Electrochemical Oxidation of 1-Phenylpyrazolidin-3-ones. Part 2.[1] 1-Aryl-4,4-dimethylpyrazolidin-3-ones

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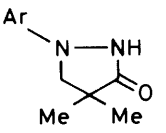
The electrochemical oxidation of 1-phenyl- and 1-(2,4-dimethylphenyl)-4,4-dimethylpyrazolidin-3-one has been studied. Nucleophilic attack on a 3-oxopyrazolidin-5-yl cation appears to be a common route to all the products which have been characterised.

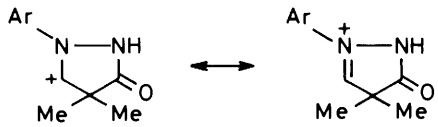
In Part 1 [1] we briefly mentioned that 4,4-dimethyl-1-phenylpyrazolidin-3-ones, on electro-oxidation in acetonitrile containing Et_4NBF_4 as the electrolyte, gave extremely complex product mixtures which we were unable to resolve. In contrast, 1-phenylpyrazolidin-3-ones possessing a readily eliminated atom or group at C(4), under the same conditions, gave a simple mixture of a 1-phenylpyrazolin-3-one and a 'dimer.' [1] In this paper we describe the electro-oxidation of 4,4-dimethyl-1-phenylpyrazolidin-3-one (1a) and 4,4-dimethyl-1-(2,4-dimethylphenyl)pyrazolidin-3-one (1b), under conditions which give greatly simplified product mixtures. All the products which have been characterised appear to be formed by nucleophilic attack at C(5) in the cation (2). A related cation is involved in the formation of 1-phenylpyrazolin-3-ones from 1-phenylpyrazolidin-3-ones which are not blocked (with respect to elimination) at C(4).[1]



(1)

a ; Ar = Ph

b ; Ar = 2,4-$Me_2C_6H_3$

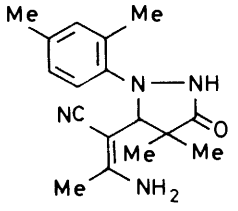


(2)

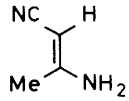
Results and Discussion

4,4-*Dimethyl*-1-(2,4-*dimethylphenyl*)*pyrazolidin*-3-*one* (1b). —When the electrolysis was performed in acetonitrile using Et_4NBF_4 as the electrolyte, a complex mixture of products was obtained, but when Et_4NCl was the electrolyte one product predominated. This was isolated and identified as 5-(2-amino-1-cyanoprop-1-enyl)-4,4-dimethyl-1-(2,4-dimethylphenyl)pyrazolidin-3-one (3).

Elemental analysis and exact mass determination of the molecular ion (*m/z* 298) in the mass spectrum of this product indicated the molecular formula $C_{17}H_{22}N_4O$. The structure was assigned on the basis of spectroscopic analysis. The 100 MHz ^1H n.m.r. spectrum [$(CD_3)_2SO$] showed the following features: two non-equivalent methyl groups at C(4) on the pyrazolidinone ring [δ 0.95 and 1.07; for (1b) these appear as one singlet at 1.01]; two aryl methyl groups [broad singlet at 2.19 identical to that for (1b)]; one vinyl methyl group (1.97, singlet), close to the methyl resonance of (*E*)-2-amino-1-cyanopropene [2] (4) (1.90); three exchangeable hydrogen signals at 6.37 (NH_2) and 9.78 (NHCO) [9.75 in (1b)]; and one methyne proton (4.11, broad singlet). The correlation of the ^{13}C resonances for (3), (1b), and (4) (*E* and *Z*) is shown in Table 1. The i.r. spectrum (Nujol mull) showed characteristic absorptions at 3 500, 3 250 (amine NH_2) [(4) has 3 450, 3 230 cm^{-1})], 3 360 (amide NH), 2 205 (CN) [(4) has 2 180 cm^{-1}], 1 700 (C=C) [(4) has 1 640 cm^{-1})], and 1 660 cm^{-1} (amide C=O). The u.v. spectrum showed $\lambda_{max.}$ (EtOH) 255 nm (ε *ca.* 25 000), in satisfactory agreement with the absorption for the two independent chromophores in (3), *viz.* (1b) has $\lambda_{max.}$ (EtOH) 248.5 nm (ε *ca.* 11 500), 1-phenylpyrazolidin-3-one has $\lambda_{max.}$ (EtOH) 247 nm (ε *ca.* 10 000) [lit.,[3] $\lambda_{max.}$ (EtOH) *ca.* 250 nm (ε *ca.* 10 000)], and 2-amino-1-cyanopropene has $\lambda_{max.}$ (EtOH) 256 nm(ε 14 500) for the high nm m.p. form (*E*-isomer) and 258 nm (ε 13 500) for the low-m.p. form (mixture of *E*- and *Z*-isomers).[4] The fragmentation pattern in the mass spectrum (Scheme 1) supports the n.m.r. evidence.



