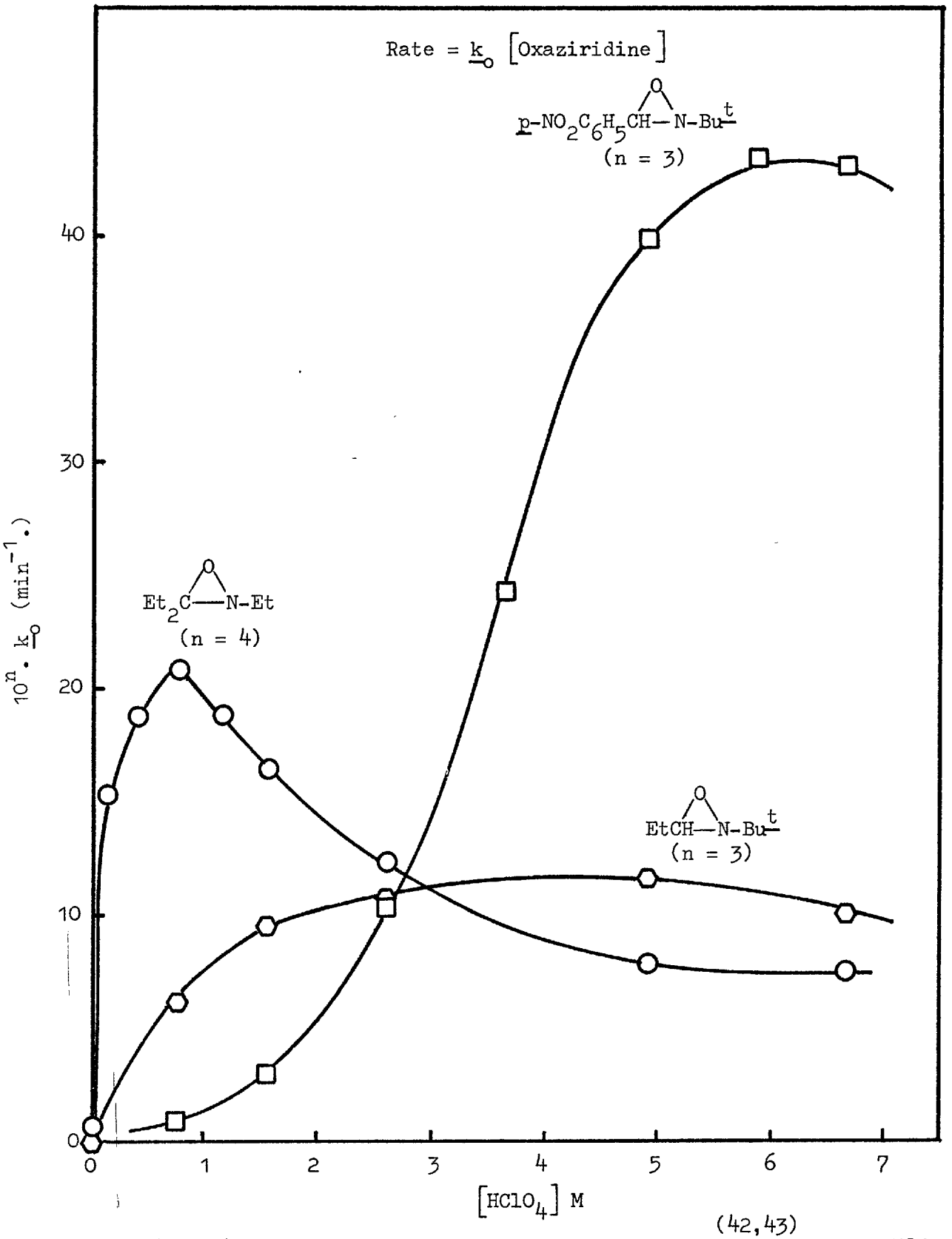


Scheme (III-7)

the oxaziridine ring cleaved by breakage of the N-O bond[6] (Scheme (III-8)).



Scheme (III-8)



(42,43)

Fig. (III-1). Acid hydrolysis of typical oxaziridines in aqueous $HClO_4$, 25°C.

Following ring opening, migration of a group α to the nitrogen atom stabilized the immonium ion (C) to give a carbonium ion (D) which in turn reacted with water to yield products. The ability of the group α to the nitrogen atom to migrate seemed to fall in order: $C_6H_5 > H > alkyl$.[6]

In order to throw some light onto the hydrolysis mechanism, Butler and Challis[42,43] made a systematic kinetic study of several oxaziridines by measuring the rates of ring opening in aqueous perchloric acid at 25°C. These workers utilised the oxaziridine's oxidising properties, already described in Section (III-1), of release of iodine from an iodide acid solution, to follow the reaction rates.

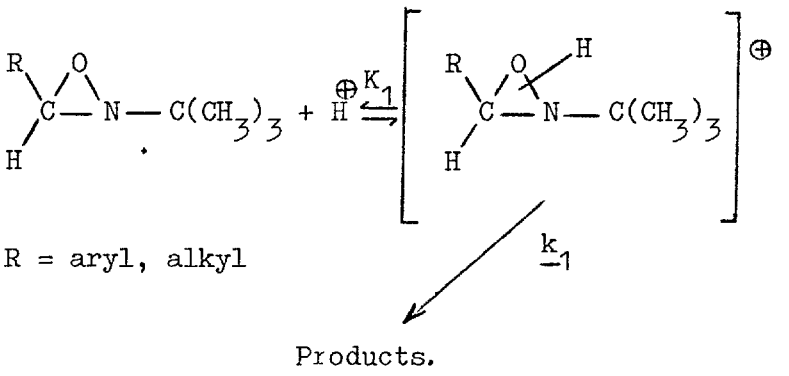
III.3.1.a 2-t-Butyloxaziridines

The results obtained with the 2-t-butyloxaziridines[42] show the existence of a rate maximum between 4 and 6M $HClO_4$. Typical profiles are shown in Fig (III-1). Similar rate maxima have been reported for the hydrolysis of amides[44,45] and more recently for the hydrolysis of hydroxamic acids[46] and attributed to the extensive protonation of the substrate. The fact that 2-t-butyloxaziridines[6,42] were not particularly susceptible to nucleophilic reagents ruled out the possibility that the origin of the maximum was the same as that found in acid hydrolysis of sulphites,[47,48] phosphates,[49] phosphinates,[50,51] and carboxylic esters.[52-54] Here the maxima result from the superposition of a specific electrolyte effect on an acid catalysed reaction (often accompanied by a considerable effect on a concurrent neutral reaction).[46]

Butler and Challis[42] showed further that the reaction was specific - rather than general - acid catalysed, and concluded that

protonation of the oxaziridines must therefore take place in a pre-equilibrium process. The maxima in the reaction rates were then attributed to complete conversion of the substrate into conjugate acid, as shown in Scheme (III-9). Confirmation of their mechanism came from studies of the solvent isotope effect. With 2-t-butyl-3-methyloxaziridines, $(k_o^{H_2O}/k_o^{D_2O}) < 1$ at low acidities, but steadily increases with acidity until 2M $HClO_4$ when $(k_o^{H_2O}/k_o^{D_2O}) = 1.2$. This is entirely consistent with a pre-equilibrium protonation, which is complete in 2M $HClO_4$.

The postulated mechanism allowed the basicities K_1 of oxaziridines to be determined from the kinetic data and the values of k_{-1}



Scheme (III-9)

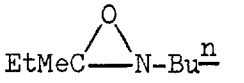
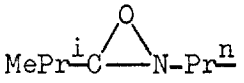
and K_1 obtained are listed for reference in Table (III-2). Alkyl substituents at the 3-position have a negligible effect on both the basicity and the rate of ring cleavage, consistent with their remote disposition to the oxygen and nitrogen atoms. Aryl substituents increase K_1 by a modest amount, as expected from comparison with benzylamines and alkylamines, and C-O fission seems to occur more readily than N-O fission, but not greatly so.[42]

Butler and Challis[42] were unable to resolve the precise structure of the conjugate acid of oxaziridines, i.e. the site of

Table (III-2)

Oxaziridine	$[HClO_4]_{max}$ (a)	$10^3 k_{o(max)}$ (min^{-1}).	m (b)	$10^3 k_1$ (c) (min^{-1}).	K_1 (c)	pK_1	Ref.
$NO_2C_6H_4$-CH(O)-N-Bu^t	5.86	43.4	1.15	43.0	63.7	-1.81	(42)
$NO_2C_6H_4$-CH(O)-N-Pr^i	6.13	14.5	0.91	28.6	254	-2.41	(43) (d)
C_6H_5-CH(O)-N-Bu^t	(e)	(e)	1.1	(1330) (f)	(313)	(-2.5)	(42) (d)
Me-CH(O)-N-Bu^t	3.95	10.7	(0.6	10.9	0.741	0.13	(42)
Et-CH(O)-N-Bu^t	4.88	11.3	(0.6)	11.5	0.814	0.19	(42)
Pr^i-CH(O)-N-Bu^t	4.88	9.05	(0.6)	9.3	2.28	-0.36	(42)
Et_2C(O)-N-Et	0.76	2.09	<0.6	4.49	2.12 (g), 2.13 (h)	-	(43)

Table (III-2) (continued)

Oxaziridine	$[HClO_4]_{max}$ (a)	$10^3\ k_{o(max)}$ (min^{-1})	m (b)	$10^3\ k_1$ (c) (min^{-1})	K_1 (c)	pK_1	Ref.
	0.73	4.18	<0.6	8.97	3.77 (g), 3.58 (h)	-	(43)
	0.72	4.95	<0.6	10.5	2.20 (g), 1.56 (h)	-	(43)

(a) In $HClO_4$ at 25°C.

(b) Slope of plot log k_o versus $(-H_o)$.

(c) Based on the h_o acidity scale.

(d) Values recalculated.

(e) Kinetic runs too fast to reach maximum of rate constants.

(f) Numbers in brackets are approximate.

(g) Equilibrium constant for the O-conjugate acid: K_1.

(h) Equilibrium constant for the N-conjugate acid: K_2.

protonation.

Though nitrogen is normally a more basic site than oxygen, and this is the experimental finding for hydroxylamines and related compounds containing both atoms,[55] there are exceptions as in the case of amides,[56] where oxygen seems to be the site of protonation, at least at high acidities.[57]

For 2-t-butyl-oxaziridines, the products can be explained most readily, as Emmons[6] noted previously, in terms of a N-O bond fission of the O-conjugate acid (Scheme (III-8)). For the 3-aryl-oxaziridines, stabilization of the incipient carbonium ion by the aryl substituent should promote C-O bond fission also of the O-conjugate acid (Scheme (III-7)). However, Butler and Challis[42,43] noted that both kinetic results and products would also be consistent with equilibrium protonation of the N atom, with this conjugate acid unreactive towards hydrolysis reagents.

A more detailed discussion about the physical evidence at present available in favour of the O or N-conjugate acids of oxaziridines will be resumed in Chapter V.

One point of major interest noted by Butler and Challis[42,43] was the acidity dependence of the hydrolysis rates. The slopes of log k_o vers. $(-H_o)$, m, are listed in Table (III-2). As can be seen, the 3-aryl-oxaziridines all have slopes close to unity. However, it is now well known that acidity dependence alone is not a sure criterion in the classification of mechanism, i.e. in distinguishing between the unimolecular pathway (A-1) and the bimolecular pathway (A-2).[58] Epoxides usually have m values close to one[59,60] but there is still a large controversy in the classification of their hydrolysis mechanism into an (A-1) or an(A-2) type.[59-65]

The same argument applies to oxaziridines. Only the 2-aryl-oxaziridines have slopes m close to unity, the others showing a lower value of m close to 0.60 or even smaller. No final conclusions can be drawn at the present stage concerning the type of mechanism involved but discussion on this important point will be continued in Chapter V.

III.3.1.b Oxaziridines without a 2-t-Butyl Group

Butler and Challis[43] showed that replacement of a 2-t-butyl group by a primary alkyl group produced more complicated kinetics. A typical rate/acidity profile for the 2,3,3-triethyl-oxaziridine, (Fig (III-1)), showed a pronounced maximum between 0.7-0.8M $HClO_4$, and a decrease in rates at higher acidities. Another different characteristic of these reactions was that the solvent isotope effect was always greater than unity, $(k_o^{H_2O}/k_o^{D_2O} > 1)$, even at low acidities.[66] This fact strongly suggested that the nucleophilicity of the solvent ($H_2\ddot{O}$ vers. $D_2\ddot{O}$) is far more important than with the 2-t-butyl-oxaziridines, where an inverse isotope effect occurred at low acidities, before complete protonation of the substrate occurred.[42]

The above evidence and also the type of products obtained in the hydrolysis (Table (III-1)) strongly suggested that protonation occurred in a pre-equilibrium step, but that the attack of solvent on the conjugate acid was also important through the whole acidity range, most especially after the maximum in the rates was reached.

Bearing this in mind, the decrease in rate constant observed can be most easily explained by the decrease in water activity, (a_w), which, within limits, expresses the availability of "free" water in a given system. As a matter of fact it is possible to fit

the experimental results with a Bunnett[67] type equation, (Eq. (III-1)), when the concentration of conjugate acid $[SH^{\oplus}]$ is very much lower than the concentration of free base $[S]$, in the pre-equilibrium step. In (Eq. (III-1)) $\underline{k}_{\psi}$ represents the rate

$$S + H^{\oplus} \underset{K_1}{\rightleftharpoons} SH^{\oplus} \xrightarrow[k_1]{} \text{Products.}$$

$$\log \underline{k}_{\psi} - \log \frac{\underline{h}_o}{\underline{h}_o + K_1} = w \log a_w + \log \underline{k}_{\psi\,max}. \qquad \text{(III-1)}$$

constant for hydrolysis after $\underline{k}_o$ was corrected with the spontaneous rate in pure water $\underline{k}_w$, i.e. $\underline{k}_{\psi} = \underline{k}_o - \underline{k}_w$, a_w is the water activity, $\underline{w}$ is a proportionality factor, K_1 is the acid dissociation constant for the protonated substrate and $\underline{h}_o$ is the Hammett acidity function value.

Obviously, (Eq. (III-1)) reduces to a much simpler expression when $[SH^{\oplus}] \gg [S]$ or when $\underline{h}_o \gg K_1$, taking then the form of (eq. (III-2)).

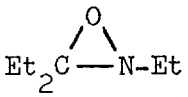
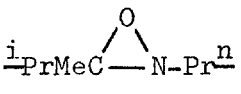
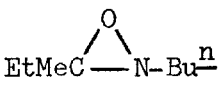
$$\log \underline{k}_{\psi} = w \log a_w + \log \underline{k}_{\psi\,max} \qquad \text{(III-2)}$$

or

$$\log \underline{k}_{\psi} = w \log a_w + C_1 \qquad \text{(III-3)}$$

When a plot of $\log \underline{k}_{\psi}$ versus $\log a_w$ was drawn for all the 2-primary alkyl-oxaziridines studied by Butler and Challis,[43] $\underline{w}$ was found not to be constant over all the acidity range considered, as can be easily seen from Table (III-3)where other typical examples are also listed. Between c a. 0.8M, $HClO_4$ and 3M,$HClO_4$, $\underline{w}$ has high values, ranging from +5.7 until +7.5. This, according to Bunnett,[68] is consistent with $H_2\ddot{O}$ acting as a proton transfer agent.

Table (III-3)

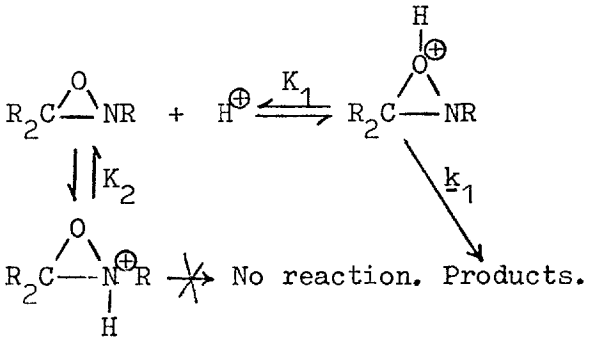
Reaction	Acidity Range	w	m
 hydrolysis	1.5-2.6M, $HClO_4$ 2.6-5.0M, $HClO_4$ 5.0-7.0M, $HClO_4$	+6.1 +3.0 +0.49	<0.6
 hydrolysis	0.72-3.95M, $HClO_4$ 3.95-6.13M, $HClO_4$	+5.7 +1.88	<0.6
 hydrolysis	0.73-2.60M, $HClO_4$ 2.60-5.86M, $HClO_4$	+7.5 +0.67	<0.6
Isopropylacetate [a] hydrolysis	0.6-8.9M, HCl	+4.62	0.42
Ethylacetate [a] hydrolysis	0.7-10.2M, HCl	+4.15	0.37
Sucrose [a] hydrolysis	0.6-5.8M, HCl	-0.43	1.02

a) Reference 67.

However at higher acidities the dependence upon the activity of water clearly decreases, and assumes low values ranging from +0.49 until +1.88. The decrease of $\underline{w}$ over the wide range of acidity considered may not be surprising since solvation in concentrated solutions will probably decrease with increasing acid concentration.[58] Several treatments,[69-72] related to equilibrium measurements for concentrated acid solutions, have tried to take this effect into account, but it would be rather ambitious at this stage to attempt a quantitative assessment on reaction rates. A more likely cause for the change in the values of $\underline{w}$ is, however, a change in mechanism, and this point will be taken up in a later chapter.

An alternative explanation[43] for the decrease in rates at high acidity was that nitrogen protonation of the oxaziridine leading to a stable conjugate acid occurred. Whether or not protonation on the nitrogen follows the $\underline{h}_o$ acidity function is not known. However, it is not unreasonable to choose the tertiary amines acidity function $\underline{h}_o'''$ to express the nitrogen protonation acidity dependence of oxaziridines. Butler and Challis,[43] therefore, translated the hydrolysis represented in Scheme (III-10) by (eq. (III-4)) and were thus able to obtain values for $\underline{k}_1$, K_1 and K_2, listed in Table (III-2).

From an inspection of the values of K_1 and K_2, (Table (III-2)), it is evident that the alkyl substituent on the nitrogen has a



Scheme (III-10)

very slight effect on the basicity. In comparison with the values obtained for the 2-t-butyl-oxaziridines, the K_1 values are slightly lower, suggesting an increase in basicity for these compounds.

$$\underline{k}_o = \frac{K_1 \underline{k}_1}{1 + K_1 \underline{h}_o + K_2 \underline{h}_o'''} \qquad \text{(III-4)}$$

$$K_1 = \frac{\left[R_2C(O^{\oplus}H)NR \right]}{\left[R_2C(O)NR \right] \underline{h}_o} \; ; \; K_2 = \frac{\left[R_2C(O)N^{\oplus}HR \right]}{\left[R_2C(O)NR \right] \underline{h}_o'''}$$

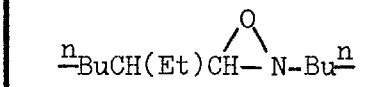
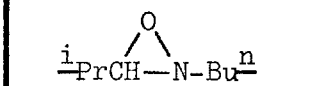
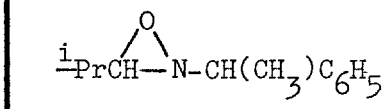
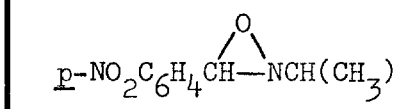
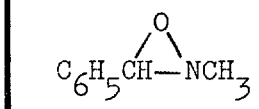
III.3.2. Basic Fission of the Oxaziridine Ring

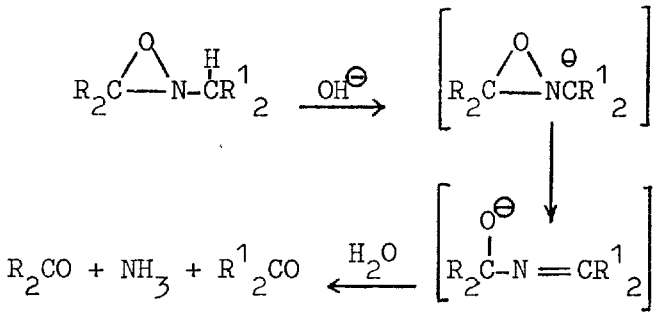
According to Emmons[6] the oxaziridine ring itself does not appear to be very reactive towards basic reagents. The same worker found that only the oxaziridines with a 2-methylene or a 2-methinyl substituent reacted vigorously with aqueous alcoholic alkali solution giving ammonia as a major product.

The mechanism postulated by Emmons[6] for the basic hydrolysis is outlined in Scheme (III-11) and is consistent with the products obtained. Proton abstraction from the carbon α to the nitrogen gave an imine which then rapidly hydrolysed to the parent carbonyl compound and ammonia.

The analyses of the carbonyl compounds formed, although difficult because these compounds undergo secondary condensation reactions, were in agreement with the proposed Scheme (III-11) as can be seen in Table (III-4).

Table (III-4)

Oxaziridine	Medium	Products	Yield	Ref.
	$OH^{\ominus}$/EtOH	NH_3	96%	6
	$OH^{\ominus}$/EtOH	NH_3	93%	6
	$OH^{\ominus}$/EtOH	NH_3 $C_6H_5COCH_3$ $(CH_3)_2CHCHO$ $(CH_3)_2CHCH=CHCOC_6H_5$	92% 25% 57% 9%	6
	$OH^{\ominus}$/EtOH	NH_3	59%	6
	$OH^{\ominus}$/H_2O	NH_3 C_6H_5CHO HCHO	80% 91% 71%	33



Scheme (III-11)

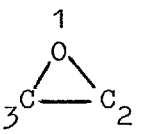
CHAPTER IV

Hydrolysis of Compounds with Related Structures to Oxaziridines

The hydrolysis of compounds with related structures to oxaziridines, such as epoxides, aziridines and diaziridines have been examined, in some cases extensively. These reactions are discussed briefly in this Chapter since they obviously give information on the behaviour of three-membered ring structures.

IV.1 Epoxides

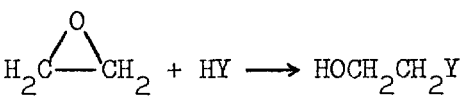
Epoxides are a three-membered ring structure of two carbon atoms and an oxygen atom, and their chemistry has been extensively



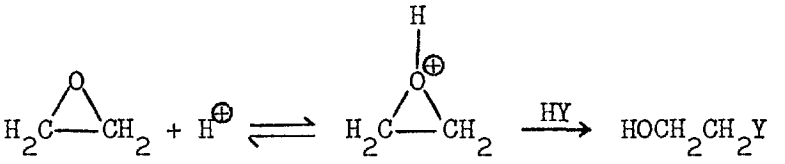
Epoxide Ring

reviewed by Winstein and Henderson,[73] Eliel[74] and Parker and Isaacs.[35]

These compounds are known to undergo several types of reactions involving ring opening and addition of a molecule of reagent HY (Scheme (IV-1)).



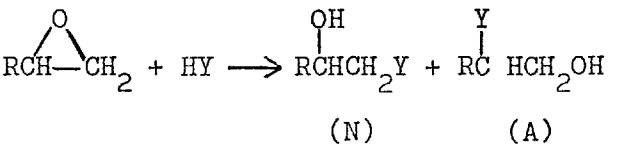
Scheme (IV-1)



Scheme (IV-2)

It was early realised,[75] however, that when HY reacted with epoxides under acidic conditions, the rate increased by a factor of 500 to 10,000, consistent with a reversible formation of the conjugate acid of the epoxides[35] (Scheme (IV-2)). Thus both the neutral epoxide and its conjugate acid may react with nucleophiles.

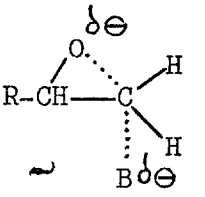
Unsymmetrically substituted epoxides may form two different products, (Scheme (IV-3)), (A) and (N) depending on which carbon atom of the ring is attacked. Krassusky[76,77] summarized the early work done with ammonia by saying that "when ammonia adds to



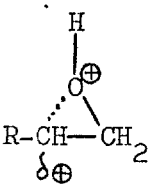
Scheme (IV-3)

unsymmetrical olefin oxides, the amino group attacks the carbon atom bearing the greater number of free hydrogen atoms", and from this follows the designation of product (N) as "normal" and product (A) as "abnormal". The fact that the type of substituents in the epoxide ring play a decisive effect on the rates of ring opening in hydrolysis has been taken as evidence for an S_N2 attack[35] by molecule or ion B involving a transition state of the type shown

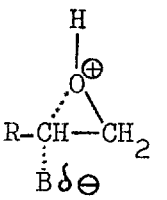
below, and this agrees with the high incidence of "normal" product



obtained. In acidic conditions, there is, however, a marked tendency towards the formation of abnormal products, which has been rationalised in terms of the inductive and hyperconjugative effects[35] of substituents (R) in transition states of the type shown below. This would allow for "abnormal" attack at the most sterically hindered carbon atom.



A-1 type



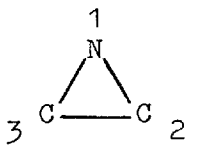
A-2 type

Brönsted and co-workers[78], found that the acid catalysed hydrolysis of epoxides was susceptible only to specific hydrogen ion catalysis, and isotope studies of the hydrolysis of isobutylene oxide and propylene oxide in water enriched with $H_2{}^{18}O$ showed that C-O bond fission occurred entirely at the most substituted carbon for the former and predominantly so for the latter.[79] The rates of hydrolysis of ten epoxides in aqueous $HClO_4$ at 0^oC were also measured and the experimental rate constants found to correlate with the H_o acidity function, the slopes of the log k_o against $(-H_o)$ plots being all in the range 0.86-1.06.[61] Pritchard and Long[59] studied the rates of hydrolysis in H_2O and D_2O at 25^oC and interpreted the

ratios ($k_o^{D_2O}/k_o^{H_2O}$) $\simeq$ 2 as indicative of a rapid pre-equilibrium for protonation before the rate determining step. On the basis of the Zücker-Hammett hypothesis, the linear correlations between log k_o and ($-H_o$) point towards an (A-1) mechanism not involving a water molecule in the rate determining step. However, independent evidence, namely the negative values[62,63] (-4 to -7.5 cal. mole.$^{-1}$deg.$^{-1}$) found for the entropy of activation, $\Delta S^{\ddagger}$, and the values obtained for the volumes of activation,[62] $\Delta V^{\ddagger}$, (-8.4 and -5.9 cm.^{3} mole.$^{-1}$), led Schaleger and Long[65] to agree that the present evidence favours the bimolecular (A-2) mechanism. Bunnett[80] found a value of w of about +2 to +3 and according to his classification this would indicate a bimolecular reaction with water acting as a nucleophile. However, a w value of approximately zero for the hydrolysis of ethylene oxide and propylene oxide may suggest that an (A-1) mechanism was operating in these cases. As a conclusion one might say that there is evidence pointing towards different types of mechanism and that Long and Paul's[62] counsel that "further study is desirable" remains appropriate.

IV.2 Aziridines

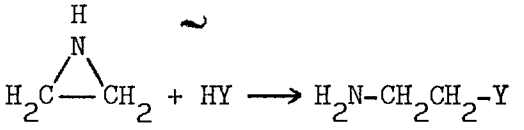
Aziridines are composed of a three-membered ring structure



Aziridine Ring

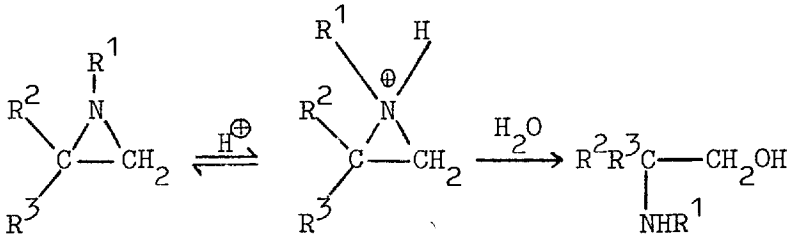
containing two carbon atoms and one nitrogen atom. They can be considered as the nitrogen analogous of epoxides and, indeed,

their properties show a striking resemblance with the latter. In particular, they undergo readily attack by nucleophiles at the carbon of the ring according to Scheme[81] (IV-4).



Scheme (IV-4)

Their hydrolysis is also catalysed by acid in low concentrations but retarded by increase of $HClO_4$ concentration above 1M.[68] Buist and Lucas,[81] and Earley, O'Rourke, Clapp, Edwards and Lawes[82] marshalled evidence that the rate determining step is S_N2 displacement of the iminium nitrogen by a water molecule (Scheme (IV-5)). The Bunnett's value[68] for $\underline{w}$ calculated for ethyleneimine hydrolysis was found to be equal to +2.5. The above facts seem to point in



Scheme (IV-5)

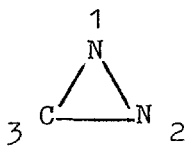
favour of a nucleophilic attack by water in the rate determining step, as for epoxides.[80]

The values of the enthalpy and entropy of activation, 23.0 kcal. mole.$^{-1}$ and -9.4 cal. mole.$^{-1}$ deg.$^{-1}$ respectively, found for the acid hydrolysis of ethylene-imine also suggest an S_N2 mechanism.[82] However, the presence of different substituents can alter the picture considerably, and Earley and co-workers[82] believed, from the values

of the activation parameters for the hydrolytic reaction and the product analysis, that the acid hydrolysis of 2,2-dimethylethyleneimine is primarily an S_N1 reaction with a small S_N2 contribution, whereas that of 2-ethylethyleneimine is primarily an S_N2 with a possible small S_N1 contribution.

IV.3 Diaziridines

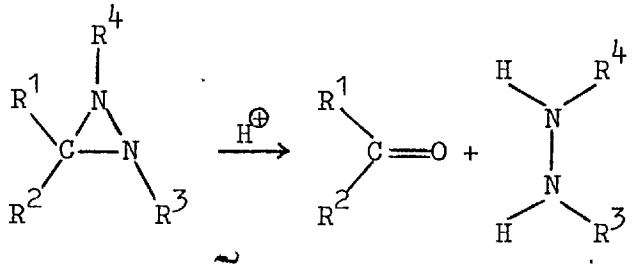
Diaziridines are compounds with a three-membered ring structure containing one carbon atom and two nitrogen atoms. They are generally more stable than oxaziridines, probably due to the lower



Diaziridine Ring

energy content of the N-N bond relative to the N-O bond.[33]

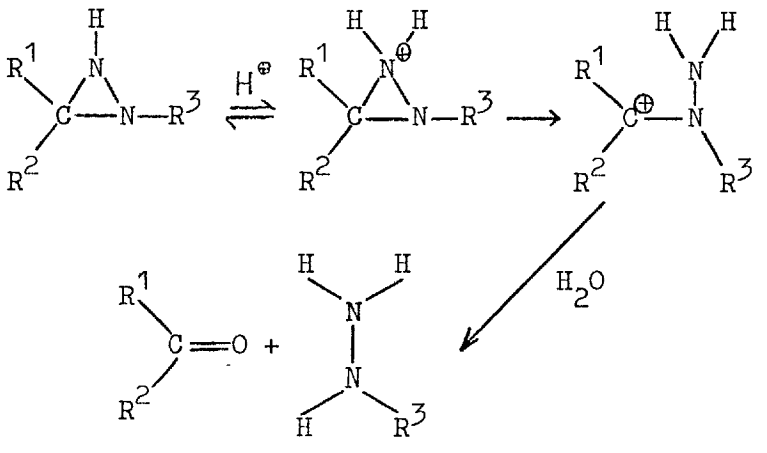
Only the hydrolytic fission of these compounds will be discussed here. As with oxaziridines, this class of compounds requires much more vigorous conditions than expected from experience with open-chain compounds or larger rings, for instance open-chain 1,1-diamines[83] which are decomposed instantaneously by dilute acids. Indeed stable salts from oxalic acid and 1,3-dialkyldiaziridines have been obtained.[84] Only when heated with aqueous mineral acids, have diaziridines been successfully cleaved to form a carbonyl compound and a substituted hydrazine[85] (Scheme (IV-6)). These reactions have been investigated kinetically,[85] and show a high temperature coefficient, an activation enthalpy in the range (23-28 kcal. mole.$^{-1}$) and a positive entropy of activation (2-6 cal. mole.$^{-1}$ deg.$^{-1}$). The influence of substitution on nitrogen



Scheme (IV-6)

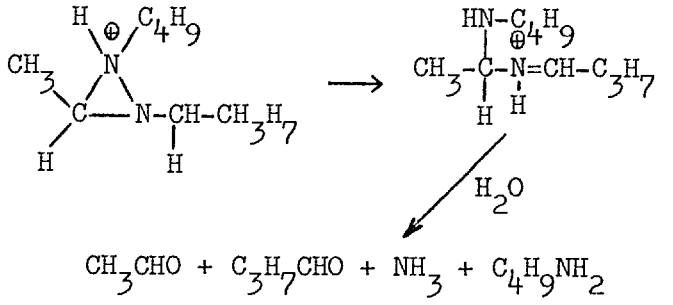
is small, the rate of hydrolysis in the weakly acid region depending only on the acid concentration. Thus the rate constants between pH7 and 3 rise by a factor of nearly 10^3, but between pH3 and 70% H_2SO_4 by only a factor of 4. The hydrolysis must therefore proceed by a pre-equilibrium for protonation which is almost complete at pH3.(33)

By contrast, substitution on the C-atom of the ring greatly affects the rates with increasing alkyl substitution strongly accelerating the hydrolysis.(86) The magnitude and direction of this substituent effect are characteristic of an S_N1 reaction, leading to the conclusion that the rate determining step of the hydrolysis is a heterolytic opening of the diaziridinium ion (Scheme (IV-7)).



Scheme (IV-7)

Hydrolysis in a weakly solvating solvent, e.g. HCl in CCl_4, proceeds via a different mechanism, with the N-N bond being broken, and perhaps synchronous migration of a hydride ion from the adjacent carbon to the nitrogen of the ring, (Scheme (IV-8)), resulting



Scheme (IV-8)

ultimately in dealkylation of this atom[86] as was the case with the 2-primary-alkyl-oxaziridines.[6,43] The possibility of this hydride migration is therefore a prerequisite for the N-N cleavage, and thus the N-N and the C-H bond must be almost parallel. When this condition is not met the compounds are stable in HCl/CCl_4.[86]

In the following Chapters, experimental results dealing with the hydrolytic cleavage of the oxaziridines, under acid and basic conditions, will be discussed. Several oxaziridines bearing different substituents attached to the ring were studied and the influence of changes in the structures can be correlated with the reactivity presented to different reagents. The bearing of these results on the mechanism of the reaction, and the properties of A-1 and A-2 reactions generally will be discussed.

Chapter V

Acid Hydrolysis of Oxaziridines

In Section (III.3.1) a survey of the work done on the acid hydrolysis of oxaziridines showed that the type of products obtained, the rate of ring opening and the mechanism of the hydrolysis were deeply dependent on the substituents attached to the oxaziridine ring, either to position 2 or to position 3. Since small changes in structure are not normally associated with very dramatic changes in mechanism it was decided to examine the influence of the substituents on the hydrolysis mechanism.

The work described in the following sections deals with investigations to determine the site of protonation as well as with the hydrolysis of oxaziridines bearing either a primary alkyl group (ethyl or benzyl) or a secondary alkyl group (isopropyl or α-phenylethyl) attached to the nitrogen atom in the ring.

All the kinetic experiments reported in this chapter were carried out at $25.0 \pm 0.1^{\circ}C$ and the rates follow Eq. (V-1):

$$\text{rate} = \underline{k}_o \left[\text{substrate}\right] \qquad \text{(V-1)}$$

where $\underline{k}_o$ is the rate constant observed for the ring opening reaction and [substrate] refers to the stoichiometric concentration of the oxaziridine.

The carbonyl products from the reaction were identified through their 2,4-dinitrophenylhydrazones and the experimental details are described in Part 3.

V.1 The Site of Protonation in Oxaziridines

Protonated organic compounds play a very important rôle as intermediates in acid-catalysed reactions and in recent years considerable attention has been devoted to finding techniques which determine their detailed structure. The tool employed with most success has been nuclear magnetic resonance spectroscopy and a review by Olah, White and O'Brien[87] compiles the most recent data available for a large range of organic compounds.

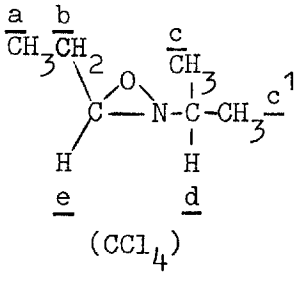
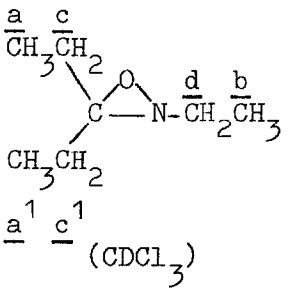
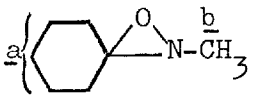
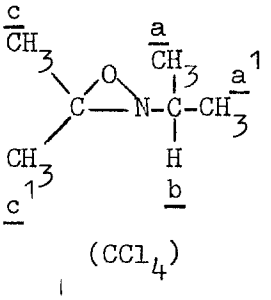
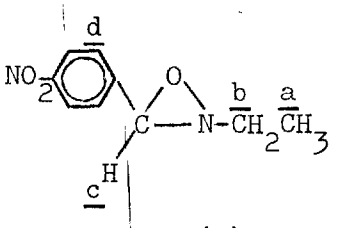
Because of its practical as well as theoretical importance, attempts were made to determine the site of protonation of the oxaziridine ring, under various conditions by n.m.r. spectroscopic examination.

The spectra of neutral oxaziridines were taken in inert solvents and the chemical shifts of proton resonances computed relative to the tetramethylsilane signal. To obtain the protonated oxaziridine, trifluoracetic acid (T.F.A.) was added to the solution, and the spectra of the conjugate acids recorded (vide Part 3).

The experimental results are summarized in Table (V-1). The spectra obtained can be seen in Fig. (V-1) to (V-5). It should be emphasised that the chemical shifts produced by the addition of trifluoracetic acid in carbon tetrachloride are the same as those found when the spectrum of the conjugate acid of the 2,3,3-triethyloxaziridine was taken in, say, 6N, D_2SO_4 (solvent D_2O), suggesting that it is not a pure medium effect which is shifting the signals downfield in the T.F.A. system (cf. Fig. (V-8), spectrum 1).

Analysis of the three last columns of Table (V-1) shows that, except for 2-ethyl-3-p-nitrophenyloxaziridine, the magnitude of the chemical shift ($\Delta\tau$) is consistent with protonation of the nitrogen atom rather than the oxygen.

