Electrochemical Studies on β-Lactams. Part 1. Electroreduction of 3-Halogeno-β-lactams

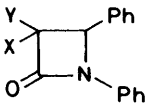
Maria Antonietta Casadei and Franco Micheletti Moracci *
Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi 'La Sapienza,' P. le Aldo Moro, 5, I-00185 Rome, Italy
Achille Inesi *
Dipartimento di Ingegneria Chimica, dei Materiali, delle Materie Prime e Metallurgia, Università degli Studi 'La Sapienza,' Via del Castro Laurenziano, 7, I-00161 Rome, Italy

The electrochemical reduction in aprotic solvents of 3-halogeno-β-lactams (**1a**—**c**) and (**2a**—**c**), with or without added proton donors or/and electrophiles, has been investigated. Without added substrates, the carbanion arising from the cleavage of the carbon–halogen bond undergoes protonation (mainly from the 'parent' molecule) and, competitively, ring-opening reactions yielding the corresponding dehalogenated β-lactam and α,β-unsaturated amide. In the presence of proton donors (CH_3CO_2H) or electrophiles (CO_2), the protonation and coupling reactions, respectively, become largely predominant, and the dehalogenated or carboxylated β-lactams are the main products. In the presence of $BrCH_2CH_2CN$ the protonation reaction is preferred, and the dehalogenated β-lactam predominates over the substitution product. The high yields of 3-carboxy-β-lactams, a class of compounds not easily accessible by chemical methods, are noteworthy from a synthetic point of view.

In connection with previous work on the electrochemical behaviour of aliphatic α-halogenoamides,[1] the electrochemical reduction of some alicyclic α-halogenoamides, the 3-halogeno-azetidin-2-ones (3-halogeno-β-lactams), was investigated. We wished to ascertain whether their reduction follows the general electrochemical behaviour of organic halogeno derivatives, and also to determine whether the electrochemical method could be usefully employed to introduce new functions into the β-lactam ring. Indeed, it is known that electroreduction of compounds of type XCR_2Y (X = Cl, Br, or I; R = H or alkyl; Y = aryl, saturated or unsaturated alkyl, or electron-withdrawing group) yields radical ($^{\bullet}CR_2Y$) and/or carbanion ($^{-}CR_2Y$) intermediates.[2] Furthermore, ionic intermediates formed upon electrochemical reduction of suitable probases have been used as reagents towards substrates (added to the electrolysed solution) that cannot be reduced at the experimental potential. This method may allow one to overcome synthetic problems which are difficult to solve by traditional chemical procedures.[3]

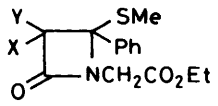
A frequently encountered problem in β-lactam chemistry concerns the introduction of a suitable function in the α-position with respect to the carbonyl group. 3-Halogeno-β-lactams, easily prepared from the corresponding halogenoacyl chlorides and imines, cannot be employed in functionalization carried out by ordinary procedures because of their low reactivity towards nucleophilic substitution of the halogen atom. Therefore, the electrochemical method was considered a better approach for this purpose.

With this aim, we have studied the electrochemical reduction of 3-halogeno- and 3,3-dihalogeno-β-lactams (**1a**—**c**) and (**2a**—**c**) in aprotic solvents. The reduction behaviour was also studied after addition to the β-lactam solution of a proton donor (CH_3CO_2H), an electrophilic reagent (CO_2), or a substrate which can behave both as an electrophile and as a proton donor [$BrCH_2CH_2CN$ (**5**)].



(1)

a ; X = Br , Y = H
b ; X = Cl , Y = H
c ; X = Y = Cl
d ; X = Y = H
e ; X = CO_2H , Y = H
f ; X = CO_2Me , Y = H
g ; X = CO_2H , Y = Cl
h ; X = $CO_2^{-}NEt_4^{+}$, Y = Cl
i ; X = CO_2Me , Y = Cl
j ; X = $[CH_2]_2CN$, Y = H



(2)

a ; X = Br , Y = H
b ; X = Cl , Y = H
c ; X = Y = Cl
d ; X = OPh , Y = H

PhCH=CHCONHPh

(3)

$PhCH_2CH_2CONHPh$

(4)

$BrCH_2CH_2CN$

(5)

Experimental

Electrochemical behaviour was investigated for solutions in *N,N*-dimethylformamide (DMF), containing tetraethylammonium perchlorate (TEAP) as supporting electrolyte, by means of polarography, coulometry, and preparative controlled-potential electrolysis (c.p.e.) at a mercury cathode. At the end of the electrolyses, the products were identified and characterized.

