Formation of Optically Active Amino-acids. Part VII.[1] An Electrochemical Synthesis of Dichlorobutyrines

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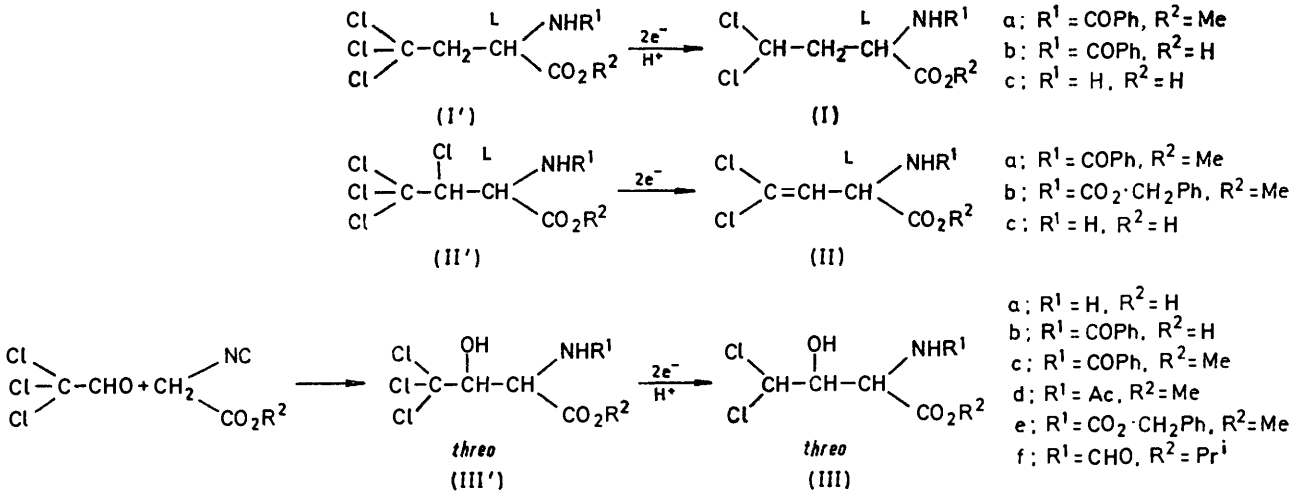
γγ-Dichloro-L-butyrines (armentomycin and its derivatives) have been synthesized electrochemically from γγγ-trichloro-L-butyrines without racemization. This method has been extended to a synthesis of βγ-unsaturated γγ-dichloro-L-butyrines and *threo*-γγ-dichloro-β-hydroxy-DL-butyrines, which are interesting as armentomycin analogues.

HALOGENO-α-AMINO-ACIDS [2] frequently act as antagonists of the naturally occurring α-amino-acids. Recently, chloro-α-amino-acids have been isolated from natural sources;[3] of these, γγ-dichloro-L-butyrine (armentomycin;[4] L-2-amino-4,4-dichlorobutanoic acid) is noteworthy because it inhibits the growth of micro-organisms such as *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Proteus mirabilis*, *etc.* However, this dichlorobutyrine skeleton has not hitherto been synthesized, probably because of its low stability, although syntheses of trichloro-[1a,5] and trifluoro-butyrines [6] have been reported.

We describe here a new electrochemical synthesis of γγ-dichloro-L-butyrines (I), βγ-unsaturated γγ-dichloro-L-butyrines (II), and *threo*-γγ-dichloro-β-hydroxy-DL-butyrines (III);† compounds (II) and (III) are of interest as armentomycin analogues.

Compounds (I) and (II) were synthesized by selective



SCHEME

reduction‡ of one C–Cl bond of a γγγ-trichloro-L-butyrine (I') and of two C–Cl bonds of a βγγγ-tetrachloro-L-butyrine (II'), respectively; the starting materials were prepared by chlorinolysis of L-methionine derivatives.[1a,5a] Compounds (III) were prepared without epimerization from *threo*-γγγ-trichloro-β-hydroxy-DL-butyrines (III').

γγ-Dichloro-L-butyrines (I).—A polarogram of *N*-benzoyl-γγγ-trichloro-L-butyrine methyl ester (I'a) in

† For convenience, we define the *threo*-isomers as those in which the disposition of the dichloromethyl group is the same as that of the methyl group in *threo*-threonine.