(3)



(4)

The configuration of the double bond in (3) has not been conclusively assigned, but we have assumed this to be the *E*-isomer shown because the olefinic methyl resonance (1.97) is closer to that of (*E*)-(4) (1.90) than to that of (*Z*)-(4) (1.77).[2] However, by analogy with (4), it is likely that the two geometrical isomers of (3) are readily interconverted in solution.

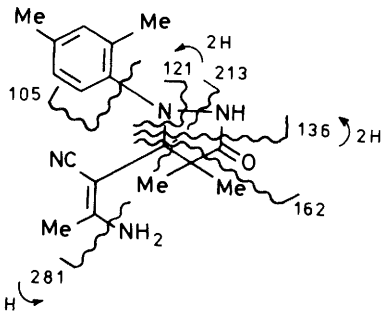
We suggest that (3) is most probably formed by nucleophilic attack of the enamine (4) on the cation (2) (Scheme 2a), the intermediate involved in the electro-oxidation of other 1-phenylpyrazolidin-3-ones.[1] In the present case the cation cannot readily eliminate from C(4) to give a pyrazolin-3-one, and therefore reacts with a nucleophile. We assume that the chloride ion, from Et_4NCl, is sufficiently basic [5] to catalyse the dimerisation of acetonitrile [6,7] to give (4). Alternatively 4-amino-2,6-dimethylpyrimidine (5), the trimer of acetonitrile,[6,7] could be the nucleophile (Scheme 2b).

4,4-*Dimethyl*-1-*phenylpyrazolidin*-3-*one* (1a).—The electro-oxidation of (1a) in acetonitrile containing either Et_4NBF_4 or

Table 1. ^{13}C N.m.r. spectra [a] of compounds (3), (1b), and (4)

	(3)	(1b)	(*E*)-(4)	(*Z*)-(4)
C=O	176.56	177.72		
-*C*Me$_2$-	44.06	40.15		
-*C*H$_2$-CMe$_2$-		66.57		
-*C*H(C)-CMe$_2$-	75.21			
-C(*C*H$_3$)$_2$-	17.46	17.74	18.92	20.86
(*C*H$_3$)$_2$C$_6$H$_3$-	19.12	20.21		
*C*H$_3$-C=C	20.22	23.73		
	25.21			
Me$_2$*C*$_6$H$_3$	117.39	116.26		
	126.48	126.63		
	129.89	128.15		
	131.76	131.92		
	132.30			
	149.48	148.35		
*C*N	122.09		122.59	120.43
C=*C*-CN	69.82		59.87	58.15
C=*C*(NH$_2$)-	156.31		163.25	162.34

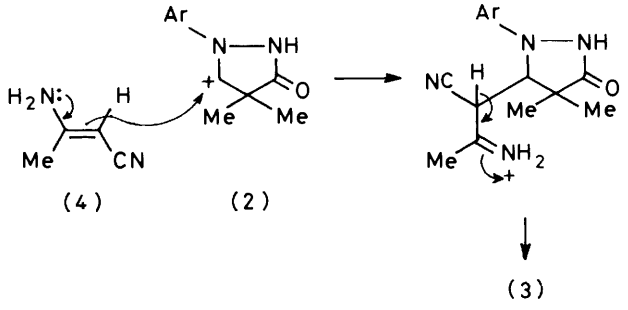
[a] In $(CD_3)_2SO$; p.p.m. from Me_4Si. The primary, secondary, or tertiary nature of the carbon atoms was confirmed by off-resonance decoupling of H.