Polarographic measurements were performed with an Amel 471 multipolarograph; the c.p.e. and coulometry were carried out with an Amel 552 potentiostat equipped with an Amel 721 integrator. The cells used for all these techniques have been already described.[4] The reference electrode was of calomel type, as described by Fujinaga;[5] its potential was −0.029 V *versus* s.c.e., and did not change during the time of our experiments; all the potential values are referred to this electrode. For the polarographic measurements, the dropping mercury electrode had a dropping time of 3.50 s and a mercury flux m = 1.45 mg s^{-1} at E −1.5 V and h 70 cm. All the electrochemical

measurements were performed at 20.0 ± 0.1 °C. DMF (Riedel-DeHaen, spectranal) and TEAP (Fluka) were purified as previously described;[4] the water content of DMF (<0.01%) was ascertained by titration according to the Karl Fischer method.

High-performance liquid chromatography (h.p.l.c.) analyses were carried out with a Perkin-Elmer system made up from a Series 4 liquid chromatograph, an LC 85B spectrophotometric detector, an LC Autocontrol, and a Sigma 15 chromatography data station. Column chromatography was carried out on Merck silica gel (70—230 mesh). M.p.s were taken with a Tottoli apparatus. I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 177 grating spectrophotometer; n.m.r. spectra were recorded for solutions in $CDCl_3$ using a Varian EM-390 spectrometer and the chemical shifts are reported relative to Me_4Si as internal standard. Mass spectra were determined at 70 eV with a Hewlett-Packard 5980A low-resolution spectrometer, equipped with a Hewlett-Packard 5934A data system.

All new compounds gave satisfactory elemental analytical data. The coupling constant between the methine hydrogen atoms at positions 3 and 4 of the β-lactam ring (*J ca.* 2 Hz) is in agreement with a *trans*-configuration.

Compounds (**1a**—**c**) were prepared by addition of triethylamine to a dichloromethane solution of *N*-benzylideneaniline and the appropriate acid chloride, according to the literature.[6] trans-3-*Bromo*-1,4-*diphenylazetidin*-2-*one* (**1a**) was obtained (35% yield) by column chromatography (chloroform as eluant) of the crude reaction mixture. The first eluted fraction was further purified by column chromatography on neutral Al_2O_3 (light petroleum–chloroform 9:1 as eluant); m.p. 93—94 °C (cyclohexane); ν̄ 1 770, 1 600, and 1 500 cm^{-1}; δ 7.5—7.0 (10 H, aromatic), 5.10 (1 H, d, H-4, *J* 2.2 Hz), and 4.62 (1 H, d, H-3, *J* 2.2 Hz); *m/z* 301 (^{79}Br, M^+) and correct pattern of isotopic abundances. *trans*-3-Chloro-1,4-diphenylazetidin-2-one (**1b**) had m.p. 90—91 °C (cyclohexane) (lit.,[6] 84—90 °C). 3,3-Dichloro-1,4-diphenylazetidin-2-one (**1c**) had m.p. 151—152 °C (cyclohexane) (lit.,[7] 150 °C).

