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ELECTRO-CARBOXYLATION OF 2-BROMOISOBUTYRAMIDES. A USEFUL SYNTHETIC WAY TO ESTER-AMIDES OF 2,2-DIMETHYLMALONIC ACID

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Abstract - The electroreduction of protic 2-bromoisobutyramides was studied in acetonitrile in the presence of carbon dioxide by means of cyclic voltammetry and controlled-potential electrolysis. The electrogeneration of the α-carbanion is followed by a fast and quantitative carboxylation at the tertiary carbon, despite the N-H acidity of the starting compounds. The carboxylate anion was trapped both after and during the electrolysis procedure by alkylating reagents. High yields of ester-amides of 2,2-dimethylmalonic acid were obtained at both mercury and platinum cathodes.

The C-X function of organic halides can be cleaved through electrochemical reduction under suitable conditions.[1] In most cases and in particular with alkyl halides, a carbanion is actually formed in an overall 2-electron process. In such a case, the use of proper electrophiles, in particular carbon dioxide, opened new synthetic pathways.[2,3] The same kind of possibility arose during our studies on the electroreduction of 2-bromoamides.[4]

2-Bromoisobutyramides **1** are easily reduced at the mercury electrode in dipolar aprotic solvents (Figure 1). According to voltammetric and coulometric results as well as to the yields and product distribution,[4] the overall process is driven by the self-protonation mechanism, in which an electrogenerated basic intermediate undergoes protonation by a parent molecule.[5] In the case of 2-bromo-amides, the carbanion **2** is electrogenerated at the first peak (see Figure 1) as a consequence of a 2-electron C-Br bond cleavage (equation 1) and cyclic voltammetry indicates that the ensuing self-protonation reaction 2) efficiently traps the carbanion even at very high potential scan rates, i.e. at very short micro-electrolysis times. The rate of reaction 2) is very high due to the strong basicity of carbanion **2** and the acidity of the amidic proton of **1** (rate constants are tipically in the 10^8 $M^{-1}s^{-1}$ range).[6] Accordingly, 1 electron per molecule is apparently consumed at the potentials of the first peak due to the transformation of half of the starting material into its conjugate base **4**. The anion **4** can be reduced at more negative potentials (second peak, Figure 1) in a similar way as its conjugate acid **1**, i.e. through a 2-electron C-Br

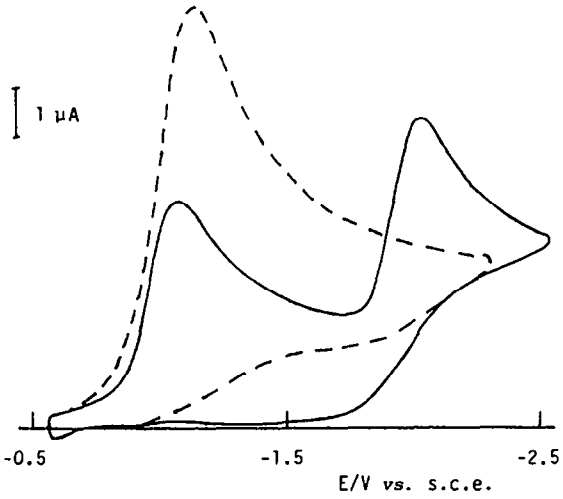
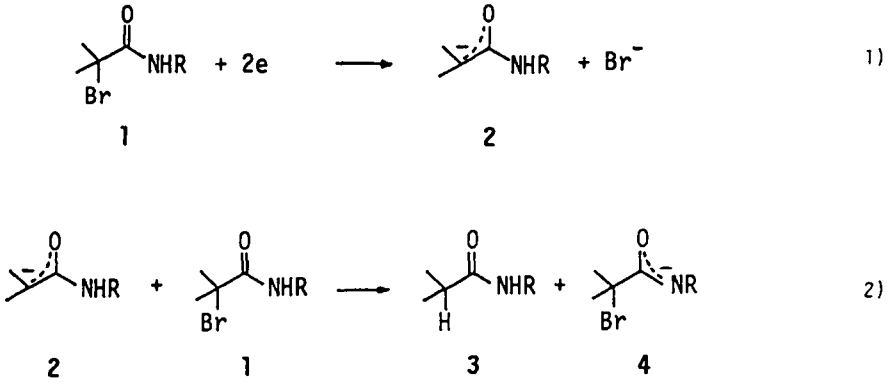


