Electrochemical Studies on Haloamides. Part 3.[1] Haloacetamides and Haloacetohydroxamates

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The electrochemical reduction of haloacetamides and acetohydroxamates **1** and **2** at a mercury cathode in DMF–0.1 mol dm^{-3} TEAP (tetraethylammonium perchlorate) solutions has been investigated.

The reduction leads to the corresponding dehalogenated products together with cyclic dimers, arising from follow-up reactions of the conjugated base of the starting compound. The same type of products, but in quite different yield, are formed when ethyl isobutyrate anion is electrogenerated in the presence of chloro derivatives **1**. The reactivity of the substrates, and in particular the structure of the dimers, primarily depends on the nature of the substituent at the amide nitrogen. Possible reaction pathways leading to the products are suggested.

The electrochemical reduction of haloamides from both a mechanistic and preparative point of view has been the subject of several studies by ourselves [1,2] and other groups.[3] The results of this research pointed to a complex reaction pathway depending on the structure of the substrate as well as on the experimental conditions. The type of the amide (whether or not it bears an acidic hydrogen at the amide nitrogen), the nature (primary, secondary or tertiary) and the position (with respect to the amide carbonyl) of the halogenated carbon, the presence of additional reducible functions, and the nature of the solvent are of major importance in determining the nature, stability and distribution of the reduction products. Nevertheless, the electrochemical behaviour of secondary and tertiary 2-bromopropanamides and isobutyramides has been well defined,[3] self-protonation and, when possible, cyclocoupling reaction with the solvent being the main pathways leading to the reaction products. These results fit in with those from basic treatment of the same substrates.[4,5] Probably owing to the greater reactivity of the substrates, intermediates and products, the available data on the electroreduction of bromoacetamides [2] do not allow the reaction pathways to be as well defined as those for the homologous haloamides, although their voltammetric data agree with those of the latter.[5] From the above information, it appears that further studies on the electroreduction of haloacetamides are necessary to better understand their behaviour.

In this paper we report the results obtained from cyclic voltammetry, coulometry and preparative controlled-potential electrolysis experiments carried out on solutions of acetamides and acetohydroxamates **1** and **2** in dipolar aprotic solvents, where the nature of the substituent at the amide nitrogen establishes the acidity of the NH group and that of the halogen affects the ability of methylene carbon to undergo nucleophilic substitution. The reactivity of **1** and **2** toward electrogenerated ethyl isobutyrate anion has been also investigated.

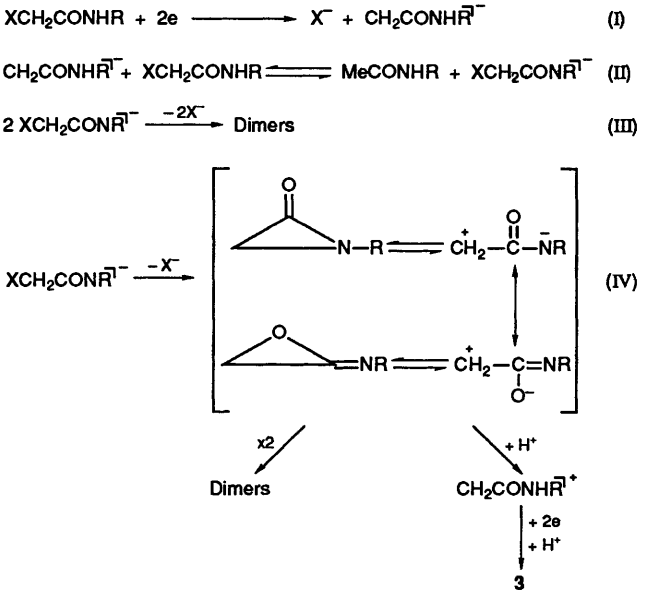
Results and Discussion

Voltammetry.—The peak potential and current intensity values pertinent to **1a–c** and **2a–c** are summarized in Table 1, together with the change of the i_p values promoted by basic (ethyl isobutyrate anion) and/or acidic (3,4-dimethylphenol)

XCH_2CONHR

1; X = Cl **a** R = OCH_2Ph
b R = CH_2Ph
2; X = Br **c** R = Ph

species. The voltammograms show one (**1a–c**) or two (**2a–c**) irreversible and diffusion controlled reduction peaks, as ascertained by routine voltammetric tests. In the case of **2b, c**, the addition of the phenol induces a sharp increase of the first peak height and the disappearance of the second. This agrees with the assignment of the first peak to the cleavage of the C–Br bond in the parent molecule and of the second one to the cleavage of the C–Br bond in its conjugated base arising from an autoprotonation reaction [2,3,5] (II in Scheme 1), which decreases the amount



