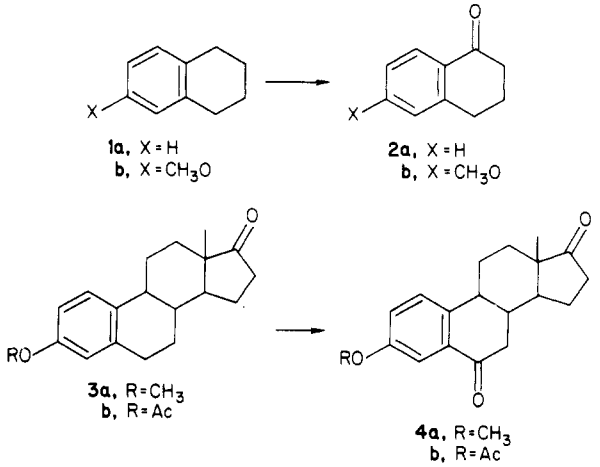
Table I. Benzylic Oxidations Using *t*-BuOOH/Cr(CO)$_6$

starting material	product	conversn, %	yield,[a] %
tetralin	α-tetralone	100	88
6-methoxytetralin	6-methoxy-α-tetralone	72	61
3a	**4a**	63	85
3b	**4b**	52	54

[a] Based on starting material consumed.

procedures,[2] even microbiological hydroxylation,[2a] have not led to convenient high yield benzylic oxidations.

We recently observed that oxidation of cycloalkenes to α,β-unsaturated ketones could be effected by *tert*-butyl hydroperoxide in the presence of chromium hexacarbonyl catalyst,[4] and we now report the use of this system for benzylic oxidation. Using this procedure, tetralin (**1a**) was



converted to α-tetralone (**2a**), 6-methoxytetralin (**1b**) to 6-methoxy-α-tetralone (**2b**), 3-methoxyestra-1,3,5(10)-trien-17-one (**3a**) to 6-oxoestrone 3-methyl ether (**4a**), and 3-acetoxyestra-1,3,5(10)-trien-17-one acetate (**3b**) to its 6-oxo derivative **4b**. The yields are summarized in Table I. While the oxidation of tetralin proceeded to completion and gave high yield of tetralone, we were unable to drive the other reactions to completion, but starting materials were easily separated, allowing isolation of pure ketones. In all cases, the yields were far superior to those obtained by chromic acid oxidation.[1]

Of particular interest is the fact that these oxidations appear to involve catalysis by Cr(0) species. While the mechanism is not yet established, it is noteworthy that the reaction medium remains almost colorless throughout, while admixture of *t*-BuOOH and chromium oxides in acetonitrile leads to deep red solutions.[5] We anticipate studying the mechanism of this interesting reaction in the near future.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 1420 spectrometer, NMR spectra on Varian XL200 spectrometer, and melting points were determined on a Fisher Johns apparatus and are uncorrected. Chromium hexacarbonyl was purchased from Strem Chemicals, and *tert*-butyl hydroperoxide (90% solution containing 5% H_2O, 5% *tert*-butyl alcohol) was purchased from Aldrich Chemical Company. Acetonitrile was distilled prior to use. All reactions were run under an atmosphere of nitrogen. (*CAUTION*: *tert*-butyl hydroperoxide may present an explosion hazard when concentrated. It is recommended that large-scale reactions be worked up using aqueous sodium metabisulfite).

Oxidation of Tetralin. To a solution of tetralin (500 mg, 3.78 mmol) in acetonitrile (25 mL) was added *tert*-butyl hydroperoxide (1.14 mL, 11.40 mmol) and chromium hexacarbonyl (250 mg, 1.14 mmol). The mixture was boiled under reflux for 23 h and then cooled to room temperature. Water (100 mL) was added and the product was extracted with ether (3 × 20 mL). The extracts were washed with water, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated to give the crude product. Purification by flash chromatography afforded pure α-tetralone (489 mg, 88%) spectroscopically identical with an authentic sample.

Oxidation of 6-Methoxytetralin. 6-Methoxytetralin (255 mg, 1.57 mmol) with *tert*-butyl hydroperoxide (0.57 ml) and chromium hexacarbonyl (124 mg, 0.56 mmol) were treated as above. Flash chromatography afforded unreacted starting material (71 mg) and 6-methoxy-α-tetralone (122 mg, 61% based on starting material consumed), identical with an authentic sample.