Compounds (**2a**—**d**) were prepared, according to the foregoing procedure, by addition of triethylamine to a benzene solution of methyl *N*-(ethoxycarbonylmethyl)thiobenzimidate[8] and the appropriate acid chloride. 3-*Bromo*-1-*ethoxycarbonylmethyl*-4-*methylthio*-4-*phenylazetidin*-2-*one* (**2a**) was obtained (50% yield) by column chromatography (chloroform–ethyl acetate 95:5 as eluant) of the crude reaction mixture; m.p. 115—116 °C (decomp.) (cyclohexane); ν̄ 1 780 and 1 740 cm^{-1}; δ 7.6—7.3 (5 H, aromatic), 5.30 (1 H, s, H-3), 4.30 (2 H, q, OCH_2), 4.25 (1 H, d, NCH_2, *J* 18 Hz), 3.90 (1 H, d, NCH_2, *J* 18 Hz), 2.23 (3 H, s, SCH_3), and 1.27 (3 H, t, CCH_3); *m/z* 310 (^{79}Br, $M^+ - SCH_3$) and correct pattern of isotopic abundances. 3-*Chloro*-1-*ethoxycarbonylmethyl*-4-*methylthio*-4-*phenylazetidin*-2-*one* (**2b**) was obtained (45% yield) by column chromatography (chloroform–ethyl acetate 95:5 as eluant) of the crude reaction mixture; m.p. 114—115 °C (cyclohexane); ν̄ 1 800 and 1 750 cm^{-1}; δ 7.6—7.3 (5 H, aromatic), 5.20 (1 H, s, H-3), 4.30 (2 H, q, OCH_2), 4.26 (1 H, d, NCH_2, *J* 18 Hz), 3.90 (1 H, d, NCH_2, *J* 18 Hz), 2.23 (3 H, s, SCH_3), and 1.30 (3 H, t, CCH_3); *m/z* 266 (^{35}Cl, $M^+ - SCH_3$) and correct pattern of isotopic abundances. 3,3-*Dichloro*-1-*ethoxycarbonylmethyl*-4-*methylthio*-4-*phenylazetidin*-2-*one* (**2c**) was obtained (70% yield) upon crystallization of the crude reaction mixture; m.p. 95—96 °C (cyclohexane); ν̄ 1 790, 1 740, and 1 730 cm^{-1}; δ 7.6—7.3 (5 H, aromatic), 4.35 (2 H, q, OCH_2), 4.28 (1 H, d, NCH_2, *J* 18 Hz), 4.06 (1 H, d, NCH_2, *J* 18 Hz), 2.23 (3 H, s, SCH_3), and 1.30 (3 H, t, CCH_3); *m/z* 300 (^{35}Cl, $M^+ - SCH_3$) and correct pattern of isotopic abundances. 1-*Ethoxycarbonylmethyl*-4-*methylthio*-3-*phenoxy*-4-*phenylazetidin*-2-*one* (**2d**) was obtained (60% yield) by column chromatography (benzene–ethyl acetate 9:1 as eluant) of the crude reaction mixture; m.p. 80—82 °C (cyclohexane); ν̄ 1 790, 1 740, 1 600, and 1 590 cm^{-1}; δ 7.6—6.8 (10 H, aromatic), 5.40 (1 H, s, H-3), 4.28 (1 H, d, NCH_2, *J* 18 Hz), 4.23 (2 H, q, OCH_2), 3.80 (1 H, d, NCH_2, *J* 18 Hz), 2.30 (3 H, s, SCH_3), and 1.28 (3 H, t, CCH_3); *m/z* 371 (M^+), 356 ($M^+ - CH_3$), and 324 ($M^+ - SCH_3$).

For the preparation of compounds (**1d**—**j**), (**3**), and (**4**), see the c.p.e. of (**1a**—**c**). The c.p.e. studies were carried out by stepwise addition of β-lactams, up to the total amount reported for the various runs, to 75 ml of DMF–0.1M-TEAP containing the added substrate when appropriate. The electrolyses were stopped when the current had dropped from its initial value of 0.3 A to 10 mA. The polarograms registered at the end of the electrolyses showed the absence of any species reducible at the potential of the experiment, and gave information on the nature and concentration of the species present in the solution, reducible at potentials more negative than that of the electrolysis.

Reduction in the Absence of Added Substrates.—Compound (**1a**) (0.60 g) was reduced at −2.0, −1.8, and −1.5 V. In the first two cases, the polarograms recorded at the end of the electrolyses showed one reduction wave at $E_{\frac{1}{2}}$ −2.7 V, coincident with that of an authentic sample of (**1d**). By comparison of the i_{lim} values, the calculated yields of (**1d**) were 35 and 45%, respectively. The solvent was removed under reduced pressure from the solution electrolysed at −2.0 V, and the residue was extracted with Et_2O (5 × 50 ml). The insoluble solid was dissolved in H_2O and extracted with $CHCl_3$ (5 × 30 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography of the residue (chloroform as eluant) gave (**1d**) (35% yield), m.p. 152—153 °C (MeOH) (lit.,[9] 153—154 °C) and (**4**) (17% yield), m.p. 95—96 °C (cyclohexane) (lit.,[10] 97 °C). The same yields were also found by quantitative h.p.l.c. analysis carried out by the internal standard method, with a Perkin-Elmer HS-3 silica column (chloroform as eluant) and a Merck Lichrosorb RT 250-4 CN 10 μm column (chloroform–hexane 4:1 as eluant) for (**1d**) and (**4**), respectively. Work-up as before of the solution electrolysed at −1.8 V gave (**1d**) (45% yield) and (**4**) (5% yield). The polarogram recorded at the end of the electrolysis carried out at −1.5 V showed three reduction waves at $E_{\frac{1}{2}}$ −1.85, −2.3, and −2.7 V. The last was coincident with that of (**1d**), the others with those of an authentic sample of (**3**), prepared according to the literature.[11] By comparison of the i_{lim} values the calculated yields of (**1d**) and (**3**) were estimated as 64 and 3%, respectively. The presence of these compounds in the reduction mixture was confirmed by h.p.l.c. analysis.