Table (V-1)

Substrate/Solvent	Protons	τ(a)	τ(b)	$\Delta\tau$	(N)(c)	(O)(d)
 (CCl_4)	a	8.93	8.77	0.16	γ	γ
	c, c^1	8.85, 8.73	8.47	0.38, 0.26	β	γ
	b	8.37	7.92	0.45	β	β
	d	7.85	6.49	1.36	α	β
	e	6.32	5.11	1.21	α	α
 ($CDCl_3$)	a, a^1	9.06, 8.94	8.87, 8.78	0.19, 0.16	γ	γ
	b	8.84	8.50	0.34	β	γ
	c, c^1	8.32	7.85	0.47	β	β
	d	7.21	6.38	0.83	α	β
 (CCl_4)	a	8.32 7.78	8.14 7.59	0.18 0.19	β,γ,ε	β,γ,ε
	b	7.38	6.78	0.60	α	β
 (CCl_4)	a, a^1	9.03, 8.88	8.68, 8.59	0.35, 0.29	β	γ
	c, c^1	8.72, 8.56	8.32, 8.27	0.40, 0.29	β	β
	b	7.00	7.04	0.56	α	β
 A,B isomers (e) (CCl_4)	(B) a	8.93	8.90	0.03	β	γ
	(A) a	8.70	8.67	0.03	β	γ
	(B) b	7.52	6.82	0.70	α	β
	(A) b	7.06	6.41	0.65	α	β
	(A) c	5.49	4.34	1.15	α	α
	(B) c	4.80	3.72	1.08	α	α
	(A,B) d	2.35-1.73	2.35-1.73	ca.0	γ,ε	γ,ε

(a) NMR in an inert solvent, TMS as internal standard, $t \simeq 43^{\circ}C$.
(b) NMR in an inert solvent to which approximately 20% of CF_3CO_2H was added, $t \simeq 43^{\circ}C$.
(c) Position of the protons relative to the nitrogen in the oxaziridine ring.
(d) Position of the protons relative to the oxygen in the oxaziridine ring.
(e) Reference (92).

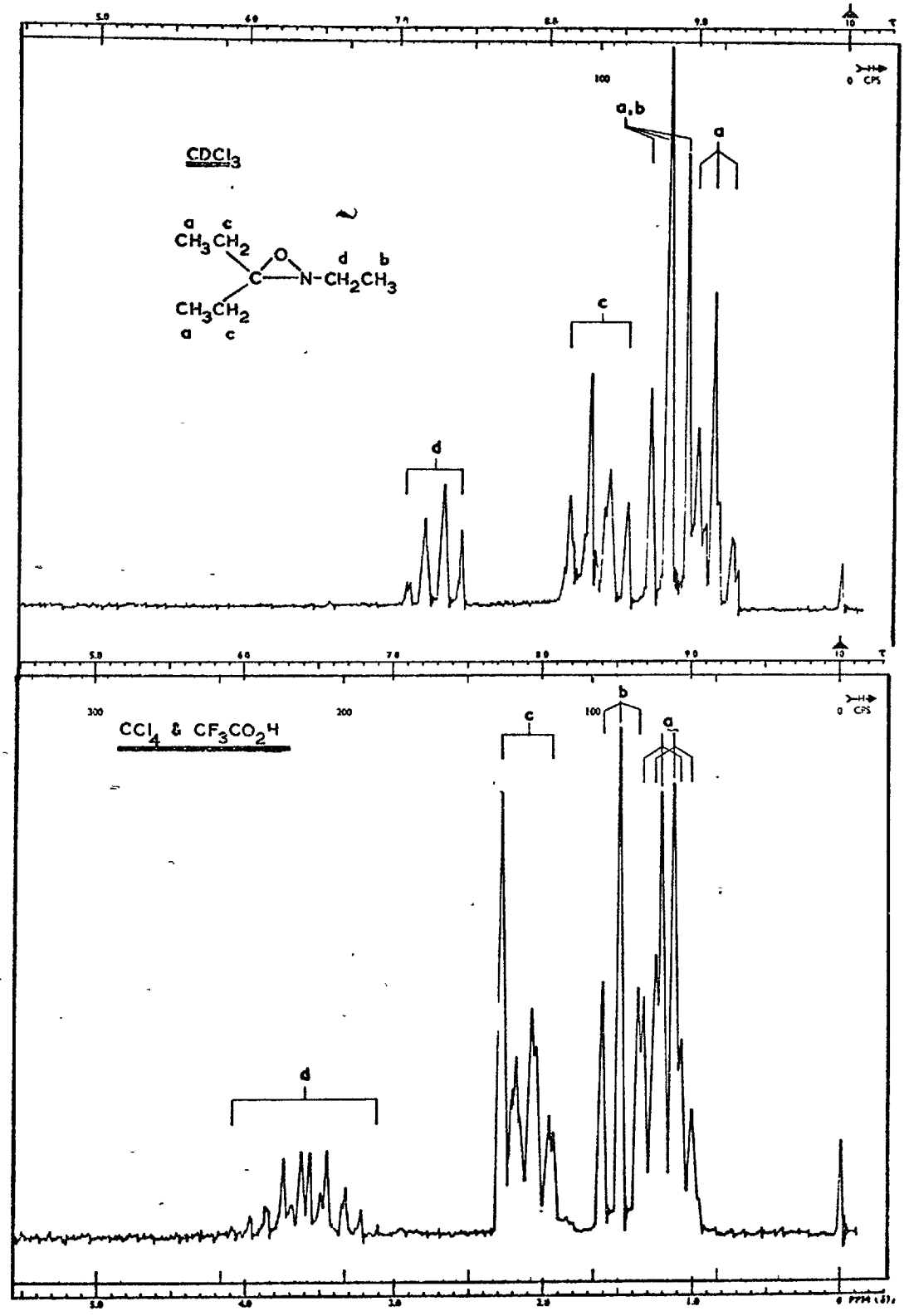


Fig. (V-1). NMR spectra of 2,3,3-triethyloxaziridine in $CDCl_3$ and in a mixture of CCl_4 and CF_3CO_2H.

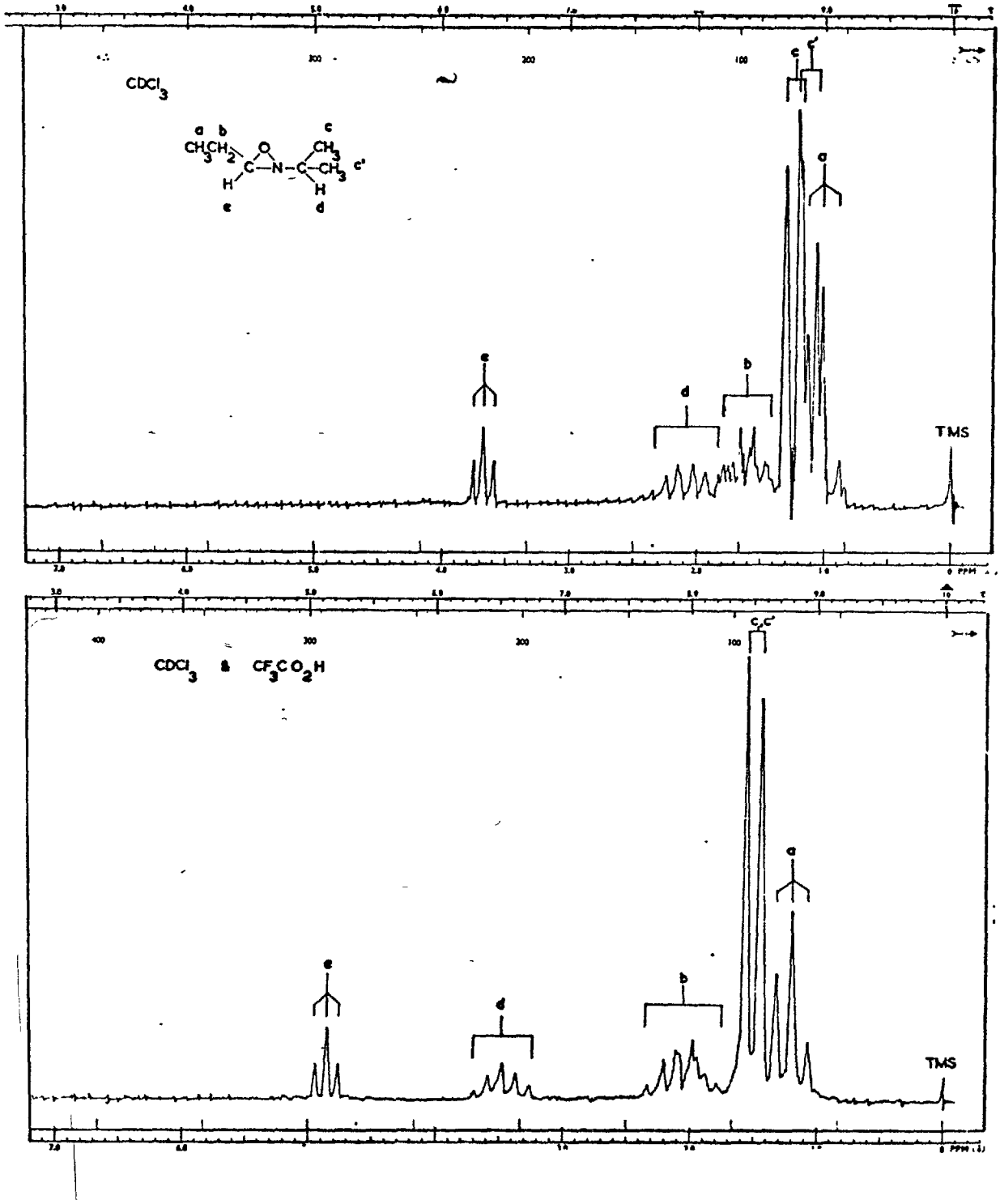


Fig. (V-2) NMR spectra of 2-isopropyl-3-ethyloxaziridine in $CDCl_3$ and a mixture of $CDCl_3$ and CF_3CO_2H.

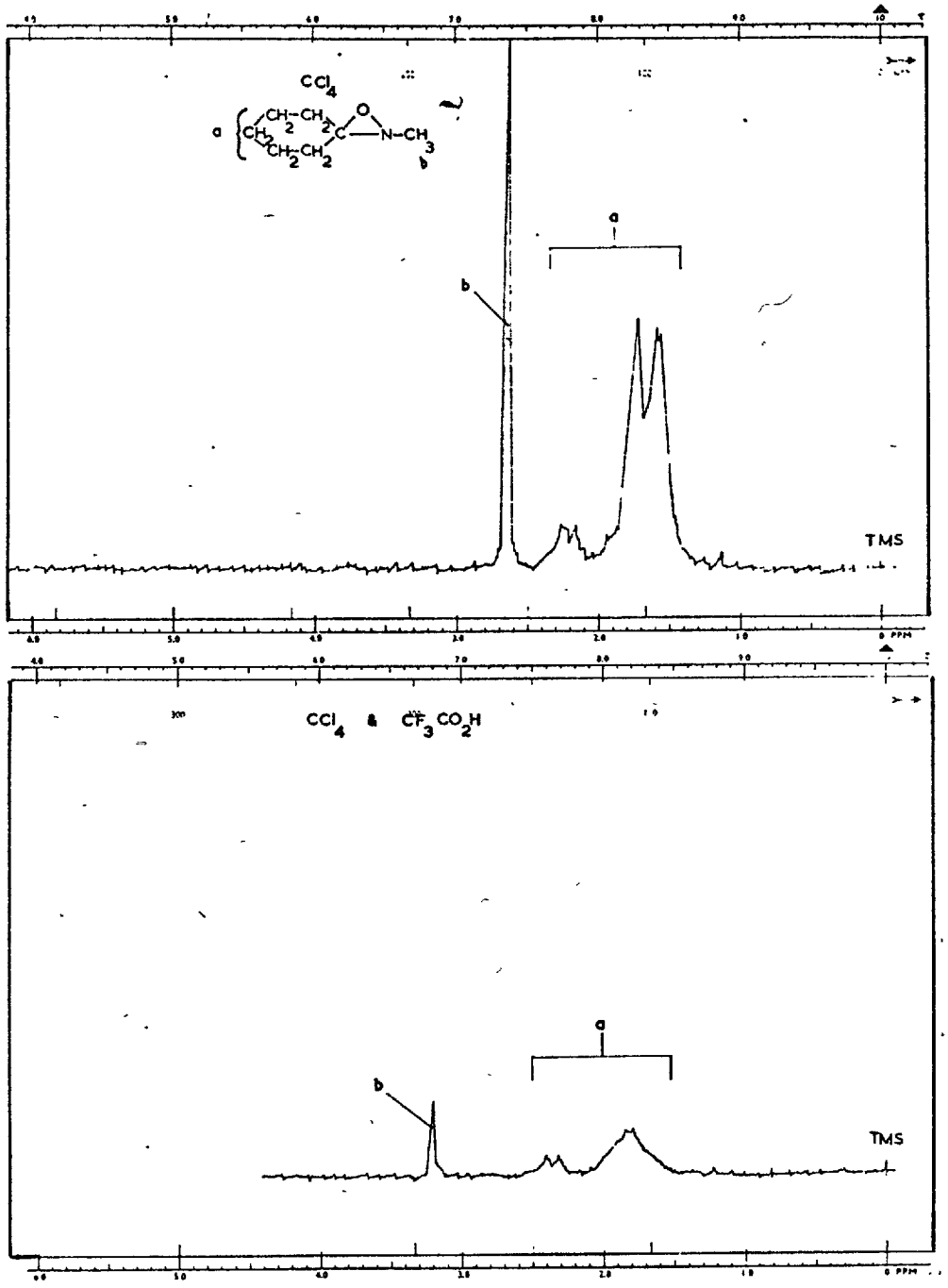


Fig. (V-3). NMR spectra of 2-methyl-3,3-pentamethyleneoxaziridine in CCl_4 and a mixture of CCl_4 and CF_3CO_2H.

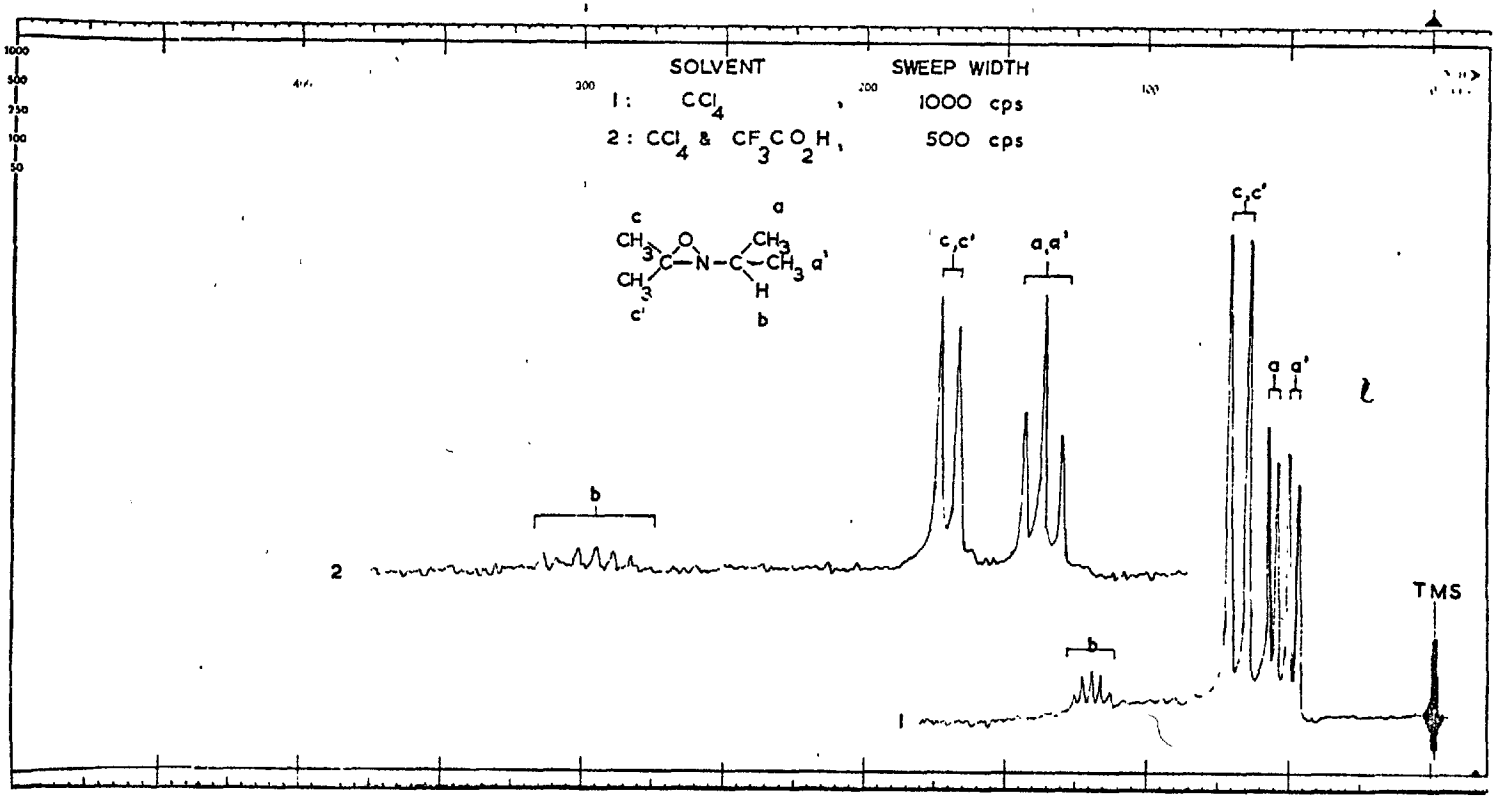


Fig. (V-4). NMR spectra of 2-isopropyl-3,3-dimethyloxaziridine in CCl_4 and a mixture of CCl_4 and CF_3CO_2H.

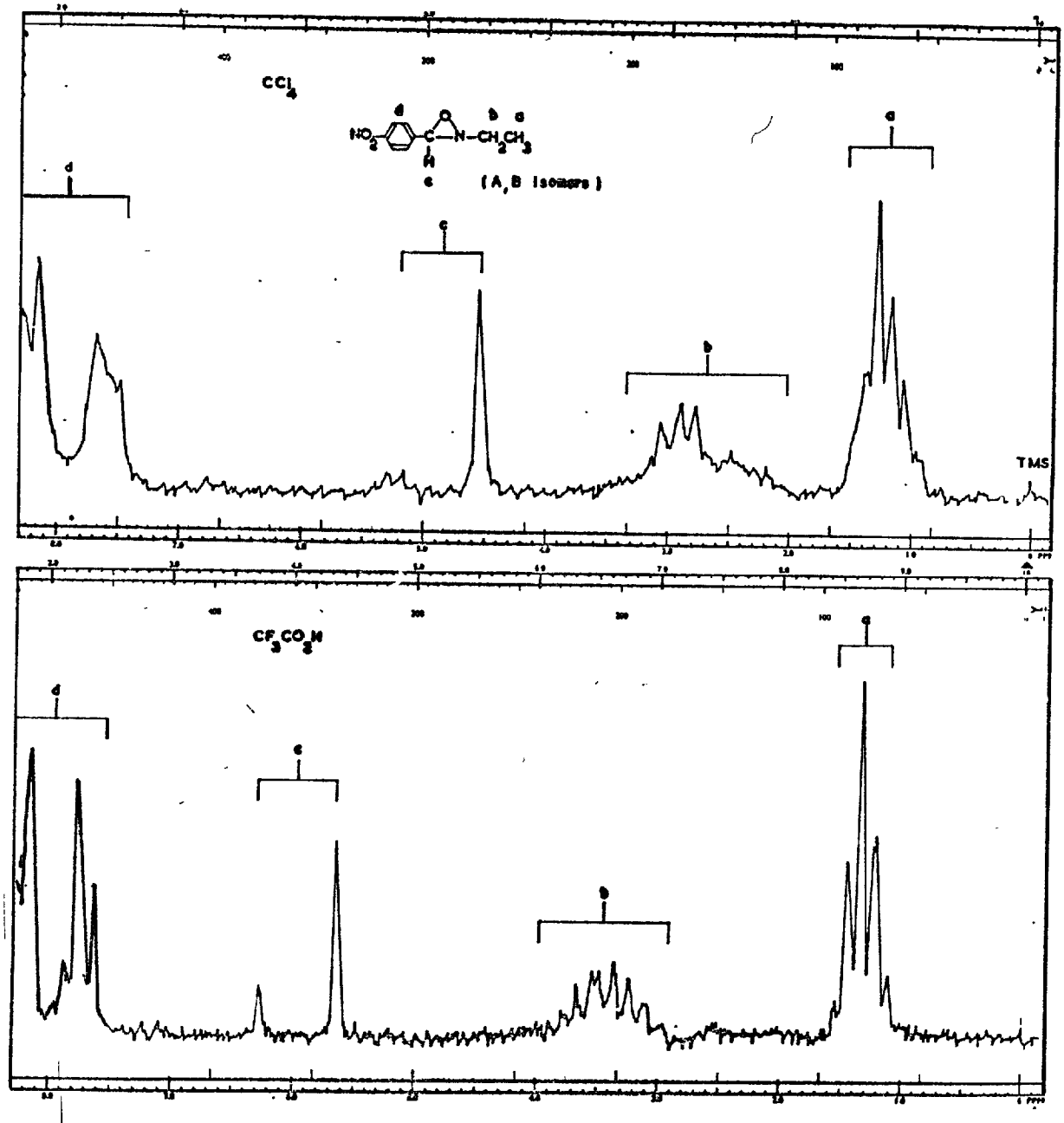
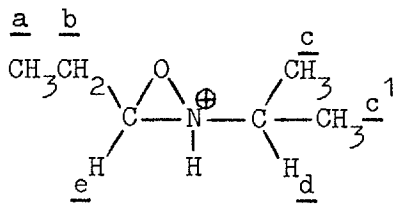
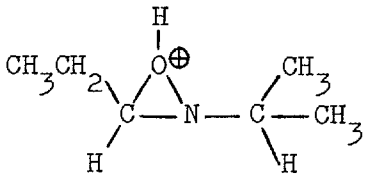


Fig. (V-5). NMR spectra of 2-ethyl-3-p-nitrophenyloxaziridine in CCl_4 and CF_3CO_2H.

It is instructive to examine the first example in detail. If it is assumed that the conjugate acid of the 2-isopropyl-3-ethyl-oxaziridine is (1), i.e. the N-protonated base, then the chemical



(1)



(2)

shifts reported are inconsistent agreement. For protons (e) and (d), both α to the positive nitrogen, $\Delta\tau$ is respectively 1.21 and 1.36, considerably higher than all the other values obtained. The methyl groups (c) and (c^1), and the methylene group (b), all β to the nitrogen atom show $\Delta\tau$ values of similar size (0.26, 0.36 and 0.45, respectively). Finally the methyl group (a), in position γ, shows the least change or addition of T.F.A. (0.16).

If, however, the O-protonated oxaziridine (2) is formed, a very poor fit is found between the $\Delta\tau$ values and the relative distance of the various hydrogens to the $\overset{\oplus}{O}$-H.

The same reasoning applied to the other oxaziridines[a] listed in Table (V-1) shows that N rather than O-protonation occurs. This is in fact not surprising. Electronegativity considerations suggest that nitrogen should be more basic than oxygen[b], and the n.m.r.

a) Except for the last compound listed (2-ethyl-3-p-nitrophenyl oxaziridine) which does not show such clear cut evidence for N protonation and could well be allocated under O protonation.

b) However, inversions to this order of basicity are known to occur with[88-91], for example, amides.

of a suitable model compound (N-methylhydroxylamine) in T.F.A. shows no signs of O-protonation occurring, the spectrum being consistent with 100% of the N-protonated species. The spectrum of the N-protonated species can easily be recognised in this case, since the coupling between the two protons on the nitrogen and the $N-CH_3$ group gives rise to a well defined triplet ($J \simeq 5$ Hz). Also the protons on the nitrogen are seen as a triplet ($J \simeq 52$ Hz) due to the quadrupole moment of this atom (Fig. (V-6)).

The same situation is not found with the oxaziridines studied. Due to the rigid structure of the three-membered ring, the slow rate of "umbrella" type of inversion around the nitrogen usually makes the n.m.r. spectra considerably more complex. It seems that at the temperature (c a. 43°C) of our experiments the complexity of the signal due to the methylene group α to the nitrogen of 2,3,3-triethyloxaziridine is caused by slow inversion (by comparison with the n.m.r. time scale) around the nitrogen (Fig. (V-1)). The complexity of this signal increases when the acid is added and becomes a well defined septet in 6N, D_2SO_4.

This slow inversion could only be observed with the 2-ethyloxaziridines. Other oxaziridines, bearing a more bulky group in the position 2, either do not invert around the nitrogen or invert too fast at the temperature studied. Recently, following the analogy of aziridines where the energy barrier for inversion is sufficiently high to allow the separation of enantiomers or diastereomers, diastereoisomerism due to non-inverting nitrogen atom has been reported for oxaziridines.[92]

Another problem with the n.m.r. spectra of the protonated oxaziridines was that no signal for the proton on the nitrogen or

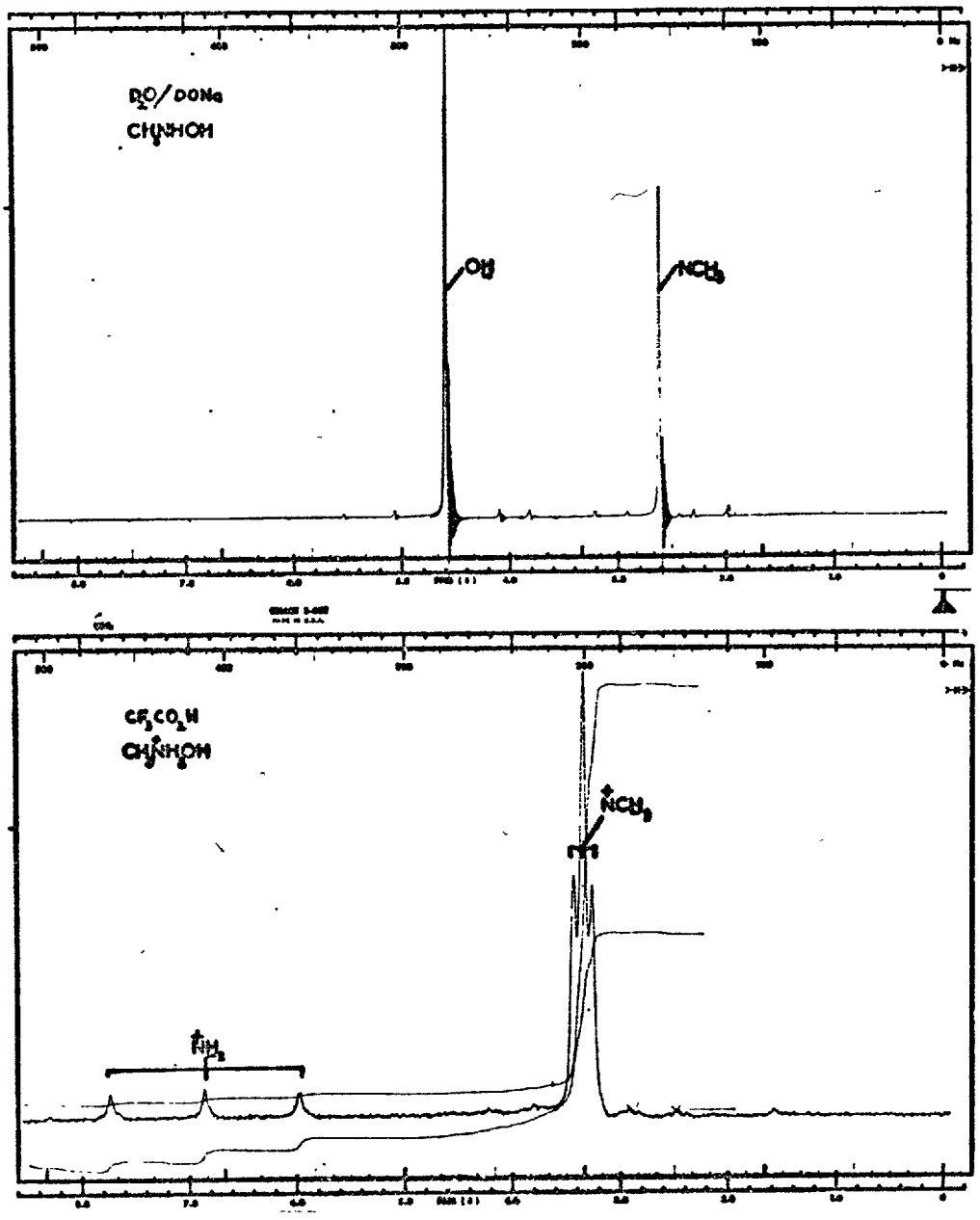
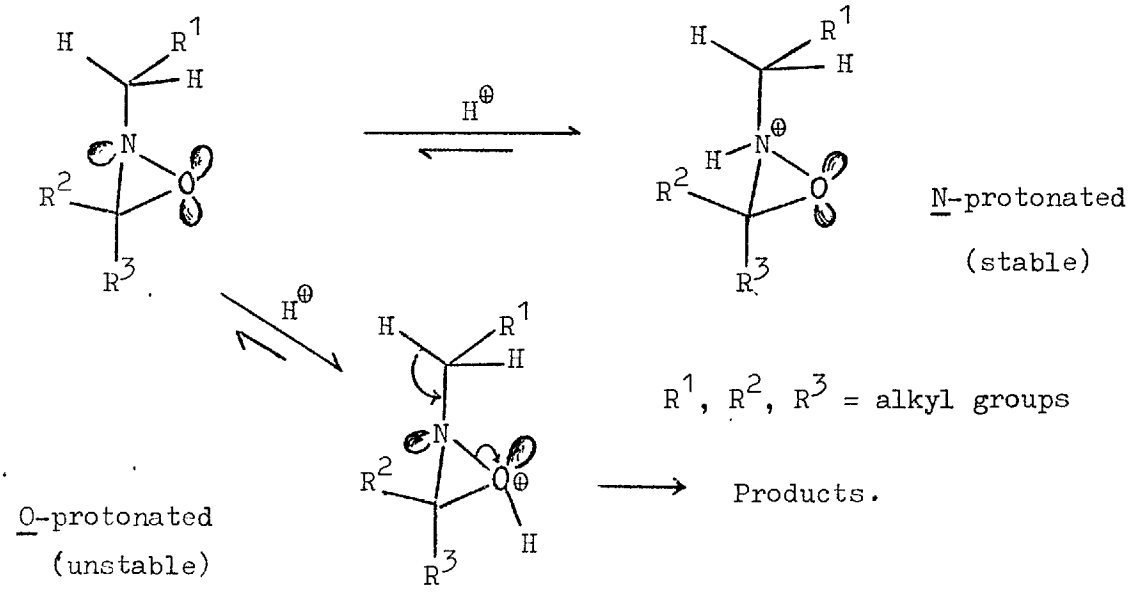


Fig. (V-6). NMR spectra of N-methylhydroxylamine in D_2O/DONa and CF_3CO_2H.

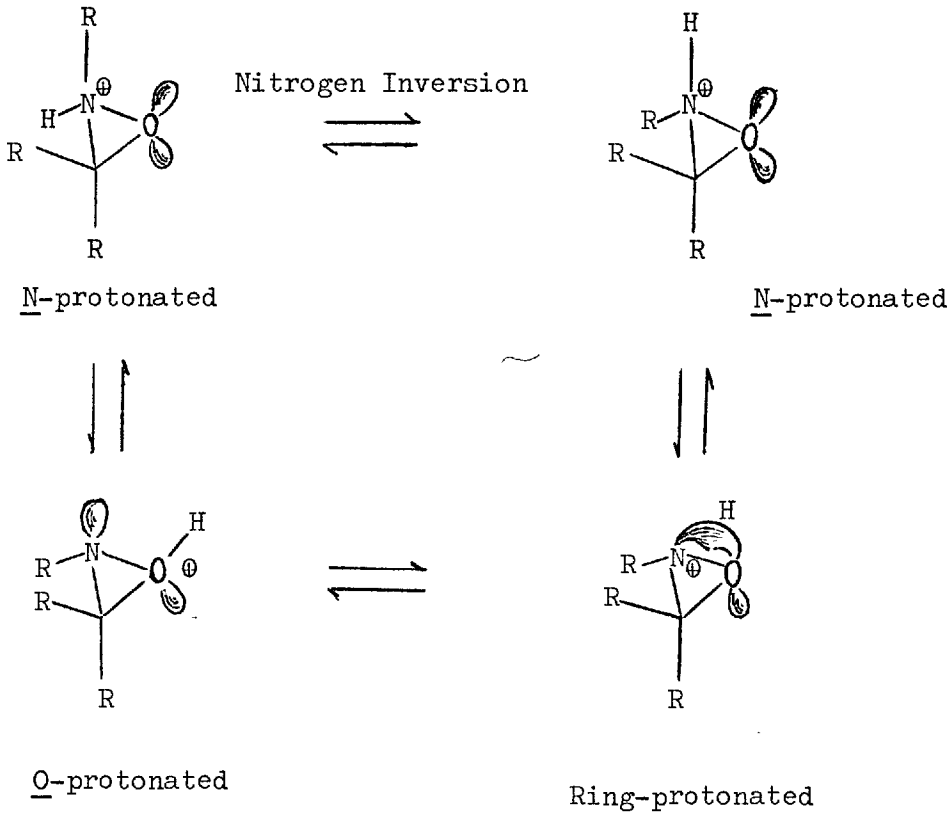
oxygen atoms could be observed. This suggests that exchange with the medium is fast since the lifetime of the acidic proton on the site of protonation[87] must be at least 10^{-1}-10^{-2} sec for observation of separate resonances in the n.m.r. spectrum.

The results point to the nitrogen atom being the site of protonation for oxaziridines with alkyl substituents in position 3 and bearing a methyl, ethyl or isopropyl group in position 2. For compounds with a 3-aryl substituent, the evidence towards N-protonation is not clear and the n.m.r. evidence does not rule out the formation of the O-conjugate acid.

Nonetheless there seems to exist a very fine balance between the basicity of the O and N atoms. Although the N-protonated species is the one apparent in n.m.r. spectra, small amounts of the O-protonated form seem to be responsible for the hydrolytic pathway shown in (Scheme (V-1)). The possibility that protonation occurs half way between the N and the O atoms cannot be dismissed "a priori" and may account for the equilibrium between the different protonated species (Scheme (V-2)).



Scheme (V-1)


Nitrogen Inversion
N-protonated
N-protonated
O-protonated
Ring-protonated

Scheme (V-2)

V.2 Results for the Hydrolysis of Oxaziridines with a Primary 2-Alkyl Group

As discussed in Section III.3.1b, the kinetics of hydrolysis of oxaziridines with a primary 2-alkyl group present special features, in particular a sharp increase in rate between 0 and 0.7-0.8 M, $HClO_4$, followed by a decrease in rates at higher acidities. Since the mechanistic implications of the rate profile were not clearly understood, further studies were desirable, particularly to clarify a) the participation of the proton α to the nitrogen atom in the ring opening process, b) the nature of the conjugate acid (N- or O-protonated) and c) the type of products obtained.

Table (V-2)

Ring Opening of 2,3,3-Triethyloxaziridine in an Aqueous Buffer of Sodium Acetate - Acetic Acid

Temperature = 25.0 ± 0.1°C

μ = 1.0, adjusted with $NaClO_4$

Buffer ratio of [NaOAc] / [HOAc] = 1

Kinetic Run	[HOAc] x10 M.	10^4 k_o $min.^{-1}$
106	10	23
110	7.0	16
109	5.0	13.5
108	3.0	8.8
107	1.0	5.7

By plotting k_o versus [HOAc] a linear plot was found - slope = 2.2×10^{-3} $mole^{-1}.l.min.^{-1}$

V.2.1 2,3,3-Triethyloxaziridine and 2-(α,α'-$\left[^2H_1\right]_2$-Ethyl)-3,3-diethyloxaziridine

One of the oxaziridines studied by Butler and Challis[43] giving the typical rate profile with a maximum at 0.7-0.8 M, $HClO_4$, was 2,3,3-triethyloxaziridine. To examine the possibility of α-proton abstraction in the rate limiting step the incidence of Brönsted acid catalysis was first investigated. Table (V-2) shows the results obtained with a sodium acetate - acetic acid buffer of ratio 1:1 at constant ionic strength (μ = 1.0, adjusted with $NaClO_4$). A plot of [HOAc] versus the experimental rate coefficient, k_o, was found to be linear with slope 2.2 x 10^{-3} $mole^{-1}.l.min^{-1}$. Thus the reaction is subject to general acid catalysis.

Table (V-3)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Hydrochloric Acid

Temperature = 25.0 $\pm$ 0.1°C

μ = 1.0, adjusted with NaCl

Kinetic Run	[HCl] x10^2 M	10^3 k_o min^{-1}.
33	10	2.2
34	1.0	1.0

In Table (V-3) kinetic runs in dilute HCl are reported. These

were aimed at studying the behaviour of this oxaziridine at pH 1 and 2. To evaluate the second order coefficient for $H_3O^{\oplus}$ catalysis (Eq. (V-2)) was used. This value ($\underline{k}_{H_3O^{\oplus}} = 1.34 \times 10^{-2}$ mole^{-1}.l.min.$^{-1}$).

$$\text{Rate} = \underline{k}_{H_3O^{\oplus}} \left[\text{oxaziridine}\right] \left[HCl\right] \qquad \text{(V-2)}$$

enables the calculation of the intercept of $\underline{k}_o$ versus $\left[HOAc\right]$ ($k_{H_3O^{\oplus}} \left[H_3O^{\oplus}\right] = 0.01 \times 10^{-3}$ min^{-1}, with $\left[H_3O^{\oplus}\right] = 6.3 \times 10^{-4}$ M) which agrees reasonably with the experimental value found if spontaneous decomposition in water is taken into account.