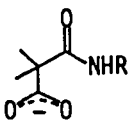
Figure 1. Cyclic voltammetries of a representative 2-bromoisobutyramide (1.14 mM $BrCMe_2CONHPh$) obtained in DMF-0.1 M Et_4NClO_4 in the absence (———) and in the presence (- - -) of acetic acid (1.2 mM) or carbon dioxide. Potential scan rate = 0.2 Vs^{-1}. T = 25° C.



bond cleavage; also in this case 1 electron per molecule is apparently consumed.[4] Proton donors stronger than the 2-bromoamides **1** block the self-protonation reaction 2), so that the isobutyramide **3** is quantitatively produced with actual consumption of 2 electrons per molecule. Accordingly, the first peak doubles while the second one disappears as anion **4** is no more forming (Figure 1, dashed curve).[4]

In the presence of carbon dioxide, the voltammetric pattern and the coulometric result change in the same way as in the presence of strong proton donors, i.e. the dashed curve in Figure 1 is exactly reproduced. On the basis of the reduction mechanism of 2-bromoisobutyramides, this behaviour can be explained by assuming that carbon dioxide quantitatively traps the carbanion **2** in dipolar aprotic solvents with formation of the carboxylate anion **5**.

The 2-electron voltammetric peak depicted in Figure 1 (dashed curve) can be observed also at



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very high scan rates, at least till about 100 Vs^{-1}, indicating that the carboxylation of carbanion **2** is fast. Hence, it was expected that, in the much longer times required by controlled potential electrolysis, the carboxylation reaction would be even more so quantitative.

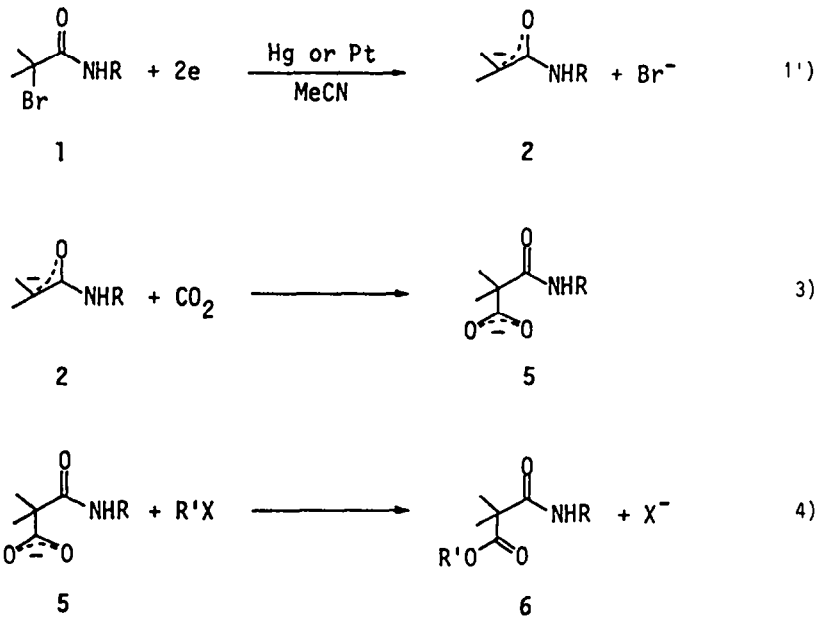
Macroelectrolyses were conducted in MeCN-0.1 M n-Bu_4NClO_4 at the mercury-pool cathode at potentials of the first peak. Carbon dioxide was slowly bubbled into the solution containing the 2-bromoamide. The substrates investigated were four representative protic 2-bromoisobutyramides: **1a**, R = Ph; **1b**, R = p-C_6H_4Cl; **1c**, R = p-C_6H_4CN; **1d**, R = CH_2Ph.