‡ The macroelectrolytic and polarographic reductions of *gem*- and *vic*-dihalides have been studied extensively to elucidate the mechanism of the electrode reactions.[7]

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[2] (*a*) 'Handbook of Biochemistry,' ed. R. C. Weast *et al.*, 1970, B-38; (*b*) H. Gershon and M. W. McNeil, *J. Medicin. Chem.*, 1973, **16**, 1407; (*c*) J. Kollonitsch, L. Barash, F. M. Kahan, and H. Kpopp, *Nature*, 1973, **243**, 346.

[3] For example, (*a*) S. Hatanaka, S. Kaneko, Y. Niimura, F. Kinoshita, and G. Soma, *Tetrahedron Letters*, 1974, 3931; (*b*) T. Shiba, Y. Mukunoki, and H. Akiyama, *ibid.*, p. 3085; (*c*) D. G. Martin, C. G. Chidester, S. A. Mizsak, D. J. Duchamp, L. Baczynkyj, W. C. Krueger, R. J. Wnuk, and P. A. Meulman, *J. Antibiotics*, 1975, **28**, 91.

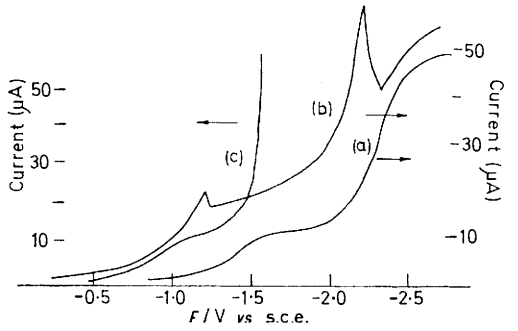
[4] A. D. Argoudelis, R. R. Herr, D. J. Mason, I. R. Pyke, and J. F. Zieserl, *Biochemistry*, 1967, **6**, 165.

[5] (*a*) Y. Urabe, T. Okawara, K. Okumura, M. Miyoshi, and K. Matsumoto, *Synthesis*, 1974, 440; (*b*) Y. Urabe, M. Miyoshi, and K. Matsumoto, *Agric. and Biol. Chem.* (*Japan*), 1975, **39**, 1085; (*c*) K. Matsumoto, Y. Urabe, Y. Ozaki, T. Iwasaki, and M. Miyoshi, *ibid.*, p. 1869.

[6] (*a*) H. M. Walborsky, M. Baum, and D. F. Loncrini, *J. Amer. Chem. Soc.*, 1955, **77**, 3637; (*b*) R. M. Babb and F. W. Bollinger, *J. Org. Chem.*, 1970, **35**, 1438.

[7] For reviews see (*a*) C. M. Bann and K. K. Barnes, 'Electrochemical Reactions in Nonaqueous Systems,' Dekker, New York, 1970, ch. 7, p. 201; (*b*) L. Eberson and H. Schafer, *Topics Current Chem.*, 1971, 131; (*c*) M. R. Rifi, in 'Organic Electrochemistry,' ed. M. M. Baizer, Dekker, New York, 1973, ch. 6, p. 279.

75% dioxan–0.1M-tetraethylammonium chloride is shown in the Figure. The half-wave potential of the first



Polarograms of compounds (I'a), (II'b), and (III'a) at 17 °C: (a) 1.9×10^{-3}M- (I'a) in 75% dioxan–0.1M-tetraethylammonium chloride; (b) 2.5×10^{-3}M- (II'b) in 75% dioxan–0.1M-tetrabutylammonium bromide; (c) 2.4×10^{-3}M- (III'a) in Clark–Lubs buffer (pH 1.94)

polarographic reduction wave, which shows an irreversible two-electron * transfer, was observed at −1.36 V *vs.* s.c.e. In dimethylformamide–tetrabutylammonium bromide, the half-wave potential was shifted to a more cathodic value (−1.60 V *vs.* s.c.e.). *N*-Benzoyl-γγγ-trichloro-L-butyrine (I'b) in 75% dioxan–0.1M-tetraethylammonium chloride and γγγ-trichloro-L-butyrine (I'c) in Clark–Lubs buffer (pH 1.94) showed half-wave potentials at −1.45 and −0.88 V *vs.* s.c.e., respectively. The first polarographic half-wave potentials of these compounds are summarized in the third column of Table 1. The second waves † appeared at potentials between −2.0 and −2.3 V *vs.* s.c.e.