To obtain direct evidence of the role of the proton $\underline{\alpha}$ to the nitrogen atom, 2-(α,α'-$\left[{}^2H_1\right]_2$-ethyl)-3,3-diethyloxaziridine was prepared and the kinetics of hydrolysis in aqueous $HClO_4$ are reported in Table (V-4). Comparison with $\underline{k}_o$ for the normal substrate[43] shows

Table (V-4)

Ring Opening of 2-(α,α'-$\left[{}^2H_1\right]_2$-Ethyl)-3,3-diethyloxaziridine in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$\left[HClO_4\right]$ 10 M	10^4 $\underline{k}_o$ min.$^{-1}$
81	66.7	6.1
78	26.1	5.8
76	7.38	8.0
77	1.06	4.6

a maximum $\underline{k}_o$ in the same region for both the dideuteriated and the normal oxaziridine, but the hydrolysis rate is considerably slower for the dideuteriated compound: the ratio $\underline{k}_o^H:\underline{k}_o^D$ is listed in the right-hand column of Table (V-5). The isotope effect observed is

Table (V-5)

Isotope Effect in the Acid Hydrolysis of 2,3,3-Triethyloxaziridine

Temperature = 25.0 ± 0.1°C

$[HClO_4]$ 10 M	$10^4\ \underline{k}_o^H$ a),b) $min.^{-1}$	$10^4\ \underline{k}_o^D$ b) $min.^{-1}$	$\underline{k}_o^H/\underline{k}_o^D$
1.06	12.3	4.6	2.7 ± 0.1
7.38	20.9	8.0	2.6 ± 0.1
26.1	12.2	5.8	2.1 ± 0.1
66.8	7.48	6.05	1.2 ± 0.1

a) Data from reference 43.

b) $\underline{k}_o^H$ and $\underline{k}_o^D$ represent the observed rate constant for 2,3,3-triethyloxaziridine and for 2-(α,α'-$[^2H_1]_2$-ethyl)-3,3-diethyloxaziridine, respectively.

not constant throughout the whole acidity range, being a maximum at the lowest acidity of 0.106 M, $HClO_4$, ($\underline{k}_o^H/\underline{k}_o^D$ = 2.7) and then decreasing slowly as the acidity increases (at the highest acidity of 6.68 M, $HClO_4$, $\underline{k}_o^H/\underline{k}_o^D$ = 1.2). A comparison between the rate

profiles of the two oxaziridines is made in Fig (V-7). Both the incidence of a maximum and the difference in rates is clearly visible.

These results show clearly that at low acidity, at least, removal of the α proton occurs in the rate limiting step. At high acidity, some additional mechanism prevails in which this step is not rate limiting. Further discussion of these findings is deferred until later.

Product Analysis

The carbonyl products of hydrolysis in c a. 1M, $HClO_4$, as identified by their 2,4-dinitrophenylhydrazones, were found to be diethylketone and acetaldehyde.

The n.m.r. spectrum of the hydrolytic reaction of 2,3,3-triethyloxaziridine in 6N, D_2SO_4, 5 minutes after mixing, when very little ring opening is known to have occurred from I_2 titration is shown in Fig. (V-8), spectrum 1. This spectrum, therefore, refers to the conjugate acid of the oxaziridine and, by the analysis of the chemical shifts, it corresponds to the N-conjugate acid (for further discussion of the site of protonation see Section (V-1)). The letters (a), (b), (c) and (d), (spectrum 1, Fig. (V-8)), against the oxaziridine formula refer to the corresponding protons in the n.m.r. spectrum. Spectrum 2 shows the type of products obtained after hydrolysis in 0.5N, D_2SO_4. Apart from the spectrum of diethylketone (τ[a]) 9.0, t, 6H; 7.4, q, 4H) and a trace of

a) τ values are only approximate since no internal standard of TMS was used in these experiments.

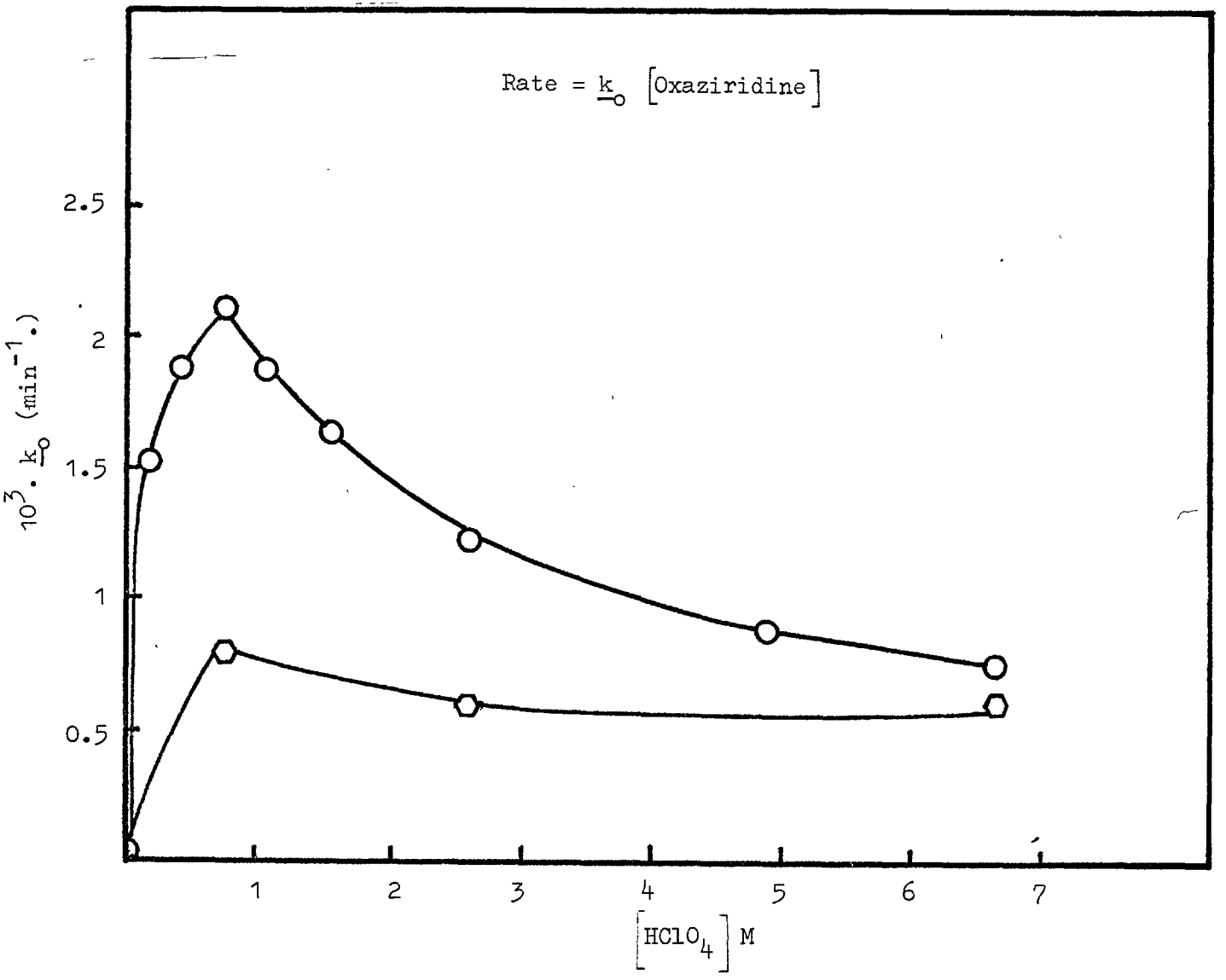


Fig. (V-7). Acid hydrolysis of 2,3,3-triethyloxaziridine (O) and 2-(α,α'-[$^2H_1$]$_2$-ethyl)-oxaziridine (⬡) in aqueous $HClO_4$, 25°C.

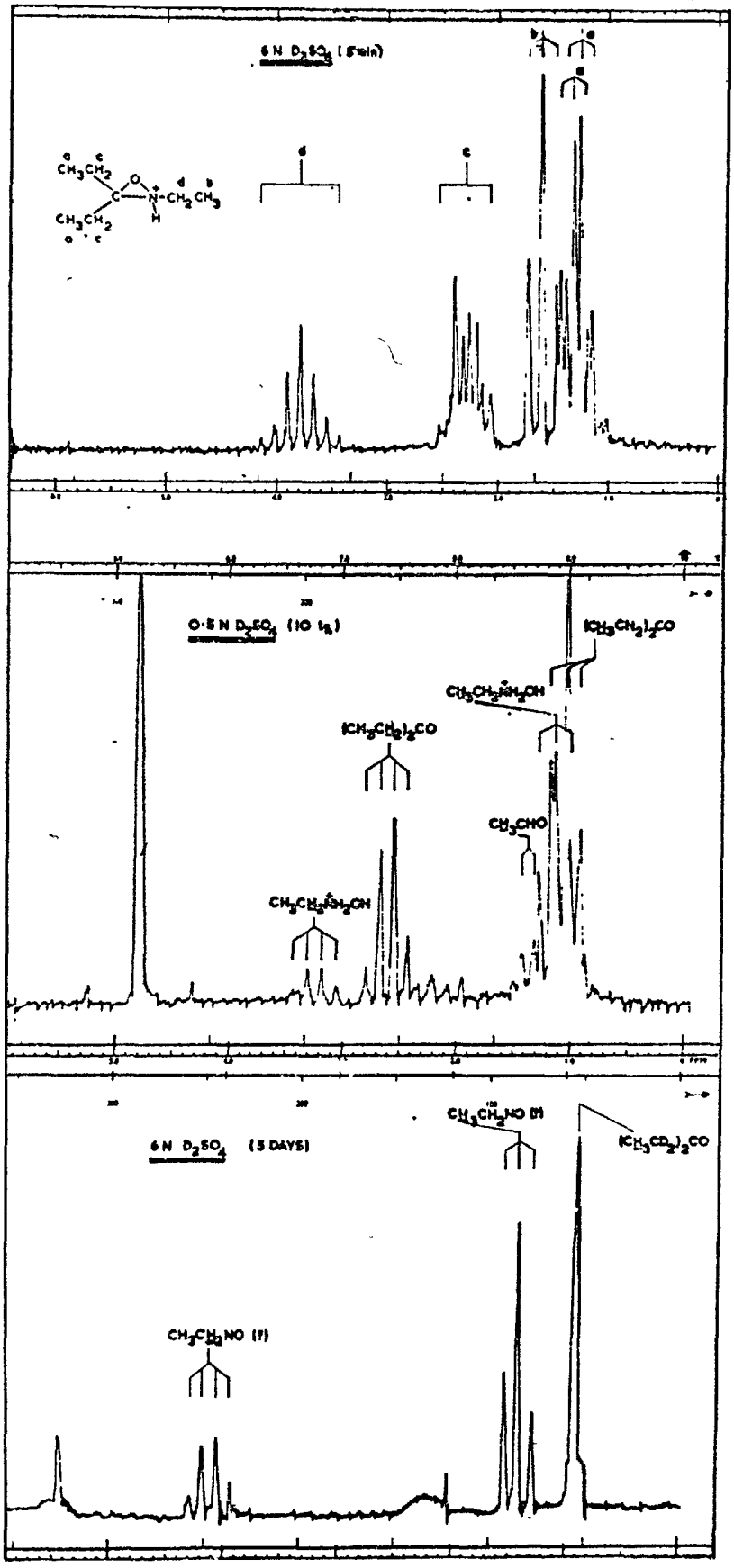


Fig. (V-8). NMR spectra of the products of the hydrolysis reaction of 2,3,3-triethyl oxaziridine in D_2SO_4/D_2O.

ethylhydroxylamine[b] (τ 8.8, t, 3H; 6.7, q, 4H), the doublet corresponding to acetaldehyde can also be seen, although the low integral reflects deuterium exchange of CH_3CHO to give CD_3CHO. Spectrum 3 shows the products obtained after allowing the hydrolysis to proceed for 5 days. This shows the presence of diethylketone (τ 9.0, s with fine splitting due to deuterium exchange of the methylene group) and an ethyl splitting pattern which can be assigned to nitrosoethane (τ 8.5, t, 3H; 5.7, q, 2H), arising probably from oxidation of the ethylhydroxylamine formed initially as a product.

The above results can be summarised by saying that the products formed at low acidity show a high incidence of diethylketone and acetaldehyde but at higher acidity the percentage of acetaldehyde diminishes and another product, probably nitrosoethane arising from oxidation of ethylhydroxylamine, is formed, both facts suggesting a change in mechanism as the acidity changes.

V.2.2 2-Ethyl-3-p-nitrophenyloxaziridine

Butler and Challis[42,43] studied the acid hydrolysis of 2-t-butyl-3-p-nitrophenyloxaziridine, 2-isopropyl-3-p-nitrophenyloxaziridine and the 2-t-butyl-3-phenyloxaziridine. The rate/acidity profile for these oxaziridines was remarkably different from those for compounds bearing 3-alkyl groups. The maximum in the rates came at acidities considerably higher (5 to 7M, $HClO_4$) than for the other oxaziridines, and their slopes, m, of log k_o versus ($-H_o$) had values close to unity. Bearing this in mind it was decided to study the 2-ethyl-3-p-nitrophenyloxaziridine, i.e. to

b) Spectrum compared with that of an authentic sample.

consider again the influence of a primary alkyl group attached to the nitrogen atom of the ring.

The results for the hydrolysis of 2-ethyl-3-p-nitrophenyl oxaziridine carried out at 25.0°C in aqueous $HClO_4$ are listed in Table (V-6). The plot of k_o versus $[HClO_4]$ is shown in Fig. (V-9), together with the data for two other oxaziridines of the same family, studied by Butler and Challis[42,43].

Table (V-6)

Hydrolysis of 2-Ethyl-3-p-nitrophenyl-oxaziridine[a] in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$[HClO_4]$ 10 M	$10^3 k_o$ $min.^{-1}$
97	1.06	1.0
98	7.38	1.1
99	15.4	1.6
100	26.1	2.7
101	46.2	3.5
102	66.7	3.0

a) Due to its low solubility this oxaziridine was first dissolved in glacial acetic acid and 0.5 ml of this solution added to the kinetic flask, kept at 25.0°C.

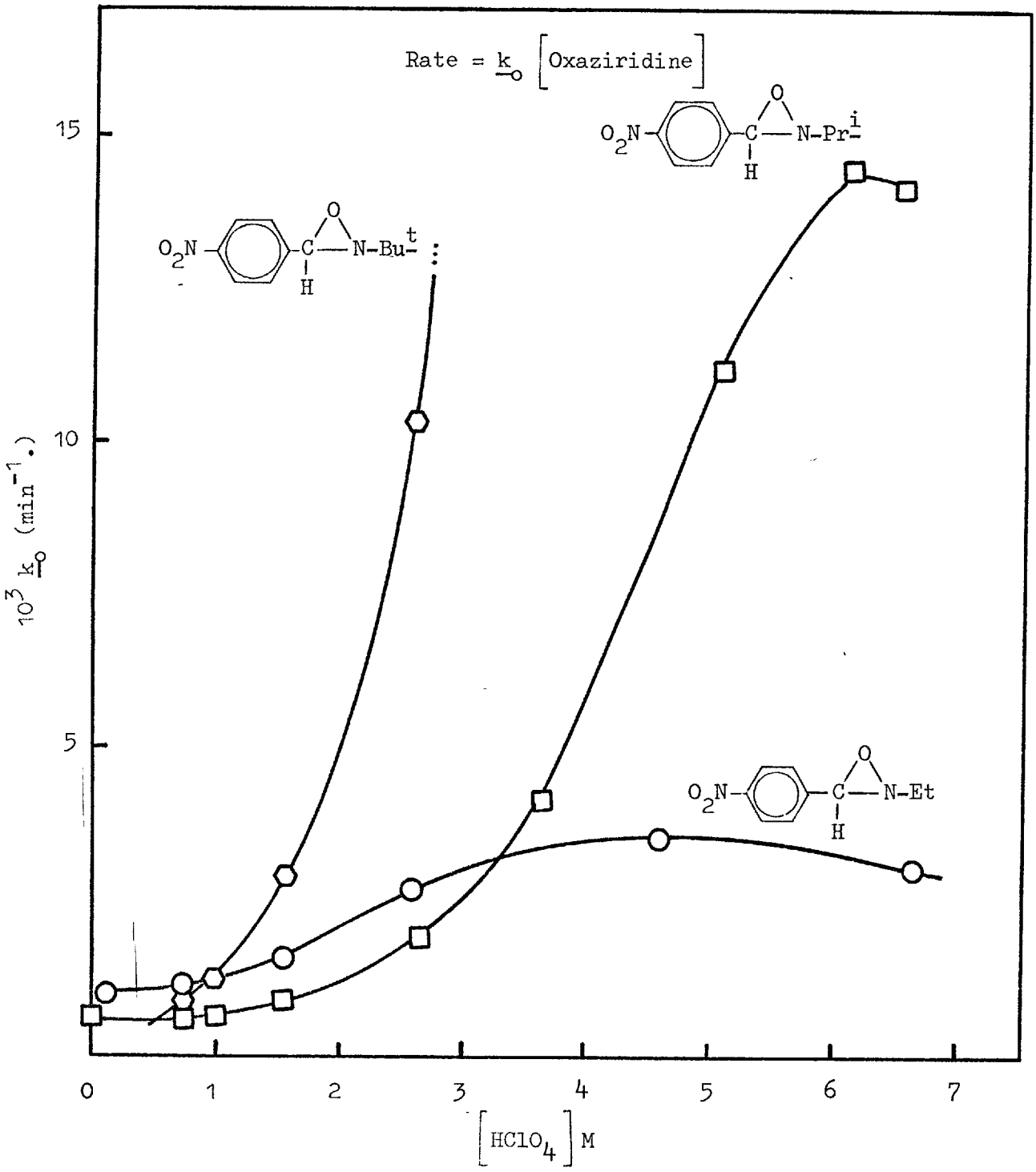


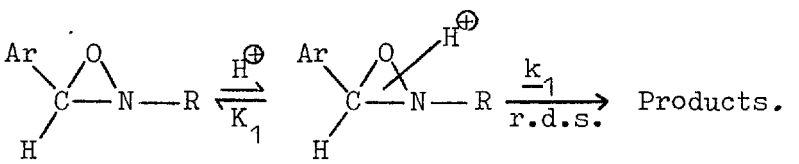
Fig. (V-9). Acid hydrolysis of several 2-alkyl-3-p-nitrophenyloxaziridines in aqueous $HClO_4$, 25°C.

A plot of log $\underline{k}_o$ versus $(-H_o)$ was linear between 0.738 and 1.5 M with a slope $\underline{m}$ = 0.90 (cf. Fig. (V-10)).

By assuming that pre-equilibrium protonation is fast, and the conjugate acid slowly decomposes to products (Scheme (V-3)), the kinetic data has been evaluated by the same method of Butler and Challis[42], using (Eq. (V-3)).

$$\frac{1}{\underline{k}_o} = \frac{1}{\underline{k}_1} + \frac{K_1}{\underline{k}_1} \cdot \frac{1}{\underline{h}_o} \qquad (V\text{-}3)$$

The two constants of interest ($\underline{k}_1$ and K_1) were obtained by plotting $1/\underline{k}_o$ versus $1/\underline{h}_o$ and determining the intercept of the vertical axis, which has the value $1/\underline{k}_1$. The slope of the linear part of the plot, equal to $K_1/\underline{k}_1$, allows the values of K_1 to be calculated once $\underline{k}_1$ is known. This yields the values of $\underline{k}_1$ = 7.1×10^{-3} min.$^{-1}$ and K_1 = 7.1*, for respectively the first order rate constant corresponding to the rate determining step (r.d.s.) after the pre-equilibrium prctonation step (Scheme (V-3)), and the



Scheme (V-3)

equilibrium constant for protonation.

* Nominally $\underline{K}_1$ is in units of (mole.$^{-1}$l.). Since $\left[H^{\oplus}\right] = \underline{h}_o$, $\underline{k}_1$ units are $\underline{h}_o^{-1}$.

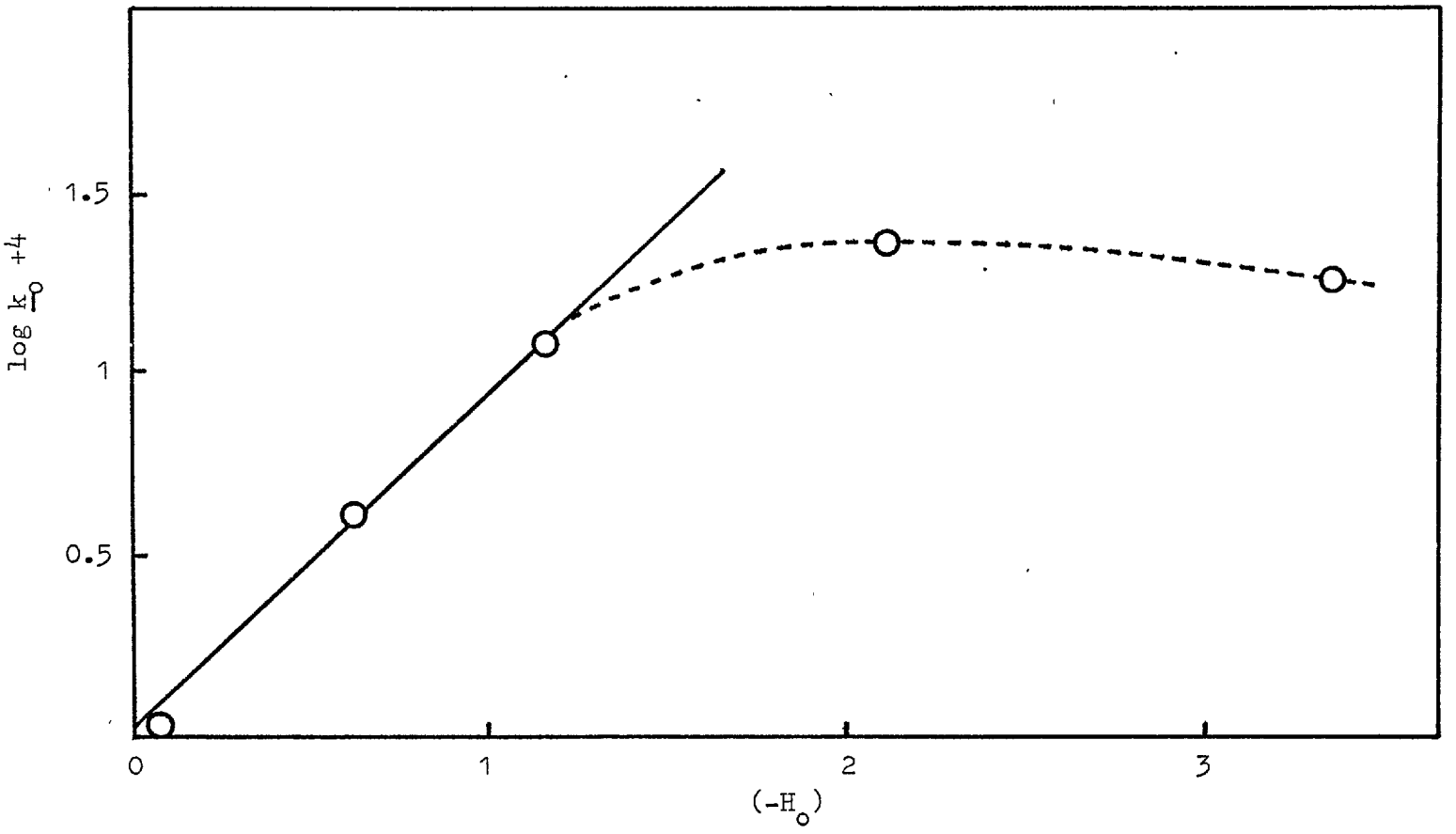


Fig. (V-10). Variation of reaction rate with (-H_o) for the hydrolysis of 2-ethyl-3-p-nitrophenyloxaziridine in aqueous $HClO_4$, 25°C.

The analysis of the carbonyl products by reaction with 2,4-dinitrophenylhydrazine in c a. 1M, $HClO_4$ showed only the presence of p-nitrobenzaldehyde. When the acid hydrolysis was carried out in TFA and followed by n.m.r. spectra as the reaction proceeded, the presence of ethylhydroxylamine was also detected as the major product resulting from the other part of the molecule.

V.2.3 2-Ethyl-3-phenyloxaziridine

The rates of hydrolysis carried out at 25.0°C in aqueous $HClO_4$ are listed in Table (V-7). A plot of the observed rate constants versus molarity of $HClO_4$ is shown in Fig (V-11).

Table (V-7)

Hydrolysis of 2-Ethyl-3-phenyloxaziridine in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$[HClO_4]$ 10 M	$10^2 k_o$ $min.^{-1}$
85	0	0.11
92	1.06	0.16
89	7.38	0.9
94	15.4	2.7
90	26.1	6.0
95	46.2	28
91	66.7	52

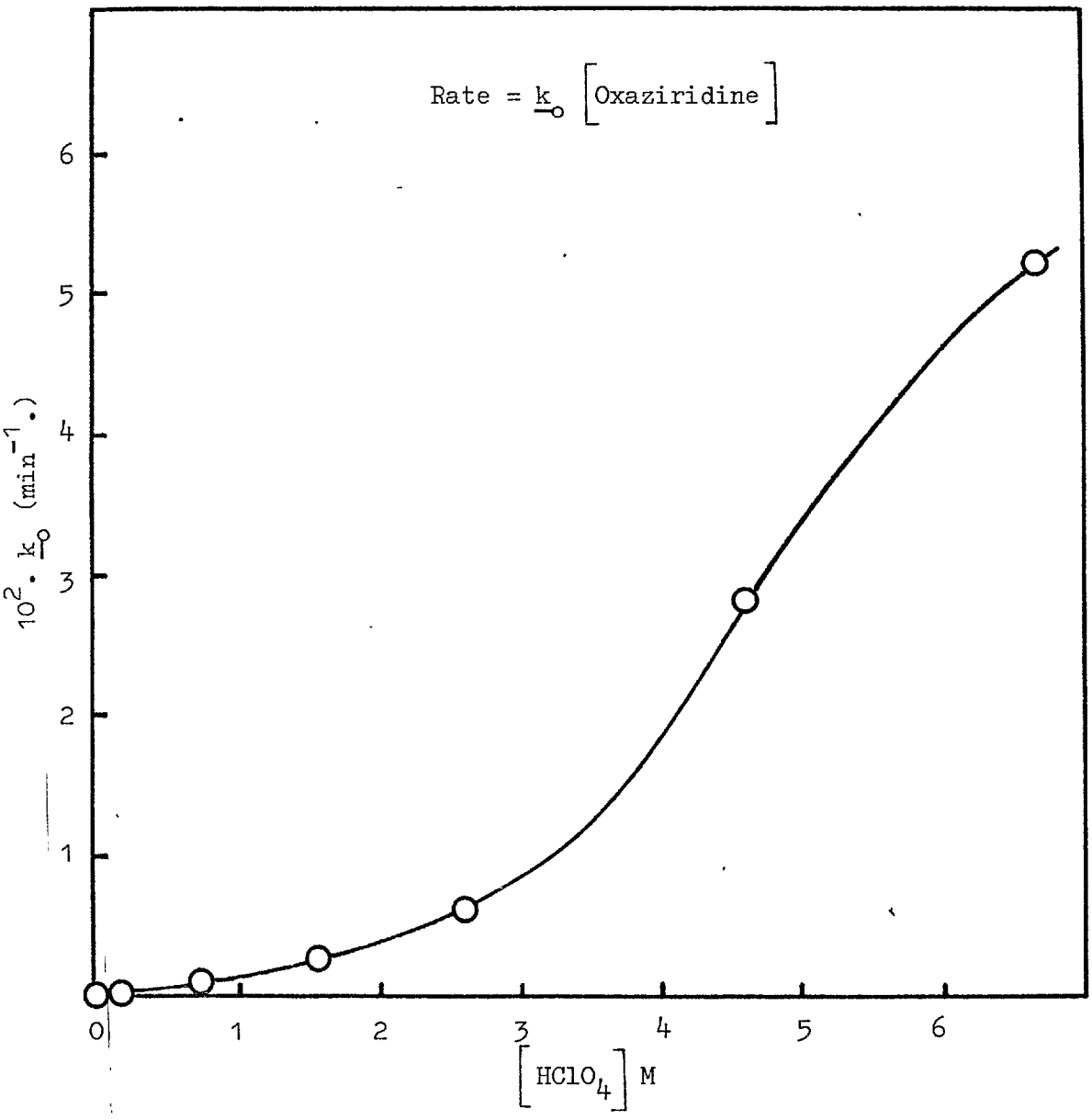


Fig. (V-11). Acid hydrolysis of 2-ethyl-3-phenyloxaziridine in aqueous $HClO_4$, 25°C.

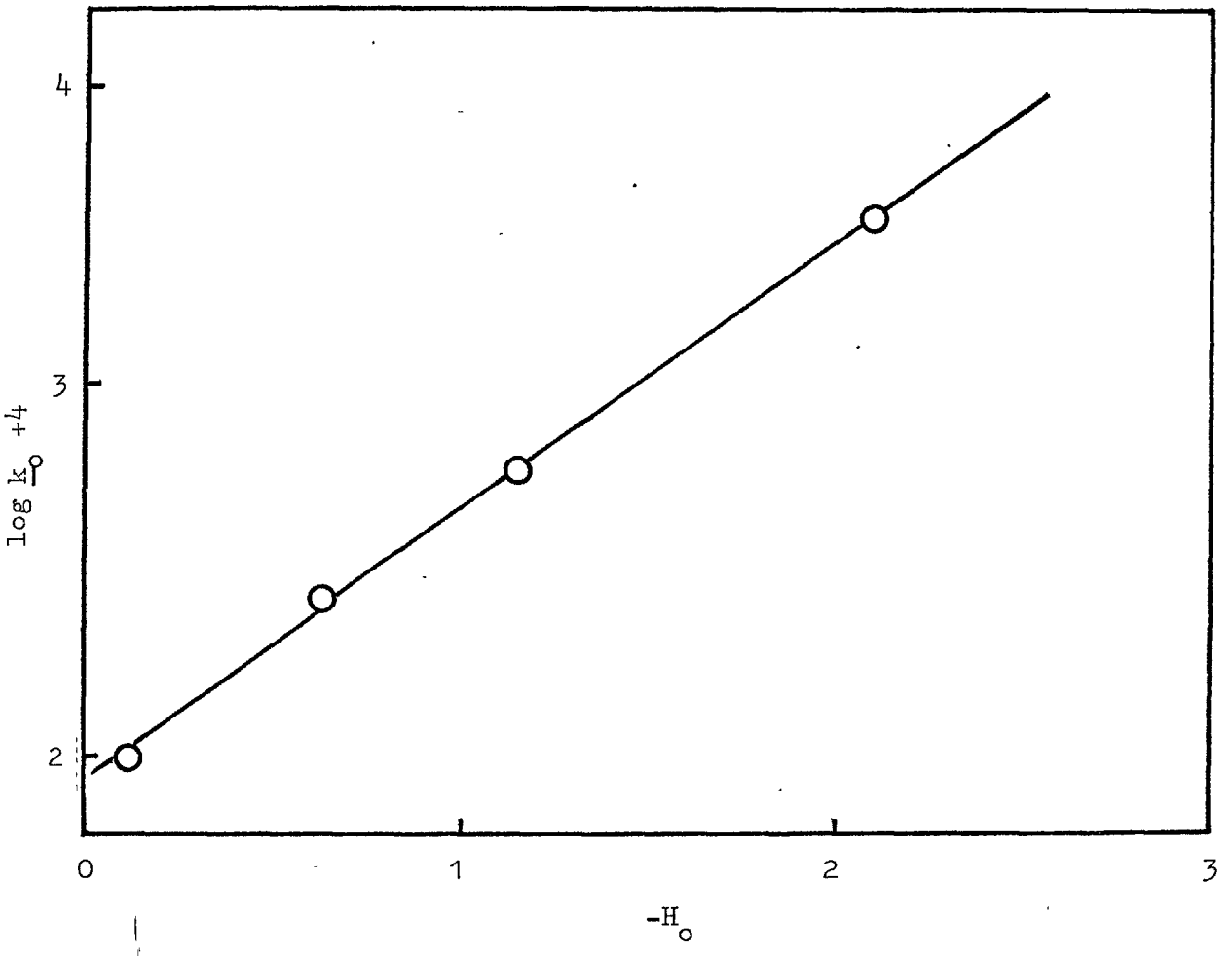


Fig. (V-12). Variation of reaction rate with ($-H_o$) for the hydrolysis of 2-ethyl-3-phenyloxaziridine in aqueous $HClO_4$, 25°C.

A plot of log $\underline{k}_o$ versus $(-H_o)$ proved to be linear in the region between 0 and 2.00 M, $HClO_4$, with a slope $\underline{m}$ of 0.70, as can be seen from Fig (V-12). Treatment of the data from Table (V-7) by a reciprocal plot (as described in the previous section) yields the values of $\underline{k}_1 = 2.5 \times 10^{-1}$ min.$^{-1}$ and $K_1 = 38.3$.

The only carbonyl product obtained by acid hydrolysis at c.a 1 M, $HClO_4$, and identified by its 2,4-dinitrophenyl hydrazone, was benzaldehyde.

When this reaction was investigated by n.m.r. spectroscopy, using 6N, D_2SO_4, benzaldehyde was again detected along with ethylhydroxylamine, in equal amounts. Since the hydrolysis was extremely fast, the n.m.r. spectra could not identify the nature of the conjugate acid. This oxaziridine proved to be very sensitive towards light, becoming progressively more yellow (probably owing to isomerisation to the corresponding nitrone[6]).

V.2.4 2-Benzyl-3,3-diethyloxaziridine

So far only oxaziridines with an ethyl group attached to position 2 have been described. It seemed interesting to replace the ethyl group by a benzyl group and study the effect of such a substitution on the rate profile as well as the products.

This was done by preparing the 2-benzyl-3,3-diethyloxaziridine and studying its acid hydrolysis in aqueous $HClO_4$ at 25.0°C. The results are listed in Table (V-8).

A plot of $\underline{k}_o$ versus $[HClO_4]$ is shown in Fig. (V-13).

A plot of log $\underline{k}_o$ versus $(-H_o)$ is linear between 0 and 0.6 M, $HClO_4$, with a slope $\underline{m}$ of 0.53.

Application of Eq. (V-3) to the kinetic data gives the values of $\underline{k}_1 = 2.78 \times 10^{-1}$ min.$^{-1}$ and $K_1 = 2.89$, calculated from the values

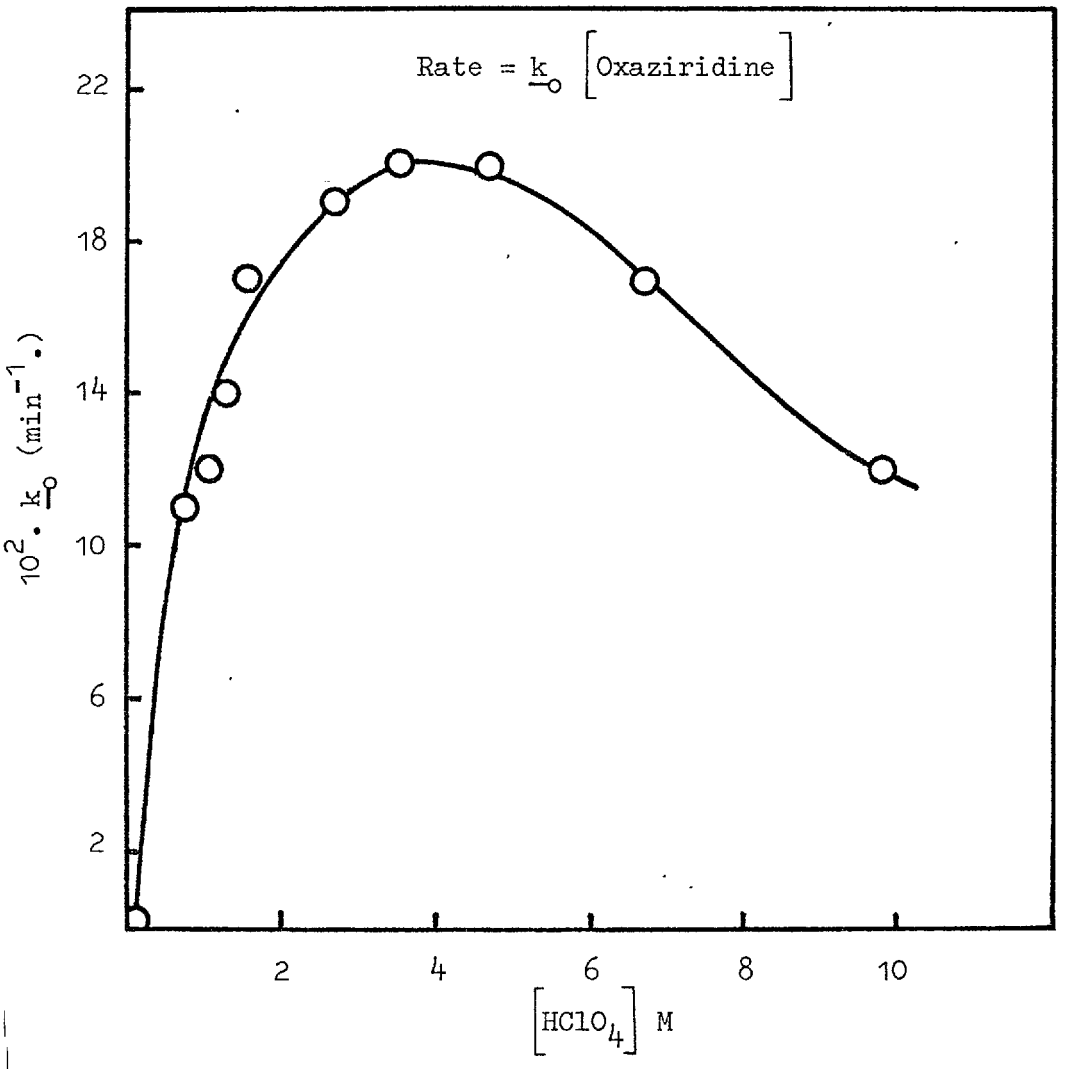


Fig. (V-13). Acid hydrolysis of 2-benzyl-3,3-diethyl-oxaziridine in aqueous $HClO_4$, 25°C.

Table (V-8)

Hydrolysis of 2-Benzyl-3,3-diethyloxaziridine in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$[HClO_4]$ 10 M	$10^2 k_o$ $min.^{-1}$
148-2 a)	0	0.28
149 b)	0.62	0.76
177	7.42	11
176	10.1	12
175	12.5	14
172	15.5	17
173	26.7	19
165	35.4	20
163	46.2	20
164	66.7	17
218	98.3	12

a) Dioxan-water (80:20).

b) Ethanol-water (40:60).

of the intercept and the slope of the linear line obtained when $1/k_o$ was plotted against $1/h_o$.

Product analysis of the carbonyl compounds formed during acid hydrolysis at ca. 3M, H_2SO_4 in H_2O-EtOH, gave quantitative amounts of formaldehyde and diethylketone in approximately equimolar concentrations.

