Electrochemical Studies on Haloamides. Part 4.[1] Reactivity of Haloacetamides and Haloacetohydroxamates Toward Electrogenerated Diethyl Malonate Anion

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The reactivity of haloacetamides and acetohydroxamates **1** and **2** toward electrogenerated diethyl malonate anion has been investigated. The course of the reaction primarily depends on the acidity of the amide NH group, which is mainly determined by the nature of the substituent, R, at the nitrogen atom. If this substituent is the same, the nature of the halogen atom also plays an important role. If the malonate anion can act as a base, products arising from follow-up reactions of the conjugated base of the substrate are formed and their structure is dependent on R. In particular, β-lactams arising from a formal insertion of a malonate residue into the amide skeleton are obtained from haloacetanilides. When the substrate cannot be deprotonated, the diethyl malonate anion behaves as a nucleophile provided that the leaving group is bromide. Chloro derivatives are rather stable toward malonate anion.

In connection with the studies described in the preceding paper, the electrochemical reduction of diethyl bromomalonate in the presence of haloacetamides and acetohydroxamates **1** and **2**, electroinactive at the working potential, has been investigated. As previously shown,[1] ethyl isobutyrate anion, electrogenerated by reduction of ethyl bromoisobutyrate, unselectively deprotonates chloro derivatives **1** to the corresponding conjugated bases, which evolve to different products depending on the nature of R. Furthermore, the reduction potential of bromoisobutyrate precludes its use in the case of bromo derivatives **2**, thus preventing the influence of the halogen on the course of the reaction from being established.[1] An electrogenerated base (EGB) of lower reactivity than isobutyrate anion is expected to discriminate between the substrates under study, depending on the acidity of NH amide group (which depends primarily on the nature of the substituent at the nitrogen atom) and/or the nature of the halogen atom.

$ClCH_2CONHR$	**1,2a**	R = OCH_2Ph
1	**b**	R = CH_2Ph
	c	R = Ph
$BrCH_2CONHR$	**2d**	R = C_6H_4-*p*-OMe
2	**e**	R = C_6H_4-*p*-CN

In this paper the results obtained using diethyl malonate anion as EGB are reported. The reduction potential value (−0.45 V) of the corresponding probase (PB), diethyl bromomalonate allows its use also in the case of bromo derivatives **2**.

Experimental

General.—HPLC analyses were carried out with a Perkin-Elmer system made up from a Series 4 LC, an LC 85B spectrophotometric detector, an LC Autocontrol, and a Sigma 15 chromatography data station on a Merck LiChrocart (250-4) RP18, 7 μm column. A mixture H_2O–CH_3CN in linear gradient from 90:10 to 10:90 in 30 min at a flow rate of 1 cm^3 min^{-1} was used as eluent. Quantitative HPLC analyses were carried out with the internal standard method. For other apparatus and methods see ref. 1.

Chemistry.—Compounds **1a–c** and **2a–c** were obtained as previously described.[1] Compounds **2d,e** were prepared using the same procedure.

N-(*p*-Methoxyphenyl)bromoacetamide **2d**. M.p. 127–129 °C ($CHCl_3$) (lit.,[2] m.p. 130.5–131.5 °C).

N-(*p*-Cyanophenyl)bromoacetamide **2e**, m.p. 163–164 °C (propan-2-ol–cyclohexane); ν_{max}/cm^{-1} 3260, 3180, 3120, 2220, 1680, 1600 and 1530; $\delta_H(CD_3COCD_3)$ 4.10 (2 H, s, CH_2Br), 7.7–8.2 (4 H, m, aromatic) and 9.8–10.2 (1 H, br s, NH).

Electrochemistry.—Controlled-potential electrolyses were carried out at −0.5 V *vs.* SCE by stepwise addition of a solution of the PB in DMF (5 cm^3) to a solution of the appropriate haloacetamide or acetohydroxamate (0.8–1.0 g) in DMF–0.1 mol dm^{-3} TEAP (50 cm^3), previously degassed and pre-electrolysed at the working potential. Each portion of the solution of PB was added when the current intensity had dropped to the value measured at the end of the pre-electrolysis. At the end of each 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 $CHCl_3$ was separated and the aqueous layer was 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 vacuum. The residues from the different extracts were analysed by TLC and ^1H NMR spectroscopy and, if identical, combined before column chromatography. Unless otherwise stated, a molar ratio [PB]/[substrate] = 1.5 was used.