Compound (**1b**) (0.77 g) was reduced at −2.3 V; the polarogram recorded at the end of the electrolysis showed one reduction wave at $E_{\frac{1}{2}}$ −2.7 V, coincident with that of (**1d**); by comparison of the i_{lim} values, the calculated yield of (**1d**) was 50%. Work-up of the electrolysed solution as before gave (**1d**) (50% yield) and (**4**) (12% yield). The yields were confirmed by h.p.l.c. analysis.

Compound (**1c**) (0.78 g) was reduced at −2.1 and −1.5 V. In the first case the polarogram recorded at the end of the electrolysis showed one reduction wave at $E_{\frac{1}{2}}$ −2.7 V, coincident with that of (**1d**). Quantitative h.p.l.c. analysis of the organic extracts, carried out as for (**1a**), showed the presence of (**1d**) and (**4**) (27 and 6% yield, respectively). The polarogram recorded at the end of the electrolysis carried out at −1.5 V showed the presence of three reduction waves at $E_{\frac{1}{2}}$ −1.85, −2.3, and −2.7 V. Work-up as before allowed the isolation of (**1b**) and (**1d**) in 20 and 14% yield, respectively.

When the methylthio-β-lactams (**2a**—**c**) were electrolysed, all gave intractable mixtures of decomposition products, probably as a result of an increase in intramolecular carbanion reactivity due to the presence at the α-position of a good leaving group

(CH_3S). Further electrolyses of compounds (**2a**—**c**) were not carried out; the investigation of these products was restricted to polarography.

Reduction in the Presence of Proton Donors.—These experiments were carried out in the presence of CH_3CO_2H, up to a tenfold molar excess. Compounds (**1a**) (0.55 g) and (**1b**) (0.55 g) were reduced at −1.3 and −2.2 V, respectively. In both cases, (**1d**) was quantitatively recovered by work-up of the reduction mixture as before. Compound (**1c**) (0.60 g) was reduced at both −2.2 and −1.5 V. In the first case, quantitative h.p.l.c. analysis of the reduction mixture showed that (**1d**) was formed quantitatively. In the case of the reduction at −1.5 V, quantitative h.p.l.c. analysis of the residue from the work-up of the electrolysed solution showed the presence of (**1b**) and (**1d**) in 55 and 30% yield, respectively.

Reduction in the Presence of CO_2.—These experiments were carried out under CO_2, in a solution previously saturated with CO_2. At the end of the electrolysis, the cathode was discharged and the solvent removed at 40—50 °C under reduced pressure. The residue was extracted with Et_2O (5 × 30 ml), the combined extracts were dried (Na_2SO_4), the solvent was evaporated off, and the residue was analysed. The solid insoluble in Et_2O was dissolved in brine, HCl was added, and the solution was extracted with $CHCl_3$ (3 × 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to leave a solid, which was further purified by crystallization.

Compound (**1a**) (0.84 g) was reduced at −1.5 V. The residue from the Et_2O solution was identified as (**1d**) (8% yield). The residue from the $CHCl_3$ solution was identified as *trans*-(**1e**) (90% yield), m.p. 76—77 °C (CCl_4); $\bar{\nu}$ 1 730 cm^{-1}; δ 9.80 (1 H, s, OH, exchanges with D_2O), 7.5—6.9 (10 H, aromatic), 5.27 (1 H, d, H-4, *J* 2 Hz), and 3.98 (1 H, d, H-3, *J* 2 Hz); *m/z* 267 (M^+).