Major mass spectral peaks

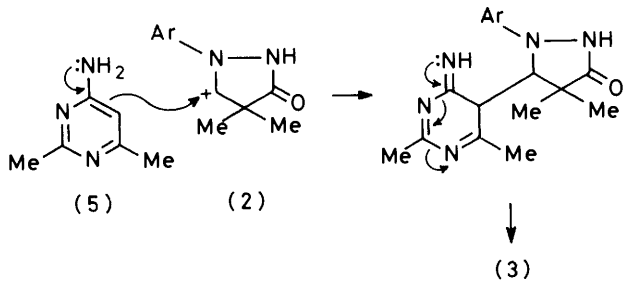
m/*z*	%
298 (*M*)	31
281	24
266	10
213	21
162	38
136 (base)	100
121	43
105	55

Scheme 1.

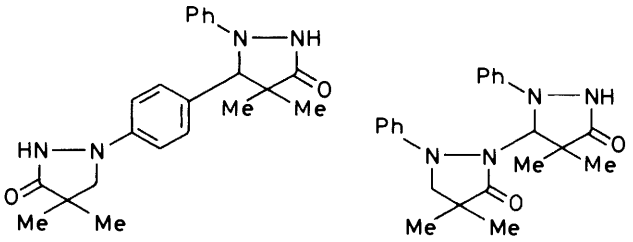


Scheme 2a.

Et_4NCl as the electrolyte gave a complex product mixture which could not be resolved. However, since we had found that 1-phenylpyrazolidin-3-one is cleanly electro-oxidised to



Scheme 2b.

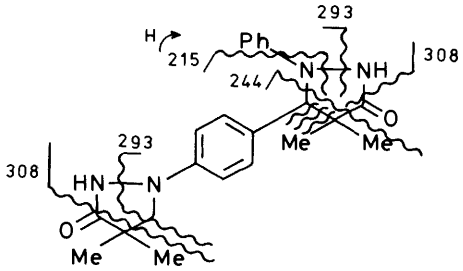


1-phenylpyrazolin-3-one in Bu_4NBF_4–CH_2Cl_2, we decided to investigate the oxidation of (1a) in this solvent also.

Under these conditions (1a) is electro-oxidised to a single product, the 'dimer' 4,4-dimethyl-5-[4-(4,4-dimethyl-3-oxopyrazolidin-1-yl)phenyl]-1-phenylpyrazolidin-3-one (6), while oxidation in the presence of base, 2,6-lutidine, gives a single isomeric product, 4,4-dimethyl-5-(4,4-dimethyl-3-oxo-1-phenylpyrazolidin-2-yl)-1-phenylpyrazolidin-3-one (7). Both products were shown to have the molecular formula $C_{22}H_{26}N_4O_2$ by elemental analysis. The full structural assignments were made on the basis of spectroscopic analysis.

The 60 MHz ^1H n.m.r. spectrum [$(CD_3)_2SO$] of (6) showed the following significant features: two equivalent methyl signals [δ 1.09, singlet; (1a) has 0.98] for the *gem*-dimethyl group in the C(5)-unsubstituted pyrazolidinone ring; two non-equivalent methyl signals (0.68 and 1.17) for the *gem*-dimethyl group in the C(5)-substituted pyrazolidinone ring, tentatively assigned *cis* and *trans*, respectively, to the C(5)-benzene ring; a methylene group [3.73, singlet; (1a) has 3.64]; a methyne proton [4.68, singlet; 1,5-diphenylpyrazolidin-3-one has C(5)H absorption at 5.03]; nine aromatic protons (6.7—7.35); and two exchangeable protons [10.4, broad singlet; NHCO; (1a) has 10.23] The i.r. spectrum (Nujol mull) had absorption at 1 690 cm^{-1} (amide C=O). The n.m.r. interpretation was supported by the fragmentation pattern in the mass spectrum (see Scheme 3). The peaks at *m*/*z* 215 and 244 are particularly diagnostic.

