ELECTROCHEMICAL OXIDATION OF 1-PHENYLPYRAZOLIDIN[redacted]-3-ONES

DAVID IAIN INNES B.Sc.

Ph.D.

UNIVERSITY OF EDINBURGH

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Abstract

The use of substituted 1-phenylpyrazolidin-3-ones as primary and superadditive developing agents is reviewed.

The electrochemical oxidation of some substituted 1-phenylpyrazolidin-3-ones in acetonitrile has been studied, using tetraethylammonium fluoroborate and tetraethylammonium chloride as the supporting electrolytes. In addition, the electrochemical oxidation of 1-phenylpyrazolidin-3-one and 4,4-dimethyl-1-phenylpyrazolidin-3-one in methylene chloride, using tetrabutylammonium fluoroborate as the supporting electrolyte, has been investigated. The preparative anodic oxidation of 1-phenylpyrazolidin-3-ones gave monomeric and/or dimeric products which were characterised using spectroscopic techniques, elemental analysis, and by reference to the published literature. The mechanism by which these compounds are formed is discussed using electroanalytical measurements as supporting evidence.

The stability of the radical cation formed after the initial oxidative charge transfer from 1-phenylpyrazolidin-3-one and from pyrazolidinones which have methyl or phenyl substitution at N(2) in neutral acetonitrile has been determined by cyclic voltammetry and a rationale is proposed for the observed order of stability.

To: Marty, Mum and Dad

DECLARATION

I declare that this thesis is of my own composition and describes my own work. Where the work of other authors is referred to, this is clearly indicated.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr A J Bellamy, since 1st October 1977, the date of my admission as a research student.

David I Innes

ACKNOWLEDGEMENTS

I should like to record my sincere gratitude to my academic supervisor, Dr A J Bellamy, for his invaluable advice and assistance during my period as a research student at the University of Edinburgh.

Thanks are also due to Dr P Hilson of the Research Division at Kodak Ltd., Harrow, for maintaining an active interest in the work I was undertaking, and to Dr T A Joslin of Diamond Shamrock Electrosearch S.A. (Geneva), formerly of Kodak Ltd., who was instrumental, along with Dr Bellamy, in setting up this project.

Finally, I should like to thank the Science Research Council for awarding me a three-year CASE studentship, and to Kodak who contributed an allowance towards the cost of copying and binding this thesis.

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CHAPTER 1

INTRODUCTION

Introduction

To date, the most common method of recording light signals is by conventional silver halide photography. Only by using silver halides can a primary, light induced effect be amplified by consumption of chemical energy up to a factor of 10^9.[1] Both the primary process and the amplification step involve the separation of charges, and the chemical reactions of charged particles. It is therefore possible to describe them in terms of electrochemistry.

The classical[2] photographic process involves the image-wise absorption of radiation by silver-halide microcrystals dispersed in a binder, usually gelatin. Absorption of as few as four photons by a single micro-crystal (though sometimes up to a hundred may be required by some crystals) render that crystal distinguishable from its neighbours by chemical means,[3] and a latent image is said to have been formed. This distinguishing process, in which silver ions in the latent image are chemically reduced, is known as development. It is generally agreed that the latent image comprises an aggregate of at least four silver atoms,[4] though it is not certain whether it is of catalytic importance in itself,[5] or owes its reactivity to some characteristic of the silver aggregate-silver halide interface.[6]

From the point of view of electrochemical models however it has been customary[1] to look at the latent image, either as directly formed, or after subsequent enlargement, as the conductor that completes the circuit between anodic and cathodic half-cell reactions, thereby allowing current to flow. That is, it is the switch which turns the redox chemistry of photographic development on or off.

There are a great number of chemical species which, acting on their own, are able to develop the latent image. Complex developers, however, ones which contain a mixture of two or more developing agents, are commonly used in conventional development systems to achieve results that cannot conveniently be obtained

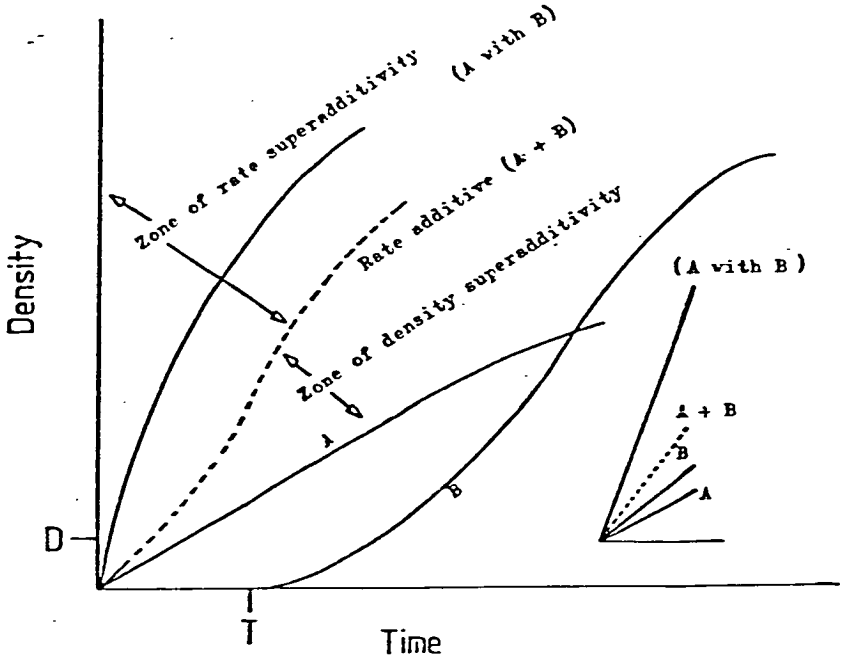
by the use of a single developing agent. These complex developers are said to display superadditivity.

Levenson[7] has conveniently separated the notion of superadditivity into two concepts:

"1. Superadditivity of densities.

This term is used to describe the joint behaviour of two developing agents, say A and B, when the density of the image obtained in a given short time of development is greater than the sum of the densities which are obtained in the same time using A and B separately on two other similar images. Figure 1 shows the course of the growth of density of three similarly exposed patches of film in developers A and B, and in the combined (A with B) developer. Developer A has a short induction time and B has a long one. In the combined developer, A initiates development rapidly so that B can participate earlier than it could otherwise. At the time T shown in the figure the developer B would have given only a trace of image on its own, whereas the density given by the (A with B) developer is greater than that given by A.

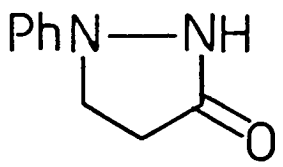
Figure 1



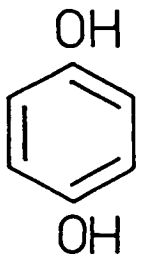
Diagrammatic time-versus-density curve for two developers with agents A and B and for the combined developer (A with B). Slope rates at a finite density D are shown inset with the arithmetic sum (A + B).

2. Superadditivity of Rates.

If a patch of exposed film has been partially developed to a density D, lower than the maximum density in any one of the developers A, B, or (A with B), and after development, the patch is washed free from all traces of used developer, and if this patch were then bathed in developer A, the course of development would be resumed at the rate (dD/dt)A. Likewise, the rates of continuation of development in solutions B and (A with B) would be (dD/dt)B and (dD/dt)(A with B). Now development by (A with B) is called superadditive in a chemical-kinetic sense if (dD/dt)(A with B) is greater than (dD/dt)A + (dD/dt)B."



(I)

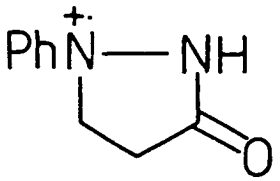


(II)

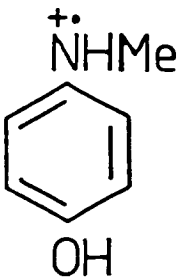
1-phenylpyrazolidin-3-one(I), while being a poor developer on its own account is effective in activating hydroquinone(II) and is used in conjunction with hydroquinone in alkaline aqueous medium as a superadditive developing agent.[8] Levenson proposed a regeneration reaction to account for the superadditive development, stating that in a superadditive combination made up of developing agents (I) and (II), superadditivity can occur when the reduced form of one of the developing agents, (for example I) reduces silver halide and the other developing agent, is able to reduce the oxidised form of I back to an active developing species.

Superadditivity could then result in one of several ways.[9] Firstly, if an oxidation product of the first developing agent

inhibits development, regeneration may effectively remove this inhibiting product from the grain by converting it back to an active developer. Secondly, regeneration could account for superadditivity if the developing agent II, which in itself develops more slowly than I, acts in solution primarily to increase the effective concentration of I in the vicinity of the developing grains. This second argument is valid only if the rate of development is primarily controlled by the rate of diffusion. Finally, reaction of the oxidised form of I with the reduced form of II to generate a more reactive reducing agent derived from I could occur.



(III)



(IV)

An alternative explanation of superadditivity suggested by James[9], involves charge-barrier depression and the promotion of adsorption of the developing agent through the formation of a positively charged oxidation intermediate. It was proposed that 1-phenylpyrazolidin-3-one, which is uncharged at low pH and at most only singly ionised at higher pH(9.0), is able to initiate development of the latent image specks, and that this reaction forms a positively charged, intermediate oxidation product (III), which reduces the charge barrier by virtue of its charge and is readily adsorbed by a silver halide grain. N-Methyl-4-amino-phenol(Metol), also forms a superadditive combination with hydroquinone, and may also form a positively charged oxidation product during development (IV). Either of these positively charged

species could thereby promote adsorption of hydroquinone the silver halide grain or serve as an electron transfer agent for development by hydroquinone. Although there is no direct evidence for the presence of (III) and (IV) in solution, their existence in the adsorbed state, where adsorption may inhibit deprotonation, has not been disproved.

The discovery of the efficacy of 1-phenylpyrazolidin-3-one and its derivatives as photographic developers was arrived at empirically and not from a fundamental, theoretical study. Therefore in order to understand the role of 1-phenylpyrazolidin-3-ones in superadditivity, the chemical and electrochemical oxidation of these compounds has been extensively studied in aqueous media.

More recently there has been interest in the use of non-aqueous developing systems and again 1-phenylpyrazolidin-3-ones have been used in this case as primary developing agents.

A preliminary investigation found that the electrochemical oxidation of the parent 1-phenylpyrazolidin-3-one in acetonitrile (assumed to be similar to the non-aqueous environment in a 'dry' developing system) was significantly different from the mechanism operating in aqueous media, and that the end products also differed[10]. It therefore appeared from these results that a more detailed study of these systems in aprotic media might provide information which would lead to a better understanding of how these developers function in non-aqueous systems.

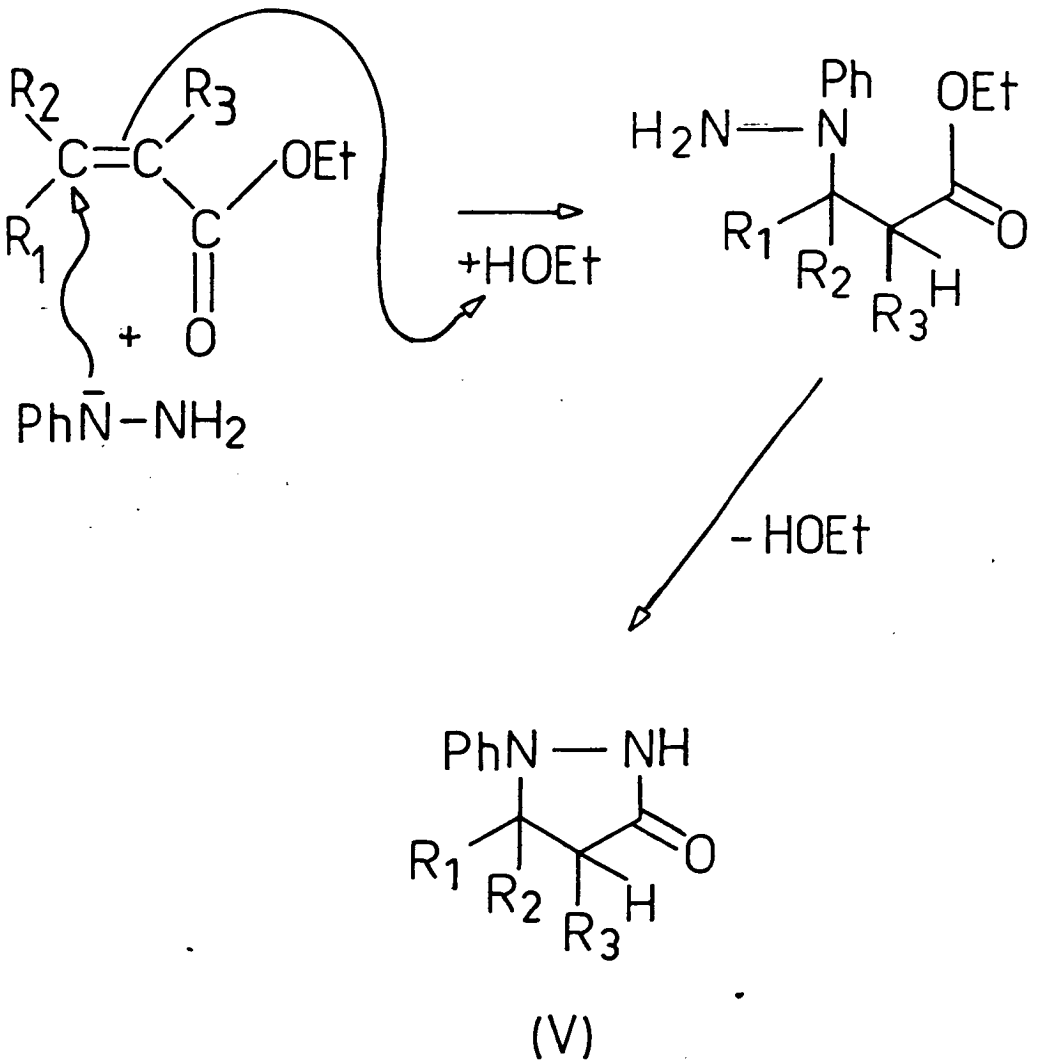
The aim of this research project, therefore, was to undertake a study of the electrochemical oxidation of 1-phenylpyrazolidin-3-ones in non-aqueous media. Of particular interest to the collaborating body (Kodak) with regard to mechanisms, products, and the stability of the intermediate radical - cations formed on oxidation, were those derivatives which have substituents at position 4 and/or in the phenyl ring.

Synthesis of 1-Phenylpyrazolidin-3-ones.

As a result of the role of the 1-phenylpyrazolidin-3-ones in photography, the literature contains numerous references to their chemical synthesis[11].

Pyrazolidin-3-ones of the general structure (V) can be most conveniently synthesised by the reaction of phenylhydrazine with α,β-unsaturated esters[12,13,14] or amides[15], under anhydrous conditions, in the presence of a strong base (typically sodium ethoxide)(Scheme 1a).

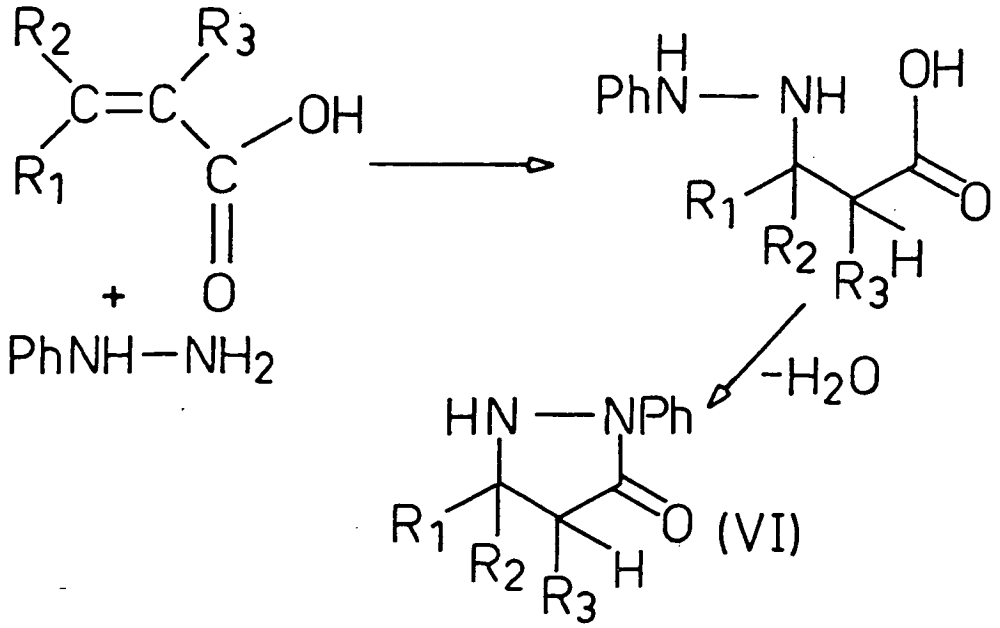
Scheme 1(a)



(V)

The reaction of α,β-unsaturated acids with phenylhydrazine in the absence of base provides pyrazolidin-5-ones (VI) as the sole product[14,16] (Scheme 1b).

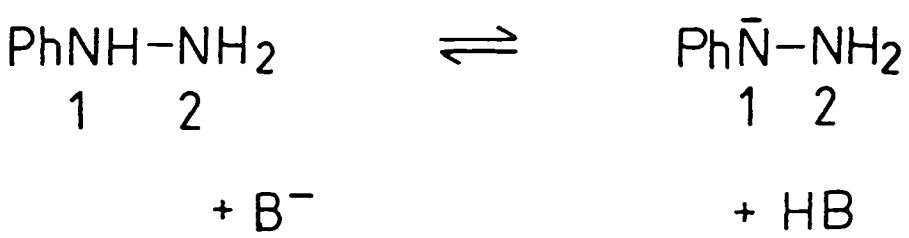
Scheme 1(b)



The mechanism of formation of these compounds has been rationalised by Boushet[14] by reference to Dorn's[17] explanation of the relative basicity of N(1) and N(2) of phenylhydrazine.

In the presence of base, N(1) is ionised preferentially, since the conjugate base $Ph\text{-}\bar{N}\text{-}NH_2$ is resonance stabilised. Reaction then takes place by Michael addition of this base to the unsaturated ester or amide. This is consistent with the observation that, as the strength of the base is increased, corresponding to an equilibrium shift to the right in Scheme 2, reaction proceeds more readily.

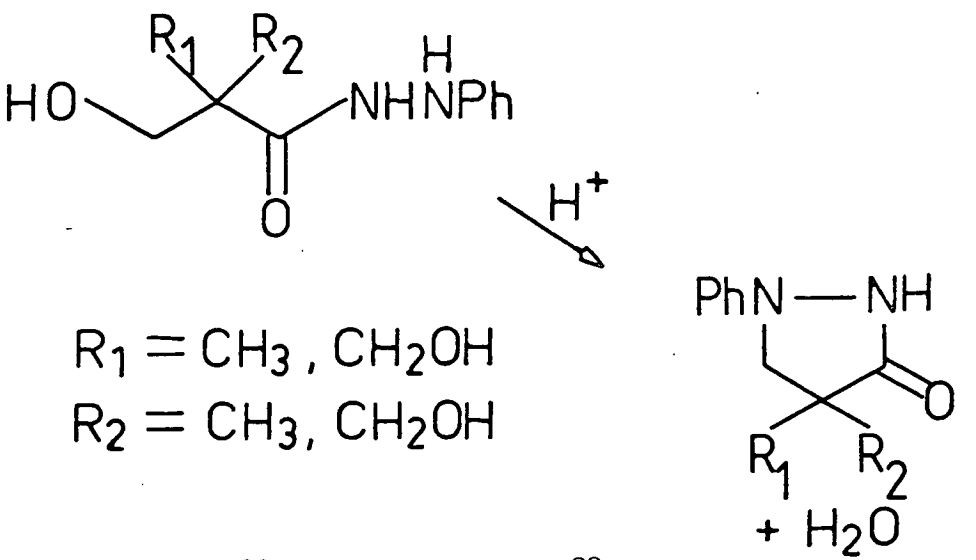
Scheme 2



Under conditions where ionisation is not induced to occur (Scheme 1b), the most nucleophilic nitrogen is N(2), N(1) being partially anilinic in character, and reaction proceeds by Michael addition to give a pyrazolidin-5-one.

A more general synthetic method[18,19,20], enabling 4,4-dimethyl, 4,4-dihydroxymethyl, and 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one, to be prepared involves acid catalysed cyclisation of the phenylhydrazides of 2,2-disubstituted-3-hydroxypropionic acids (Scheme 3).

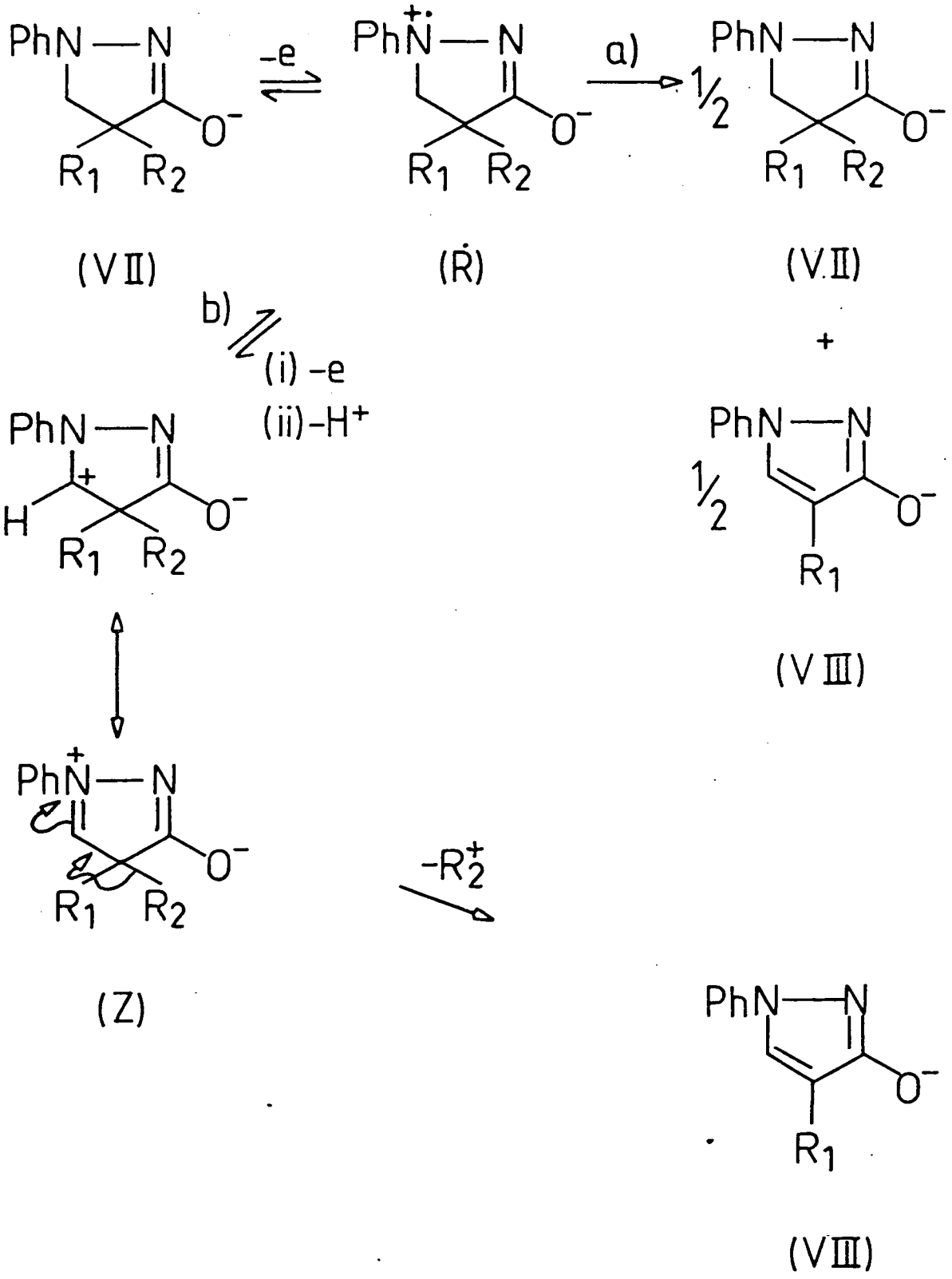
Scheme 3



The use of polyphosphoric[19], or p-toluene[20] sulphonic acid, as the catalyst allows high yields of the pyrazolidin-3-ones to be obtained without concomitant hydrolysis of the phenylhydrazides.

The parent compound has also been synthesised by base catalysed reaction of ethyl 3-ethoxypropionoate[21] with phenylhydrazine, and by thermal reaction of methyl and butyl 3-chloropropionoate[22] with phenylhydrazine. These methods are not however general for other 4 and 5 substituted derivatives, and give lower yields of product than the general methods already described.

Scheme 4


PhN—N
-e
PhN—N
a)
1/2
PhN—N
O⁻
R1 R2
(VII)
(Ṙ)
(VII)
b)
(i) -e
(ii) -H+
+
PhN—N
H
1/2
PhN—N
R1
(VIII)
PhN—N
-R2+
PhN—N
(Z)
PhN—N
R1
(VIII)

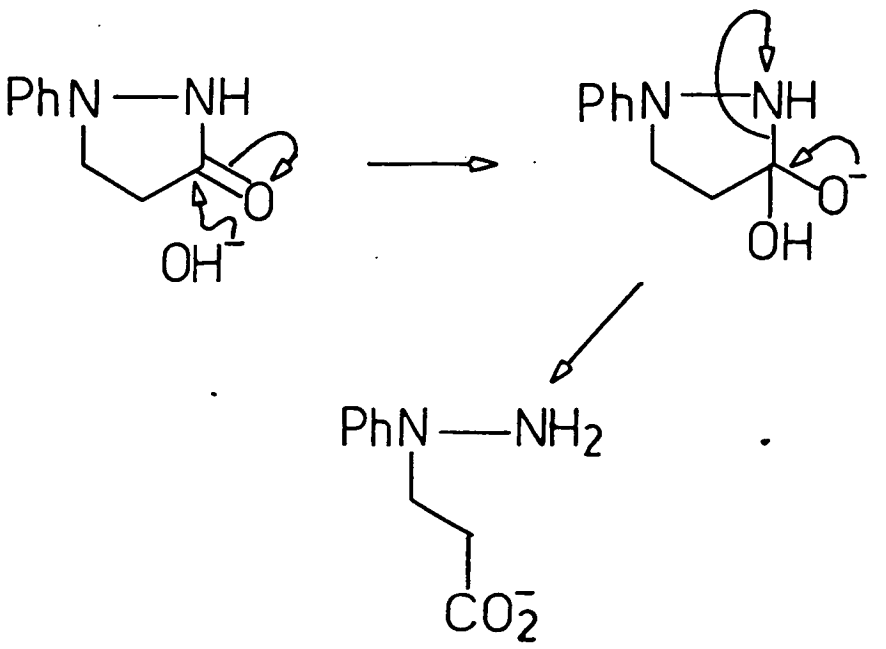
Oxidation of 1-Phenylpyrazolidin-3-ones in Aqueous Media.

Because the reducing characteristics of the molecules involved in the photographic developing process is important, and the existence of a stable radical[23] or mono-electronic oxidation state is a prerequesite of a superadditive developing agent, the oxidation of 1-phenylpyrazolidin-3-ones has been studied in aqueous solution by both chemical and electrochemical methods.

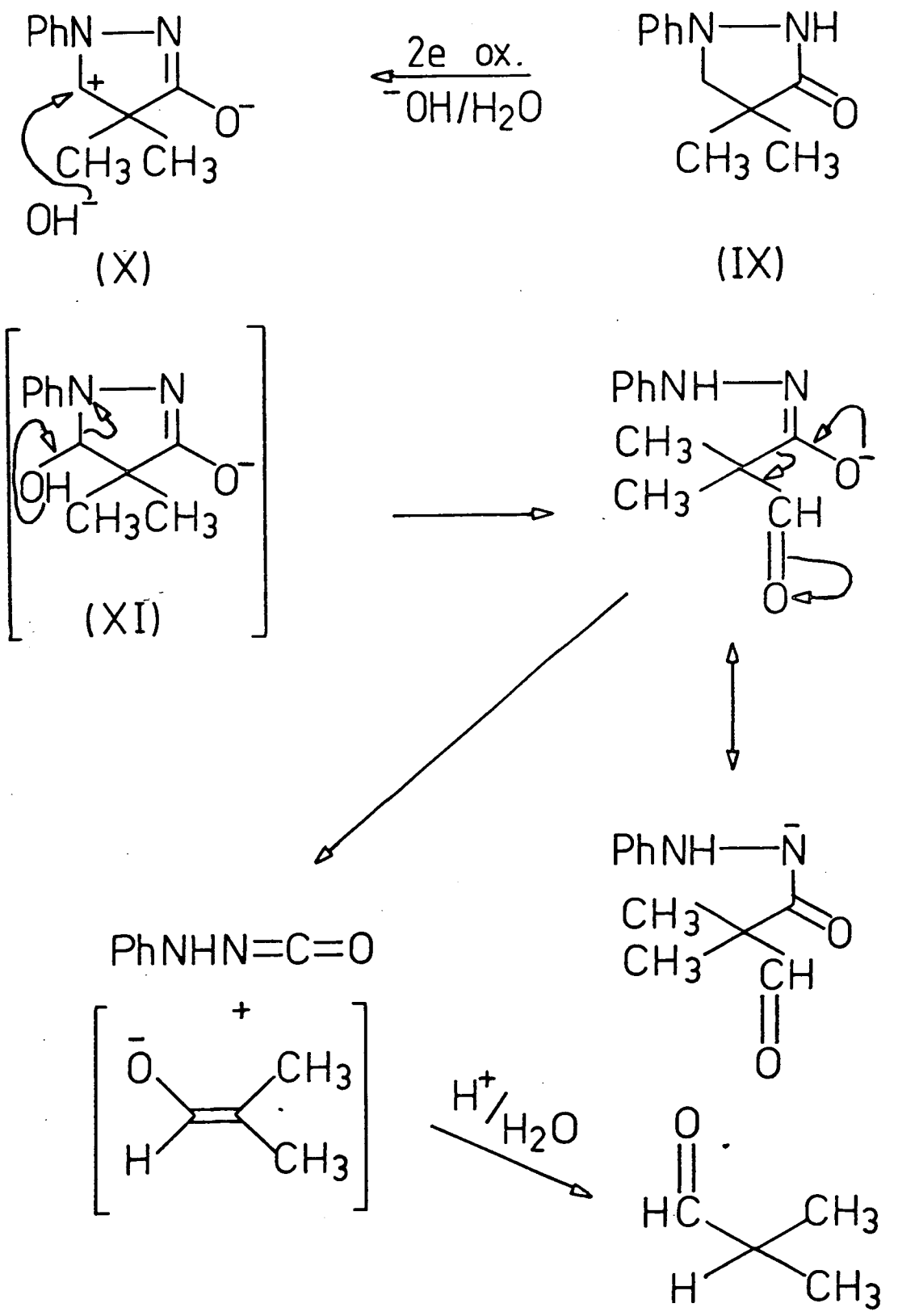
The initial 1-electron oxidation of 1-phenylpyrazolidin-3-one in aqueous alkaline media has been shown to yield a radical species(R), which undergoes a second order dismutation reaction[24-29].

This oxidation has been studied by Battaglia[29] who used electrochemical, stop-flow, and gas-chromatographic techniques to confirm the mechanism shown in Scheme 4a.(R^1=R^2=H); (VII) is the ionised form of 1-phenylpyrazolidin-3-one predominant in solutions of pH greater than 9.35, the pk of 1-phenylpyrazolidin-3-one[27]. At high pH(14), a second oxidation of the radical(R) occurs to give a resonance stabilised intermediate(Z)[30] which rapidly loses a proton to give the same product (VIII). Unfortunately the parent compound is unstable in alkaline solution and undergoes ring cleavage (Scheme 5).

Scheme 5



Scheme 6


PhN—N
2e ox.
⁻OH/H₂O
PhN—NH
CH₃ CH₃
(X)
(IX)
PhNH—N
CH₃
CH₃
CH
PhNH—N̄
PhNHN=C=O
H⁺/H₂O
HC
CH₃
H

The inclusion of a 4-methyl, or a 4-hydroxymethyl group into the molecule greatly increases its long-term stability in alkaline solutions, thereby increasing the usefulness of this class of compound as a developer. 4,4-Disubstituted derivatives are particularly effective. A study of the oxidation of these derivatives at high pH resulted in the mechanism(Scheme 4) being postulated as general for those compounds having at least one leaving group at C(4) (R^1 = CH_3, CH_2OH, H ; R^2 = CH_2OH, H).[31] 4,4-Dimethyl-1-phenylpyrazolidin-3-one (IX) however has no readily available leaving group at C(4), and oxidation of this compound under mild conditions in alkaline solution leads to cleavage of the pyrazolidinone ring to give benzene, nitrogen, isobutyraldehyde, carbon dioxide, and a resinous polymeric material as major products, along with small amounts of acetone, formaldehyde, and biphenyl.[32]

It was proposed that, on oxidation, a reactive intermediate is formed (X) (Scheme 6) which reacts with hydroxide ion to give a short-lived unstable species (XI), which ring opens expelling isobutyraldehyde. The formation of the other oxidation products was thought to be due to further hydrolysis and oxidation of the fragment which remains after loss of isobutyraldehyde.

The oxidation of 1-phenylpyrazolidin-3-one has also been accomplished by U.V. irradiation of aqueous solutions.[33] Flash photolytic experiments indicated that the primary oxidation product, a free radical, undergoes dismutation to yield starting material and 1-phenylpyrazolin-3-one, in a similar manner to that shown in Scheme 4a.

In strong aqueous acid, the oxidation mechanism is more complicated with dimeric, polymeric, and stable radical, species being formed.[34,35]

Electrochemical Oxidation of 1-Phenylpyrazolidin-3-one in Acetonitrile.

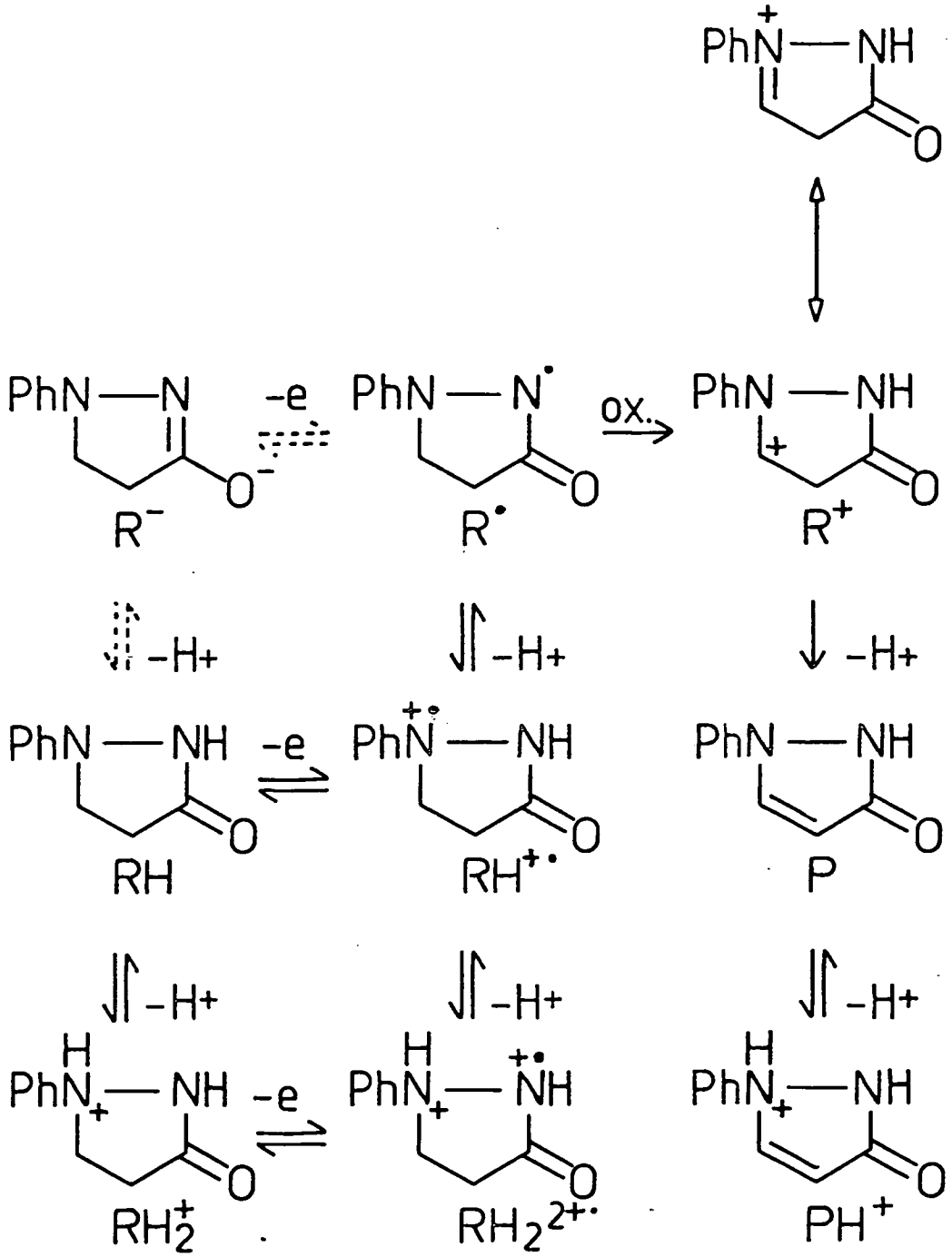
In a previous study[10], it has been shown that the electrochemical oxidation of 1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium perchlorate as the supporting electrolyte is more complex than that observed in aqueous alkali, with the aprotic nature of the solvent leading to the formation of protonated intermediates and products.

Cyclic voltammetry indicated that 0.61 V and 0.84 V (vs. SCE), two distinct oxidative processes were occurring, corresponding to the oxidation of the unprotonated and the protonated pyrazolidinone respectively. Controlled potential electrolyses at these potentials showed that both processes resulted in the same products being formed, viz. 1-phenylpyrazolin-3-one (P; major product) and a dimer, 3-anilino-N-4-(3-oxopyrazolin-1-yl) phenylpropionamide (XIII; minor product). The most likely mechanism which would explain the electrochemical formation of the monomer (P) was described by the authors in the form of a sequence of squares (Scheme 7).

In neutral acetonitrile solution the pyrazolidinone (RH) is initially oxidised via a reversible one-electron process to the radical cation ($RH^{+\cdot}$) which can undergo proton loss to give the neutral acylhydrazyl radical ($R^{\cdot}$).

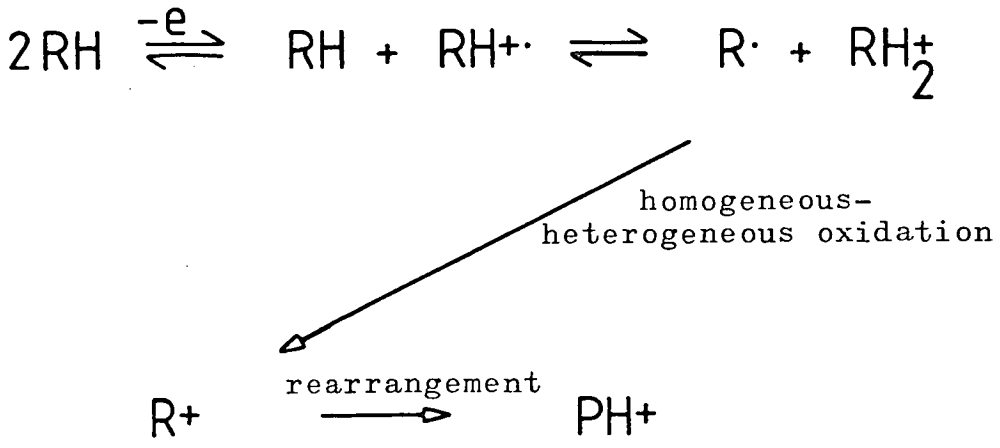
In aqueous alkaline solution, a further oxidation wave at a potential between the waves for the oxidation of the pyrazolidinone (RH) and the pyrazolinone (P) is observed. In acetonitrile, however, no oxidation wave which could be attributed to the further oxidation of the radical ($R^{\cdot}$) was observed between these potentials. This suggested that the radical ($R^{\cdot}$) was being oxidised at the same potential as (RH).