Investigation of the products of the acid hydrolysis at room temperature by u.v. spectroscopy showed that there is some benzaldehyde formed at low acidity, 39% at 0.101 M, $HClO_4$ and 5.9% at 4.43 M, $HClO_4$. At high acidities the u.v. shows clearly the fine structure of the spectrum of the anilinium ion formed in the reaction (Table (V-9)).

Table (V-9)

Product Analysis of the Acid Hydrolysis of 2-Benzyl-3,3-diethyloxaziridine

$[HClO_4]$ 10 M	C_B a) 10^4 M	C_A a) 10^4 M	C_B/C_t a) in (%)
0 b)	13	0	100%
1.01	5.1	7.9	39%
9.70	1.7	11	13%
25.5	0.98	12	7.5%
44.3	0.77	12	5.9%

a) $C_B = [\text{Benzaldehyde}]$

$C_A = [\text{Aniline}]$

$C_t = [\text{total concentration of oxaziridine}] = 1.3 \times 10^{-3}$M

b) In $[NaOH] = 0.0098$M

V.3 Results of the Acid Hydrolysis of Oxaziridines with 2-Isopropyl and 2-(α-Phenylethyl) Groups

V.3.1 2-Isopropyl-3-ethyloxaziridine

After studying oxaziridines with primary alkyl groups attached to position 2, it is interesting to speculate the effect of a secondary alkyl group on both the rates and products of hydrolysis. An obvious question is whether they behave like the 2-primary alkyl oxaziridines or like the 2-t-butyloxaziridine where migration of a methyl group α to the nitrogen atom seems to be the dominating feature under acidic conditions.(6, 42)

To clarify this point, the 2-isopropyl-3-ethyloxaziridine was prepared and the hydrolysis reaction in aqueous perchloric acid was studied at 25.0°C. The results of the kinetic experiments are listed in Table (V-10).

Table (V-10)

Hydrolysis of 2-Isopropyl-3-ethyloxaziridine in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$[HClO_4]$ 10 M	$10^4 k_o$ $min.^{-1}$
137	0	1.95
138	1.06	4.19
139	7.38	19.7
146	10.1	28.0
145	12.5	34.0
140	15.4	40.6
141	26.7	52.5
142	46.2	51.6
144	66.7	40.8

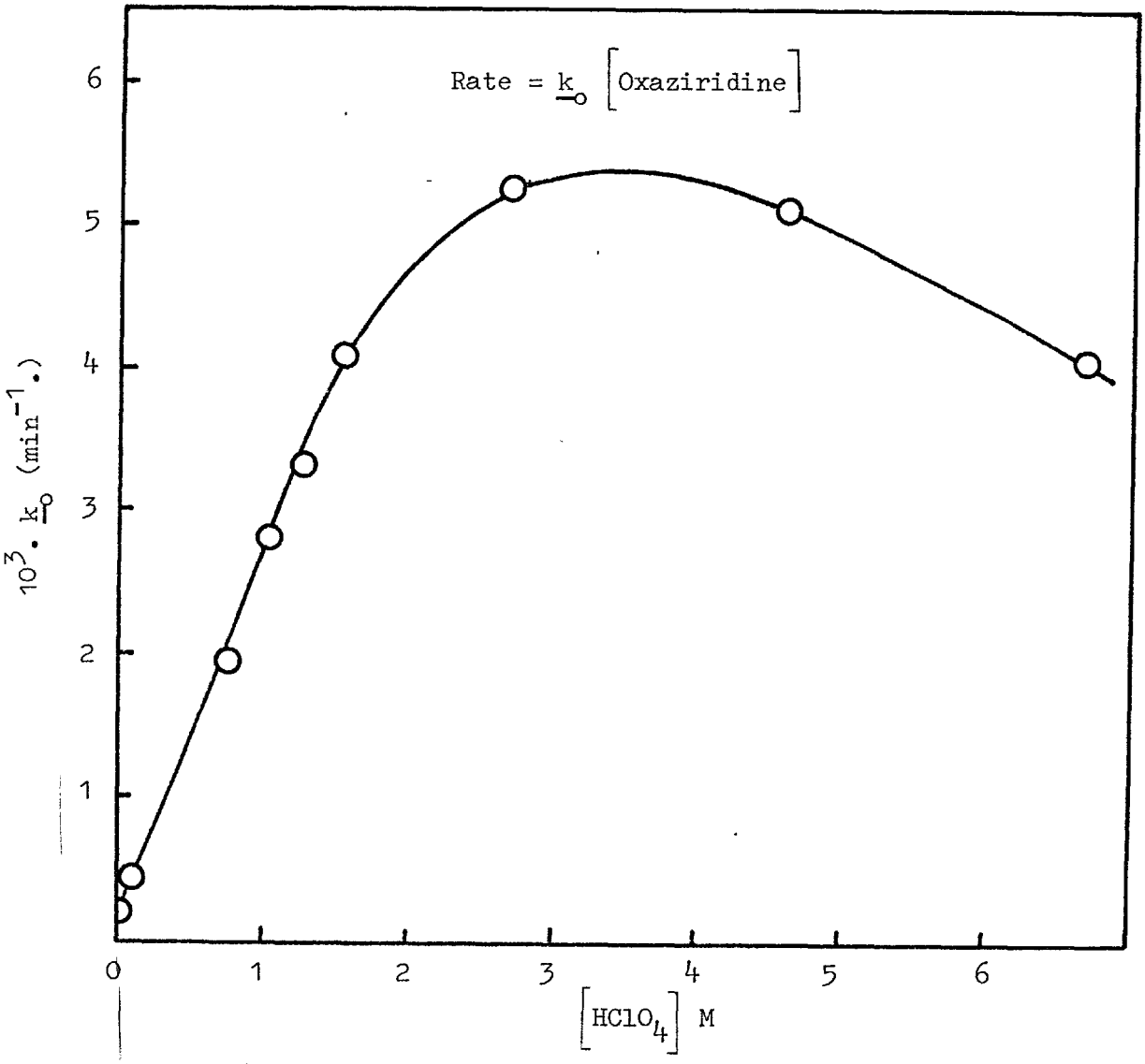


Fig. (V-14). Acid hydrolysis of 2-isopropyl-3-ethyloxaziridine in aqueous $HClO_4$, 25°C.

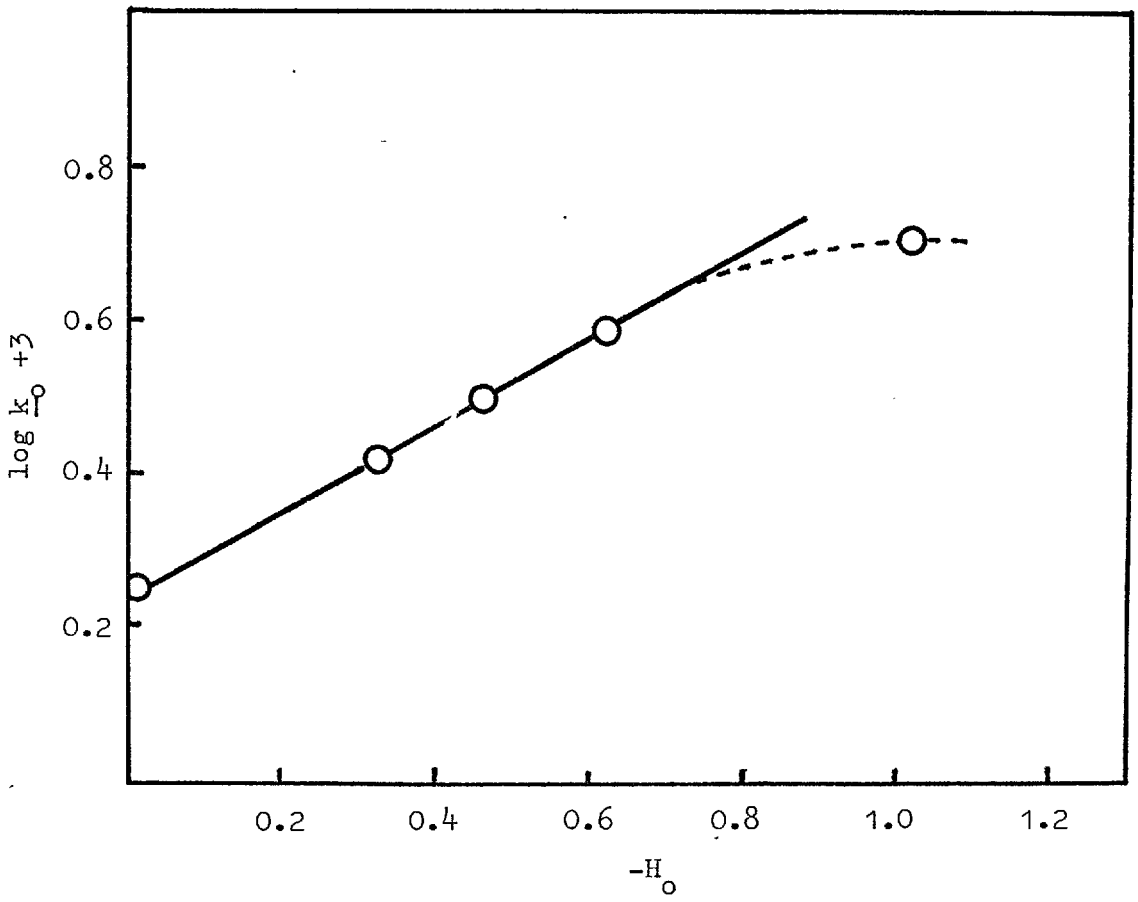


Fig. (V-15). Variation of reaction rate with ($-H_o$) for the hydrolysis of 2-isopropyl-3-ethyloxaziridine in aqueous $HClO_4$, 25°C.

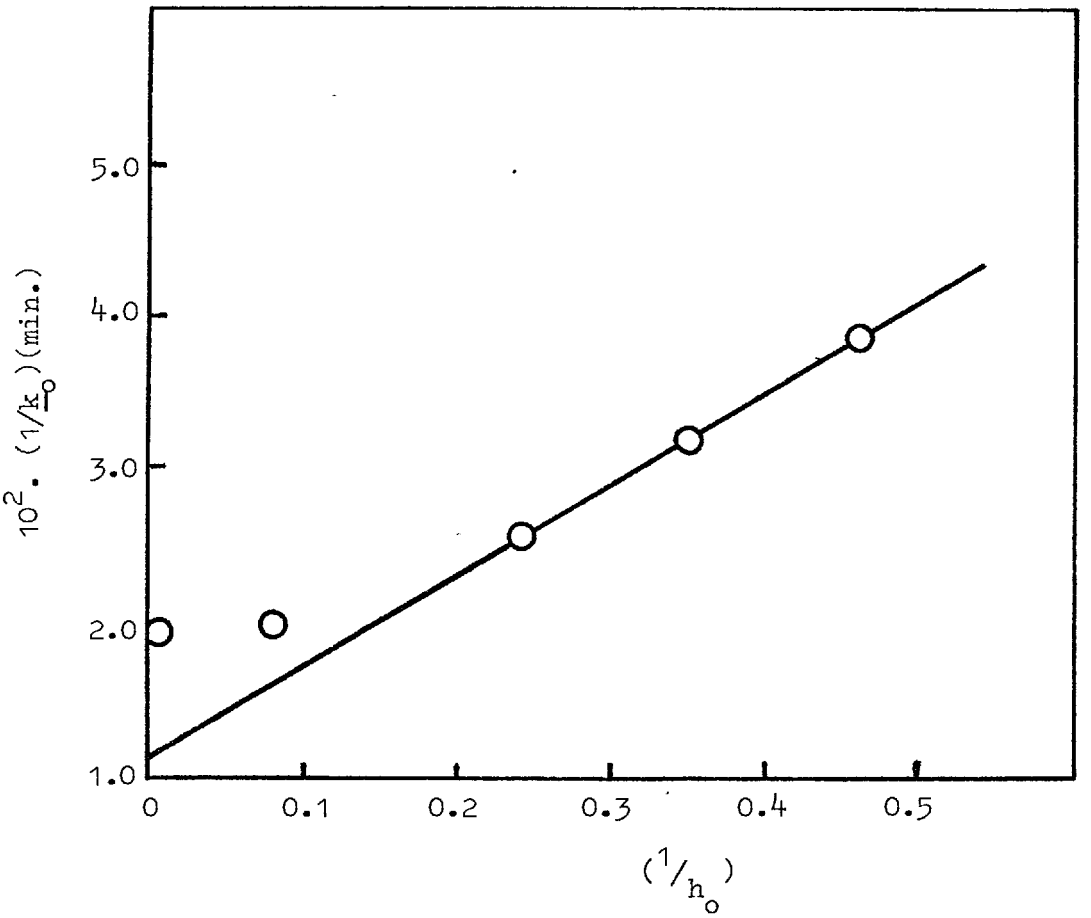


Fig. (V-16). Reciprocal plot for the acid hydrolysis of 2-isopropyl-3-ethyloxaziridine in aqueous $HClO_4$, 25°C.

The rate profile ($\underline{k}_o$ versus $[HClO_4]$) is shown in Fig. (V-14), where a steady increase of $\underline{k}_o$ from 0 to 3M, $HClO_4$, a limiting value between 3 and 4.5 M, $HClO_4$, and a decreasing $\underline{k}_o$ at acidities higher than 4.5M are all apparent. A similar rate profile[42] was obtained for 2-t-butyl-3-alkyl-oxaziridines mentioned in Section (III.3.1.a).

The full implication of this fact will be discussed later.

The plot of log $\underline{k}_o$ versus $(-H_o)$ is shown in Fig. (V-15). This is linear with a slope $\underline{m}$ of 0.58 for the ascending values of $\underline{k}_o$.

Application of Eq. (V-3) to the kinetic data (the reciprocal plot is shown in Fig. (V-16)) gives values of $\underline{k}_1 = 8.62 \times 10^{-3}$ min^{-1} and $K_1 = 0.501$ for this compound.

The carbonyl products obtained from acid hydrolysis in c a. 1 M, $HClO_4$, and identified by their 2,4-dinitrophenyl hydrazones, were propionaldehyde and acetaldehyde. When the reaction was followed by n.m.r. spectroscopy, using T.F.A. as solvent, evidence was obtained for the formation of methylamine, which is consistent with extensive methyl migration from the 2-isopropyl group to the nitrogen in the ring.

V.3.2 2-(α-Phenylethyl)-3,3-diethyloxaziridine

The observation of extensive methyl migration to nitrogen for the hydrolysis of the 2-isopropyl-3-ethyloxaziridine suggested examination of the migratory aptitudes of an aryl relative to an alkyl group. Accordingly, 2-(α-phenylethyl)-3,3-diethyloxaziridine was prepared and the hydrolysis kinetics examined in aqueous $HClO_4$ at 25.0°C as before(Table (V-11)).

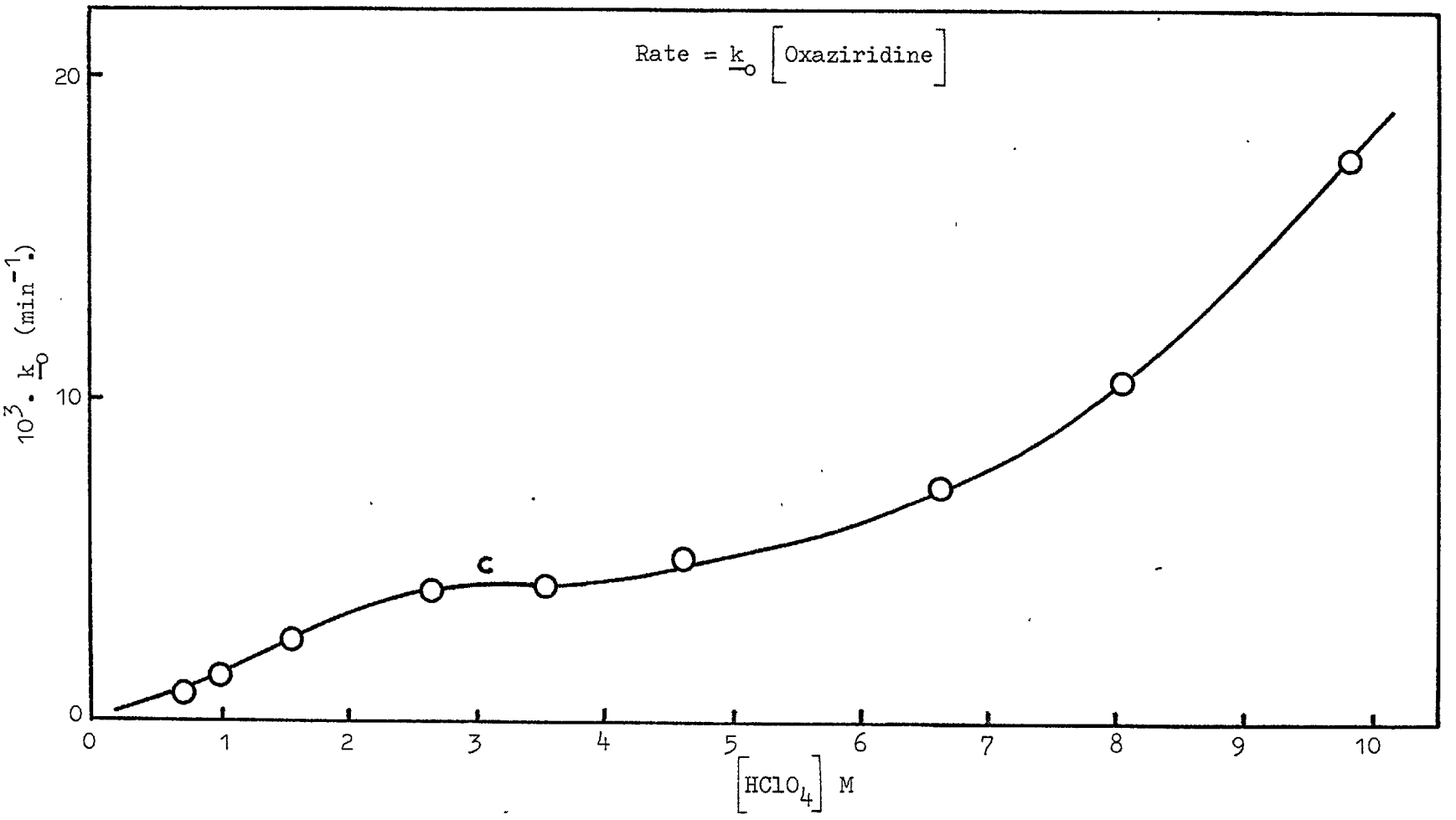


Fig. (V-17). Acid hydrolysis of 2-(α-phenylethyl)-3,3-diethyloxaziridine in aqueous $HClO_4$, 25°C.

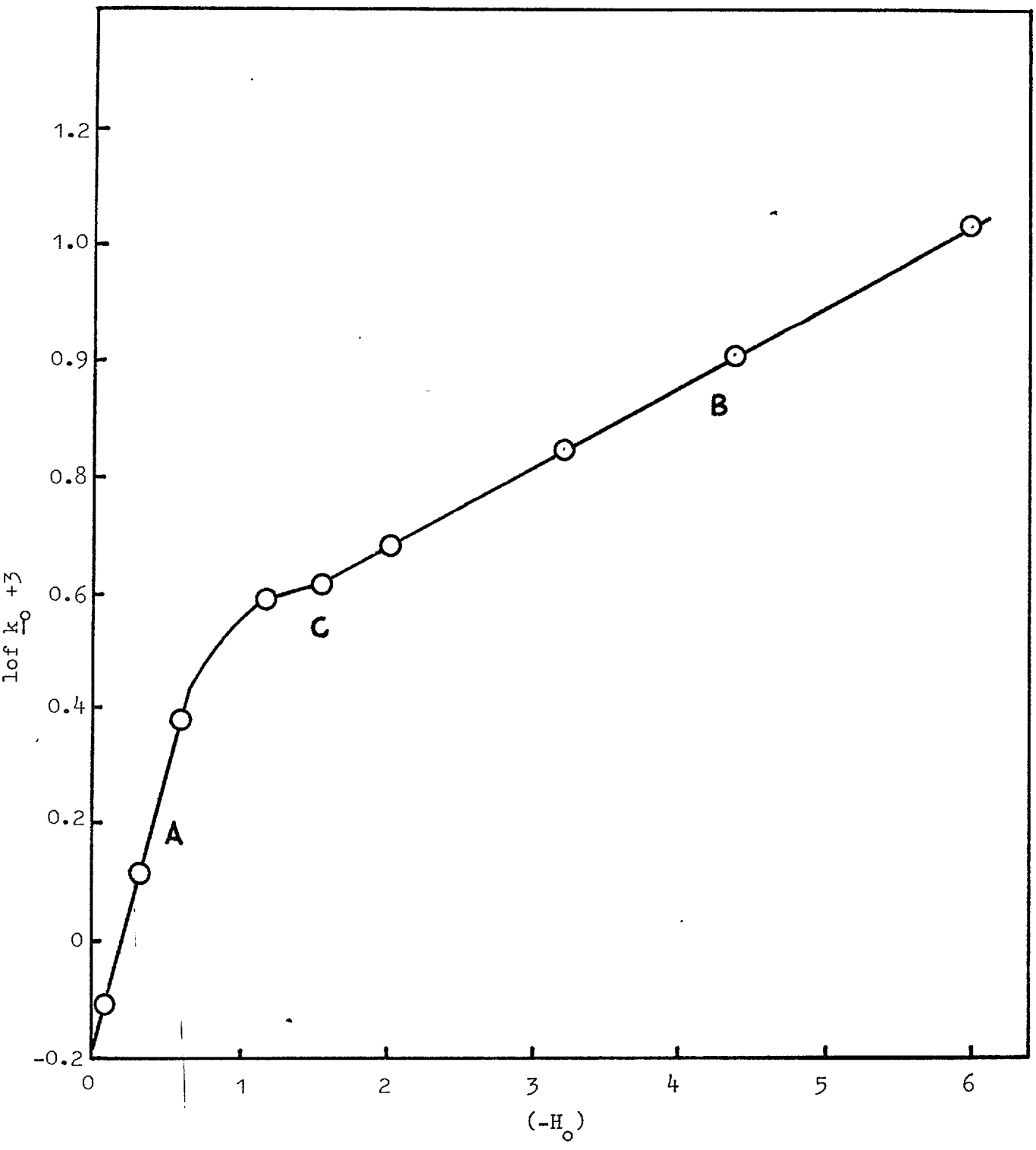


Fig. (V-18). Variation of reaction rate with $(-H_o)$ for the hydrolysis of 2-(α-phenylethyl)-3,3-diethyloxaziridine in aqueous $HClO_4$, 25°C

Table (V-11)

Hydrolysis of 2-(α-Phenylethyl)-
3,3-diethyloxaziridine in Aqueous Perchloric Acid

Temperature = 25.0 ± 0.1°C

Kinetic Run	$[HClO_4]$ 10 M	10^3 k_o $min.^{-1}$
194	7.42	0.75
195	10.1	1.3
197	15.5	2.4
198, 202	26.7	3.9
199	35.4	4.1
200	46.2	4.9
201	66.4	7.2
203	80.7	11
204	98.3	17

Fig. (V-17) shows the usual rate profile of k_o versus $[HClO_4]$.

The acidity dependence of log k_o on $(-H_o)$ is shown in Fig. (V-18). Two linear sections, marked A and B are apparent, which have slopes m of 0.89 abd 0.14, respectively. In between these linear sections there is an inflexion point C which corresponds to that observed in k_o versus $[HClO_4]$ plot, marked with the same letter.

Application of Eq. (V-3) to the kinetic data below the point

of inflexion gives values of $\underline{k}_1 = 5.0 \times 10^{-2}$ min.$^{-1}$ and $K_1 = 82$ for this compound.

The carbonyl products obtained from the acid hydrolysis (c a. 1 M, $HClO_4$) of this oxaziridine are diethylketone and acetaldehyde as identified by their 2,4-dinitrophenylhydrazine derivatives. By u.v. spectroscopy aniline could be detected, but no evidence of acetophenone formation could be found, suggesting extensive phenyl migration over the whole acidity range studied (0.1 to 6 M, $HClO_4$).

N.m.r. spectroscopy was not very helpful in this particular case. Using a 29% solution of D_2SO_4 in D_2O, and a temperature close to 0°C, only the products of decomposition could be observed suggesting, as was already the case with the 2-benzyl-3,3-diethyloxaziridine, a very unstable conjugate acid.

V.4 Discussion of the Results

V.4.1 The Acid Hydrolysis of Oxaziridines with a Primary 2-Alkyl Group

Previous investigations and the present results show that the simplest kinetic results and hydrolysis products are obtained with compounds bearing an aryl substituent at the 3 position. Accordingly, these compounds are discussed first.

Comparison of the results in Sections V.2.2 and V.2.3, for 2-ethyl-3-phenyloxaziridine and 2-ethyl-3-p-nitrophenyloxaziridine, with those of Butler and Challis[42] shows that the precise nature of the 2 substituent has little bearing on either the form of the acid catalysis of 3-aryl oxaziridines or the nature of the products. In all cases investigated, the rate rises smoothly with $[HClO_4]$ to

Table (V-12)

Oxaziridine	$[HClO_4]_{max}$ (a)	$10^3 k_{o(max)}$ ($min.^{-1}$)	m (b)	$10^3 k_1$ ($min.^{-1}$) (c)	K_1 (c)	pK_1 (c)	Ref.
$NO_2C_6H_4CH(O)N\text{-}Bu^t$	5.86	43.4	1.15	43.0	63.7	-1.80	42
$NO_2C_6H_4CH(O)N\text{-}Pr^i$	6.13	14.5	0.91	28.6	254	-2.40	43
$NO_2C_6H_5CH(O)N\text{-}Et$	4.62	3.5	0.90	7.1	7.1	-0.85	-
$C_6H_5CH(O)N\text{-}Bu^t$	(d)	(d)	(1.1)	(1330) (e)	(313)	(-2.5)	42
$C_6H_5CH(O)N\text{-}Et$	(d)	(d)	(0.70)	(250)	(38.3)	(-1.6)	-

(a) In aqueous $HClO_4$ at 25°C.

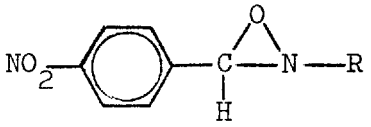
(b) Slope of plot log k_o versus $(-H_o)$.

(c) Based on the h_o scale.

(d) Kinetic runs too fast to be followed at high acidities.

(e) Numbers in brackets represent approximate values.

reach a maximum value, at an acidity which is generally higher than that for compounds without the 3-aryl substituent. A comparison of the rate profiles for the three oxaziridines (1), (2) and (3), is shown in Fig. (V-9).



R { (1): Ethyl
(2): Isopropyl
(3): t-Butyl

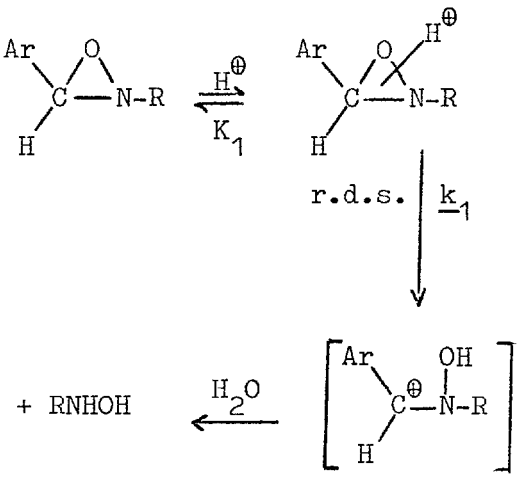
It is evident and interesting that the 2-substituent affects the reactivity. This trend is also reflected in plots of log k_o versus $(-H_o)$. These are linear for all the 3-aryl compounds studied, but their slopes decrease with decreasing substitution of the 2 alkyl substituent (Table (V-12)). Generally, however, the magnitude of the slopes is close to 1, and in this respect the results are similar to those for epoxides.[35] On the bases of the Zücker-Hammett hypothesis, this would be evidence for an A-1 type of reaction, although more recent developments, as discussed in Chapters III and IV, suggest the acidity dependence is not a good criterion of mechanism. However, these results do show that the reaction is acid catalysed, and that formation of the conjugate acid is complete in 4-6 M, $HClO_4$.

Values of the equilibrium constant for protonation (K_1) and the decomposition rate of the conjugate acid (k_1) are summarized in Table (V-12) for the 2 aryl compounds. Several trends are

apparent. Decomposition of 3-phenyl compounds is generally faster than their 3-p-nitrophenyl counterparts - this implies that the 3 carbon atom is electron deficient in the transition state. As noted before, k_1 decreases steadily with decreasing substitution of the 2 substituent, but the same trend is not observed for the equilibrium constant K_1 (in this case : 2-Et < 2-t-Bu < 2-i-Pr).

The products obtained from all the 3-aryl oxaziridines (aromatic aldehyde and alkyl hydroxylamine) do not appear to depend on the 2-substituent or the acidity of the medium. They imply cleavage of the C-O or C-N bonds and this is consistent with the formation of an electron deficient 3 carbon atom.

The mechanism proposed by Butler and Challis[42] is given in Scheme (V-4):

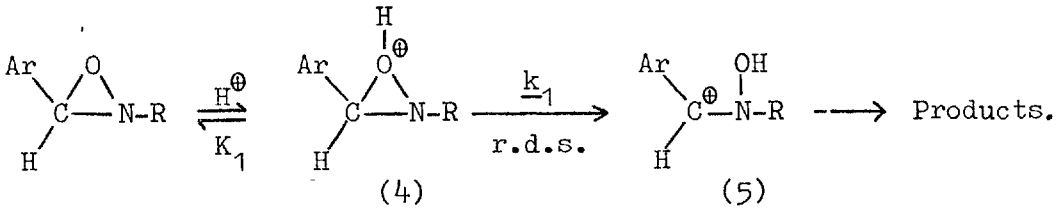


Scheme (V-4)

it is necessary first to see how the present results fit in with their postulates. They assumed reaction via the O-conjugate acid by analogy with other oxaziridines, although with the 3-aryl compounds this is not required to explain the products (i.e. cleavage of the C-N

bond of the N-conjugate acid would also lead to aromatic aldehydes). Direct examination of conjugate acid species by n.m.r., as discussed in Section (V.1), gives no definite evidence for the conjugate acid structure.

The influence of 2-alkyl substituents seems to throw some light on this problem.



(4) (5)

(1) R=Et

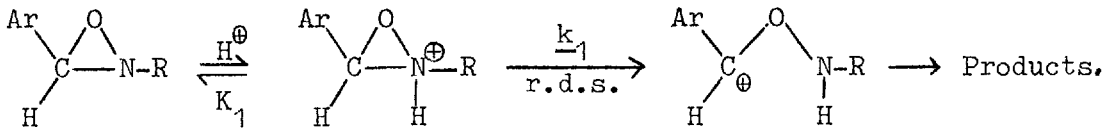
(2) R=i-Pr

(3) R=t-Bu

Scheme (V-5)

Let us assume(Scheme (V-5)) that the only conjugate acid present in the system corresponds to the O-protonated species (4), which in turn opens by cleavage of the C-O bond of the ring yielding a carbonium type of intermediate (5). When R changes, becoming Et, i-Pr or t-Bu, the values of K_1 and k_1 should show very little effect, k_1 increasing slightly in the order t-Bu> i-Pr > Et due to the inductive effect of R on the cleavage of the C-O bond. However, the results reported show an appreciable variation of K_1 and a very marked variation for k_1, which, though in the order predicted by the above argument, is far too great to

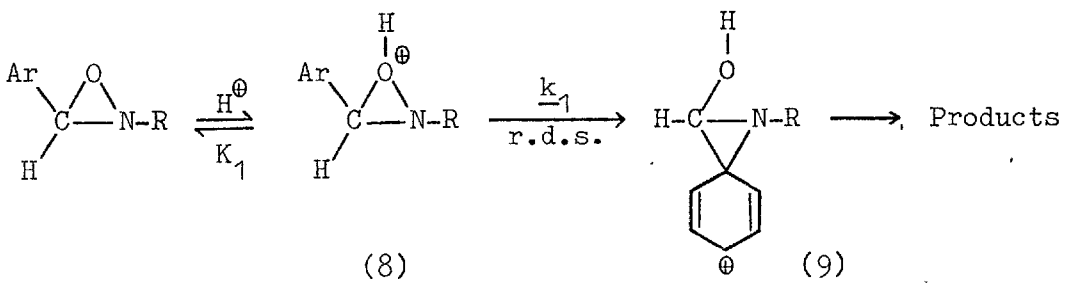
be a result of a pure inductive effect transmitted through the nitrogen atom.



(6) (7)

Scheme (V-6)

Let us consider now that instead of an O-conjugate acid, the reactive species in the reaction corresponds to the N-conjugate acid (6), as is represented in Scheme (V-6). Substituent effects of the R group on the value of K_1 should be small. This can be demonstrated by the pK_a values for t-Bu NH_2, i-PrNH_2 and EtNH_2, 10.68, 10.69 and 10.70, respectively[93], showing a very little change due to the nature of the alkyl group attached to the nitrogen atom. The values of k_1 also should be only slightly perturbed, but the order of magnitude should then be t-Bu < i-Pr < Et, i.e. the reverse of the one observed experimentally.



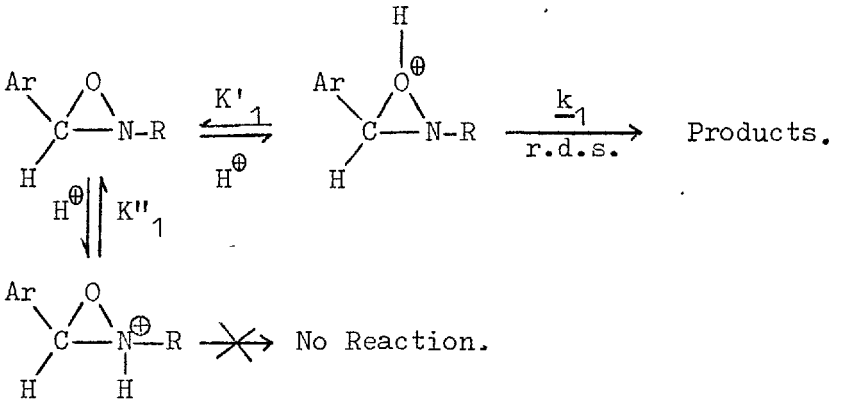
(8) (9)

Scheme (V-7)

Finally, if instead of the cleavage of the C-O bond of the O-conjugate acid, (8), extensive phenyl participation occurs, to yield the intermediate (9) (Scheme (V-7)), only slight changes

should be apparent in K_1, but the values of k_1 would probably vary greatly due to steric interaction, in the order t-Bu < i-Pr< Et, which does not agree with the experimental observations.

These considerations suggest that neither the O-protonated species nor the N-protonated conjugate acid by themselves can explain the results satisfactorily.



Scheme (V-8)

If, however, it is assumed, that both conjugate acids, N- and O-, are present in equilibrium in the reaction mixture (Scheme (V-8)), but that only the O-protonated species is reactive, the results may be easily rationalised. For compound (3), where R=t-Bu, the predominant equilibrium refers to the O-protonated species, K'_1, since protonation of the nitrogen is hindered by the bulkiness of the t-Bu group. Since this species is the one which successfully leads to reaction, the corresponding k_1 is the maximum observed. For compound (1), where R=Et, the predominant equilibrium refers to the N-protonated species, K''_1, since protonation of the nitrogen is no longer impeded by steric congestion. However, since the N-conjugate acid does not lead to reaction, the corresponding k_1 value should be minimal. Compound (2) should

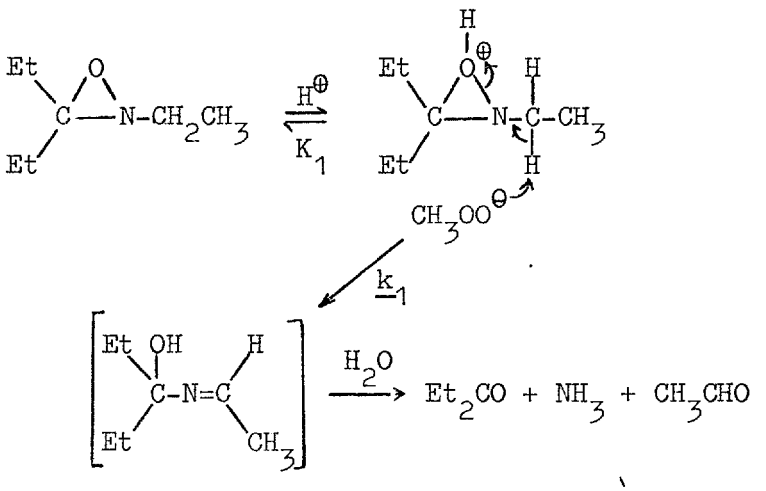
show an intermediate behaviour, and this is in fact observed. The values of K_1, which show an increase in the order i-Pr > t-Bu> Et, probably reflect the perturbation resulting from the fact that for (1) K_1 refers mainly to an $\overset{\oplus}{N}H$ cation and for (3) K_1 refers mainly to an $\overset{\oplus}{O}H$ cation, with K_1 for compound (2) referring to both types of conjugate acid.

In conclusion, the bulk of the evidence points to the scheme outlined by Butler and Challis[43] in which the reaction intermediate is the O-conjugate acid. However, for the primary 2-alkyl groups, N-protonation also occurs but does not lead to reaction.

It must be also mentioned that Emmons[6] suggested that nitrones might be intermediates on the reaction path for acid hydrolysis. If so, then they are not kinetically significant. This is apparent because the reaction rates are measured from the loss of oxaziridine reactant, and the formation of nitrones will only affect the kinetics if they are in equilibrium with the substrate. Independent checks have shown that nitrones are not converted to oxaziridines under the conditions of our experiments. The reaction mixtures were also examined by u.v. and n.m.r. for the presence of nitrones, but they were not detected.

Butler and Challis[43] also examined the hydrolysis of 3-alkyl oxaziridines bearing a primary 2-alkyl substituent. As discussed previously, the kinetics observed were unusual and the mechanism was unclear. The work reported in Section (V.2.1) concerning the acid hydrolysis of 2,3,3-triethyloxaziridine and 2-(α,α'-$\left[{}^2H_1\right]_2$-ethyl)-3,3-diethyloxaziridine was designed to resolve these difficulties. The rates of ring opening in dilute hydrochloric

acid (Table (V-3)) are in good agreement with the corresponding values obtained with acetic acid (Table (V-2)). The observation of general acid catalysis for 2,3,3-triethyloxaziridine shows that some kind of proton transfer is rate limiting. Since the conjugate acid is known to be formed very rapidly in a pre-equilibrium step, it seems likely that the catalysis arises from $OAc^{\ominus}$ abstraction of a proton from the conjugate acid itself, rather than proton donation by HOAc. The most likely proton to be removed in order to explain the products is the one $\underline{\alpha}$ to the nitrogen atom (Scheme (V-9)).