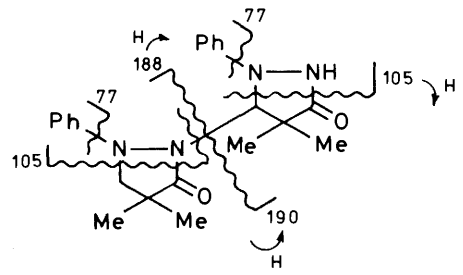
The 100 MHz ^1H n.m.r. spectrum ($CDCl_3$) of (7) showed the following significant features: 4 non-equivalent methyl groups [δ 1.10, 1.15, 1.18, and 1.26, all singlets; the methyl groups in the C(5)-unsubstituted pyrazolidinone ring are probably non-equivalent in this case because there is restricted rotation about the inter-ring C–N bond and they are closer to the chiral centre]; two non-equivalent methylene protons (doublets at 3.50 and 3.86, J_{gem} 12 Hz; non-equivalent for the reasons given above); a methyne proton [5.73, singlet; at higher frequency than the corresponding proton in (6) due to the second adjacent nitrogen atom]; and ten aromatic protons (6.8—7.4). The correlation of the ^{13}C resonances of (7) and (1a) is shown in Table 2. The i.r. spectrum (Nujol mull) showed



Major mass spectral peaks

m/z	%
378 (*M*, base)	100
308	56
293	13
244	35
215	25
131	19

Scheme 3.



Major mass spectral peaks

m/z	%
378 (*M*)	<5
190 (base)	100
188	61
146	33
105	39
77	94

Scheme 4.

absorptions at 3 420 (amide NH), and 1 715 and 1 680 cm^{-1} [tertiary and secondary amide C=O, respectively; 2-methyl-1-phenylpyrazolidin-3-one and (1a) have 1 725 and 1 690 cm^{-1}, respectively]. The mass spectrum showed a very weak molecular ion (*m/z* 378), the principal fragmentation occurring at the inter-ring C–N bond to give peaks at *m/z* 190 and 188 (see Scheme 4).

The formation of these two ' dimers ' may be rationalised in a similar manner to that for (3). In the case of (6) the nucleophile is the parent molecule, *viz.* electrophilic substitution occurs on the phenyl group of the parent by C(5) of the cation (2) (Scheme 5), while for (7) the nucleophile is presumably the conjugate base of the parent molecule, 2,6-lutidine, effecting deprotonation (Scheme 6). In both cases this route is followed because C(4) is blocked with respect to elimination to give a pyrazolinone. It is likely that when lutidine is present, it is the conjugate base of (1a) which is oxidised at the electrode (see Part 3 [8]).

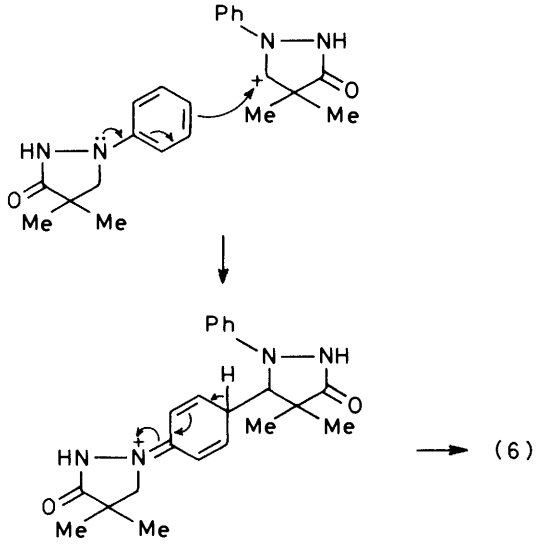
Experimental

For the treatment of acetonitrile and Et_4NCl before use, and the electrolysis procedure, see Part 1.[1] The pyrazolidin-3-ones

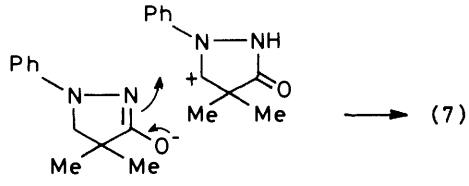
Table 2. ^{13}C Spectra [a] of compounds (7) and (1a)