Scheme 7


PhN—NH
O
PhN—N
-e
O⁻
R⁻
PhN—N•
O
R•
ox.
PhN—NH
+
O
R⁺
-H+
-H+
-H+
PhN—NH
O
RH
-e
PhN—NH
O
RH+•
PhN—NH
O
P
-H+
-H+
-H+
H
PhN—NH
+
O
RH2+
-e
H
PhN—NH
+
O
RH2 2+•
H
PhN—NH
+
O
PH+

Steady-state experiments with a rotating-disc electrode indicated that 1-electron is being transferred during the initial oxidative process(0.61V). This result was explained by the mechanism in Scheme 8.

Scheme 8

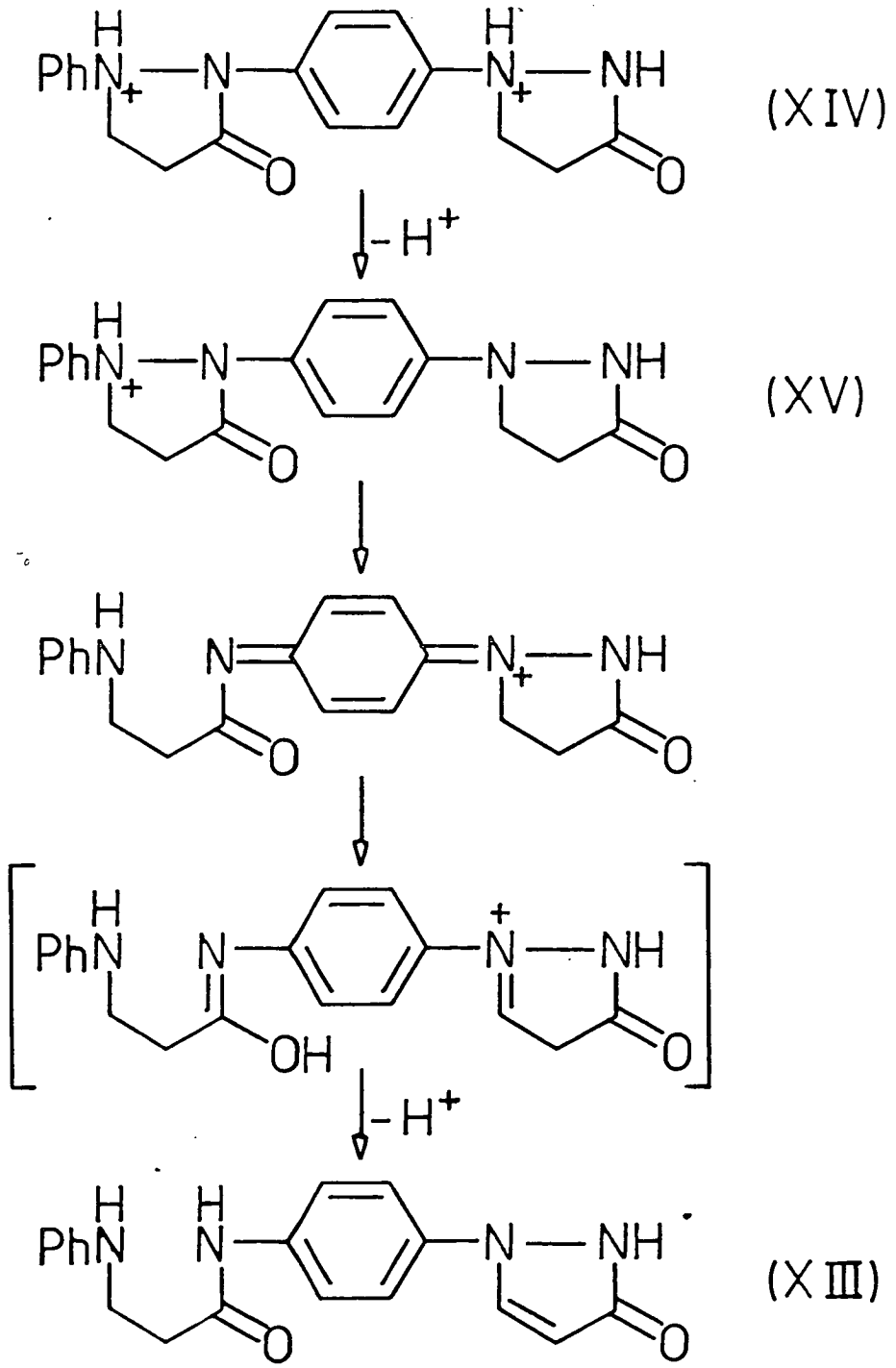


The overall reaction thus corresponds to a 1-electron transfer per molecule of RH as the protonated pyrazolidinone(RH_2^+) is not electroactive at 0.61V. Similar mechanisms had previously been reported for the oxidation of aniline[36] and phenylhydrazine[37] in acetonitrile.

At potentials where the protonated pyrazolidinone(RH_2^+) is electroactive(0.82V), coulometric experiments indicated that the number of electrons transferred per molecule approached 2 , in agreement with this mechanism (Scheme 8). The addition of perchloric acid to a neutral solution of 1,1-diphenylhydrazine[38] gives analagous electrochemical results.

The mode of formation of the dimeric oxidation product (XIII) was postulated to occur via the intermediary dimeric species (XIV), and (XV) (Scheme 9).

Scheme 9



A study[39] has also been made of the electrochemical oxidation of 1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium chloride as the supporting electrolyte. Cyclic voltammograms obtained from this system showed a single, irreversible, 2-electron oxidation peak which was 100mV cathodic of that obtained using tetraethylammonium perchlorate as the supporting electrolyte.

Controlled potential electrolysis of the pyrazolidinone(RH) at this potential, gave one product, 1-phenylpyrazolin-3-one(P), in almost quantitative current yield by a 2-electron oxidation.

Since the probability of 2 electrons tunnelling simultaneously between an ion and a metal electrode is extremely low[40], the authors postulated a multi-step oxidation mechanism consistent with their experimental results (Scheme 10)

Scheme 10

$$RH \xrightarrow{\text{r.d.s.}} RH^{+\cdot} + e$$

$$RH^{+\cdot} + Cl^- \xrightarrow{\text{fast}} R^{\cdot} + HCl$$

$$R^{\cdot} \xrightarrow{\text{fast}} R^+ + e$$

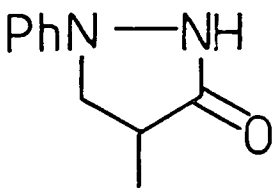
$$R^+ + Cl^- \longrightarrow P + HCl$$

In this mechanism chloride ion is acting as a strong base in agreement with the observation[41, 42] that hydrogen chloride is 99% associated in acetonitrile, with a pK. of 9.0. The authors however rejected the suggestion that the pyrazolidinone is initially ionised by chloride ion in acetonitrile on the basis of voltammetric and spectroscopic evidence.

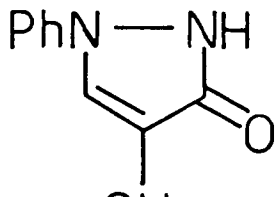
CHAPTER 2

RESULTS OF THE PREPARATIVE ANODIC OXIDATION OF SOME 1-ARYLPYRAZOLIDIN-3-ONES IN APROTIC SOLVENTS

Controlled potential electrolyses were performed on solutions of 1-arylpyrazolidin-3-ones which were either mono- or di- substituted at either C(4) or C(5), or substituted in the phenyl ring. Electrolysis potentials were chosen which were anodic of the peak current recorded by cyclic voltammetry. The detailed cyclic voltammetric behaviour of these compounds is discussed in Chapters 3 and 4.



(XVI)



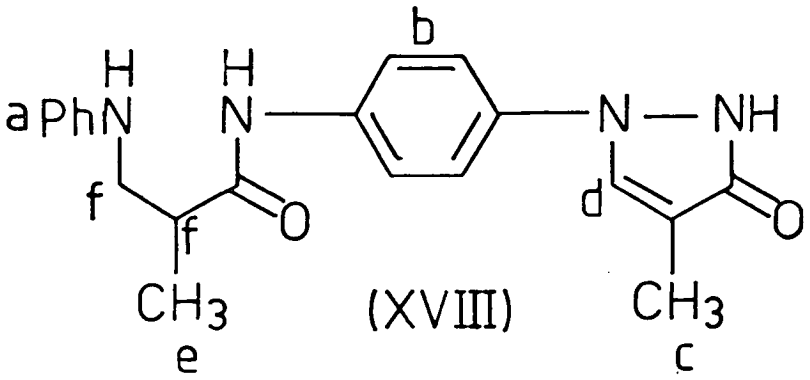
(XVII)

2.1. - Electrochemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one (XVI) in acetonitrile:- The electrochemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one (XVI) in acetonitrile containing tetraethylammonium chloride as the supporting electrolyte gave one product, 4-methyl-1-phenylpyrazolin-3-one (XVII). This product was identified by comparing its physical properties, and its i.r., n.m.r., and mass spectra with those of an authentic sample prepared by the chemical oxidation of an aqueous solution of XVI using ferric chloride[43], by elemental analysis, and by reference to the published literature[44].

By contrast, the electrochemical oxidation of XVI in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte gave a mixture of 2 major products, XVII and a dimer identified as 3-anilino-2-methyl-N-[4-(4-methyl-3-oxopyrazolin-1-yl)phenyl]propionamide (XVIII) on the basis of i.r., n.m.r., and mass spectroscopic evidence. Elemental analysis of this product indicated a molecular formula of $C_{20}H_{22}N_4O_2$, and this was consistent with the parent ion peak (P+) in the mass spectrum at m/e = 350. In addition the 100 MHz ^1H n.m.r. spectrum of this dimer clearly showed the following characteristic features.

Two separate groups of resonances were apparent in the aromatic region of the spectrum, a monosubstituted phenyl ring (δ6.40-7.20)(protons a; Table 1), and the AA'BB' pattern characteristic of a p-disubstituted phenyl ring (δ7.59, J= 10 Hz)(protons b; Table 1). The presence in the structure of a methyl substituted pyrazolinone ring was indicated by the exact correspondence of the methyl resonance of XVII with a singlet methyl resonance at δ1.93 in the ^{1}H n.m.r. spectrum of the dimer(protons c; Table 1), and the olefinic proton at C(5) in XVII with a singlet resonance at δ7.75 (proton d; Table 1). Another methyl resonance consisted of a doublet resonance (δ1.22, J= 6 Hz) in the region characteristic of a methyl group attached to a saturated carbon(protons e; Table 1). The coupling constant(J= 6 Hz) is consistent with that due to an adjacent proton. In addition there were 2 resonances attributable to exchangeable protons(δ9.67 and 9.45-10.00). Unfortunately the methylene and methyne regions of the spectrum were obscured by water in the deuterated dimethyl sulphoxide used. The infra-red spectrum, however, was also consistent with this structure; it showed absorbances at 3430 cm^{-1}, due to the NH stretch of a secondary amide, and at 3300 cm^{-1}, due to the NH stretch of a secondary amine, as well as a weak absorption at 2730 cm^{-1} due to H-bonded OH, and a strong peak at 1660 cm^{-1} attributed to the carbonyl stretch of an amide.

Table 1

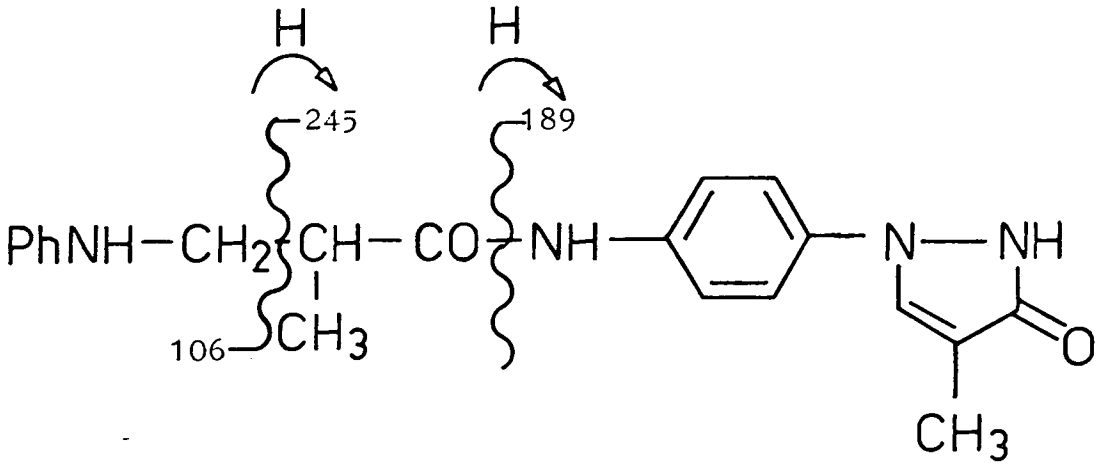


100 MHz ^{1}H n.m.r. resonances of XVIII

Proton	Shift (δ)	Multiplicity
a	6.40-7.20	Multiplet
b	7.59	AA 'BB'
c	1.93	Singlet
d	7.75	Singlet
e	1.22	Doublet
f	2.30-3.00	Multiplet

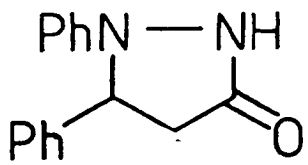
The analysis of the mass spectrum of this dimeric product was consistent with the compound having the assigned structure, XVIII. The parent ion (m/e = 350) fragmented to give ions at m/e = 245, 189, and 106. This fragmentation pattern, shown in Figure 2, is similar to that proposed for dimer XIII, formed on oxidation of 1-phenylpyrazolidin-3-one in acetonitrile[10].

Figure 2

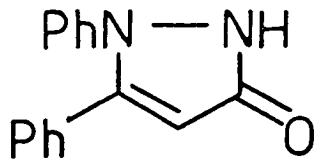


$P^+ = 350$

(XVIII)



(XIX)

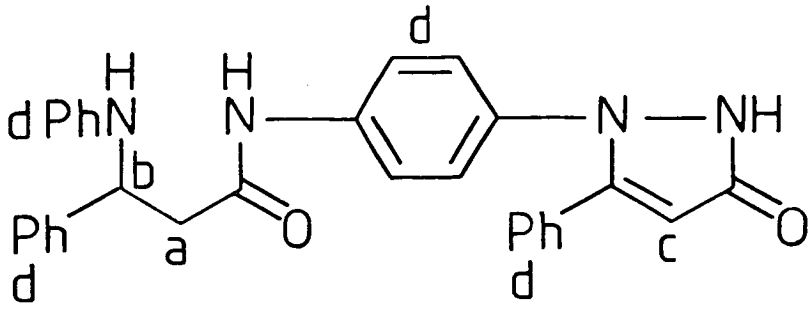


(XX)

2.2. - Electrochemical oxidation of 1,5-diphenylpyrazolidin-3-one (XIX) in acetonitrile:- The electrochemical oxidation of 1,5-diphenylpyrazolidin-3-one in acetonitrile containing tetraethylammonium chloride as the supporting electrolyte as in the case of 4-methyl-1-phenylpyrazolidin-3-one, gave only one product, 1,5-diphenylpyrazolin-3-one (XX). This product was also identified by comparing its physical properties, and its n.m.r., i.r., and mass spectra with those of an authentic sample prepared by the chemical odixation of an aqueous solution of XIX with ferric chloride[43], by elemental analysis, and by reference to the published literature[45].

The electrochemical oxidation of XIX in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte gave a mixture of 2 major products, XX and a dimer identified as 3-anilino-3-phenyl-N-[4-(5-phenyl-3-oxopyrazolin-1-yl)phenyl]propionamide (XXI) on the basis of i.r., n.m.r., and mass spectroscopic evidence. An exact mass determination of the parent ion peak (P^+ = 474) in the mass spectrum of the dimer indicated that the compound had the formula $C_{30}H_{26}N_4O_2$. Although the 100 MHz ^1H n.m.r. spectrum of this dimer was not interpretable, the 360 MHz spectrum clearly showed the following features (Table 2). The two symmetrical doublet of doublet resonances at δ2.876 (J = 1.44 Hz, 0.58 Hz) and 2.995 (J = 1.44 Hz, 0.79 Hz) were assigned to methylene protons (protons a, Table 2). Another resonance at δ5.024, also a doublet of doublets (J = 0.79 Hz, 0.58 Hz) was coupled to both of the other methylene resonances, (proton b, Table 2). The singlet at δ6.000 (proton c, Table 2) was assigned to the proton attached to unsaturated C(4). The two exchangeable protons atδ5.960 and 9.839 were not assigned.

Table 2



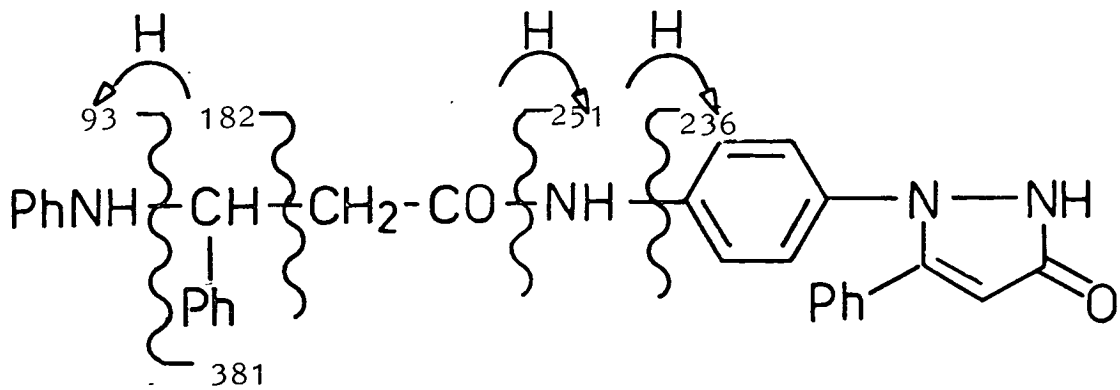
(XXI)

360 MHz ^{1}H n.m.r. resonances of XXI

Proton	Shift (δ)	Multiplicity
a	2.876	Doublet of doublets
a	2.995	Doublet of doublets
b	5.024	Doublet of doublets
c	6.000	Singlet
d	6.606-7.613	Multiplet

The infra-red spectrum showed an absorbance at 3320 cm^{-1} attributed to the NH stretch of a secondary amine, an absorbance at 2580 cm^{-1} due to hydrogen bonded OH, and a strong peak at 1665 cm^{-1} attributed to the carbonyl stretch of an amide.

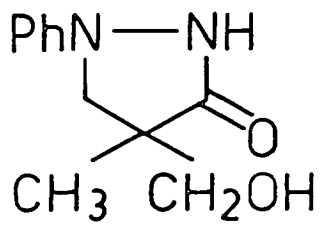
Figure 3



$P^+ = 474$

(XXI)

The analysis of the mass spectrum of this dimeric compound was also consistent with it having the structure XXI. The principal fragmentation pattern is shown in Figure 3.

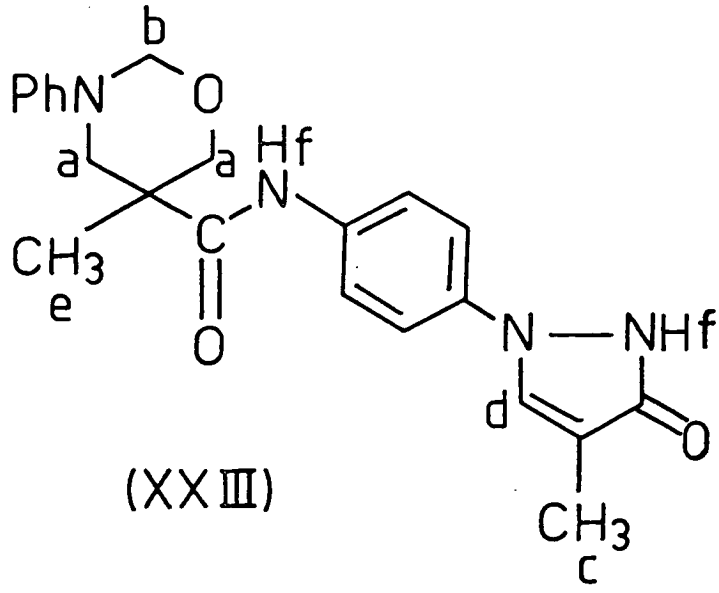


(XXII)

2.3. - Electrochemical oxidation of 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one (XXII) in acetonitrile:- The electrochemical oxidation of XXII in acetonitrile containing tetraethylammonium chloride as the supporting electrolyte also gave one product, 4-methyl-1-phenylpyrazolin-3-one(XVII). This compound was identified by comparing its physical properties, and its n.m.r. and i.r. spectra with that of an authentic sample (Section 2.1).

The electrochemical oxidation of XXII in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte gave a mixture of two products, XVII, and a dimer which was identified as 1-(5-methyl-3-phenyltetrahydro-1,3-oxazin-5-yl)-N-[4-(4-methyl-3-oxopyrazolin-1-yl)phenyl] formamide (XXIII), on the basis of i.r., n.m.r. and mass spectroscopic evidence. An exact mass determination of the parent ion peak (P+ = 392), and elemental analysis indicated that the dimer had the formula $C_{22}H_{24}N_4O_3$. The 100 MHz ^1H n.m.r. spectrum showed the following features (Table 3). Four methylene protons, giving rise to characteristic AB doublets, were apparent in positions characteristic of methylene protons attached to a hetero-atom (δ3.47, 3.66, 3.92, 4.22)(protons a; Table 3). The coupling constants for these four doublets were 12 and 13 Hz. A further broad AB pattern was also present further downfield, and centred on δ4.82. This chemical shift is characteristic of a methylene group attached to two electron rich heteroatoms (protons b; Table 3). In addition the spectrum indicated the presence of a 4-methyl-1-phenylpyrazolidin-3-one moiety viz a singlet methyl resonance at δ1.90 and an olefinic proton resonance at δ7.90. A methyl group

Table 3



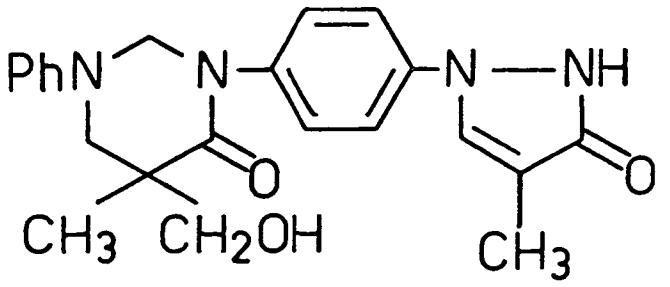
(XXIII)

100 MHz ^{1}H n.m.r. resonances of XXIII

Proton	Shift (δ)	Multiplicity
a	3.47	Doublet
a	3.66	Doublet
a	3.92	Doublet
a	4.22	Doublet
b	4.82	AB (broad)
c	1.90	Singlet
d	7.90	Singlet
e	1.16	Singlet
f	9.36	Broad
f	10.02	Broad

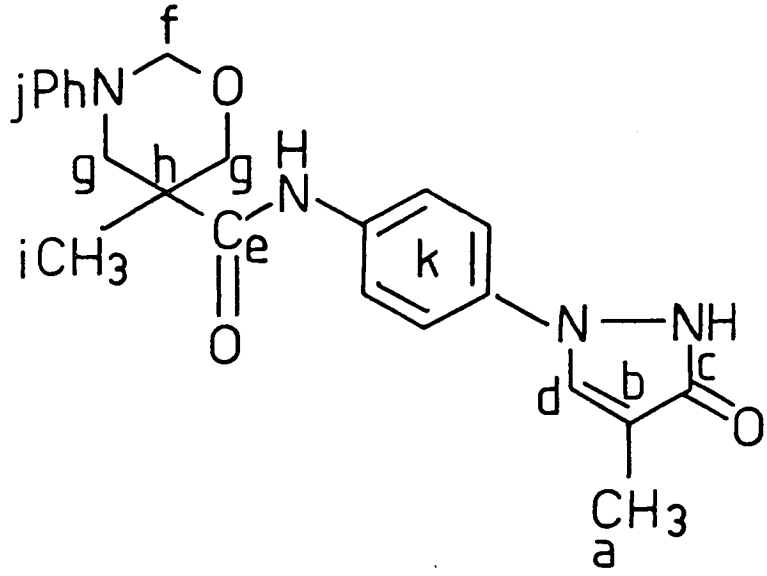
attached to a saturated carbon, a singlet resonance at δ1.16 (protons e; Table 3), and two exchangeable hydrogens at δ9.36 and δ10.02, were also indicated. The i.r. spectrum of this compound clearly showed the following features; an absorbance at 3340 cm^{-1} due to the NH stretch of a secondary amide, a strong absorbance at 1665 cm^{-1} due to the carbonyl stretch of a secondary amide, and weak peaks at 2620 cm^{-1} and 2720 cm^{-1} indicating the presence of strongly H-bonded OH.

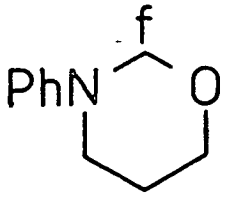
From the preceding spectroscopic evidence it was initially thought possible that the compound could have one of two structures, XXIII, or XXIV. However, the structure XXIII was finally assigned to the dimer by comparing its n.m.r. resonances with those of a model compound, tetrahydro-3-phenyl-1,3-oxazine (XXV). The position of the methylene resonance (δ4.82) in the ^{1}H n.m.r. spectrum of the dimer, exactly corresponded to the position of the methylene resonance attributable to the protons at C(2) in the model compound, XXV. In addition, by comparing the ^{13}C n.m.r. spectrum of the dimer with those of methyl-1-phenylpyrazolin-3-one (XVII), tetrahydro-3-phenyl-1,3-oxazine (XXV), and 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one (XXII), a complete assignment was made which was consistent with the structure, XXIII; this is detailed in Table 4.



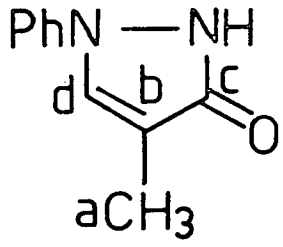
(XXIV)

Table 4

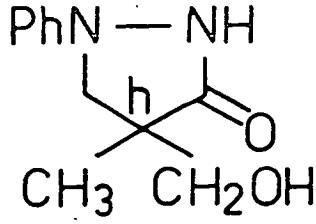




(XXV)



(XVII)



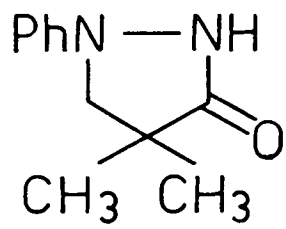
(XXII)

^{13}C n.m.r. resonances of XXIII compared to those of XXV, XVII and XXII

Carbon	XXIII	shift (ppm) XXV	XVII	XXII
a	7.10		7.12	
b	126.40		126.59	
c	161.34		161.63	

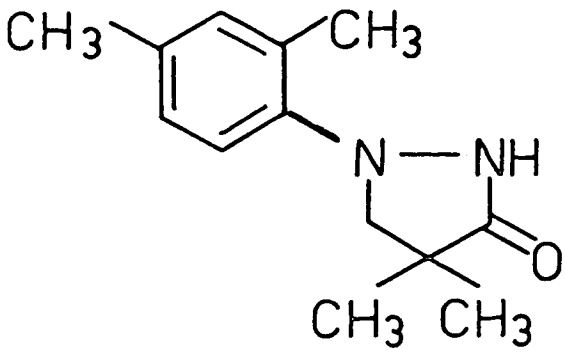
Table 4 (contd.)

Carbon	shift (ppm) XXIII	XXV	XVII	XXII
d	103.00		103.51	
e	172.50			
f	80.53	80.77		
g	72.99			
g	55.31			
h	42.41			47.00
i	19.86			
j	148.44	148.69		
j	129.11	128.96		
j	119.66	119.30		
j	116.39 or 116.59	117.07		
k	135.95			
k	135.07			
k	121.35			
k	116.39 or 116.59			



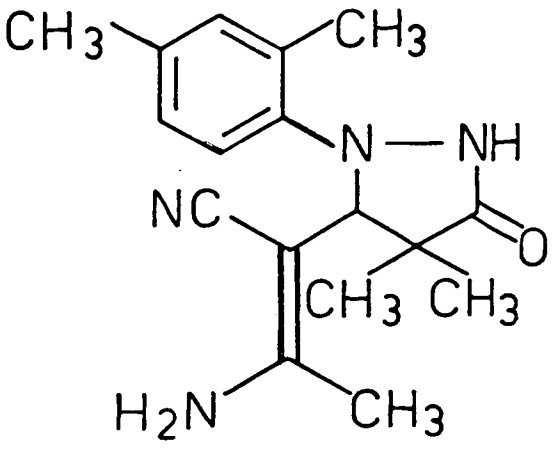
(XXVI)

2.4. - The electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one (XXVI) in acetonitrile:- Controlled potential oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one (XXVI) in acetonitrile containing tetraethylammonium fluoroborate or tetraethylammonium chloride as the supporting electrolyte gave a complex mixture of products. H.p.l.c. analysis of the former electrolysis solution indicated that the solution contained more than 24 different products, while similar analysis of the latter electrolysis solution indicated that there was no significant simplification of the product mixture using the different electrolyte. It was not possible to separate and characterise any of these products.

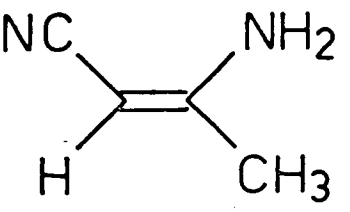


(XXVII)

2.5. - Electrochemical oxidation of 4,4-dimethyl-1-(2,4-dimethyl)-phenylpyrazolidin-3-one (XXVII) in acetonitrile:- The electrochemical oxidation of XXVII in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte gave a complex mixture of products as determined by h.p.l.c. However, h.p.l.c. analysis of the electrolysis solution when tetraethylammonium chloride was used as the supporting electrolyte indicated that one product predominated. This was isolated and identified as 4,4-dimethyl-1-(2,4-dimethyl-phenyl)-5-(1-cyano-2-amino prop-1-en-1-yl)pyrazolidin-3-one (XXVIII) on the basis of i.r., n.m.r., and mass spectroscopic evidence, and by elemental analysis. The elemental analysis of this compound indicated that it had a molecular formula of $C_{17}H_{22}N_4O$, which was consistent with the parent ion peak in the mass spectrum at m/e = 298. The ^1H n.m.r. spectrum (100 MHz) indicated the presence of 5 methyl groups. The resonances at δ0.95 and 1.07 corresponded to the methyl proton resonances at C(4); that these groups absorbed at different chemical shifts indicated that on oxidation the plane of symmetry of the parent molecule had been destroyed; the ^1H n.m.r. spectrum of the parent molecule showed a singlet resonance at δ1.01. The broad singlet at δ2.19 in the ^1H n.m.r. spectrum of XXVII assigned to the methyl groups at C(2) and C(4) in the phenyl ring attached to N(1) was also present in the ^1H n.m.r. spectrum of XXVIII.



(XXVIII)



(XXIX)

The broadness of this singlet is due to the accidental coincidence of these two methyl resonances. One further methyl proton resonance was apparent at δ1.97, close to that of the methyl resonance in the ^{1}H n.m.r. spectrum of cis-1-cyano-2-aminoprop-1-ene(XXIX). Three exchangeable hydrogen resonances were also present in the spectrum. Two, observed as a broad singlet at δ6.37, were assigned to the amine protons analagous to those in structure XXIX. The third, at δ9.78, was assigned to the amide hydrogen at N(2). There was also a broad singlet in the methyne region of the spectrum due to the proton at C(5) of XXVIII. Aromatic proton resonances were also present in the spectrum at the same frequency as those in the starting compound (δ6.80 - 7.20). Table 5 summarises the 100 MHz ^{1}H n.m.r. resonances of compound XXVIII, and compares them to those of the starting material (XXVII) and compound XXIX.

Table 5

100 MHz ^{1}H n.m.r. resonances of XXVIII compared to those of XXVII and XXIX

PROTON	Shift/ δ (Multiplicity) XXVIII	XXVII	XXIX
$C\underline{H}_3$-aromatic	2.18 (singlet)	2.19 (singlet)	
$(C\underline{H}_3)_2$-aliphatic	0.95 (singlet) 1.07 (singlet)	1.01 (singlet)	
$C\underline{H}_3C{=}C$	1.97 (singlet)		2.00 (singlet)
$C\underline{H}_2CH_2$		3.33 (singlet)	
C<u>H</u>RCH	4.11 (singlet)		
C<u>H</u>-aromatic	6.80-7.20 (multiplet)	6.80-7.14 (multiplet)	
exchangeable N<u>H</u>/O<u>H</u>	6.37 (singlet) 9.78 (singlet)	9.75 (singlet)	

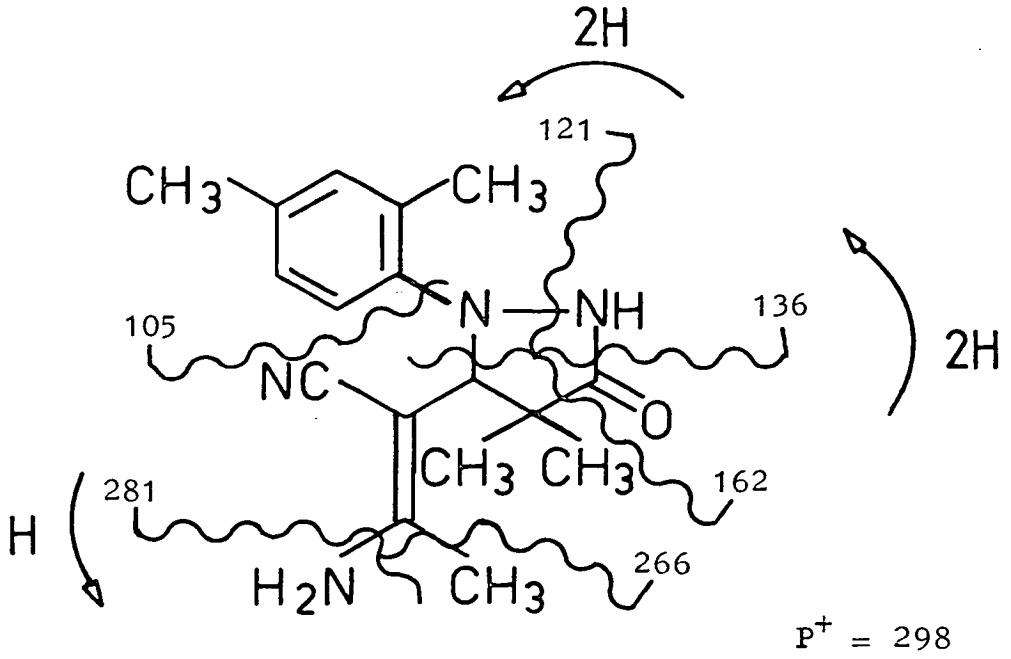
The ^{13}C n.m.r spectrum of XXVIII confirmed the assignment. A complete assignment of the ^{13}C resonances was made (Table 6) by comparison with the corresponding resonances of XXVII and XXIX, and by performing off-resonance experiments to determine the primary, secondary, or tertiary nature of the carbon atoms. The mass spectrum fragmentation pattern of XXVIII is shown in Figure 4. The molecule fragments by the same route as other 1-arylpyrazolidin-3-ones after loss of the group at C(5). An exact mass determination of the parent ion peak (P+ = 298) confirmed that the molecular formula was $C_{17}H_{22}N_4O$. In addition, the infra-red spectrum clearly showed the following features; absorbances at 3500 and 3250 cm^{-1} characteristic of a primary amine NH stretch (XXIX; 3450 and 3230 cm^{-1}), an absorbance at 3360 cm^{-1} characteristic of an amide NH stretch, a strong absorbance at 2205 cm^{-1} due to a nitrile group stretch (XXIX; 2180 cm^{-1}), a strong absorbance at 1700 cm^{-1} due to double bond stretch (XXIX; 1640 cm^{-1}), and a strong absorbance at 1660 cm^{-1} due to the stretch of an amide carbonyl.

Table 6

^{13}C n.m.r. resonances of XXVIII compared to those of XXIX and XXVII

Carbon	shift (ppm) XXVIII	XXIX	XXVII
>C=O	176.56		177.72
-C-	44.06		40.15
$>CH_2$			66.57
>CHR	75.21		
$>C=CNH_2$	156.31	163.25	
$CH_3C=C<$	25.21	18.92	
$(CH_3)_2C<$	20.22		23.73
CH_3-aromatic	19.12 17.46		20.21 17.74
-CN	122.09	122.46	
>C=C< aromatic	149.48 132.30 131.76 129.89 126.48 117.39		148.35 131.92 (quaternary 2(C)) 128.15 126.63 116.26
$NCC=CNH_2$ (R, CH_3)	69.82	59.87 or 58.15	

Figure 4



(XXVIII)

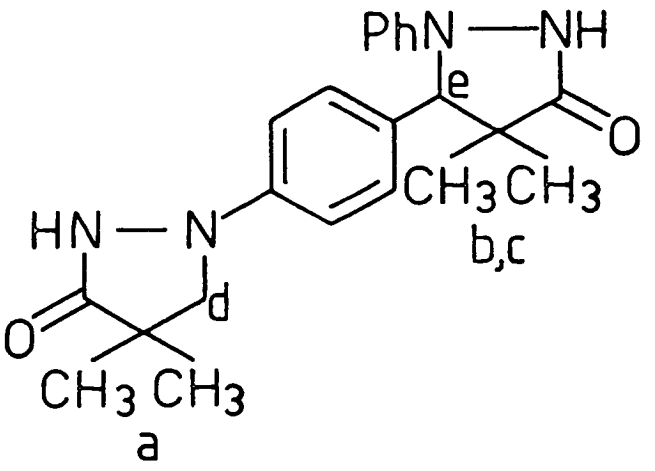
The configuration about the double bond in XXVIII has not been absolutely assigned. However, it is clear from the ^{1}H n.m.r. spectrum that only one isomer is present. The structure of XXVIII as drawn is likely to be more stable because of hydrogen bonding between the cyano and amino groups. Conn and Taurins[99] have investigated the cis/trans isomerisation of 1-cyano-2-aminoprop-1-ene (XXIX) and concluded that the cis form is more stable. XXIX was prepared under conditions which Conn and Taurins[99] described as favouring formation of the cis isomer; a comparison of the methyl resonances in the ^{1}H n.m.r. spectrum indicated that the methyl resonance of the cis form was close to that of the side-group methyl resonance in the n.m.r. spectrum of XXVIII (Table 5), whereas the methyl resonance of the less stable trans form occurred at a lower frequency (δ1.87).

2.6. - Electrochemical oxidation of 1-phenylpyrazolidin-3-one in methylene chloride:- The electrochemical oxidation of 1-phenylpyrazolidin-3-one in methylene chloride containing tetrabutylammonium fluoroborate as the supporting electrolyte gave one product, 1-phenylpyrazolin-3-one which was identified by comparing its physical properties and spectra with that of an authentic sample prepared by chemical oxidation[43].

2.7. - Electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one (XXVI) in methylene chloride:- In contrast to the results described in Section 2.6, and to the previously described behaviour of XXVI in acetonitrile (Section 2.4), the electrochemical oxidation of XXVI in methylene chloride containing tetrabutylammonium fluoroborate as the supporting electrolyte, gave only one product. This was a dimer of XXVI and was identified as 4,4-dimethyl-1-phenyl-5-[4'-(4,4-dimethyl-3-oxopyrazolidin-1-yl)]phenylpyrazolidin-3-one (XXX). When the oxidation was carried out in the presence of the base, 2,6-lutidine, a different dimer was isolated as the only product of the oxidation and this was identified as 4,4-dimethyl-5-(4,4-dimethyl-1-phenyl-3-oxopyrazolidin-2-yl)-1-phenylpyrazolidin-3-one (XXXI). Both of these dimeric structures were assigned on the basis of i.r., n.m.r. and mass spectroscopic evidence, and by elemental analysis.