Macroelectrolyses of these compounds were carried out by the controlled potential method at cathodic potentials near the first polarographic reduction waves. The conditions are summarized in Table 1. The electrolysis of compound (I'a) in 75% dioxan–tetraethylammonium chloride at the cathodic potential of −1.35 V *vs.* s.c.e. (mercury pool cathode) caused selective reduction of one of the three C–Cl bonds to afford *N*-benzoyl-γγ-dichloro-L-butyrine methyl ester (Ia) in 46% yield. The use of methanolic 0.01N-hydrochloric acid instead of the above catholyte increased the yield to 92%. Compound (I'b), electrolysed at −1.45 V *vs.* s.c.e., gave *N*-benzoyl-γγ-dichloro-L-butyrine (Ib) in 52% yield. The lower yield in 75% dioxan–tetraethylammonium chloride is presumably due to decomposition of the product by the cathodic solution, which gradually becomes alkaline during the electrolysis. Therefore, the pH of the cathodic solution should be maintained below 7 during the electrolysis by addition of acetic acid.

The dichloro-products synthesized from compounds (I'a and b) were dehalogenated by hydrogenation over palladium–charcoal. It was confirmed by comparing the specific rotations of the products with those of authentic specimens that optical activity was retained during the electrolyses.

The electrolysis of compound (I'a) in the non-aqueous catholyte of dimethylformamide–tetrabutylammonium bromide afforded only the dichloro-product; no dimer was detected. This indicates that compound (I'a) is reduced *via* a two-electron transfer to give a carbanion which is basic enough to abstract a proton from the supporting electrolyte and/or the solvent.[8]

In the case of γγγ-trichloro-L-butyrine (I'c), aqueous 0.01N-hydrochloric acid was used as the catholyte. Electrolysis at −1.30 V *vs.* s.c.e. gave γγ-dichloro-L-butyrine (armentomycin) (Ic) in 98% yield.[1b]

TABLE 1

Electrolysis conditions

		Polarography [a]	Macroelectrolyses				
					Cathode Potential		Yield
Run	Compd.	$E_{\frac{1}{2}}$/ V *vs.* s.c.e.	Solvent	Electrolyte	(V *vs.* s.c.e.)	Product	(%)
1	(I'a)	−1.36	75% Dioxan [b]	TEA Cl [c]	−1.35	(Ia)	46
2	(I'a)	*d*	Dioxan–MeOH (1 : 3)	Conc. HCl	−1.20	(Ia)	92
3	(I'a)	−1.60	Me_2N·CHO	TBA Br [c]	−1.60	(Ia)	63
4	(I'b)	−1.45	75% Dioxan	TEA Cl	−1.45	(Ib)	52
5	(I'c)	−0.88	aq. 0.01N-HCl	HCl	−1.30	(Ic)	98
6	(II'a)	−1.05	75% Dioxan	TBA Br	−1.20	(IIa)	53
7	(II'a)	*d*	MeOH–H_2O (3 : 1)	Conc. HCl [g]	−0.95	(IIa)	87
8	(II'b)	−1.22 [h]	MeOH–H_2O (3 : 1)	Conc. HCl [g]	−1.22	(IIb)	92
9	(III'a)	−0.90 [f]	aq. 0.01N-HCl		−1.35	(IIIa)	95
10	(III'b)	−1.63	75% Dioxan	TEA Cl	−1.55	(IIIb)	95
11	(III'c)	−1.43	75% Dioxan	TEA Cl	−1.45	(IIIc)	92
12	(III'd)	−1.52	75% Dioxan	TEA Cl	−1.55	(IIId)	89
13	(III'e)	−1.50	75% Dioxan	TEA Cl	−1.45	(IIIe)	90
14	(III'f)	−1.42	75% Dioxan	TEA Cl	−1.40	(IIIf)	87

In runs 10—14 cathodic solutions were neutralized with acetic acid during the electrolyses.

[a] The polarograms were measured in the same solvent–supporting electrolyte systems as used for macroelectrolyses. The half-wave potentials ($E_{\frac{1}{2}}$) are those of the first polarographic reduction waves. [b] 25% H_2O. [c] Tetraethylammonium chloride. [d] Did not show a clear limiting current. [e] Tetrabutylammonium bromide. [f] Measured in Clark–Lubs buffer (pH 1.94). [g] 0.6 ml of 12N-HCl in 80 ml of solvent. [h] Measured in 75% dioxan–0.1M-tetraethylammonium chloride.

