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A NEW SYNTHESIS OF ARMENTOMYCIN AND ITS ANALOG[1]

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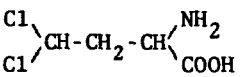
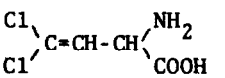
Halogenoamino acids[2a-b] are well-known to be strong antibacterial agents in both of the free and the combined states.[3a-c] Of these amino acids, Armentomycin (L-2-amino-4,4-dichlorobutanoic acid) [I] which was isolated from the culture broth of *Streptomyces armentosus var. armentosus*[4a-b] is particularly noteworthy because it inhibits the growth of several microorganisms such as *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Proteus mirabilis*, etc.. However, a chemical synthesis of Armentomycin has not yet been achieved.

In the previous papers from this laboratory,[5a-b] we have reported that optically active L-2-amino-4,4,4-trichlorobutanoic acid [III], its derivatives, and L-2-amino-3,4,4,4-tetrachlorobutanoic acid derivative [IV] were synthesized by the chlorinolysis of L-methionine derivative with molecular chlorine. Although a selective reduction of one C-Cl bond of compound [III] and compound [IV] would lead directly to Armentomycin and its analog, such a technique could hardly be found in ordinary chemical methods.[6]

The present paper describes an electrochemical synthesis of Armentomycin through selective reduction of the one C-Cl bond of compound [III]. This method was extended to a synthesis of the Armentomycin analog (L-2-amino-4,4-dichloro-3-butenoic acid) [II] which would possess a similar antibacterial activity.



[I]



[II]

The reduction wave of the polarogram of compound [III] at pH 1.94 appeared at the half-wave potential of -0.88 V. vs. S.C.E.. This wave showed an irreversible two-electrons wave.[7] The whole polarogram pattern is shown in Fig..

The macroelectrolysis was carried out by controlled potential electrolysis using a three-compartments cell[8] at the cathodic potential of the first polarographic reduction wave in which only the first wave was reduced but not the more cathodic waves.

Compound [III] (400 mg) was electrolyzed in 50 ml of 0.01 N HCl at the

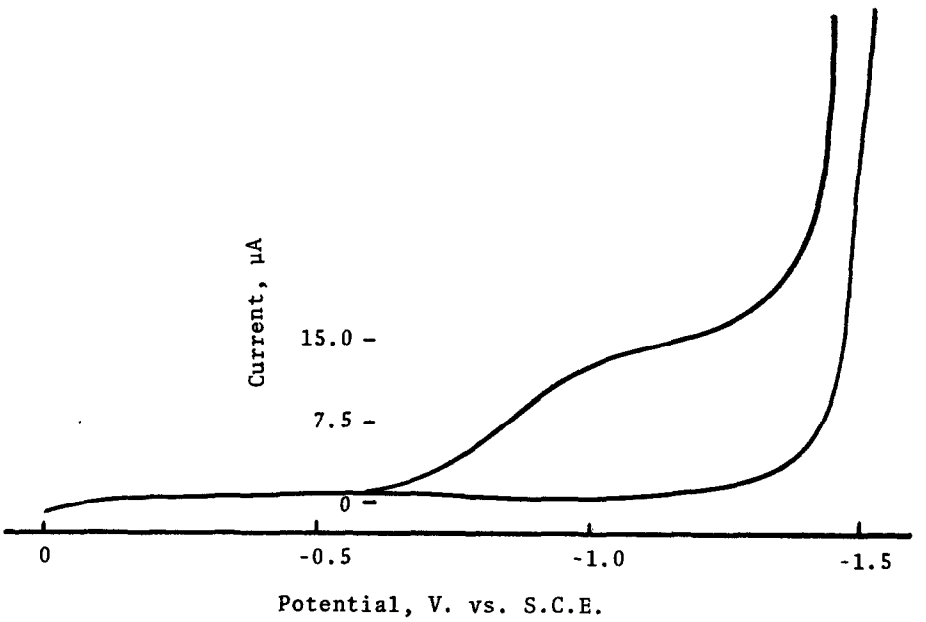
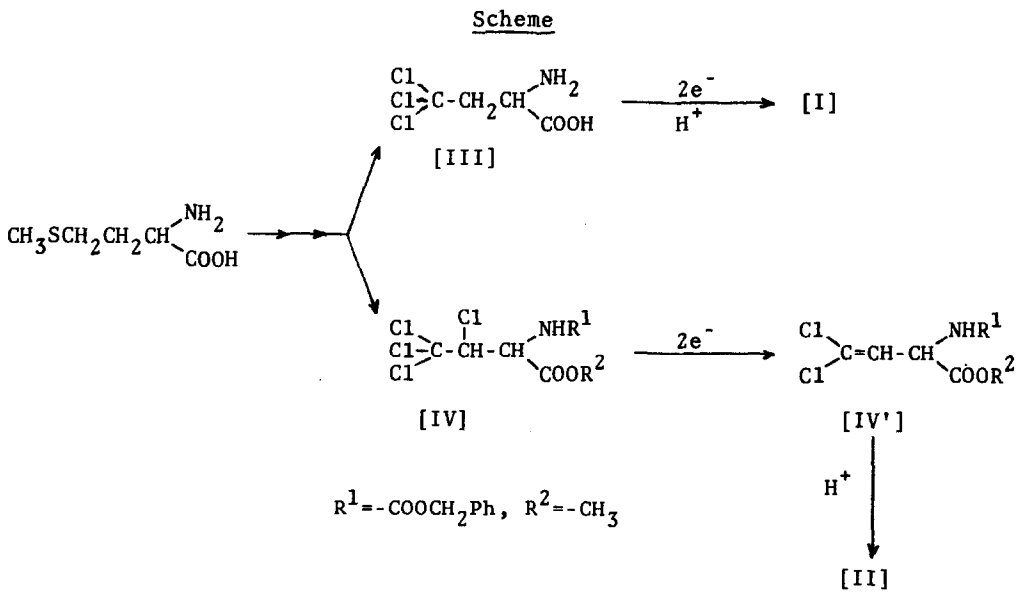