Preliminary experiments were carried out on compounds **1a** at the substrate concentration usually selected in controlled-potential electrolyses, i.e. 10^{-2} M. The charge consumption of 2.0 $Fmol^{-1}$ showed that the quantitative formation of the carbanion and its reaction with carbon dioxide were taking place as in cyclic voltammetry experiments, in which the concentration of the bromoamide is typically 10^{-3} M. Moreover, it was also evident that the carboxylate eventually formed was not involved in a further reaction with the starting material itself which, in principle, might act as an alkylating reagent.[3] In the latter case, in fact, a fraction of the bromoamide would have been deactivated towards reduction at the working potential with decrease of the apparent number of electrons exchanged. However, only the isobutyranilide **3a** was obtained after acidification of the mixture, due to the spontaneous decarboxylation of malonamic acids.[7] As the conjugate acid of **5** is hardly isolable, the stability of the carboxylate anion **5** itself was investigated for some substrates by means of h.p.l.c.. Typical analyses were performed as follows. Samples of the electrolytic solution were collected during the electrolysis and directly analyzed without any pretreatment with strong acids. The chromatograms revealed the presence of three species: the unreacted 2-bromoisobutyramide **1**, the isobutyramide **3**, and a third peak assigned to the ion-paired carboxylate **5**. By using calibration curves, the percentage of **3** was observed to increase during the electrolysis to reach 20-30% yield at the end of the electroreduction, meaning that the decarboxylation process occurs also under the basic conditions in which anion **5** is formed. The peak assigned to the carboxylate **5** disappeared when the electrolysed solution was treated with a strong acid and, accordingly, the peak of **3** proportionally increased. Therefore, in order to obtain an isolable product, the carboxylate anion **5** was trapped with alkylating reagents such as MeI, $PhCH_2Br$ or $PhCH_2Cl$. The n-Bu_4N^+ cation of the electrolyte was kept constant in order to have a good nucleophilicity of carboxylate **5**, loosely paired with such a counter-ion. In Table 1 are reported the electrochemical data and product distributions obtained through direct h.p.l.c. of the reaction mixture and ^1H n.m.r. of the oil obtained after elimination of the solvent and electrolyte.

The reported data show that the alkylation of the carboxylate anion **5** into the pertinent ester **6** is quite efficient and almost quantitative with respect to the carboxylate concentration, which was evaluated in most of the experiments just before injecting the alkylating reagent. H.p.l.c. measurements carried out during the chemical reaction (substrate **1a**, expt 1, 3), indicated that, after adding MeI or $PhCH_2Br$, 90% conversion of anion **5a** into the methyl or benzyl esters was reached in 18 and 15 min, respectively. During this time, no more than 5% of the carboxylate **5a** was

lost due to the decarboxylation reaction. When the water content of the solvent-electrolyte system was reduced to minimum values by using activated alumina (see Experimental), the extent of the decarboxylation was also reduced (expt 2, 7, 9), although no attempt was made to focus on such an aspect from a mechanistic point of view. As expected from the fact that no products ascribable to interaction with the mercury electrode were observed upon macroreduction of 2-bromoamides,[4] the use of a platinum grid cathode led to the same product distribution (expt 4, 8).

On the basis of the above results, the electrocarboxylation-alkylation process can be represented by the reaction sequence 1', 3, 4):



where R' is Me or CH_2Ph and X is the appropriate halogen (see Table 1).

The finding that the self-protonation reaction 2) is totally suppressed upon electrolysis in the presence of CO_2, along with the known values of the self-protonation rate constant and the concentration of CO_2 in MeCN-0.1 M n-Bu_4NClO_4 (ca. 3 x 10^{-2} M at 25° C)[8] lead to a rough calculation of the minimum value of the rate constant of the carboxylation 3), i.e. about 10^8 $M^{-1}s^{-1}$ for having a rate of at least 15-fold the self-protonation rate. On the other hand, as indicated by h.p.l.c., the O-alkylation reaction 4) is quite slow compared to step 3). On these grounds, a one-pot electrosynthesis of the esters of malonamic acids was envisaged. Compound **1a** was again chosen as the trial material. In a preliminary experiment, its reduction was studied in the presence of benzyl chloride, which is unreducible at the first wave of compound **1a**. Cyclic voltammetry indicated that benzyl chloride is unable to react directly with the electrogenerated carbanion **2**, the self-protonation reaction being quantitatively operative. Subsequently, macro-reduction of **1a** in the presence of both carbon dioxide and benzyl chloride led to a good yield of the benzyl ester **6** (expt 5), although the reaction needed several hours (h.p.l.c. analysis). Therefore, in order to trap the greatest amount of the carboxylate during the electrolysis procedure, the above approach was turned to benzyl bromide which is much more reactive

Table 1. Electrochemical data and product distribution in the electrocarboxylation-alkylation of 2-bromoisobutyramides **1a-d**.