Oxidation of 3-Methoxyestra-1,3,5(10)-trien-17-one. Estrone 3-methyl ether (300 mg, 1.05 mmol) was treated with *tert*-butyl hydroperoxide (0.32 mL, 3.18 mmol) and chromium hexacarbonyl (69 mg, 0.31 mmol) as above (reflux, 29 h). Flash chromatography gave unreacted starting material (110 mg) and 3-methoxyestra-1,3,5(10)-triene-6,17-dione (**4a**) (169 mg, 85% based on starting material consumed): Mp 144–145 °C (lit.[1] mp 144–145 °C; IR ($CHCl_3$) ν_{max} 1740, 1685 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 7.58 (1 H, d, J = 2.9 Hz), 7.35 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.9 Hz), 3.86 (3 H, s), 2.88 (1 H, dd, J = 16.5, 3 Hz), 0.93 (3 H, s), 2.6–1.1 (methylenes, etc.).

Oxidation of 3-Acetoxyestra-1,3,5(10)-trien-17-one. Estrone acetate (100 mg, 0.32 mmol) was treated with *tert*-butyl hydroperoxide (0.10 mL, 1.0 mmol) and chromium hexacarbonyl (21 mg, 0.09 mmol) as described above (reflux 24 h). Purification by preparative TLC afforded unreacted starting material (48 mg) and 3-acetoxyestra-1,3,5(10)-triene-6,17-dione (**4b**) (29 mg, 54% based on starting material consumed): IR ($CHCl_3$) ν_{max} 1765, 1740, 1687, 1613 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 7.77 (1 H, d, J = 2.5 Hz), 7.46 (1 H, d, J = 8 Hz), 7.28 (1 H, dd, J = 8, 2.5 Hz), 2.88 (1 H, dd, J = 16.5, 3.5 Hz), 2.32 (3 H, s), 0.92 (3 H, s), 2.6–1.1 (methylenes, etc.).

Acknowledgment. This research was supported by a grant from the U.S. Public Health Service (NIH Grant #GM30373). High field NMR spectra were obtained on a Varian XL200 spectrometer purchased with the aid of a grant from the U.S. Public Health Service (NIH #RR-01689).

Registry No. **1a**, 119-64-2; **1b**, 1730-48-9; **2a**, 529-34-0; **2b**, 1078-19-9; **3a**, 1624-62-0; **3b**, 901-93-9; **4a**, 19115-79-8; **4b**, 7323-89-9; *t*-BuOOH, 75-91-2; $Cr(CO)_6$, 13007-92-6.

(4) Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235. Pearson, A. J.; Chen, Y. S.; Han, G. R.; Hsu, S. Y.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 267.

(5) During attempts to modify and optimize this procedure, we have found that $Cr(CO)_5(CH_3CN)$ reacts instantly with *t*-BuOOH to give a brown material, presumably an oxide of chromium. Use of this mixture does lead to benzylic oxidation, but several other products are also obtained. This is in contrast to $Cr(CO)_6$ which does not give any colored substances even on prolonged heating with *t*-BuOOH in acetonitrile.

A Convenient Method for the Preparation of N-Blocked Amino Acids

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Carbamates have been used to protect the amino function of α-amino acids since Bergmann and Zervas[1] first investigated the use of the benzyloxycarbonyl (Cbz) group in 1932. These groups are most commonly introduced by

(1) Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.

0022-3263/85/1950-2792$01.50/0

Table I. Preparation of Benzyloxycarbonyl (Cbz) Derivatives

amino acid	% yield in EtOAc	mp, °C	mp, °C (lit.)	optical rotatns[a] $[\alpha]_D^{25}$	optical rotatns[a] $[\alpha]_D^{25}$ (lit.)
L-Ala	46	86–87	87[b]	−14.2	−13.9 (c 2, HOAc)[b]
Gly	41	118–120	120[b]		
L-His	31	164–166 dec	166–167 dec[c]	−25.2	−25.0 (c 6, 6 N HCl)[c]
L-Leu	48	oil[f]	d		
D,L-Met	31	113	112[c]		
L-Phe	67	88	88–89[d]	+5.2	+5.1 (c 2, EtOH)[d]
L-Pro	32	75–76	76–77[d]	−61.8	−61.7 (c 5, HOAc)[d]
L-Val	57	66	66–67[d]	+0.2	+0.1 (c 2, EtOH)[d]