Scheme (V-9)

Examination of 2-(α,α'-$\left[{}^{2}H_{1}\right]_{2}$-ethyl)-3,3-diethyloxaziridine confirms this suggestion, as the reduction in rate (relative to the undeuteriated compound) of 2.6 to 2.7, between 0 and 0.738 M, $HClO_4$, is indicative of a substantial primary isotope effect. Thus the proton $\underline{\alpha}$ to the nitrogen must be removed in the rate determining step, probably synchronously with the opening of the oxaziridine ring.

The decrease of the primary isotope effect at high acidities must imply either a change of r.d.s. or a change in mechanism of ring cleavage. The first explanation can be ruled out by the following arguments. It is unlikely that in conditions of increasing acidity, protonation of the oxaziridine becomes rate limiting. For steps subsequent to removal of the α-proton to be rate-limiting, the intermediate structure $R_2\overset{OH}{\overset{|}{C}}-N = CR'_2$ must be in equilibrium with the oxaziridine. This is not impossible but seems unlikely in aqueous solution. Also no synthetic pathway of this kind has been reported. It seems more likely that the decrease in primary isotope effect arises from a change in mechanism. Two factors could initiate this change. One is that as the acidity is raised, the amount of $H_2\ddot{O}$ available for proton removal decreases. This factor is consistent with the decrease in reaction rates observed at high acidities and also accounts for the unusual solvent isotope effect reported for 2-n-butyl-3-methyl-3-ethyl-oxaziridine by Butler and Challis[43]. Support for this interpretation comes from the analysis of rates in terms of a_{H_2O}. The decrease in rate is accounted for by a term involving $a^{W}_{H_2O}$, i.e., the reaction follows (Eq. (V-4)):

$$\text{Rate} = k' \left[\text{oxaziridine}\right]\left[H^{\oplus}\right]\left[a_{H_2O}\right]^{W} \qquad (V\text{-}4)$$

Fig (V-19) shows the type of linearity obtained for primary 2-alkyloxaziridines when log k_ψ (k_ψ is the observed k_o corrected for the spontaneous rate in H_2O) is plotted against log a_{H_2O}.

The second factor influencing the magnitude of the primary isotope effect must be the formation of the N-conjugate acid. It was shown in Chapter V, Section (V.1), that at high acidities this is the predominant form of the substrate. In this circumstance,

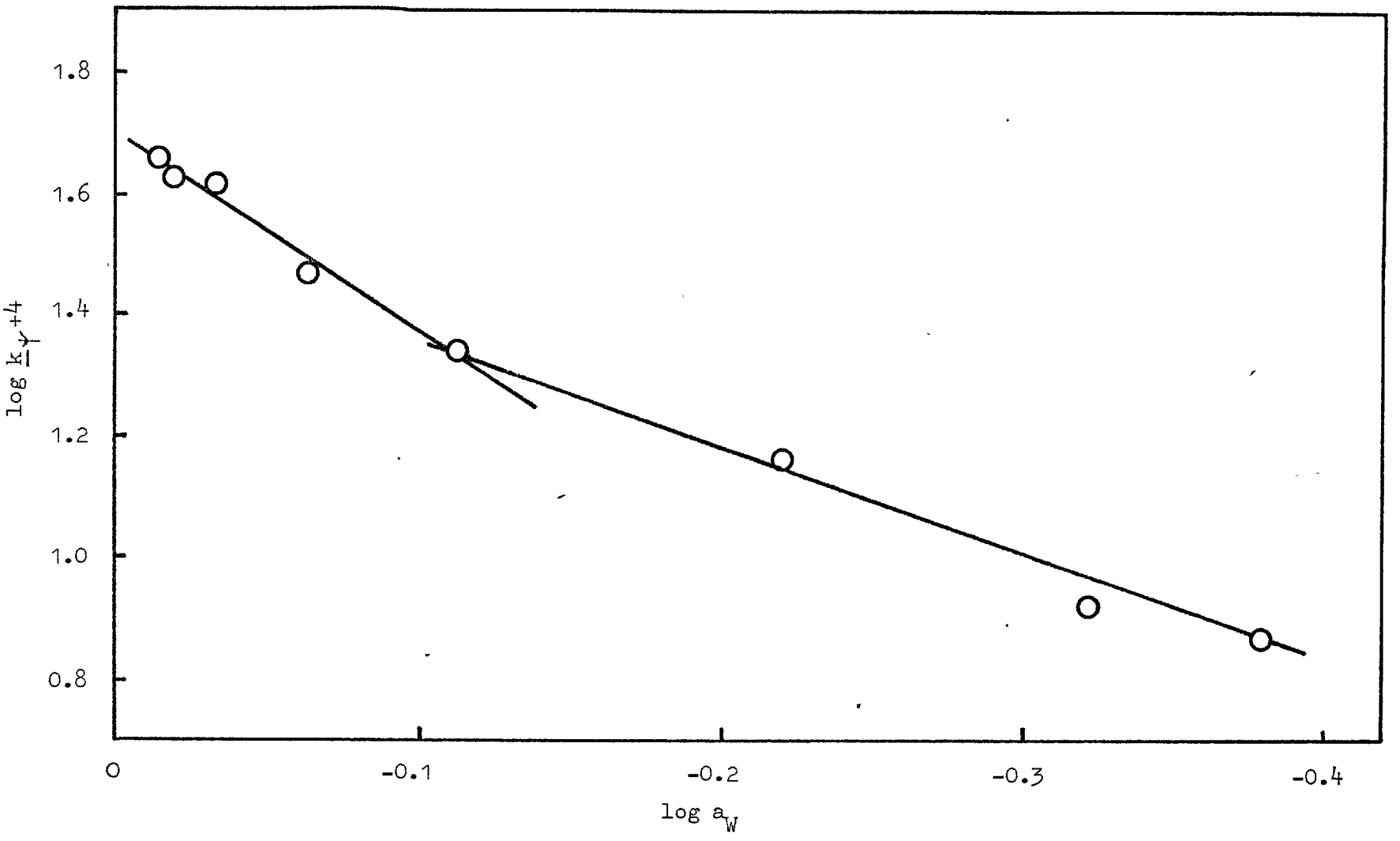
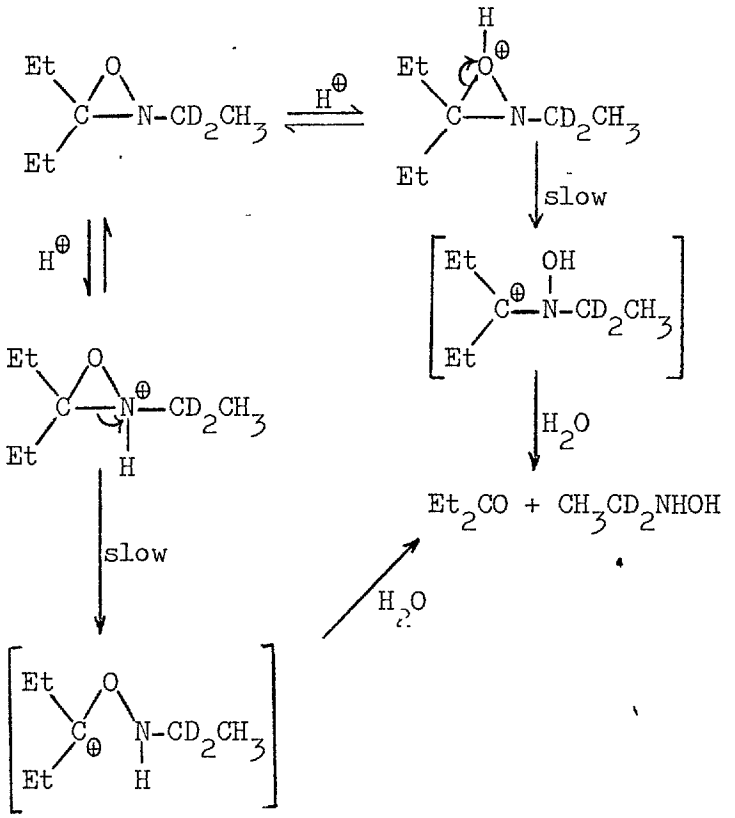


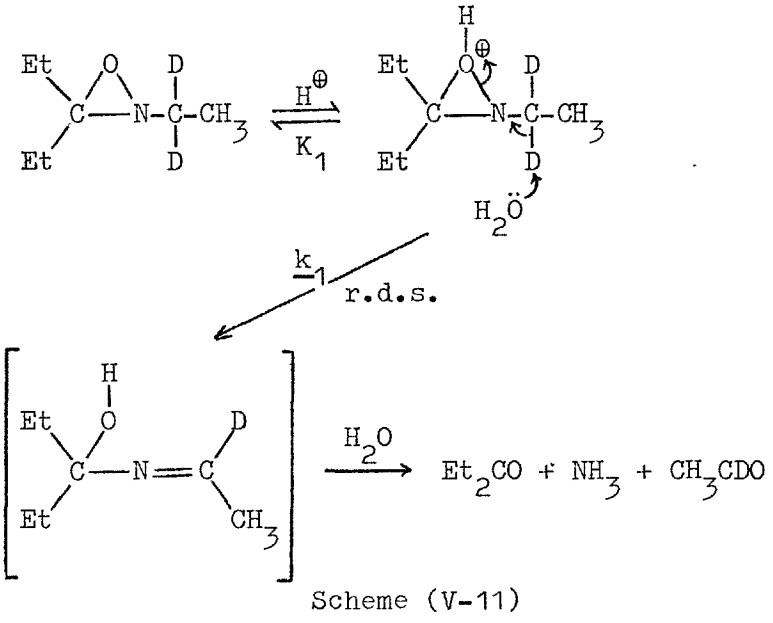
Fig. (V-19). Test of equation (III - 3) for the hydrolysis of 2-n-butyl-3-methyl-3-ethyl-oxaziridine in aqueous sulphuric acid, 25°C.

removal of the α-proton is inhibited and a new reaction pathway occurs, leading to the formation of ethylhydroxylamine as the major product. This new mechanism is more complex. It may involve a thermal process via the nitrone or one (or both) of the heterolytic pathways outlined in Scheme (V-10). The present results do not permit a clear distinction to be made.



Scheme (V-10)

Our conclusion for the primary 2-alkyl oxaziridines is that the O-protonated conjugate acid is the reactive species. Its formation gives additional driving force for ring opening by formation of the imine structure (Scheme (V-11)).

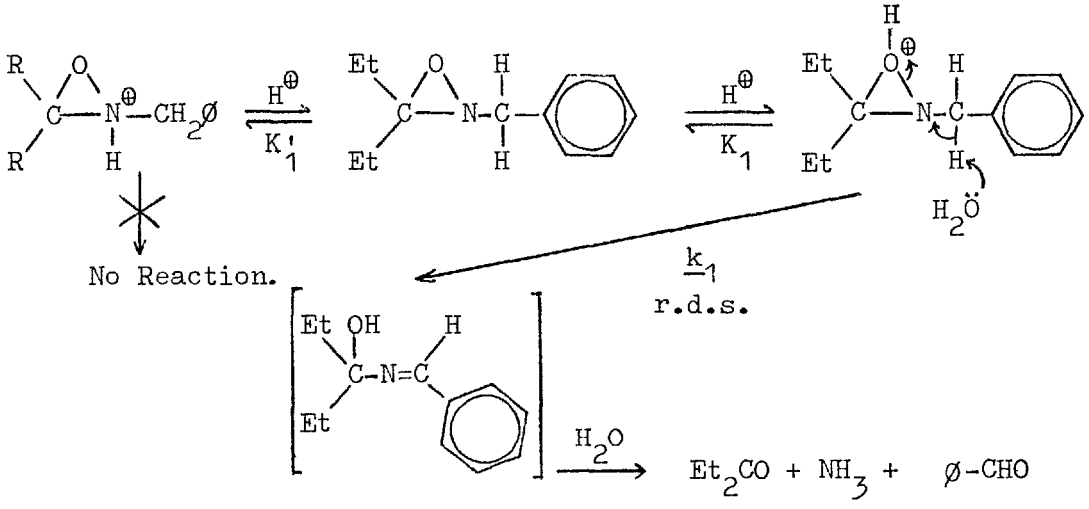


Scheme (V-11)

The N-protonated conjugate acid can only lead to ring opening by an increase of steric strain. When the nitrogen atom becomes protonated, its almost tetrahedral structure will add to the already high energy content of the three-membered ring.

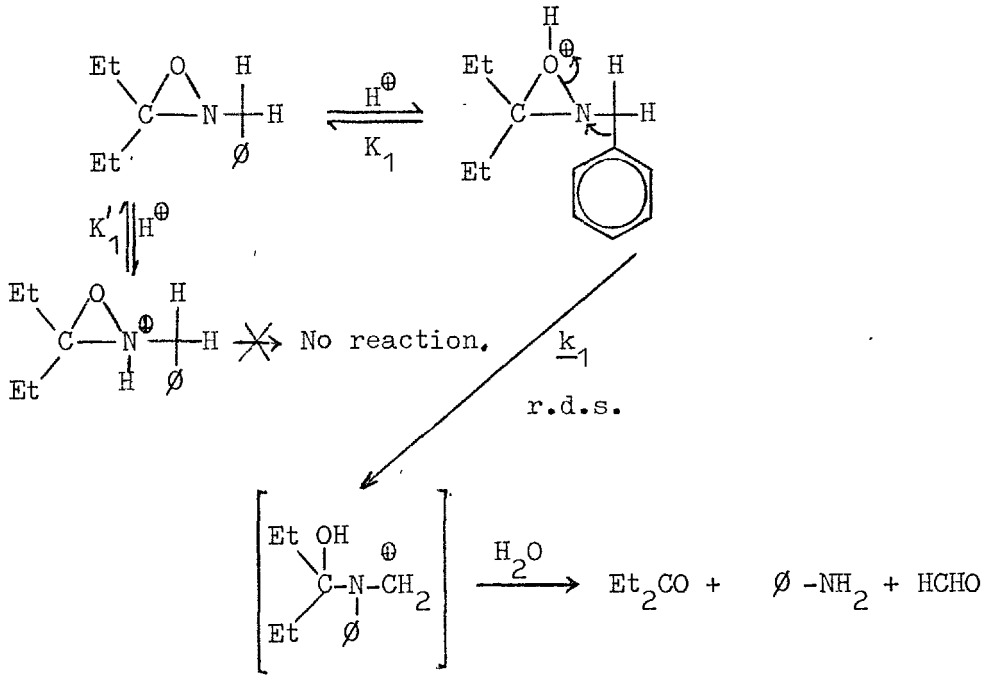
Having determined the role played by the α-proton to nitrogen, the importance of solvent basicity and the implications of the structure of the oxaziridine conjugate acid, we are in a better position to understand the influence of an aryl group α to the nitrogen on the hydrolysis kinetics. The profile shown in Fig (V-13) shows an increase in reaction rate at low acid concentrations, reaching a maximum at 3.54 M, $HClO_4$, and then a very gradual fall off in rates at acidities above 5 M, $HClO_4$. This is consistent with rapid protonation occurring in a pre-equilibrium step. The profile, however, is very different from the one found for the 2,3,3-triethyl-oxaziridine but markedly resembles that for the 2-t-butyl-3-alkyl-oxaziridines, where extensive methyl migration occurs. Analysis of the products shows clearly that α-proton abstraction from the O-conjugate acid leading to benzaldehyde (Scheme (V-12)) is only

important at very dilute acid concentration (at 0.101 M $HClO_4$,



Scheme (V-12)

only 39% of benzaldehyde is formed) and that phenyl migration occurs with increasing facility throughout the whole acidity range becoming the exclusive pathway above 4-5 M, $HClO_4$ (Scheme (V-13)). As for

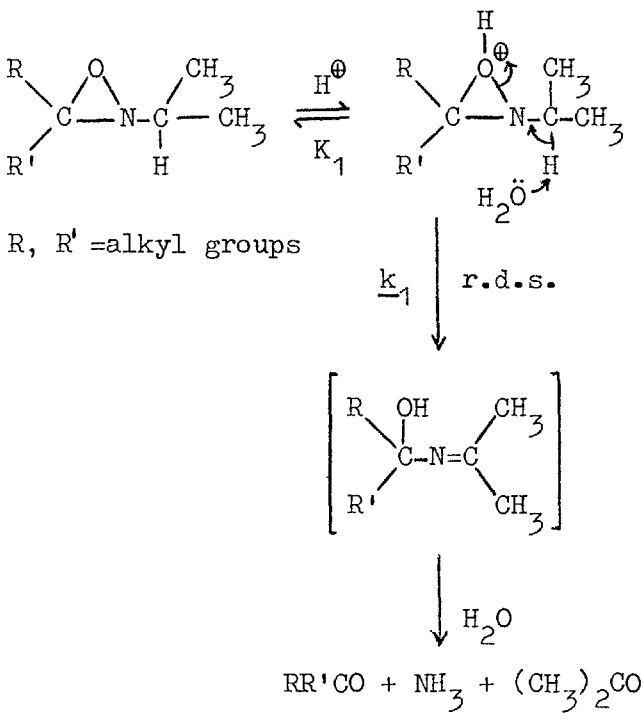


Scheme (V-13)

the primary 2-alkyl oxaziridines, the products for either pathway are best explained in terms of an O-protonated oxaziridine though probably, as in the case of the 2-t-butyloxaziridines, this is in equilibrium with a small amount of the N-conjugate acid*(Scheme (V-13)). Further implications of exclusive phenyl migration at high acidities will be dealt with in the following section.

V.4.2 The Acid Hydrolysis of Oxaziridines with 2-Isopropyl and 2-α-Phenylethyl Groups.

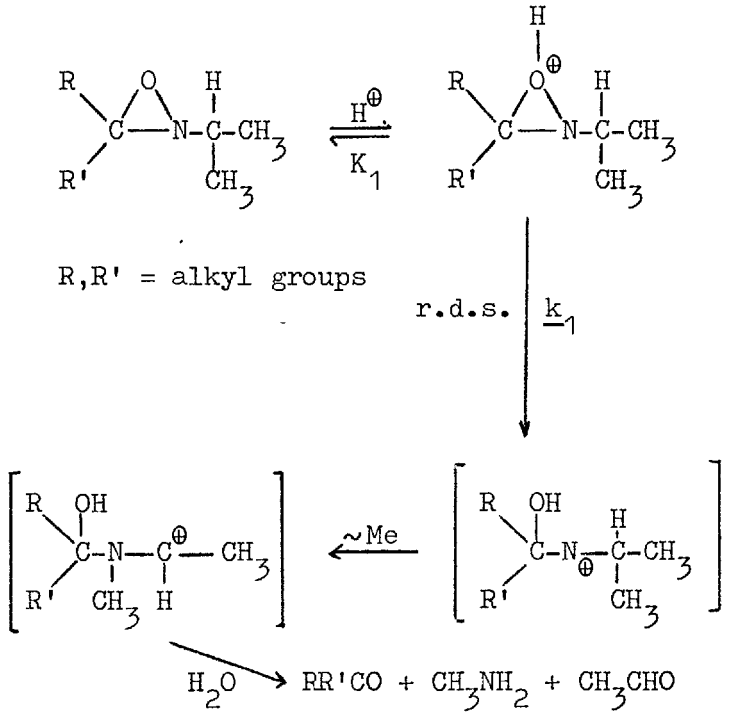
In the light of the previous discussion, two potential pathways for decomposition of these oxaziridines are possible. The first, as shown in Scheme (V-14) involves $H^{\oplus}$ abstraction, as



Scheme (V-14)

* N.m.r. analysis could not detect either of the two forms of the conjugate acid due to the instability of this oxaziridine under acid conditions.

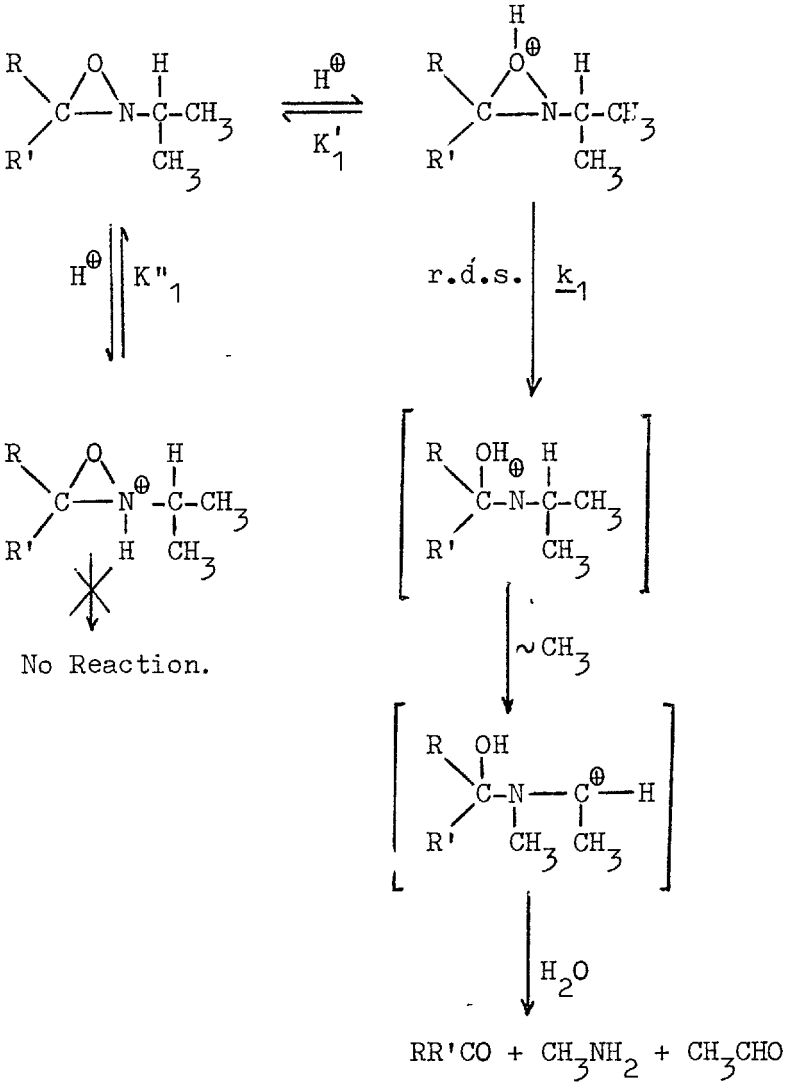
observed for compounds bearing a primary 2-alkyl substituent. The second resembles the pathway found for the 2-t-butyl-3-alkyloxaziridines,[6,42] involving a methyl migration to the nitrogen atom (Scheme (V-15)). Both the analysis of the products obtained in the



Scheme (V-15)

acid hydrolysis of 2-isopropyl-3-ethyloxaziridine (propionaldehyde and acetaldehyde, cf. Section (V.3.1)) and the rate/acidity profile, (Fig. (V-14), which is similar to that for 2-t-butyl-3-alkyl-oxaziridines, (Fig. (I-1)), are consistent with a pre-equilibrium protonation step followed by collapse of the ring by N-O bond fission to give an electron deficient immonium ion species, with migration (perhaps synchronous) of the α methyl group[42] (i.e. Scheme (V-15)). Of course, although the products are best rationalised in terms of an O-conjugate acid, the N-protonated species is the one

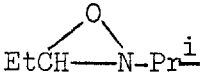
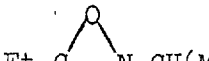
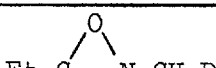
observed by n.m.r. spectroscopy. This suggests, as for the other oxaziridines discussed previously (Section V.4.1), that an equilibrium between the O- and N- conjugate forms exists, but that the N-protonated does not lead to reaction (Scheme (V-16)).



Scheme (V-16)

Not surprisingly the K_1 value, as well as the $\underline{k}_1$ rate constant, are very close to those found for the 2-t-butyl-3-alkyloxaziridines (Tables (III-2) and (V-13)).

Table (V-13)

Oxaziridine	$[HClO_4]_{max}$ (a)	$10^3\ k_{o(max)}$ ($min.^{-1}$)	m (b)	$10^3\ k_1$ ($min.^{-1}$) (c)	K_1 (c)	pK_1 (c)
	2.67	5.25	0.58	8.62	0.501	+0.30
	3.54 (d)	-	0.89	50	82	-1.9
	3.54	200	0.53	278	2.89	-0.46

(a) In aqueous $HClO_4$, at 25°C.

(b) Slope of plot log k_o versus $(-H_o)$.

(c) Based on the h_o scale.

(d) Inflexion point (see Section (V.3.2)).

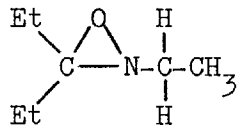
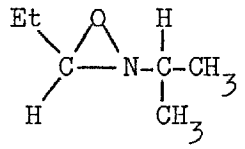
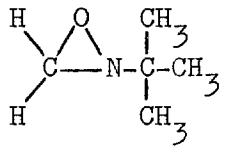
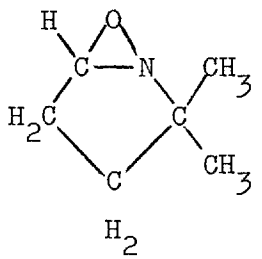
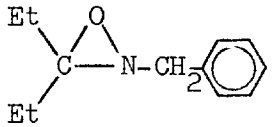
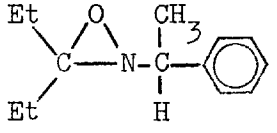
Our interest in the migratory aptitudes of groups $\underline{\alpha}$ to the $\underline{N}$ atom of the ring encouraged study of the 2-(α-phenylethyl)-3,3-diethyloxaziridine, the results obtained being summarized in Section V.3.2. The kinetic acidity profile is somewhat different to that for 2-isopropyl-3-ethyloxaziridine showing an inflexion point at c a. 3M, $HClO_4$, then a very gradual increase in the reaction rates (Fig. (V-17)). Below the inflexion point, the slope of log $\underline{k}_o$ versus $(-H_o)$ has a value of 0.89. This suggests that, as for the other oxaziridines, there is rapid equilibrium protonation before rate determining breakdown of the conjugate acid. However, once protonation is complete the rate still increases with a small dependence on $(-H_o)$. Product analysis shows no apparent change of mechanism. Unlike the situation for 2-benzyl-3,3-diethyloxaziridine, where proton abstraction initially occurs side by side with phenyl migration but decreases at high acidity, for 2-(α-phenylethyl)-3,3-diethyl-oxaziridine the products derive from exclusive phenyl migration at all acidities studied. Aniline is thus formed throughout the whole acidity range.

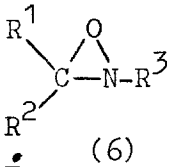
It is interesting at this point to take a closer look at the migratory aptitudes of the different groups in the oxaziridine acid hydrolysis.* A summary of the rearrangements occurring in the acid hydrolysis of 3-alkyloxaziridines is shown in Table (V-14). It is evident that, in the case of 2,3,3-triethyloxaziridine, for example, the migration of a methyl group would lead to the formation of a

* In the following discussion concerning the migratory aptitudes of the different groups α to the $\underline{N}$ atom of the oxaziridine ring, the abstraction of the $\underline{\alpha}$ hydrogen, will, for the sake of simplicity, simply be described as an hydrogen migration or "hydride shift".

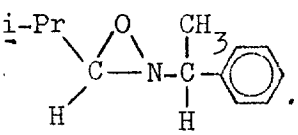
Table (V-14)

Rearrangement of the group R^3 [a] in oxaziridines acid hydrolysis

Oxaziridine	Groups α to the N	Group Shifted to the N	Carbonium ion intermediate	Ref.
	H CH_3	H	$-C^{\oplus}H-CH_3$	(43)
	H CH_3	CH_3	$-C^{\oplus}H-CH_3$	-
	CH_3	CH_3	$-C^{\oplus}(CH_3)-CH_3$	(6)
	CH_3 CH_2-R	CH_3	$-C^{\oplus}(CH_3)-CH_2$-R	(16)
	H 	H  b)	$-C^{\oplus}H-H$	-
	H CH_3, 	c) 	$-C^{\oplus}H-CH_3$	-

a) 

b) Predominantly phenyl migration at high acidities.

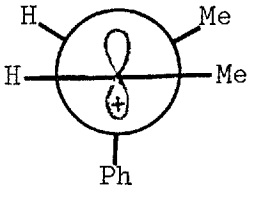
c) Emmons (6) found the same behaviour present in .

highly unstable primary carbonium ion.

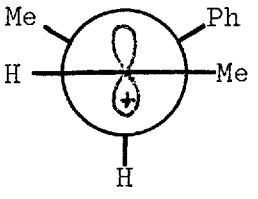
Examination of the other oxaziridines listed shows the normal order of migration aptitudes is as follows: Ph > CH_3 > R-CH_2 > H, except when migration of a group α to the nitrogen would generate an unstable primary carbonium ion, in which case "the hydride shift" becomes important, at least in dilute acid. However, for 2-isopropyl-3-ethyloxaziridine, it is the CH_3 group, and not hydrogen that migrates, although this does not produce the most stable carbonium ion structure. Thus some factor other than carbonium ion structure is important in this case.

It is interesting at this stage to notice that the normal order is similar to that found for reactions of a different type. For example, in the case of 3-phenyl-2-butylamine, PhCHMe-CHMeNH$_2$, deamination (with HNO_2 in acetic acid) can proceed with either phenyl, methyl or hydride migration in the order Ph > Me > H.[94] The mechanistic implications of these results are not yet entirely clear and several factors seemed to be involved. Interestingly enough, there are marked differences between the acetolysis of the diazonium ion, PhCHMeCHMeN$_2^{\oplus}$, and that of the corresponding tosylate, PhCHMeCHMeOTos.[95] When the leaving group is N_2, then a phenyl, a methyl, or a hydrogen may migrate; whereas with OTos$^{\ominus}$ as the leaving group, only phenyl shifts. This suggests that OTos$^{\ominus}$ must be pushed from the α position of the tosylate by the α-phenyl group, whereas the unusual stability of the nitrogen molecule allows it to depart from the diazonium ion without the benefit of anchimeric assistance, leaving behind a classical carbonium ion.[96-a)] In the latter case, the group that migrates is very probably that parallel to the empty p orbital of the α-carbon in the carbonium

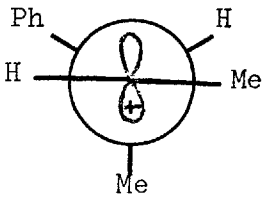
ion[96-b]. Thus there is a steric requirement that may influence the migratory aptitudes.



Ph migration



H migration

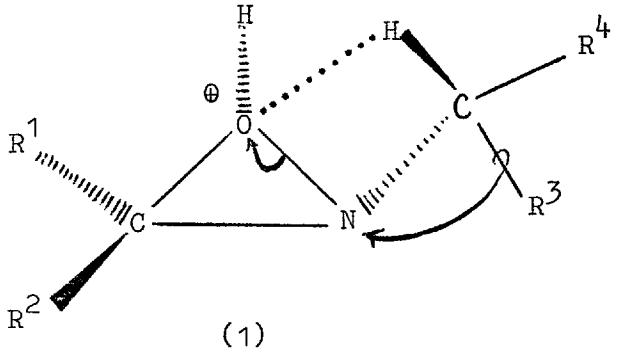


CH_3 migration

It seems that of all factors, two are most important in determining which group is going to migrate in the acid hydrolysis of 3-alkyl oxaziridines, namely the stereochemistry of the compound at the moment of migration and the intrinsic stability of the incipient carbonium ion formed. One additional factor for oxaziridine hydrolysis is the basicity of the solvent, already considered in relation to proton abstraction from primary 2-alkyl oxaziridines.

It therefore seems probable that steric factors partly account for the exclusive Me migration for 2-isopropyl-3-ethyloxaziridine and exclusive Ph migration for 2-(α-phenylethyl)-3,3-diethyloxaziridine. These would fix the most stable conformation of the oxaziridine as that where the α-H to the nitrogen is adjacent to the ring oxygen (1). Thus only the Me group and the Ph group in the above compounds are in the correct position for backside attack on the N of the conjugate acid intermediate.

The reason for the rate increase at high acidity for 2-(α-phenylethyl)-3,3-diethyloxaziridine is not entirely clear. However,



(1)

Only R^3 migrates

since conformational factors appear to be important in this case, it is likely that increasing the acidity also increases the concentration of reactive conformer.

Chapter VI

Basic and Nucleophilic Ring Cleavage of Oxaziridines

The results reported here and discussed in the following sections are concerned with either basic or nucleophilic catalysed ring opening of the oxaziridine ring. A range of catalysts have been studied and the oxaziridine structure varied. Most of the kinetic experiments were carried out at 25.0 $\pm$ 0.1°C and the rates always followed (Eq. (VI-1)).

$$\text{Rate} = \underline{k}_o[\text{substrate}] \qquad \text{(VI-1)}$$

where $\underline{k}_o$ is the rate constant observed for the opening of the ring and [substrate] refers to the stoichiometric concentration of oxaziridine.

The product analyses were carried out as described in Part 3, mainly by the chromatographic analysis of the carbonyl products formed during hydrolysis (t.l.c.), but other techniques were also used, namely n.m.r. and u.v. spectroscopy.

VI.1 The Experimental Data

VI.1.1 2,3,3-Triethyloxaziridine

VI.1.1.1 Kinetic Results

Kinetic studies of reactions between 2,3,3-triethyloxaziridine and aqueous solutions of sodium hydroxide, sodium deuteroxide, sodium phenoxide, dimethylamine, piperidine, 2,6-dimethylpiperidine, potassium cyanide, potassium iodide and potassium thiocyanate are reported in this section.

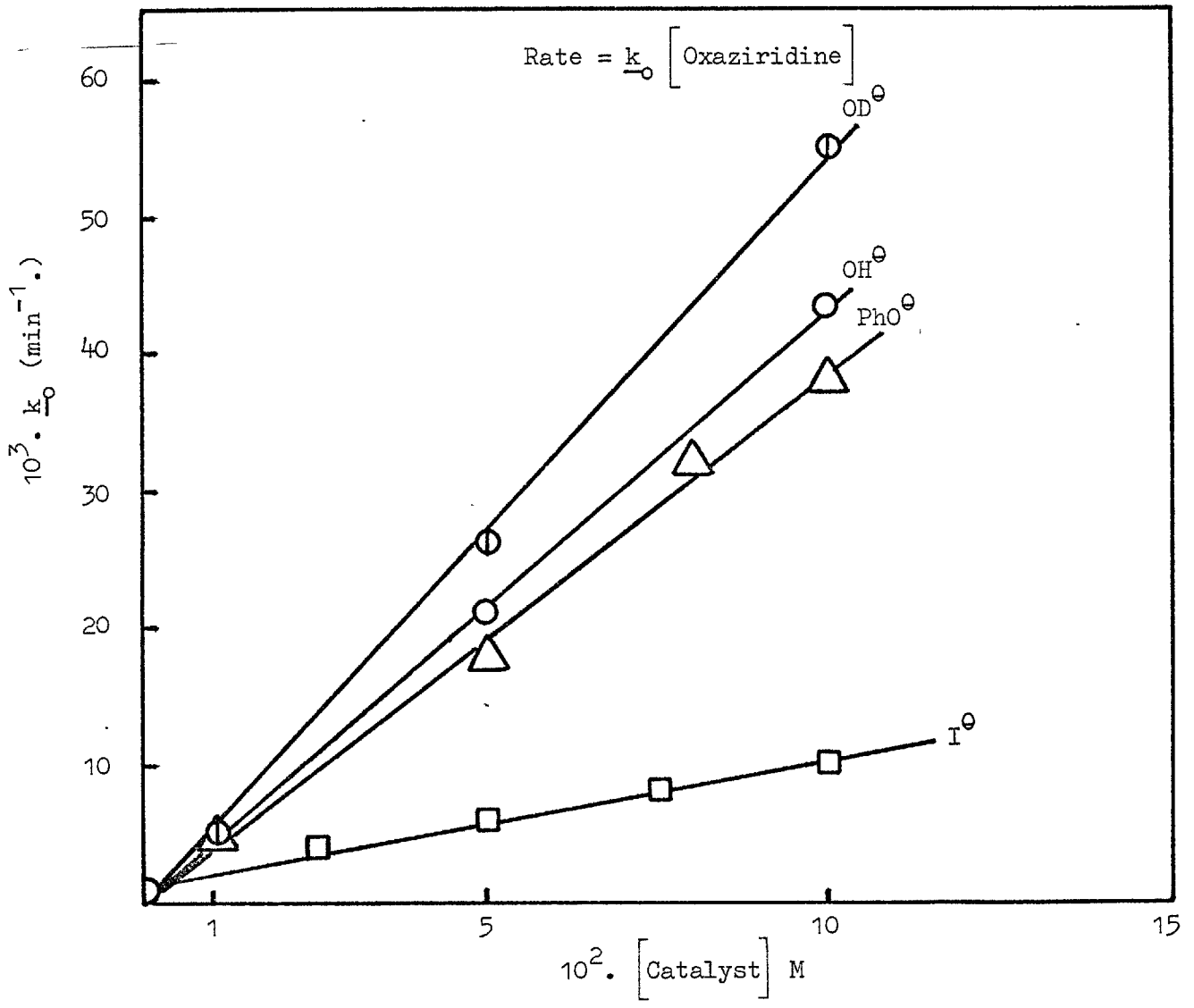


Fig. (VI-1a). Variation of reaction rate for the hydrolysis of 2,3,3-triethyloxaziridine with catalyst concentration.