Substrate	Expt	Potential[a] (V)	Charge[b] ($Fmol^{-1}$)	Alkylating reagent	Products, yield (%)[b] h.p.l.c.[c] **3**	**6**	^{1}H n.m.r.[c] **3**	**6**
1a	1[d]	- 1.1	2.03	MeI	29	71	30	70
	2[d]	- 1.1	1.99	MeI	23	77	24	76
	3	- 1.1	2.05	$PhCH_2Br$[f]	30	70	25	75
	4[e]	- 1.6	3.14	$PhCH_2Br$[f]	10	90	-	-
	5	- 1.1	1.95	$PhCH_2Cl$[f]	26	74	-	-
1b	6[d]	- 1.0	2.00	MeI	30	70	29	71
	7[d]	- 1.0	2.00	MeI	24	76	20	80
	8[e]	- 1.4	2.19	MeI	30	70	-	-
1c	9[d]	- 0.9	2.02	MeI	-	-	10	90
1d	10[g]	- 1.4	1.97	MeI	-	-	25	75

[a] All potentials are quoted against the saturated calomel electrode. [b] In some cases, coulometric data and yields were averaged from two or more electrolyses. [c] H.p.l.c. and ^{1}H n.m.r. yields were calculated from the electrolysed solution and the product mixture, respectively; the h.p.l.c. yields calculated before and after the elimination of the solvent and the electrolyte were identical. [d] The solvent-electrolyte system was carefully anhydrified by using activated alumina. [e] Platinum cathode. [f] Alkylating agent injected before the electrolysis procedure. [g] Preliminary experiment: the ester was not isolated but recognized on the basis of the ^{1}H n.m.r. spectrum.

towards the carboxylate. The reduction of benzyl bromide, however, is about 1 V easier than that of benzyl chloride.[9] In order to avoid the loss of an excess of charge for reducing also benzyl bromide, the macroelectrolysis of **1a** was carried out at the platinum electrode in the presence of the alkylating reagent in only two-fold amount (expt 4). As shown in Table 1, the result of the one-pot strategy is successful, even if no pre-treatment of the solvent-electrolyte system with activated alumina was done. Moreover, the concentration of the alkylating reagent can be kept somewhat lower than in the two-step synthesis. In fact, the carboxylate moving from the electrode surface is actually at a very low concentration owing to the dilution, and for most of the electrolysis time the molar ratio is more in favour of benzyl bromide than the stoicheiometry would suggest. Of course, the coulometry shows that a sensible fraction of charge is consumed in reducing benzyl bromide (3.14 instead of 2.0 $Fmol^{-1}$). As expected,[3] the ensuing electrocarboxylation produces tetrabutylammonium phenylacetate and the self-alkylation product, i.e. benzyl phenylacetate.

The two-step synthesis realized in most of the runs is comparable with the electrosyntheses of the diesters of malonic acid obtained in the presence of CO_2 either through electrocleavage of the C-NMe_3^+ function in an α-ammonium ester[10] or α-proton abstraction in ethyl phenylacetate by means of electrogenerated bases.[11] The one-pot strategy is feasible provided that the O-alkylating reagent is i) almost unreducible at the electrolysis potential and ii) unable to compete with carbon dioxide in front of the carbanion. Usually, electrocarboxylations of organic halides are suffering the problem that about half of the starting material acts as an alkylating reagent in front of the electrogenerated carboxylate,[2,3] a fact that severely limits possible applications. Sacrificial anodes overcome this problem through the formation of unreactive carboxylate salts in high yields.[12] In this respect, the electrocarboxylation of 2-bromoamides represents one of the very few examples in which the latter approach is unnecessary as no self-alkylation products were observed in the present research. On the other hand, the use of sacrificial anodes is unpractical

in this case as it reduces the nucleophilicity of the carboxylate in front of exogenous alkylating reagents. In fact, the esterification is to be preferred because the carboxylate or the ensuing acid obtained upon working up are suffering intrinsic instability. Therefore, it seems that the present approach is better suited when the electrosynthesis of malonic acid derivatives is envisaged.