[a] Measurements (in deg) were taken in the same solvents and at the same concentration that had been reported in the literature. [b] Reference 1. [c] Patchornik, A.; Berger, A.; Katchalski, E. *J. Am. Chem. Soc.* **1957**, *79*, 6416. [d] Grassmann, W.; Wuncsh, E. *Chem. Ber.* **1958**, *91*, 462. [e] Dekker, C. A.; Fruton, J. S. *J. Biol. Chem.* **1948**, *173*, 471. [f] R_f 0.25 with 6:4:0.1 hexane–ethyl acetate–acetic acid as eluant.

Schotten–Baumann procedures.[2] The *tert*-butoxycarbonyl (*t*-Boc) and Cbz groups have been used extensively for the preparation of peptides. For other applications, however, additional versatility may be required so that specific amino functions can be selectively deblocked. The 2,2,2-trichloroethoxycarbonyl (Tcc) group, first introduced by Woodward in his total synthesis of Cephalosporin C,[3] was of interest to us since it would confer substantial lipophilicity to N-blocked tyrosine derivatives we wished to prepare and could be selectively removed by Zn^0. Despite numerous attempts and strict adherence to prescribed procedures, satisfactory yields of the desired *O*-benzyl-*N*-Tcc-L-tyrosine could not be obtained with trichloroethyl chloroformate under Schotten–Baumann conditions using Na_2CO_3 as base.

During our investigation of the formation of *N*-Tcc amino acids, we noted a report by Ronwin[4] describing the direct acylation of amino acids with acid chlorides in the absence of added base. We now report that this method can be used to effect the formation of carbamate derivatives in moderate to high yield. The method is general for amino acids and can be used for the preparation of many carbamates which are obtainable from their corresponding chloroformates. Although many of these derivatives are accessible by the conventional Schotten–Baumann procedures, we find that the method we have developed is more convenient and isolation of the product is simple. Furthermore, in the case of *O*-benzyl-*N*-Tcc-L-tyrosine, this direct acylation procedure gives an 85% yield whereas Schotten–Baumann conditions afforded only modest yields (5–25%).

The new, preparative procedure involves simply refluxing a suspension of the amino acid in dry ethyl acetate containing 1 equiv of the requisite chloroformate. The reaction requires no attention while in progress; the product is isolated by filtration of the unreacted starting material, now the hydrochloride salt, followed by concentration of the filtrate. Purification of the product can be achieved by either trituration or recrystallization.

We investigated several means of enhancing the yields, but all had nominal effect. The substitution of dry THF[5] for EtOAc as a solvent increased yields approximately 10% in reactions employing amino acids with the least solubility in organic solvents (i.e., Gly and Ala). The yield can be enhanced marginally (ca. 5%) by the addition of the thermally labile chloroformates in aliquots over the course of the reaction. The addition of an equivalent of base (triethylamine or pyridine) or acylation catalysts (such as (dimethylamino)pyridine) also failed to markedly increase the yields. Generally, the more polar amino acids gave yields in the range of 30–70% (see Table I), while the most lipophilic ones gave yields approaching quantitative (see the Experimental Section).

Experimental Section

General Procedures. Amino acids were purchased from Sigma Chemical Co. and were used without purification; they were ground to a powder with mortar and pestle to increase surface area. Chloroformates were purchased from Aldrich Chemical Co. and were also used without purification. Reagent grade solvents were purchased from Burdick and Jackson. Thin-layer chromatography was done on Analtech Uniplate 250 μm silica gel plates. Melting points were determined on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 241MC Polarimeter at 23 °C at the concentrations indicated. NMR and IR spectra were recorded for all compounds and were consistent with the assigned structures; the data is reported where pertinent. ^1H NMR spectra were recorded on a Varian EM-390 90-MHz spectrometer in $CDCl_3$ with tetramethylsilane as a standard. Mass spectra were recorded on a Finnegan 3300 mass spectrometer operating in the CI mode for compound 1 or a Varian MAT CH5 DF mass spectrometer operating in the FD mode for compounds 2 and 3. Elemental analyses were performed by the Analytical, Physical and Structural Chemistry Department of Smith Kline and French Laboratories.