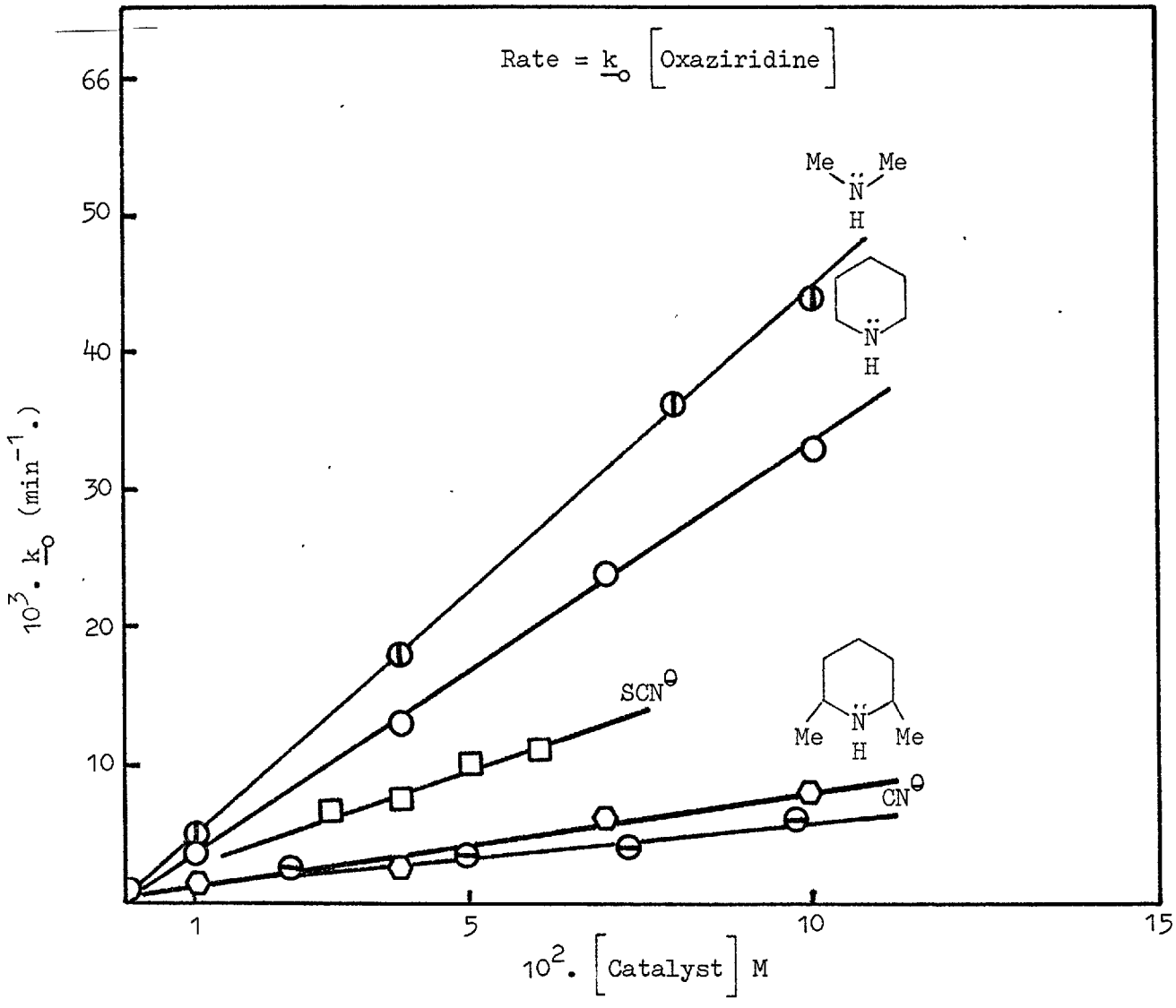


Fig. (VI-1b). Variation of reaction rate for the hydrolysis of 2,3,3-triethyloxaziridine with catalyst concentration.

All the runs were carried out at 25.0 $\pm$ 0.1°C, in different concentrations of the catalysts (normally ranging from 1.0×10^{-2}M to 10×10^{-2}M), whereas the concentration of oxaziridine was kept to about 6×10^{-3}M to ensure reasonable pseudo first order conditions where the catalysts were consumed by reaction products or by the oxaziridine itself. The ionic strength, μ, was kept constant by addition of NaCl or $NaClO_4$.

First-order rate coefficients, $\underline{k}_o$, for each kinetic run are reported in Tables (VI-1) to (VI-10).* Second-order rate coefficients, $\underline{k}_2^{Cat.}$, for each catalyst, (Eq. (VI-2)),

$$\text{Rate} = \underline{k}_2^{Cat.} [\text{oxaziridine}][\text{catalyst}] \qquad \text{(VI-2)}$$

were obtained from the slope of the best straight line, for plots of $\underline{k}_o$ versus [catalyst]. These plots are shown in Fig (VI-1a) and (VI-1b), and values of $\underline{k}_2^{cat.}$ are given at the foot of each Table. It is apparent that both basic and nucleophilic catalysts are effective for the reaction.

VI.1.1.2 Solvent Isotope Effect

Table (VI-11) correlates the data for $\underline{k}_o$ observed in H_2O and D_2O. The solvent isotope ratio ($\underline{k}_o^{D_2O}/\underline{k}_o^{H_2O}$) is listed in the third column of the table, and its magnitude lies in the range 1.10 to 1.26. These are noticeably larger than the value of 0.73 found for the spontaneous decomposition in pure water (pH $\simeq$ 7), suggesting that

* The term buffer ratio refers to the ratio $(HA)/(A^{\ominus})$, i.e. the ratio of the concentration of the buffer acid to the concentration of its conjugate base.

Table (VI-1)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Sodium Hydroxide

Temperature = 25.0 ± 0.1°C μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOH] x 10^2M	10^3 $\underline{k}_o$ $min.^{-1}$
5	10	45
6	10	42
7	5.0	21
8	1.0	4.8
16[a]	1.0	4.7
*[b]	0	0.55

$\underline{k}_2^{OH^\ominus}$ = 4.3 x 10^{-1} $mole^{-1}$. l. min^{-1}.

a) μ = 1.0

b) Reference (43).

Table (VI-2)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous Sodium Deuteroxide

Temperature = 25.0 ± 0.1°C μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOD] x 10^2M	10^3 k_o $min.^{-1}$
192[a]	20	110
188	10	55
189	5.0	27
190	1.0	5.3
191	0	0.4

$k_2^{OD^\ominus}$ = 5.5 x 10^{-1} $mole^{-1}$. l. min^{-1}.

$k_2^{OD^\ominus}/k_2^{OH^\ominus}$ = 1.3 ± 0.1.

a) μ = 0.20

Table (VI-3)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Sodium Phenoxide

Temperature = 25.0 ± 0.1°C μ = 0.10, adjusted
Buffer ratio [PhOH] / [NaPhO] = 1 with NaCl

Kinetic Run	[NaPhO] x 10^2 M	10^3 k_o $min.^{-1}$
9	10	37
10	8.0	32
11	4.0	18
12	1.0	5.3
29[a)]	10	37

$k_2^{PhO^\ominus}$ = 3.7 x 10^{-1} $mole^{-1}$. l. min^{-1}.

a) 5 ml of an ethanolic saturated solution of galvinoxyl added.

Table (VI-4)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous Sodium Phenoxide

Temperature = 25.0 ± 0.1°C μ = 0.10, adjusted

Buffer ratio [PhOH]/[NaPhO] = 6 with NaCl

Kinetic Run	[NaPhO] x 10^2M	10^3 k_o $min.^{-1}$
27	7.0	23
22	5.0	19
23	4.0	16
26	1.0	4.9

$k_2^{PhO^\ominus}$ = 3.6 x 10^{-1} $mole^{-1}$. l. min^{-1}.

Table (VI-5)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Dimethylamine

Temperature = 25.0 ± 0.1°C μ = 0.10, adjusted with NaCl

Buffer ratio [Dimethylamine]/[Dimethylammonium chloride] = 1

Kinetic Run	$[Me_2\ddot{N}H]$ x 10^2M	10^3 k_o $min.^{-1}$
15	10	44
17	8.0	36
18	4.0	18
19	1.0	4.8

$k_2^{Me_2\ddot{N}H}$ = 4.3 x 10^{-1} $mole^{-1}$. l. min^{-1}.

Table (VI-6)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous Piperidine

Temperature = 25.0 ± 0.1°C

μ = 0.20, adjusted with NaCl

pH = 10.9 ± 0.1

Kinetic Run	[P] * x 10^2M	[$PH^{\oplus}$]* x10^2M	10^3 k_o $min.^{-1}$
129	10	9.7	33
126	7.0	6.7	24
127	4.0	3.7	13
128	1.0	0.7	3.1

k_2^P = 3.0 x 10^{-1} $mole^{-1}$. l. min^{-1}.

*) P ≡ piperidine; $PH^{\oplus}$ ≡ piperidinium ion.

Table (VI-7)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous 2,6-Dimethylpiperidine

Temperature = 25.0 ± 0.1°C

μ = 0.20, adjusted with NaCl

pH = 11.1 ± 0.1

Kinetic Run	[DMP]* x10^2 M	[$DMPH^{\oplus}$]* x10^2 M	10^3 k_o $min.^{-1}$
130	10	9.8	7.7
131	7.0	6.8	6.0
132	4.0	3.8	3.6
133	1.0	0.8	2.0

k_2^{DMP} = 7.8 x 10^{-2} $mole^{-1}$. l. min^{-1}.

*) DMP ≡ 2,6-Dimethylpiperidine; $DMPH^{\oplus}$ ≡ 2,6-Dimethylpiperidinium ion.

Table (VI-8)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Potassium Cyanide

Temperature = $25.0 \pm 0.1^{\circ}C$

$\mu = 0.38$, adjusted with $NaClO_4$

pH = 10.4 ± 0.1, $\left[Na_3PO_4\right] = 0.0095$ M, $\left[Na_2HPO_4\right] = 0.095$ M

Kinetic Run	[KCN] $\times 10^2$ M	$10^3 k_o$ $min.^{-1}$
116	9.7	6.2
117	7.3	4.2
118	4.9	3.5
119	2.4	2.7

$k_2^{CN^{\ominus}} = 5.6 \times 10^{-2}$ mole^{-1}. l. min^{-1}.

Table (VI-9)

Ring Opening of 2,3,3-Triethyloxaziridine in Aqueous Potassium Iodide

Temperature = 25.0 ± 0.1°C

Kinetic Run	[KI] $\times 10^2$ M	$10^3 k_o$ $min.^{-1}$
55	10	10
57	7.5	8.2
56	5.0	5.9
58	2.5	3.8

$k_2^{I^\ominus} = 1.0 \times 10^{-1}$ mole^{-1}. l. min^{-1}.

Table (VI-10)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous Potassium Thiocyanate

Temperature = 25.0 ± 0.1C

Kinetic Run	[KSCN] x10^2 M	[KI] x10^2 M	$10^3(\underline{k}_o - \underline{k}_2^{I^\ominus}[I^\ominus])$ $min.^{-1}$
72	6.0	5.0	11
69	5.0	5.0	10
71	4.0	5.0	7.5
70	3.0	5.0	7.0

$$k_o = \underline{k}_2^{SCN^\ominus}[SCN^\ominus] + \underline{k}_2^{I^\ominus}[I^\ominus]$$

$$\underline{k}_2^{SCN^\ominus} = 1.8 \times 10^{-1} \text{ mole}^{-1}. \text{ l. min}^{-1}.$$

Table (VI-11)

Solvent Isotope Effect for the basic hydrolysis of 2,3,3-triethyloxaziridine

Temperature = 25.0 ± 0.1°C

$[OH^{\ominus}(D)]$ x10^{2} M	$10^{3}\ k_o^{H_2O}$ [a] $min.^{-1}$	$10^{3}\ k_o^{D_2O}$ [b] $min.^{-1}$	$k_c^{D_2O}/k_o^{H_2O}$
20	87 [c]	110	1.26 ± 0.05
10	44	55	1.25 ± 0.05
5.0	21	27	1.26 ± 0.05
1.0	4.8	5.3	1.10 ± 0.05
0	0.55 [d]	0.40	0.73 ± 0.05 [e]

a) $k_o^{H_2O}$ represents the rate constant in $OH^{\ominus}/H_2O$.

b) $k_o^{D_2O}$ represents the rate constant in $OD^{\ominus}/D_2O$.

c) Calculated from the expression $k_o = k_o^{H_2O} + k_2^{OH^{\ominus}}[OH^{\ominus}]$, with $k_2^{OH^{\ominus}} = 4.3 \times 10^{-1}$ mole^{-1}. l. min^{-1}.

d) Reference (43).

e) Reference (97).

the chemical process under consideration is somewhat different. The latter agrees well with the value of 0.74, reported for the decomposition in water of 2-n-butyl-3-methyloxaziridine[97]. Further discussion of this point will be deferred until later.

VI.1.1.3 Thermodynamic Parameters

The hydrolysis of 2,3,3-triethyloxaziridine (5.0×10^{-2}M, NaOH and NaPhO) was studied at different temperatures. The experimental results are listed in Tables (VI-12) and VI-13).

Thermodynamic parameters were calculated from Eq. (VI-3), where

$$\underline{k}_2 = \underline{K} \left(\frac{kT}{h}\right) e^{\Delta S^{\ddagger}/R} \; e^{- E_a^{\ddagger}/RT} \qquad \text{(VI-3)}$$

$\underline{k}_2$ is the bimolecular rate coefficient computed at temperature $\underline{T}$ (^{o}K), $\underline{R}$ is the gas constant, $\underline{K}$ is the transmission coefficient, and $\underline{E}_a^{\ddagger}$ and $\underline{\Delta S}^{\ddagger}$ are, respectively, the energy of activation and the entropy of activation.

In practice plots of log $\underline{k}_2$ vers. 1/T, were drawn to give good straight lines as can be seen in Fig. (VI-2) and (VI-3). The slopes ($=E_a^{\ddagger}/2.303R$) yielded values of $\underline{E}_a^{\ddagger}$ and direct substitution in (Eq. (VI-3)) yielded the values of $\underline{\Delta S}^{\ddagger}$. The values obtained are also reported in Tables (VI-12) and (VI-13).

Calculation of the thermodynamic parameters, $\underline{\Delta H}^{\ddagger}$, and $\underline{\Delta F}^{\ddagger}$ (respectively enthalpy and free energy of activation) were made from (Eq. (VI-4)) and (Eq. (VI-5)). The values are

$$\Delta H^{\ddagger} = E_a^{\ddagger} - RT \qquad \text{(VI-4)}$$

$$\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad \text{(VI-5)}$$

Table (VI-12)

Ring Opening of 2,3,3-Triethyloxaziridine

in Aqueous Sodium Hydroxide at Different Temperatures

μ = 0.10 throughout, adjusted with NaCl

Kinetic Run	[NaOH] x10^2 M	Temperature ^oK	10^3 k_o $min.^{-1}$
209	5.0	308.50	49
210	5.0	308.50	50
208	5.0	299.75	25
7	5.0	298.00	21
211	5.0	275.70	3.6
212	5.0	275.70	3.6

$E_a^{\ddagger} = 13.3 \pm 1.3$ kcal mole^{-1}

$\Delta H^{\ddagger} = 12.7 \pm 1.3$ kcal mole^{-1}

$\Delta S^{\ddagger} = -25.6 \pm 0.1$ cal degree^{-1} mole^{-1}

$\Delta F^{\ddagger} = 20.2 \pm 1.3$ kcal mole^{-1}

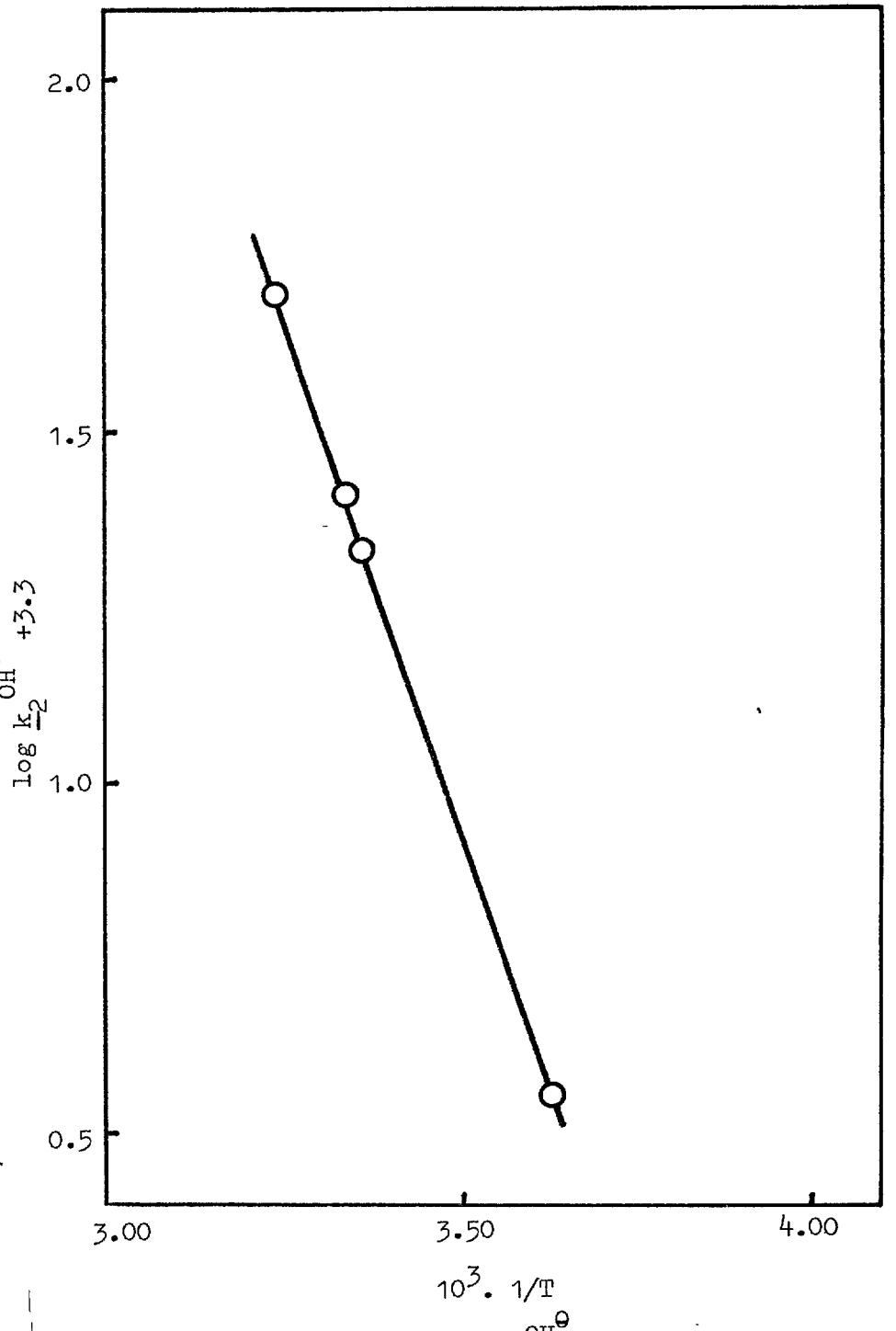


Fig. (VI-2). Variation of $k_2^{OH^\ominus}$ with temperature.

Table (VI-13)

Ring Opening of 2,3,3-Triethyloxaziridine
in Aqueous Sodium Phenoxide at Different Temperatures

Buffer ratio of $[PhOH]/[NaPhO] = 1$

$\mu = 0.10$ throughout, adjusted with NaCl

Kinetic Run	$[NaPhO]$ $\times 10^2$ M	Temperature $^\circ K$	$10^3 \underline{k}_o$ min^{-1}
214	5.0	310.70	60
215	5.0	310.70	59
216	5.0	302.45	30
*	5.0	298.00	22[a)]
217	5.0	279.00	4.4

$$E_a^{\ddagger} = 14.2 \pm 0.2 \text{ kcal mole}^{-1}$$
$$\Delta H^{\ddagger} = 13.6 \pm 0.2 \text{ kcal mole}^{-1}$$
$$\Delta S^{\ddagger} = -22.6 \pm 0.1 \text{ cal degree}^{-1} \text{ mole}^{-1}$$
$$\Delta F^{\ddagger} = 20.4 \pm 0.2 \text{ kcal mole}^{-1}$$

a) Calculated from plot $\underline{k}_o$ versus $[NaPhO]$ at 298.00°K, using the expression $\underline{k}_o = \underline{k}_o^{H_2O} + \underline{k}_2^{PhO^\ominus}[PhO^\ominus]$, with $\underline{k}_2^{PhO^\ominus} = 3.7 \times 10^{-1}$ mole. l. min^{-1}.

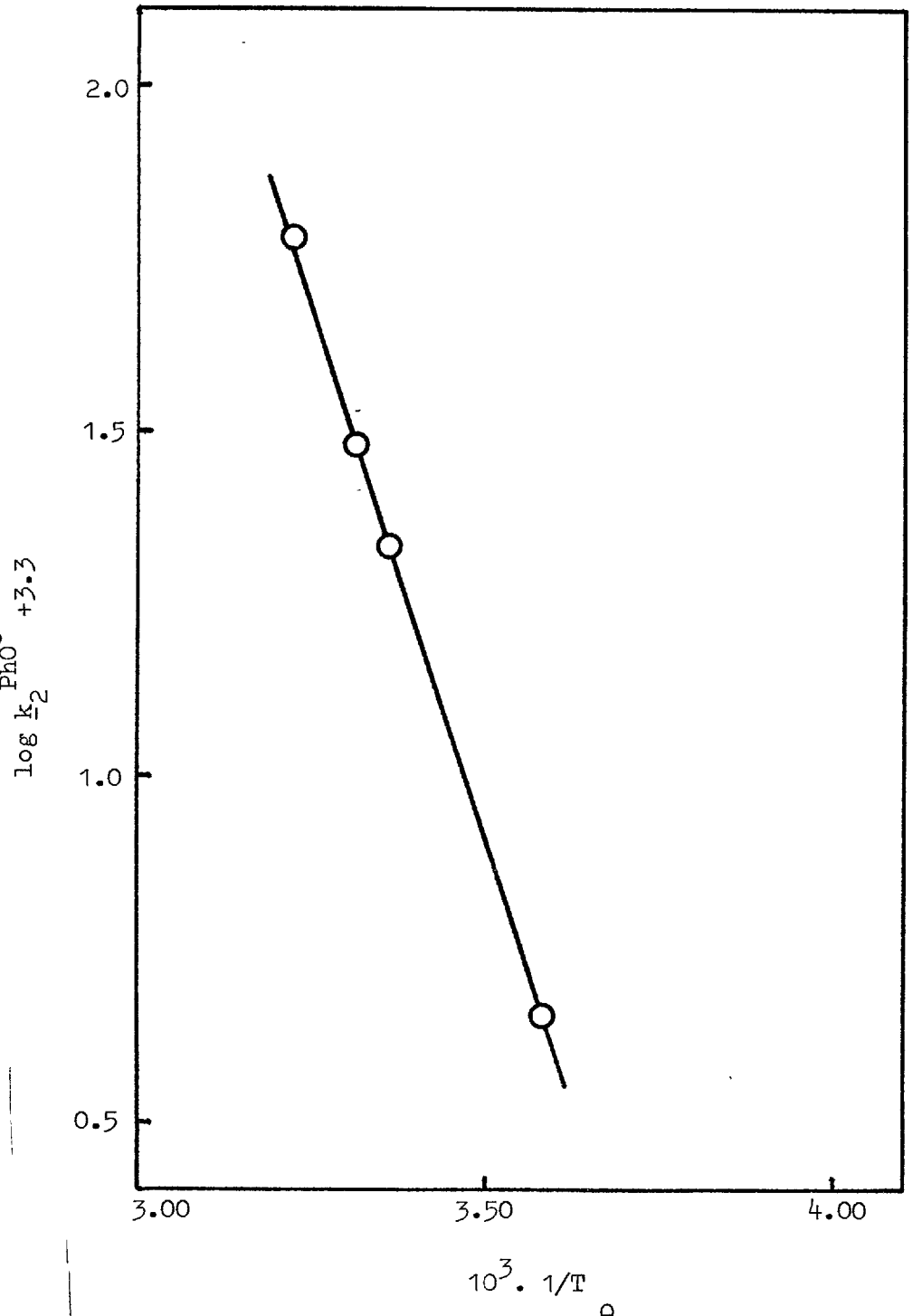


Fig. (VI-3). Variation of $k_2^{PhO^\ominus}$ with temperature.

also reported in Tables (VI-12) and (VI-13).

VI.1:1.4 Product Analysis

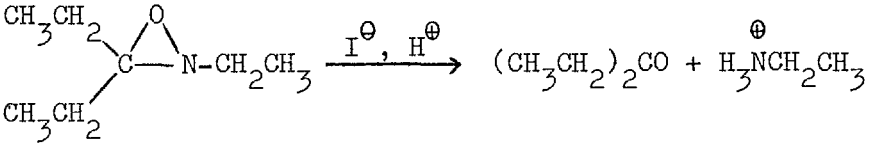
The experimental details of the way in which the products of the reactions were identifiedare described in full in Part 3.

The reactions of 2,3,3-triethyloxaziridine in basic medium with (0.05M) NaOH, NaOD, NaOPh, and with the buffer solutions of dimethylamine, piperidine and 2,6-dimethylpiperidine and cyanide yield diethylketone and acetaldehyde, in c.a. 1:1 mixture; these were identified by t.l.c. by comparison with authentic samples.

The reaction with iodide in neutral media gave diethylketone and acetaldehyde as well as iodine and iodoform.

The iodine, however, which came from an oxidation process was consumed as the hydrolysis reaction proceeded and a detectable amount of iodoform was found when the reactions were followed to completion.

In acid conditions, however, a simple redox reaction occurs, as was pointed out in Part 1, and instead of this side product, 2,3,3-triethyloxaziridine simply yields diethylketone and ethylamine in a 1:1 ratio (Scheme (VI-1)).



Scheme (VI-1)

The reaction with thiocyanate-ion also seemed to follow a complex process since, in spite of the fact that diethylketone and

acetaldehyde could be found among the hydrolytic products, oxidation of thiocyanate ion to thiocyanogen could be detected by the formation of a red colour (one of the first decomposition products of thiocyanogen) followed by precipitation of a yellow, sulphur-containing compound.

A complex oxidation pathway was noticed to occur to a small extent in the reaction between 2,3,3-triethyloxaziridine and phenoxide ion since an intense blue coloured product ($\lambda = 632$ nm), probably arising from oxidative coupling of the phenol, was seen at an early stage of the kinetic run. Under acidic conditions this blue compound changed to red, but attempts to isolate it from the remaining products were unsuccessful owing to its instability. Invariably the residue was a brown polymer which n.m.r. spectroscopy showed to be mainly composed of <u>para-para</u> coupled products.

Attempts to detect products arising from nucleophilic attack on the nitrogen of the oxaziridine ring were unsuccessful. Several attempts were made, especially with piperidine, but no N-N coupled products could be found.

The reactions of 2,3-3-triethyloxaziridine in $OD^{\ominus}/D_2O$ were followed by n.m.r. spectroscopy. By comparison of the n.m.r. signals and chemical shifts with the n.m.r. spectra of authentics, it was shown that the products were the same as those detected by t.l.c. for the corresponding reactions in aqueous solutions, apart from the exchange of labile <u>H</u> atoms in the products.

VI.1.2 <u>2-(α,α'-$\left[^2H_1\right]_2$-Ethyl)-3,3-diethyloxaziridine</u>

<u>Kinetic Results and Isotope Effects</u>

Kinetic results of the ring-opening reaction of 2-(α,α'-$\left[^2H_1\right]_2$-

ethyl)-3,3-diethyloxaziridine catalysed by aqueous NaOH, NaOPh and KI are listed in Tables (VI-14), (VI-15) and (VI-16) respectively.

Comparison of these results with those for the normal substrate yields values of $\underline{k}_o^H/\underline{k}_o^D$ which are listed in Table (VI-17). As can be seen, there is a large primary isotope effect for the reaction with $OH^\ominus$ and $PhO^\ominus$ (4.8 and 3.7 respectively) but no isotope effect for the reaction with $I^\ominus$ (0.8 ~ 1). The full implication of these data will be discussed later.

VI.1.3 2-Ethyl-3-phenyloxaziridine, 2-Ethyl-3-p-nitrophenyloxaziridine and 2-t-Butyl-3-p-nitrophenyloxaziridine

Kinetic results for the ring opening reaction of 2-ethyl-3-phenyloxaziridine in aqueous NaOH, at 25.0 ± 0.1°C and constant ionic strength (μ = 0.10) are listed in Table (VI-18).

The product analysis, carried out by analysis of the hydrazones of the carbonyl compounds formed in the hydrolysis with 0.05 M, NaOH (after the reaction mixture was acidified), showed the presence of benzaldehyde and acetaldehyde, though the quantity of acetaldehyde formed seemed to be slightly less than the quantity of benzaldehyde (approximately 40% less), due to decomposition of the oxaziridine ring through more than one pathway.

Kinetic study of 2-ethyl-3-p-nitrophenyloxaziridine in aqueous NaOH was also attempted but not very reliable data could be obtained due to the very low solubility of this compound. However, a rough value for $\underline{k}_2^{OH^\ominus}$ could be estimated as 1.4 $mole^{-1}$. l. min^{-1}. Analysis of the products with 0.05 M, NaOH showed the presence of p-nitrobenzaldehyde and acetaldehyde.

Table (VI-14)

Ring Opening of 2-(α,α'-$[^2H_1]_2$-Ethyl)-3,3-Diethyloxaziridine in Aqueous Sodium Hydroxide

Temperature = 25.0 ± 0.1°C

μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOH] x10^2 M	10^3 k_o min^{-1}
74	10	9.2
73	5.0	4.5

$k_2^{OH^\ominus}$ = 9.1 x 10^{-2} $mole^{-1}$. l. min^{-1}.

Table (VI-15)

Ring Opening of 2-(α,α'-$[^2H_1]_2$-Ethyl)-3,3-Diethyloxaziridine in Aqueous Sodium Phenoxide

Temperature = 25.0 ± 0.1°C

Buffer ratio of [PhOH]:[NaPhO] = 1

μ = 0.10, adjusted with NaCl

Kinetic Run	[NaPhO] x10^2 M	10^3 k_o min^{-1}
79	10	10
80	4.0	4.9

$k_2^{PhO^\ominus}$ = 8.5 x 10^{-2} $mole^{-1}$. l. min^{-1}.

Table (VI-16)

Ring Opening of 2-(α,α'-$[^2H_1]_2$-Ethyl)-3,3-Diethyloxaziridine in Aqueous Potassium Iodide

Temperature = 25.0 ± 0.1°C

Kinetic Run	[KI] x10^2 M	10^3 k_o min^{-1}
75;82	10	12

$k_2^{I^\ominus}$ = 1.2 x 10^{-1} $mole^{-1}$. l. min^{-1}.

Table (VI-17)

Primary Isotope Effect Observed with

2-(α,α'-[$^{2}H_{1}$][$^{2}H_{2}$]-ethyl)-3,3-diethyloxaziridine

Catalyst	$10^{3}\ k_{o}^{H}$ (*) ($min.^{-1}$)	$10^{3}\ k_{o}^{D}$ (*) ($min.^{-1}$)	k_{o}^{H}/k_{o}^{D}
NaOH , 0.10 M	44	9.2	4.8 ± 0.3
NaOH , 0.05 M	21	4.5	4.7 ± 0.3
NaPhO , 0.10 M	37	10	3.7 ± 0.3
NaPhO , 0.10 M	18	4.9	3.7 ± 0.3
KI, 0.10 M	10	12	0.8 ± 0.3

(*) k_{o}^{H} and k_{o}^{D} represent the first order rates for respectively the normal and the dideuterated oxaziridine.

Table (VI-18)

Ring Opening of 2-Ethyl-3-phenyloxaziridine in Aqueous Sodium Hydroxide

Temperature = 25.0 ± 0.1°C

μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOH] x10^2 M	10^3 k_o $min.^{-1}$
88	10	60
87	5.0	32
86	1.0	7.0

$k_2^{OH^\ominus}$ = 6.0 x 10^{-1} $mole^{-1}$. l. min^{-1}.

An interesting point with this last oxaziridine is the way it is attacked by amines. In fact, when the reaction between, say, piperidine and 2-ethyl-3-p-nitrophenyloxaziridine in $(CD_3)_2CO$ is carried at room temperature the loss of the n.m.r. signals at 4.5-5.5 τ due to the 3-proton in the oxaziridine ring (in fact there are two signals, one due to the cis isomer and the other due to the trans; see n.m.r. data in Part 3) was complete in c.a. 5 minutes. The colour of the reaction mixture changed from almost colourless to deep brown and t.l.c. analysis showed to be a complex mixture of several compounds, out of which p-nitrobenzaldehyde (63.4%) could be detected as a major constituent.

The basic hydrolysis of 2-t-butyl-3-p-nitrophenyloxaziridine was also studied but the reaction proved to be too slow ($k_2^{OH^\ominus}$ approximately 1.0×10^{-4} $mole^{-1}$. l. min^{-1}.), which shows the great stability of this oxaziridine to basic reagents, which is in accord with Emmons' observations[6].

The reaction at room temperature between neat piperidine and this last oxaziridine was also followed by t.l.c. and found to be very slow, with almost no isomerization of the oxaziridine to the corresponding amide after 24 hr. (Rubottom[98] found that the reaction between this oxaziridine and sodium hydride in hexamethylphosphoramide at room temperature yield 78.5% of the isomeric amide in c.a. 5 minutes, and from this observation concluded that the proton in the ring of this oxaziridine is very susceptible to basic attack).

VI.1.4 2-Benzyl-3,3-diethyloxaziridine

Kinetic results for the base catalysed ring opening of 2-

benzyl-3,3-diethyloxaziridine in aqueous NaOH, at 25.0 ± 0.1°C and constant ionic strength, are listed in Table (VI-19).

Analysis of the carbonyl products formed in ca. IN, NaOH, by preparation of their DNP derivatives after acidification of the reaction mixture, showed the presence of benzaldehyde and diethylketone in quantitative yields. Benzaldehyde was also detected by u.v. spectroscopy (λ = 249 nm), in a quantitative yield, when a reaction of this oxaziridine in 0.01, NaOH was carried out to infinity.

VI.1.5 2-Isopropyl-3-ethyloxaziridine and 2-t-Butyl-3-ethyloxaziridine

The influence of changing the substituent on the nitrogen atom from a primary alkyl group to a secondary one was of some interest, thus 2-isopropyl-3-ethyloxaziridine was prepared and the results of the kinetic runs, carried out in aqueous NaOH, at 25.0 ± 0.1°C and constant ionic strength, are listed in Table (VI-20).

Analysis of the carbonyl compounds formed in basic media (c.a. o.o5 M, NaOH), by formation of DNP derivatives showed the presence of propionaldehyde and acetone in approximately equal amounts.

The kinetics of the basic decomposition of 2-t-butyl-3-ethyloxaziridine were also studied in aqueous NaOH (0.10 M) and aqueous NaOPh (0.10 M) and the respective rate constants obtained were 8.3×10^{-5} min^{-1}. and 5.7×10^{-5} min^{-1}. These rates correspond to very slow reactions and are close to the spontaneous rate for these compounds in pure H_2O (pH 7). There seems to be little base catalysis.

Table (VI-19)

Ring Opening of 2-Benzyl-3,3-diethyloxaziridine in Aqueous Sodium Hydroxide

Temperature = 25.0 $\pm$ 0.1°C

μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOH] x10^2 M	10x k_o min^{-1}
186-187	5.0	6.5 a)
185	2.0	2.4
178	1.0	1.6

$k_2^{OH^\ominus}$ = 1.3 x 10 $mole^{-1}$. l. min^{-1}.

a) Average of runs 186 and 187.

Table (VI-20)

Ring Opening of 2-Isopropyl-3-ethyloxaziridine in Aqueous Sodium Hydroxide

Temperature = 25.0 ± 0.1°C

μ = 0.10, adjusted with NaCl

Kinetic Run	[NaOH] x10^2 M	10^4 k_o $min.^{-1}$
134	10	20
135	5.0	11
136	1.0	4.1

$k_2^{OH^\ominus}$ = 1.7 x 10^{-2} $mole^{-1}$. l. min^{-1}.

VI.2 Discussion of the Results

VI.2.1 Catalysis by Hydroxide Ion

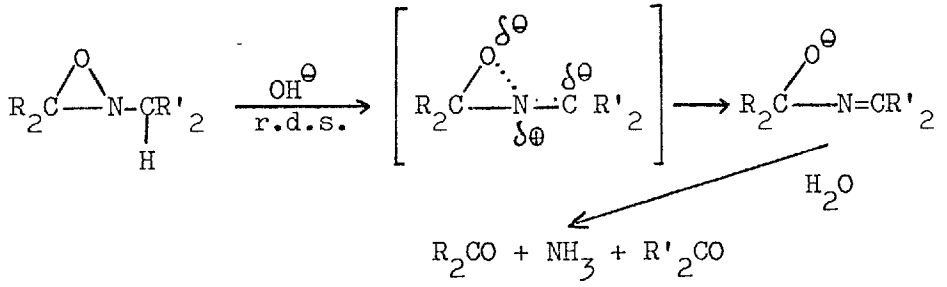
Emmons[6] showed that a primary or secondary alkyl group attached to the nitrogen atom of the ring is essential for the base catalysed hydrolysis of oxaziridines. In fact, 2-t-butyl-oxaziridines were found to be extremely stable in basic media.

The introduction of deuterium in the place of the hydrogens α to the nitrogen of the ring reduces the rate of hydrolysis by a factor of 4.7, (see Tables (VI-17) and (VI-21)), i.e. the reaction is subject to a primary isotope effect. This observation permits important conclusions concerning the mechanism to be made. It shows that the α-proton is removed in the rate determining step, and probably synchronously with the opening of the oxaziridine ring (by virtue of the fact that the kinetic experiments are followed by utilising the oxidative property of oxaziridines which is related with the integrity of the three-membered ring). It seems unlikely that proton removal and ring opening could be stepwise because the three-membered ring is a highly strained structure and rupture should be fast.

The solvent isotope effects for the 2,3,3-triethyloxaziridine computed from the rate coefficients in H_2O and D_2O are listed in Table (VI-11). They are consistent with values reported for other hydroxide ion catalysed C-H abstraction reactions, which show $k_o^{D_2O}/k_o^{H_2O}$ values in the range 1.2-1.4[99]. Thus hydroxide ion catalysis usually leads to a faster reaction in D_2O than in H_2O, and this is normally explained in terms of the effectiveness as basic catalysts of the pairs $OH^{\ominus}$-$OD^{\ominus}$ and H_2O-D_2O.[99]

The thermodynamic parameters for the reaction of 2,3,3-triethyloxaziridine in aqueous NaOH are also illuminating as far as the mechanism of the reaction is concerned. Of the values obtained (listed below Table (V-12)), that of -25.6 cal degree^{-1} mole^{-1}. for the entropy of activation, $\Delta S^{\ddagger}$, is indicative of a highly organized transition state and seems to point to a bimolecular mechanism.

These results suggest that the mechanism of the hydroxide ion catalysed reaction (Scheme (VI-2)) involves rate limiting abstrac-



Scheme (VI-2)

tion of a hydrogen atom α to the nitrogen of the neutral oxaziridine, followed by rapid collapse to the products.