Compound (**1e**) was quantitatively converted into its methyl ester on refluxing (2 h) in MeOH–HCl; *trans*-(**1f**) showed $\bar{\nu}$ 1 755 and 1 725 cm^{-1}; δ 7.5—7.0 (10 H, aromatic), 5.27 (1 H, d, H-4, *J* 2 Hz), 4.00 (1 H, d, H-3, *J* 2 Hz), and 3.83 (3 H, s, CH_3); *m/z* 281 (M^+).

Compound (**1b**) (0.94 g) was reduced at −2.0 V. The residues from Et_2O and $CHCl_3$ solutions were identified as (**1d**) (5% yield) and *trans*-(**1e**) (95% yield), respectively.

Compound (**1c**) (0.61 g) was reduced at −1.5 V. A sample of the electrolysed solution was evaporated under vacuum to dryness; the residue was extracted with Et_2O (5 × 30 ml), and the insoluble solid dissolved in DMF–0.1M-TEAP. The polarogram recorded on this solution showed two reduction waves at $E_{\frac{1}{2}}$ −2.15 and −2.7 V. The remaining electrolysed solution was treated as before. Quantitative h.p.l.c. analysis of the residue from the Et_2O solution showed the presence of (**1b**) and (**1d**) in 7 and 3% yield, respectively. The residue from the $CHCl_3$ solution was identified as (**1g**) (81% yield), m.p. 189—190 °C (hexane–CH_2Cl_2); $\bar{\nu}$ 1 760 and 1 715 cm^{-1}; δ 9.78 (1 H, s, OH, exchanges with D_2O), 7.6—7.1 (10 H, aromatic), and 5.76 (1 H, s, H-4); *m/z* 301 (^{35}Cl, M^+) and correct pattern of isotopic abundances.

Compound (**1g**) was quantitatively converted into its methyl ester on refluxing (2 h) in MeOH–HCl: (**1i**) had m.p. 120—121 °C (cyclohexane); $\bar{\nu}$ 1 760 and 1 730 cm^{-1}; δ 7.6—7.1 (10 H, aromatic), 5.73 (1 H, s, H-4), and 3.90 (3 H, s, CH_3); *m/z* 315 (^{35}Cl, M^+) and correct pattern of isotopic abundances.

The reduction potential values of compounds (**1e**) and (**1g**) were measured after the isolation of the products. They could not be obtained *in situ* at the end of the electrolysis because traces of CO_2 are present in the DMF solution even after long nitrogen bubbling, and hinder a correct measurement of $E_{\frac{1}{2}}$.

Table 1. Half-wave potentials $E_{\frac{1}{2}}$/V (*versus* s.c.e.) and current function values I^* of β-lactams (**1**) and (**2**) (1.0 × 10^{-3}M) in DMF–0.1M-TEAP solutions

Compd.	$E'_{\frac{1}{2}}$	$E''_{\frac{1}{2}}$	$E'''_{\frac{1}{2}}$	I^{*a}	$I^{*a,b}$	$I^{*a,c}$
(**1a**)	−1.0		−2.7	1.98	2.31	2.31
(**1b**)	−1.85		−2.7	1.87	2.58	2.69
(**1c**)	−1.35	−2.0	−2.7	2.31	2.53	2.58
(**1d**)			−2.7			
(**1e**)		−2.2	−2.7			
(**1g**)	−1.25	−2.2	−2.7			
(**1h**)		−2.15	−2.7			
(**1i**)	−1.3		−2.7			
(**2a**)	−1.3		−2.5	1.9	1.9	
(**2b**)		−2.15	−2.5	2.7	2.7	
(**2c**)	−1.4	−2.2	−2.5	2.9	2.9	
(**2d**)			−2.45			

[a] $I^* = i_{lim}/m^{2/3}t^{1/6}C$(μA dm^3 $mmol^{-1}$ $mg^{-2/3}$ $s^{1/2}$) (first wave). [b] Upon addition of CH_3CO_2H [3,4-xylenol in the case of (**2b**)] (1.0 × 10^{-2} M). [c] Upon addition of CO_2 (saturated DMF solution).