General Procedure for the Preparation of Cbz Derivatives. The amino acid (0.5 g) was suspended in EtOAc (50 mL). The mixture was stirred and heated at reflux for 30 min to fully saturate the solvent with the amino acid. The refluxing suspension was then treated with 1 equiv of the desired chloroformate and was allowed to continue refluxing overnight. At this time the solid amino acid hydrochloride was removed by filtration and the filtrate was concentrated. Purification could be effected either by trituration or by crystallization from appropriate solvents. See Table I for yields and analytical data.

***O*-Benzyl-*N*-Tcc-L-tyrosine (1).** *O*-Benzyltyrosine (15 g, 55.2 mmol) was suspended in dry EtOAc (750 mL) with stirring and heated at reflux for 30 min. The mixture was treated with 2,2,2-trichloroethyl chloroformate (7.6 mL, 55.2 mmol) and heated at reflux overnight. Filtration of the remaining solid and concentration of the filtrate left 1 as an off-white solid: 21.1 g (85%); ^1H NMR ($CDCl_3$) δ 8.4 (s, 1 H), 7.9–7.15 (complex m, 9 H), 5.8 (br d, J = 8 Hz, 1 H), 5.2 (s, 2 H), 5.0–4.4 (complex m, 3 H), 3.2 (d, J = 4 Hz, 2 H); IR (Nujol mull) 1755, 1735 cm^{-1}; $[\alpha]^{25}_D$ −1.79 ($CHCl_3$); mp 111 °C; mass spectrum, m/e 447 ($M + H^+$).

Anal. Calcd for $C_{19}H_{18}NO_5Cl_3$: C, 51.08; H, 4.06; N, 3.13. Found: C, 51.26; H, 4.41; N, 3.13.

***S*-Trityl-*N*-Tcc-L-cysteine (2).** To a stirring suspension of *S*-trityl-L-cysteine (0.363 g, 0.001 mol) in 20 mL of dry EtOAc was added 2,2,2-trichloroethyl chloroformate (0.138 mL, 0.212 g, 0.001 mol). The mixture was then heated at reflux for 15 h. After

(2) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. 2, pp 887–901.
(3) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.
(4) (a) Ronwin, E. *J. Org. Chem.* **1953**, *18*, 127. (b) *Ibid.* **1953**, *18*, (c) *Ibid.* **1957**, *22*, 1180. (d) Ronwin, E.; Warren, C. *Ibid.* **1964**, *29*, 2276. (e) Ronwin, E.; Horn, D. *Ibid.* **1965**, *30*, 2821.
(5) Although Ronwin[4e] suggested that dioxane should be the best solvent for his direct acylation reactions, we elected to use THF since dioxane is a suspected carcinogen.

the mixture was cooled, EtOAc was removed by concentration in vacuo. The product was dried under high vacuum to yield an off-white, gummy solid: 0.613 g (~100%): ^{1}H NMR ($CDCl_3$) δ 9.3 (br s, 1 H), 7.6 – 7.1 (m, 15 H), 4.35 (br m, 1 H), 5.36 (d, J = 8.5 Hz, 1 H), 4.8 (s, 2 H), 2.75 (d of d, J = 6 Hz, 1 Hz, 2 H); IR 1745, 1730 cm^{-1}; $[\alpha]^{25}_D$ +7.78 ($CHCl_3$); mass spectrum, m/e 537 (M^+); R_f 0.3 with 80:20:0.1 cyclohexane–ethyl acetate–acetic acid as eluant.