Scheme 1

of starting amide available for the reduction. In the presence of an added proton donor, the autoprotonation reaction is suppressed: as a consequence, all the starting amide is reduced

Table 1 Voltammetric data for solutions of **1a–c** and **2a–c** in DMF–0.1 mol dm^{-3} TEAP ($c = 1 \times 10^{-3}$ mol dm^{-3}, $v = 0.2$ V s^{-1}, Hg cathode)

Substrate	$-E_{p1}$/V	i_{p1}/μA	$i_{p1}{}^{a}$/μA	$i_{p1}{}^{b}$/μA	$-E_{p2}$/V	i_{p2}/μA	$i_{p2}{}^{b}$/μA
1a	2.02	4.00	0	4.00	—	—	—
1b	2.14	4.32	0	9.12	—	—	—
1c	1.98	3.64	0	5.61	—	—	—
2a	1.18	3.20	—[c]	2.64	2.32	3.84	3.76
2b	1.32	3.52	—[c]	7.20	2.41	2.64	0
2c	1.13	3.44	—[c]	5.52	2.08	3.32	0

[a] Value measured after addition of equimolar amount of ethyl 2-bromoisobutyrate. [b] Value measured after addition of equimolar amount of 3,4-dimethylphenol. [c] The peak potential value of the probase (−1.3 V) makes impossible its use with this substrate.

Table 2 Distribution and yields of the products from the electroreduction of **1a–c** and **2a–c** (Hg cathode, DMF–0.1 mol dm^{-3} TEAP)

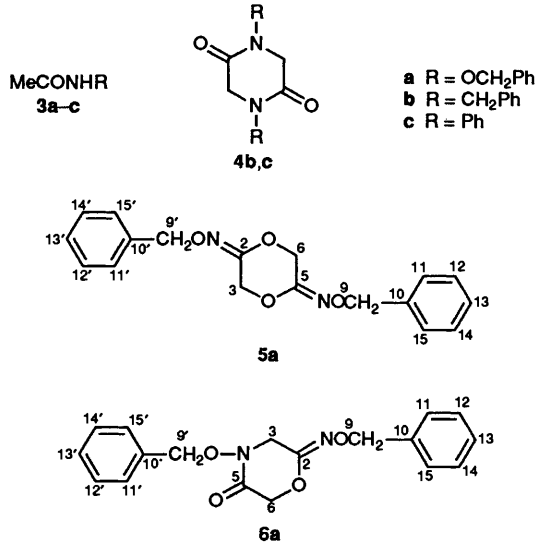
			Yield (%)					
Substrate	$-E$/V	n_{app}	**1**	**2**	**3**	**4**	**5**	**6**
1a	2.0	1	**1a** (30)	—	**3a** (48)	—	**5a** (5)	**6a** (10)
2a	1.3	1.1	—	**2a** (15)	**3a** (49)	—	**5a** (5)	**6a** (16)
1b	2.2	1.1	—	—	**3b** (43)	**4b** (35)	—	—
2b	1.5	1	—	—	**3b** (45)	**4b** (34)	—	—
1c	2.1	1	**1c** (4)	—	**3c** (45)	**4c** (25)	—	—
2c	1.1	1	—	—	**3c** (45)	**4c** (35)	—	—

(the height of the first peak increases) and its conjugated base is no longer formed (the second peak disappears). In the case of **2a**, the addition of the phenol causes no significant changes in the current intensity of either the first and the second peak. This apparently anomalous behaviour can be explained taking into account that hydroxamates have acidity constants of the same order or greater [18] than those of phenols so that, in the case of **2a**, the autoprotonation reaction can also occur in the presence of the added proton donor.