* *n* Values were determined by microcoulometry.

† In the polarogram of compound (I'a), a hydrogen wave due to the carboxylic acid was observed at −1.8 V *vs.* s.c.e. The cathodic limit of the polarographic measurement in Clark–Lubs buffer (pH 1.94) was −1.4 V *vs.* s.c.e.

[8] (*a*) S. Warzonek, E. W. Balaha, R. Berkey, and M. E. Runner, *J. Electrochem. Soc.*, 1967, **107**, 537; (*b*) A. J. Fry and R. G. Reed, *J. Amer. Chem. Soc.*, 1969, **91**, 6488.

βγ-Unsaturated γγ-Dichloro-L-butyrines (II).—A polarogram of *N*-benzyloxycarbonyl-βγγγ-tetrachloro-L-butyrine methyl ester (II'b) in 75% dioxan–tetrabutylammonium bromide is shown in the Figure. The first polarographic half-wave potential was observed at −1.22 V *vs.* s.c.e. That of the *N*-benzoyl analogue (II'a) is −1.22 V *vs.* s.c.e. The second polarographic waves of these compounds appeared between −1.9 and −2.3 V *vs.* s.c.e. The macroelectrolyses were carried out at the first polarographic reduction waves. The conditions are given in Table 1.

The *N*-benzoyl-derivative (II'a) gave the βγ-unsaturated γγ-dichloro-L-butyrine (IIa) (53%), identified from its mass and n.m.r. spectra and elemental analysis. The product of electrolysis with methanolic hydrogen chloride instead of 75% dioxan–tetraethylammonium chloride as catholyte was the same, obtained in 87% yield. The *N*-benzyloxycarbonyl derivative (II'b) afforded the corresponding olefinic compound (IIb). In the above reactions, trichloro-products resulting from cleavage of one C–Cl bond were not formed, even in a strongly protic solvent such as methanolic hydrogen chloride or methanolic sulphuric acid. This suggests that olefin formation occurs *via* concerted dehalogenation involving vicinal chlorine atoms with a two-electron transfer, but not *via* a carbanionic intermediate generated by a two-electron transfer to one C–Cl bond of the tetrachloro-compound.[9]

Hydrolysis of compound (IIb) with 6N-hydrochloric acid gave the optically pure βγ-unsaturated γγ-dichloro-L-butyrine (IIc).[1b]

threo-*γγ-Dichloro-β-hydroxy-DL-butyrines* (III).—In biological systems *threo*-β-hydroxy-amino-acids sometimes play a more important role than the *erythro*-isomers. However, it is more difficult to synthesize *threo*-isomers stereoselectively.

It has already been reported[1a,5] that *threo*-γγγ-trichloro-β-hydroxybutyrines are obtained with complete stereoselectivity *via* an oxazoline by the reaction of chloral with isocyano-acetates. The above electrochemical method was applied to these products to synthesize *threo*-γγ-dichloro-β-hydroxy-DL-butyrines.

The first polarographic half-wave potential of γγγ-trichlorothreonine (III'a) in Clark–Lubs buffer (pH 1.94) appeared at −0.90 V *vs.* s.c.e. (see Figure). The derivatives (III'b—f) showed half-wave potentials near −1.5 V *vs.* s.c.e. in 75% dioxan–tetraethylammonium chloride (Table 1). The macroelectrolyses were carried out by a procedure similar to that described in the previous sections. The conditions are summarized in Table 1. The cathodic solutions were neutralized with acetic acid during the electrolyses, because the products (IIIa—f) are unstable under basic conditions. The reactions proceeded easily with good current efficiencies and the yields were 85—95%.

The dichloro-product (IIIe) possesses a stronger growth inhibitory activity than armentomycin against *Pseudomonas aeruginosa*.

EXPERIMENTAL

M.p.s were measured with a Yamato apparatus. I.r. spectra were recorded with a Shimadzu IR-27G spectrophotometer, and n.m.r. spectra with a Hitachi–Perkin-Elmer R-20A high resolution spectrometer (tetramethylsilane as internal standard). Optical rotations were measured (2 cm cell) with a JASCO DIP-4 automatic polarimeter. R_F Values for paper partition chromatography were obtained with Toyo Filter No. 51. Polarograms were taken at 17 °C by use of three electrodes with a Yanako P-8 polarograph attached to a Yanako 101 recorder. The dropping mercury electrode had the following characteristics on open circuit: at h 30.0 cm, t 9.54 s drop^{-1}, and m 2.28 mg s^{-1} in 75% dioxan–0.1M-tetraethylammonium chloride saturated with nitrogen; at h 80.0 cm, t 3.4 s drop^{-1}, and m 0.816 mg s^{-1} in Clark–Lubs buffer (pH 1.94). The macroelectrolyses were carried out by use of a Hokuto Potentio-Galvanostat PGS-2500 (2.5 A; 55 V). The other parts of the electrolysis apparatus were as described before[10] except that the area of mercury pool cathode was 37 cm^2.