Reduction of the PB in the presence of **1a**. Column chromatography of the combined residues from Et_2O and $CHCl_3$ extracts ($CHCl_3$–AcOEt 85:15 as eluent) gave 90% recovery of starting **1a**.

Reduction of the PB in the presence of **1b**. Column chromato-

graphy of the combined residues from Et_2O and $CHCl_3$ extracts (CH_2Cl_2–Me_2CO 98:2 as eluent) gave 90% recovery of starting **1b**.

Reduction of the PB in the presence of **1c**. HPLC analysis carried out by comparison with authentic samples showed the presence, in the crude reduction mixture, of starting **1c**, acetanilide **3c** and 4,4-bis(ethoxycarbonyl)-1-phenylazetidin-2-one **7c**.[3] Quantitative HPLC analysis gave the following products distribution: **1c**: 80%, **3c**: 2% and **7c**: 7%.

Reduction of the PB in the presence of **2a**. Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts ($CHCl_3$–AcOEt 85:15 as eluent) gave starting **2a** (9%), **3a** (7%), **5a**[1] (37%) and **6a**[1] (6%). Column chromatography of the residue from $CHCl_3$ extract after acidification (same eluent) gave **2a** (30%) and **3a** (4%).

Reduction of the PB in the presence of **2b**. Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts ($CHCl_3$–AcOEt 95:5 as eluent) gave *N*-benzylacetamide **3b**[4] (8%) and 2,7-dibenzyl-2,7-diazaspiro-[4.4]nonane-1,3,6,8-tetraone **4b**[5] (70%).

Reduction of the PB in the presence of **2c**. This experiment has been carried out at different PB/substrate molar ratios to optimize the yield of β-lactam (Table 2). In all cases, the crude reduction mixture was resolved by column chromatography ($CHCl_3$–AcOEt 9:1 as eluent) of the combined residues from the Et_2O and $CHCl_3$ extracts. When the usual 1.5 molar ratio was used, the following product distribution was found: starting **2c**: 26%; **3c**: 24%, **7c**: 41%.

Reduction of the PB in the presence of **2d**. A 2:1 PB/substrate molar ratio was used. Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts (light petroleum–AcOEt 7:3 as eluent) gave *N*-(*p*-methoxyphenyl)-acetamide **3d**[6] (37%) and 4,4-bis(ethoxycarbonyl)-1-(*p*-methoxyphenyl)azetidin-2-one **7d**[7] (29%).

Reduction of the PB in the presence of **2e**. A 2:1 PB/substrate molar ratio was used. Column chromatography of the combined residues from the Et_2O and $CHCl_3$ extracts (light petroleum–AcOEt 7:3 as eluent) gave starting **2e** (29%) and 4,4-bis(ethoxycarbonyl)-1-(*p*-cyanophenyl)azetidin-2-one **7e** (69%). Small amounts (*ca.* 1%) of *N*-(*p*-cyanophenyl)acetamide **3e**[8] were detected in the crude reduction mixture by HPLC.

Independent Synthesis of **4b**.—A mixture of diethyl malonate (1.0 mmol) and NaH (2.0 mmol) in DMF (2 cm^3) was added stepwise to a solution of *N*-benzylbromoacetamide **2b** (1.0 mmol) in DMF (3 cm^3) maintained at room temperature. After the mixture had been stirred for 1.5 h, the solvent was evaporated under reduced pressure, $CHCl_3$ was added to the residue, and the mixture repeatedly extracted with water. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. Column chromatography of the residue (CH_2Cl_2–AcOEt 9:1 as eluent) gave *N*-benzyl-3-ethoxycarbonylsuccinimide **9b** (40%) and 2,7-dibenzyl-2,7-diazaspiro[4.4]-nonane-1,3,6,8-tetraone **4b** (10%).