The ^{1}H 60 MHz n.m.r. spectrum of XXX clearly showed the following features. In the methyl region of the spectrum there were three singlet resonances. One, at δ1.09, integrated for $2CH_3$ and was assigned to protons a (Table 7) by comparison with the corresponding resonance for XXVI (δ0.98). Two other singlet methyl resonances were apparent. The rather high field resonance of one, at δ0.68, provided evidence for the presence of an adjacent aryl group at C(5), the latter producing a neighbouring anisotropic shift of the resonance due to the methyl group cis to the phenyl group (protons b; Table 7).

Table 7

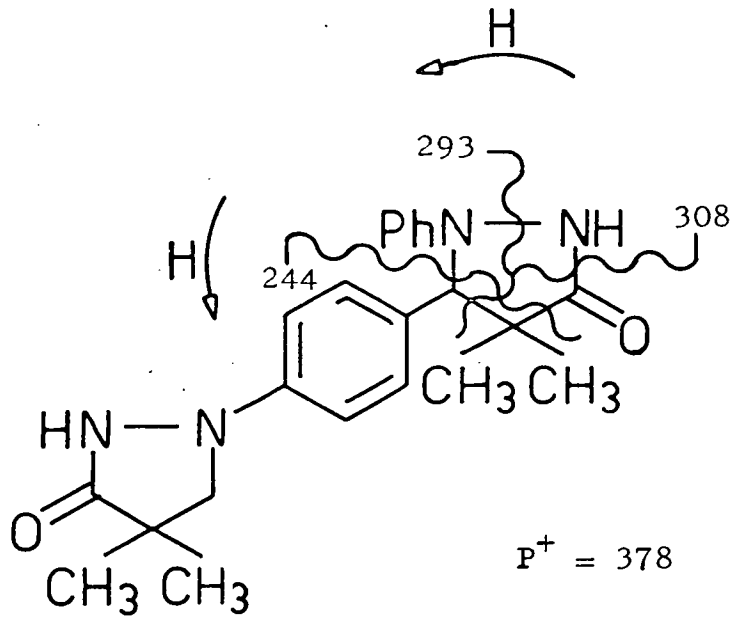


(XXX)

60 MHz ^{1}H n.m.r. resonances of XXX

Proton	Shift (δ)	Multiplicity
a	1.09	Singlet
b	0.68	Singlet
c	1.17	Singlet
d	3.73	Singlet
e	4.68	Singlet

Figure 5



(XXX)

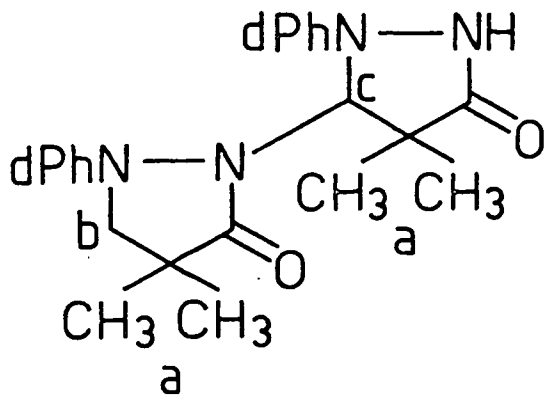
i.e. magnetic shielding of a methyl group at C(4) positioned centrally above the plane of the aryl ring at C(5). The singlet methyl resonance at lower field (δ1.17), is correspondingly due to deshielding of the other methyl group at C(4), i.e. trans to the phenyl ring at C(5) (protons c; Table 7). There were two other singlet resonances in the ^{1}H n.m.r. spectrum of XXX. The singlet at δ3.73 was attributed to a methylene group (protons d; Table 7) in a similar magnetic environment to that of the methylene group at C(5) in the parent compound (XXVI), which gave rise to a singlet at δ3.64, and the singlet at δ4.68 in the methyne region of the spectrum was assigned to proton e (Table 7), adjacent to the phenyl ring at C(5). In addition, the aromatic region of the spectrum showed a multiplet resonance which integrated for 9 protons, and a broad peak centred on δ10.40 accounted for the 2 exchangeable NH protons. The i.r. spectrum of compound XXX showed one strong absorbance at 1690 cm^{-1}, due to the carbonyl stretch of a secondary amide. The structure was confirmed by the principal breakdown pattern in the mass spectrum

which is shown in Figure 5. The occurrence of a fragment at m/e = 244 is further strong evidence for the proposed structure. In addition, elemental analysis indicated that the molecular formula was $C_{22}H_{26}N_4O_2$. Elemental analysis of XXXI indicated that this dimer also had a molecular formula of $C_{22}H_{26}N_4O_2$. The 100 MHz ^1H n.m.r. spectrum, however, showed the presence of four methyl groups in different magnetic environments (protons a; Table 8). There were also two methylene doublet resonances centred on δ3.50 (J = 12 Hz) and 3.86 (J = 12 HZ)(protons b; Table 8). A further singlet resonance was observed at δ5.73. This was assigned to the proton at C(5) (proton c; Table 8), and indicated that dimerisation of the starting material had occurred through C(5). That this dimerisation had occurred through an amide nitrogen was evident from the occurrence of a carbonyl stretching band at 1715 cm^{-1} in the i.r. spectrum, and the aromatic region of the ^1H n.m.r. spectrum (protons d; Table 8) integrating for 10 protons. The proposal that coupling had occurred in this manner also explains the non-equivalence of both the methyl and methylene resonances in the ^1H n.m.r. spectrum. The pyrazolidinyl group in XXX is attached to C(5) through a phenyl ring which allows free rotation about the bond between C(4') and N(1") resulting in the magnetic equivalence in the ^1H n.m.r. spectrum of the methyl protons attached to C(4") and the methylene protons at C(5").

In contrast, the pyrazolidinyl group in XXXI is coupled to C(5) directly through N(2'). Free rotation about this bond does not occur due to steric hindrance and results in all methyl protons and the protons at C(5') in the ^1H n.m.r. spectrum of XXXI appearing at different frequencies. Also present in the i.r. spectrum of XXXI was an absorbance at 1680 cm^{-1} due to the carbonyl stretch of a secondary amide, and an absorbance at 3420 cm^{-1} due to the NH stretch of a secondary amide.

The principal fragmentation pattern in the mass spectrum is shown in Figure 6; the parent ion peak (P+ = 378) was very weak and gave rise to a principal fragmentation at the N-C bond at C(5), thus supporting the structural assignment.

Table 8

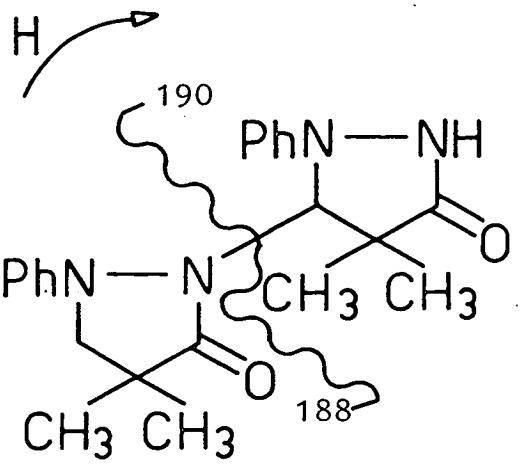


(XXXI)

100 MHz ^{1}H n.m.r. resonances of XXXI

Proton	Shift (δ)	Multiplicity
a	1.10	Singlet
a	1.15	Singlet
a	1.18	Singlet
a	1.26	Singlet
b	3.50	Doublet
b	3.86	Doublet
c	5.73	Singlet
d	6.80-7.40	Multiplet

Figure 6



$P^+ = 378$

(XXXI)

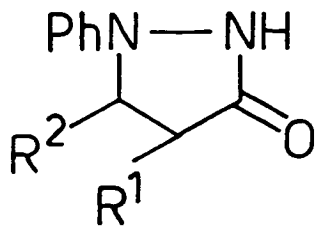
CHAPTER 3

DISCUSSION OF THE MECHANISM OF THE ELECTROCHEMICAL OXIDATION OF 1-PHENYLPYRAZOLIDIN-3-ONES IN APROTIC SOLVENTS

3.1. - Initial oxidative charge transfer in neutral acetonitrile:-
The electrochemical oxidation of 1-phenylpyrazolidin-3-one and some of its derivatives (RH)(Table 9) in neutral acetonitrile has been shown to yield two products (Chapter 2), the corresponding pyrazolin-3-one(P) as the major product, and a dimeric compound (D). Electrochemical oxidation of 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one (XXII) under identical conditions also gives the corresponding pyrazolin-3-one(XVII) and a dimeric compound which has been assigned the structure XXIII (Chapter 2). The formation of the major product, P, has previously been rationalised in terms of a sequence of squares[10] (Scheme 8), although it has not been determined whether further oxidation of the neutral acylhydrazyl radical, $R^{\bullet}$, occurs by heterogeneous charge transfer, or by disproportionation in solution.

In an attempt to differentiate between these possibilities cyclic and linear sweep voltammograms were obtained from solutions of 1-phenylpyrazolidin-3-one in acetonitrile, using tetraethylammonium fluoroborate as the supporting electrolyte, under conditions of varying concentration (c), sweep rate ($\underline{v}$), and concentration of added base, recording changes in anodic peak potential ($E_{p,a}$), anodic peak current ($i_{p,a}$), and reversibility ($i_{p,c}/i_{p,a}$).

Cyclic voltammograms, obtained from a 1mM solution of 1-phenylpyrazolidin-3-one in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte (0.4M), with a sweep rate of 0.1 $V.s^{-1}$, and a voltage range of -1.2 V to +1.2 V, showed an initial oxidation wave at 0.264 V vs. $Ag/AgNO_3$, with a half-peak potential at 0.180 V.

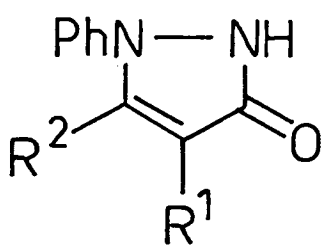


(RH)

Table 9

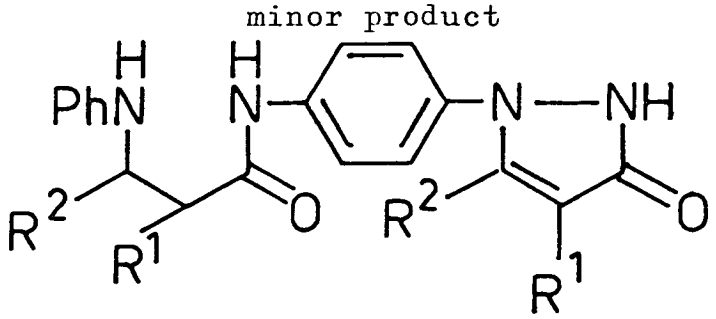
R^1	R^2
H	H(10)
CH_3	H
H	Ph

major product

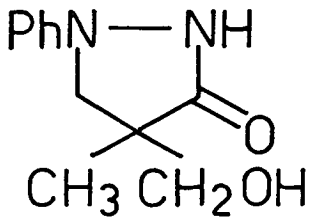


(P)

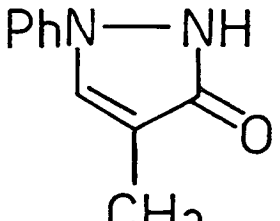
minor product



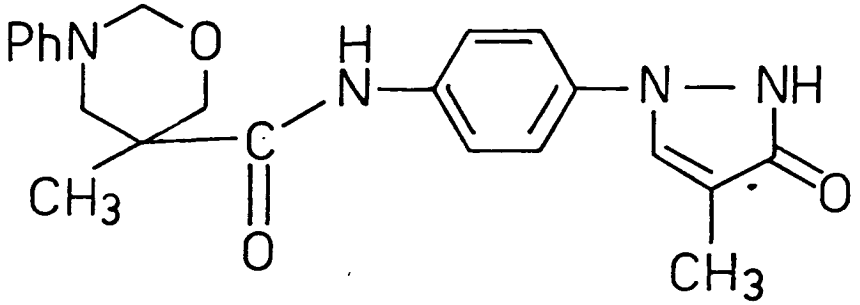
(D)



(XXII)



(XVII)



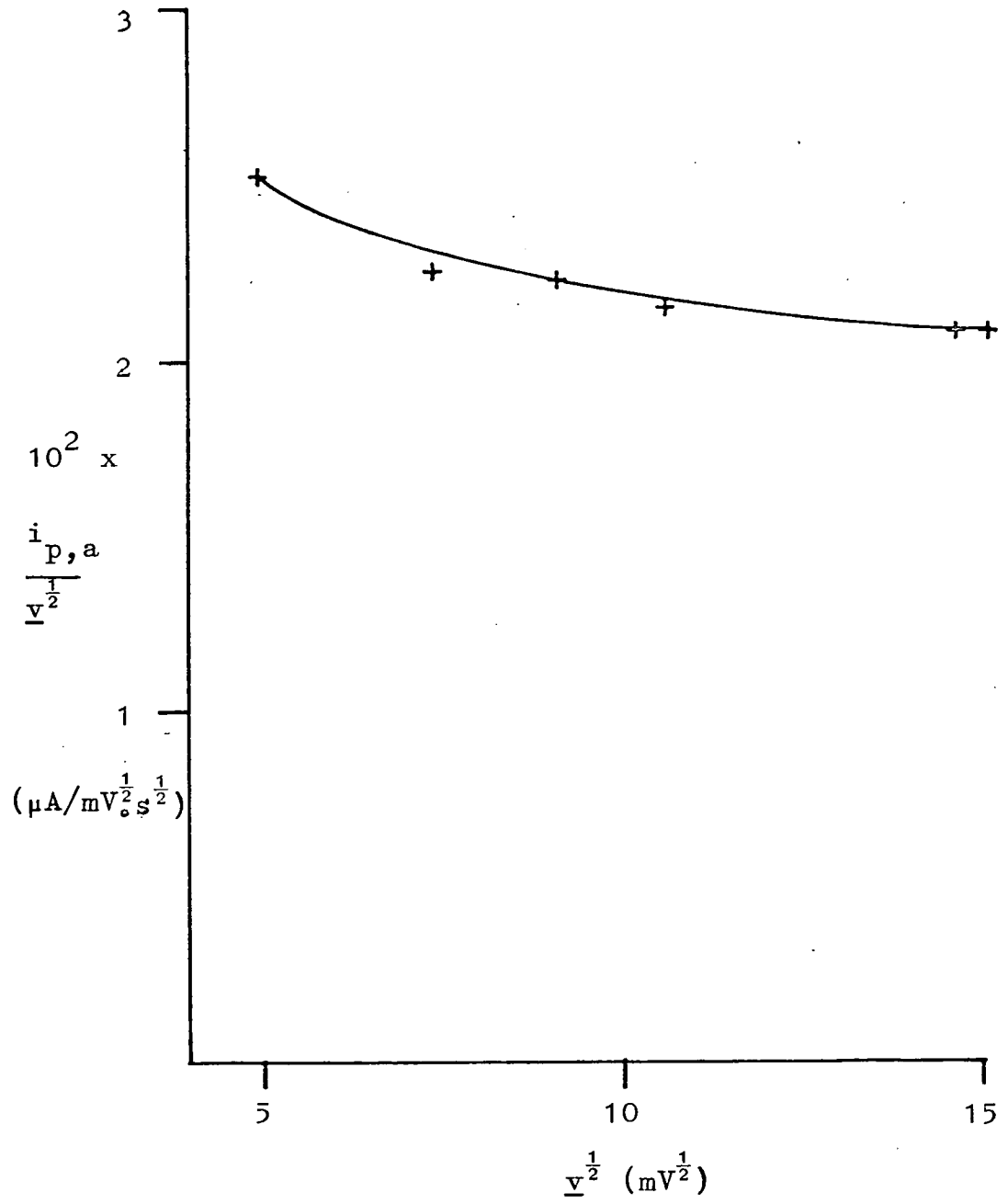
(XXIII)

No cathodic current due to the reversible reduction of the initial oxidation product was observed at this concentration and at this sweep rate. However, on increasing the sweep rate ($\underline{v}$), an anodic shift of the wave was observed along with an increase in cathodic current. The anodic current function, $i_{p,a}\underline{v}^{-\frac{1}{2}}$, decreased with an increase in sweep rate ($\underline{v}$)(Figure 7). Comparing the anodic peak current with that of a known one electron system, the oxidation of ferrocene in acetonitrile[47], gave a concentration normalised current ratio (N, Equation 1) of 1.54(0.93mM 1-phenylpyrazolidin-3-one; 1.34mM ferrocene). The sweep rate was identical in both determinations ($0.1\ V.s^{-1}$).

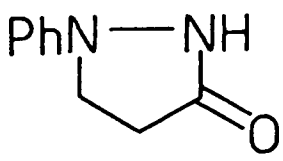
$$N = \frac{n^{3/2}\ D^{1/2}\ (\text{pyrazolidin-3-one})}{D^{\frac{1}{2}}\ (\text{ferrocene})} \qquad 1$$

Assuming that there is no significant difference in the diffusion co-efficients of 1-phenylpyrazolidin-3-one and ferrocene, the anodic peak corresponding to the initial oxidation of 1-phenylpyrazolidin-3-one involves the transfer of more than 1 electron/molecule. In addition, as the sweep rate was increased the anodic current approached that of a 1 electron oxidation. These experimental observations are consistent with the proposal[10], that an irreversible, fast, following chemical reaction occurs after the initial electron transfer[48], giving a species which is further oxidised either at the electrode surface (Scheme 11; ECE), or in solution by a solution electron transfer, the latter resulting in an increase in depolariser concentration in the vicinity of the electrode surface (disproportionation). It is possible to formulate 4 mechanisms by which a second electron transfer can occur to give the observed major product of the macro-scale electrolysis, and which are consistent with the electroanalytical behaviour of these compounds. (Schemes 11-14). It had previously been reported that at low sweep rates ($30\ mV.s^{-1}$), a second oxidation wave, previously assigned to the oxidation of the protonated pyrazolidinone, $RH_2^{+\cdot}$ (Scheme 8), appears at a more anodic potential[10]. This anodic peak was not observed at the low substrate concentration used in the present study.

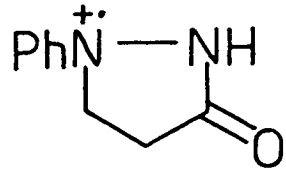
Figure 7



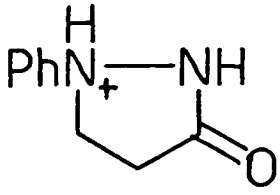
Plot of $i_{p,a}/v^{\frac{1}{2}}$ against $v^{\frac{1}{2}}$ obtained from a 1.30mM solution of 1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate (0.4M) as the supporting electrolyte.



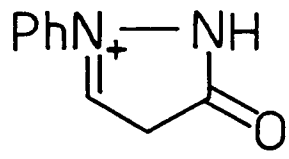
(RH)



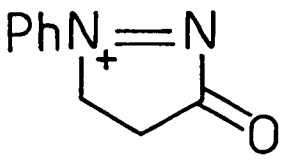
$(\dot{R}H)^{+}$



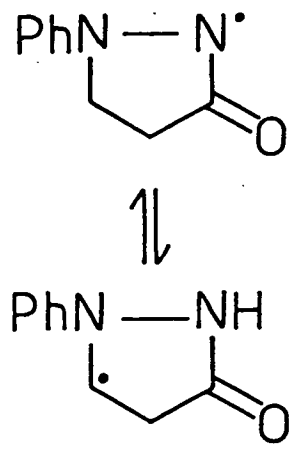
$(\dot{R}H_2)^{+}$



$(\dot{R})^{+}$

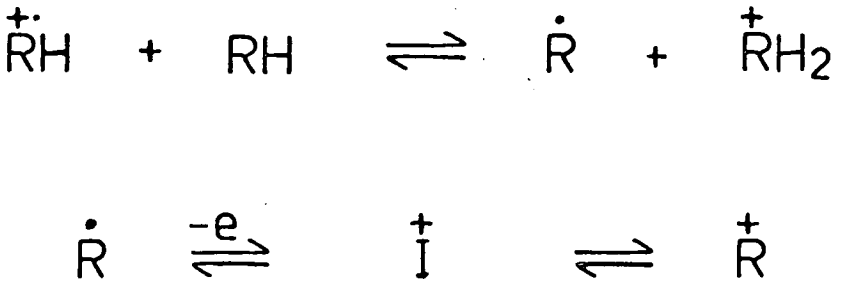


$(\dot{I})^{+}$

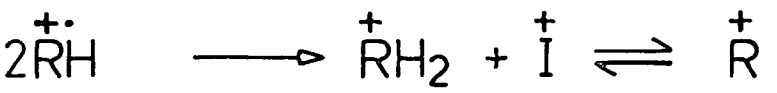


(Ṙ)

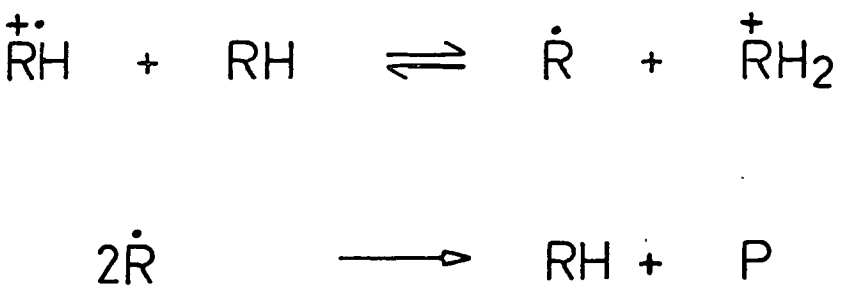
Scheme 11



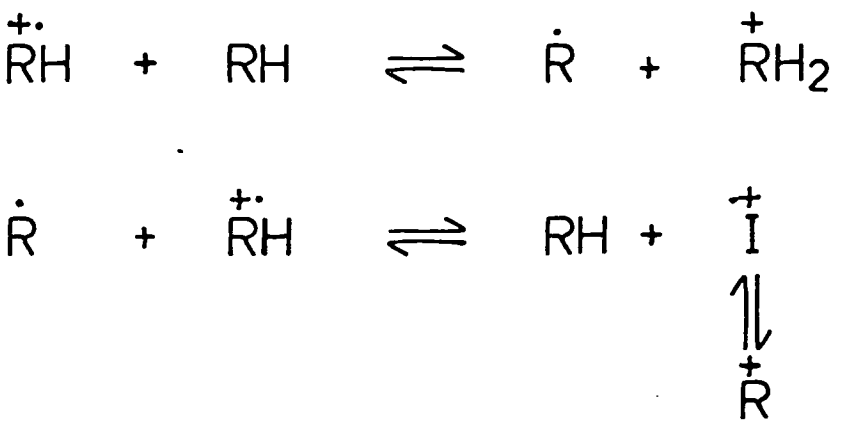
Scheme 12



Scheme 13



Scheme 14



As this latter peak had been observed at higher substrate concentrations (10^{-2}M), linear sweep voltammograms were obtained as a function of concentration (Figure 8), at constant sweep rate (100 mV.s^{-1}), to determine whether the occurrence of the second peak was concentration dependent, and to observe any dependence of the peak potential upon concentration. At low concentrations, the plot of $E_{p,a}$ of the first peak against log c (Figure 9) is a straight line, with a slope of 39 mV per decade change in concentration. Above around 2mM, however, there is no peak potential shift with concentration, but at this concentration a second wave appears at a more anodic potential which corresponds to the oxidation of protonated substrate.

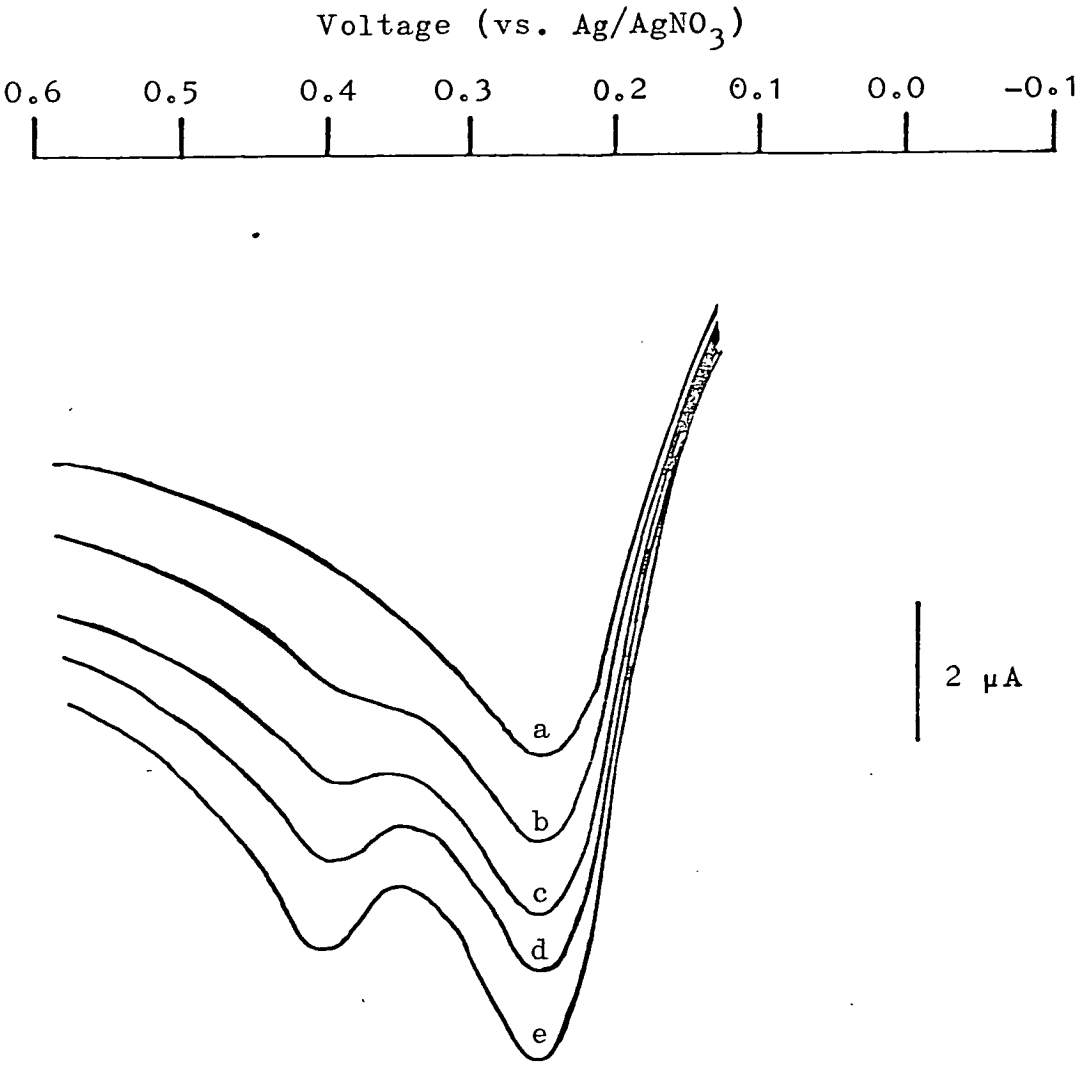
A plot of the peak current ($i_{p,a}$) of the initial wave against concentration at constant sweep rate (Figure 10) showed a linear dependence at low concentrations of substrate, as predicted from the Randles-Sevcik equation (Equation 2[49,50]), for an ECE process where $n_1 = n_2 = 1$[51].

$$i_p = k(n_1 + n_2) A D_o^{\frac{1}{2}} C_o v^{\frac{1}{2}} \qquad \text{Equation 2}$$

taking $D = 2.07 \times 10^{-5}$ cm^2 s^{-1} [10], $A = 3.2 \times 10^{-3} cm^2$ (Chapter 5), $k = 2.69 \times 10^8$ (current in μA)[52].

Since at low concentrations the current is that of a 2 electron oxidation/molecule of substrate, and since protonated pyrazolidinone is not detected by voltammetry at concentrations below 2mM (Figure 8), Schemes 11-14 are not feasible mechanisms. It is probable that at low concentrations a trace impurity is altering the oxidation mechanism, resulting in the appearance of a 2 electron wave. There are two possible mechanisms involving a basic impurity in the voltammetric solution which could account for the linear concentration dependence of the peak current at low concentrations. These mechanisms are shown in Schemes 15 and 16.

Figure 8

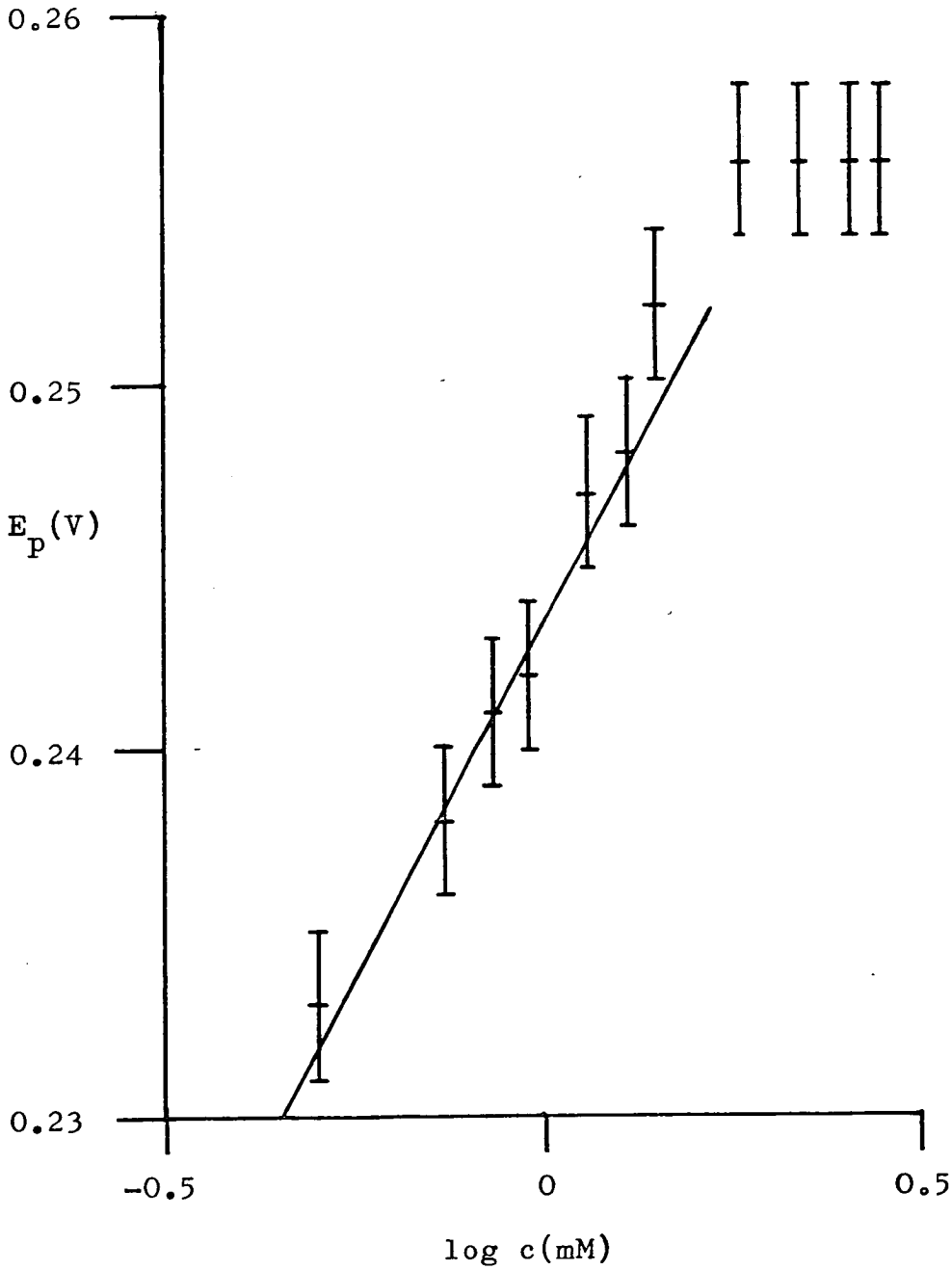


1-phenylpyrazolidin-3-one concentration (mM)

a 1.81
b 2.19
c 2.54
d 2.87
e 3.18

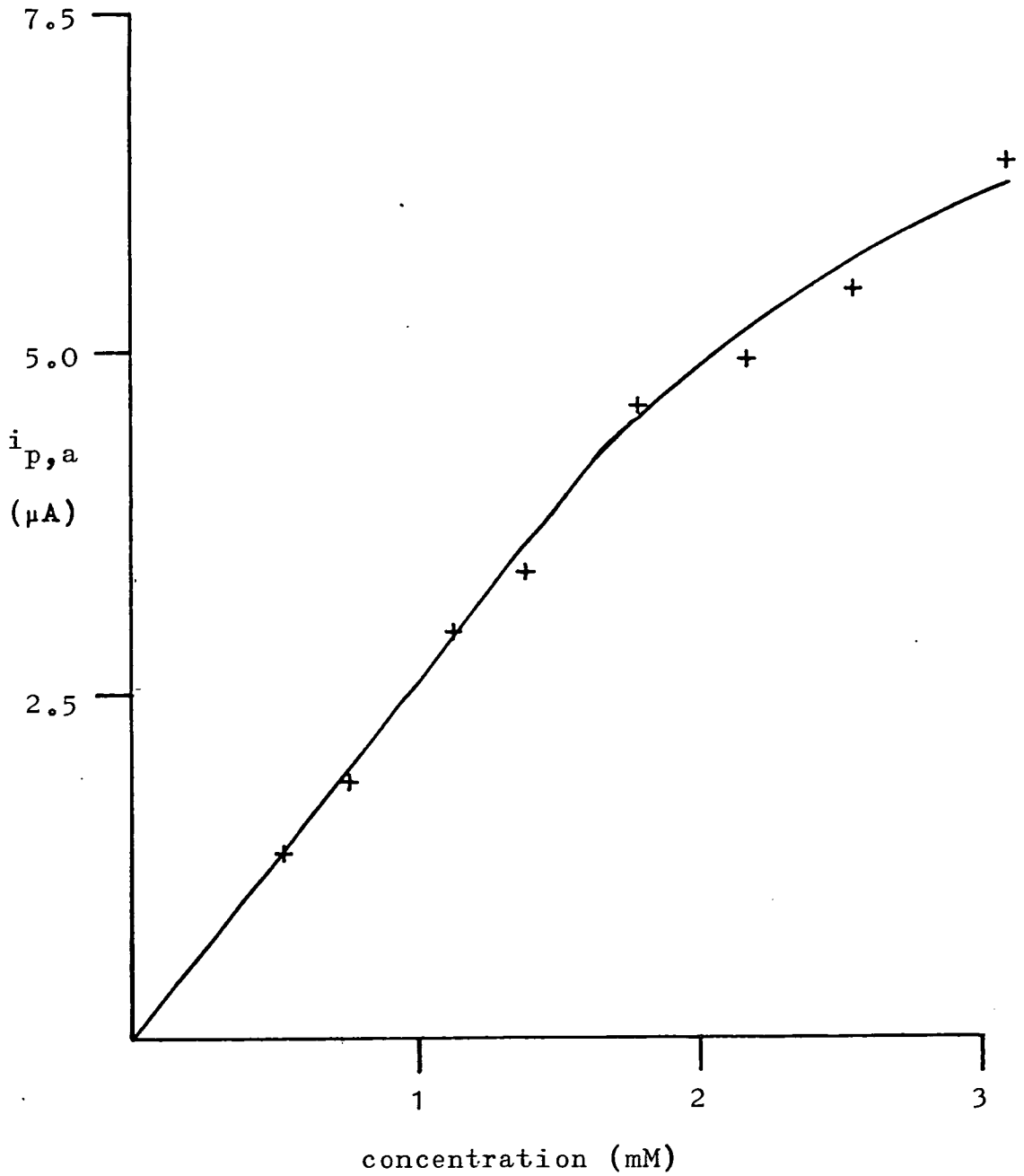
$\underline{v}$ = 100 $mV.s^{-1}$

Figure 9



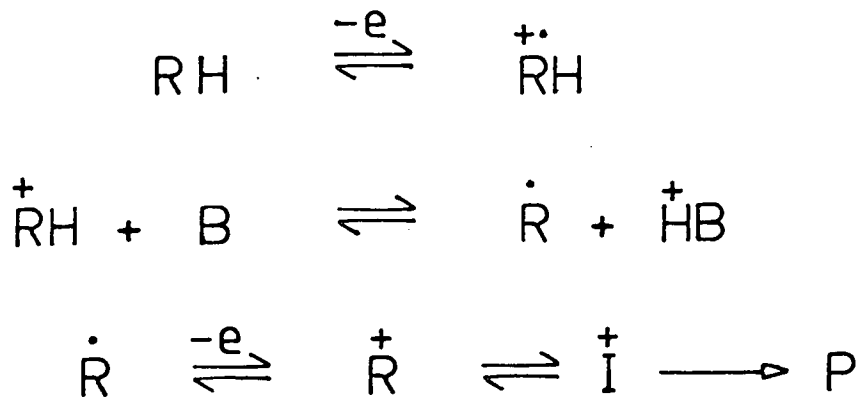
$\underline{v}$ = 100 $mV.s^{-1}$

Figure 10

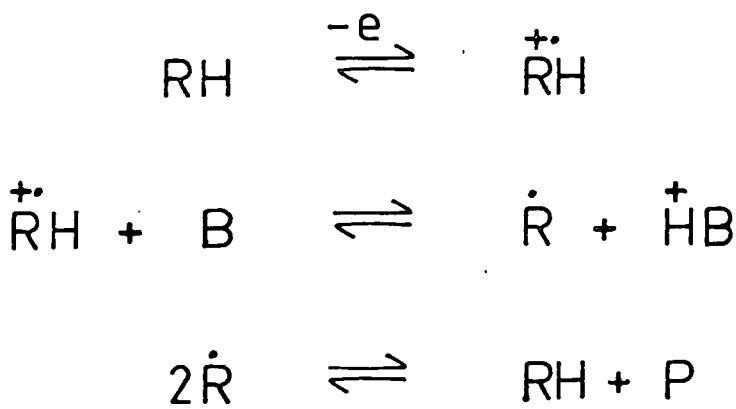


$\underline{v}$ = 100 $mV.s^{-1}$

Scheme 15



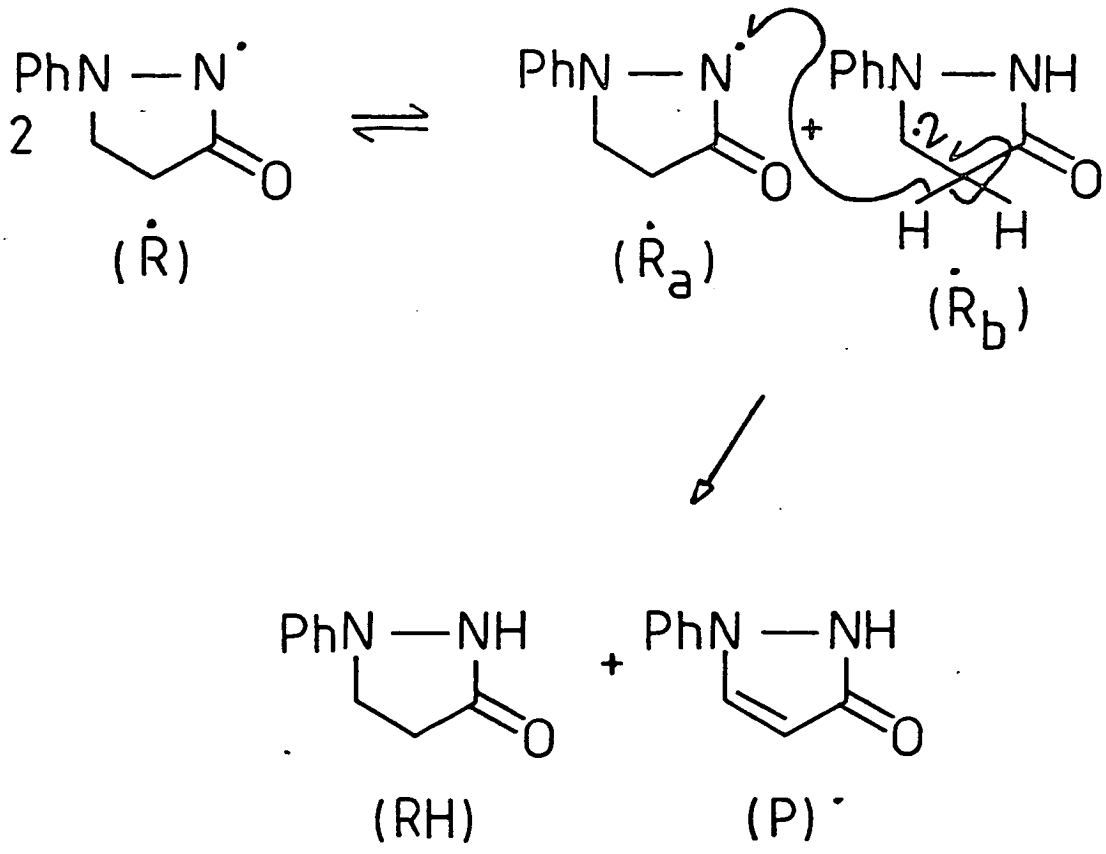
Scheme 16



Scheme 15 shows an ECE process by which the protonated acylhydrazyl radical, $RH^{+\bullet}$, is deprotonated by the basic impurity, B. The generated acylhydrazyl radical, R., is then further oxidised at the electrode surface, to the intermediate I^+, which rearranges to R^+, and after proton loss yields the major product, P. The proposal that the acylhydrazyl radical $R^\bullet$ is oxidisable at the potential at which RH shows a voltammetric response[39] (Section 3.3) is consistent with this mechanism.