The voltammograms of chloro derivatives **1a–c** show only one reduction peak, which can be ascribed to the C–Cl bond reduction in the parent molecule. In this case, the cleavage of the C–Cl bond in the conjugated base, whose formation must be presumed to occur in analogy with bromoamides **2**, takes place at potential values beyond the range accessible in the adopted experimental conditions. The addition of 3,4-dimethylphenol causes, in the voltammograms of **1a–c**, effects identical to those observed for **2a–c**: the height of the first (only) peak increases in the case of **1b, c** and is unaffected in the case of **1a**. The reduction potential values of **1a–c** (*ca.* −2 V) allows the study of the influence on their voltammograms of the electrogenerated base (EGB) arising from the selected probase (PB), ethyl 2-bromoisobutyrate ($E_p = -1.3$ V). In any case, on addition of the PB the reduction peak of **1a–c** disappears, which proves the effectiveness of the EGB to deprotonate all chloroamides under study.

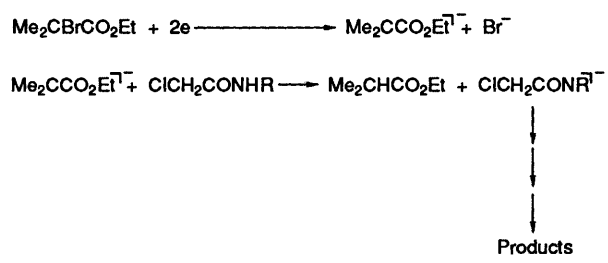
The above interpretation of the voltammetric data is substantiated from controlled-potential electrolysis experiments.

Macroscale electrolysis. Direct reduction at an Hg cathode in DMF–0.1 mol dm^{-3} TEAP (tetraethylammonium perchlorate) solutions of all haloamides **1** and **2** uses 1F per mol of substrate and affords almost theoretical yields (43–49%) of **3** (Table 2) through the autoprotonation reaction (II) of the carbanion derived from two-electron cleavage of C–X bond (I, Scheme 1). In addition to **3**, dimeric compounds arising from the conjugated base of the starting amide are also formed. Irrespective of the nature of X, they are piperazine **4** when R = benzyl or phenyl and a mixture of 1,4-dioxane **5** and 1,4-oxazine **6** when R = benzyloxy. Concerning the formation of the dimers, two reaction pathways can be considered: (i) an intermolecular nucleophilic substitution involving two molecules of conjugated base (III, Scheme 1) or (ii) an initially



intramolecular substitution giving reactive intermediates as α-lactams or iminoxiranes (or the dipolar tautomers), followed by dimerization (IV, Scheme 1). Although no conclusive evidence is available, some data acquired in the reduction of bromoisobutyrate in the presence of **1** support the existence of dipolar ions as intermediates (see later). Concerning the nature of the dimers, it appears that ionic structures involving a negative charge on the oxygen atom play a more significant role in the case of hydroxamates (*i.e.* **1a**, **2a**) than in that of amides. Possibly, the inductive effect of the alkoxy substituent lowers the reactivity of the nitrogen side of the ambident nucleophilic site of the dipole, promoting the intervention of the oxygen in the dimerization reaction.

As shown by voltammetry (Table 1), if the selected PB ethyl bromoisobutyrate is electrochemically reduced in the presence of **1a–c**, the correspondent EGB is able to deprotonate all substrates. The so formed conjugated bases (Scheme 2) follow qualitatively and quantitatively quite different fates depending, once again, on R: high yields of 1,4-piperazine dimers **4** are obtained in the case of **1b, c** whereas only low yield of a mixture



Scheme 2

of 1,4-dioxane **5** and 1,4-oxazine **6** are obtained from **1a**.* In all cases, small amounts of dehalogenated products **3** are also isolated (Table 3).

The formation of **3** in the EGB promoted reaction of **1** is important from a mechanistic point of view. In fact, the possibility that **3** can arise by direct reduction of **1** can be excluded on the basis of the large difference between the reduction potential of **1** (Table 1) and the working potential (−1.3 V). Moreover, the substrates under study are unlikely to undergo electron transfer in a homogeneous phase.

Therefore, the formation of **3** points to the existence of dipolar intermediates whose protonation, in competition with alkylation, yields a carbonium ion, which can be easily reduced at the working potential (Scheme 1).

Table 3 Distribution and yields of the products from the electroreduction of ethyl 2-bromoisobutyrate in the presence of **1a–c** (Hg cathode, DMF–0.1 mol dm^{-3} TEAP, $E = -1.3$ V, molar ratio PB/**1** = 1.5)

	Yield (%)				
Substrate	**1**	**3**	**4**	**5**	**6**
1a	**1a** (38)	**3a** (14)	—	**5a** (5)	**6a** (10)
1b	—	**3b** (17)	**4b** (50)	—	—
1c[a]	**1c** (3)	**3c** (2)	**4c** (75)	—	—

[a] [PB]/[**1c**] = 1.1.