As a conclusion from the present study, the rather acidic 2-bromoamides 1 are successfully carboxylated at the tertiary carbon, the electrochemical methodology allowing to obtain useful information on the reactivity of intermediates and a facile synthesis where carbon dioxide is used as an active co-reagent.

EXPERIMENTAL

Melting points were determined with a Reichert-Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C n.m.r. spectra were recorded on a Bruker AC 200 MHz spectrometer, using $CDCl_3$ or Me_2SO-d_6 as solvents; chemical shifts are in δ p.p.m. downfield from tetramethylsilane used as internal standard. Uncoupled ^{13}C chemical shifts are reported: the ^{1}H-^{13}C coupled spectra fitted the assignations and are not reported. Mass spectrometry was performed with a Varian CH7 high-resolution spectrometer. I.r. spectra were measured with a Perkin-Elmer 299 B spectrometer.

The electrolysed solutions were analyzed by h.p.l.c. using a Perkin-Elmer Series 4 liquid chromatograph, equipped with an LC-85 autocontrol u.v. detector and a Perkin-Elmer 3700 data station for chromatogram analysis. A 4.6 mm diameter, 15 cm length stainless steel column packed with ODS2, 5 µm mean particle size, was employed. A 5 cm pre-column was always used, all other specifications being as above. The eluting solution was 45% acetonitrile - 55% water. In expt 4, two of the products had almost the same retention time so that a 60% aceconitrile - 40% water mobile phase was used. Quantitative analysis was based on calibration curves constructed with solutions of authentic specimens.

Samples were purified until they gave a single spot in t.l.c., using 0.25 mm SiO_2 layers (Merck) and the mixture acetate:toluene (1:4). Column chromatography was performed using columns of SiO_2 (Merck, KG-60), with the same eluent.

Solvent, Electrolyte, and Electrophiles.

Acetonitrile (Merck, uvasol grade) was used as received. Tetrabutylammonium perchlorate was prepared by neutralizing the corresponding hydroxide (Fluka) with perchloric acid. The salt was recrystallized from water-ethanol and carefully dried under vacuum at 60° C. Methyl iodide (Merck), benzyl bromide (Merck), and benzyl chloride (Erba) were used as received. Carbon dioxide (99.998%) was supplied by SIAD.

Electrochemical Apparatus.

A conventional three-electrode cell was used and measurements were carried out in MeCN-0.1 M n-Bu_4NClO_4 at 25° C. In some instances, the anhydricity of the medium was kept at minimum values by repetitive cycling of the solvent-electrolyte solution through an Al_2O_3 column. Neutral alumina (Merck, activity grade I) was activated overnight at 350° C.

The preparation of the mercury microelectrode employed in voltammetric measurements has been described.[4] Controlled potential electrolyses were carried out at a stirred mercury-pool cathode (ca. 7 cm^2) and/or a platinum grid (ca. 20 cm^2). The counter-electrode (platinized platinum) and the reference electrode (Ag/AgCl) have been described.[13] Potential values are quoted against the saturated aqueous calomel electrode (s.c.e.).

All measurements were carried out with conventional instrumentation: PAR 173/179 potentiostat-digital coulometer, PAR 175 universal programmer, Nicolet 3091 digital oscilloscope, and Amel 863 X/Y recorder.

General Method for the Electrosynthesis of Ester-amides of 2,2-Dimethylmalonic Acid.

In controlled-potential electrolyses, the concentration of the 2-bromoisobutyramide was ca. 1×10^{-2} M and more than one addition was made after the first electrolysis in nearly all of the runs. The solution was always purged from oxygen by means of argon bubbling. Subsequently, carbon dioxide was bubbled into the solution till the end of the electrolysis. In all the electrolyses the limiting reduction current was allowed to decay to about 2% of the initial value, i.e. the electroreduction was quantitative as also supported by the analysis of the reaction mixture.