Fig. Polarogram of L-2-amino-4,4,4-trichlorobutanoic acid [III] in Clark-Lubs buffer (pH 1.94) at 17°C. h=80 cm, t=3.4 sec/a drop, m=2.28 mg/sec (open circuit). Curve a: compound [III], 2.4 x 10^{-3}M; Curve b: base line.

Scheme



cathodic potential of -1.30 V. vs. S.C.E. until the electrolysis current (300-400 mA) reached to the back current (70 mA). The catholyte was evaporated to dryness under reduced pressure below 45°C to give colorless crystals of Armentomycin hydrochloride in 98% yield (390 mg). The hydrochloride was dissolved in 10 ml of distilled water, and the solution was passed through Amberlite IR-45 (OH^- form, 1.0 x 10 cm). The column was further washed with distilled water, and the washings were evaporated to dryness under reduced pressure below 45°C to afford colorless crystals of Armentomycin in 86% yield (calculated from [III]) (280 mg). The crystals decompose at 153°C. IR and NMR spectra were identical with those reported by A. D. Argoudelis *et al.*.[4a-b] The elemental analysis was in good agreement with that calculated for Armentomycin. The specific rotation, $[\alpha]_D^{25}$ +25.7° (c=0.7 aqueous HCl, pH 1.0), was almost the same value as that[9] of Armentomycin.

In order to obtain the Armentomycin analog, methyl L-2-N-benzyloxycarbonyl-amino-3,4,4,4-tetrachlorobutanoate [V][10] (400 mg) was electrolyzed. The electrolysis was carried out in 80 ml of 75% aqueous methanol containing 0.6 ml of 12 N HCl at -1.22 V. vs. S.C.E. to afford compound [IV'] in 92% yield (300 mg). Pure crystals melt at 121-2°C. Elemental analysis, found: C, 53.25; H, 4.18; N, 4.52; Cl, 22.46. $C_{13}H_{13}O_4NCl_2$ requires: C, 53.14; H, 4.09; N, 4.40; Cl, 22.33. NMR ($CDCl_3$) δ 7.35 (s, 5H, arom), 5.90 (d, 1H, -C=C-H, J=8.2 Hz), 5.60 (broad, 1H, NH), 5.19 (d, 1H, CH, J=8.2 Hz), 5.12 (s, 2H, CH_2), 3.77 (s, 3H, CH_3). IR (nujol) 3340, 1748, 1682, 1632 cm^{-1}. The mass spectrum showed M^+ ion peak at m/e = 317 and the isotope peaks of chlorine atoms consisted of $M^+ + 2$ and $M^+ + 4$. The specific rotation, $[\alpha]_D^{26}$, showed -11.85° (c=0.46, MeOH). The hydrogenation of the olefinic compound [IV'] was carried out using 5% palladium on charcoal to afford methyl L-2-aminobutanoate hydrochloride which was identical with that of an authentic specimen in the specific rotation.