An alternative mechanism (Scheme 16) involves the rapid disproportionation (DISP) of 2 acylhydrazyl radicals, $R^\bullet$. This mechanism requires that the form of $R^\bullet$ with the radical centre on N(2) ($R^\bullet_a$; Scheme 17) reacts with a radical centred on C(5) ($R^\bullet_b$; Scheme 17). $R^\bullet_b$ could be formed either by a Hoffmann-Loffler[53] type intramolecular rearrangement of $R^\bullet_a$, or directly as a product of the initial electron transfer.

Scheme 17



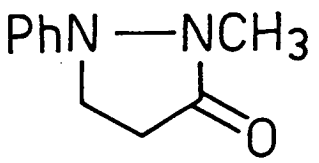
On balance, however, at the low concentrations which correspond to the linear portion of Figure 9 an ECE process involving heterogeneous charge transfer, is more likely to occur than second-order disproportionation of 2 neutral acylhydrazyl radicals $R^{\bullet}$.

The existence of a basic impurity in the voltammetric solutions can best be explained by the presence of trace amounts of water in the acetonitrile which was used for the electroanalytical work, although experimental precautions had been taken to ensure the solvent was dry, and was not exposed to the atmosphere. Water has been shown to be a strong base in acetronitrile by Kolthoff[41,42,54]. As the concentration of the pyrazolidinone is increased (Figure 10), the current deviates from that corresponding to a 2-electron ECE oxidation of substrate[51], and the peak (Figure 8) due to oxidation of protonated pyrazolidinone RH_2^+ appears. The occurrence of protonated pyrazolidinone RH_2, can be explained by Schemes 11 and 13. In these mechanisms, as there is insufficient basic impurity in the voltammetric solution to effect the deprotonation of the radical cation, $RH^{+\bullet}$, the substrate itself, RH, acts as a base. An alternative mechanism (Scheme 12) involves the disproportionation of 2 radical cations, $RH^{+\bullet}$, to the protonated pyrazolidinone, RH_2^+, and the intermediate, I^+.

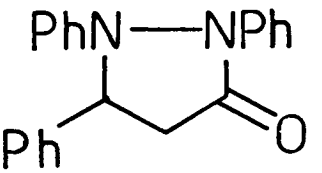
Joslin and Baigrie[10] have previously discounted the latter mechanism on the grounds that while in acetonitrile no peak was observed which could be attributed to the heterogeneous oxidation of the radical cation $RH^{+\bullet}$, this mechanism implies an easy homogeneous route (Scheme 12). As cyclic voltammetry indicated that the radical dication, $RH_2^{\bullet 2+}$, formed by oxidation of protonated pyrazolidinone, RH_2^+, in acidic acenonitrile, was more stable than the radical cation, $RH^{+\bullet}$, was in neutral solution, the authors argued that disproportionation, as set out in Scheme 12, was less acceptable than that shown in Scheme 13. However, studies on the electrochemical oxidation of the RH in aqueous alkali[30] have shown that radical disproportionation ($R^{\bullet}$; Scheme 4a) occurs after the initial oxidative electron transfer even although a second heterogeneous electron transfer (Scheme 4b) occurs at a potential which is 0.52 V more anodic than the first electron transfer. The fact that the radical dication in acidic

acetonitrile is more stable than the radical cation is in neutral acetonitrile, does not detract therefore from the plausibility of this disproportion mechanism (Scheme 12). However, it would appear reasonable to assume on the basis of coulombic repulsion, that disproportionation between two dications is less likely to occur than disproportionation between two monocations.

The experimental observations (a) that at low concentration of RH (Figure 9), in the presence of a basic impurity the diffusion current is that of a two electron ECE process, while at higher concentrations of RH, a wave due to protonated pyrazolidinone, RH_2^+ appears, (b) that the current due to the oxidation of unprotonated pyrazolidinone, RH, approaches that expected for a 1 electron oxidation at high concentration of RH, and (c) that the anodic current function ($i_{p,a} \cdot v^{-\frac{1}{2}}$) decreases with an increase in sweep rate at a concentration at which the protonated pyrazolidinone RH_2^+ is not observed, leads to the conclusion that deprotonation of RH is the most probable rate-limiting step in the overall oxidation mechanism. Alternatively if disproportionation of the radical cation $RH^{+\cdot}$ contributes significantly to the overall oxidation mechanism at high concentrations, then the experimental evidence points to this as being the rate-limiting step of this route (Scheme 12).



(XXXII)



(XXXIII)

In order to determine the effect on the voltammetric behaviour of 1-phenylpyrazolidin-3-one of alkyl and aryl substitution at N(2), cyclic voltammograms were obtained from solutions of 2-methyl-1-phenylpyrazolidin-3-one (XXXII), and 1,2,5-triphenylpyrazolidin-3-one (XXXIII) in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte.

Both of these compounds exhibit electrochemical reversibility at a sweep rate as low as 0.1 $V.s^{-1}$. This suggests that the chemical reaction which normally occurs after the initial electron transfer involves the amide hydrogen at N(2). This is consistent again with both the mechanisms shown in Schemes 11 and 12, although for disproportionation of two radical cations ($RH^{+}\cdot$; Scheme 12) to occur, the reaction must be disproportionation to yield intermediate I^{+}, since if disproportionation to give intermediate R^{+} was the rate-determining step of the reaction the electrochemical reversibility of the pyrazolidinone would be unaffected by substitution at N(2).

A controlled potential electrolysis of 2-methyl-1-phenyl pyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte did not produce an isolable product. Qualitative straight-phase h.p.l.c. analysis of the oxidation product showed only the presence of starting material and reverse-phase h.p.l.c. indicated that the reaction mixture contained over 11 high polarity products. This indicated that the radical cation generated on electrolysis did not react to give stable products on the time-scale of a macro-scale electrolysis.

Saveant and his co-workers[55,56,57] have published diagnostic criteria for distinguishing between various mechanistic possibilities and identifying the rate limiting step in electrochemical reactions, and these theoretical analyses have been successfully applied to other electrochemical systems[58,59]. The theory of their analysis, however, requires that the electrochemical oxidation gives rise to deprotonation reactions which are first order[56,57], and the proton donor/acceptor concentration is assumed to be large enough in comparison to the initial concentration of depolariser so as to remain practically unaffected by the course of the electrolysis. In the present study the acidity of the medium varied with the concentration of substrate RH since the substrate itself was acting as a base and

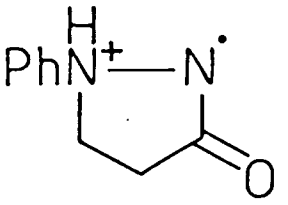
the system was unbuffered. In addition, Figures 9 and 10 suggest that the presence of a trace impurity acting as a proton acceptor changes the oxidation mechanism, and that deprotonation of the radical cation, $RH^{+}\cdot$ is a second order process, as is disproportionation of the radical cation $RH^{+}\cdot$. Thus the concentration, in this case, cannot be used as a prime variable to differentiate between the ECE and DISP mechanisms[56,57].

3.2. - Dimer formation in neutral acetonitrile:- The previous study of the electrochemical oxidation of RH in acetonitrile suggested that the formation of the dimeric species (Scheme 9; XIII) occurred as a result of rearrangement of intermediary dimers XIV and XV[10]. The authors stated that they thought that a key role in the formation of these dimers (XIV, XV) was played by the radical cation, XXXIV, as no dimeric product was observed when the oxidation was carried out in the presence of base[39]. They also stated that as the dimer XIII was not formed during the initial stages of the electrolysis (up to 15% 2-electron oxidation), its formation was dependent on the increased acidity of the electrolysis medium as the electrolysis proceeded. It was proposed that the formation of the intermediary dimers XIV and XV was brought about by reaction of the radical cation XXXIV in one of three ways (Scheme 18). There are, however, certain aspects of this mechanism which make it improbable.

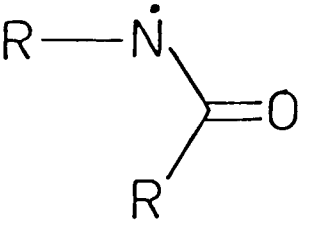
The radical cation intermediate XXXIV can be considered as an acylaminyl radical[60] (XXXV), as protonation of N(1), removes the possibility of mesomeric interaction of the lone pair on N(1) with the orbitals of N(2). Acylaminyl radicals have been extensively studied and the evidence to date suggests a π structure for the electronic ground state[60,61] (Figure 11). It has been shown [53,62] that acylaminyl radicals undergo Hoffmann-Loffler intramolecular rearrangements of the type already discussed[63] (Scheme 17) and abstract hydrogens such as allylic hydrogens. It has also been shown[53] that acylaminyl radicals do not add readily to double bonds, presumably as a result of repulsion of the σ_N lone pair and the electron-rich double bond.

The published literature on the chemical behaviour of radicals similar to XXXIV therefore argues against the radical cation XXXIV, if it exists in the acetonitrile solution at all, reacting in the ways shown in Scheme 18.

One further aspect of the proposed mechanism is at variance with the experimental observations in the present study. It was proposed[10] that dimer XIII was formed by rearrangement of the intermediary dimer XV. However, h.p.l.c. analysis of the electrolysis solution during the course of a controlled potential electrolysis of 4-methyl-1-phenylpyrazolodin-3-one in acetonitrile showed only the presence of starting material, pyrazolinone, and the dimer XVIII. There was no evidence of intermediary dimers.

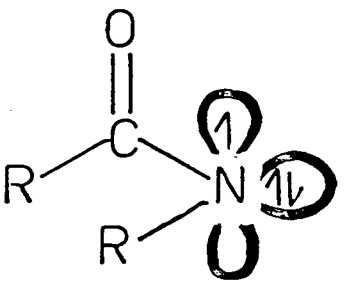


(XXXIV)

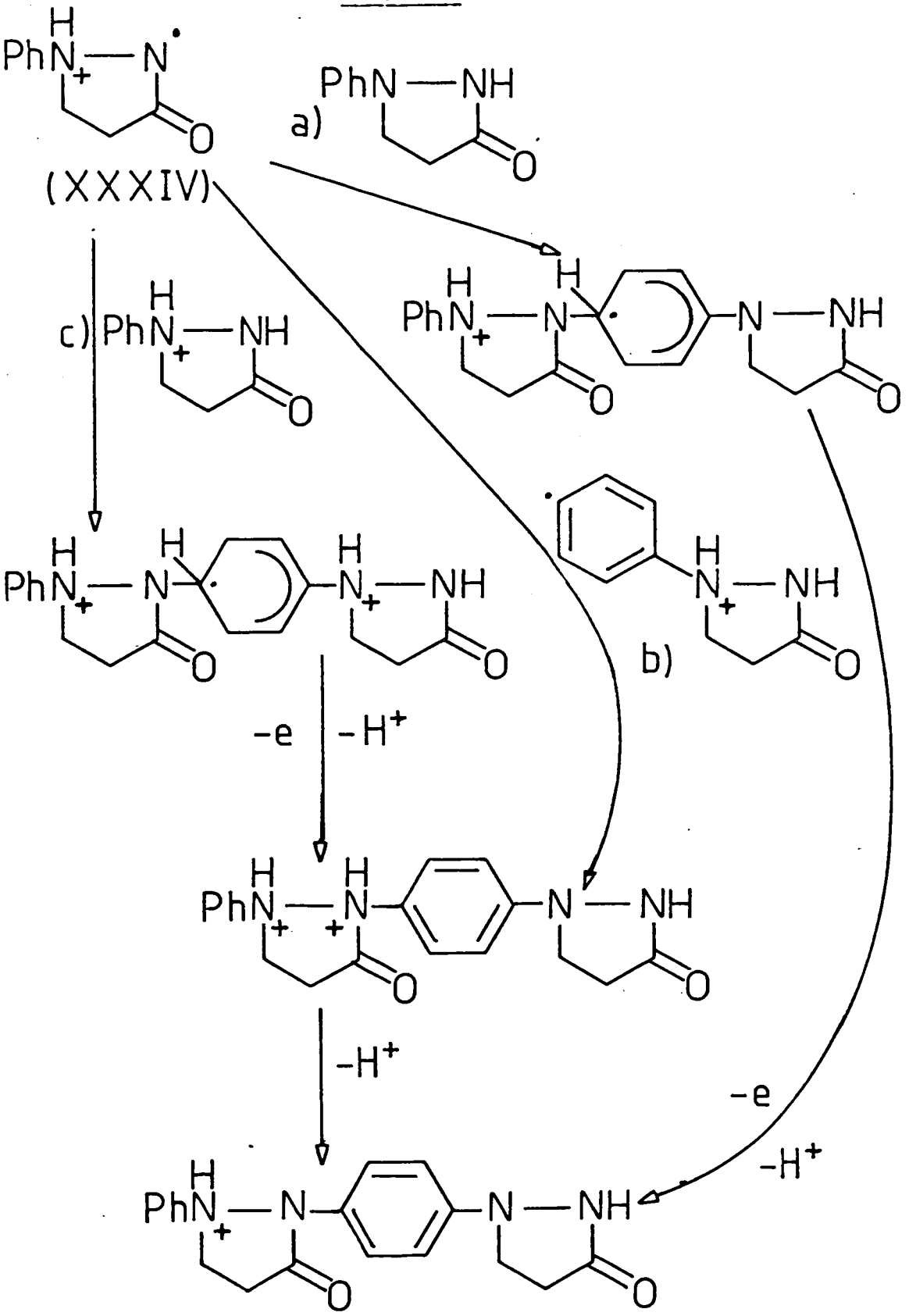


(XXXV)

Figure 11



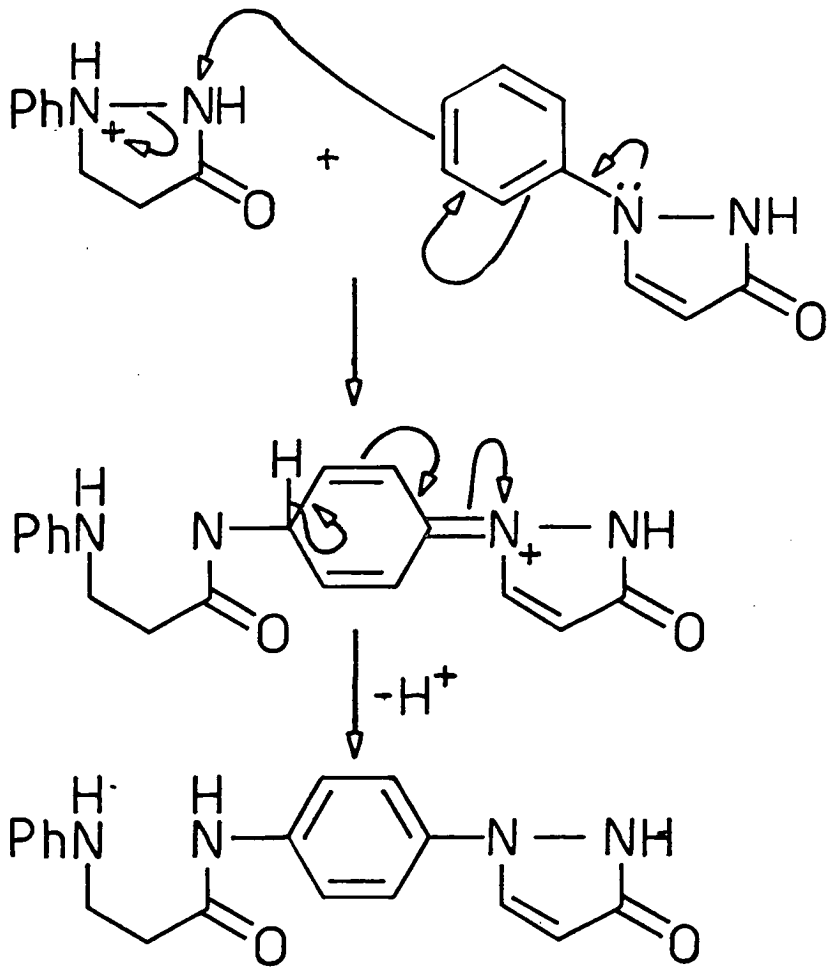
Scheme 18



In an attempt to rationalise the production of the dimer during the course of an electrolysis, two experimental facts were considered particularly important:

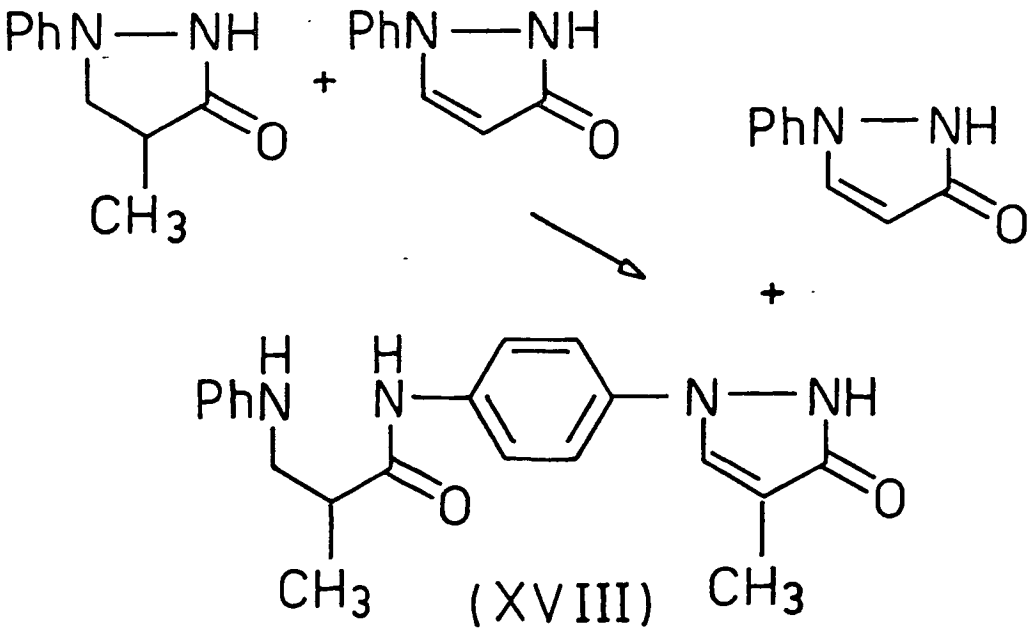
1. The dimer is not formed in the initial stages of the electrolysis, i.e. when the acidity of the solution and the concentration of pyrazolinone is low.
2. The dimer is not formed from pyrazolidinones which cannot oxidise directly to pyrazolinones, e.g. 4,4-dimethyl-1-phenylpyrazolidin-3-one, due to position 4 being blocked. These facts suggested that acid catalysed addition of pyrazolidinone to pyrazolinone might be occurring (Scheme 19). However, attempts to achieve such a reaction under various conditions of acidity and reactant concentration were unsuccessful, suggesting that reaction of discrete monomers as shown in Scheme 19 was not responsible for dimer formation in the electrolysis solution.

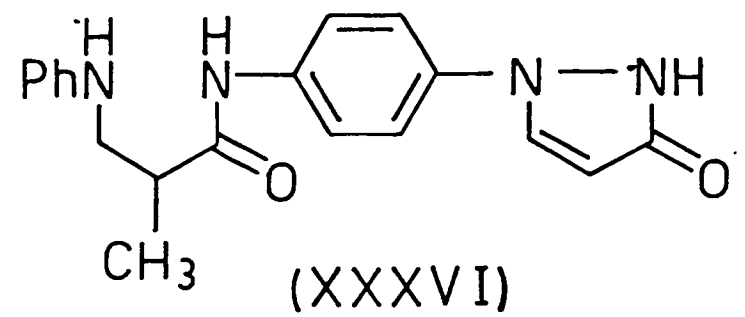
Scheme 19



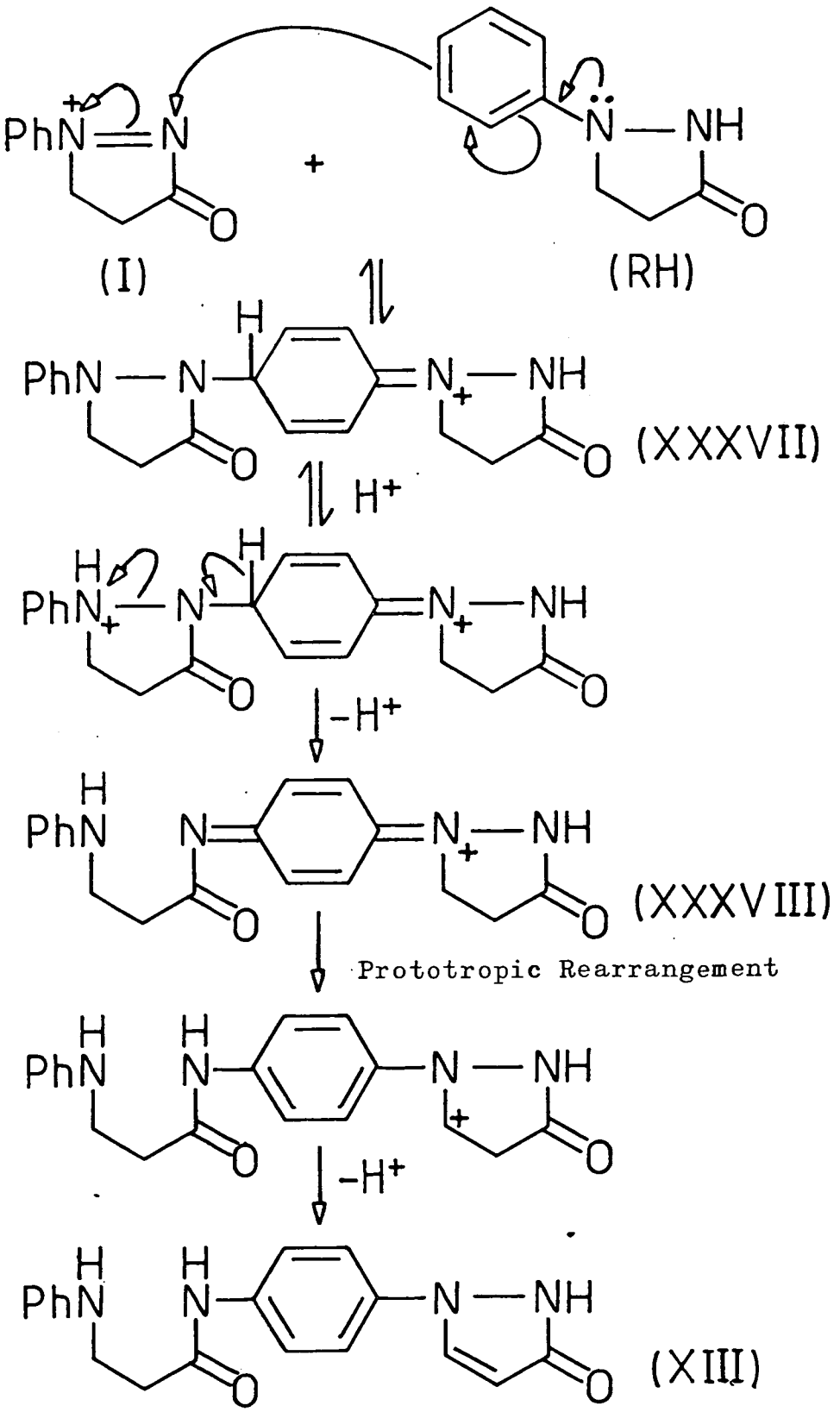
To test the suggestion that prior formation of a pyrazolinone ring may be necessary for dimerisation to occur, a controlled potential electrolysis was performed on 4-methyl-1-phenylpyrazolidin-3-one under conditions which had previously led to isolation of the dimer XVIII in the presence of an equivalent amount of 1-phenylpyrazolin-3-one (Scheme 20) in the anodic working electrode compartment. If prior formation of the pyrazolinone ring was necessary for dimerisation to occur it was expected that a crossed-dimer of the form XXXVI, as well as the normal dimer XVIII, would be detected as an electrolysis product. H.p.l.c. analysis of the electrolysis mixture showed the presence of three compounds, 1-phenylpyrazolin-3-one, 4-methyl-1-phenylpyrazolin-3-one, and a third compound which was isolated by chromatography and found to be the dimer XVIII. The presence of the crossed-dimer XXXVI was not detected. It was clear from this experiment that the pyrazolinone ring in the dimer is formed after initial dimerisation has taken place.

Scheme 20





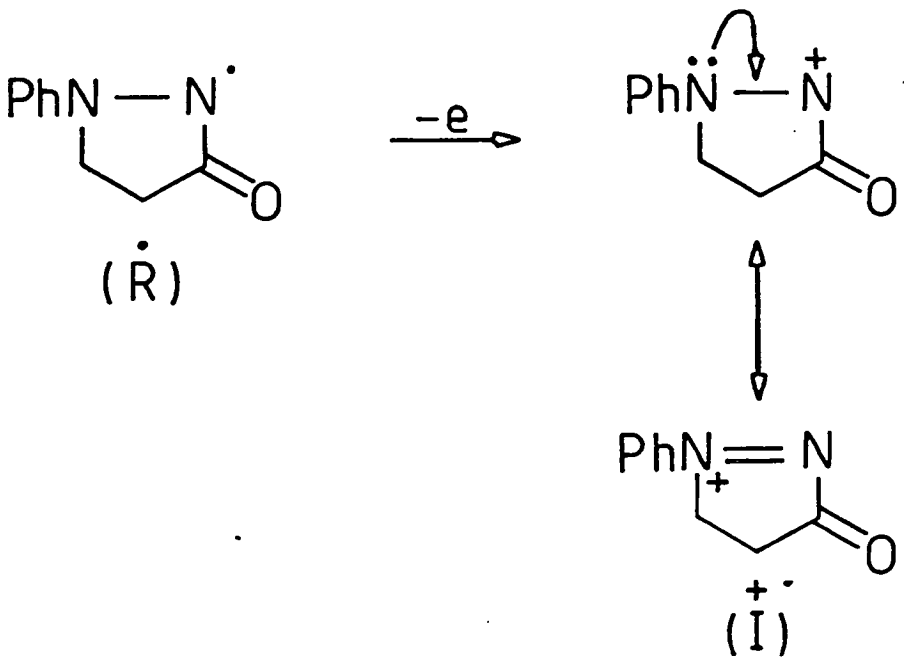
Scheme 21



An alternative mechanism for the formation of these dimeric products is shown in Scheme 21. This mechanism does not involve acylaminyl radical addition to a phenyl ring, nor does it require the prior formation of a pyrazolinone ring. It also explains why the dimers are not present in the electrolysis mixture during the early stages of the electrolysis, when the acidity of the medium is low, as protonation of N(1) is necessary for cleavage of the bond between N(1) and N(2) to occur.

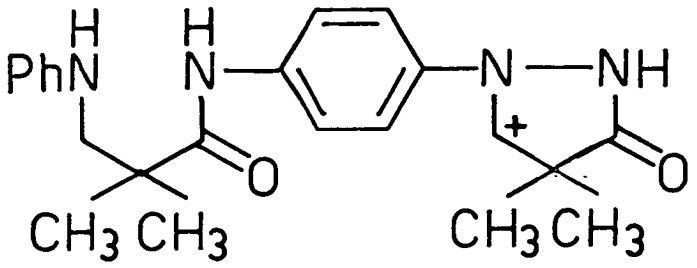
It is proposed that a primary product of 2 electron oxidation of 1-phenylpyrazolidin-3-ones in acetonitrile is the intermediate I^+, which is formed either by heterogeneous oxidation of the radical $R^\bullet$ (Scheme 11), or disproportionation of two radical cations $RH^{+\bullet}$ (Scheme 12). The disproportionation of two neutral radicals $R^\bullet$ (Scheme 13) would result in direct formation of the pyrazolinone P and pyrazolidinone RH. The proposed initial product of the second heterogeneous electron transfer I^+ requires that N(2) is positively charged, which would be expected to be a very unstable arrangement. However, the lone pair on N(1) is available to both induce the charge transfer to occur and to stabilise the intermediate I^+ (Scheme 22).

Scheme 22



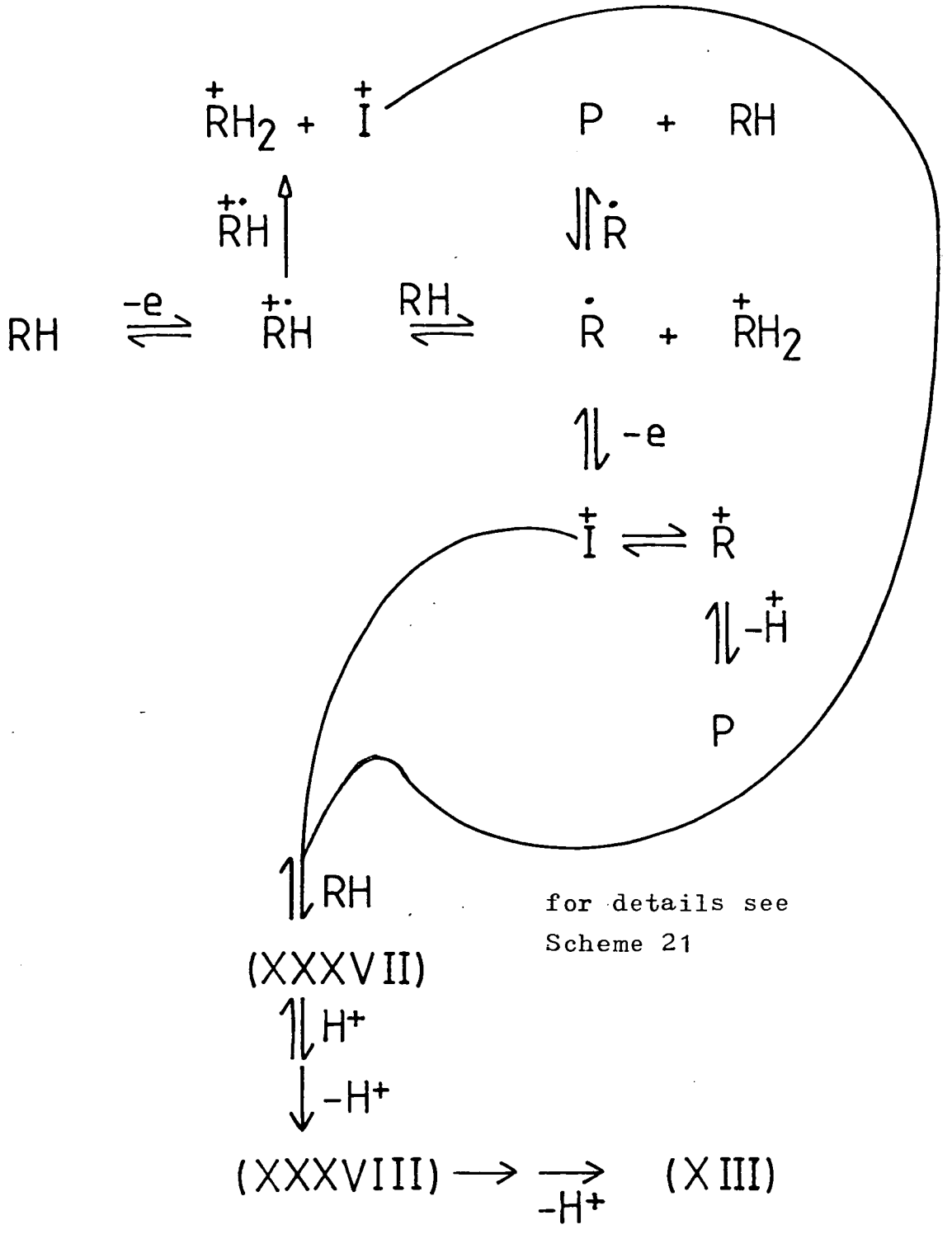
Disproportionation of two radical cations RH^+ (Scheme 12) would give the proposed intermediate, I^+, directly by abstraction of the hydrogen on N(2) of one of the radical cations by the other. It is then suggested that the intermediate I^+ can either rearrange by hydride transfer to R^+, which loses a proton to yield P, the major product of the electrolysis, or react with RH in a reversible step to give the intermediate XXXVII. The latter, on protonation, rearranges irreversibly to XXXVIII. Prototropic rearrangement followed by proton loss then gives the observed dimer. In the presence of base the monomer (P) would be the only product of the electrolysis since the irreversible rearrangement of the intermediate XXXVII can only occur after protonation. This is borne out by electrolysis in the presence of base; when tetraethylammonium chloride is used as the supporting electrolyte only the monomer P is detected as a product. The observation that no major product is detected on electrolysis of 4,4-dimethyl-1-phenylpyrazolidin-3-one (XXVI) in neutral acetonitrile is consistent with the mechanism shown in Scheme 21. The intermediate (XXXIX) proposed by this mechanism has no leaving group at C(4') and therefore cannot form a pyrazolinone ring.

Scheme 23 summarises the mechanisms which have been discussed so far in this chapter.



(XXXIX)

Scheme 23


RH2+ + I+
P + RH
RH
-e
RH
RH
R + RH2+
-e
I+ R+
-H+
P
RH
for details see Scheme 21
(XXXVII)
H+
-H+
(XXXVIII)
(XIII)
-H+

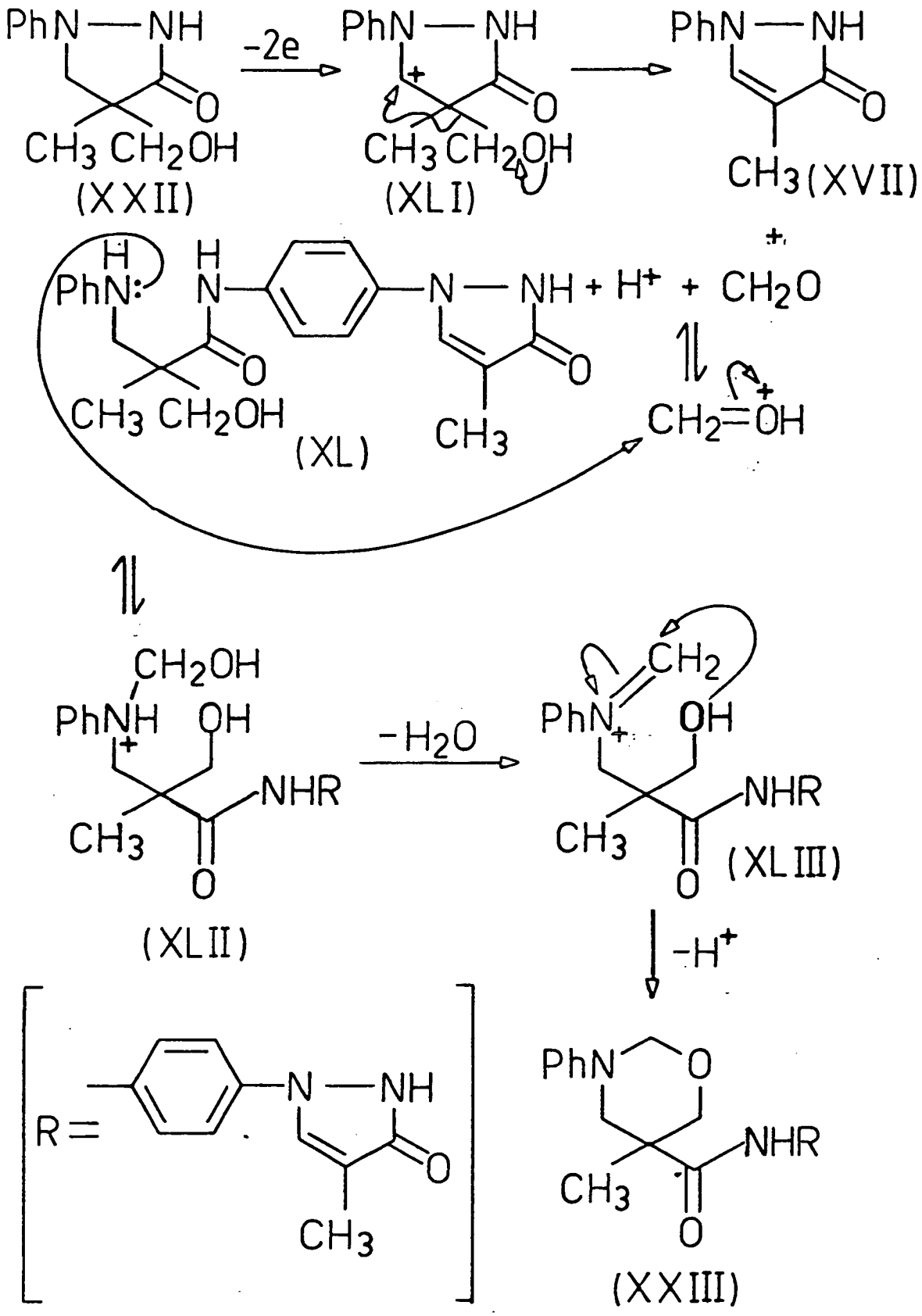
The electrochemical oxidation of 4-hydroxymethyl-4-methyl-1-phenyl-pyrazolidin-3-one XXII in neutral acetonitrile did not produce the dimer (XL) analagous to those which had been produced on oxidation of the other pyrazolidinones. Instead, as well as 4-methylpyrazolin-3-one, a dimer was isolated which has been assigned the structure XXIII, on the basis of i.r., n.m.r., and mass spectroscopic evidence (Chapter 2).

The formation of the pyrazolinone XVII can be rationalised as loss of a molecule of formaldehyde, and a proton from the cation, XLI (Scheme 24), which is obtained on oxidation of the pyrazolidinone.

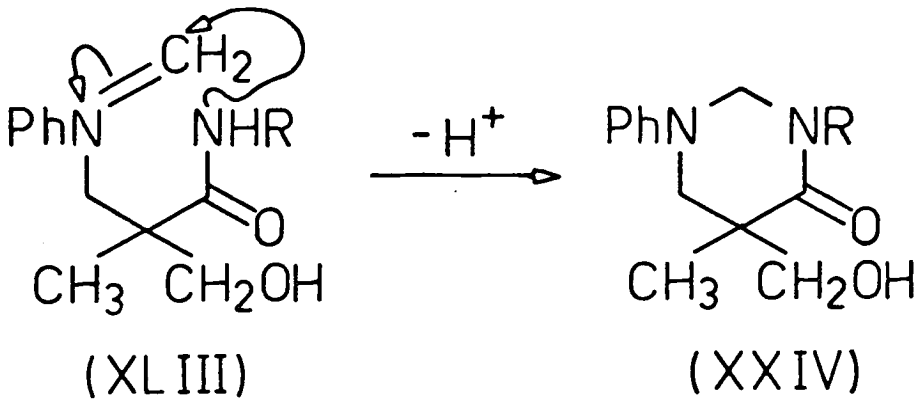
A possible mechanism (Scheme 24) to account for the dimeric product involves Mannich[64,65,66] type reaction of formaldehyde, under acidic conditions, with the dimer XL, which was not isolated, nor detected in the electrolysis solution, but which was expected by comparison with the oxidative behaviour of the pyrazolidinones which had been previously studied. The aryl amine nitrogen in dimer XL can be thought of as a Mannich base which reacts with formaldehyde in the manner shown in Scheme 24. The intermediate XLII dehydrates to the imminium cation, XLIII, which then reacts with the alcoholic oxygen to give the product XXIII. Alternatively the amide nitrogen in the intermediate XLIII (Scheme 25) could also act as a nucleophile to give the structure XXIV.