	(7)	(1a)
$(CH_3)_2C$	17.79	23.05
	23.52	
	25.90	
$(CH_3)_2C$	43.47	40.43
$C\text{-}CH_2\text{-}N$	68.87	65.99
$N\text{-}CH(C)\text{-}N$	84.94	
Aromatic *C* (*o*, *m*, *p*)	113.25	114.93
	117.97	120.78
	120.93	129.11
	122.78	
	128.65	
	129.36	
Aromatic *C*–N	149.93	152.00
	152.41	
NHCO	175.75	177.93
	179.54	

[a] In $(CD_3)_2SO$; p.p.m. from Me_4Si.



Scheme 5.



Scheme 6.

(1a) and (1b) were supplied by Eastman Kodak Ltd. H.p.l.c. analyses were performed either on Hypersil (5 μm) with either ethyl acetate (50% water-saturated) or a mixture of ethanol (10—15%) and hexane containing 0.3% water was the eluant, or on Partisil octadecyl silicate (5 μm; reverse phase) with 0.01M-NaH_2PO_4 (buffered at pH 3.1) in 1 : 3 acetonitrile–water as the eluant.

Electrolysis of 4,4-*Dimethyl*-1-(2,4-*dimethylphenyl*)*pyrazolidin*-3-*one* (1b).—Oxidation of (1b) (0.9 g, 4.1 mmol) at +0.3 V in 0.3M-Et_4NCl in acetonitrile (50 ml) was terminated after 3 F mol^{-1} has passed. The anodic solution was evaporated to

dryness, water (100 ml) was added, and the undissolved yellow solid (0.69 g) was filtered off and dried. H.p.l.c. analysis indicated that the solid was a mixture of one major product and at least five minor products. The major product was isolated by chromatography on silica gel grade III (50 × 2.5 cm). Elution with light petroleum (b.p. 40—60 °C)—ethyl acetate (1 : 1) gave two fractions: (i) four of the minor products, and (ii) 5-(2-*amino*-1-*cyanoprop*-1-*enyl*)-4,4-*dimethyl*-1-(2,4-*dimethylphenyl*)*pyrazolidin*-3-*one* (3) (0.19 g), m.p. 219 °C (Found: C, 68.2; H, 7.4; N, 18.55%; M^+, 298.177 567. $C_{17}H_{22}N_4O$ requires C, 68.45; H, 7.4; N, 18.8%; *M*, 298.179 352).

2-*Amino*-1-*cyanoprop*-1-*ene* (4).[3]—A mixture of sodium (15.6 g, 0.6 g atom), acetonitrile (49.5 g, 1.21 mol), and benzene (160 ml) was refluxed during 3 h. The solid which separated was filtered off and recrystallised from chloroform–light petroleum (b.p 40—60 °C) to give 2-amino-1-cyanoprop-1-ene (10.9 g, 22%).

A freshly prepared solution of a stored sample was >95% *E*-isomer (by ^{1}H n.m.r. spectroscopy). In $(CD_3)_2SO$, this slowly isomerised to an equilibrium mixture of 65% *E*- and 35% *Z*-isomer (Me absorptions 1.90 and 1.77, respectively; HC absorptions 3.91 and 3.61, respectively; lit.,[2] 65% *E*-isomer, 1.91, 1.77, 3.91, and 3.61, respectively). In C_6H_6 the system equilibrated to 30% *E*- and 70% *Z*-isomer (Me absorptions 1.43 and 0.99, respectively; HC absorptions 3.56 and 3.33, respectively; lit.,[2] 66% *E*-isomer, 1.37, 0.90, 3.49, and 3.22, respectively; lit.,[9] 35% *E*-isomer, 1.50, 1.03, 3.64, and 3.36, respectively). In both solutions, addition of acetic acid increased the rate of isomerisation, but did not affect the position of the equilibrium.

Our observations of the ^{1}H n.m.r. spectra in $(CD_3)_2SO$ are in complete agreement with previous assignments based on nuclear Overhauser effect (n.O.e.) experiments.[2] For the measurements in C_6H_6 there is some inconsistency between our results and those of other workers.[2,9] It is not clear if the spectroscopic assignments [2] in this case are based on n.O.e. experiments, or simply on analogy with the $(CD_3)_2SO$ results. If the spectroscopic assignments [2] are correct, and we think this is the case, then the equilibrated system in C_6H_6 favours the *Z*-isomer (our results and those in ref. 9; ref. 2 reports the *E*-isomer as being predominant).