Experimental

General.—Column chromatography was carried out on Merck silica gel (70–230 mesh, 100 g per 1 g substrate), using a mixture $CHCl_3$–AcOEt 85:15 as eluent. In some cases, more polar products were eluted with AcOEt or Me_2CO. M.p.s were taken with a Tottoli apparatus, and are uncorrected. IR spectra were recorded with a Perkin-Elmer 281B grating spectrophotometer as Nujol mulls; ^1H NMR 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. ^{13}C NMR were recorded for solutions in $CDCl_3$ using a Varian XL300 spectrometer. All J values are given in Hz. Mass spectra were recorded with a VG ZAB 2F spectrometer using both EI (70 eV) and CI (CH_4) techniques. All new compounds gave satisfactory elemental analyses (C ±0.3%; H ±0.2%; N, ±0.2%).

Voltammetric measurements were carried out at an Amel 498 sessile mercury drop electrode with an Amel 552 potentiostat equipped with an Amel 566 function generator and an Amel 563 multipurpose unit; the curves were displayed on an Amel 863 recorder. Controlled-potential electrolysis and coulometry were carried out at a mercury pool cathode with an Amel 552 potentiostat equipped with an Amel 721 integrator. The catholyte was degassed and pre-electrolysed at the working potential before the addition of the depolarizer. The cells used for all these techniques have already been described.[6] The reference electrode was of the calomel type described by Fujinaga,[7] its potential was −0.029 V *vs.* SCE. *N,N*-Dimethylformamide (DMF, Riedel- de Häen spectranal), was distilled under reduced pressure from activated (500 °C, 24 h) alumina. Tetraethylammonium perchlorate (TEAP, Fluka) was purified as previously described.[6] All electrochemical measurements were performed at 20.0 ± 0.1 °C in DMF–0.1 mol dm^{-3} TEAP solution percolated through activated alumina just before use.

Syntheses.—Haloacetohydroxamates **1a**,**2a** and haloacetamides **1b**,**c** and **2b**,**c** were prepared by allowing equimolar amounts of chloro(bromo)acetyl chloride(bromide) and the corresponding primary amine to react in the presence of triethylamine (110%) in $CHCl_3$ solution whilst the solution was cooled. After extraction with water, 1 mol dm^{-3} HCl, water, sat. aqueous $NaHCO_3$ and water, the solvent was removed, and the residue resolved by column chromatography. The products were further purified by crystallization from cyclohexane (from a mixture benzene–cyclohexane in the case of **1c**).

1a: M.p. 102–103 °C (lit.,[8] m.p. 105 °C); **2a**:[9] m.p. 98–99 °C; ν_{max}/cm^{-1} 3150 and 1695; δ_H 3.77 (2 H, s, CH_2Br), 4.93 (2 H, s, CH_2O) and 7.44 (5 H, s, aromatic); **1b**: m.p. 93–94 °C (lit.,[10] m.p. 93.5–94.5 °C); **2b**: m.p. 107–108 °C (lit.,[11] m.p. 109.5–110.5 °C); **1c**: m.p. 131–132 °C (lit.,[12] m.p. 134.5 °C); **2c**: m.p. 131 °C (lit.,[13] m.p. 130–131 °C).

Electrochemistry.—The controlled-potential electrolyses were carried out by stepwise addition of the depolarizer (0.8–1.0 g) to DMF–0.1 mol dm^{-3} TEAP (60–80 cm^3) in such a way that its concentration did not exceed 1×10^{-2} mol dm^{-3}. Each addition was made when the value of the current had dropped to that measured at the end of the pre-electrolysis (10 mA). The values of the working potential and n_{app} (number of Faraday × mol^{-1} obtained by coulometry) are given for each run. At the end of the electrolysis, the DMF solution was separated from the cathode, the solvent removed at 40–45 °C under reduced pressure, and the residue extracted with Et_2O (5 × 30 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated to constant weight under reduced pressure. A mixture $CHCl_3$–H_2O (1:1, 60 cm^3) was added to the solid insoluble in ether, the chloroform was separated and the water further extracted with the same solvent (3 × 30 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated to constant weight under reduced pressure. The aqueous phase was acidified (H_2SO_4) and extracted with $CHCl_3$ (3 × 30 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated to constant weight under reduced pressure. The residues from the different extracts were analysed by TLC and ^1H NMR and, if identical, combined before column chromatography.