Although the weight of spectroscopic evidence (Chapter 2) is against XXIV being the structure of the isolated dimer, the literature does contain an example of an intermolecular Mannich reaction of pyrazolidin-3-one (XLIV) with formaldehyde to give XLV[91]. In this case the amide nitrogen N(2) provides the nucleophilic site. Further evidence to support the spectroscopic evidence for XXIII as being the correct structure for the isolated dimeric product was obtained from model reactions. Formaldehyde readily reacted with 3-anilinopropanol to give tetrahydro-3-phenyl-1,3-oxazine[67] (Scheme 26), but it was not possible to make formaldehyde react with N-phenyl-3-anilinopropionamide (Scheme 27), even under conditions which were much more severe than those which would be encountered in an electrolysis solution.

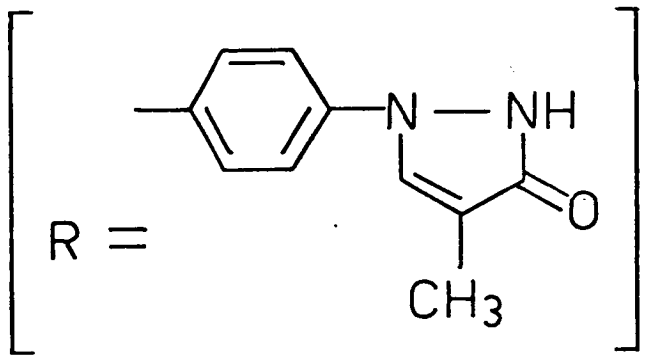
Scheme 24

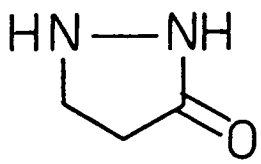

PhN — NH
-2e
CH3 CH2OH
(XXII)
(XLI)
CH3 (XVII)
+ H+ + CH2O
(XL)
CH2=OH
CH2OH
PhNH OH
NHR
CH3
(XLII)
-H2O
CH2
(XLIII)
-H+
R=
(XXIII)

Scheme 25

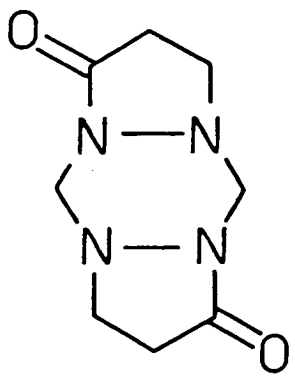


(XLIII) (XXIV)



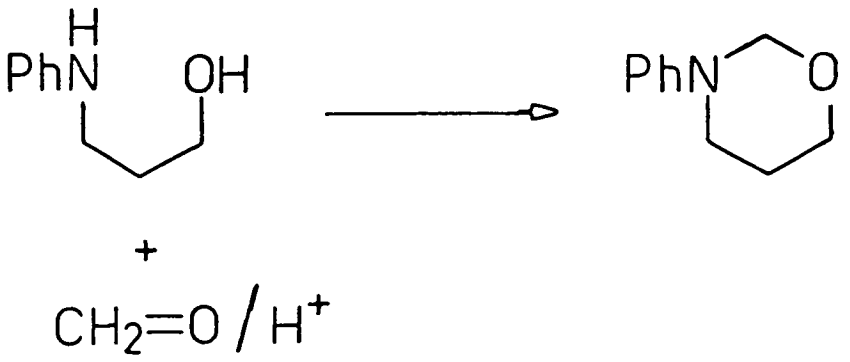


(XLIV)

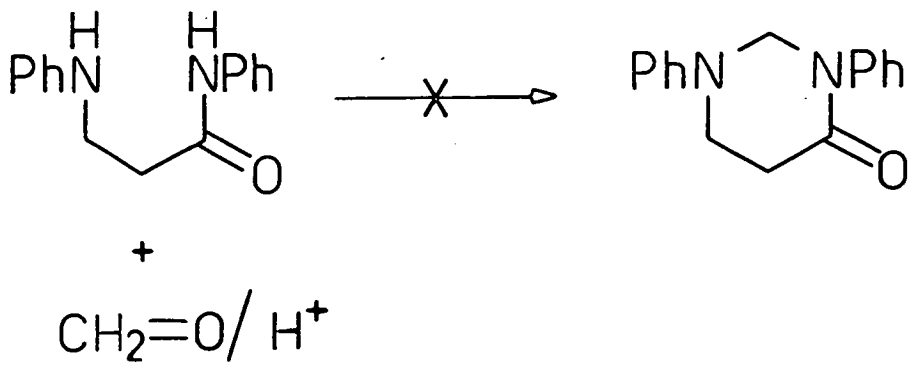


(XLV)

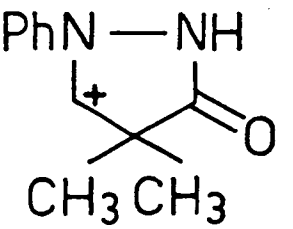
Scheme 26



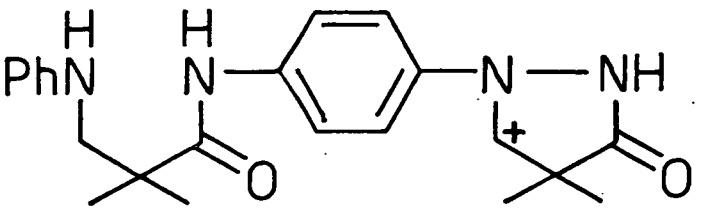
Scheme 27



3.3. - Anodic oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in methylene chloride:- As has already been described (Chapter 2) the electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one (XXVI) in neutral acetonitrile gives a complex mixture of products, 24 of which can be detected by high resolution h.p.l.c. Since the absence of a leaving group at position 4 prohibits the formation of a pyrazolinone ring directly, it can be inferred that the cation XLVI or the intermediate XXXIX react in some way with the solvent or take part in further coupling reactions. It was felt that the inclusion of methyl groups at positions 2 and 4 of the phenyl ring would block coupling reactions at those positions and would lead to a simpler product mixture on electrolysis. However, this did not occur to any significant extent.



(XLVI)



(XXXIX)

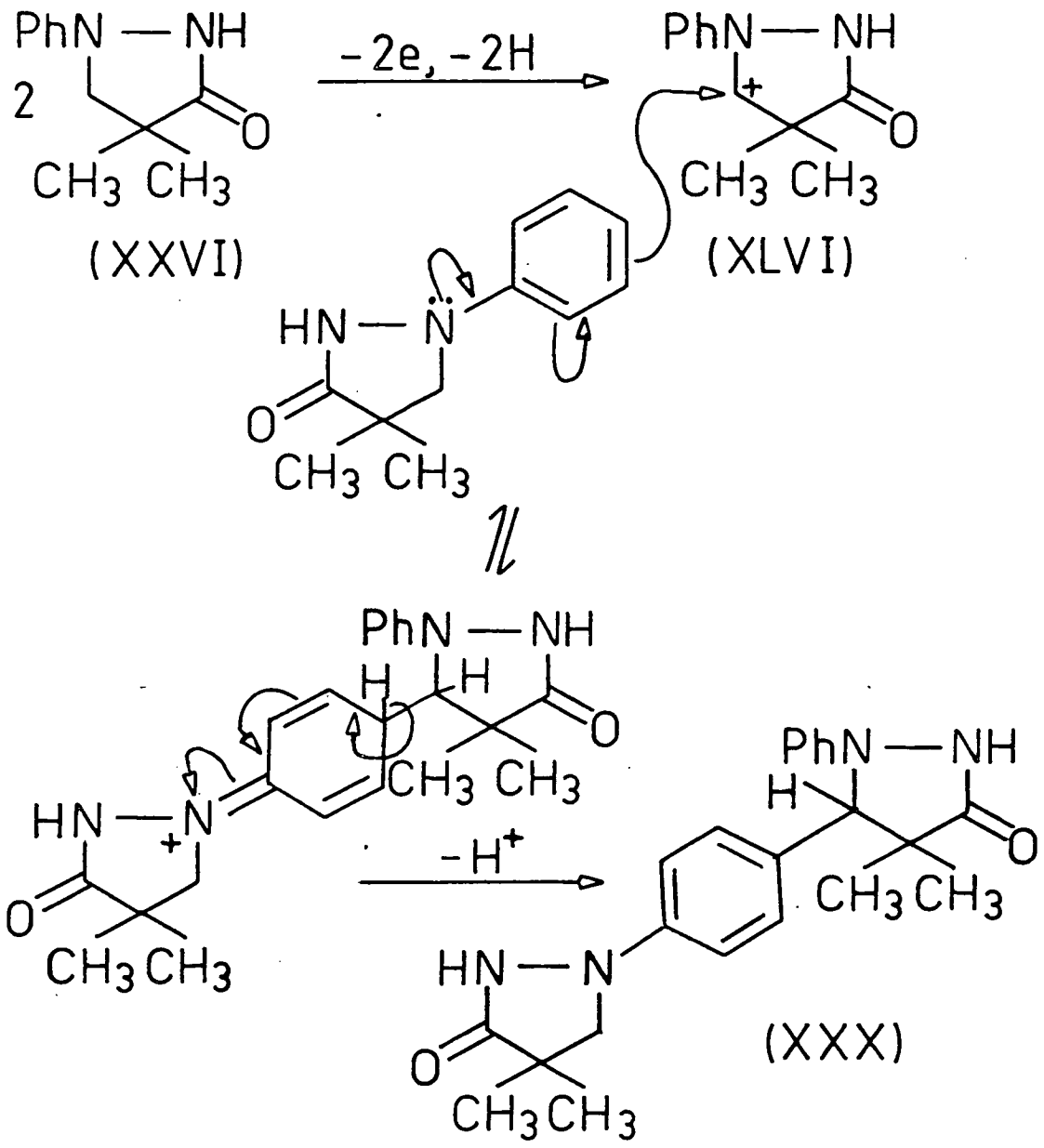
The observation that 4,4-dimethyl-1-(2,4-dimethyl)phenyl pyrazolidin-3-one is oxidised in acetonitrile containing tetraethylammonium chloride as supporting electrolyte to give a product which can be rationalised by a mechanism involving attack of either a dimer or trimer of acetonitrile, on the intermediate X (Scheme31), indicated that in the absence of a leaving group at

position 4, the solvent or a solvent derived oligomer is a strong enough nucleophile to attack the generated cation. Extending this reasoning it was felt that if the electrolyses were performed in a medium which had no nucleophiles of appreciable strength present, the substrate itself could act as a nucleophile towards the cation formed on anodic oxidation. From other studies on the anodic oxidation of organic compounds in media of low nucleophilicity, e.g. methylene chloride[68,69], nitrobenzene[70], methylene chloride was chosen as the solvent and tetrabutyl ammonium fluoroborate as the supporting electrolyte. The anodic limit for methylene chloride is reported to be 1.8V(vs SCE)[71], and for tetrabutylammonium fluoroborate 2.9V(vs Ag/Ag^{+})[72].

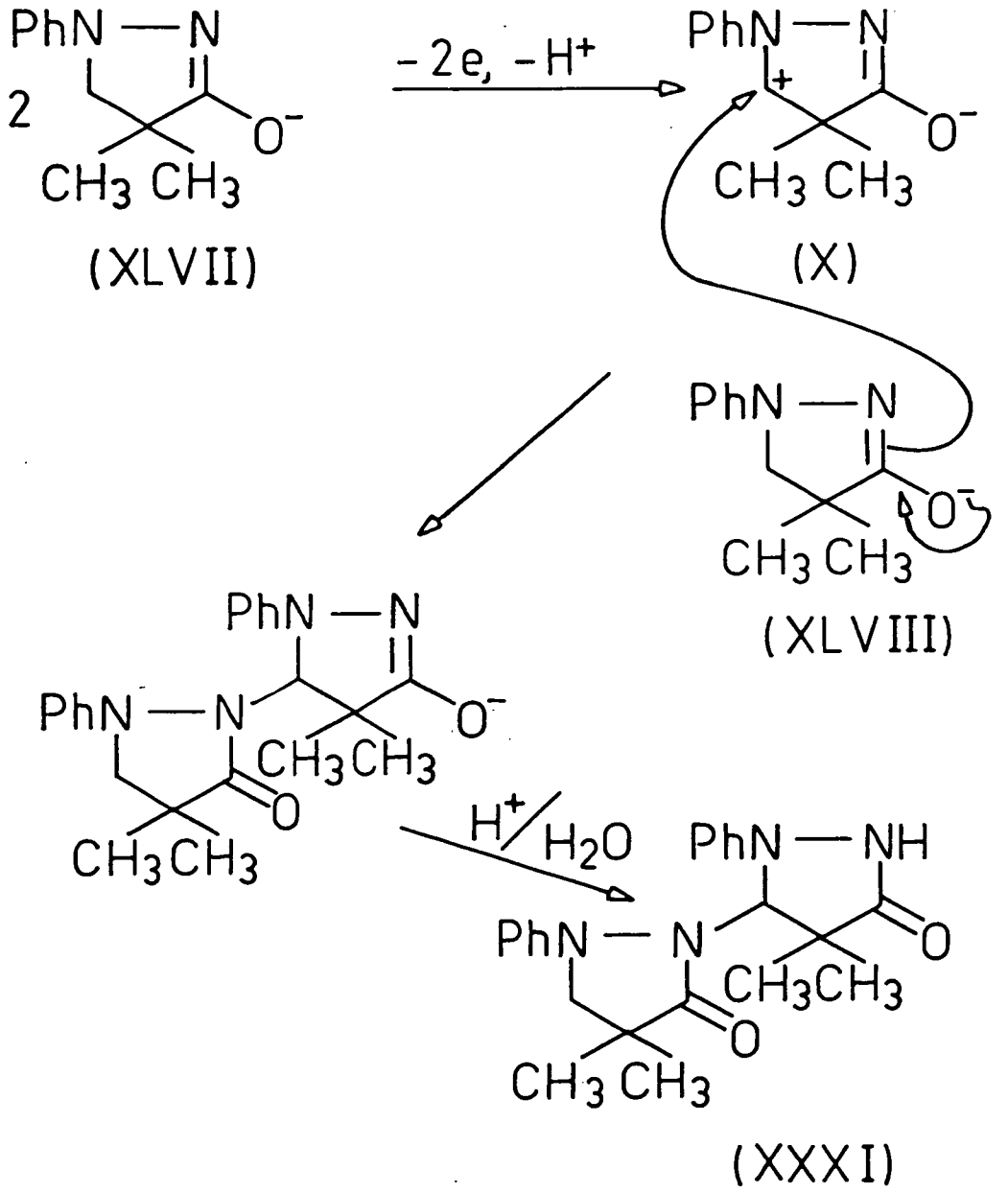
As already described (Chapter 2) the electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in methylene chloride containing tetrabutylammonium fluoroborate as supporting electrolyte does give a dimer as the sole product (XXX). The formation of this product can be rationalised by the mechanism shown in Scheme 28, which proposes that in the absence of any other nucleophiles the phenyl ring of one molecule of substrate, which is activated by N(1), attacks the cation (XLVI) generated by 2 electron oxidation. Proton loss and the accompanying rearomatisation of the p-disubstituted phenyl ring gives the dimer XXX.

When the electrolysis was carried out in methylene chloride in the presence of the base 2,6-lutidine (2,6-dimethyl pyridine), a dimer, isomeric with XXX, was isolated and assigned the structure XXXI (Chapter 2). The formation of this dimer can be rationalised by the mechanism shown in Scheme 29 which involves attack of the anion XLVII on the electron deficient carbon (C(5)) of the 2 electron oxidation product X. Coupling, promoted by the negative charge on the oxygen at C(3), is effected through N(2) of XLVII. In contrast, the anodic oxidation of 1-phenylpyrazolidin-3-one in under identical conditions gave as sole product the monomer, 1-phenylpyrazolin-3-one.

Scheme 28

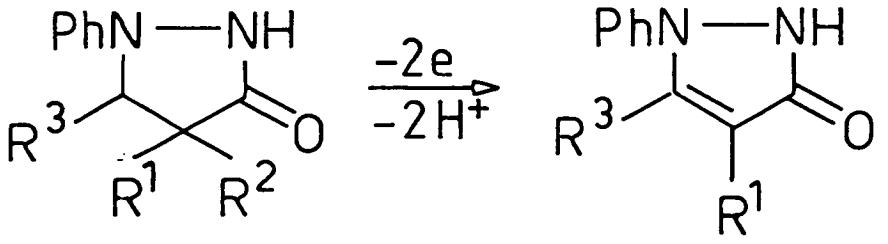

PhN — NH
2
CH3 CH3
(XXVI)
-2e, -2H
PhN — NH
CH3 CH3
(XLVI)
HN — N
CH3 CH3
PhN — NH
CH3 CH3
HN — N
-H+
PhN — NH
CH3 CH3
HN — N
(XXX)
CH3 CH3

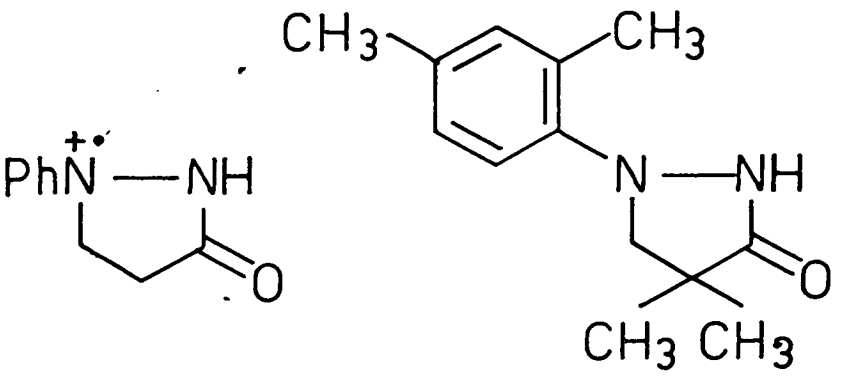
Scheme 29


PhN — N
2
O⁻
CH3 CH3
(XLVII)
-2e, -H+
PhN — N
+
O⁻
CH3 CH3
(X)
PhN — N
O⁻
CH3 CH3
(XLVIII)
PhN — N
PhN — N
O⁻
CH3CH3
O
CH3CH3
H+/H2O
PhN — NH
PhN — N
O
CH3CH3
O
CH3 CH3
(XXXI)

3.4. - Anodic oxidation of 1-phenylpyrazolidin-3-ones in acetonitrile containing tetraethylammonium chloride as the supporting electrolyte:- A description of a previous study[39] of the electrochemical oxidation of 1-phenylpyrazolidin-3-one has already been included in the Introduction. The authors found that a controlled potential electrolysis of 1-phenylpyrazolidin-3-one in acetonitrile (0.5M) with tetraethylammonium chloride (0.5M) as the supporting electrolyte gave an almost quantitative current yield of 1-phenylpyrazolin-3-one (Scheme 30), ($R^1 = R^2 = R^3 = H$). The anolyte remained colourless throughout the electrolysis and no red colour, believed to be due to the radical cation III was observed at the electrode surface.

Scheme 30





(III) (XXVII)

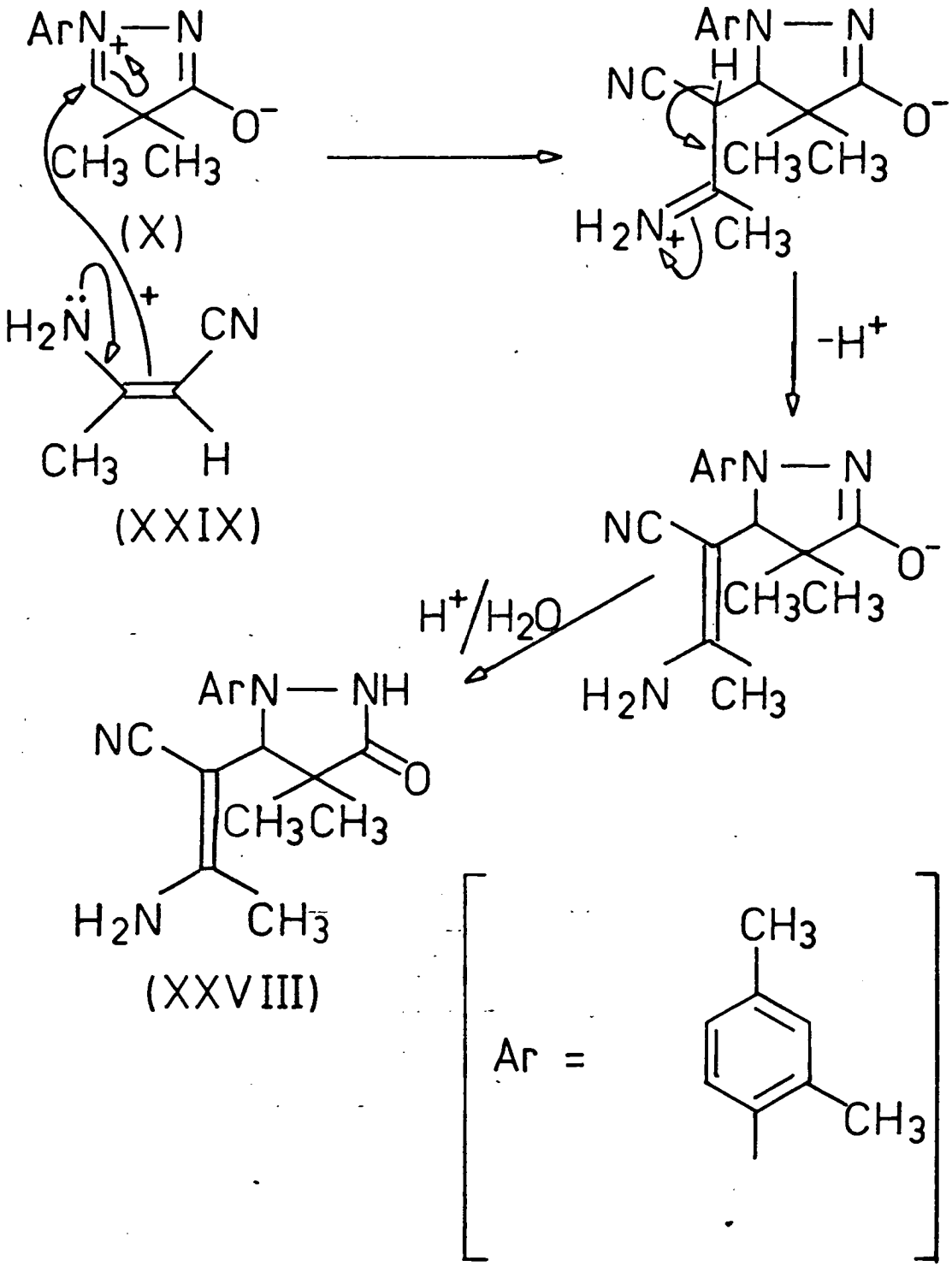
In this present study, controlled potential electrolyses were performed on solutions of 4-methyl-1-phenylpyrazolidin-3-one (R^1 = Me, R^2 = R^3 = H, (Scheme 30)), 1,5-diphenylpyrazolidin-3-one (R^1 = R^2 = H, R^3 = Ph, (Scheme 30)), and 4-hydroxymethyl-4-methylpyrazolidin-3-one (R^1 = CH_3, R^2 = CH_2OH, R^3 = H, (Scheme 30)), in acetonitrile using tetraethylammonium chloride as the supporting electrolyte. In all these cases near quantitative yields of the corresponding 1-phenylpyrazolin-3-ones were obtained (Scheme 30).

As was the case in neutral acetonitrile, the anodic oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in acetonitrile containing tetraethylammonium chloride as supporting electrolyte, gave a complex mixture of products. However, when positions 2 and 4 of the phenyl ring were blocked with methyl groups as in XXVII, an isolable product was obtained which has been assigned the structure XXVIII (Chapter 2). It is not certain how this product is formed, although it is possible to rationalise its formation as the reaction of the cation X with either a dimer XXIX (Scheme 31a), or a trimer XLVIII (Scheme 31b) of acetonitrile. It was thought possible that a free radical mechanism similar to that reported for the formation of 1-cyano-2-aminoprop-1-ene XXIX from acetonitrile and sodium metal[46], may have resulted in the discrete existence of the dimer XXIX in the electrolysis solution. To explore this possibility a controlled potential electrolysis of 4,4-dimethyl-1-phenylpyrazolidin-3-one was performed in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte, with an equivalent amount in the anodic compartment of 1-cyano-2-aminoprop-1-ene XXIX. However, this electrolysis still produced a mixture of products, and the h.p.l.c. analysis of the electrolysis solution did not show a major product peak which could be attributed to the addition of 1-cyano-2-aminoprop-1-ene (XXIX) to position 5 of the pyrazolidinone.

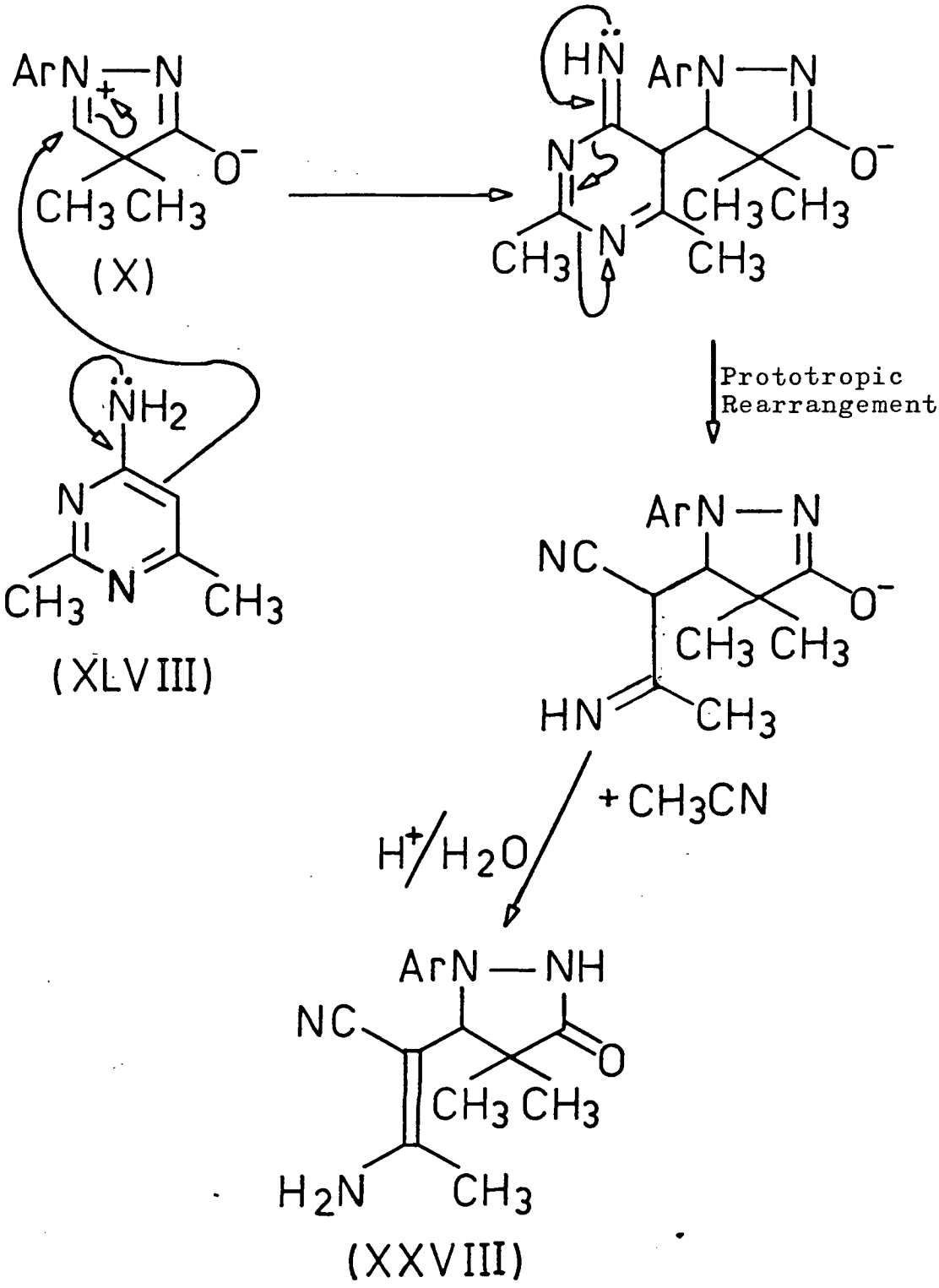
The fact that there is no dimeric product when the electrolysis is performed in the presence of chloride ion is in agreement with the mechanism proposed in (Scheme 23) for the formation of dimers via an intermediate I^+, and is in agreement with Kolthoff[41], who found that chloride ion is a strong base in acetonitrile.

Kolthoff[41] has found that in not too dilute solutions (around 10^{-5}M), the dissociation of hydrochloric acid in acetonitrile is not accounted for by the simple reaction (Equation 3).

Scheme 31a


ArN — N
CH3 CH3
O⁻
(X)
H2N
CN
CH3
H
(XXIX)
NC
H
H2N
CH3
-H+
H+/H2O
NH
O
(XXVIII)
Ar =
CH3

Scheme 31b


ArN—N
CH3 CH3
(X)
HN
ArN—N
N
CH3 N CH3
CH3 CH3
Prototropic Rearrangement
NH2
N
CH3 N CH3
(XLVIII)
ArN—N
NC
CH3 CH3
HN CH3
+CH3CN
H+/H2O
ArN—NH
NC
CH3 CH3
H2N CH3
(XXVIII)

$$HCl \rightleftharpoons H^+ + Cl^- \qquad 3$$

As acetonitrile is a poor solvating agent, the Cl ions are stabilised by association with HCl (Equation 4).

$$2HCl \rightleftharpoons H^+ + ClHCl^- \qquad 4$$

Thus the lack of H-bonding of the anions by the solvent counter-balances the dielectric effect on the dissociation. By studying the acid-base equilibria of hydrogen chloride in acetonitrile Kolthoff[41] has evaluated the simple dissociation constant (K_{HCl}) to be 1.15 x 10^{-9} giving a pK_{HA} of 8.94.

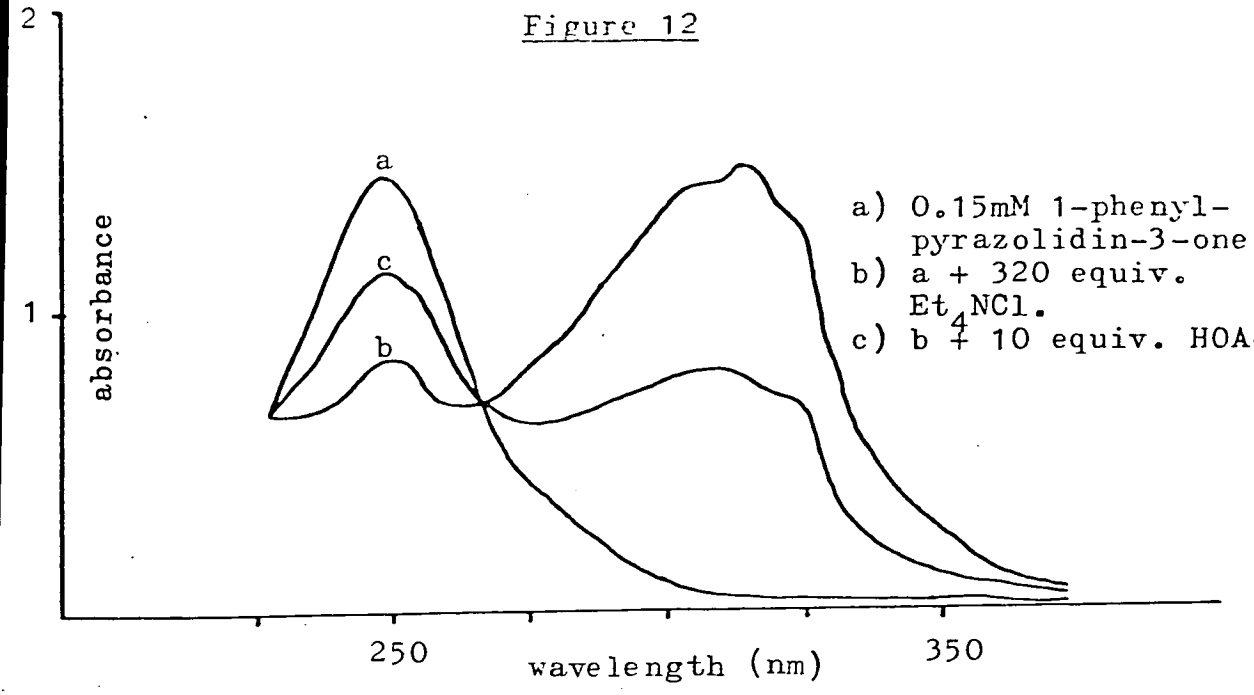
Baigrie and Joslin[39] have made the observation that in acetonitrile solution containing tetraethylammonium chloride, 1-phenylpyrazolidin-3-one is not ionised, and have based their proposed mechanism of oxidation (Scheme 10) on this fact. However, the fact that chloride is such a strong base in acetonitrile prompted the following re-examination of their evidence for un-ionised substrate being present.

The evidence that Baigrie and Joslin[39] put forward to support their claim that 1-phenylpyrazolidin-3-one was not ionised by tetraethyl-ammonium chloride in acetonitrile solution was based on their observation that the U.V. spectrum of 1-phenylpyrazolidin-3-one (λ_{max} 245nm) in acetonitrile was not changed on addition of excess chloride ions, although the anion appeared (λ_{max} 261nm) on addition of sodium hydride. On re-examining this U.V. evidence it was found that 1-phenylpyrazolidin-3-one (0.15 mM) in acetonitrile exhibited a maximum absorbance at 247 nm (ε = 9530)(Figure 12a).. On addition of a solution of anhydrous tetraethylammonium chloride in acetonitrile the intensity of this peak decreased and a new series of bands appeared around 305-325 nm. These peaks reached a maximum intensity after 320 equivalents (1 equivalent $\simeq$ 0.15mM) of tetraethylammonium chloride had been added (Figure 12b). This spectrum, however was not stable.

The peak around 315 nm decreased and a new peak around 275-280 nm increased with time (Figure 13c). However, if the incremental addition of tetraethylammonium chloride was effected quickly, and the spectra run without delay, the series of curves which were obtained passed through a single isosbestic point (Figure 14). If acetic acid (40 equivalents) was added to the solution immediately after the addition of 320 equivalents of tetraethylammonium chloride, the broad band around 320 nm decreased and was replaced by a double band (315-325 nm) of lower intensity and a single band at 250 nm (Figure 12 c). If the addition of acetic acid was delayed (10 minutes to 3 hours), the addition then gave a less intense double peak (315-325 nm), and a new band around 275 nm appeared instead of the one at 250 nm. On standing the double peak (315-325 nm) slowly decreased. The U.V. spectra which were obtained when a solution of 1-phenylpyrazolidin-3-one in acetonitrile was treated with sodium hydride, were essentially the same as those just described. The U.V. spectrum of 1-phenylpyrazolin-3-one (0.15mM) in acetonitrile showed a maximum absorbance at 269 nm (ε = 21200); addition of tetraethylammonium chloride caused this band to decrease and two new bands to appear (283 nm and 320 nm).

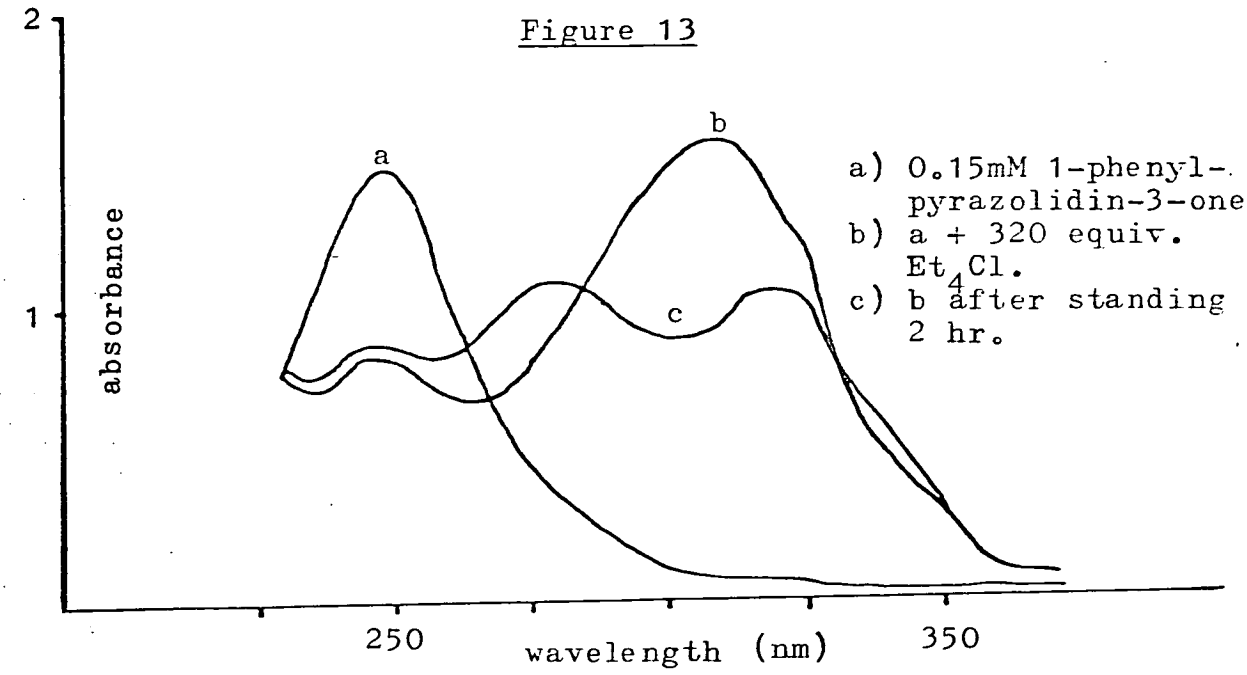
These results are significantly different from those obtained by Baigrie and Joslin[39], and show that addition of tetraethylammonium chloride to a solution of 1-phenylpyrazolidin-3-one in acetonitrile does cause ionisation of NH (Scheme 32). If acetic acid is added to the solution immediately the anion is reprotonated (Scheme 32). However, if the addition of acetic acid is delayed, the anion is oxidised to the anion of the pyrazolin-3-one by air, so that on reprotonation by acetic acid the spectrum of the pyrazolin-3-one is produced (Scheme 33). The inexact correspondence of the product spectra and the spectra obtained from pure compounds could be due to medium effects[76]. While the bulk of the band at 315-325 nm is due to the anion of 1-phenylpyrazolidin-3-one or 1-phenylpyrazolin-3-one (Figure 12 b), there are also superimposed minor bands which remain for some time after acidification and have not been accounted for (Figure 12 c). Also, addition of tetraethylammonium chloride to a solution of 1-phenylpyrazolin-3-one, causes ionisation of NH, which is reprotonated by acetic acid (Scheme 34). It also appears from this study that 1-phenylpyrazolin-3-one exists in neutral acetonitrile solution as the keto-tautomer (Scheme 34). Previous studies[73,74,75] of the ultra-

Figure 12



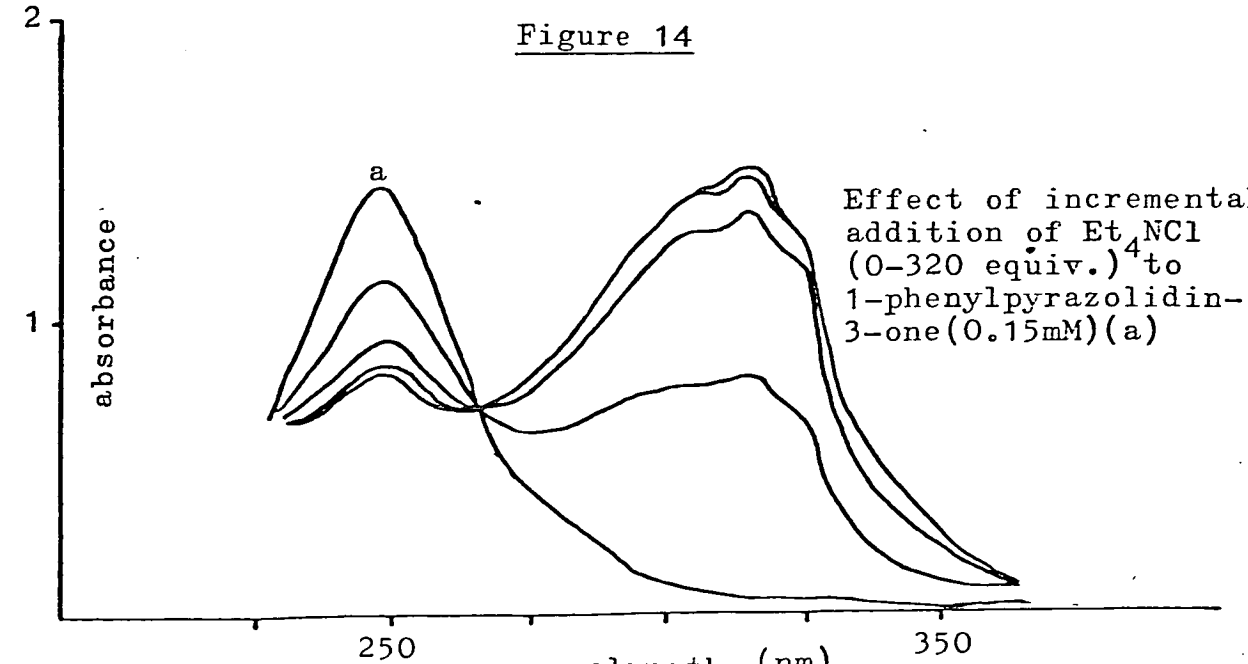
a) 0.15mM 1-phenyl-pyrazolidin-3-one.
b) a + 320 equiv. Et_4NCl.
c) b + 10 equiv. HOAc.