9b: M.p. 74–75 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1785, 1740 and 1710; δ_H 1.26 (3 H, t, CH_3), 2.79 (1 H, dd, $J_{3,4cis}$ 9, $J_{4,4}$ 18, 4-H), 3.12 (1 H, dd, $J_{3,4trans}$ 6, $J_{4,4}$ 18, 4-H), 3.73 (1 H, dd, *J* 6 and 9, 3-H), 4.25 (2 H, q, OCH_2), 4.65 (2 H, s, NCH_2) and 7.2–7.5 (5 H, m, aromatic).

A mixture of diethyl malonate (0.4 mmol) and NaH (0.8 mmol) in DMF (2 cm^3) was added dropwise to a solution of **9b** (0.4 mmol) and **2b** (0.4 mmol) in DMF (3 cm^3) maintained at room temperature. After being stirred for 1.5 h, the reaction mixture was worked-up as before. On the basis of IR and ^1H NMR spectra, the residue from the $CHCl_3$ phase was **4b**.

In order to understand the reaction pathways leading to β-lactams **7** and spiro compound **4**, separate chemical and electrochemical experiments were performed, giving the following information: (i) diethyl bromomalonate and bromoacetanilide (equimolar, DMF, room temp., 1 h) do not react at all; (ii) no β-lactam formation occurs when: (a) bromoacetanilide (1.05 mmol) was allowed to react with a mixture of diethyl malonate (1.06 mmol) and NaH (1.04 mmol) in DMF (25 cm^3) at room temp. for 1 h (some amount of 1,4-diphenylpiperazine-2,5-dione **8c**[9] was formed); (b) diethyl bromomalonate (1.0 mmol) was allowed to react with a mixture of acetanilide (1.0 mmol) and NaH (1.0 mmol) in DMF (25 cm^3) at room temp. for 1 h or with a mixture of acetanilide (0.3 mmol) and butyllithium (0.7 mmol) in THF (5 cm^3) at room temp. for 2 h; (c) diethyl bromomalonate (1.5 mmol) was reduced at −0.5 V in the presence of acetanilide (1.0 mmol) under the electroreduction conditions given before (some amount of tetraethyl ethane-1,1,2,2-tetracarboxylate was recovered together with starting **3c**). On the other hand, β-lactam **7c** was isolated from the following reaction.

A mixture of diethyl malonate (1.06 mmol) and NaH (1.04 mmol) in DMF (5 cm^3) was added stepwise to a solution of bromoacetanilide (1.05 mmol) and diethyl bromomalonate (1.05 mmol) in DMF (25 cm^3) maintained at room temperature. After the mixture had been stirred for 30 min, the solvent was evaporated under reduced pressure, $CHCl_3$ was added to the residue, and the mixture repeatedly extracted with water. The organic phase was dried (Na_2SO_4), and the solvent evaporated under reduced pressure. HPLC analysis and IR (ν_{CO}) and ^1H NMR ($\delta_{3\text{-}H}$) spectra of the residue showed the presence of β-lactam **7c**. Quantitative HPLC analysis gave the yields: 46% starting **2c** and 26% β-lactam **7c**.

Results and Discussion

Voltammetry.—The peak potential and current intensity values pertinent to **1a–c** and **2a–c** are summarized in Table 1,

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

Substrate	$-E_{p1}$/V	i_{p1}/μA	$i_{p1}{}^a$/μA	$-E_{p2}$/V	i_{p2}/μA	$i_{p2}{}^a$/μA
1a	2.02	4.00	0	—	—	—
1b	2.14	4.32	7.28	—	—	—
1c	1.98	3.64	6.08	—	—	—
2a	1.18	3.20	0	2.32	3.84	5.12
2b	1.32	3.52	6.24	2.41	2.64	0
2c	1.13	3.44	4.64	2.08	3.32	0.24

[a] Value measured after addition of equimolar amount of diethyl bromomalonate.

together with the change of the i_p values promoted by addition of diethyl bromomalonate (PB). A general discussion of the voltammetric behaviour of the haloamides under study both alone and in the presence of basic (ethyl isobutyrate anion) or acidic (3,4-dimethylphenol) species has been presented in the preceding paper.[1] In this instance, we direct our attention to the effect of added PB on the current intensities at the peak potentials.