Reduction of Haloacetohydroxamates **1a**, **2a** *and Acetamides* **1b**,**c** *and* **2b**,**c**.—*Benzyl chloroacetohydroxamate* **1a**. The title compound was reduced at −2.0 V ($n_{app} = 1$). Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts gave starting **1a** (5%), benzyl acetohydroxamate **3a**[14] (40%), 2,5-bis(benzyloxyimino)-1,4-dioxane **5a** (5%) and 4-benzyloxy-2-benzyloxyimino-1,4-oxazin-5-one **6a** (10%). Column chromatography of the residue from the $CHCl_3$ extract after acidification gave starting **1a** (25%) and **3a** (8%).

5a: M.p. 125–127 °C; ν_{max}/cm^{-1} 1660 and 1600; δ_H 4.73 (4 H, s, 3-H + 6-H), 5.00 (4 H, s, 9-H + 9′-H) and 7.36 (10 H, s, aromatic); δ_C 62.79 (C-3 + C-6), 76.80 (C-9 + C-9′), 128.09–128.79 (C-11 ÷ C-15 + C-11′ ÷ C-15′), 137.07 (C-10 + C-10′) and 148.22 (C-2 + C-5); m/z (EI) 326 (M^+).

* The low conversion yield of **1a** can be ascribed to the concomitant effects of a lower reactivity of both the leaving and alkylating groups.

6a: M.p. 104–105 °C; ν_{max}/cm^{-1} 1690 and 1660; δ_H 4.04 (2 H, s, 3-H), 4.63 (2 H, s, 6-H), 4.97 (2 H, s, 9-H or 9′-H), 5.03 (2 H, s, 9′-H or 9-H), 7.36 (5 H, s, aromatic) and 7.39 (5 H, s, aromatic); δ_C 47.76 (C-3), 68.10 (C-6), 76.58 (C-9 or C-9′), 76.68 (C-9′ or C-9), 128.06–129.58 (C-11 ÷ C-15 + C-11′ ÷ C-15′), 134.20 (C-10′ or C-10), 137.16 (C-10 or C-10′), 147.04 (C-2) and 163.89 (C-5); *m/z* (CI) 327 ($M^+ + 1$).

Benzyl bromoacetohydroxamate **2a**. The title compound was reduced at −1.3 V (n_{app} = 1.1). Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts gave **3a** (35%), **5a** (5%) and **6a** (16%). Column chromatography of the residue from $CHCl_3$ extract after acidification gave starting **2a** (15%) and **3a** (14%).

N-*Benzylchloroacetamide* **1b**. The title compound was reduced at −2.2 V (n_{app} = 1.1). Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts gave *N*-benzylacetamide **3b**[15] (43%) and 1,4-dibenzylpiperazine-2,5-dione **4b**[16] (35%).

N-*Benzylbromoacetamide* **2b**. The title compound was reduced at −1.5 V (n_{app} = 1). Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts gave **3b** (45%) and **4b** (34%).

Chloroacetanilide **1c**. The title compound was reduced at −2.1 V (n_{app} = 1). Column chromatography of the residue from Et_2O extract gave starting **1c** (4%) and acetanilide **3c** (45%). The residue from $CHCl_3$ extract was 1,4-diphenylpiperazine-2,5-dione **4c**[17] (25%).

Bromoacetanilide **2c**. The title compound was reduced at −1.1 V (n_{app} = 1). Column chromatography of the residue from Et_2O extract gave **3c** (45%). The residue from $CHCl_3$ extract was **4c** (35%).

Reduction of Ethyl Bromoisobutyrate in the Presence of **1a–c**.—In these experiments, the catholyte was a solution of chloro derivative in DMF–0.1 mol dm^{-3} TEAP previously degassed and pre-electrolysed at −1.3 V. The probase was added as DMF solution (10 cm^3) in five aliquots. Each portion was added when the current had dropped to the value measured at the end of the pre-electrolysis. The work-up of the reaction mixture was identical with that of direct reduction of the substrates. The products isolated and their yield, are reported in Table 3. Compounds **1a** and **3a** were recovered in the organic extracts both before (10 and 12%, respectively) and after acidification (28 and 2%, respectively).

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