Electrolysis of 4,4-*Dimethyl*-1-*phenylpyrazolidin*-3-*one* (1a) *in Acetonitrile*.—Oxidation of (1a) (1.90 g, 0.02 mol) at +0.4 V in 0.2M-Et_4NBF_4 in acetonitrile (50 ml) was terminated after 1.8 F mol^{-1} had passed. After a typical isolation procedure, the product was analysed by reverse-phase h.p.l.c. and shown to consist of at least 24 products.

A similar electrolysis in which Et_4NCl was the electrolyte gave an equally complex product mixture.

Electrolysis of 1-*Phenylpyrazolidin*-3-*one in Methylene Dichloride*.—Oxidation of 1-phenylpyrazolidin-3-one (1.62 g, 0.01 mol) in 0.5M-Bu_4NBF_4 in methylene dichloride (50 ml) at a controlled current of 45 mA was terminated after 0.72 F mol^{-1} had passed. The crude product was shown (h.p.l.c. analysis) to be a mixture of 1-phenylpyrazolidin-3-one and 1-phenylpyrazolin-3-one, and these were separated by chromatography on silica gel grade III (65 × 2.5 cm). Elution with ether gave the pyrazolin-3-one (0.33 g, 21% yield; 58% current yield), m.p. 151—153 °C (lit.,[10] 154 °C), and further elution with ethyl acetate gave starting material (0.40 g, 25%).

Electrolysis of 4,4-*Dimethyl*-1-*phenylpyrazolidin*-3-*one* (1a) *in Methylene Dichloride*.—(a) *Without* 2,6-*lutidine*. Oxidation of (1a) (1.90 g, 0.01 mol) at +0.5 V in 0.5M-Bu_4NBF_4 in methylene dichloride (50 ml) was terminated after 0.7 F mol^{-1} has passed, due to passivation of the electrode. The anodic solution was poured into water (100 ml), the organic layer was separated, and the aqueous layer was neutralised with sodium carbonate. After further extraction with methylene dichloride, the combined organic layers were dried (4 Å molecular sieve) and then concentrated. The residue was chromatographed on silica gel grade III (100 × 2.5 cm). Elution with ether gave two fractions: (i) (1a) (0.48 g, 25%), and (ii) 4,4-*dimethyl*-5-[4-(4,4-*dimethyl*-3-*oxopyrazolidin*-1-*yl*)*phenyl*]-1-*phenylpyrazolidin*-3-*one* (6) (0.22 g, 12% yield; 65% current yield), m.p. 203—205 °C (from ethanol) (Found: C, 69.6; H, 6.95; N, 14.6. $C_{22}H_{26}N_4O_2$ requires C, 69.85; H, 6.9; N, 14.8%), *m/z* 378 (*M*).

(b) *With* 2,6-*lutidine*. Oxidation of (1a) (1.90 g, 0.01 mol) and 2,6-lutidine (2.14 g, 0.02 mol) in 0.5M-Bu_4NBF_4 in methylene dichloride (50 ml) was terminated after 0.88 F mol^{-1} had passed. The anodic solution was concentrated by rotary evaporation and the resultant red oil was extracted with light petroleum (b.p. 60—80 °C) to remove lutidine. The remaining yellow solid was chromatographed on silica gel grade III (100 × 2.5 cm). Elution with ether gave 4,4-*dimethyl*-5-(4,4-*dimethyl*-3-*oxo*-1-*phenylpyrazolidin*-2-*yl*)-1-*phenylpyrazolidin*-3-*one* (7) (0.50 g, 26% yield; 59% current yield), m.p. 173—176 °C (from chloroform–hexane) (Found: C, 69.65; H, 6.95; N, 14.6%; M^+, 378.203 974. $C_{22}H_{26}N_4O_2$ requires C, 69.85; H, 6.9; N, 14.8%; *M*, 378.205 564).

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