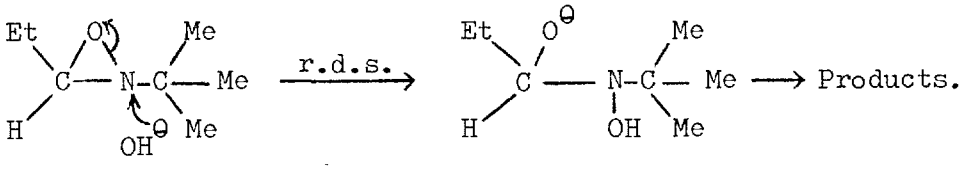
In the light of this deduction, it is possible to account for structural effects on the rate of hydrolysis. Oxaziridines with an ethyl or benzyl group attached to the nitrogen are the most reactive followed by the 2-isopropyl compound and then the 2-t-butyl compounds. Second order rate coefficients for catalysis by hydroxide ion for different oxaziridines are listed in Table (VI-21). The reactivity is exemplified by the rate ratios listed in the 3rd column, obtained by dividing the second-order rate coefficient for each oxaziridine by the value found for 2,3,3-triethyloxaziridine. As can be easily

seen all oxaziridines with a 2-primary alkyl group irrespective of other substituents show rates of decomposition of the same order of magnitude. Rate ratios for other compounds are best understood in terms of the expected stability of the carbanion resulting from α-proton abstraction, written in the last column of Table (VI-21). Compounds with a 2-t-butyl group obviously cannot react by this pathway and the observed rate in aqueous sodium hydroxide must arise from either thermal decomposition or the acid catalysed pathway with H_2O as catalyst (this will be very slow).

The observation that 2-isopropyl-3-ethyloxaziridine reacts 25 times slower than 2,3,3-triethyloxaziridine probably reflects steric hindrance to proton abstraction from the carbon atom with the gem-dimethyl group attached to it.

The high reactivity of the benzyl compound is expected from the resonance stabilization of the carbanion by the phenyl substituent. By analogy this is reflected in the higher acidity of phenoxide ion relative to methoxide ion (e.g. $Ph\text{-}O^{\ominus}$ $pK_A \simeq 10$ and $CH_3\text{-}O^{\ominus}$ $pK_A \simeq 18$).

From the above facts, it can be concluded that the hydroxide ion catalysed hydrolysis of oxaziridines involves the mechanism outlined in Scheme (VI-2), which is similar to that suggested by Emmons[6]. There is so far no evidence that $OH^{\ominus}$ attacks the oxaziridine ring directly, at the nitrogen or carbon atoms, (Scheme (VI-3)), as might be expected by analogy with reactions of epoxides. There is no evidence that $OH^{\ominus}$ is a nucleophilic catalyst in these reactions.



Scheme (VI-3)

Table (VI-21)

The Reactivity of Different Oxaziridines towards Hydroxide Ion ($t = 25.0 \pm 0.1^{\circ}C$)

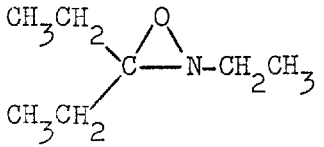
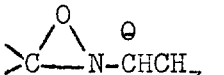
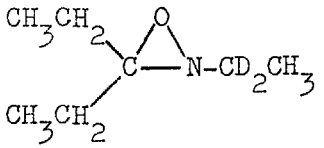
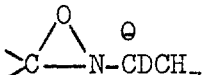
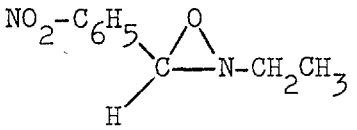
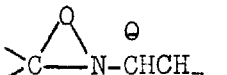
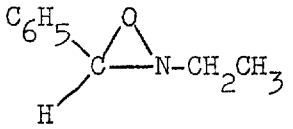
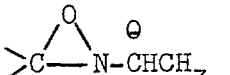
Substrate	$k_2^{OH^{\ominus}}$ mole^{-1}. l. min^{-1}.	Relative Reactivity Towards 2,3,3-Triethyloxaziridine	Hypothetical carbanion intermediate[b]
	4.3×10^{-1}	1	
	9.1×10^{-2}	0.2	
	(1.4)[a]	(3.3)	
	6.0×10^{-1}	1.4	

Table (VI-21) (continued)

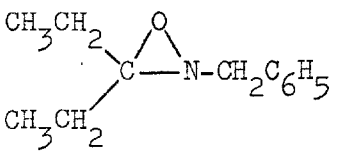
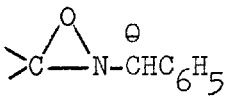
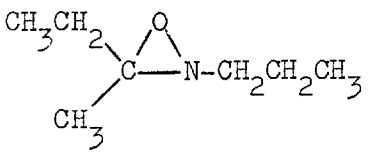
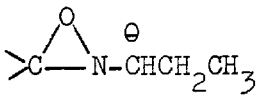
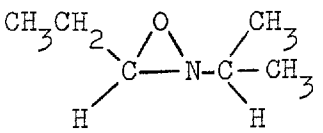
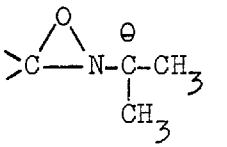
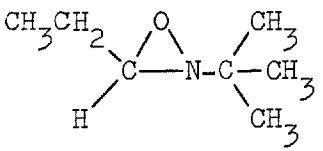
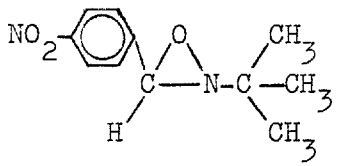
Substrate	$\underline{k}_2^{OH^{\ominus}}$ mole^{-1}. l. min^{-1}.	Relative Reactivity Towards 2,3,3-Triethyloxaziridine	Hypothetical carbanion intermediate[b]
	1.3 x 10	30	
	(5×10^{-1})[c]	(1.2)	
	1.7×10^{-2}	0.04	
	(8×10^{-4})[b]	(0.2×10^{-2})	-

Table (VI-21) (continued)

Substrate	$\underline{k}_2^{OH^\ominus}$ $mole^{-1}.\ l.\ min^{-1}.$	Relative Reactivity Towards 2,3,3-Triethyloxaziridine	Hypothetical carbanion intermediate[b]
	(1×10^{-4})[a]	(0.2×10^{-3})	-

a) Numbers in brackets are only approximate.

b) See Schemes (VI-2) and (VI-3).

c) $\underline{k}_2^{OH^\ominus} = 3.4 \times 10^{-1}$ $mole^{-1}.\ l.\ min^{-1}$ from reference (100).

VI.2.2 Reaction of 2,3,3-Triethyloxaziridine with Other Basic and Nucleophilic Catalysts

The conclusion that $OH^{\ominus}$ does not react via a nucleophilic pathway is not surprising in view of its strongly basic but weakly nucleophilic properties. Accordingly, reactions by several other reagents were also studied some of which had basic character (eg. phenoxide ion, dimethylamine, piperidine, 2,6-dimethylpiperidine) and other which were powerful nucleophiles (e.g. iodide ion, cyanide ion and thiocyanate ion).

The oxaziridine chosen for this study was the 2,3,3-triethyloxaziridine since the $OH^{\ominus}$ catalysed hydrolysis for this compound had been thoroughly investigated. Second order coefficients, k_2^N, obtained from data in Tables (VI-1) to (VI-10) are summarized in Table (VI-22).

A conventional Brönsted plot, obtained by plotting log k_2^N versus pK_A is shown in Fig (VI-4). A single line cannot be drawn satisfactorily through all the points.

The best straight line through most of the data has a low slope of 0.03, and this clearly shows that the rate constants bear little or no relationship with the pK_A'S of the catalysts. This is not entirely surprising as the reaction between iodide ion or thiocyanate ion and 2,3,3-triethyloxaziridine gave products arising from a total redox reaction in the iodide case, and a partial redox reaction in the thiocyanate occurring side by side with the normal basic hydrolytic pathway. Nonetheless, the similar reactivity of $PhO^{\ominus}$, $OH^{\ominus}$ and Me_2NH catalysts is puzzling unless these too react by different mechanisms.

However, the phenoxide ion reaction shows a primary isotope effect of 3.7 (Table (VI-17)), indicating that proton abstraction

Table (VI-22)

Nucleophilic Ring Opening of 2,3,3-Triethyloxaziridine

(25.0 ± 0.1°C)

Catalysts	pK_A	H_N [a]	E_N [b]	$10^{-1}\ k_2$ ($mole^{-1}.\ l.\ min^{-1}.$)
$OH^{\ominus}$	15.74	17.48	1.65	4.3
$PhO^{\ominus}$ (1) [d]	10.00	11.74	1.46	3.7
$PhO^{\ominus}$ (6) [d]	10.00	11.74	1.46	3.6
Me_2NH	10.73	12.47	(1.84) [c]	4.3
Piperidine	11.12	12.86	-	3.0
2,6-Dimethylpiperidine	11.07	12.81	-	7.8×10^{-1}
Cyanide	9.14	10.88	2.79	5.6×10^{-1}
Iodide	(-10.74)	(-9.00)	2.06	1.0
Thiocyanate	(- 0.74)	(1.00)	1.83	1.8
H_2O	-1.74	0.00	0.00	0.099×10^{-2}

a) $H_N = pK_A + 1.74$; $E_N = E_O + 2.60$; E_N is the standard electrode potential of the nucleophile $X^{\ominus}$ in the equilibrium reaction $2X^{\ominus} \rightleftharpoons X_2 + 2e^{\ominus}$, relative to that of a similar equilibrium for water[101].

b) E_N values taken from reference (101); numbers in brackets represent estimates.

c) E_N value for NH_3.

d) $PhO^{\ominus}$ (1) and $PhO^{\ominus}$ (6) represent buffer ratios of $[PhOH]/[PhO^{\ominus}]$ of respectively 1 and 6.

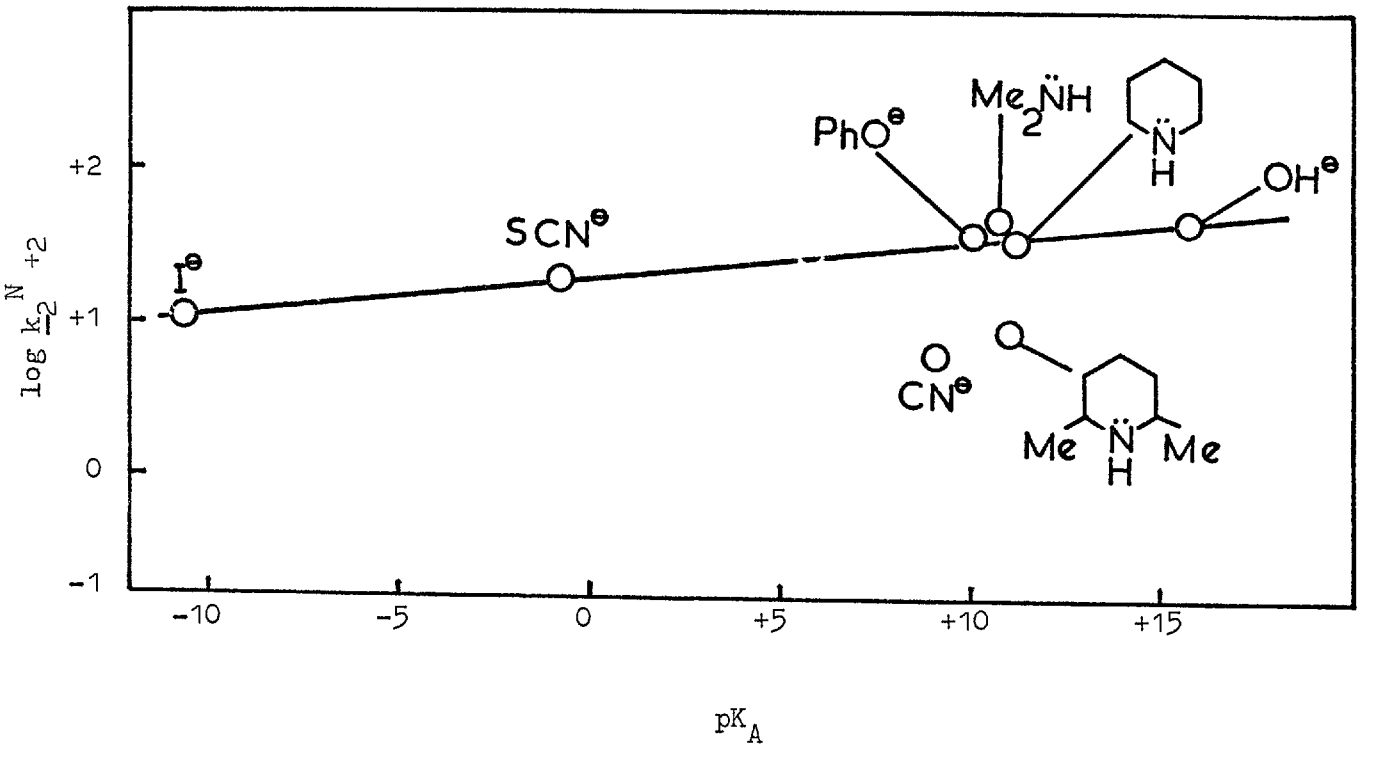
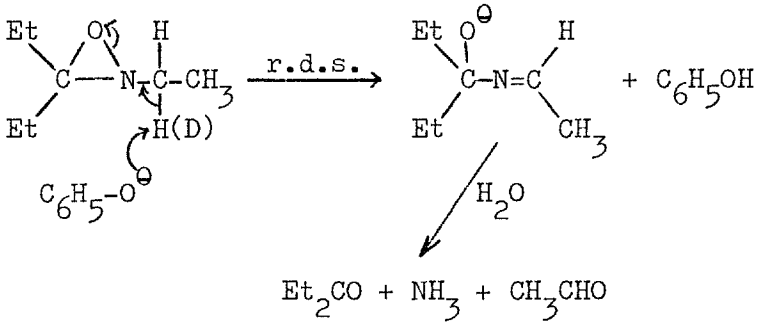


Fig. (VI-4). Brönsted plot for the hydrolysis of 2,3,3-triethyloxaziridine (25°C).

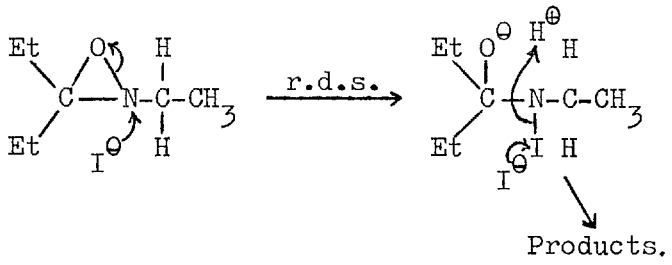
from the neutral oxaziridine* by the phenoxide ion is important. Also the thermodynamic parameters for the reaction, particularly a negative entropy of activation, $\Delta S^{\neq}$, of -22.6 cal. degree^{-1}. mole^{-1}, are close to those for hydroxide ion (Tables (VI-12) and (VI-13)). Radicals seem not to be involved in the reaction as an e.s.r. spectrum of the reaction between 2,3,3-triethyloxaziridine and $PhO^{\ominus}$ showed no signs of the presence of radicals. Also addition of galvinoxyl, a powerful radical trap, to the kinetic run did not alter the rate of the reaction (Table (VI-3)). Therefore the mechanism is probably the one outlined in Scheme (VI-4).



Scheme (VI-4)

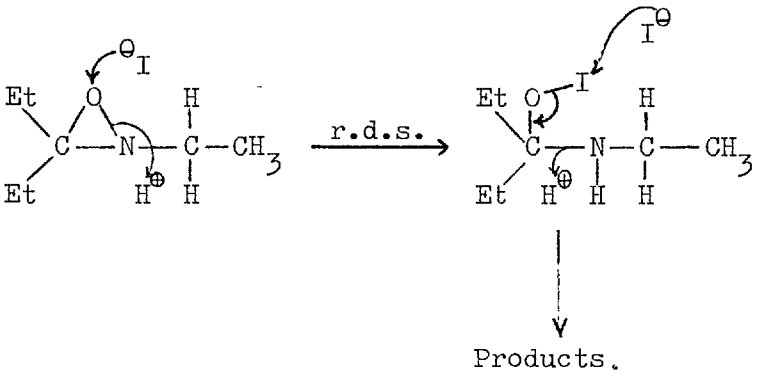
In the case of iodide ion catalysis no primary isotope effect ($0.8 \div 1$, Table (VI-17)) was observed and an altogether different type of product resulted: this suggests a mechanism involving either direct attack on the nitrogen or the oxygen atoms of the ring as outlined in Scheme (VI-5) and (VI-6). Although both mechanisms

* No PhOH catalysis was found in this reaction.



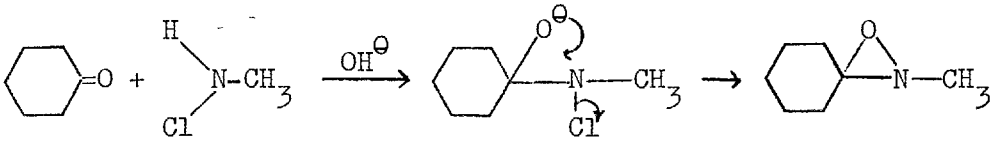
Scheme (VI-5)

are feasible, there are more arguments in favour of Scheme (VI-5). This mechanism is the reverse process to Schmitz's method (discussed



Scheme (VI-6)

in Part 1, Section I.3) for the preparation of oxaziridines (Scheme (VI-7).



Scheme (VI-7)

It also provides an explanation why the reaction with iodide ion is slower with oxaziridines bearing a 2-t-butyl group, where steric congestion of the nitrogen, but not of the oxygen atom, is considerable.

The fact that nucleophilic attack on N seems to be important for some catalysts, in addition to base-catalysed hydrolysis, suggests the application of the Edward's oxi-base equation[102,103] (Eq. (VI-6)) which correlates nucleophilic reactivity with a linear combination of two model processes.

$$\log(k_2^N/k_2^O) = aE_N + bH_N \qquad \text{(VI-6)}$$

In the above equation k_2^N refers to a process in which the substance Nu is the nucleophile, and k_2^O refers to the analogous processes in which water is the nucleophile. H_N is a measure of the basicity of the nucleophile, defined by (Eq. (VI-7)) and E_N is the standard

$$H_N \equiv pK_A + 1.74 \qquad \text{(VI-7)}$$

electrode potential of the reagent Nu^- in the equilibrium (Eq. (VI-8)), relative to that of a similar equilibrium for water[102,103].

$$2Nu^{\ominus} \overset{E^o}{\rightleftharpoons} Nu_2 + 2e^{\ominus} \qquad \text{(VI-8)}$$

$$2H_2O \rightleftharpoons H_4O_2^{2\oplus} + 2e^{\ominus};\ E^o = -2.60v$$

E_N is defined by (Eq. (VI-9)).

$$E_N \equiv E^o + 2.60 \qquad \text{(VI-9)}$$

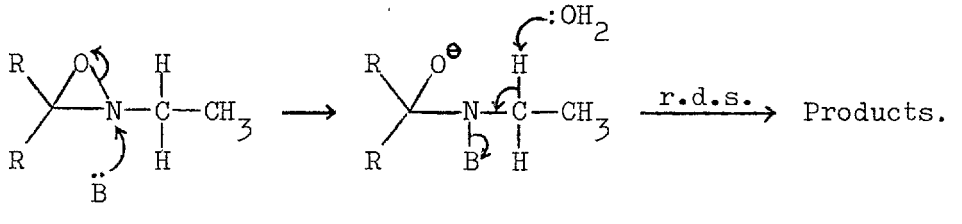
The parameters a and b are empirical and characteristic of the substrate undergoing reaction with the nucleophile.

For practical purposes (Eq.(VI-6)) can be written as (Eq. (VI-10))

so that determination of the parameters a and b can be made by plotting $\left\{(1/E_N)\ \log(k_2^N/k_2^o)\right\}$ versus $\left\{H_N/E_N\right\}$, as shown in Fig. (VI-5). In this plot the values of E_N of piperidine and dimethyl-

$$\frac{1}{E_N}\ \log\frac{k_2^N}{k_2^o} = a + b\ \frac{H_N}{E_N} \qquad \text{(VI-10)}$$

amine were assumed to be the same as for ammonia and as a result these points are only approximate. The value of b, calculated from the slope of the plot is 0.095, and the value of a, calculated from the intercept is 0.78. These coefficients provide a rough guide to the extent to which the base catalysed pathway and the nucleophilic pathway contribute to the overall rate. Clearly the nucleophilic pathway is very important. This still leaves the question of why large isotope effects, indicative of a base catalysed proton abstraction are observed for the phenolate ion reaction. It is possible that even phenoxide and hydroxide ions attack the N atom, to give an intermediate that suffers base catalysed proton abstraction in the slow step (Scheme (VI-7). However direct evidence for this pathway is lacking. For example no hydrazine products could be



Scheme (VI-7)

found for catalysis by amines, although evidence of p-coupling was found for the phenolate ion reactions and there was no evidence of a second order dependence on $PhO^{\ominus}$ as might be expected for this

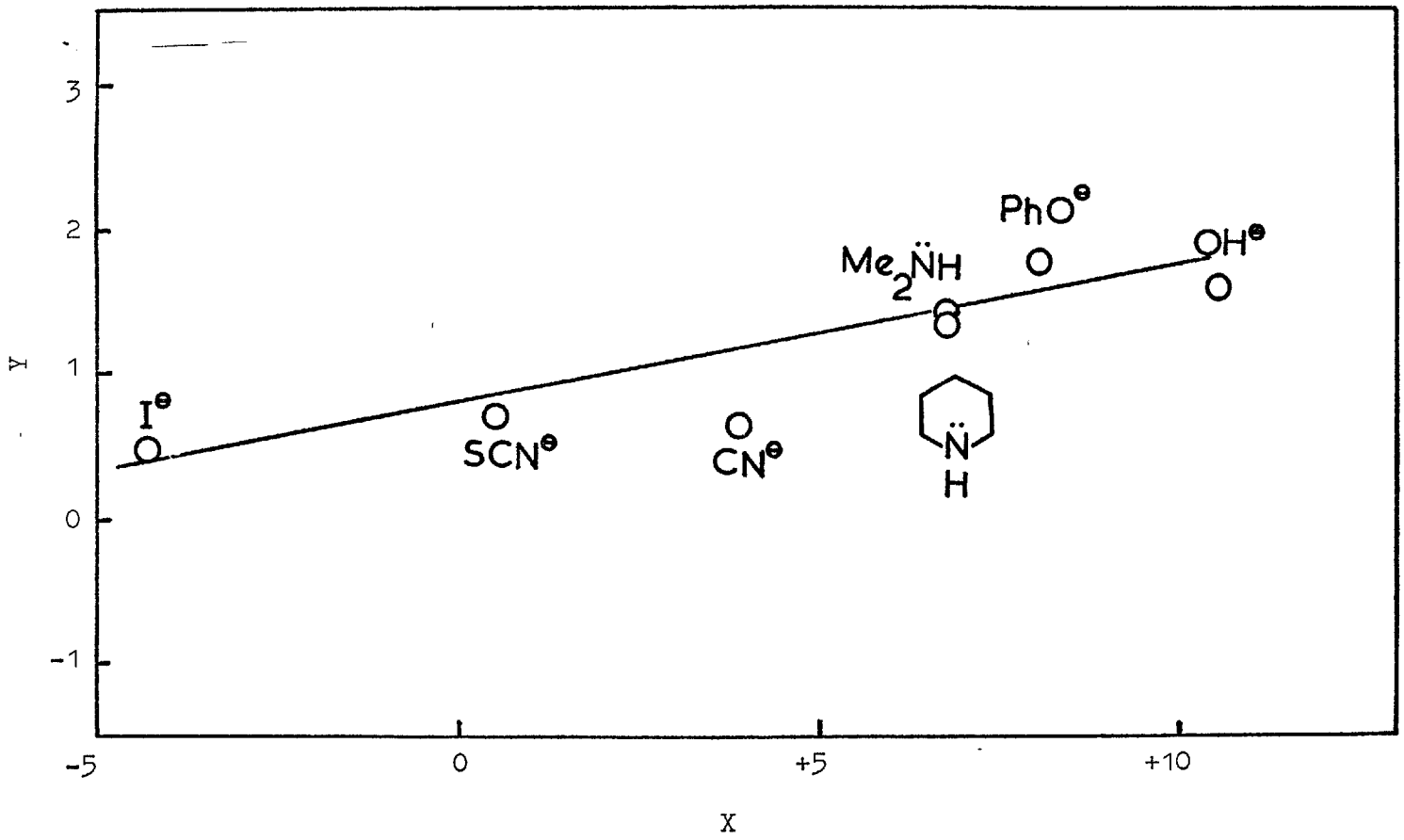


Fig. (VI-5). Application of Edward's equation to the hydrolysis of 2,3,3-triethyloxaziridine (25°C): $X=H_N/E_N$, $Y=1/E_N \log(k_2^N/k_2^o)$.

mechanism.

Conclusion

The experimental results show that the base catalysed ring opening of oxaziridines is primarily a function of their structure, and that it is usually a heterolytic bimolecular process, involving rate-limiting abstraction of the proton $\underline{\alpha}$ to the nitrogen atom of the ring.

A conventional Brönsted plot does not give a satisfactory correlation for all points: it shows a β of 0.03, indicating very little influence of basicity in the rates of ring opening.

A more satisfactory correlation was obtained by the use of Edward's equation of nucleophilicity. The parameters $\underline{a}$ and $\underline{b}$ are consistent with two different mechanisms operating, and show that the reaction is more sensitive to the nucleophilicity of the catalyst than its basicity.

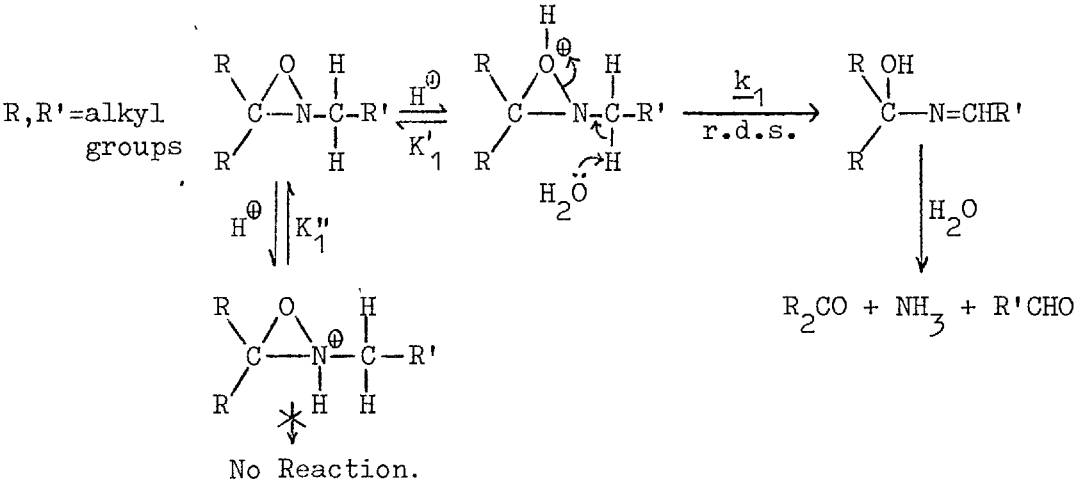
Chapter VII

Conclusions from the Study of Hydrolysis of Oxaziridines

The hydrolysis of several oxaziridines was studied under acid and basic conditions.

The acid hydrolysis seems to proceed with a rapid pre-equilibrium for protonation, followed by the breakdown of the conjugate acid.

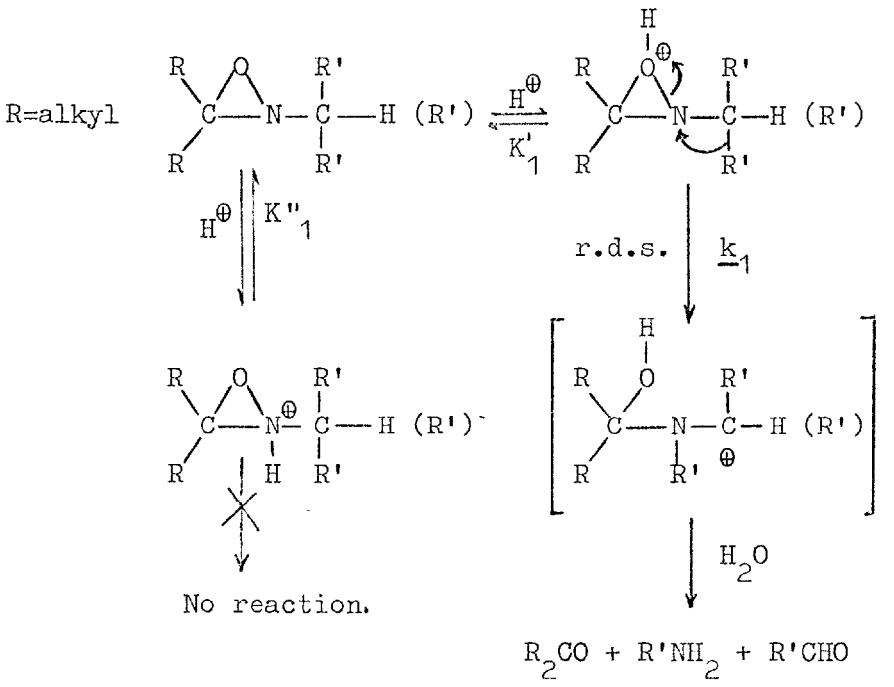
Two possible forms of the conjugate acid seem to be present, the N-protonated and the O-protonated. The N-protonated form is stable and does not lead to reaction. The O-conjugate acid is the form which successfully leads to reaction by N-O cleavage, synchronous with α-proton abstraction by a water molecule, acting as a base (Scheme (VII-1)) as in the case of the primary 2-alkyl



Scheme (VII-1)

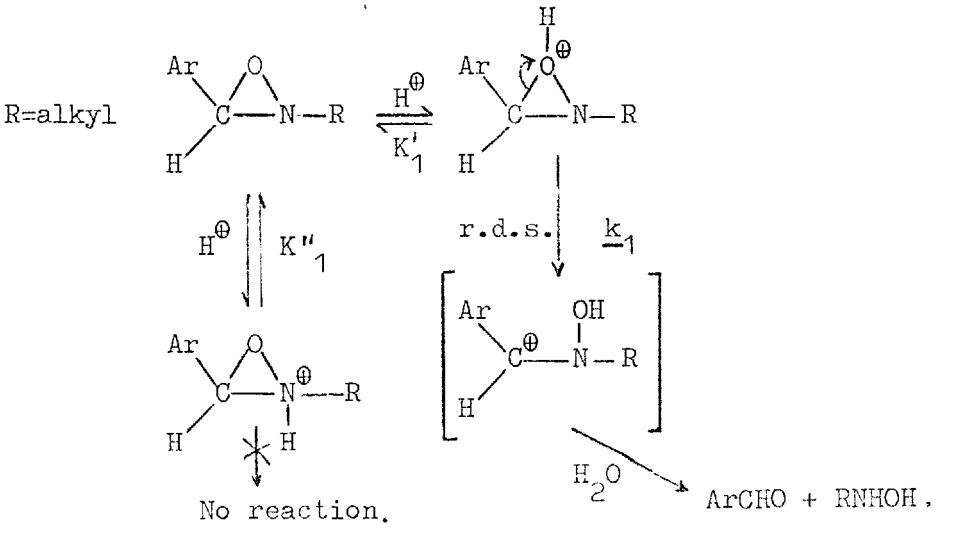
oxaziridines, or by extensive migration of a group α to the electron deficient nitrogen of the ring (Scheme (VII-2)) as in

the case of the secondary 2-alkyl oxaziridines or tertiary 2-alkyl oxaziridines.



Scheme (VII-2)

When there is an aryl group in position 3 the O-conjugate acid tends to break by C-O bond cleavage as in this case there is a possibility of stabilization of the developing carbonium ion. (Scheme (VII-3)).



Scheme (VII-3)

All oxaziridines proved to be weak bases, their pK_As ranging from -2.5 to +0.30.

The dependence of the acid hydrolysis on the H_o function proved to be intermediate between 0.90 and 0.53, and thus no clear cut mechanism basedon the Zücker-Hammett hypothesis could be assigned.

Bunnett treatment of the data for the primary 2-alkyl oxaziridines showed w values in the range of +5.7 to +7.5 at intermediate acidities which according to Bunnett classification correspond to an acid catalysed reaction in which water is acting as a proton transfer agent.

All the previous findings agree well with the work of Butler and Challis[42,43] and of Emmons[6].

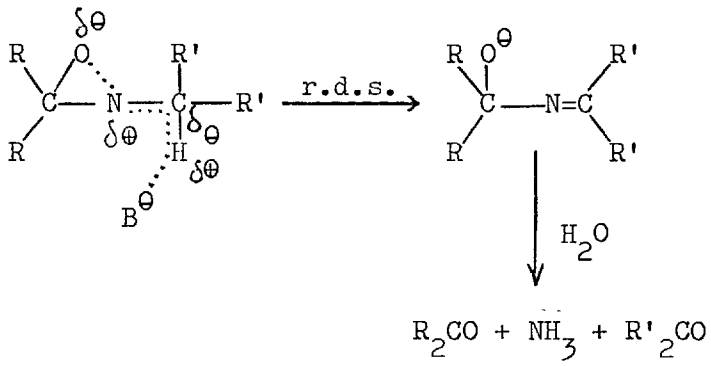
The basic hydrolysis proved to be a heterolytic bimolecular process, involving rate-limiting abstraction of the proton α to the N atom of the ring of the neutral oxaziridine.

A plausible mechanism is the one outlined in Scheme (VII-4), which is close to that postulated by Emmons[6].

There was no evidence in favour of $OH^{\ominus}$ acting as a nucleophile towards the C or N atoms of the ring as in the case of epoxides[35].

Structural differences in the nature of R' are shown in the differences in the rates and can be easily explained in terms of the stability of the incipient carbanion $\left[RRC\overset{O}{\diagup\diagdown}N\text{-}CR'R'\right]^{\ominus}$ formed by α-proton abstraction.

Finally, the products of hydrolysis can be easily accounted for



Scheme (VII-4)

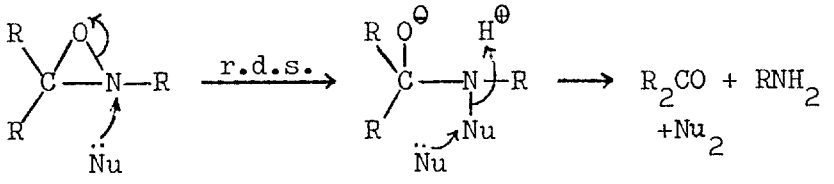
by the above scheme.

The finding that $OH^{\ominus}$ did not act as a nucleophile led to the investigation of the reactions between 2,3,3-triethyloxaziridine and different nucleophiles, some with partial basic character.

A satisfactory correlation was obtained when Edward's oxi-base equation was applied. The parameters a and b are consistent with the existence of a basic pathway and a nucleophilic one of much more importance.

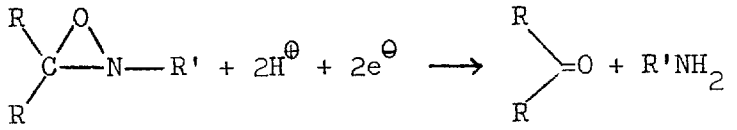
Though nucleophilic attack can operate at the C,O or N atoms of the oxaziridine ring, attack at N seems likely as it constitutes the reverse of Schmitz's method for the preparation of oxaziridines from ketones and chloramines.[21-24] Another piece of evidence in favour of N-attack is the fact that 2-t-butyloxaziridines release iodine at a much slower rate than primary 2-alkyloxaziridines; steric congestion around the N atom seems to be responsible for this fact.

A possible mechanism is outlined in Scheme (VII-5). It is



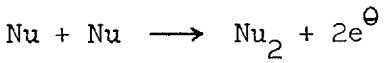
Scheme (VII-5)

formally equivalent to a redox reaction where the oxaziridine gets reduced (Scheme (VI-6)) and the nucleophile



Scheme (VII-6)

Nu oxidised (Scheme (VII-7)).



Scheme (VII-7)

Though it was not possible to isolate and characterise all the products from the nucleophilic reactions these were invariably connected with the presence of an oxidation process involving the nucleophile.

PART 3

E X P E R I M E N T A L

CHAPTER VIII

The Experimental Details

The experimental details concerning the preparation and purification of oxaziridines and other reagents, kinetic methods, product analysis and the method of investigating the site of protonation of the substrates are described in the following sections.

All the u.v. spectra were measured with either a Unicam SP-700 or a Unicam SP-1800 spectrophotometer; n.m.r. spectra were obtained with a Varian T-60, a Varian A-60 (by Mrs A.I. Boston) or with a Varian HA-100 instrument (by Dr L.M. Twanmoh and Mr P.N. Jenkins). Infrared spectra were obtained (normally as a thin film or as a Nujol mull between two sodium chloride plates) with a Perkin-Elmer 700 and a Unicam SP-800 instrument. The refractive indices were measured with a Hilger and Watts refractometer. Melting points were taken on a Kofler melting point apparatus and are uncorrected. Mass spectra were obtained with a M.S.9 high resolution mass spectrometer (by Mrs J. Lee and Mr J. Bilton) using direct sample injection. Thin layer chromatography was carried out on Silica Gel G (Merck) plates, developed (15 cm) with benzene-dichloromethane (1:1). The pH measurements were carried out with a Radiometer PHM 26. Microanalyses were performed by the analysts of Imperial College Chemistry Department Microanalysis Service.

VIII.1 Preparation and Purification of Materials

VIII.1.1 Substrates

Preparation of Imines - The imines employed as starting materials were all prepared by condensation of the appropriate amine and ketone or aldehyde.(104)

Since the preparative procedures of these compounds were generally very similar only a typical example will be described.

Preparation of Isoamylidene-ethylamine - 99.0g (2.2 moles) of ethylamine were cooled in an ice-bath. 172g (2.0 moles) of diethyl-ketone were added dropwise over a period of three hours while the contents were stirred vigorously. The reagents were left in contact at room temperature for four days with occasional shaking. Then sodium hydroxide pellets (c.a. 3g) were added and the aqueous layer which subsequently formed was separated. The reaction mixture was distilled to give 55g of imine. b.p. $60^{\circ}/69$mm, $n_{20^{\circ}.5}$ 1.4230.

Physical data of all the imines prepared are listed in Table (VIII-1).

Preparation of Oxaziridines - Oxaziridines were prepared following the procedure of Emmons(6) by oxidation of the corresponding imine with peracetic acid. A typical oxidation will only be described. Due to their marked instability they were stored in the dark at c.a. -5°C and used within a few weeks of preparation.