The macroscale reduction was carried out at a potential slightly negative with respect to the potential value of the first peak, the easiness of the reduction being **1c** > **1b** > **1a** > **1d**. At the platinum electrode the reduction requires more negative values. The alkylating reagent, i.e. MeI,

$PhCH_2Br$, or $PhCH_2Cl$, was added in seven- to ten-fold amount, unless otherwise stated, when the electrolysis was accomplished. In expt 4 and 5, $PhCH_2Br$ and $PhCH_2Cl$, respectively, were already present in the solution to be electrolysed (two- and eight-fold amount, respectively). In most of the runs, h.p.l.c. measurements were made during and/or at the end of the macroreduction as well as during the reaction with the alkylating reagent.

At the end of the esterification, the solvent (20-30 ml) was removed in rotavapor at 30° C. The residue was extracted with anhydrous ethyl ether, leaving the supporting electrolyte undissolved. The ethereal extract was dried ($MgSO_4$) and concentrated to yield the oily product mixture. The identification of the products was carried out through inspection of t.l.c. plates (u.v. light, iodine vapours) and ^1H n.m.r. spectra in comparison with authentic specimens. The major product, i.e. the malonamic esters **6**, were isolated by column chromatography and characterized by ^1H and ^{13}C n.m.r., i.r., m.p., mass spectrometry (M^+) and/or microanalysis.

Known Compounds.

The following compounds were prepared as described in the literature or electrosynthetized. Some unreported spectral data are given.

2-Bromo-2-methylpropananilide **1a**.[14]

2-Bromo-4'-chloro-2-methylpropananilide **1b**.[15]

2-Bromo-2-methyl-N-benzylpropanamide **1d**.[14]

2-Methylpropananilide **3a**;[14] ^{13}C n.m.r.: $\delta(CDCl_3)$ 19.60 (Me_2), 36.27 (CH), 120.20 ($C_{2'}$, $C_{6'}$), 124.05 ($C_{4'}$), 128.78 ($C_{3'}$, $C_{5'}$), 138.26 ($C_{1'}$), 176.23 (CO).

4'-Chloro-2-methylpropananilide **3b**:[16] ^1H n.m.r.: $\delta(CDCl_3)$ 1.20 (6H, d, Me_2), 2.50 (1H, sept, CH), 7.27 (4H, A_2B_2, C_6H_4); ^{13}C n.m.r.: $\delta(CDCl_3)$ 19.56 (Me_2), 36.50 (CH), 121.32 ($C_{2'}$, $C_{6'}$), 128.87 ($C_{3'}$, $C_{5'}$), 129.08 ($C_{4'}$), 136.68 ($C_{1'}$), 175.79 (CO).

2-Methyl-N-benzylpropanamide **3d**.[14]

3-Anilino-2,2-dimethyl-3-oxo-propanoic acid, methyl ester **6** (R = Ph, R'= Me). Expt 2: the electrolytic cell was charged with MeCN-0.1 M $n\text{-}Bu_4NClO_4$ (40 ml) and the solution was twice cycled through a column of activated alumina. Subsequently, a sample of 2-bromo-2-methylpropananilide **1a** (51.8 mg, 0.21 mmol) was added to the solution and electrolysed (Hg pool) at -1.1 V. At the end of the electrolysis, a second sample of **1a** (53.8 mg, 0.22 mmol) was introduced into the cell and the electrolysis was repeated as above. The electroreduction took 1.99 $Fmol^{-1}$. Methyl iodide (0.27 ml, 4.4 mmol) was injected into the cell. After 1 h, the solution was concentrated to dryness and extracted with dry diethyl ether (20 ml); the extract was dried and concentrated to yield an oily mixture whose ^1H n.m.r. spectrum showed the presence of the title ester **6** (76%) and the isobutyranilide **3a** (24%). The oil was fractionated by column chromatography. Compound **6** was obtained as colourless prisms, m.p. 78-79° C:[17] $\nu_{max.}(CDCl_3)$ 3340 (NH), 1710 (ester CO), 1670 cm^{-1} (amide CO). ^1H n.m.r.: $\delta(CDCl_3)$ 1.56 (6H, s, Me_2), 3.78 (3H, s, MeO), 7.3 (5H, m, Ph), 8.58 (1H, br s, NH). ^{13}C n.m.r.: $\delta(CDCl_3)$ 23.72 (Me_2), 50.66 ($\underline{C}Me_2$), 52.85 (MeO), 120.20 ($C_{2'}$, $C_{6'}$), 124.29 ($C_{4'}$), 128.83 ($C_{3'}$, $C_{5'}$), 138.02 ($C_{1'}$), 170.07 ($\underline{CO}_2$), 175.53 (CON).