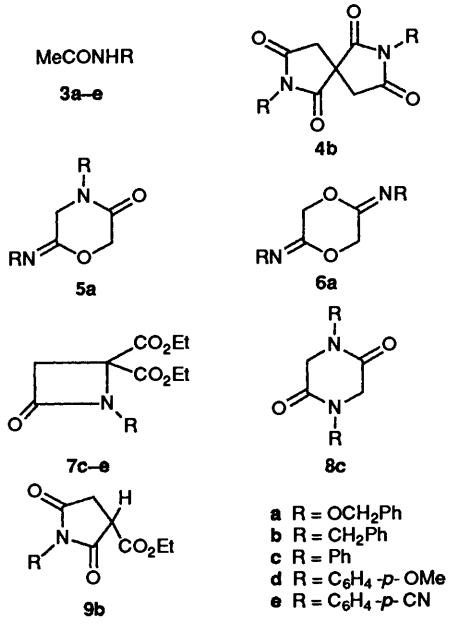
In the presence of PB, the current values of the only (**1b,c**) or the first (**2b,c**) peak sharply increase, whereas the second peak of **2b** disappears and that of **2c** strongly reduces. On the contrary, on addition of the PB the first (or the only) peak of **1,2a** disappears and the current value of the second peak of **2a** is enhanced. According to the proposed picture,[1] it appears that electrogenerated diethyl malonate anion (EGB) cannot deprotonate amides **1b,c** and **2b**, in which case the PB and/or products arising from its reduction behave as proton donors totally suppressing the autoprotonation reaction,[1] whereas in the case of **2c** small amounts of its conjugated base survive the

Table 2 Distribution and yield of the products from the electroreduction of diethyl bromomalonate (PB) in the presence of **1a–c** and **2a–e** (DMF–0.1 mol dm^{-3} TEAP, $E = -0.5$ V *vs.* SCE, Hg cathode)

Substrate	[PB]/[Sub]	Products (yield, %)
1a	1.5	**1a** (90)
1b	1.5	**1b** (90)
1c	1.5	**1c** (80), **3c** (2), **7c** (7)
2a	1.5	**2a** (39), **3a** (11), **5a** (37), **6a** (6)
2b	1.5	**3b** (8), **4b** (70)
2c	1.0	**2c** (45), **3c** (12), **7c** (20)
2c	1.5	**2c** (26), **3c** (24), **7c** (41)
2c	2.0	**3c** (26), **7c** (52)
2d	2.0	**3d** (37), **7d** (29)
2e	2.0	**2e** (29), **3e** (1), **7e** (69)

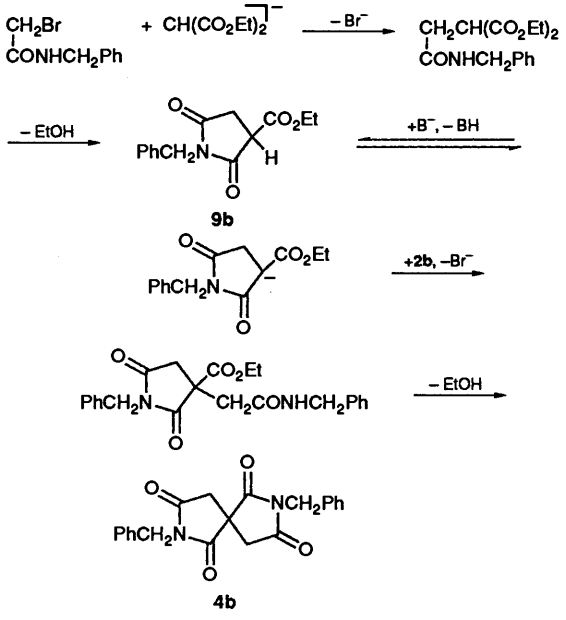
presence of EGB. In contrast, the latter is able to convert hydroxamates **1,2a** into the corresponding halogenated anions, which are responsible for the reduction peak at more negative potential. From the foregoing, it is evident that in contrast with the isobutyrate anion,[1] the diethyl malonate anion can discriminate amides from hydroxamates on the basis of their different acidity. As we can see later, further information on the different reactivity of the substrates under study toward malonate anion, as determined from the nature of the halogen atom as well, can be drawn from macroscale electrolysis experiments.