Figure 13



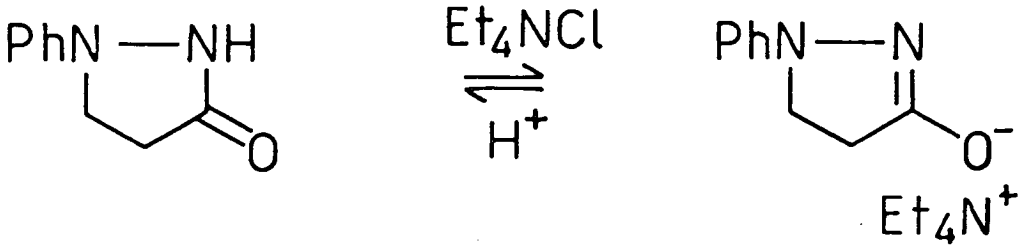
a) 0.15mM 1-phenyl-pyrazolidin-3-one.
b) a + 320 equiv. Et_4Cl.
c) b after standing for 2 hr.

Figure 14

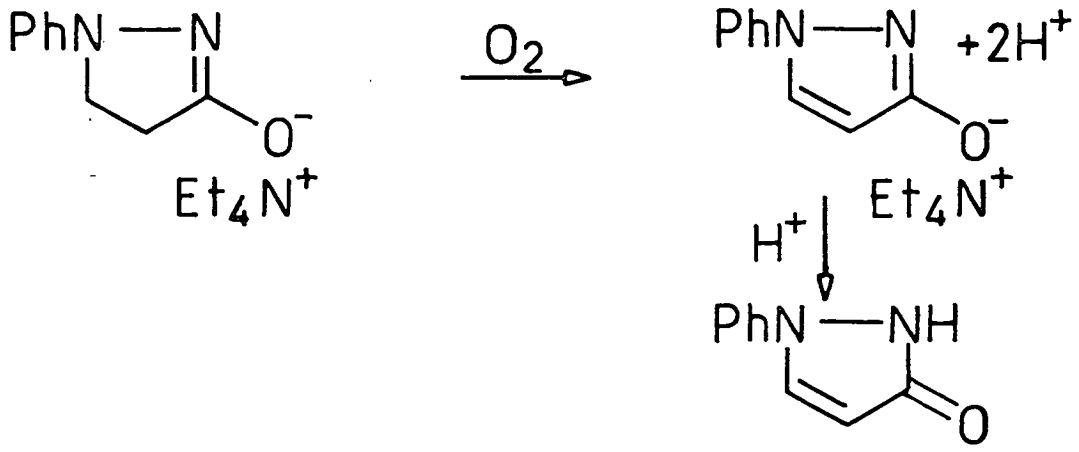


Effect of incremental addition of Et_4NCl (0-320 equiv.) to 1-phenylpyrazolidin-3-one(0.15mM)(a)

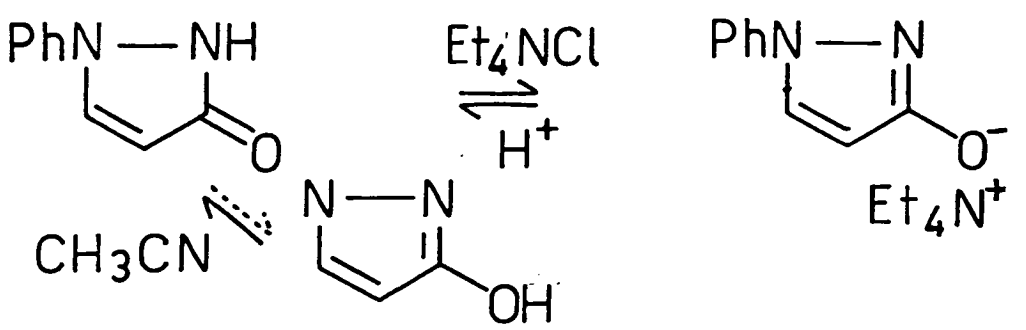
Scheme 32



Scheme 33



Scheme 34



violet absorbances of other pyrazolinones have assigned absorbances between 240 nm and 270 nm to $\rangle C{=}C\langle$. If the enol tautomer had been present under these conditions an absorbance corresponding to $\rangle C{=}N-$ would have been observed at 295-325nm. This absorbance is in fact observed, as expected, on ionisation of both the pyrazolin-3-one (Scheme 34) and the pyrazolidin-3-one (Scheme 32).

Since tetraethylammonium chloride is very hygroscopic, a possible cause of the difference between the present results and those of Baigrie and Joslin[39] is that the non-anhydrous salts may have been used in their U.V. experiments. This was shown to be the case by adding $Et_4NCl.H_2O$ to a solution of 1-phenylpyrazolidin-3-one (0.15mM) in acetonitrile. It was indeed found that there was no change in the U.V. spectra; thus monohydrated tetraethylammonium chloride is not a strong enough base in acetonitrile to ionise the pyrazolidinone. This may be due to the fact that the water present in solution stabilises the Cl^- ion by hydrogen bonding, thus lowering its basicity (Equation 5).

$$Et_4NCl{:}H_2O \xrightarrow{CH_3CN} Et_4N^+ + ClH_2O^- \quad - \quad 5$$

The absorbance that they observed at $\lambda_{max} = 261$ nm on addition of sodium hydride to a solution of 1-phenylpyrazolidin-3-one in acetonitrile, and wrongly attributed to the anion, is probably due to 1-phenylpyrazolin-3-one, as it has already been shown in this study (Figure 13 C) that the anion of 1-phenylpyrazolidin-3-one is readily oxidised by air to the pyrazolinone.

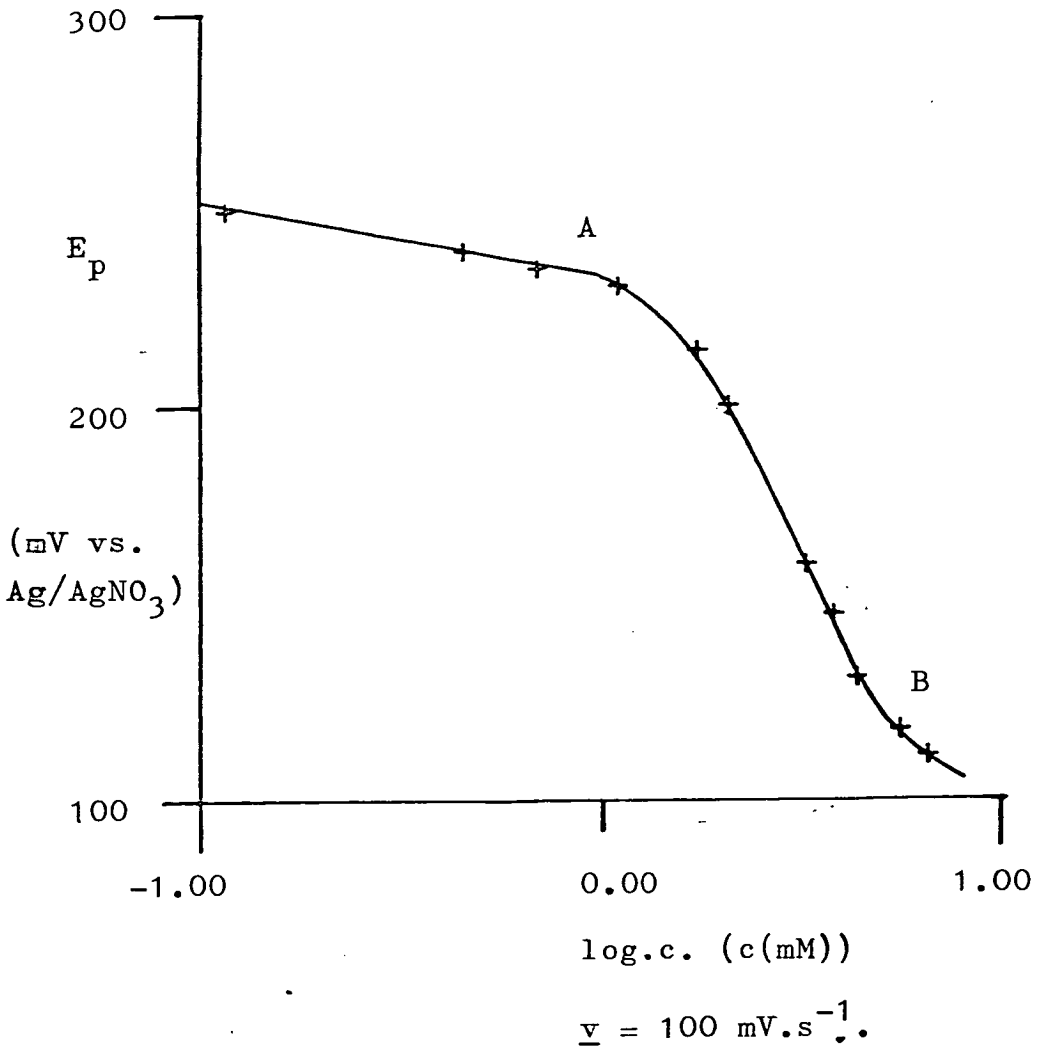
The final piece of evidence which Baigrie and Joslin[39] put forward to support their claim that the anion of 1-phenylpyrazolidin-3-one was not present in acetonitrile solution containing tetraethylammonium chloride was the observation that cyclic voltammetry of this solution showed an ill-defined cathodic wave at -0.4V vs. SCE on the reverse cathodic sweep. As this wave corresponded to a similar wave observed

on addition of concentrated hydrochloric acid to a solution of tetraethylammonium perchlorate in acetonitrile, and as it was not observed until an anodic scan had taken place in voltammetry of the pyrazolidinone solution, the wave was assigned to reduction of hydrochloric acid generated after, and not before, electron transfer (Scheme 11). In the present study, this cathodic wave has not fully been explained although a similar wave was observed in cyclic voltammograms of 1-phenylpyrazolidin-3-one in acetonitrile containing tetraethylammonium fluoroborate as the supporting electrolyte. In a recent study of the electrochemical oxidation of some methylbenzenes in acetonitrile, a cathodic wave has been reported at approximately the same potential and has been attributed to the reduction of hydrogen ion[77].

The overall reaction shown in Scheme 30 involves a two electron oxidation. Baigrie and Joslin[39] in their paper had reported that cyclic voltammograms obtained for 10^{-2}M solutions of 1-phenylpyrazolidin-3-one in acetonitrile containing tetraethylammonium choride as the supporting electrolyte, showed a single 2 electron anodic wave, which was irreversible at 100 $V.s^{-1}$. This wave had an $E_{p,a}$ which was around 100 mV cathodic of the peak potential which they had previously observed using tetraethylammonium perchlorate as supporting electrolyte. It was decided to study this shift quantatively to determine whether any further information on the oxidative process could be extracted from voltammograms obtained under conditions of varying basicity.

Linear sweep voltammograms were run on a solution of 1-phenylpyrazolidin-3-one (1mM) in acetonitrile containing tetraethylammonium fluoroborate (0.4M) as the supporting electrolyte. Tetraethylammonium chloride was added incrementally (0.1mM - 10mM) and a shift of peak potential was observed from 0.265V(0mM Et_4NCl) to 0.100V(8.0mM Et_4NCl) vs. $Ag/AgNO_3$ ($\underline{v}$ =111 $mV.s^{-1}$). Although no well defined pre-peak which could be attributed to the oxidation of the conjugate base of pyrazolidinone was apparent, a distinct broadening of the peak occurred between approximately 2-5mM tetraethylammonium chloride. On further addition of base the peak sharpened and continued to shift cathodically. The variation of peak potential (Ep) with log Et_4NCl is shown in Figure 15. The region AB corresponds to peak broadening and shows that at a base concentration

Figure 15


300
200
100
E_p
(mV vs. $Ag/AgNO_3$)
A
B
-1.00
0.00
1.00
log.c. (c(mM))
$\underline{v}$ = 100 mV.s^{-1}.

of above approximately 2mM the rate of change of peak potential ($\delta Ep/\delta(\log Et_4NCl)$) increases. The broadening can best be explained by the coexistence of both RH and R^-, with R^- being oxidised at a slightly lower potential. As pre-ionisation of the substrate has been shown to occur when dry Et_4NCl is used as the supporting electrolyte, it is necessary to modify Scheme 10 to include the formation of R^- (Scheme 35).

Therefore it can be concluded that for a 1mM solution of 1-phenylpyrazolidin-3-one in acetonitrile, no significant ionisation of the depolariser occurs up to a concentration of tetraethylammonium chloride of approximately 2mM, and Scheme 10 is valid. However, at concentrations of tetraethylammonium chloride of above 10mM, the oxidation mechanism will be that shown in Scheme 35, with pre-ionisation of the pyrazolidinone occuring before oxidation. At intermediate supporting electrolyte concentration corresponding to the region of greatest change in Figure 15, both mechanisms will operate simultaneously due to the coexistence of RH and R^- in the electrolysis solution.

Scheme 10

$$RH \xrightarrow{\text{R.D.S.}} \overset{+\cdot}{R}H + e$$

$$\overset{+\cdot}{R}H + Cl^- \xrightarrow{\text{fast}} \dot{R} + HCl$$

$$\dot{R} \xrightarrow{\text{fast}} \overset{+}{R} + e \qquad -E_1$$

$$\overset{+}{R} + Cl^- \longrightarrow P \quad HCl$$

Scheme 35

$$RH \quad Cl^- \rightleftharpoons R^- + HCl$$

$$R^- \xrightarrow[\text{R.D.S.}]{\text{fast}} \dot{R} + e \qquad -E_2$$

$$R \longrightarrow \overset{+}{R} + e$$

$$\overset{+}{R} + Cl^- \longrightarrow P + HCl$$

$$E_2 < E_1$$

CHAPTER 4

THE STABILITY OF THE INITIAL MONOELECTRONIC OXIDATION PRODUCT OF SOME PYRAZOLIDINONES IN NEUTRAL ACETONITRILE

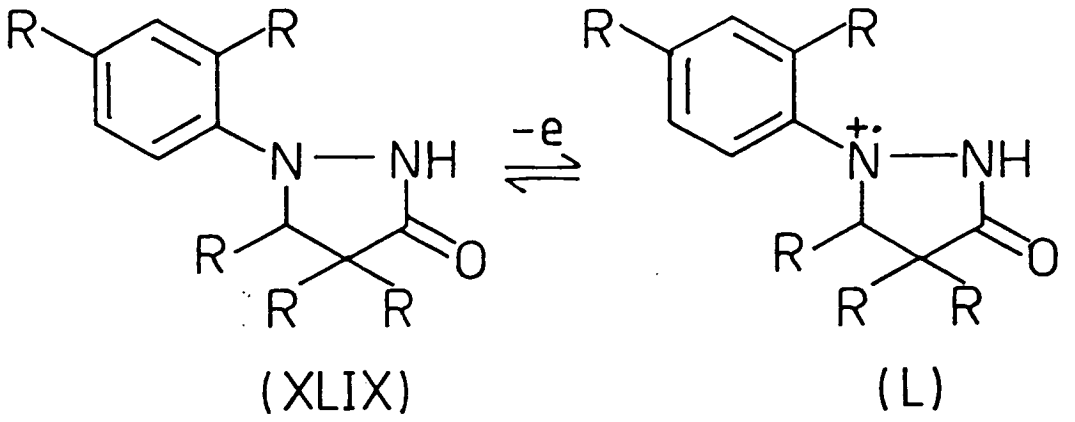
An important factor to be considered in the mechanism of development, and in particular of superadditive development (Chapter 1), is the stability of the species initially generated on monoelectronic oxidation of the developing agent.[78] It has been found that in alkaline aqueous solution the stability of the radical cation is dependent upon the nature of the substituents at position 4 and/or 5 in the pyrazolidinone ring (Scheme 36), and that there is good correlation between this stability, measured as the magnitude of the second order rate constant for disproportionation (Scheme 37) and the effectiveness of these derivatives as superadditive developing agents[25].

A study of the stability of the monoelectronic oxidation products of some 1-arylpyrazolidin-3-ones in acetonitrile was undertaken. The criterion used for the comparison of these compounds was the magnitude of sweep rate which was necessary to observe by cyclic voltammetry an $i_{p,c}/i_{p,a} = 0.75$ for the first electron transfer. It has been shown (Chapter 3) that the presence of a basic, trace impurity, which is probably water, in the solvent/electrolyte system, interferes with the oxidation mechanism by deprotonating the radical cation (L). This effect is concentration dependent, however, (Figure 10) and so cyclic voltammograms were obtained at a relatively high concentration (5mM). At this concentration, the effect of this basic impurity would be minimal. The electroanalytical experiments were conducted under standard conditions, with the same batch of supporting electrolyte being used for all voltammetric experiments.

The compounds which were chosen for this study are shown in Table 10. Also tabulated is the sweep rate necessary to obtain $i_{p,c}/i_{p,a} = 0.75$ (75% reversibility), which was determined from the empirical formula given by Nicholson[79] (Equation 6).

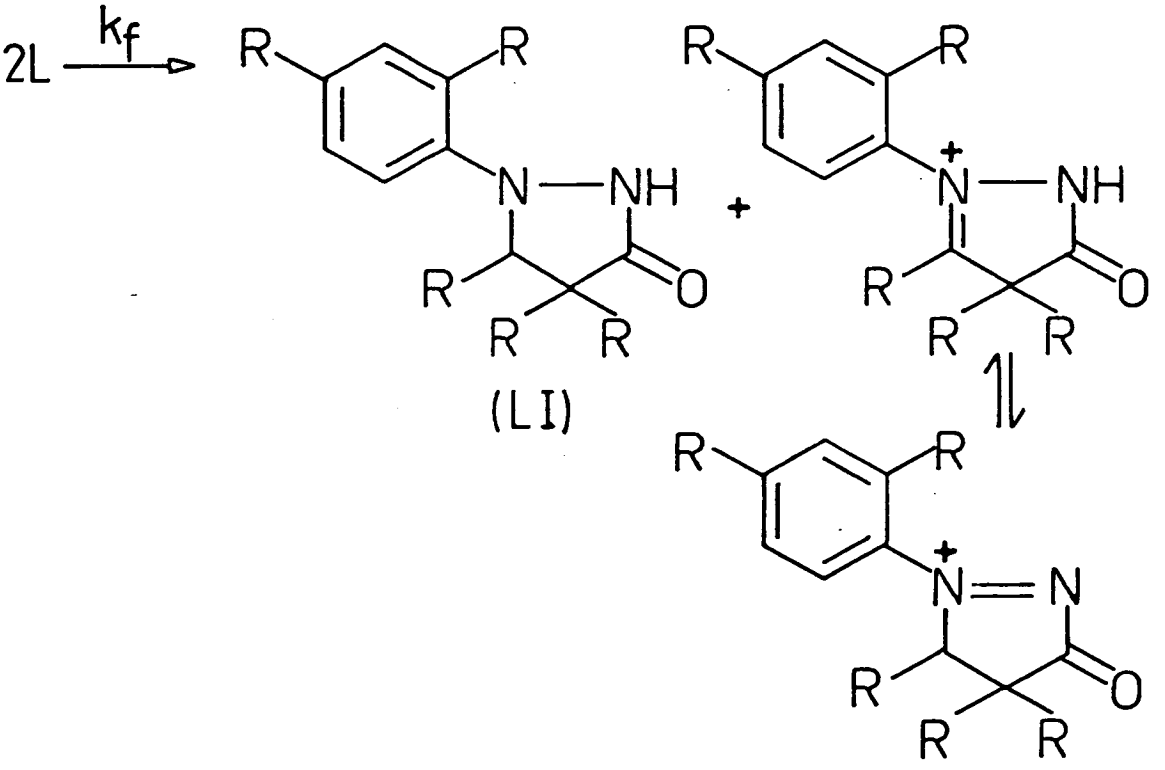
$$i_{p,c}/i_{p,a} = (i_{cp})_o/(i_{ap})_o + 0.485(i_{sp})_o/(i_{ap})_o + 0.086 \qquad - 6$$

Scheme 36



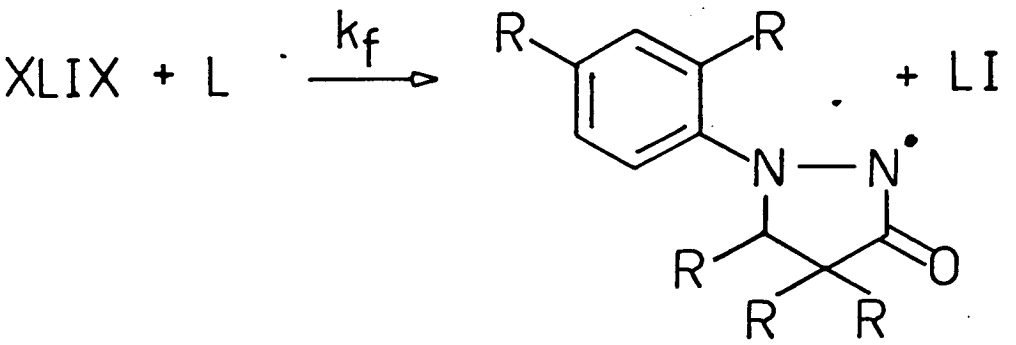
(XLIX) (L)

Scheme 37



(LI)

Scheme 38



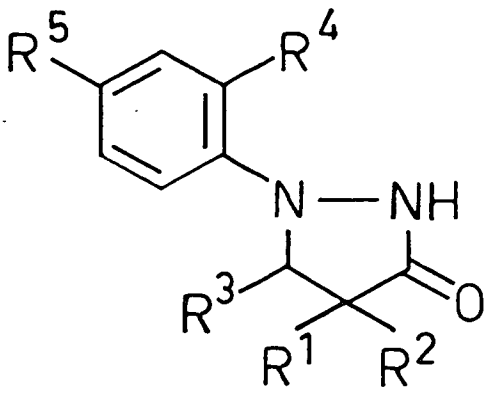
The terms in Equation 6 have the significance shown in Figure 16, and the potential from $E_{p,a}$ to the switching potential, E_s, was kept constant at 300 mV for each compound. The stability of the radical cation, L, in acetonitrile solution is dependent on the magnitude of the second order rate constant, k_f, in either of Schemes 37 or 38. The standard of reversibility was set at 0.75 as this ratio falls within the region of maximum rate of change of the function $i_{p,c}/i_{p,a}$ vs. log $k_f\tau$ for an irreversible chemical reaction following electron transfer[48]. From Table 10 it can be seen that the stability of the initial monoelectronic oxidation product of the pyrazolidinone derivatives in neutral acetonitrile are in the sequence shown in Scheme 39.

The difference in the stabilities of the cation radicals of the three 1-phenylpyrazolidin-3-ones in Table 10 which show an electrochemically reversible electron transfer in acetonitrile is not as great as the differences in stability which 4 and 5 substituted 1-phenylpyrazolidin-3-ones exhibit in aqueous alkali. In aqueous alkali it has been shown that the only chemical reaction occurring after charge transfer is disproportionation by electron transfer and that substitution at positions 4 and 5 in the pyrazolidinone ring causes the rate constant for dismutation to vary over several orders of magnitude[25].

The stabilities of the radical cations which were studied in acetonitrile are all very similar suggesting that perhaps the disporportionation of 2 radical cations is not an important reaction. If disproportionation were significant, then inclusion of a relatively bulky phenyl group at position 5 might be expected to sterically inhibit disproportionation and make the radical cation more stable. In fact, the reverse is observed experimentally (Table 10).

An alternative explanation for the slightly different stabilities of the radical cations, and one which is consistent with the deprotonation mechanism (Scheme 38) is that the different stabilities of the pyrazolidinones with substituents at positions 4 and 5 is due to slight variations in the basicity of the pyrazolidinones. There is very little difference in the reversible electrochemical potentials ($E_{p,a}$) of the compounds in Table 10, and, since these potential

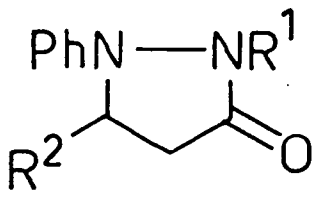
Table 10



R^1	R^2	R^3	R^4	R^5	$\underline{v}^*(V.s^{-1})$
H	H	H	H	H	2.55
CH_3	CH_3	H	H	H	1.65
H	H	Ph	H	H	3.30
CH_3	CH_3	H	CH_3	CH_3	quasi-reversible

*Sweep rate at which ip,c/ip,a = 0.75

Table 11



R^1	R^2	$E_{(p,c)}$(reversible)($\underline{v}$ vs. Ag/Ag NO_3)
H	H	0.250 (at 2.55 $V.s^{-1}$)
Me	H	0.530 *
Ph	Ph	0.760 *

*Show electrochemical reversibility at sweep rates as low as 0.1 $V.s^{-1}$

Scheme 39

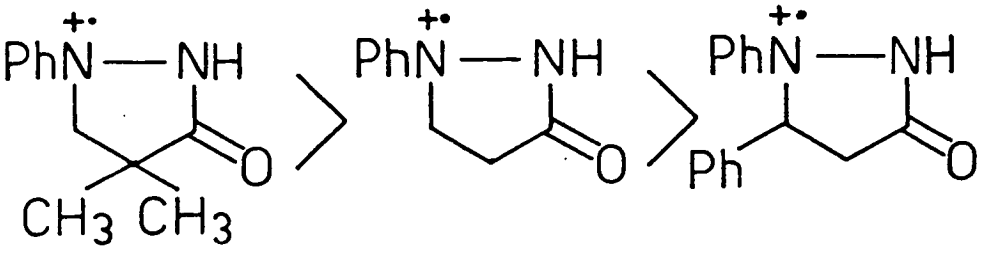
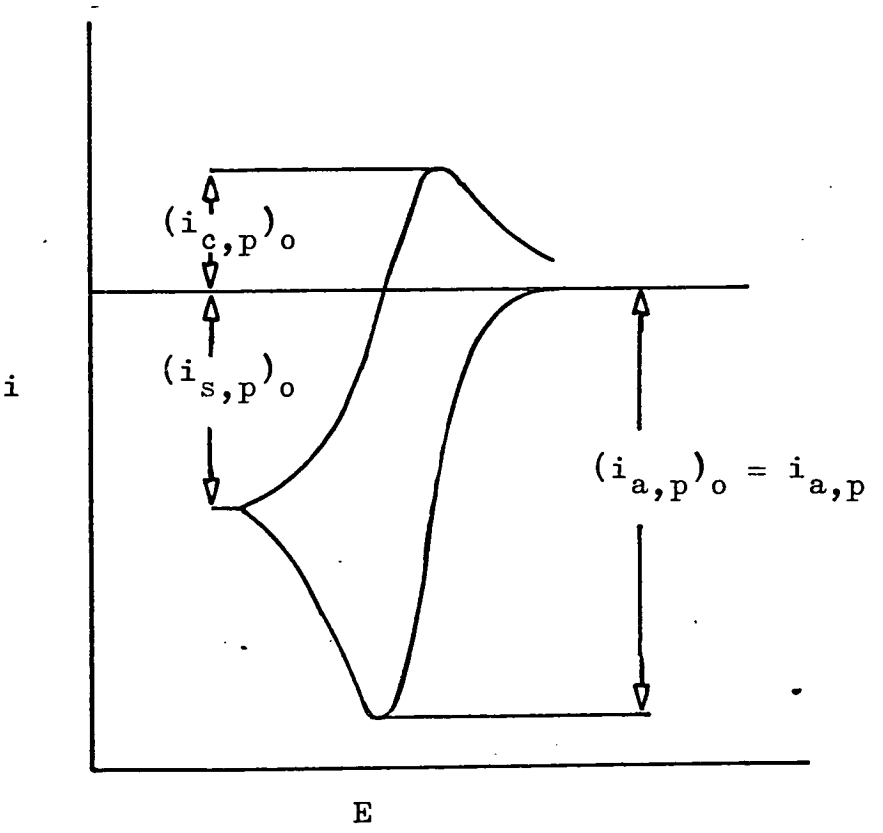


Figure 16



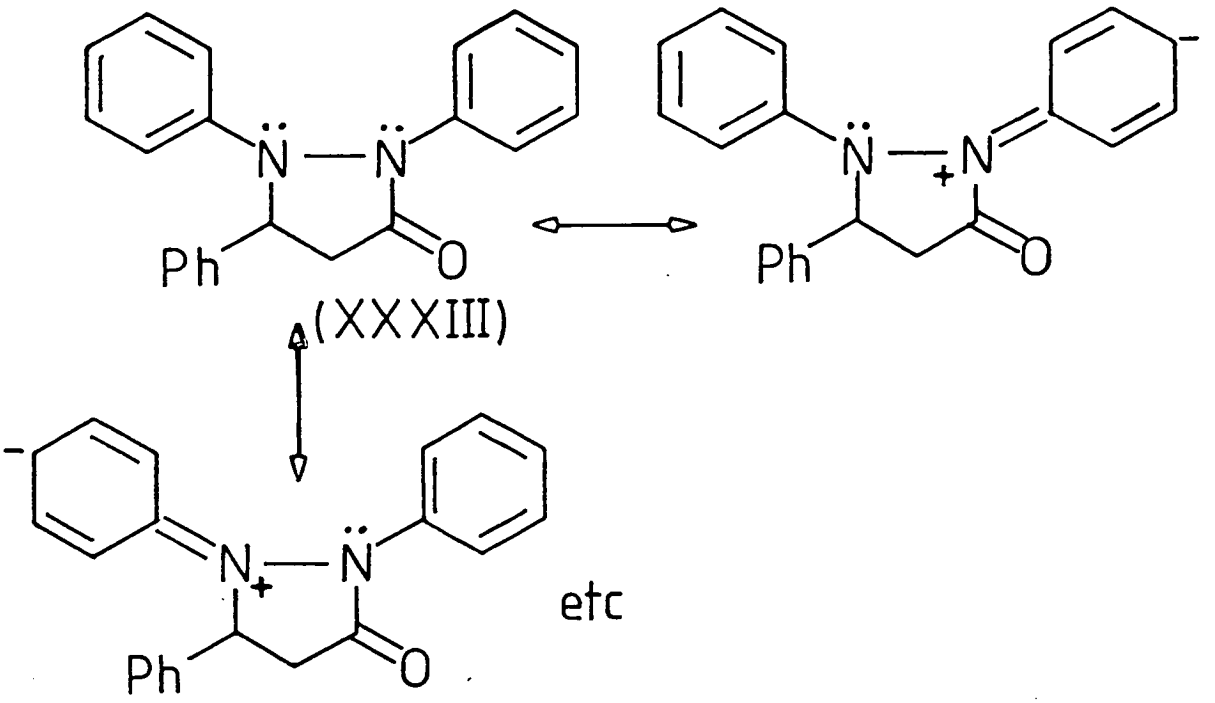
determinations were carried out in different batches of acetonitrile, it was not considered advisable to place too much significance on the slight potential differences which were recorded.

Alkyl or aryl substitution at N(2), however, does produce a significant shift of the reversible peak potential ($E_{p,a}$). The different reversible potentials ($E_{p,a}$) recorded for the pyrazolidinones in Table 11 correlate well with expectations based upon the availibility of lone pair electrons in the substrate and the stabilising influences in the cation radical.

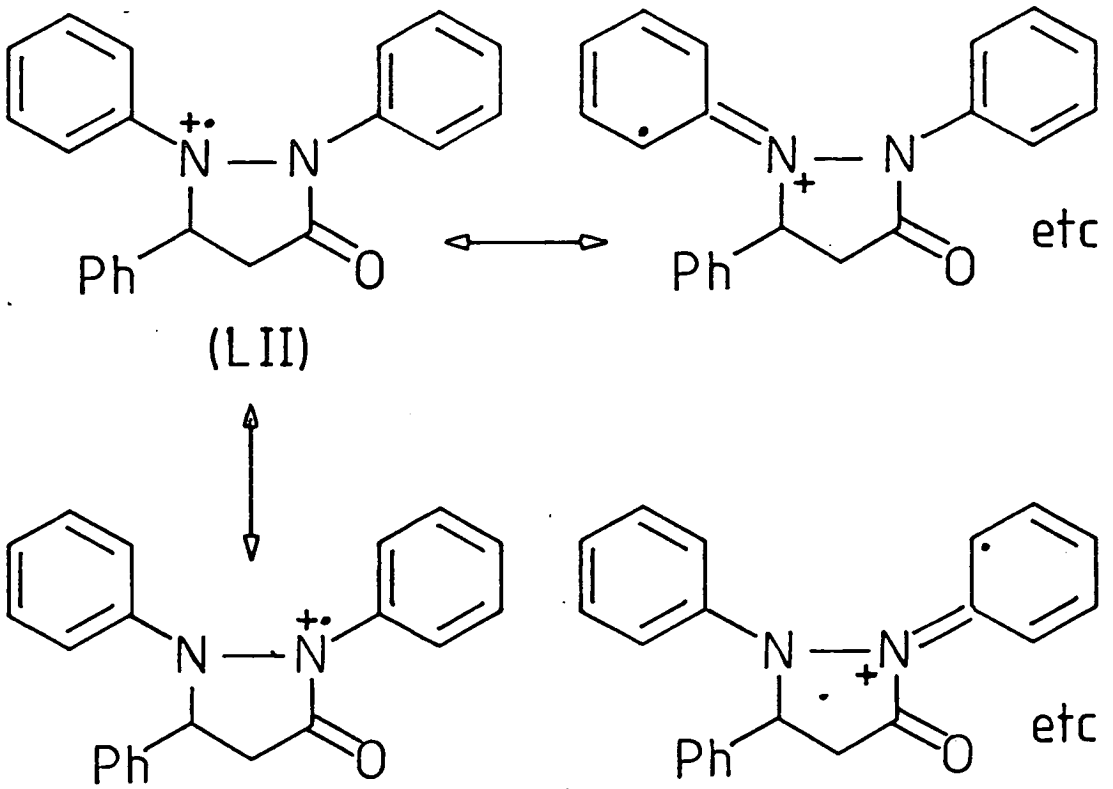
Ground state delocalisation of the available lone pairs in compound (XXXIII) makes it potentially harder for oxidative charge transfer to occur (Scheme 40). However, the corresponding radical cation (LII) is also stabilised by the presence of both phenyl groups at N(1) and N(2) (Scheme 41). In contrast, the ground state of compound (XXXII) has only one phenyl group to take part in mesomeric delocalisation of the electrons available for transfer, and there is a positive inductive effect associated with the methyl group on N(2) (Scheme 42). The corresponding radical cation (LIII) is stabilised both by mesomeric stabilisation from the phenyl group on N(1), and by the inductive effect of the methyl group on N(2) (Scheme 43). Therefore the greater mesomeric stabilisation which occurs in both the ground state of XXXIII and the radical cation, LII, in comparison to XXXII and LIII is reflected in the more positive reversible peak potential which is observed for XXXIII (Table 11).

The ground state of 1-phenylpyrazolidin-3-one (I) is also stabilised by the delocalisation of the lone pair electrons into the phenyl group at N(1) (Scheme 44). This phenyl group also contributes to stabilisation of the corresponding radical cation, III (Scheme 45). The hydrogen present at N(2), however, cannot contribute to the stabilisation of either the ground state pyrazolidin-3-one or the radical cation. This lower degree of stabilisation is reflected in the less positive reversible peak potential ($E_{p,a}$) observed for this compound in comparison to that recorded for both XXXII and XXXIII.