3(4'-Chloroanilino)2,2-dimethyl-3-oxo-propanoic acid, methyl ester **6** (R = $p\text{-}C_6H_4Cl$, R'= Me).[17] Expt 7: same procedure as above. Two samples of 2-bromo-4'-chloro-2-methylpropananilide **1b** (74.4 mg, 0.27 mmol; 76.7 mg, 0.28 mmol) were electroreduced at -1.0 V with overall consumption of 2.00 $Fmol^{-1}$. The esterification was carried out with methyl iodide (0.34 ml, 5.5 mmol). After 1 h the solution was concentrated to dryness and the residue was extracted with ether (20 ml). Concentration gave an oil (105 mg) consisting of the title ester **6** and **3b**: ^1H n.m.r. yields were 80 and 20%, respectively. Compound **6** has the following ^1H n.m.r. spectrum: $\delta(CDCl_3)$ 1.56 (6H, s, Me_2), 3.79 (3H, s, MeO), 7.38 (4H, A_2B_2, C_6H_4), 8.77 (1H, s, NH).

New Compounds.

2-Bromo-4'-cyano-2-methylpropananilide **1c**. Following the procedure reported for analogues, a solution of 2-bromo-2-methyl-propanoyl bromide (6.9 g, 0.03 mol) in $CHCl_3$ (10 ml) was added under stirring during 20 min to a solution of p-aminobenzonitrile (3.54 g, 0.03 mol) and triethylamine (3.03 g, 0.03 mol) in $CHCl_3$ (18 ml), and stirring was continued for 20 h. The mixture was washed (water, 1 N HCl 5x40 ml, water, saturated aqueous $NaHCO_3$, water), dried on Na_2SO_4 and concentrated to dryness. The oil was triturated with light petroleum (b.p. 40-60° C) and the undissolved solid (5.8 g, 72%) was recrystallized from ethanol-water. Colourless prisms, m.p. 128-130° C; $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 2240 (CN), and 1700 cm^{-1} (CO). ^1H n.m.r.: $\delta(CDCl_3)$ 2.05 (6H, s, Me_2), 7.68 (4H, A_2B_2, C_6H_4), 8.68 (1H, s, NH); $\delta(Me_2SO\text{-}d_6)$ 2.01 (6H, s, Me_2), 7.86 (4H, A_2B_2, C_6H_4), 10.26 (1H, s, NH; exchange with D_2O takes more than 24 h). ^{13}C n.m.r.: $\delta(CDCl_3)$ 32.20 (Me_2), 61.95 ($\underline{C}Me_2$), 107.61 (CN), 119.83 ($C_{2'}$, $C_{6'}$), 133.20 ($C_{3'}$, $C_{5'}$), 141.51 ($C_{1'}$), 170.35 (CO)(Found C, 49.24; H, 4.14; N, 10.46; Br, 29.66. $C_{11}H_{11}BrN_2O$ requires C, 49.47; H, 4.12; N, 10.49; Br, 29.93%).

4'-Cyano-2-methylpropananilide **3c**. A solution of 2-methyl-propanoyl chloride (2.1 g, 0.02 mol) in $CHCl_3$ (10 ml) was added in 5 min under stirring to a solution of 4-amino-benzonitrile (2.4 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in $CHCl_3$ (45 ml). The mixture was stirred overnight, washed and dried as for compound **1c**, and concentrated to yield a solid (2.7 g, 73%) that was recrystallized from ethanol-water. Colourless prisms, m.p. 112-113° C; ν_{max} ($CHCl_3$) 3440 (NH), 2230 (CN), 1700 cm^{-1} (CO). ^1H n.m.r.: $\delta(CDCl_3)$ 1.26 (6H, d, Me_2), 2.57 (1H, sept, CH), 7.66 (4H, A_2B_2,

C_6H_4), 7.8 (1H, br s, NH; exchanges with D_2O in 4-5 h); δ (Me_2SO-d_6) 1.12 (6H, d, Me_2), 2.63 (1H, sept, CH), 7.78 (4H, degen. A_2B_2, C_6H_4), 10.29 (1H, s, NH; exchanges with D_2O in 3 min). ^{13}C n.m.r.: δ ($CDCl_3$) 19.48 (Me_2), 36.46 (CH), 106.15 ($C_{4'}$), 119.19 (CN), 119.78 ($C_{2'}$, $C_{6'}$), 133.16 ($C_{3'}$, $C_{5'}$), 142.86 ($C_{1'}$), 176.78 (CO)(Found C, 69.87; H, 6.34; N, 14.90. $C_{11}H_{12}N_2O$ requires C, 70.19; H, 6.43; N, 14.88%).