Reduction in the Presence of $BrCH_2CH_2CN$ (**5**).—This substrate was selected to test the reactivity of the carbanion arising from the cleavage of the carbon–halogen bond, because it can undergo both acid–base and nucleophilic substitution reactions. The β-lactam (**1a**) (0.76 g) was reduced at −1.5 V in the presence of a twofold molar excess of (**5**). Gas chromatographic analysis of the electrolysed solution showed the presence of acrylonitrile in 35% yield, calculated on the basis of starting bromonitrile, and h.p.l.c. analysis showed the presence of (**1d**) (88% yield), an unidentified product (A) (having higher retention time), the peak area of which accounts for about 5% of the total, and minor amounts of several other unidentified products. Column chromatography ($CHCl_3$ as eluant) of the residue from the electrolysed solution allowed the separation of (**1d**) (83% yield) and a fraction of inseparable products containing compound (A) as the major component. This fraction showed $\bar{\nu}$ 2 230 and 1 740 cm^{-1}; δ 7.5—7.0 (10 H), 4.80 (1 H), 2.75 (2 H), and 1.35 (2 H), and *m/z* 276. On this basis, structure (**1j**) was assigned to compound (A).

Results and Discussion

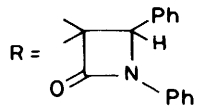
In polarographic analysis 3-halogeno-β-lactams (**1a**—**b**) and (**2a**—**b**) show two reduction waves, whereas 3,3-dihalogeno-β-lactams (**1c**) and (**2c**) show three reduction waves. In all the cases considered, the most negative potential waves coincide with those of β-lactams (**1d**) and (**2d**), whereas the second wave potentials ($E_{\frac{1}{2}}$) of (**1c**) and (**2c**) coincide with those of the corresponding monohalogeno-β-lactams (**1b**) and (**2b**) (Table 1). All the waves are irreversible and diffusion-controlled, as deduced by the usual polarographic tests. Table 1 shows how the current function I^*, referred to the first reduction wave, is modified by addition of the substrate.

C.p.e. of the monohalogeno- and dihalogeno-β-lactams was carried out at potential values corresponding to the diffusion plateau of the first and of both the first and the second reduction waves, respectively. In all cases, the potential was not negative enough to promote the reduction of any substrate added to the solution (Tables 1 and 2). The corresponding coulometric measurements allowed us to obtain n_{app} values and to establish how these values are affected by the presence of any substrate during the reduction. At the end of the electrolyses, the content of the solutions was determined by polarography, and by isolation and characterization of the products (see Experimental section and Table 2). The polarographic investigation was carried out for all the halogeno-β-lactams, whereas the c.p.e., in

Table 2. Coulometric data and yields of the products from the electroreduction (mercury cathode) of β-lactams (**1**) in DMF–0.1M-TEAP, in the absence and presence of proton donor or electrophile

Compd.	Added substrate	E/V	n_{app}	Products (% yield)
(**1a**)		−1.5	1.3	(**1d**) (64) + (**3**) (3)
(**1a**)		−1.8	1.2	(**1d**) (45) + (**4**) (5)
(**1a**)		−2.0	1.3	(**1d**) (35) + (**4**) (17)
(**1a**)	CH_3CO_2H	−1.3	1.9	(**1d**) (100)
(**1a**)	$Br[CH_2]_2CN$	−1.5	1.9	(**1d**) (88) + (**1j**) (5)[a]
(**1a**)	CO_2	−1.5	2.1	(**1d**) (8) + (**1e**) (90)
(**1b**)		−2.3	1.2	(**1d**) (50) + (**4**) (12)
(**1b**)	CH_3CO_2H	−2.2	2.0	(**1d**) (99)
(**1b**)	CO_2	−2.0	2.0	(**1d**) (5) + (**1e**) (95)
(**1c**)		−1.5	2.0	(**1b**) (20) + (**1d**) (14)
(**1c**)		−2.1	2.4	(**1d**) (27) + (**4**) (6)
(**1c**)	CH_3CO_2H	−1.5	2.3	(**1b**) (55) + (**1d**) (30)
(**1c**)	CH_3CO_2H	−2.2	4.3	(**1d**) (98)
(**1c**)	CO_2	−1.5	2.0	(**1b**) (7) + (**1d**) (3) + (**1g**) (81)

[a] Acrylonitrile (35% yield based on bromo nitrile) was also formed.