Reagents.—Dimethylformamide was dried over sodium sulphate for 3 days and distilled (b.p. 152—153 °C). Dioxan was dried over sodium flakes and distilled after refluxing with sodium (b.p. 100.5—101 °C). Tetraethylammonium chloride was dried over phosphorus pentaoxide under reduced pressure for 3 days. Tetrabutylammonium bromide was recrystallized twice from ethyl acetate and dried.

Starting Materials.—Compounds (I'), (II'), and (III') were synthesized as described previously.[1a,5] Compound (I'b) was prepared as follows: compound (I'a) (0.2 g) suspended in N-sodium hydroxide (4 ml) was stirred at room temperature for 12 h. The solution was acidified (to Congo Red) with 6N-hydrochloric acid and shaken with ethyl acetate. The ethyl acetate layer was washed with water, dried, and evaporated to dryness to give crystals. Recrystallization from ethanol–water afforded *N-benzoyl-γγγ-trichloro-L-butyrine* (I'b) (0.16 g, 85%), m.p. 196—197 °C (decomp.); δ[$(CD_3)_2SO$] 9.01 (1 H, d, NH), 7.45—7.75 (5 H, m, aromatic), 4.90 (1 H, m, CH), and 3.45 (2 H, d, CH_2) (Found: C, 42.7; H, 3.45; Cl, 33.85; N, 4.45. $C_{11}H_{10}Cl_3NO_3$ requires C, 42.55; H, 3.25; Cl, 34.25; N, 4.5%).

General Electrolysis Procedure.—The electrolysis cell, thermometer, stirrer, *etc.*, which had been oven-dried for 6 h, were quickly assembled in a water-bath under dry nitrogen. The saturated calomel electrode was fixed 1 mm above the mercury pool cathode. Then, the catholyte was put in the cathodic compartment, while the anolyte (same solvent–supporting electrolyte composition) was placed in the anodic compartment so as to make its height identical with that of the catholyte. Dried nitrogen was bubbled through the catholyte for at least 15 min before electrolysis. Pre-electrolysis procedure was always employed to remove impurities. The other conditions are listed in Table 1. The substrate was added in portions to the catholyte to maintain a current of 300—600 mA. More electrolyte was added periodically to the anolyte to maintain its level. In the use of 75% dioxan–tetraethylammonium chloride (runs 10—14 in Table 1), acetic acid was added dropwise during the electrolysis to keep the pH of the catholyte at 6—7.

A. F. Fry, 'Synthetic Organic Electrochemistry,' Harper and Row, New York, 1972, p. 180.

[10] T. Iwasaki and K. Harada, *J.C.S. Chem. Comm.*, 1974, 338.

Detailed Procedures of Representive Runs.—Preparation of N-benzoyl-γγ-dichloro-L-butyrine methyl ester (Ia) (i) (*run* 1). The electrolysis was discontinued when the current reached 50 mA, and acetic acid (0.5 ml) was added to the catholyte. The catholyte was evaporated to dryness *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with water, dried ($MgSO_4$), and evaporated. The resulting crystals were recrystallized from ethyl acetate–n-hexane to afford the *product* (Ia) (46%), $\nu_{max.}$ (Nujol) 3 300, 1 735, and 1 635 cm^{-1}; $\delta(CDCl_3)$ 7.35—7.90 (5 H, m, aromatic), 7.1 (1 H, d, NH), 5.90 (1 H) t, CHCl), 4.99 (1 H, m, CH·NH), and 3.80 (3 H, s, OMe) (see Table 2).