The olefinic compound [IV'] (300 mg) was further hydrolyzed with 6N HCl at 85°C for 4 hrs. The reaction mixture was evaporated to dryness under reduced pressure below 45°C. The residue was treated with Amberlite IR-45 (OH^- form, 1.5 x 10 cm) as above, and the eluate was evaporated to dryness under reduced pressure below 40°C. The resulting crystals were recrystallized from water-acetone to afford compound [II] in 69% yield (110 mg). Pure crystals decompose at 142-154°C. Elemental analysis, found: C, 28.10; H, 2.82; N, 8.29; Cl, 41.90. $C_3H_4O_2NCl_2$ requires: C, 28.25; H, 2.94; N, 8.24; Cl, 41.76. NMR ($CF_3COOD + D_2O$) δ 6.18 (d, 1H, -C=C-H, J=9.5 Hz), 5.71 (d, 1H, CH, J=9.5 Hz). The specific rotation, $[\alpha]_D^{25}$, showed + 13.39° (c=0.45, 0.1 N HCl).

It may be concluded that this electrochemical method will be useful for the synthesis of Armentomycin and its optically active analog from L-trichloro- and L-tetrachloroamino acid prepared by the chlorinolysis of L-methionine derivative.

The authors thank Drs. T. Takayanagi and I. Chibata for their encouragement throughout this study.

References and Footnotes

1. Formation of Optically Active Amino Acids. 7. Part 6: see reference 5b.
2. a) Halogenoamino acids are listed in the Table of "Handbook of Biochemistry" Edited by R. C. Weast *et al.*, B-38 (1970); b) Most recently, an interesting halogenoamino acid was reported. S. Hatanaka, S. Kaneko, Y. Niimura, F. Kinoshita, and G. Soma, Tetrahedron Lett., 3931 (1974).
3. For example, a) H. Gershon and M. W. McNeil, J. Med. Chem., 16 1407 (1973); b) J. Kollonitsch, L. Barash, F. M. Kahan, and H. Kropp, Nature, 243 346 (1973); c) T. Shiba, Y. Mukunoki, and H. Akiyama, Tetrahedron Lett., 3085 (1974).
4. a) A. D. Argoudelis, R. R. Harr, D. J. Mason, I. R. Pyke, and J. F. Sieserl, Biochemistry, 6 165 (1967); b) A. D. Argoudelis, R. R. Herr, and D. J. Mason, Japanese Patent, S46-15676 (1971).
5. a) Y. Urabe, T. Okawara, K. Okumura, M. Miyoshi, and K. Matsumoto, Synthesis, 440 (1974); b) Y. Urabe, M. Miyoshi, and K. Matsumoto, Agr. Biol. Chem., submitted for publication.
6. Catalytic hydrogenolysis of L-2-amino-4,4,4-trichlorobutanoic acid gave a mixture of the starting material, 2-amino-4,4-dichlorobutanoic acid, and 2-aminobutanoic acid. It was difficult to separate the dichloro compound from the others.
7. n-Values were determined by microcoulometry.
8. T. Iwasaki and K. Harada, J. Chem. Soc., Chem. Comm., 338 (1974).
9. The reported value is $[\alpha]_D^{25}$ +26.2° (c=0.74. aqueous HCl at pH 1.0). See references 4a-b.
10. The polarogram of compound (IV) in 75% aqueous methanol containing 0.6 ml of 36% HCl and 0.1 M tetraethylammonium chloride did not show a clear limiting current. However, electrons transfer occurred from the cathodic potential of -0.5 V. vs. S.C.E..