(a)
$$RCl_2 + e \xrightarrow{E_1} RCl_2^{-\bullet}$$
$$RCl_2^{-\bullet} \longrightarrow RCl^{\bullet} + Cl^-$$
$$RCl^{\bullet} + e \xrightarrow{E_2} RCl^- \qquad E_2 > E_1$$
$$RCl^- + H^+ \longrightarrow RHCl$$
$$RHCl + e \xrightarrow{E_3} \qquad E_3 < E_1$$
$$RHCl + RCl_2^{-\bullet} \rightleftharpoons RHCl^{-\bullet} + RCl_2$$
$$RHCl^{-\bullet} \longrightarrow RH^{\bullet} + Cl^-$$
$$RH^{\bullet} + RCl_2^{-\bullet} \rightleftharpoons RH^- + RCl_2$$
$$RH^{\bullet} + e \xrightarrow{E_4} RH^- \qquad E_4 > E_1$$
$$RH^- + H^+ \longrightarrow RH_2$$

(b)
$$RCl_2 + 2e \xrightarrow{E_1} RCl^- + Cl^-$$
$$RCl^- + H^+ \longrightarrow RHCl$$
$$RCl^- \longrightarrow R + Cl^-$$
$$R + 2e + 2H^+ \xrightarrow{E_5} RH_2 \qquad E_5 > E_1$$

Scheme 1.

the presence or in the absence of substrates, was performed with compounds (**1a**—**c**) only. Analysis of the electrolysed solutions revealed that halogen–carbon bond cleavage had occurred; reduction of compounds (**1a** and **b**) gave the corresponding hydrogenated compound (**1d**) together with products formed by cleavage of the β-lactam ring, while reduction of (**1c**) yielded products the structure of which depended on the electrolysis potential. The presence of proton donors always caused a considerable increase in the n_{app} values, and ensured that hydrogenated compounds were largely prevalent in the reduction mixture. On the whole, these results are in agreement with those already described for other organic halogeno derivatives;[1,2] in the absence of proton donors the carbanion formed upon cleavage of the halogen–carbon bond is protonated by the 'parent' molecule and also, to a lesser extent, by the solvent and/or the supporting electrolyte. However, several features of this β-lactam reduction are worthy of further discussion. First, compound (**1d**) is formed upon reduction of (**1c**) both in the presence and in the absence of a proton donor, although the potential (E −1.5 V) is not negative enough to allow the direct reduction of (**1b**) at the electrode (E −1.85 V). In agreement with the fact that the second C–Cl bond also is partially reduced, the n_{app} value, as measured in the reduction of (**1c**) at −1.5 V in the absence of a proton donor (n_{app} 2.0), is considerably higher than that measured during the reduction of (**1a**) (n_{app} 1.3) or (**1b**) (n_{app} 1.2).

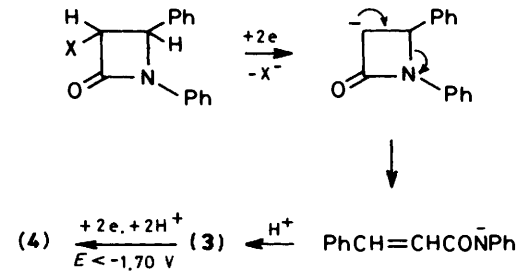
The available data do not allow us to draw a final conclusion about the formation mechanism of (**1d**) in the reduction of (**1c**) at the first wave potential. Nevertheless, two hypotheses can be put forward. (i) The formation of (**1d**) follows the occurrence of electron exchanges in solution between the anion radical $RCl_2^{-\bullet}$ and RHCl, which therefore is an intermediate [Scheme 1(a)]. This hypothesis is in agreement with earlier suggestions about aromatic radical anions and radical anions from the reduction of dibromo esters,[12] as well as with voltammetric analyses we have carried out on DMF–0.1M-TEAP solutions of (**1c**) (h.d.m.e. cathode, sweep rate 200 mV s^{-1}, E_p' −1.38, E_p'' −1.89, E_p''' −2.64 V) in the absence and presence of (**1b**) (E_p' −1.89, E_p'' −2.64 V). In fact, on addition of (**1b**) the first peak current of (**1c**) increases in proportion to the concentration ratio of the two β-lactams.[13] (ii) Alternatively, the formation of (**1d**) may be explained by a reaction pathway involving carbene intermediates [Scheme 1(b)]. In this case, the electrochemically generated carbanion (e.g.c.) RCl^- may competitively undergo protonation to (**1b**) and cleavage into chloride ion and a carbene (R) which, following reduction and protonation, yields (**1d**). The latter hypothesis, especially when the reduction is carried out in the absence of proton donors, agrees with previous suggestions for the cathodic reaction of geminal polyhalogeno derivatives.[14]

When the reduction of (**1c**) is carried out in the absence of proton donors, protonation of the intermediates by the 'parent' molecule necessarily involves the positon 4 of the latter, in the absence of hydrogen atoms in the more acidic position 3 of the β-lactam ring.