Preparation of 2,3,3-Triethyloxaziridine - A peracetic acid solution was prepared first by mixing carefully 11.5 ml of hydrogen peroxide (90%) with 60g of acetic anhydride containing 2 drops of concentrated sulphuric acid. This was added dropwise to an ice-cooled solution of isoamylidene-ethylamine (55g). The reaction

Table (VIII-1)

Physical Properties of Imines, $R^1R^2C{=}NR^3$

			B.p.			Lit. B.p.		
R^1	R^2	R^3	°C	Mm	n(°C)	°C	Mm	Ref.
Et	Me	n-Bu	152	760	1.4235 (24.0)	151	760	(42)
Et	Et	Et	60	96	1.4230 (20.5)	52-54	54	(6)
Et	H	t-Bu	104	760	1.4072 (22.5)	104	760	(42)
Et	Et	$CH_2C_6H_5$ a)	65	0.4	1.5254 (15.5)	-	-	-
Et	Et	$CH(CH_3)C_6H_5$	65	0.1	1.5135 (20.5)	64	0.2	(6)
Et	H	i-Pr b)	91-93	760	-	-	-	-
p-$O_2NC_6H_4$	H	Et	75.5	M.p.	-	75-76	M.p.	(6)
p-$O_2NC_6H_4$	H	tBu	74	M.p.	-	74-75	M.p.	(6)
C_6H_5	H	Et	80	10	1.5400 (22.5)	101	13	(105)

a) Infrared stretching (C=N) at 1660 cm^{-1}.

b) Infrared stretching (C=N) at 1660 cm^{-1}.

mixture was stirred until the temperature had risen to above 25°C and was then washed in succession with distilled water (200 ml), cooled 15% ammonia solution (2 x 100 ml), cooled 10% sulphuric acid solution (50 ml) and distilled water again (100 ml). It was then dried over magnesium sulphate and distilled under reduced pressure. The yield of the crude product was 33 g, which was then distilled under reduced pressure, b.p. 40°/10 mm, $n_{20.5}$ 1.4218. NMR described in Table (VIII-3).

The only oxaziridine which was not obtained by oxidation of the corresponding imine was 2-methyl-3,3-pentamethyleneoxaziridine. In this case a procedure described by Schmitz[21] was used as described below.

Preparation of 2-Methyl-3,3-pentamethyleneoxaziridine - An ether solution of N-chloromethylamine was first prepared by adding 12% aqueous sodium hypochlorite (265 ml) to 10% aqueous methylamine (125 ml) over a period of about 5 minutes. The chloramine was extracted with ether (3 x 100 ml), washed with a saturated solution of potassium bicarbonate and dried over anhydrous potassium carbonate. The amount of N-chloramine in the ether solution was determined by titrating the iodine released from KI against $Na_2S_2O_3$. The yield of product was 0.99 mole. The N-chloramine solution was used shortly after being prepared.

To 40 ml (0.4 moles) of cyclohexanone, cooled to ice-temperature, 250 ml of 2N sodium hydroxide, was added, followed by 0.5 moles of N-chloromethylamine in c a. 300 mls of ether. The reaction mixture was stirred and allowed to reach room temperature. The ether phase was separated and washed first with cold 1N acetic acid solution (2 x 100 ml), then cold sodium bicarbonate saturated solution (100 ml) and finally dried overnight with anhydrous potassium carbonate. The ether was removed under reduced pressure, to yield

29.0 g of crude product, 2-methyl-3,3-pentamethyleneoxaziridine. The compound was distilled under reduced pressure, b.p. 63-64°/13 mm, n_{23}^{o} 1.4570, active oxygen 90.0%, NMR described in Table (VIII-3).

Preparation of 2-($\alpha_1\alpha'$-$\left[{}^{2}H_1\right]_2$-Ethyl)-3,3-diethyloxaziridine - This oxaziridine was prepared by the usual oxidation of the deuteriated imine with peracetic acid as described previously. The deuteriated imine was obtained from the corresponding amine, itself prepared by reduction of the deuteriated nitroethane with tin and hydrochloric acid.

Preparation of $\alpha_1\alpha'$-$\left[{}^{2}H_1\right]_2$-nitroethane - A small piece of clean sodium was added cautiously to 500 ml of heavy water (D_2O) containing approximately 0.99 atom fraction of deuterium. The pH of the solution was checked and found to be approximately 11. Then 45.0 g (0.57 moles) of nitroethane was added and the mixture was gently heated until the solvent refluxed with efficient stirring for c a. 18 hours. The heterogeneous reaction mixture was then cooled with ice and several drops of concentrated deuteriosulphuric acid[a)] were added to neutralize the base. The layer corresponding to the deuteriated nitroethane was separated and the aqueous phase was further extracted with anhydrous diethylether(2 x 100 ml). The solvent was evaporated under reduced pressure and the nitroethane was distilled at atmospheric pressure: The yield of product 34.8 g, b.p. 112-114°C, n_{18}^{o} 1.3940, NMR showed complete disappearance of hydrogens α to the nitro group and collapse of the ethyl pattern to a singlet, corresponding to the methyl group.

a) Kindly supplied by Dr B.C. Challis.

Reduction of α, α'-$\left[^2H_1\right]_2$-Nitroethane - To 275.0 g (1.52 mole) of granulated tin, 30 ml of water, 40.0 g (0.52 mole) of α, α'-$\left[^2H_1\right]_2$-nitroethane and, dropwise, 459 ml (3.12 mole) of concentrated hydrochloric acid were successively added. The well stirred reaction mixture was heated gently at 50°C for two days until all the tin dissolved. Then 176 g (4.68 mole) of sodium hydroxide pellets were added to the ice-cooled reaction mixture to neutralise the α, α'-$\left[^2H_1\right]_2$-ethylamine hydrochloride. The amine (17.0 g) was driven off by heating the reaction mixture at about 60°C and bubbling nitrogen gas through the system, then dried in a column packed with sodium hydroxide pellets and collected in two liquid air traps. An n.m.r. spectrum of the amine hydrochloride in trifluoroacetic acid showed no trace of the methylene protons $\underline{\alpha}$ to the amino group, confirming complete exchange with deuterium.

Condensation of α, α'-$\left[^2H_1\right]_2$-Ethylamine with Diethylketone - To 17.0 g (0.38 mole) of α, α'-$\left[^2H_1\right]_2$-ethylamine was added 42.1 g (0.49 mole) of diethylketone and these reagents were left in contact for six days, with occasional shaking. Some sodium hydroxide pellets were subsequently added, the aqueous layer which separated was discarded and the imine was distilled under atmospheric pressure. The product yield was 10.0 g, b.p. 154°/760 mm, NMR (TMS as internal standard) showed the following signals and chemical shifts: τ 8.85, dbl. trip., (6H); 8.80, s., (3H); 7.67, dbl. qu., (4H).

Preparation of 2-(α, α'-$\left[^2H_1\right]_2$-Ethyl)-3,3-diethyloxaziridine - The deuteriated imine, previously described, was oxidised using the normal procedure and the 2-(α, α'-$\left[^2H_1\right]_2$-ethyl)-3,3-diethyl-oxaziridine was obtained. The yield was c a. 2 g, b.p. 40°C/10 mm;

Table (VIII-2)

Physical Properties of Oxaziridines[a], $R^1R^2C\overset{O}{\diagup\!\diagdown}NR^3$

R^1	R^2	R^3	B.p. °C	B.p. Mm	n(°C)	Active Oxygen	Lit. B.p. °C	Lit. B.p. Mm	Ref.
Et	Me	n-Bu	60	10	-	88%	52	7	42
Et	Et	Et	40	10	1.4218 (20.5)	100%	62	19	6
Et	H	t-Bu	45	0.9	1.4240 (20.0)	74%	56	25	42
Et	Et	$CH_2C_6H_5$[b]	75-76	1.35×10^{-4}	1.5258 (22.2)	89%	-	-	-
Et	Et	$CH(CH_3)C_6H_5$	55-56	4.00×10^{-4}	1.5122 (20.0)	103%	-	-	6
Et	H	i-Pr[c]	50	20	1.4149 (25.0)	96%	-	-	-
p-$O_2NC_6H_4$	H	Et	42-43	M.p.	-	100%	34-35	M.p.	6
p-$O_2NC_6H_4$	H	t-Bu	62-63	M.p.	-	108%	65-67	M.p.	6
C_6H_5	H	Et[d]	73	1.7	1.5202 (22.5)	97%	-	-	-

Table (VIII-2) (continued)

R^1	R^2	R^3	M.p. °C	M.p. Mm	n(°C)	Active Oxygen	Lit. B.p. °C	Lit. B.p. Mm	Ref.
$-(CH_2)_5-$		Me	64	13	1.4570 (23.0)	90%	53-54	8	21

a) NMR data listed in Table (VIII-3).
Infrared spectra showed a peak at c.a. 1400 cm^{-1}.

b) Microanalysis, calculated for $C_{12}H_{17}NO$: C, 73.35; H, 8.96; N, 7.32;
Found: C, 75. 64; H, 8.89; N, 7.46.

c) Microanalysis, calculated for $C_6H_{13}NO$: C, 62.57; H, 11.37; N, 12.16;
Found: C, 62.51; H, 11.25; N, 12.13.

d) This oxaziridine proved to be very unstable. The NMR and IR spectra were both consistent with its structure but both showed traces of benzaldehyde that could not be removed by successive destillations.

Table (VIII-3)

NMR Data for Several Oxaziridines, $R^1R^2C(O)NR^3$

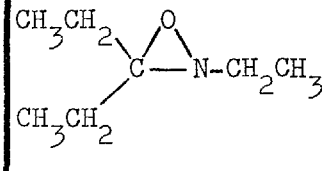
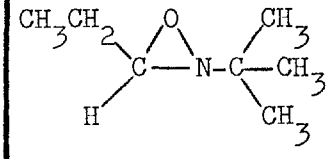
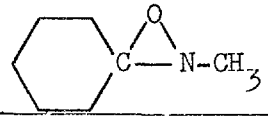
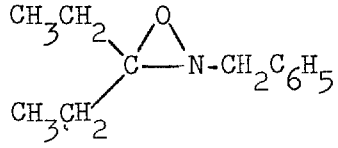
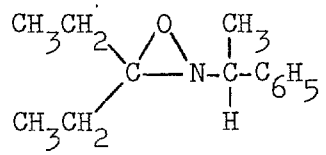
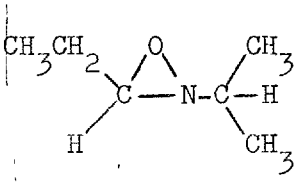
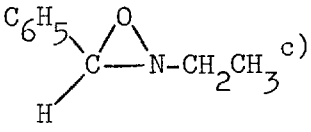
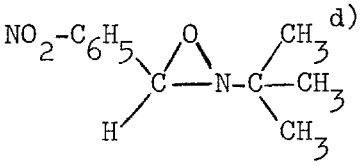
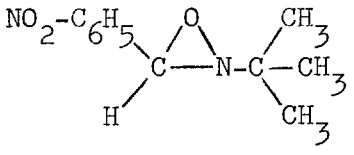
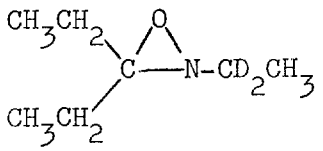
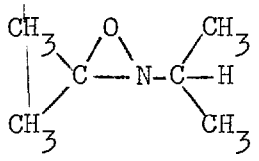
Compound	Solvent	Chemical Shift[a] (τ)	Multiplicity of peaks	Integration
	CCl_4	9.06	3	6
		8.94	3	
		8.83	3	3
		8.32	m[b]	4
		7.21	4	2
	$CDCl_3$	9.00	1	9
		8.92	3	3
		8.44	m	2
		6.16	3	1
	CCl_4	8.40	m	10
		7.43	1	1
	$CDCl_3$	9.10	3	6
		8.95	3	
		8.21	m	4
		6.05	1	2
		2.65	1	5
	CCl_4	9.25	3	6
		9.17	3	
		8.52	2	3
		8.44	m	4
		6.45	4	1
		2.71	1	5
	$CDCl_3$	8.93	3	3
		8.85	2	6
		8.73	2	
		8.37	m	2
		7.85	7	1
		6.32	3	1

Table (VIII-3) (continued)

Compound	Solvent	Chemical Shift[a] (τ)	Multiplicity of peaks	Integration
 A,B	CCl_4	A-9.17	3	3
		B-8.94	3	3
		A-7.76	m	2
		B-7.45	m	2
		B-5.83	1	1
$\frac{B}{A} = 1.9$		A-5.07	1	1
		A,B-2.80	1	5
 A,B	CCl_4	A-8.93	3	3
		B-8.70	3	3
		A-7.52	m	2
		B-7.16	m	2
		B-5.49	1	1
$\frac{B}{A} = 2.2$		A-4.80	1	1
		A,B-2.42-1.73	m	4
	$CDCl_3$	8.83	1	9
		5.18	1.	1
		1.69-2.42	m	4
	CCl_4	9.06	3	6
		8.94	3	
		8.83	1	3
		8.32	4	4
	$CDCl_3$	8.92	2	3
		8.76	2	3
		8.50	2	6
		7.40	7	1

a) Referred to the TMS signal (internal standard).
b) m=multiplet; chemical shift referred to the centre of the multiplet.
c) Cis- and trans- forms apparent; (A,B).
d) Cis and trans forms apparent (A,B); reference (92).

NMR data listed in Table (VIII-3), active oxygen 70% (this oxaziridine was slightly contaminated with diethylketone); mass spectra showed M^+ 131.

Physical data of all the oxaziridines prepared are listed in Tables (VIII-2) and (VIII-3).

VIII.1.2 Reagents

"Analar" grade perchloric, hydrochloric, sulphuric and glacial acids, obtained from Hopkin and Williams Ltd., were used without further purification. Standard solutions of these acids were prepared by dilution with de-ionised water which had been boiled-out to remove oxygen and then kept under nitrogen. Their concentrations were checked by titration against B.D.H. standard sodium hydroxide solutions using either phenolphthalein or methyl red as indicators.

All buffer solutions were made by adding measured amounts of B.D.H. standard sodium hydroxide to a measured amount of the buffer acid concerned. The phenol buffers were made by the same method, using freshly made stock solutions of "AnalaR" grade phenol, to avoid decomposition.

Salts like sodium chloride, sodium perchlorate, potassium iodide, potassium thiocyanate, potassium cyanide, trisodium phosphate and monosodium phosphate were "AnalaR" grade and were used without further purification.

Piperidine, 2,6-dimethylpiperidine and dimethylamine were purified via recrystallization of their hydrochlorides. They were easily prepared by addition of a 6N, methanolic solution of hydrochloric acid into an ice-cooled ethereal solution of the respective amine. The hydrochloride salt precipitated in a state of high purity

but when necessary was further recrystallised from anhydrous ethanol.

The amines and carbonyl compounds employed in the preparation of the imines were carefully dried and distilled prior to use.

Hydrogen peroxide (90%), used in the preparation of peracetic acid, was kindly supplied by Laporte Industries Ltd.

Deuterium oxide, supplied by Koch Light, contained 99.7% deuterium and was used without further purification.

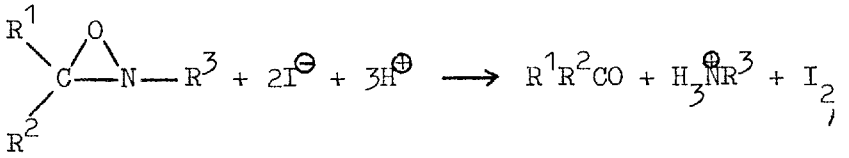
The solutions of sodium deuteroxide were prepared by dissolving a calculated amount of sodium metal in deuterium oxide and titrating the solution with standard hydrochloric acid, using phenolphtalein as indicator. In these kinetic runs the scale of the reaction was reduced by half.

All other reagents and solvents were used as commercially available and without further purification.

VIII.2 The Kinetic Details

VIII.2.1 The Kinetic Method

The rates of hydrolysis of oxaziridines in aqueous acid solution at 25°C were determined by utilising their oxidising properties, namely the ability to oxidise iodide ion to iodine under acid conditions. The iodine so liberated can then be titrated with sodium thiosulphate using sodium starch glycollate as indicator (Schemes (VIII-1) and (VIII-2)).



Scheme (VIII-1)

$$I_2 + 2S_2O_3^{2\ominus} \longrightarrow 2I^{\ominus} + S_4O_6^{2\ominus}$$

Scheme (VIII-2)

In practice a c a. 5 x 10^{-3}M solution of oxaziridine in perchloric acid (100 mls) was prepared by direct addition of substrate to the reaction flask, kept at 25.0°C, followed by efficient shaking to dissolve the compound. The kinetic flask was returned to the thermostat tank to equilibrate thermally before samples were taken (usually 4 min. was allowed for this when the half life of the reaction under study was longer than 40 minutes). The time of removing the first aliquot was taken as time zero. The rate of decomposition of the oxaziridine was followed by taking successive aliquots of 10 mls at timed intervals and running them into a mixture of 10% potassium iodide (1 ml) and sodium bicarbonate (c a. 0.5 g). As noted above, under acid conditions the unhydrolysed oxaziridine releases iodine from the iodide solution, while the bicarbonate reacts to give off carbon dioxide, which displaces any oxygen from the titrating vessel and minimises release of iodine by aerial oxidation (Scheme (VIII-3)). Also the excess

$$4I^{\ominus} + O_2 + 4H^{\oplus} \longrightarrow 2I_2 + 2H_2O$$

Scheme (VIII-3)

potassium iodide minimises loss of iodine due to its appreciable volatility, by forming the stable tri-iodide ion $I_3^{\ominus}$ (Scheme (VIII-4)).

$$I_2 + I^{\ominus} \longrightarrow I_3^{\ominus}$$

Scheme (VIII-4)

After allowing the quenched reaction sample to stand for 5 minutes, it was diluted with 30 ml of water (deionised, boiled for 10 minutes to remove dissolved oxygen and kept under nitrogen) and the liberated iodine was titrated with 0.01N sodium thiosulphate to the starch end point.

The time required for the unhydrolysed oxaziridine to react with potassium iodide in the quenching solution was found to depend on the structure of oxaziridine. For those bearing a primary alkyl (or benzyl) group attached to the nitrogen of the ring, the standard time of 5 minutes was sufficient. However, the release of iodine from oxaziridine bearing an isopropyl or a t-butyl group on nitrogen was found to be much slower and the quenching period had to be increased to 15 minutes and 30 minutes respectively. This does not appear to affect the accuracy of the method, which is reasonable because the rates of hydrolysis of these compounds in dilute aqueous acid are known to be very slow.

The hydrolysis rates of oxaziridines in aqueous alkaline or neutral solutions were measured by the method described above with a slight alteration. The aliquots were withdrawn at timed intervals but the quenching mixture, apart from 2 ml of 10% potassium iodide solution and 0.5 g of sodium bicarbonate also contained 10 ml of glacial acetic acid to acidify the media. The iodine was then titrated with sodium thiosulphate as described above.

The runs performed with potassium iodide were followed basically by the same method except for the fact that since iodine was itself a by-product of the reaction, it was first titrated with sodium thiosulphate under basic conditions. Then 10 ml of glacial acetic acid were added and the unhydrolysed oxaziridine was estimated by

this second titre of thiosulphate.

The time allowed for the quenching reaction to proceed was essentially the same as for the acid hydrolysis.

All runs were done under pseudo-first order conditions, by working with a concentration of oxaziridine at least 10 times less than the concentration of the catalyst. When the concentration of catalyst ($SCN^{\ominus}$, $CN^{\ominus}$ and $I^{\ominus}$) was of the order of 10^{-2}M, the conditions for application of pseudo-first order kinetics were not fully met, due to consumption of catalyst during the reaction, probably because of interaction with the products. The problem was, however, partially solved, by lowering the initial concentration of oxaziridine.

First order rate constants for the disappearance of substrate were obtained by plotting the "log." of "titre" (ml) of thiosulphate against "time" and drawing the best straight line through the experimental points.

An infinity point was taken after 10 half-lives and usually indicated complete hydrolysis of the substrate.

Temperature at which the runs were done was usually $25.0^{\circ} \pm 0.1^{\circ}C$, although some kinetic runs were carried out at different temperatures to determine the enthalpy and entropy of the reaction.

When buffers were used, the value of the pH, calculated by the use of Sörensen equation, found to be in close agreement with that measured experimentally with the pH-meter.

VIII.2.2 Typical Kinetic Runs in Acidic Solution

To illustrate the conditions under which the reactions were studied some examples are given overleaf.

The results refer to an observed first order rate coefficient (k_o) defined by (Eq. (VIII-1))

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous buffer of acetate-acetic acid

Run 109

$[CH_3COONa]$ = 0.5M Temperature = 25.0°C

$[CH_3COOH]$ = 0.5M

Ionic strength 1.0, adjusted with $NaClO_4$

$[Na_2S_2O_3]$ = 0.010N

Time (hours)	a_t (ml)	% Reaction	$10^2 . k_o$ ($hr.^{-1}$)
0.00	15.40	-	-
3.03	12.13	20.7	8.0
4.57	10.65	31.0	8.1
6.67	8.90	42.5	8.3
8.00	8.14	47.4	8.1
11.98	5.89	62.1	8.1
23.92	2.30	85.6	8.1
∞	0.09	-	-

Mean value of k_o = 8.1×10^{-2} $hr.^{-1}$ = 1.4×10^{-3} $min.^{-1}$

Hydrolysis of 2-(α,α'-$\left[{}^{2}H_{1}\right]_{2}$-Ethyl)-3,3-diethyloxaziridine in aqueous $HClO_4$

Run 78

$[HClO_4]$ = 2.61M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (hours)	a_t (ml)	% Reaction	$10^2 \cdot k_o$ ($hour^{-1}$)
0.00	8.20	-	-
2.38	7.77	5.2	2.3
4.53	6.68	18.5	4.5
6.80	6.42	21.7	3.6
8.62	6.05	26.2	3.5
12.80	5.19	36.7	3.6
24.25	3.67	55.2	3.3
∞	0.00	-	-

Mean value of k_o = 3.5×10^{-2} hr^{-1} = 5.8×10^{-4} min^{-1}.

Hydrolysis of 2-Ethyl-3-phenyloxaziridine in aqueous $HClO_4$

Run 89

$[HClO_4]$ = 0.738M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (Minutes)	a_t (ml)	% Reaction	$10^2 . k_o$ ($min.^{-1}$)
0.0	14.19	-	-
19.8	11.73	17.3	1.0
41.5	9.33	34.2	1.0
68.8	7.74	45.5	0.9
131.0	5.07	64.3	0.8
173.0	3.82	73.1	0.8
225.0	2.59	81.7	0.8
∞	0.00	-	-

Mean value of $k_o = 0.9 \times 10^{-2}$ $min.^{-1}$

Hydrolysis of 2-Ethyl-3-p-nitrophenyloxaziridine in aqueous $HClO_4$

Run 101

$[HClO_4]$ = 4.62M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (Minutes)	a_t (ml)	% Reaction	$10^3 . k_o$ ($min.^{-1}$)
0	14.32	-	-
53	11.92	16.8	3.4
132	9.03	36.9	3.5
191	6.80	52.5	3.9
257	5.69	60.3	3.6
304	4.99	65.1	3.5
372	3.90	72.8	3.5
∞	0.00	-	-

Mean value of k_o = 3.5×10^{-3} $min.^{-1}$

Hydrolysis of 2-Isopropyl-3-ethyloxaziridine in aqueous $HClO_4$

Run 145

$[HClO_4]$ = 1.25M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^3 . k_o$ ($min.^{-1}$)
0.0	11.30	-	-
50.8	9.50	15.9	3.4
106.3	7.80	22.1	3.5
150.3	6.72	40.5	3.4
207.3	5.69	49.6	3.3
278.8	4.53	59.9	3.3
330.3	3.90	65.5	3.2
∞	0.00	-	-

Mean value of k_o = 3.4×10^{-3} $min.^{-1}$

Hydrolysis of 2-Benzyl-3,3-diethyloxaziridine in aqueous $HClO_4$

Run 172

$[HClO_4]$ = 1.55M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	10. k_o ($min.^{-1}$)
0.00	3.05	-	-
1.25	2.53	17.0	1.5
2.33	2.12	30.5	1.6
3.58	1.61	47.2	1.8
4.75	1.40	54.1	1.7
6.00	1.11	62.6	1.7
7.25	0.89	70.8	1.7
∞	0.00	-	-

Mean value of k_o = 1.7×10^{-1} $min.^{-1}$

Hydrolysis of 2-(α-Phenylethyl)-3,3-diethyloxaziridine in aqueous $HClO_4$

Run 201

$[HClO_4]$ = 6.64M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^3 k_o$ ($min.^{-1}$)
0	4.80	-	-
22	4.20	12.5	6.0
42	3.49	27.3	7.6
105	2.32	51.7	6.9
140	1.81	62.3	7.0
162	1.47	69.4	7.3
223	1.05	78.1	6.8
∞	0.00	-	-

Mean value of k_o = 7.2×10^{-3} $min.^{-1}$

$$\text{rate} = -\frac{d(\text{oxaziridine})}{dt} = \underline{k}_o \left[\text{oxaziridine}\right]_t \qquad \text{(VIII-1)}$$

In practice, $\underline{k}_o$ was calculated from the integrated first order rate expression (Eq. (VIII-2)), where, $\underline{a}_o$, $\underline{a}_t$ and $\underline{a}_\infty$, represent the

$$k_o = 2.303 \frac{\left\{\log\left[a_o - a_\infty\right] - \log\left[a_t - a_\infty\right]\right\}}{(t - t_o)} \qquad \text{(VIII-2)}$$

concentration of oxaziridine, as expressed by the titre of sodium thiosulphate solution used to titrate the iodine liberated, at the initial time $\underline{t}_o$, at time $\underline{t}$ and at infinity, $\underline{t}_\infty$, of the reaction course respectively.

VIII.2.3 Precision of the Measured Rate Coefficient

The main course of error probably lies in aerial oxidation of $I^{\ominus}$ that may occur during quenching, as well as further hydrolysis during this period. To minimise the first factor, sodium hydrogen carbonate was added to the quenching mixture and the CO_2 evolved displaced the oxygen from the titration vessel. After the evolution of CO_2, this vessel was tightly stopped until the contents were titrated.

The second error was minimised by keeping the quenching period short. The titres were reproducible and the rate coefficients show no appreciable perturbation.

The estimated errors in the rate coefficients were $\pm$6%, though in the case of 2-ethyl-3-p-nitrophenyloxaziridine, 2-ethyl-3-phenyloxaziridine, 2-benzyl-3,3-diethyloxaziridine and 2-(α-phenylethyl)-3,3-diethyloxaziridine, due to their low solubility in aqueous solution, which expressed itself in the low titres of

thiosulphate used, the reproducibility cannot be better than $\pm$15%.

VIII.2.4 Typical Kinetic Run for the Alkaline Hydrolysis

To illustrate the conditions in which the reactions were studied some examples are given in the following pages. Whenever possible the ionic strength of the reaction mixture was kept constant by addition of a neutral salt, normally sodium chloride or sodium perchlorate.

VIII.2.5 Precision of the Measured Rate Coefficient

The main source of error is, as for the runs under acidic conditions, the liberation of iodine due to aerial oxidation and reaction occurring during the quenching period. The same method of adding sodium bicarbonate to the quenching mixture was adopted. Another problem which interfered with some of the kinetic runs was secondary reactions between the iodine liberated and the catalyst nucleophile. This problem was particularly severe with thiocyanate ion and the observed rate constants with this catalyst must be interpreted with some reserve, the reproducibility being $\pm$20%. For the other catalysts the average reproducibility is usually $\pm$6%, but higher ($\pm$15%) for experiments performed with oxaziridines of low solubility.

VIII.3 The Product Analysis

The carbonyl products of hydrolysis under acidic conditions were determined by performing the reaction with various concentrations (0.7 to c.a. 2M) perchloric acid containing 2,4-dinitrophenylhydrazine.[42] The oxaziridine being analysed was alternatively added directly to the stock acid solution of 2,4-dinitrophenyl-

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous NaOD

Run 189

$[NaOD]$ = 0.05M Temperature = 25.0°C

Ionic strength 0.10, adjusted with NaCl

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^2 . k_o$ ($min.^{-1}$)
0.00	6.23	-	-
2.25	5.78	7.2	3.3
11.92	4.49	27.9	2.7
20.09	3.59	42.4	2.7
28.42	2.87	53.9	2.7
37.50	2.31	62.9	2.6
45.92	1.80	71.1	2.7
∞	0.00	-	-

Mean value of k_o = 2.7×10^{-2} $min.^{-1}$

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous NaOH

Run 208

$[NaOH]$ = 0.05M Temperature = 26.75°C

Ionic strength 0.10, adjusted with NaCl

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^2 . k_o$ ($min.^{-1}$)
0.00	10.56	-	-
2.77	9.91	6.2	2.3
10.83	8.13	23.0	2.4
18.50	6.70	36.6	2.5
29.17	5.10	51.7	2.5
36.75	4.15	60.7	2.5
47.50	3.15	70.2	2.6
∞	0.00	-	-

Mean value of k_o = 2.5×10^{-2} $min.^{-1}$

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous solution of 2,6-dimethylpiperdine

Run 130

[2,6-dimethylpiperidine] = 0.10M Temperature = 25.0°C

Buffer ratio of [2,6-dimethylpiperidine]: [2,6-dimethylpiperidinium ion] = 1.024

Ionic strength 0.20, adjusted with NaCl.

$[Na_2S_2O_3]$ =0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^3 . k_o$ ($min.^{-1}$)
0.00	11.80	-	-
2.67	11.60	1.7	6.0
13.00	10.56	10.5	8.5
24.09	9.76	17.1	7.8
40.67	8.52	27.8	8.0
72.67	6.73	43.0	7.7
109.67	5.03	57.4	7.8
151.67	3.65	69.1	7.7
∞	0.00	-	-

Mean value of k_o = 7.7×10^{-3} min^{-1}

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous KCN

Run 118

$[KCN]$ = 0.097M Temperature = 25.0°C

Buffer of Na_3PO_4 and Na_2HPO_4 used to keep the pH constant (10.4).

Ionic strength o.38, adjusted with $NaClO_4$

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^3 . \underline{k}_o$ ($min.^{-1}$)
0	17.64	-	-
53	14.15	19.8	4.1
92	12.86	27.1	3.4
143	10.45	40.8	3.6
203	8.77	50.3	3.4
297	6.18	65.0	3.5
357	4.65	73.6	3.7
∞	0.00	-	-

Mean value of $\underline{k}_o = 3.5 \times 10^{-3}$ $min.^{-1}$

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous solution of KI

Run 55

$[KI]$ = 0.10M Temperature = 25.0°C

$[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^2 . k_o$ ($min.^{-1}$)
0.00	14.80	-	-
11.75	12.87	13.0	1.2
23.50	11.66	21.2	1.0
39.50	10.18	31.2	0.9
61.00	8.14	45.0	1.0
75.17	7.00	52.7	1.0
89.50	5.97	59.7	1.0
104.00	5.25	64.5	1.0
120.00	4.58	69.1	1.0
∞	0.00	-	-

Mean value of k_o = 1.0×10^{-2} $min.^{-1}$

Hydrolysis of 2,3,3-Triethyloxaziridine in aqueous solution of KSCN and KI

Run 69

$[KSCN]$ = 0.05M Temperature = 25.0°C

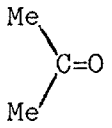
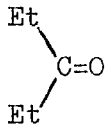
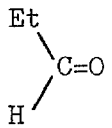
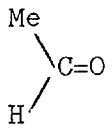
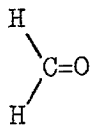
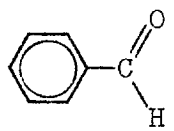
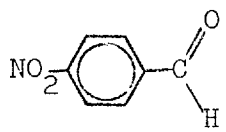
$[KI]$ = 0.05M $[Na_2S_2O_3]$ = 0.010N

Time (minutes)	a_t (ml)	% Reaction	$10^2 . k_{-o}$ (min^{-1}.)
0.00	12.91	-	-
8.00	11.77	8.8	1.2
15.75	10.73	16.9	1.2
24.50	9.32	27.8	1.3
32.00	8.42	34.8	1.3
40.25	7.30	43.5	1.4
49.00	6.40	50.4	1.4
∞	0.00	-	-

Mean value of k_{-o} = 1.3×10^{-2} min^{-1}.

Table (VIII-4)

2,4-Dinitrophenylhydrazones[106]

Corresponding Carbonyl Compound	Colour	m.p.
	yellow	128
	orange	156
	orange	155
	yellow	168
	yellow	166
	orange	237
	yellow	320

hydrazine[a] at 25.0°C. The hydrolysis was allowed to proceed until the reaction reached completion. The insoluble 2,4-dinitrophenylhydrazones, which precipitated as a bulky orange-yellow precipitate, were subsequently filtered off, and examined by t.l.c. silica gel SG (Merck) plates. Ether was used to dissolve the precipitates and to spot the plates. The chromatograms were developed 15 cm using a mixture of methylene chloride-benzene (50:50). The hydrazones were identified by spotting the plates with authentic samples, prepared according to Vogel[106].

In one case (2-isopropyl-3-ethyloxaziridine) the products of hydrolysis could not be separated on silica plates but those prepared from Bentonite Kieselguhr (1:1) with chloroform-ethanol (90:10) did separate the products, propionaldehyde and acetone.

The physical data relative to the 2,4-dinitrophenyl hydrazones are listed in Table (VIII-4).

U.v. spectroscopy was particularly helpful in determining the relative percentages of benzaldehyde and aniline formed in the acid hydrolysis of 2-benzyl-3,3-diethyloxaziridine. A typical experiment will be described: a stock solution of benzyl-3,3-diethyloxaziridine was prepared by weighing 149.55mg of this compound and dissolving it in 25ml of ethanol. 1ml of this stock solution was added to 25ml of 1.01M, $HClO_4$, and the reaction allowed to reach infinity. A u.v. spectrum of the reaction mixture was taken and the optical density at 250nm was

a) The stock solution of 2,4-dinitrophenylhydrazine was prepared by dissolving 0.25g of 2,4-dinitrophenylhydrazine in a mixture of 42 ml of concentrated sulphuric acid and 50 ml of water by warming on a water bath: the cold solution was then diluted to 250 ml with distilled water.

found to be 2.10. This value was then substituted in (Eq. (VIII-3)) and the values of C_B (molar concentration of benzaldehyde) and C_A

$$(O.D.)_\lambda = \varepsilon_{\lambda,B} C_B + \varepsilon_{\lambda,A} C_A \qquad \text{(VIII-3)}$$

$(O.D.)_\lambda$ = optical density at wavelength λ.

$\varepsilon_{\lambda,B}$, $\varepsilon_{\lambda,A}$ = extinction coefficients at wavelength λ for the two compounds.

C_A, C_B = concentrations of aniline and benzaldehyde

(molar concentration of aniline) computed using $\varepsilon_B = 1.15 \times 10^4$ mole^{-1}.l.cm^{-1}. and $\varepsilon_A = 134$ mole^{-1}.l.cm^{-1}. as respectively the extinction coefficients of benzaldehyde[107] and aniline[108] at 250 nm and taking into account that $C_A + C_B$ is equal to the total concentration of oxaziridine. The ratio C_A/C_B in this case was 6.6. An independent check on the total concentration of oxaziridine was made by carrying out the reaction in 0.0098 N, NaOH and measuring the total amount of benzaldehyde formed ($C_B = 1.3 \times 10^{-3}$M, $C_A = 0$). The accuracy of the method is ca. $\pm$10%.

N.m.r. spectroscopy was also utilized to some extent. The product analysis was carried out by following the course of the reaction in the n.m.r. tube with suitable catalysts (D_2SO_4 in D_2O, KI in D_2O and NaOD in D_2O). The signals obtained as well as the integration curves were compared with those of authentics.

VIII.4 The Site of Protonation

The method for determining the site of protonation in oxaziridines consisted in taking the n.m.r. spectrum of the oxaziridine in an inert solvent (CCl_4 or $CDCl_3$) and noting the chemical shifts

of the different signals corresponding to the different protons, relative to an internal standard of tetramethylsilane (TMS). Then trifluoracetic acid (TFA) was added carefully to the n.m.r. tube with cooling and the spectrum of the conjugate acid of the oxaziridine recorded. The new chemical shifts, also referred to the same internal standard of TMS, were compared with those corresponding to the free base and from the differences observed the site of the positive charge could be allocated. In some cases, spectra were taken of the conjugate acid in TFA solution alone.

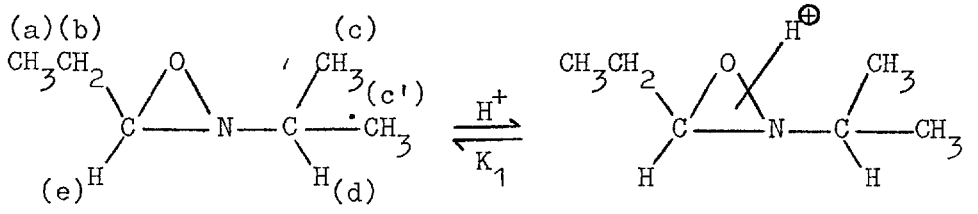
The data for all the oxaziridines concerned are listed in Part 2, so only a typical example is given in Table (VIII-5). The values of τ registered refer to the middle of the n.m.r. signal when this one has multiplicity higher than 2.

This method has the obvious limitations of being only applicable to oxaziridines which bear α-H relative to the ring nitrogen atom, and have a sufficiently slow rate of decomposition in T.F.A. to allow the n.m.r. spectra to be recorded. Fortunately this is true for several 2,3,3-trialkyloxaziridines, specially those with a primary alkyl group attached to the nitrogen atom of the ring. In these cases the method could be applied with reasonable success.

The precision of the chemical shifts is within $\pm$0.02 τ units and so the precision of the reported chemical shifts differences, $\Delta\tau$, is within $\pm$0.04 .

Table (VIII-5)

Protonation of 2-Isopropyl-3-ethyloxaziridine



Protons	τ a)	τ b)	$\Delta\tau$
(a)	8.93	8.77	0.16
(c), (c')	8.85, 8.73	8.47	0.38, 0.26
(b)	8.37	7.92	0.45
(d)	7.85	6.49	1.36
(e)	6.32	5.11	1.21

a) Spectra in $CDCl_3$, at c a. 43°C (Varian A-60)
(TMS as internal standard)

b) Spectra run in $CDCl_3$:CF_3CO_2H (1:1), at c a. 43°C.
(TMS as internal standard)

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