TABLE 2

Characterisation of electrolysis products

Compd.	M.p. (°C)	Optical rotation	Formula	Analysis (%) [a] C	H	N	Cl
(Ia)	103—104 (decomp.)	$[\alpha]_D^{27}$ −46.4 (*c* 0.55 in MeOH)	$C_{12}H_{13}Cl_2O_3$	49.6	4.5	4.8	24.4
				49.4	4.45	4.7	24.6
(Ib)	128—130	$[\alpha]_D^{27}$ 34.6 (*c* 0.71 in MeOH)	$C_{11}H_{11}Cl_2NO_3$	47.85	4.0	5.05	25.7
				47.75	4.15	5.1	25.4
(IIa)	118	$[\alpha]_D^{23}$ −9.5 (*c* 1.0 in MeOH)	$C_{12}H_{11}Cl_2O_3N$	50.0	3.8	4.85	24.65
				50.2	3.8	4.8	24.8
(IIIa)	148 (decomp.)		$C_4H_7NO_3Cl_2$	25.55	3.75	7.45	37.7
				25.85	3.9	7.3	37.5
(IIIb)	126—127		$C_{11}H_{11}NO_4Cl_2$	45.25	3.8	4.8	24.25
				45.5	3.8	4.8	24.3
(IIIc)	107—109		$C_{12}H_{13}NO_4Cl_2$	47.1	4.3	4.6	23.15
				47.45	4.45	4.45	23.25
(IIId)	147—149		$C_7H_{11}NO_4Cl_2$	34.35	4.55	5.75	29.05
				34.4	4.6	5.7	29.35
(IIIe)	130—131		$C_{13}H_{15}NO_5Cl_2$	46.45	4.5	4.15	21.1
				46.25	4.75	4.3	21.45
(IIIf)	102—104		$C_8H_{13}NO_4Cl_2$	37.35	5.1	4.45	27.5
				37.1	5.15	4.65	27.7

[a] Upper line 'required'; lower line 'found'.

(ii) (*run* 2). After the electrolysis was over, the catholyte was evaporated to dryness *in vacuo*. The resulting crystals were recrystallized from ethyl acetate–n-hexane to give the compound (Ia) (92%), identical with that obtained in run 1.

Preparation of N-benzoyl-γγ-dichloro-L-butyrine (Ib) (*run* 4). The procedure after the electrolysis was the same as that in run 1. *Compound* (Ib) (52%) showed $\nu_{max.}$ (Nujol) 3 400, 1 745, and 1 640 cm^{-1}; $\delta[(CD_3)_2SO]$ 8.79 (1 H, d, NH), 7.4—8.05 (5 H, m, aromatic), 6.28 (1 H, t, CHCl), 4.71 (1 H, m, CH), and 2.77 (2 H, q, CH_2).

Preparation of armentomycin (Ic) (*run* 5). The experimental procedure has already been reported.[1b]

Preparation of methyl 2-benzamido-4,4-dichlorobut-3-enoate (IIa) (*run* 7). The electrolysis was carried out in 75% methanol (80 ml) containing 12N-hydrochloric acid (0.6 ml) at −0.95 V *vs.* s.c.e. The cathodic solution was evaporated to afford *compound* (IIa) (87%), $\nu_{max.}$ (Nujol) 3 300, 1 743, 1 635, and 1 605 cm^{-1}; $\delta(CDCl_3)$ 7.30—7.95 (5 H, m, aromatic), 7.0br (1 H, d, *J* 6.5 Hz, NH), 6.02 (1 H, d, *J* 9.0 Hz, C=CH), 5.5 (1 H, q, *J* 9.0 and 6.5 Hz, CH), and 3.81 (3 H, s, CH_3).

Preparation of γγ-dichlorothreonine (IIIa) (*run* 9). The procedure after the electrolysis was the same as that described in run 5. The *product* showed $\delta(CF_3{\cdot}CO_2D{-}D_2O)$ 6.13 (1 H, d, *J* 3.4 Hz), and 4.70—4.91 (2 H, m), and R_F 0.46 in paper chromatography (Shaw–Fox solvent [11]). It was converted into *threo*-threonine by hydrogenation over palladium–charcoal in the presence of 2 mol. equiv. of sodium hydrogen carbonate. No *allo*-threonine was observed.

Preparation of compounds (IIIb—f). The procedures after the electrolyses were the same as that in run 1. M.p.s and elemental analyses are given in Table 2.

We thank Drs. T. Takayanagi, I. Chibata, and M. Matsuoka for encouragement and interest.

[5/1827 *Received*, 22*nd September*, 1975]

[11] K. N. F. Shaw and S. W. Fox, *J. Amer. Chem. Soc.*, 1953, **75**, 3421.