Macroscale electrolysis. The nature and yield of the products from controlled-potential electrolyses of the PB in the presence of chloro (**1a–c**) and bromo (**2a–e**) derivatives are reported in Table 2. The peculiar features of such data are (i) the (almost) complete stability of **1a–c**, (ii) the formation of diazaspirononane **4b** from benzylbromoacetamide **2b** and (iii) the formation of β-lactams **7c–e** from the corresponding acetanilides. As to the formation of cyclic dimers **5** and **6** (from **2a**) and of



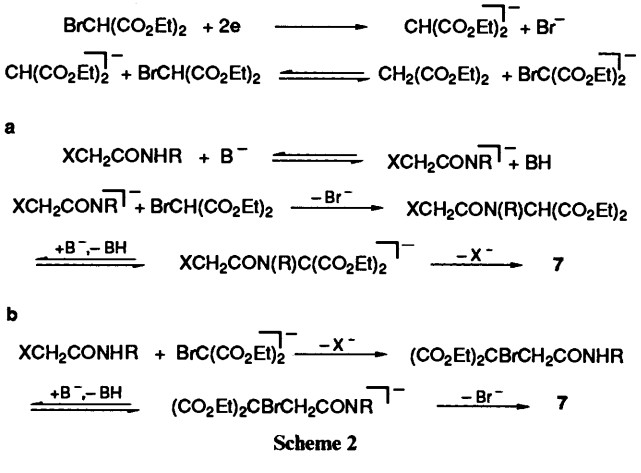
dehalogenated compounds **3** (in all cases where reaction occurs) a possible explanation has been given in the preceding paper.[1] Concerning the stability of chloro compounds **1a–c** toward diethyl malonate anion, it should be noted that the data from macroscale electrolysis agree with the voltammetric data in the case of **1b,c** but not of **1a**. As stated before, the voltammetry points to a deprotonation of this substrate by the EGB, whereas the work-up of the electrolysed solution allows almost quantitative recovery of unchanged **1a**. This is a typical example of results obtained on a macroscale which differ from those predicted on the basis of microscale experiments.[10]

The substituent at the nitrogen atom being the same, the nature of the halogen atom also has an important effect on the reactivity of haloacetamides as evidenced by the stability of **1b** if compared with the total conversion of **2b**. *N*-Benzylhaloacetamides are not acidic enough to be deprotonated to any significant extent by the EGB; however, provided that a bromine atom is present at the carbon adjacent to the carbonyl group, its nucleophilic displacement occurs leading, after a multistep process, to **4b**. On the basis of separate runs (see Experimental section), we propose that such a process involves succinimide **9b** as a stable intermediate, as depicted in Scheme 1.



Scheme 1

From a synthetic point of view, the most interesting aspect of this work is the formation of β-lactams **7c–e** from the corresponding bromoacetanilides. Formally, the conversion of **1,2** into **7** involves 'insertion' of a malonate framework into the amide skeleton and could, in principle, take place through different reaction pathways, two of which are depicted in Scheme 2. According to route **a**, preliminary *N*-alkylation of



Scheme 2

the conjugated base of the substrate by unreduced PB affords *N*-bis(ethoxycarbonyl)methylhaloacetanilides which cyclize to

β-lactams **7** following base-promoted ionization of methine carbon.*

Alternatively (route **b**), *C*-alkylation of the substrate by brominated malonate anion gives β,β-bis(ethoxycarbonyl)-β-bromopropanamides, whose cyclization follows deprotonation of amide nitrogen.†

The observed increase in the yield of β-lactam with electron withdrawing substituent *para* to the nitrogen atom supports the intervention of anionic intermediates. While the present data do not allow discrimination between the two possible reaction pathways, nevertheless they show that the presence of both diethyl malonate anion and bromomalonate is a necessary condition for the conversion of acetanilides into β-lactams to take place.

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* Electrosynthesis of β-lactams through C_3–C_4 bond formation has been described.[3,7]

† Electrosynthesis of β-lactams through N–C_4 bond formation has been described.[11]

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