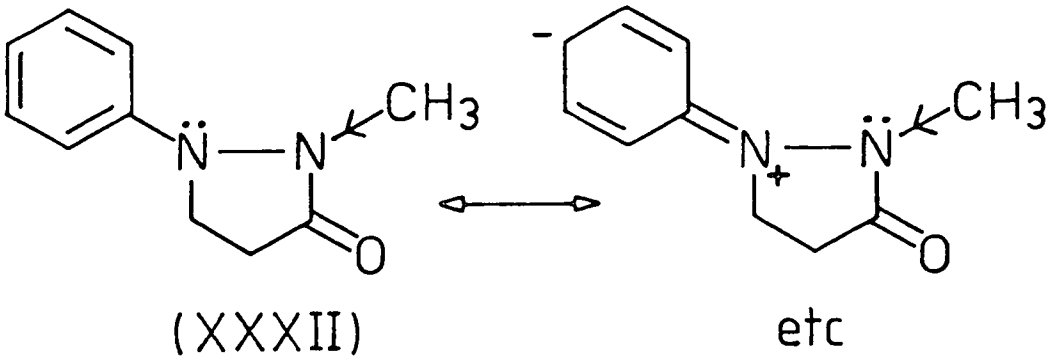
Scheme 40



Scheme 41

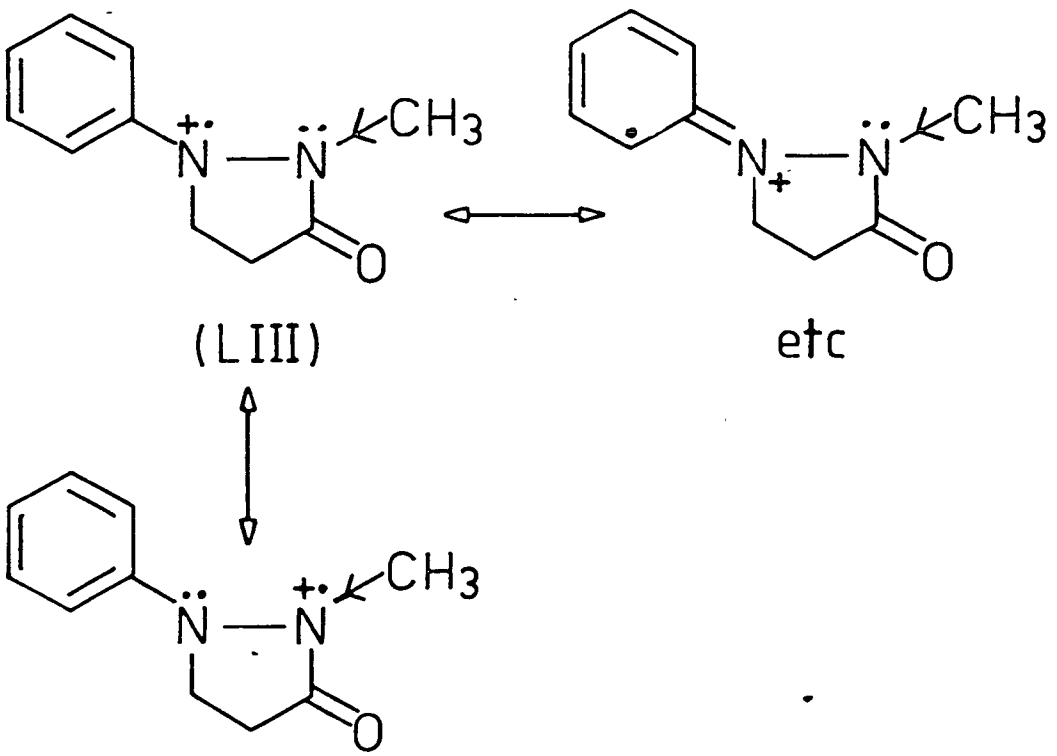


Scheme 42



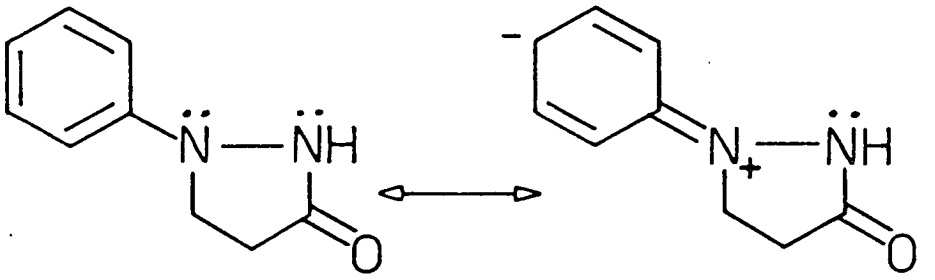
(XXXII) etc

Scheme 43



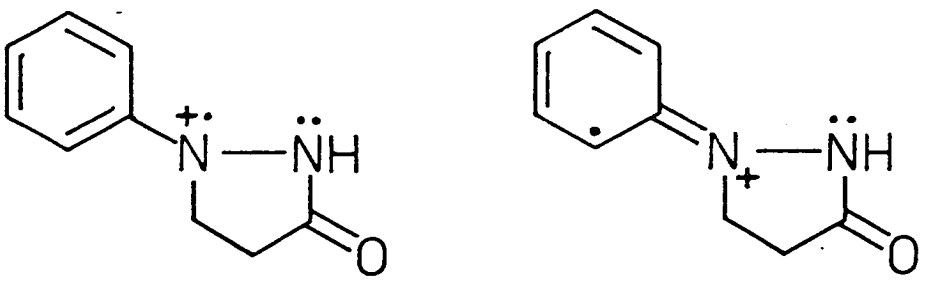
(LIII) etc

Scheme 44

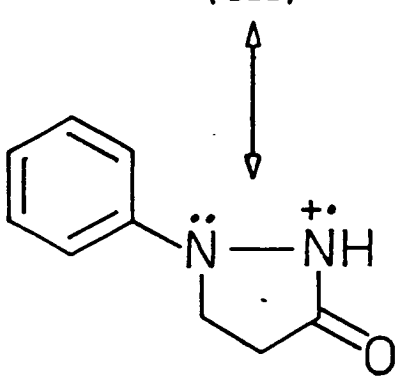


(I) etc

Scheme 45



(III) etc



In summary, therefore, the difference in the reversible peak potential ($E_{p,a}$), and the degree of electrochemical reversibility ($i_{p,c}/i_{p,a}$) shown in Table 11 can best be rationalised by considering the effect of the groups at N(1) and N(2) on, (i) the availability of electrons for charge transfer in the ground state, and (ii) the stability of the radical cation generated by monoelectronic oxidation.

CHAPTER 5

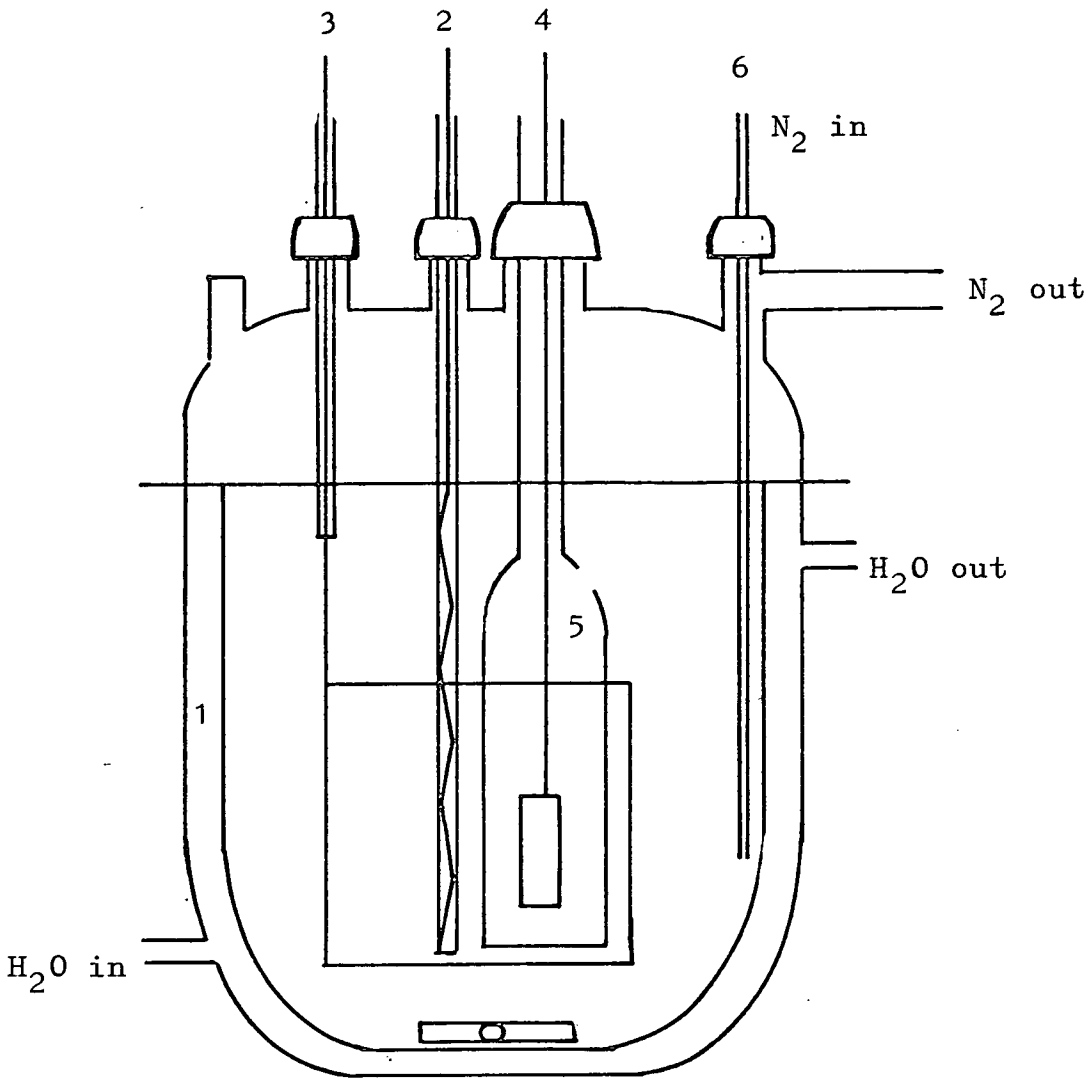
EXPERIMENTAL

Instrumentation:- ^{1}H Nuclear magnetic resonance spectra were recorded on a Varian Associates EM 360 (60 MHz), a Varian Associates HA 100 (100 MHz), or a Bruker WH 360 (360 MHz) spectrometer. ^{13}C Nuclear magnetic resonance spectra were recorded on a Varian Associates CFT-20 spectrometer system. N.m.r. samples were run as solutions (1-10%) in deuterated solvents with tetramethylsilane as internal reference; chemical shifts are given in ppm. The following abbreviations are used to describe n.m.r. resonances; singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m). Infra-red spectra were recorded on a Perkin-Elmer 157G grating spectrophotometer. Suffixes to infra-red bands are abbreviated; weak(w), medium(m), strong(s). Elemental analyses were obtained using a Perkin-Elmer 240 elemental analyser. Mass spectra were run on an AEI MS 902 double focussing mass spectrometer. Melting points were obtained on a Reichart hot-stage microscope system and are uncorrected.

Controlled potential and controlled current electrolyses were performed using a Chemical Electronics type TR 70/2A, or a Hermes control series 50, 100V/0.5A potentiostat. Current integration was effected by using either a hydrogen-nitrogen gas-coulometer[80] or a homebuilt electronic integrator[81]. Controlled potential electrolyses were performed in the cell illustrated in Figure 17. The working electrode was a platinum cage, the secondary electrode a platinum strip and the reference electrode a cracked glass Ag electrode in 0.1M $AgNO_3$.

Routine high performance liquid chromatography (h.p.l.c.) was carried out using a 100 x 5 mm stainless steel column, slurry packed with Hypersil (5 μ), at ambient temperature, in conjunction with a Chromatronix model 3100 liquid chromatograph. Compound detection was effected by an ultra-violet detector operating at 254 or 280 nm, connected to a dual channel absorbance amplifier and Servoscribe type RE 511 chart recorder. Reverse-phase h.p.l.c. was carried out using the above system in conjunction with a 100 x 5 mm stainless steel column packed with Partisil octadecylsilicate (ODS, 5 μ). In all straight phase analyses the elutant was either ethyl acetate (50% water saturated), or a mixture of ethanol (10-15%) and hexane containing 0.3% water. The solvent for reverse-phase h.p.l.c. was methanol (0-90%) in water. In

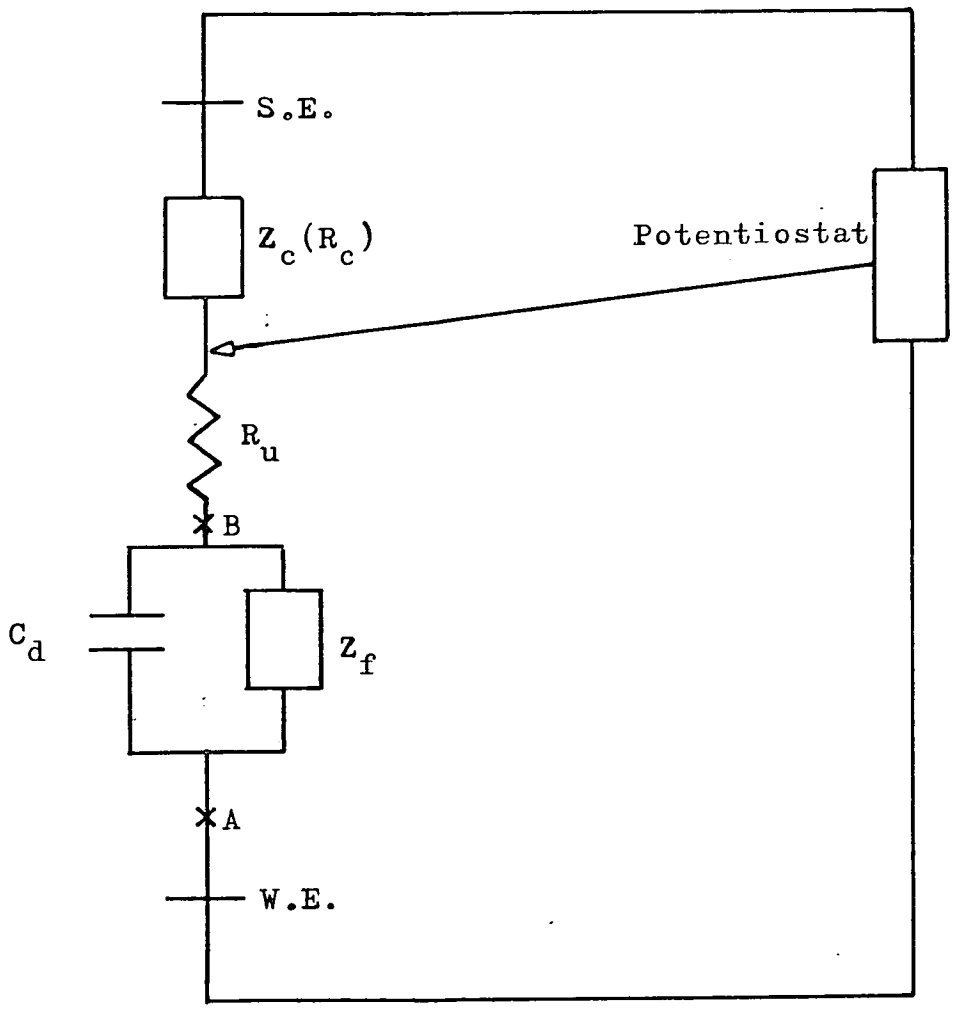
Figure 17



Preparative Electrolysis Cell

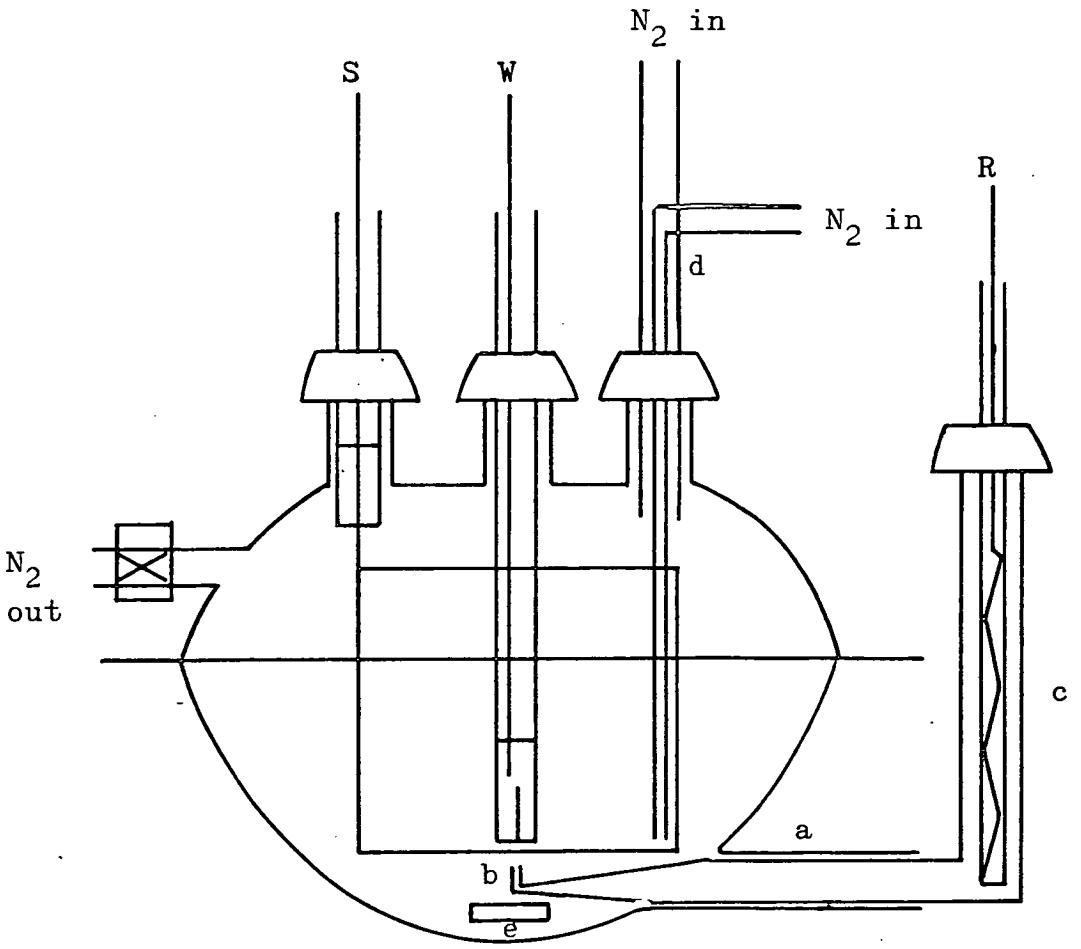
1) Water jacket
2) R.E.
3) W.E.
4) S.E.
5) Secondary compartment
6) N_2 bubbler

Figure 18[83]



Cd	=	double layer capacitance
R_u	=	uncompensated resistance
$Z_{c(Rc)}$	=	compensated
W.E.	=	working electrode
S.E.	=	Secondary electrode
R.E.	=	reference electrode

Figure 19



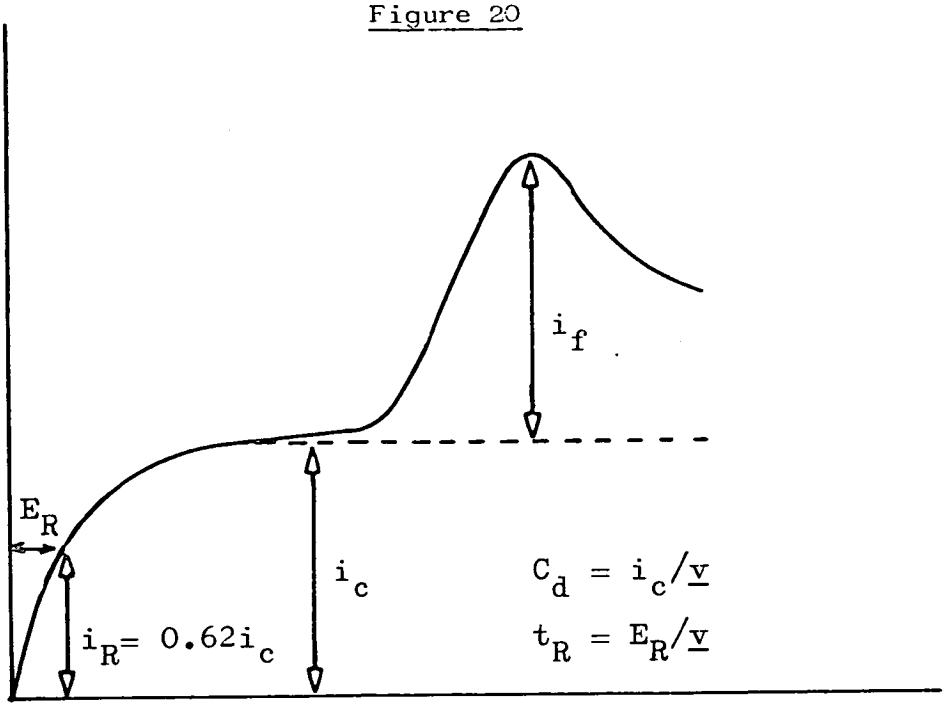
W = Working Electrode

S = Secondary Electrode

R = Reference Electrode

a) 'Chance' syringe barrel incorporated into lower flange
b) Luggin Capillary
c) Reference Cell
d) Nitrogen inlet
e) Magnetic Stirrer

Figure 20



Schematic representation of faradaic and double-layer charging currents[84]

quantitative analyses, peak areas were evaluated by weighing the peaks after cutting out.

The product mixture obtained from the oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in acetonitrile, using tetraethylammonium fluoroborate as the supporting electrolyte was analysed by Dr R Wall on a 100 x 5 mm stainless steel column, slurry packed with ODS Hypersil. The elutant consisted of 25% acetonitrile in water, containing 0.01M NaH_2PO_4, and buffered at pH 3.10.

Voltammetry:- The use of a potentiostat with a three electrode configuration in linear sweep voltammetry (LSV), or cyclic voltammetry (CV) does not fully eliminate the effect on polarisation curves of uncompensated resistance (R_u). The potentiostat effectively compensates for solution resistance (Rc) between the secondary and reference electrodes by ensuring that the potential difference between the working and reference electrodes is approximately equal to the voltage delivered by the sweep generator. There still exists, however, an uncompensated resistance (R_u) due to that part of the solution between the working and reference electrodes[82]. It is possible to draw a three electrode LSV/CV experiment as an equivalent circuit[83] (Figure 18).

In linear sweep voltammetry, the potential difference (E) applied between the working electrode and the reference electrode (between A and B in Figure 18) is scanned linearly with time[84].

The aim of the experiment is to apply a certain potential difference between the working electrode and the adjacent solution, and positioning the reference electrode close to the working electrode is an approximation to this.

For an anodic sweep

$$E = E_i + \underline{v}t$$

(E_i = initial potential, $\underline{v}$ = sweep rate, t = time)

However, the presence of uncompensated resistance (R_u) in the cell reduces the actual potential between the working electrode and adjacent solution by an amount $R_u(i_c + i_f)$(i_c = double layer charging current, i_f faradaic current).
i.e.

$$E' = E_i + vt - R_u(i_c + i_f)$$

The observable effects of this ohmic drop[82,84] on the polarisation curve when a faradaic current flows through the working electrode are, a decrease of the peak current, an enlargement of the peak width, and a shift of the peak potential to larger values (anodic for oxidative processes, cathodic for reductive processes). The magnitude of these effects increases with i_f, and, consequently with those variables in the LSV experiment which serve to increase i_f, the depolariser concentration, the electrode surface area, and the sweep rate.

The uncompensated resistance is also dependent on cell geometry[82,85] and the physical distance of the working electrode from the reference electrode sampling point. As the equipment available to perform electroanalytical experiments did not include a positive[82,83,86,87,88] feedback loop which allows electronic compensation to be effected for the hitherto uncompensated resistance, it was necessary to design a cell which minimised this resistance by placing the reference electrode sampling point as close as possible to the working electrode surface, without screening it and thus interfering with the diffusion of electroactive species[82,85,87]. It was also necessary to define the geometry of the cell to enable experiments to be performed under reproducible conditions.

The cell which was used for cyclic and linear sweep voltammetry is shown in Figure 19. The working electrode was a platinum wire sealed into soft glass tubing. The end of the electrode was first polished with graded emery paper, and then 3 micron alumina until the platinum surface appeared scratch-free on optical inspection with a magnifying glass (5x). The surface area of the electrode was

determined to be 0.38 mm^2 from the Randles-Sevcik equation[49,50] (Equation 7) using linear sweep voltammograms on a 1mM solution of ferrocene (D taken as 2.4×10^{-5} [89] $cm^2\ s^{-1}$) in acetonitrile with 0.4M tetraethylammonium fluoroborate as the supporting electrolyte.

$$A = k i_p / N^{3/2} D_o^{1/2} C_o v^{1/2} \qquad -7$$

A = electrode area

i_p = peak current

= sweep rate

k = constant

By optical measurement the diameter of the wire used in the electrode was 0.64 mm, giving a cross-sectional area of 0.32 mm^2. This working electrode was sealed with 'Araldite', into a plastic Quickfit SQ screw-top, with the electrode surface horizontal. The secondary electrode was a platinum cage which symmetrically surrounded the working electrode disc.

The reference electrode was Ag/0.1M $AgNO_3$ in CH_3CN contained in a separate compartment which was connected by means of a cracked glass seal, and a Luggin capillary, to a point approximately 2 mm from the working electrode surface. The reference electrode compartment was constructed from a 'Chance' 2 ml glass syringe, the outer part of which was incorporated into the lower flange case; this allowed the capillary tip to be placed directly underneath the working electrode disc.

With the cell set up as shown in Figure 19 the residual uncompensated resistance was measured using the method of Saveant[83,84] (Figure 20). The cell and reference compartment contained 0.4M tetraethylammonium fluoroborate as supporting electrolyte in acetonitrile[90]. In order to obtain a measurable value of the double layer charging current (i_c) it was necessary to perform linear sweep voltammetry at a high sweep rate (500 V/s). For this experiment a PAR™ Model 170 Electrochemistry System, coupled to a Physical Data Inc Model 512A transient store with playback facility was used. This system enabled a high sweep rate

voltammogram to be initially stored, and then played back at a speed within the response capabilities of the X-Y recorder. With ferrocene (1mM) as the depolariser, the linear sweep voltammogram at 500 V/s showed a double-layer charging current (i_c) of 84.0 μA. As $C_d = i_c/\underline{v}$, the double-layer capacitance (C_d) was calculated to be 1.68×10^{-7} F. The double layer response time (t) was found by measuring the point on the initial rising portion of the curve where the current is 63.2% of that on the plateau[83]. This gave a value for t_r of 1.22×10^{-4} s. The value of the uncompensated resistance in the cell under these conditions was calculated to be 728 Ω, using the equation $R_u = t_r/C_d$.

Knowing the value of the uncompensated resistance present in the cell for a 0.4M solution of tetraethylammonium fluoroborate in acetonitrile, a correction term (Equation 8) could be applied to peak potential measurements made under the same solvent/supporting electrolyte conditions, if this was found to be significant.

$$E_p = R_u[0.68(i_c)_o + 1.26i_p] \quad ((i_c)_o = \text{double layer charging current at foot of faradaic wave; } ip = \text{total peak current}) \quad - 8$$

Voltammetry was performed on solutions (25-35 ml) of supporting electrolyte (0.1-0.4M) in acetonitrile or methylene chloride containing the depolariser (0.1-10 mM). The solutions were thoroughly de-aerated by passing a stream of nitrogen gas through the solution for at least 10 minutes prior to recording the voltammograms. The nitrogen stream was presaturated with the appropriate solvent by passing it through a solvent bubbler. Presaturation of the stream in this way minimised the possibility of solvent evaporation from the cell during a series of sweeps. A solvent-saturated, nitrogen atmosphere was maintained over the solution during the recording of voltammograms. Between each sweep the solution was stirred magnetically, and nitrogen bubbled through the solution for 30 seconds. The solution was then left for a further 30 seconds to allow it to become quiescent.

Voltammetric experiments were carried out using either a home-built potentiastatic sweep unit or a Chemical Electronics TR 70/2A potentiostat driven by a Chemical Electronics Waveform Generator Type RB1. Voltammograms were recorded on either a Hewlett-Packard

7045A or a Bryans Model 26000 A4 X-Y recorder for slow sweep rates, or on a Tektronik 5103N storage oscilloscope for high sweep rates. The leads from the potentiostat to the cell, and from the potentiostat to the recorder were of co-axial cable, the outer sheath of which was connected to a single earth through which all electronic equipment was grounded. This earthing procedure was used in an attempt to reduce the 50 Hz mains hum which was superimposed on the Y response of the Bryans Model 26000 A4 X-Y recorder when it was used in conjunction with the Chemical Electronics TR 70/2A potentiostat and Chemical Electronics Waveform Generator Type RB1. Although using one earth greatly reduced this interference on the Y signal of the Bryans recorder, it did not totally eliminate it; therefore for slow sweep rate voltammetry (100 $mV.s^{-1}$) it was found that the Hewlett-Packard recorder, although less sensitive, provided the most reproducible voltammograms.

Chemicals:- 1-phenylpyrazolidin-3-one, 4-methyl-1-phenylpyrazolidin-3-one, 4,4-dimethyl-1-phenylpyrazolidin-3-one, 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one, and 4,4-dimethyl-1-(2,4-dimethyl) phenylpyrazolidin-3-one were supplied by Eastman Kodak Ltd. Tetraethylammonium chloride was obtained from BDH Chemicals Ltd as the monohydrate, and was dehydrated by storing in a vacuum desiccator over phosphorus pentoxide for seven days. (d_6-DMSO) was dried by standing over 3A molecular sieve.

Spectroscopic data:- 1-Phenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ2.34(t, 2H, J = 3.5 Hz, $-\underline{CH}_2-CH_2-$), 3.74 (t, 2H, J - 3.5 Hz, $-CH_2-\underline{CH}_2-$), 6.75-7.33 (m, 5H, aromatic), 10.16(broad s, 1H, NH); ^{13}C n.m.r. (d_6-DMSO) δ 29.98($\underline{CH}_2$), 53.64($\underline{CH}_2$), 115.69 (aromatic $\underline{C}$), 121.31 (aromatic $\underline{C}$), 129.02 (aromatic $\underline{C}$), 151.83 (aromatic $\underline{C}$), 173.94 ($\underline{C}$=O); i.r.ν_{max}^{nujol} 1690 cm^{-1}(s, amide carbonyl); mass spec. m/e = 162.

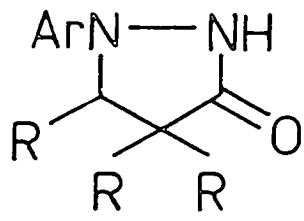
4-Methyl-1-phenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz) (d_6-DMSO) δ0.97 (d, 3H, J = 3.5 Hz, $-CH\underline{CH}_3$), 2.29-2.73 (m, 1H, $-CH_2-\underline{CH}CH_3-$), 3.29 (t, 1H, J = 5 Hz, $-H\underline{CH}-CHCH_3-$), 3.98 (d of d, 1H, J = 5,3.5 Hz, $-\underline{HCH}-CHCH_3-$), 6.73-7.35 (m, 5H aromatic), 10.18 (broad s, 1H, $N\underline{H}$); ^{13}C n.m.r. (d_6-DMSO) δ13.69($\underline{CH}_3$), 35.13($-\underline{CH}CH_3-$), 61.18($\underline{CH}_2$), 115.75(aromatic $\underline{C}$), 121.38(aromatic $\underline{C}$), 129.13(aromatic $\underline{C}$), 151.98(aromatic $\underline{C}$), 176.30($\underline{C}$=O); i.r. ν_{max}^{nujol} 3150(m, NH), 1690 cm^{-1}(s, amide carbonyl); mass spec. m/e = 176.

4,4-Dimethyl-1-phenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz) (d_6-DMSO) δ0.98(s, 6H, $2\underline{CH}_3$), 3.64(s, 2H, $\underline{CH}_2$), 6.74-7.36 (m, 5H, aromatic), 10.23(broad s, 1H, $N\underline{H}$); ^{13}C n.m.r. (d_6-DMSO) δ23.05($2\underline{CH}_3$), 40.43($-\underline{C}(CH_3)_2-$), 65.99($\underline{CH}_2$), 114.93(aromatic $\underline{C}$), 120.78(aromatic $\underline{C}$), 129.11(aromatic $\underline{C}$), 152.00 (aromatic $\underline{C}$), 177.93($\underline{C}$=O); i.r.ν_{max}^{nujol} 3150(m, NH), 1690 cm^{-1}(s, amide carbonyl); mass spec. m/e = 190

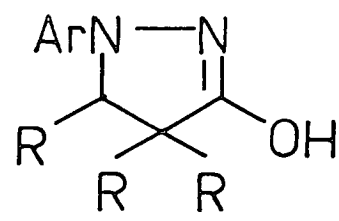
4,4-Dimethyl-1-(2,4-dimethyl)phenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ1.01(s, 6H, $2CH_3$), 2.19(s, 6H, aromatic $2CH_3$), 3.33(s, 2H, CH_2), 6.82-7.14(m, 3H, aromatic), 9.75(broad s, 1H, NH); ^{13}C n.m.r. (d_6-DMSO) δ17.79($ArCH_3$), 20.25($ArCH_3$), 23.78($2CH_3$), 40.17($-C(CH_3)_2-$), 66.53(CH_2), 116.26(aromatic C), 126.67(aromatic C), 128.14(aromatic C), 131.93(aromatic C) 148.36(aromatic C), 177.75(C = O); i.r.ν_{max}^{nujol} 3160(m, NH), 1690 cm^{-1}(s, amide carbonyl); mass spec. m/e = 218.

4-Hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ0.97(s, 3H, CH_3), 3.10-3.45(m, 2H, CH_2OH), 3.54(d(AB), 1H, J = 5 Hz, -HCH-), 3.96(d(AB), 1H, J = 5 Hz, -HCH-), 4.93(broad t, 1H, CH_2OH), 6.74-7.38(m, 5H, aromatic); ^{13}C n.m.r. (d_6-DMSO) δ19.16(CH_3), 47.00($-C(CH_3)(CH_2OH)-$), 61.66(CH_2), 64.30(CH_2), 115.15(aromatic C), 120.99(aromatic C), 129.31(aromatic C), 152.41(aromatic C), 176.45(C = O); i.r.ν_{max}^{nujol} 3430(s, OH), 3150(m, NH), 1670cm^{-1}(s, amide carbonyl); mass spec. m/e = 206.

1,5-Diphenylpyrazolidin-3-one; ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ2.25(d of d, 1H, J = 8,1.5Hz, -CH(Ph).HCH-), 3.19(d of d, 1H, J = 8,4.5Hz, -CH(Ph).HCH-), 5.03(d of d, 1H, J = 4.5, 1.5 Hz, -CH(Ph).HCH-), 6.80-7.69(m, 10H, aromatic); i.r.ν_{max}^{nujol} 3260(w, NH), 1695 cm^{-1}(s, amide carbonyl); mass spec. m/e = 238.



(LIV)



(LV)

Although compounds of the general structure, LIV, have been referred to as 1-arylpyrazolin-3-ones, their nujol mull i.r. spectra do not show absorptions in the carbonyl stretching region. On the other hand, there is present a strong absorption band at around 1600 cm^{-1} due to C=N- stretch, and a broad absorption band at around 2500-2800 cm^{-1} which may be attributed to strongly H-bonded OH stretchings. Thus in the crystalline state these compounds exist as 1,4-disubstituted-3-hydroxypyrazoles (LV)[92].

Purification of acetonitrile:- Acetonitrile (Fisons SLR grade) was purified by a method similar to that of Clark et al[93].

Acetonitrile (2 l.) was refluxed with a mixture of potassium permanganate (20 g) and sodium carbonate (10 g) for one hour. After filtration to remove insoluble inorganic material the filtrate was acidified with concentrated sulphuric acid and distilled quickly under dry nitrogen. The first and last 200 ml (10%) of distillate were discarded. The acetonitrile was then distilled using a 50 cm Vigreux column at 5 $ml.min^{-1}$, again discarding the first and last 10% fractions. Throughout this second distillation the still-head temperature remained at $80^{o}C$.

Preparation of tetraethylammonium fluoroborate:- 40% Aqueous fluoroboric acid (30 ml) was added slowly with stirring to 20% aqueous tetraethylammonium hydroxide (100 ml). Water was removed on a rotary evaporator leaving wet, white crystals which were recrystallised twice from ethanol, washed with ether (5 ml) and dried over calcium chloride in a desiccator under vacuum (22.0 g, 56%); m.p. $> 360^{o}C$(lit. 377-$8^{o}C$(decomp.)).

Preparation of tetrabutylammonium fluoroborate:- 40% Aqueous tetrabutylammonium hydroxide (20 ml) was neutralised with 40% aqueous fluoroboric acid (20 ml). The solid which precipitated was collected by suction filtration, was washed with water and recrystallised from a mixture of ethanol and water. The product was dried over phosphorus pentoxide in a desiccator under vacuum (6.2 g); m.p. 160-$2^{o}C$(lit. 162-$2.5^{o}C$)[94].

Preparation of 1,5-diphenylpyrazolidin-3-one (by the method of Kendall, Duffin and Axford[95]):- Sodium (3.0 g) was dissolved in absolute ethanol (100 ml) and phenylhydrazine (10.0 ml, 0.10 mol) was added, followed by ethyl cinnamate (16.6 ml, 0.10 mol). The resultant solution was refluxed for 16 h, and then all the volatile material was removed on a rotary evaporator at 100°C. The residue was dissolved in water (50 ml) and the solution was saturated with carbon dioxide at 0°C. The precipitated white crystalline mass was recrystallised from toluene, and then from methanol and water, to give microcrystals of 1,5-diphenylpyrazolidin-3-one (17.40 g, 73%); m.p. (160-1°C (lit.[95] 159°C(benzene)); ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ 2.25(d of d, 1H, J = 8, 1.5 Hz, RCH-HCH-), 3.19(d of d, 1H, J = 8, 4.5 Hz, R-CH-HCH-), 5.03(d of d, 1H, J = 4.5, 1.5 Hz, R-CH-HCH-), 6.80-7.69(m, 10H, aromatic; i.r. ν_{max}^{nujol} 3260 (w, NH), 1695 cm^{-1} (s, amide carbonyl).

Preparation of 1,2,5-triphenylpyrazolidin-3-one:- Sodium (3.0 g) was dissolved in absolute ethanol (100 ml) and 1,2-diphenylhydrazine (19.00 g, 0.1 mol) was added, followed by ethyl cinnamate (16.6 ml, 0.1 mol). The mixture was refluxed for 24 h, and was then evaporated on a rotary evaporator to remove volatile material, and poured into water (250 ml). After neutralisation with acetic acid, the oily product was extracted from the aqueous layer with ethyl acetate; cinnamic acid, a side product of the reaction was distilled off under reduced pressure (2.05 g, 14%); b.p. 120-5°C/ 2 mm Hg. The solidified acid was collected and washed with a mixture of benzene and petroleum ether (b.p. 40-60°C) to remove azobenzene. White crystals of cinnamic acid remained; m.p. 131°C (lit.[96] 134-6°C). The brown, tarry residue (13.47 g) which did not distil over under the above conditions was pre-deposited on to silica gel (60 g) and introduced on to the top of a silica column (grade III, 1 m x 4 cm). Elution with ethyl acetate-petroleum ether (b.p. 40-60°C)(1:4) gave an initial

fraction which contained a yellow oil (6.97 g, 22%). This oil was further purified by distillation (250°C/0.1 mm Hg) to yield 1,2,5-triphenylpyrazolidin-3-one as an oil which solidified to a resin-like material at room temperature (1.82 g); ^{1}H n.m.r. (100 MHz) δ2.64(d, 1H, J = 8 Hz, Ph-CH-HCH-), ($CDCl_3$), 3.47(d of d, 1H, J = 8, 4Hz, Ph-CH-HCH-), 4.97(d, 1H J = 4 Hz, Ph-CH-HCH-), 6.88-7.89 (m, 15H aromatic); i.r.ν_{max}^{nujol} 1720 cm^{-1} (s, carbonyl); mass spec. m/e = 314, exact mass = 314.142891, $C_{21}H_{18}N_2O$ requires 314.141905 (error 4 ppm); found, C 80.02, H 5.63, N 8.65%, $C_{21}H_{18}N_2O$ requires C 80.25, H 5.73, N 8.92%.

Attempted preparation of 2-methyl-1-phenylpyrazolidin-3-one (by the method of Bouchet, Elguero and Jacquier[14]):-
1-Phenylpyrazolidin-3-one (1.62 g. 0.01 mol), was added to methyl iodide (10 ml) and the mixture was refluxed for 3 h.

The methyl iodide was then evaporated on a rotary evaporator leaving unreacted 1-phenylpyrazolidin-3-one (1.56 g); m.p. 120-2°C (lit. 123°C). H.p.l.c. qualitative analysis of this solid indicated that it contained only unreacted starting material.

Preparation of 2-methyl-1-phenylpyrazolidin-3-one:-
1-Phenylpyrazolidin-3-one (4.86 g, 0.03 mol), was added to potassium carbonate (8.28 g, 0.02 mol) and methyl iodide (4.50 g, 0.03 mol), and the mixture was stirred for 16 h. It was then poured into water (200 ml), and the alkaline, aqueous layer was extracted with ethyl acetate (6 x 50 ml). The organic extract was evaporated on a rotary evaporator to leave an oil which was distilled under reduced pressure. The fraction (2.85 g, 53%)(b.p. 95-110°C/0.1 mm), was found by h.p.l.c. qualitative analysis to be predominantly 2-methyl-1-phenylpyrazolidin-3-one. The required product was

further purified by chromatography (silica gel grade III, 1 x 25 cm. column). On elution with methylene chloride a green oil (0.16 g), was obtained as the first fraction. 2-Methyl-1-phenylpyrazolidin-3-one, an oil which crystallised on standing (1.42 g), was the second fraction; m.p. 28°C; ^{1}H n.m.r. (100 MHz)($CDCl_3$) δ2.53(t, 2H, J = 3.5 Hz, -CH_2-), 3.05(s, 3H, N-CH_3), 3.82(t, 2H, J = 3.5 Hz, -CH_2-); 13C n.m.r. (d_6-DMSO) δ26.88, 30.53, 55.14, 118.23, 123.21, 129.30, 150.11, 172.13. 6.85-7.47 (m, 5H, aromatic); i.r. ν_{max}^{film} 1725 cm^{-1}(s, carbonyl); mass spec. m/e = 176.