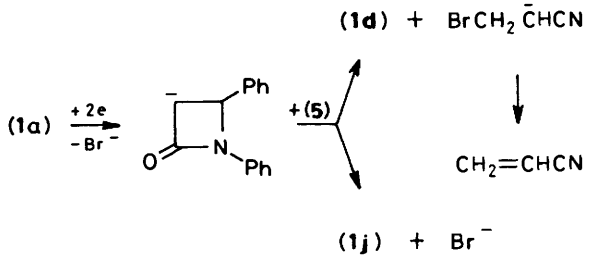
As already suggested for the methylthio-β-lactams (**2a**—**c**), proton abstraction from position 4 of (**1c**) can be assisted by a β-elimination reaction, with subsequent formation of an unstable azetinone derivative. Its decomposition could explain the formation of large amounts of unidentified by-products in the reduction of (**1c**).

Moreover, the intramolecular reactivity of the e.g.c. should explain the formation of the saturated amide (**4**) in the reduction carried out in the absence of proton donors (Scheme 2).

The unsaturated amide (**3**) was prepared and its polarographic features were determined ($E_{\frac{1}{2}}$ −1.85 and −2.3 V; first reduction wave foot potential −1.70 V). Scheme 2, where an example of electrochemically induced C–N bond cleavage is depicted, was verified by carrying out the reduction of (**1a**) at three different potentials: −1.5, −1.8, and −2.0 V. In agreement with the proposed reaction pathway, the presence of the unsaturated amide (**3**) and, at the same time, the absence of the saturated amide (**4**) (Table 2) was observed after the reduction at −1.5 V only. Furthermore, the yield of (**1d**) decreases whenever the



Scheme 2.



Scheme 3.

reduction is carried out at a potential more negative than −1.70 V, *i.e.* at potentials allowing further reduction of (**3**). Indeed, the latter requires the 'parent' molecule (**1**) as the protonating agent, thus decreasing the availability of (**1**) for the protonation of the e.g.c.

The reduction of a compound in the presence of CO_2 has been often suggested as a suitable procedure to introduce a carboxy group.[3,15] This procedure is always successful whenever carbanionic intermediates are involved in the electrochemical process, and it has become a reliable test to ascertain the formation of such an intermediate. The reduction of (**1a**—**c**) in the presence of CO_2 gives rise to the corresponding 3-carboxy-β-lactams (**1e** and **g**) in high yields, with complete retention of configuration at C-3. If the half-wave potential values of products (**1g**) and (**1i**) are compared with those of the products present in the electrolysed solution before the addition of the acid, it can be deduced that (**1g**) is present in the solution as the anion (**1h**); therefore, the latter cannot be protonated by any compound in the solution. It should be noted that, under these reaction conditions, the primary products of the carboxylation reaction are carboxylate anions like (**1h**); this fact seems to be particularly important in connection with the overall reaction yield, mainly in the carboxylation of (**1c**). Indeed, anionic compounds such as (**1h**) cannot be further reduced at the electrolysis potential, in contrast with the corresponding neutral molecules such as (**1g**) (Table 1). Thus, the carboxylation reaction of the β-lactams under study provides useful information concerning its reaction mechanism, since the carbon–halogen bond reduction is proved to occur *via* a carbanion mechanism. Furthermore, this reaction allows one to functionalize the β-lactam nucleus, giving 3-carboxy-β-lactams, that are not easily obtained by conventional chemical procedures. Another attempt to functionalize the β-lactam ring involved reducing (**1a**) in the presence of (**5**). The main product of this reaction is (**1d**), obtained together with minor amounts of the coupling product (**1j**). Acrylonitrile, formed from a β-elimination of the conjugate base of (**5**), is a secondary product.

These results show that in the presence of substrates which can act at the same time as proton donors and electrophiles, the e.g.c. is more effective as a base than as a nucleophile. Therefore, it appears that only electrophilic reagents lacking sufficiently acidic hydrogen atoms can be chosen to functionalize the β-lactam ring.

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