3-Anilino-2,2-dimethyl-3-oxo-propanoic acid, phenylmethyl ester **6** (R = Ph, R'= CH_2Ph). Expt 3: a sample of 2-bromo-2-methylpropananilide **1a** (48.9 mg, 0.20 mmol) dissolved in MeCN-0.1 M n-Bu_4NClO_4 (20 ml) was electrolysed (Hg pool) at -1.1 V. When the electrolysis was accomplished, a second sample (53.4 mg, 0.22 mmol) was added and the electrolysis was repeated as above. 2.05 $Fmol^{-1}$ were consumed. Benzyl bromide was added in eight-fold amount. Evaporation of MeCN gave an oil that was triturated with petroleum ether (4 x 10 ml) to remove benzyl bromide: the undissolved mixture was fractionally extracted with ethyl ether (5 x 10 ml) to yield 5 fractions of crude **6** (72 mg). The first fraction (34 mg) was purified through column chromatography to yield a pure sample; the other fractions contained **6** admixed with **3a**. The benzyl ester **6** was obtained as colourless prisms, m.p. 42-43° C; $\nu_{max.}$ (KBr) 3300 (NH), 1730 (ester CO), 1650 and 1600 cm^{-1} (amide CO); ^1H n.m.r.: δ ($CDCl_3$) 1.57 (6H, s, Me_2), 5.22 (2H, s, CH_2), 7.34 (5H, s, Ph), 7.3 (5H, m, Ph), 8.38 (1H, s, NH). Mass spectrum m/z 297 (M^+). (Found C, 72.43; H, 6.50; N, 4.76. $C_{18}H_{19}NO_3$ requires C, 72.72; H, 6.44; N, 4.71%).

3(4'-Cyanoanilino)2,2-dimethyl-3-oxo-propanoic acid, methyl ester **6** (R = p-C_6H_4CN, R'= Me). Expt 9: 2-bromo-4'-cyano-2-methylpropananilide **1c** was electrolysed at -0.9 V in two runs (75.2 mg, 0.28 mmol; 65.4 mg, 0.24 mmol) with overall consumption of 2.02 $Fmol^{-1}$. Methyl iodide (0.23 ml, 3.68 mmol) was subsequently added. The solvent was evaporated and the residue was extracted with ethyl ether to yield a crude oil (111 mg). Column cromatography gave **6** as colourless prisms, m.p. 82-83° C; $\nu_{max.}$ ($CDCl_3$) 3330 (NH), 1720 (ester CO), 1670 cm^{-1} (amide CO); ^1H n.m.r.: δ ($CDCl_3$) 1.57 (6H, s, Me_2), 3.81 (3H, s, MeO), 7.66 (4H, A_2B_2, C_6H_4), 9.20 (1H, br s, NH). Mass spectrum m/z 246 (M^+).

2,2-Dimethyl-3-oxo-3-phenylmethylamino-propanoic acid, methyl ester **6** (R = CH_2Ph, R'= Me). Expt 10: 2-bromo-2-methyl-N-benzylpropanamide **1d** (103.2 mg, 0.40 mmol) was electrolysed at -1.4 V with consumption of 1.97 $Fmol^{-1}$. Methyl iodide was added in seven-fold amount. The solution was treated as above to yield a crude oil (67 mg). The ^1H n.m.r. spectrum of the oil led to the following product distribution. 2,2-Dimethyl-3-oxo-3-phenylmethylamino-propanoic acid, methyl ester **6** (75%): ^1H n.m.r., δ ($CDCl_3$) 1.48 (6H, s, Me_2), 3.72 (3H, s, MeO), 4.44 (2H, d, CH_2), 6.75 (1H, br s, NH), 7.30 (5H, s, Ph); N-benzylisobutyramide **3d** (25%).

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