Preparation of N-anilino-trans-but-2-enamide[97]:- Thionyl chloride (30 ml) was added to trans-but-2-enoic acid (8.6 g, 0.1 mol) and the mixture was refluxed until evolution of hydrogen chloride ceased (ca. 0.5 h). The excess of thionyl chloride was distilled off (b.p. 60-85°C) and the brown residue was cooled to room temperature, dissolved in ether (40 ml), and added to phenylhydrazine (20 ml, 21.6 g, 0.2 mol) in ether (100 ml) with stirring. The temperature of the reaction mixture was not allowed to rise above 10°C during this addition. After the slurry had been stirred for a further hour, a white solid was filtered off and added to cold, saturated, aqueous sodium bicarbonate (200 ml). The mixture was stirred until effervescence ceased. The solid product was collected by suction filtration, was washed with water (100 ml), and recrystallised from ethyl acetate to yield white needles of N-anilino-trans-but-2-enamide (4.26 g, 24%); m.p. 191-3°C(lit[97,98] 190°C); ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ1.81 (d of d, 3H, J = 3.5, 1Hz, CH_3), 5.96(d of q, 1H, J = 7.5, 1 Hz, olefinic CH), 6.52-7.26(m, 6H, 5 aromatic + 1 olefinic CH), 7.70(broad s, 1H, NH), 9.66(broad s, 1H, NH); i.r. ν_{max}^{nujol} 3300 (s, NH), 3240 (s, NH), 1670(m, amide carbonyl) 1620 cm^{-1}(s, >C=C< conjugated with carbonyl); mass spec. m/e = 176. Found, C 68.29, H 6.92, N 15.91%, $C_{10}H_{12}N_2O$ requires, C 68.18 H 6.82, N 15.91%. One attempt to obtain 5-methyl-1-phenyl pyrazolidin-3-one by the method of Kendall, Duffin, and Axford[95]

gave N-anilino-trans-but-2-enamide (18%) as sole reaction product; m.p. 187-8°C (benzene)(lit.[98] 190°C); ^{1}H n.m.r. (100 MHz)(d_6-DMSO) δ1.181(d, 3H, J = 3.5 Hz, CH_3-), 5.96(broad d of d, 1H, olefinic CH), 6.52=7.26(m, 6H, 5 aromatic + 1 olefinic CH), 7.70(broad s, 1H, NH), 9.66(broad s, 1H, NH); i.r. ν_{max}^{nujol} 3300 (s, NH), 3240 (s, NH), 1665 (s, amide carbonyl), 1620 cm^{-1} (s, >C=C< conjugated with carbonyl); mass spec. m/e = 176. Found, C 68.10, H 6.87, N 15.84%, $C_{10}H_{12}N_2O$ requires, C 68.18, H 6.82, N 15.91%; ^{13}C n.m.r. (d_6-DMSO) δ 17.59, 112.09, 112.32, 118.63, 123.75, 128.76, 139.23, 149.43, 165.01.

Preparation of 1-cyano-2-aminoprop-1-ene (by the method of Conn and Taurins[46,99]):- Acetonitrile (49.5 g, 1.21 mol), was added over 0.5 h to sodium (15.6 g, 0.60/g atoms) in dry benzene (160 ml), and the mixture was refluxed for 3 h. The solid which precipitated was collected and recrystallised from a mixture of chloroform and petroleum ether (b.p. 40-60°C) to yield a mixture of cis-and trans-1-cyano-2-aminoprop-1-ene (10.90 g, 22%); ^{1}H n.m.r. (60 MHz)(CD_3CN) δ1.87(s, 3H, CH_3, cis-isomer, 47%), 2.00(s, 3H, CH_3, trans-isomer, 53%), 3.77(s, 1H, CH, cis-isomer), 4.10(s, 1H, CH, trans-isomer), 5.26(broad s, 2H, NH_2, both isomers).

Chemical oxidation of 1-phenylpyrazolidin-3-one to 1-phenylpyrazolin-3-one[43]:- 1-Phenylpyrazolidin-3-one (10 g, 0.062 mol) was dissolved in water under reflux (250 ml), and ferric chloride (12 g, 0.075 mol) in water (100 ml) was added. The resultant mixture was stirred and allowed to cool to room temperature. The solid which had precipitated was collected, washed with water, and recrystallised from water to give needles of 1-phenylpyrazolin-3-one (4.16 g, 42%); m.p. 151-153°C (lit.[43] 154°C); ^{1}H.n.m.r. (60 MHz)(d_6-DMSO) δ 5.92 (d, 1H, olefinic CH), 7.10-8.15 (m, 5H, aromatic), 8.32 (d, 1H, olefinic CH).

Chemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one to 4-methyl-1-phenylpyrazolin-3-one:- 4-Methyl-1-phenylpyrazolidin-3-one (5 g, 0.028 mol) was mixed with water (150 ml) and ferric chloride (4.6 g, 0.028 mol) in water (100 ml) was added. The mixture was stirred under reflux for 5 min and then left to cool to room temperature. The solid which precipitated was collected and recrystallised from ethanol to yield needles of 4-methyl-1-phenylpyrazolin-3-one (1.76 g, 36%); m.p. 207-210°C (lit.[44] 210°C); ^{1}H n.m.r. (60 MHz)(d_6-DMSO) δ 1.97(s, 3H, CH_3), 7.10-7.80 (m, 5H, aromatic), 8.03 (s, 1H, olefinic CH); ^{13}C n.m.r. (d_6-DMSO) δ 7.12, 103.51, 116.32, 124.08, 126.59, 129.43, 140.09, 161.63.

Chemical oxidation of 1,5-diphenylpyrazolidin-3-one to 1,5-diphenylpyrazolin-3-one:- 1,5-Diphenylpyrazolidin-3-one (0.24 g, 0.001 mol) was dissolved in water (20 ml), and p-benzoquinone (0.22 g, 0.002 mol) was added to the solution. On heating on a water-bath a white solid precipitated which was collected and recrystallised from a mixture of dimethylformamide and methanol to give white plates of 1,5-diphenylpyrazolidin-3-one (0.18 g, 75%); m.p. 256-257°C (lit.[45] 255-6°C); ^{1}H n.m.r. (100 MHz) (d_6-DMSO) δ6.03 (s, 1H, olefinic CH), 7.15-7.55 (m, 10H, aromatic); i.r.ν_{max}^{nujol} 2580 cm^{-1} (w, strongly H-bonded OH); mass spec. m/e = 236. Found, C 75.99, H 5.10, N 11.71, $C_{15}H_{12}N_2O$ requires, C 76.27, H 5.08, N 11.86%.

Preparation of 3-anilinopropan-1-ol, (i) by the method of Rindfuss[100]:- A mixture of aniline (12 g, 0.13 mol), 3-chloropropan-1-ol (12.5 g, 0.13 mol), and sodium carbonate (12.5 g, 0.13 mol) was refluxed for 3 h. After cooling, the insoluble inorganic material was filtered off, was washed with ether, and the combined filtrates were evaporated on a rotary evaporator. The viscous oil which remained was distilled. The first fraction (b.p. 138-142°C/1.4 mm Hg) containing aniline and 3-anilinopropan-1-ol was discarded. The second fraction (b.p. 142-145°C/1.4 mm) contained predominantly 3-anilinopropan-1-ol (5.2 g, 27%). The n.m.r. spectrum of this fraction showed that it still contained impurities. These were removed, sacrificing yield for purity, by dissolving the crude alcohol (3.5 g) in ether (10 ml), extracting with 0.1M hydrochloric acid (10 ml), neutralising the aqueous layer with sodium carbonate, and back extracting into ether (10 ml). Evaporation of the solvent yielded a straw-coloured liquid (0.6 g) which was 3-anilinopropan-1-ol, ^{1}H n.m.r. (60 MHz) (CCl_4) δ1.26-1.85 (m, 2H, $-CH_2-\underline{CH}_2-CH_2-$), 2.96(t, 2H, J = 7 Hz, $-\underline{CH}_2-CH_2-$), 3.48(t, 2H, J = 7 Hz, $-\underline{CH}_2-CH_2-$), 4.00(broad s, 2H, O<u>H</u> N<u>H</u>), 6.19-7.28(m, 5H, aromatic); i.r. ν_{max}^{film} 3350 cm^{-1} (s, OH).

(ii) by the method of Kon and Roberts[67]:- 3-Chloropropan-1-ol (11.81 g, 0.125 mol), was added to a mixture of aniline (23.25 g, 0.250 mol) and water (2.25 g, 0.125 mol) during 1 h. The temperature of the reaction mixture was kept at 140°C during the addition, and then the mixture was refluxed for 1 h. After the resultant oil had cooled to room temperature, 1.0M sodium hydroxide (150 ml), was added and the mixture was extracted with ether. The ether layer was evaporated on a rotary evaporator leaving a brown oil which was purified by distillation at reduced pressure. The fraction(b.p. 128-135°C/1.1 mm); was 3-anilinopropan-1-ol (10.65 g, 56%); ^{1}H n.m.r. (60 MHz)(CCl_4) (identical to that previously reported for the alcohol prepared by the method of Rindfuss[100]).

Preparation of N-Phenyl-3-anilinopropionamide (by the method of Autenrieth and Pretzell[101]):- Acrylic acid (7 g, 0.1 mol) was added to aniline (23 g, 0.25 mol), and the mixture was refluxed (180-190°C) for 3 h. After cooling, 20% aqueous hydrochloric acid (30 ml) was added, and the crude hydrochloride which precipitated was collected. This was stirred with 20% aqueous sodium hydroxide (20 ml) for 0.5 h to generate the free base, which was collected, washed with water, and recrystallised twice from ethanol and water to yield N-phenyl-3-anilinopropionamide (1.40 g, 6%); m.p. 89-91°C (lit. 91-3°C); ^{1}H n.m.r. (100 MHz)(CD_3CN) δ 2.58(t, 2H, J = 6 Hz), ($-CH_2-CH_2-$), 3.41(t, 2H, J = 6 Hz, $-CH_2-CH_2-$), 4.37(broad s, 1H, NH), 6.50-7.66 (m, 10H, aromatic), 8.48(broad s, 1H, NH); i.r. ν_{max}^{nujol} 3380 (w, NH), 330 (m, NH), 1660 cm^{-1} (s, amide carbonyl); mass spec. m/e = 240. Found, C 75.26, H 6.56, N 11.86%, $C_{15}H_{16}N_2O$ requires C 75.00, H 6.67, N 11.67%. When this experiment was repeated, the anilide of 3-anilinopropanoic acid was obtained in a higher yield (33%).

Preparation of tetrahydro-3-phenyl-1,3-oxazine (by the method of Kon and Roberts[67]):- 3-Anilinopropan-1-ol (0.6 g, 0.004 mol) was stirred with an excess of 40% aqueous formaldehyde solution (10 ml) for 72 h. The solution was then extracted with ether (3 x 10 ml), and the combined extracts were evaporated on a rotary evaporator to yield a yellow oil. This was purified by distillation (microdistillation apparatus) to give tetrahydro-3-phenyl-1,3-oxazine (90 mg), ^{1}H n.m.r. (60 MHz)(d_6-DMSO) δ1.38-1.85 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 3.54 (t, 2H, J = 5 Hz, $-\underline{CH_2}-CH_2$), 3.86 (t, 2H, J = 5 Hz, $-\underline{CH_2}-CH_2-$), 4.86 (broad s, 2H, $O-\underline{CH_2}-N$), 6.63-7.47 (m, 5H, aromatic); ^{13}C n.m.r. (d_6-DMSO), 23.78 ($-\underline{CH_2}-$), 48.15($-\underline{CH_2}-$), 67.39($-\underline{CH_2}-$), 80.77 ($N-\underline{CH_2}-O$), 117.07 (aromatic C), 119.30 (aromatic C), 128.96 (aromatic C), 148.69 (aromatic C). i.r. ν_{max}^{film} no OH band. The preparation was repeated on a larger scale to quantify the experiment. The alcohol (4.0 g, 0.027 ml) produced an oil (3.7 g) which on distillation gave tetrahydro-3-phenyl-1,3-oxazine (2.8 g, 70%) as the first fraction, b.p. 82-85°C/0.4 mm; ^{1}H n.m.r. (60 MHz)(CCl_4) consistent with those reported above.

Attempted reaction of formaldehyde with N-phenyl-3-anilino-propionamide:- Aqueous 37% formaldehyde was added to N-phenyl-3-anilinopropionamide in acetonitrile followed by 40% aqueous fluoroboric acid. The solution was stirred. The specific reaction conditions are shown in the Table below:

	Formaldehyde /g(m.mol)	Amide /g(m.mol)	Aceto-nitrile ml	Fluoroboric acid /g(mol)	Temp., Time /°C, h
(i)	0.13 (1.6)	0.40 (1.6)	25	0.50 (3.0)	20, 1
(ii)	0.26 (3.3)	0.70 (3.3)	15	0.50 (3.0)	20, 1
(iii)	0.16 (2.0)	0.48 (2.0)	25	-	20, 24
(iv)	0.80 (10.0)	0.48 (2.0)	25	-	80, 1
(v)	0.80 (10.0)	0.48 (2.0)	25	-	20, 1
(vi)	40 ml(excess)	1.00 (4.2)	25	-	20, 1

The work-up consisted of evaporation of the solvent, addition of water (40 ml), neutralisation of the aqueous layer (if necessary) with sodium corbonate, and extraction with ethyl acetate. H.p.l.c. qualitative analysis of these extracts showed that only starting material was present. Under the conditions specified in (iv), formaldehyde polymerised to paraformaldehyde which separated out in the reflux condenser. (vi) corresponds to the reaction conditions under which 3-anilinopropan-1-ol reacts with formaldehyde to give tetrahydro-3-phenyl-1,3-oxazine.

Attempted acid-catalysed reaction of 1-phenylpyrazolidin-3-one with 1-phenylpyrazolin-3-one in acetonitrile:- 1-Phenylpyrazolidin-3-one (1.00 g, 0.006 mol) was added to 1-phenylpyrazolin-3-one (1.00 g, 0.006 mol) in acetonitrile (50 ml). A 2 ml sample was removed from the reaction flask and evaporated on a rotary evaporator. 60% Aqueous perchloric acid (1.00 g, 0.0062 mol) was added with stirring to the remaining solution and further 2 ml samples were removed after 0.5, 5, and 72 h. After evaporation on a rotary evaporator, the ^{1}H n.m.r. spectra (d_6-DMSO) were compared to that of the initial control sample. This indicated that no reaction had taken place.

Electrochemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.6 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (2.17 g, 0.1M) in acetonitrile (100 ml) with the anodic working electrode compartment containing 4-methyl-1-phenylpyrazolidin-3-one (1.76 g, 0.01 mol). After a current equivalent to 50% of a 2-electron oxidation had passed, the solution from the working electrode compartment was removed, was reduced in volume on a rotary evaporator (30 ml) and poured into water (200 ml). A white precipitate was formed. The resultant mixture was neutralised with sodium carbonate and extracted with ethyl acetate (6 x 25 ml). After evaporating off the solvent from the organic extracts, the remaining red oil was dissolved in the minimum amount of hot methanol and poured into water (150 ml). The precipitated white solid (0.50 g) was collected, and dried in a desiccator. H.p.l.c. analysis of this solid indicated that it contained two main products, one of which corresponded to 4-methyl-1-phenylpyrazolin-3-one by h.p.l.c. comparison with an authentic sample.

Separation of these two components was effected by column chromatography (silica gel grade III, 50 x 2.5 cm. column). The solid (0.50 g) was predeposited on silica gel (2.50 g) and the column was eluted with ethyl acetate:petroleum ether (b.p. 40-60°C)(1:4) to give 4-methyl-1-phenylpyrazolin-3-one (0.10 g); m.p. 208-210°C (lit.[44] 210°C); i.r. ν_{max}^{nujol} 2620 (w), 2720 cm^{-1}(w), (strongly H-bonded OH); mass spec, m/e = 174.

By increasing the elutant polarity to ethyl acetate-petroleum-ether (b.p. 40-60°C)(2-3) a second fraction was obtained containing 3-anilino-2-methyl-N-[4-(4-methyl-3-oxopyrazolin-1-yl)phenyl] propionamide(0.10 g) which was recrystallised from methanol-water; m.p. 223-6°C; ^1H n.m.r. (100 MHz)(d_6-DMSO) δ1.21 (d, J = 6 Hz, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.70-3.68 (m, 3H, CH_2 and CH), 6.40-7.20 (m, 5H, aromatic), 7.59 (d of d, AA'BB' system, J = 10 Hz, 4H, para-disubstituted benzene ring), 9.67 (broad s, 1H, OH), 9.45-10.00 (broad s, 1H, NH); i.r. ν_{max}^{nujol} 3430 (w, 2° amide), 3300 (m, 2° amine), 2730 (w, H-bonded OH), 1660 cm^{-1} (s, amide carbonyl); mass spec, m/e = 350. Found, C 68.73, H 6.21, N 16.18%, $C_{20}H_{22}N_4O_2$ requires, C 68.55, H 6.33, N 15.99%

The electrolysis was repeated under the following conditions. The anolyte contained 0.88 g of 4-methyl-1-phenylpyrazolidin-3-one, with the cell in total containing tetraethylammonium fluoroborate (1.08 g, 0.1M) in acetonitrile (50 ml). On exhaustive electrolysis, current equivalent to 60% of a 2-electron electrolysis flowed. The solution from the working electrode compartment was evaporated to dryness and the residue was mixed with water (20 ml). After the mixture had been neutralised with sodium carbonate, the solid which remained was collected, washed with water (30 ml), and dried at 80°C over phosphorus pentoxide. Quantitative h.p.l.c. analysis of this solid (0.811 g) using phenacene as the internal standard showed that it contained 0.244 g of 4-methyl-1-phenylpyrazolin-3-one (47% current yield) and 0.166 g of 3-anilino-2-methyl-N-[4-(4-methyl-3-oxopyrazolin-1-yl)phenyl] propionamide (19% current yield).

Electrochemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte, with equimolar 1-phenylpyrazolin-3-one present in the working electrode compartment:- A controlled potential electrolysis was performed at 0.6 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (2.17 g, 0.2M) in acetonitrile (50 ml) with the anodic working electrode compartment containing 4-methyl-1-phenylpyrazolidin-3-one (0.88 g, 0.002 mol) and 1-phenylpyrazolin-3-one (0.81 g, 0.002 mol). After a current equivalent to 71% of a 2-electron oxidation had passed, the solution from the working electrode compartment was reduced in volume on a rotary evaporator (30 ml), and poured into water (150 ml). A white precipitate formed. The resultant mixture was neutralised with sodium carbonate and extracted into ethyl acetate (6 x 25 ml). The solvent was evaporated on a rotary evaporator to leave an orange solid which was predeposited on silica gel from methanol, and introduced at the top of a silica gel column (grade III, 2.5 x 50 cm).

Elution with ethyl acetate-petroleum ether (b.p. 40-60°C)(1:4) gave a white solid (0.86 g). H.p.l.c. qualitative analysis of this solid indicated that it contained a mixture of 4-methyl-1-phenylpyrazolin-3-one, and 1-phenylpyrazolin-3-one. On increasing the elutant polarity to ethyl acetate-petroleum ether (b.p. 40-60°C)(2:3) a second fraction was collected which contained 3-anilino-2-methyl-N-4-[(4-methyl-3-oxopyrazolin-1-yl)phenyl] propionamide (0.10 g); ^{1}H n.m.r. spectra identical to that previously reported, no trace of the crossed dimer observed; mass spec. m/e = 350, no measurable peak at (M-14). The dimer (50 mg) was recrystallised from a mixture of methanol and water to give white microcrystals; m.p. 225-7°C.

Electrochemical oxidation of 1,5-diphenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.6 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (1.08 g, 0.1M) in acetonitrile (50 ml) with the anodic working electrode compartment containing 1,5-diphenylpyrazolidin-3-one (1.29 g, 0.005 mol). After a current equivalent to 60% of a 2-electron conversion had passed, the solution from the working electrode compartment was separated and concentrated to 5 ml on a rotary evaporator. Water (50 ml) was added to the resultant red tar, and the product was extracted into ethyl acetate (6 x 10 ml). The combined extracts were dried over magnesium sulphate before being predeposited on silica gel (5 g, grade III). H.p.l.c. qualitative analysis of the extract indicated that it contained two main products, one of which corresponded to 1,5-diphenylpyrazolin-3-one.

Separation of these two components was effected by column chromatography (silica gel grade III, 50 x 2.5 cm column). The column was eluted with ethyl acetate-petroleum ether (b.p. 40-60°C) (3:7) to give a pink solid which was recrystallised from ethanol to yield 1,5-diphenylpyrazolin-3-one (0.15 g); m.p. 248-250°C (lit.[45] 251°C); ^{1}H n.m.r. (60 MHz)(d_6-DMSO) δ6.07 (s, 1H,

olefinic CH), 6.85-7.70 (m, 10H, aromatic); i.r. ν_{max}^{nujol} 2580 cm^{-1} (m, strongly H-bonded OH). Elution with methanol gave a red tar which did not solidify on trituration. The tar (0.50 g) was dissolved in the minimum amount of hot methylene chloride and added to the top of a small silica gel column (grade III, 1.5 x 25 cm). Elution with chloroform yielded a red oil which solidified on trituration with ether (0.081 g). This solid (50 mg) was recrystallised from a mixture of THF, toluene and hexane to give microcrystals of 3-anilino-3-phenyl-N-[4-(5-phenyl-3-oxopyrazolin-1-yl)phenyl] propionamide (38 mg); ^{1}H n.m.r. (360 MHz)(d_6-DMSO) δ 2.876 (d of d, 1H, J = 1.44, 0.58 Hz, HCH), 2.995 (d of d, 1H, J = 1.44, 0.70 Hz, HCH), 5.024 (d of d, 1H, J = 0.79, 0.58 Hz, PhCH), 5.960 (broad s, 1H, NH), 6.000 (s, 1H, olefinic CH), 6.606-7.613 (m, 19H, aromatic), 9.839 (s, 1H, OH); i.r. ν_{max}^{nujol} 3320 (m, 2° NH), 2580 (w, strongly H-bonded OH), 1665 cm^{-1} (m, amide carbonyl); mass spec. m/e = 474, exact mass = 474.205408, $C_{30}H_{26}N_4O_2$ requires 474.205564 (error 1 ppm).

Electrochemical oxidation of 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.6 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (2.17 g, 0.1M) in acetonitrile (100 ml) with the anodic working electrode compartment containing 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one (2.06 g, 0.01 mol). After a current equivalent to 70% of a 2-electron conversion had passed, the solution from the working electrode compartment was separated, reduced in volume on a rotary evaporator to 5 ml and then poured into water (200 ml). An off-white solid was collected (1.32 g). H.p.l.c. qualitative analysis of this solid indicated that it contained two main components, one of which corresponded to 4-methyl-1-phenylpyrazolin-3-one by h.p.l.c. comparison with an authentic sample. Separation of these two components was effected by column chromatography

(silica gel Grade III, 1 m x 2.5 cm column). The solid was predeposited on silica gel from methanol and introduced at the top of the column. On elution with ethyl acetate-petroleum ether (b.p. 40-60°C)(3:7) gave 4-methyl-1-phenylpyrazolin-3-one (0.30 g); m.p. 207-209°C (lit.[44] 210°C); ^{1}H n.m.r. (60 MHz)(d_6-DMSO), δ 2.02 (s, 3H, CH_3), 6.87-7.87 (m, 5H, aromatic), 8.02 (s, 1H, olefinic CH); i.r.ν_{max}^{nujol} 2620 cm^{-1} (w, strongly H-bonded OH). The elutant polarity was increased to ethyl acetate-petroleum ether (b.p. 40-60°C)(3:2) and a second fraction gave 1-(5-methyl-3-phenyltetrahydro-1,3-oxazin-5-yl)-N-[4-(4-methyl-3-oxopyrazolin-1-yl)phenyl] formamide (0.31 g); m.p. 172-4°C; ^{1}H n.m.r. (d_6-DMSO) (100 MHz), δ 1.16 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 3.47 (d, 1H, J = 13 Hz, CH(AB)), 3.66 (d, 1H, J = 12 Hz, CH(A'B')), 3.92 (d, 1H, J = 13 Hz, CH(AB)), 4.22 (d, 1H, J = 12 Hz, CH(A'B')), 4.82 (broad AB, 2H, $-CH_2-N$), 6.65-7.30 (m, 5H, aromatic), 7.48 (broad s, 4H, N- para-disubstituted benzene ring), 7.90 (s, 1H, olefinic CH), 9.36 (broad s, 1H NH), 10.02 (broad s, 1H, OH); ^{13}C n.m.r. (d_6-DMSO) δ 7.10($-CH_3$), 19.86 ($-CH_3$), 42.41(-C-), 55.31 (R-CH_2-N(O)), 72.99 (R-CH_2-N(O)), 80.53 (N-CH_2-O), 103.00 (-CH = CR-), 116.39 116.59 119.66 121.35 (aromatic C), 126.40 (-CMe = CH-), 129.11 135.07 135.95 148.44 (aromatic C), 161.34 (=COH-R), 172.50 (NH-CO-R); i.r.ν_{max}^{nujol} 3340 (m, amide NH), 2620, 2720 (w, strongly H-bonded OH), 1665 cm^{-1} (amide carbonyl); mass spec. m/e = 392, exact mass = 392.183964, $C_{22}H_{24}N_4O_3$ requires 392.184829 (error 3 ppm).

Electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.4 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (2.17 g, 0.2M) in acetonitrile (50 ml) with the anodic working electrode compartment

containing 4,4-dimethyl-1-phenylpyrazolidin-3-one (1.90 g, 0.02 mol). After a current equivalent to 90% of a 2-electron oxidation had passed, the solution from the working electrode compartment was reduced in volume to 5 ml on a rotary evaporator and poured into water (100 ml). The solution was neutralised with sodium carbonate and extracted with ethyl acetate (6 x 25 ml). Qualitative analysis of this extract by high resolution variable wavelength reverse-phase h.p.l.c. (ODS, pH 3.10, 0.01M NaH_2PO_4, CH_3CN - H_2O (1:3) 223 nm), indicated that it contained a complex mixture of products (min. 24).

Electrochemical oxidation of 2-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.6 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium fluoroborate (2.17 g, 0.2M) in acetonitrile (50 ml) with the working electrode compartment containing 2-methyl-1-phenylpyrazolidin-3-one (1.76 g, 0.01 mol). After a current equivalent to 100% of a 2-electron oxidation had passed, the solution from the working electrode compartment was evaporated to dryness on a rotary evaporator, water (100 ml) was added, and the mixture was neutralised with sodium carbonate. Extraction with ethyl acetate (6 x 25 ml) yielded a red oil. Qualitative straight-phase h.p.l.c. analysis of this oil showed only the presence of the starting material. However, reverse-phase h.p.l.c. showed that the oil was a complex mixture of high polarity products (11 detectable).

Electrochemical oxidation of 4-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium chloride as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.3 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium chloride (2.0 g, 0.085M) in acetonitrile (100 ml) with the anodic working electrode compartment containing 4-methyl-1-phenylpyrazolidin-3-one (1.76 g, 0.01 mol). After a current equivalent to 75% of a 2-electron oxidation had passed, the solution from the working electrode compartment was reduced in volume on a rotary evaporator to 5 - 10 ml and poured into water (200 ml). A white solid separated which was isolated, washed with petroleum ether (b.p. 40-60°C) and dried by suction. H.p.l.c. indicated that this compound was pure 4-methyl-1-phenylpyrazolin-3-one by comparing its retention time with that of an authentic sample. This material was recrystallised from ethanol to yield white needles; m.p. 210-212°C (lit.[44] 210°C); ^{1}H n.m.r. (100 MHz) ($CDCl_3$), δ1.94 (s, 3H, $\underline{CH}_3$), 7.01-7.75 (m, 5H, aromatic), 8.00 (s, 1H, olefinic CH); i.r. ν_{max}^{nujol} 2620 (w), 2720 cm^{-1} (w), (strongly H-bonded OH); mass spec. m/e = 174.

Electrochemical oxidation of 1,5-diphenylpyrazolidin-3-one in acetonitrile using tetraethylammonium chloride as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.3 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium chloride (0.85 g, 0.068M), in acetonitrile (50 ml) with the anodic working electrode compartment containing 1,5-diphenylpyrazolidin-3-one (1.18 g, 0.005 mol). After a current equivalent to 75% of a 2-electron oxidation had passed, the solution from the working electrode compartment was evaporated to dryness and the solid which remained was recrystallised from ethanol to give needles of 1,5-diphenylpyrazolin-3-one (0.71 g, 80% current yield); m.p. 248-250°C (lit.[45] 251°C); ^{1}H n.m.r. (60 MHz)(d_6-DMSO), δ6.07 (s, 1H, olefinic $\underline{CH}$), 6.85-7.90 (m, 10H, aromatic); i.r. ν_{max}^{nujol} 2580 cm^{-1} (m, strongly H-bonded OH).

Electrochemical oxidation of 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one in acetonitrile using tetraethylammonium chloride as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.3 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium chloride (1.03 g, 0.086M) in acetonitrile (50 ml) with the anodic working electrode compartment containing 4-hydroxymethyl-4-methyl-1-phenylpyrazolidin-3-one (1.06 g, 0.005 mol). After a current equivalent to 50% of a 2-electron oxidation had passed, the solution from the working electrode compartment was reduced in volume on a rotary evaporator to 5-10 ml and poured into water (200 ml). A white solid separated which was extracted into ethyl acetate (6 x 25 ml). H.p.l.c. analysis indicated that the sole product of the reaction was 4-methyl-1-phenylpyrazolidin-3-one by comparison with an authentic sample.

Electrochemical oxidation of 4,4-dimethyl-1-(2,4-dimethylphenyl) pyrazolidin-3-one in acetonitrile using tetraethylammonium chloride as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.3 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetraethylammonium chloride (3.5 g, 0.3M) in acetonitrile (50 ml) with the anodic working electrode compartment containing 4,4-dimethyl-1-(2,4-dimethylphenyl)pyrazolidin-3-one (0.9 g, 0.0041 mol). After a current equivalent to a 3-electron oxidation had passed, the solution from the working electrode compartment was evaporated to dryness and water (100 ml) was added to dissolve the supporting electrolyte. The yellow solid which remained (0.69 g), was collected and dried over phosphorus pentoxide. H.p.l.c. qualitative analysis of this solid indicated that it contained one major product and at least five minor products.

Separation of these components was effected by column chromatography (silica gel grade III, 50 x 2.5 cm). The solid was predeposited on silica gel from methanol and the column was eluted with ethyl acetate-petroleum ether (b.p. 40-60°C)(1:1). The first fraction which was collected contained four of the minor components (h.p.l.c.). The second fraction contained 4,4-dimethyl-1-(2,4-dimethylphenyl)-5-(1-cyano-2-aminoprop-1-en-1-yl) pyrazolidin-3-one (0.19 g); m.p. 219/°C (decomp.); ^{1}H n.m.r. (100 MHz)(d_6-DMSO),δ0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.18 (s, 6H, $2CH_3$), 4.11 (s, 1H, CH), 6.80-7.20 (m, 3H, aromatic), 6.37 (broad s, 2H, NH_2), 9.78 (broad s, 1H, NH); ^{13}C n.m.r. (d_6-DMSO) δ17.46 (CH_3), 19.12 (CH_3), 20.22 ($2CH_3$), 25.21 (CH_3), 44.06 (-C-), 69.82, 75.21, 117.39 (aromatic C), 122.09, 126.48, 129.89, 131.76, 132.30, 147.48 (aromatic C), 156.31, 176.56; i.r. ν_{max}^{nujol} 3500 (m, NH_2) 3360 (m, amide NH), 3250 (m, NH_2), 2205 (s, C = N), 1700 (s, >C=C-N), 1660 cm^{-1} (s, amide carbonyl); mass spec. m/e = 298, exact mass = 298.177567, $C_{17}H_{22}N_4O$ requires 298.179352 (error 6 ppm); Found, C 68.18, H 7.40, N 18.56%, $C_{17}H_{22}N_4O$ requires C 68.46, H 7.38, N 18.79.

Electrochemical oxidation of 1-phenylpyrazolidin-3-one in methylene chloride using tetrabutylammonium fluoroborate as the supporting electrolyte:- A controlled current electrolysis was performed (50 ml) in a divided glass cell containing tetrabutylammonium fluoroborate (8.35 g, 0.5M) in methylene chloride (50 ml) with the anodic working electrode compartment containing 1-phenylpyrazolidin-3-one (1.62 g, 0.01 mol). After a current equivalent to 36% of a 2-electron oxidation had passed, the solution from the working electrode compartment was evaporated on a rotary evaporator. A yellow solid remained (9.17 g). H.p.l.c. qualitative analysis of this solid indicated that it contained 1-phenylpyrazolidin-3-one, 1-phenylpyrazolin-3-one and supporting electrolyte. Separation of these components was

effected by column chromatography (silica gel, grade III, 65 x 2.5 cm). The solid was dissolved in the minimum amount of methylene chloride and introduced at the top of the column. Elution with ether gave 1-phenylpyrazolin-3-one (0.33 g, 61%); m.p. 151-3°C(lit.[43] 154°C); ^{1}H n.m.r. (60 MHz)(d_6-DMSO) δ 5.95 (d, 1H, J = 1.5Hz, olefinic CH), 7.15-7.67 (m, 5H, aromatic), 7.73 (d, 1H, J = 1.5 Hz, olefinic CH); i.r. ν_{max}^{nujol} 2530 cm^{-1} (w, strongly H-bonded OH); mass spec. m/e = 160. The column was then flushed with ethyl acetate to give a solid (3.30 g) which was extracted with hot ether (2 x 30 ml). The ethereal solution contained unreacted starting material (0.40 g). H.p.l.c. retention times and spectroscopic characteristics were identical to those previously reported for 1-phenylpyrazolidin-3-one.

Electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in methylene chloride using tetrabutylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.5 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetrabutylammonium fluoroborate (8.35 g, 0.5M) in methylene chloride (50 ml) with the anodic working electrode compartment containing 4,4-dimethyl-1-phenylpyrazolidin-3-one (1.90 g, 0.01 mol). The working electrode became passivated, stopping the electrolysis after a current equivalent to 35% of a 2-electron oxidation had passed. The solution from the working electrode compartment was poured into water (100 ml) and the aqueous layer was neutralised with sodium carbonate. After washing the aqueous layer with methylene chloride (50 ml) the combined organic layers were dried over 4°A molecular sieve and the solvent was evaporated on a rotary evaporator to leave a yellow solid (7.19 g). H.p.l.c. qualitative analysis of this solid indicated that it contained starting material, supporting electrolyte and one electrolysis product. Separation of these components was effected by

column chromatography (silica gel, grade III, 1 m x 2.5 cm). The solid was dissolved in the minimum amount of methylene chloride and introduced at the top of the column. On elution with ether a fraction was collected which contained a yellow solid (0.48 g). H.p.l.c. indicated that this solid was 4,4-dimethyl-1-phenylpyrazolidin-3-one. A second fraction was collected which contained another solid (0.22 g). This was recrystallised from ethanol to give microcrystals of 4,4-dimethyl-1-phenyl-5-[4'-(4,4-dimethyl-3-oxopyrazolin-1-yl)] phenylpyrazolidin-3-one; m.p. 203-205°C; ^{1}H n.m.r. (60 MHz) (d_6-DMSO), δ0.68 (s, 3H, $C\underline{H}_3$), 1.09 (s, 6H, $2C\underline{H}_3$), 1.17 (s, 3H, $C\underline{H}_3$), 3.73 (s, 2H, $C\underline{H}_2$), 4.68 (s, 1H, C$\underline{H}$), 6.70-7.35 (m, 9H, aromatic), 10.40 (broad s, 2H, N$\underline{H}$), (the ^{1}H n.m.r. spectrum was initially very broad but sharpened after the nujol solution was left over sodium dithionite for 3 days); i.r. ν_{max} 1690 cm^{-1} (s, amide carbonyl); mass spec. m/e - 378. Found C 69.59, H 6.95, N 14.58%, $C_{22}H_{26}N_4O_2$ requires C 69.84, H 6.88, N 14.81%.

Electrochemical oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one in methylene chloride in the presence of 2,6-lutidine, using tetrabutylammonium fluoroborate as the supporting electrolyte:- A controlled potential electrolysis was performed at 0.5 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetrabutylammonium fluoroborate (8.35 g, 0.5M), in methylene chloride (50 ml) with the anodic working electrode compartment containing 4,4-dimethyl-1-phenylpyrazolidin-3-one (1.90 g, 0.01 mol) and 2,6-lutidine (2.14 g, 0.02 mol). After a current equivalent to 44% of a 2-electron oxidation had passed, the solution from the working electrode compartment was evaporated at 100°C on a rotary evaporator. The resultant red oil was extracted with petroleum ether (b.p. 60-80°C to remove lutidine. The yellow solid which remained was dissolved in the minimum amount of hot methylene chloride and introduced at the top of a silica gel column (grade III, 1 m x 2.5 cm). Elution with ether gave

4,4-dimethyl-5-(4,4-dimethyl-1-phenyl-3-oxopyrazolidin-2-yl)-1-phenylpyrazolidin-3-one (0.50 g), which was recrystallised from a mixture of chloroform and hexane; m.p. 173-6°C; ^{1}H n.m.r. (100 MHz)($CDCl_3$) δ 1.10 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 3.50 (d, 1H, J = 12 Hz, HCH), 3.86 (d, 1H, J = 12 Hz, methylene HCH), 5.73 (s, 1H, CH), 6.80-7.40 (m, 10H, aromatic); ^{13}C n.m.r. (d_6-DMSO) δ 17.79(CH_3), 23.52((CH_3)$_2$), 25.90 (CH_3), 43.47 (-C(CH_3)$_2$), 68.87 (CH_2), 84.94 (-C-N), 113.25, 117.97, 120.93, 122.78, 128.65, 129.36 (aromatic C), 149.93, 152.41 (=C-N aromatic), 175.75, 179.54 (C=O); i.r, ν_{max}^{nujol} 3420 (m, 2° amide), 1715 (s, carbonyl), 1680 cm^{-1} (s, carbonyl); mass spec. m/e = 378, exact mass = 378.203974, $C_{22}H_{26}N_4O_2$ requires 378.205564 (error 5 ppm). Found, C 69.65, H 6.97, N 14.62%, $C_{22}H_{26}N_4O_2$ requires C 69.85, H 6.88, N 14.81%.

Attempted electrochemical oxidation of 2-methyl-1-phenylpyrazolidin-3-one in methylene chloride using tetrabutylammonium fluoroborate as the supporting electrolyte:- On attempting a controlled potential electrolysis at 0.5 V (vs. $Ag/AgNO_3$) in a divided glass cell containing tetrabutylammonium fluoroborate (8.35 g, 0.5M), in methylene chloride (50 ml) with the anodic working electrode compartment containing 2-methyl-1-phenylpyrazolidin-3-one (1.76 g, 0.01 mol), the working electrode became passivated after a current equivalent to 6% of a 2-electron oxidation had passed.

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I attended the following lecture courses and conferences during my period as a research student.

"Electroanalytical Chemistry," Dr A. J. Bellamy, E.U.C.D., October 1977.

"Computer Programming using Fortran," Dr C. N. M. Pounder, E.U.C.D., December 1977.

"Nuclear Magnetic Resonance Spectroscopy," E.U.C.D., March 1978.

"Basic and Advanced Stereochemistry," Dr H. MacNab, E.U.C.D., May 1978.

"Mass Spectroscopy," Prof. J. H. Beynon(University College, Swansea), E.U.C.D., 19th./20th. December 1978.

"The Society of Chemical Industry's Electrochemical Technology Group Symposium on Electro-Organic Process Technology," The Electricity Council Research Centre, Capenhurst, 23rd./24th. April 1979.

"High Performance Liquid Chromatography," Analytical Division of the Chemical Society, Wolfson Liquid Chromatography Unit, Edinburgh University, 9th.-13th July 1979.

"SRC/CRAC Graduate School," King's College, Cambridge, 16th.-22nd. September, 1979.

"Organic Research Seminars," E.U.C.D., 1978-79.

"Industrial Inorganic Chemistry," Dr H. L. Roberts(I.C.I. Mond Division), E.U.C.D., March 1980.