***N*-((Allyloxy)carbonyl)-*S*-trityl-L-cysteine (3).** A suspension of *S*-tritylcysteine (5.45 g, 15 mmol) in EtOAc (300 mL) was treated with allyl chloroformate (3.16 g, 26 mmol, 1.75 equiv) and then heated at reflux for 24 h to give a yellow solution. Evaporation of the solvent in vacuo gave a yellow oily solid: 6.1 g (91%); ^{1}H NMR ($CDCl_3$) δ 9.15 (br s, 1 H), 7.6–7.1 (m, 15 H), 6.05–5.65 (m, 1 H), 5.3 (d, J = 9 Hz, 1 H), 5.3–5.1 (m, 2 H), 4.55 (d, J = 4 Hz, 2 H), 4.2 (m, 1 H), 2.7 (d, J = 5 Hz, 2 Hz); IR 1745, 1730 cm^{-1}; mass spectrum, m/e 447 ($M + H^+$); R_f 0.33 with 8:2:0.1 cyclohexane–ethyl acetate–acetic acid as eluant.

Acknowledgment. We thank Mr. M. Howard for the preparation of **2** and **3**, Mr. G. Roberts and Ms. M. Mentzer for mass spectral analysis, Ms. E. Reich for microanalyses, and Dr. L. Kruse for helpful discussions.

Registry No. **1**, 37888-25-8; **2**, 96845-11-3; **3**, 96865-72-4; Cbz-L-Ala-OH, 1142-20-7; Cbz-Gly-OH, 1138-80-3; Cbz-L-His-OH, 14997-58-1; Cbz-L-Leu-OH, 2018-66-8; Cbz-DL-Met-OH, 4434-61-1; Cbz-L-Phe-OH, 1161-13-3; Cbz-L-Pro-OH, 1148-11-4; Cbz-L-Val-OH, 1149-26-4; L-Ala-OH, 56-41-7; Gly-OH, 56-40-6; L-His-OH, 71-00-1; L-Leu-OH, 61-90-5; DL-Met-OH, 59-51-8; L-Phe-OH, 63-91-2; L-Pro-OH, 147-85-3; L-Val-OH, 72-18-4; *O*-benzyltyrosine, 16652-64-5; 2,2,2-trichloroethyl chloroformate, 17341-93-4; *S*-trityl-L-cysteine, 2799-07-7; allyl chloroformate, 2937-50-0; benzyl chloroformate, 501-53-1.

Thiol–Disulfide Exchange Reactions of Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide Studied by ^{1}H Nuclear Magnetic Resonance Spectroscopy

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Recently, 1-methyl-1*H*-tetrazole-5-thiol (**1**) and its disulfide **2** have been proposed to inhibit in vitro an enzyme system for the γ-carboxylation of the glutamyl residue of a model prothrombin precursor.[1] Since little was known about their chemical properties, we examined them in detail using NMR and UV spectroscopies as well as polarography. Here, we report observations that oxidation of **1** giving **2** is more difficult than that of dithiothreitol **3**, that decomposition of **2** giving **1** and **6** in neutral aqueous solution proceeds rapidly, that facile thiol–disulfide exchange reactions of **2** with **1** and **3** proceed in $CDCl_3$, and that the latter reaction, carried out in neutral aqueous solution, precedes the decomposition, if the concentrations of **2** and **3** are above 1.0 mmol/L.

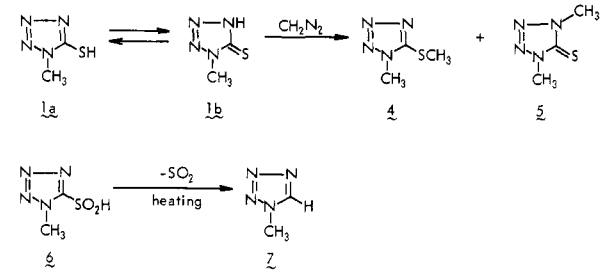
Disulfide **2** was prepared by oxidizing **1** with ferric chloride, mp 112.5–113.0 °C.[3] Spectral data for **1**, which predominantly takes a thioamide form,[2] and **2** are shown in Table I. The fact that the potentials observed at pH 7.0 for **1** ($E_{1/2}^{oxd}$ = –0.08 V vs. SCE) and **2** ($E_{1/2}^{red}$ = ca. –0.3 V vs. SCE[3]) are respectively differentiated from the $E_{1/2}^{oxd}$ values for **3** or cysteine[4] (–0.465 or –0.46 V, respectively) and from the $E_{1/2}^{red}$ values for **10** or cystine[4] (–0.965 or –0.86 V, respectively) suggests that **1** possesses poor susceptibility to oxidation and high reducibility. In fact, although oxygen oxidation of **3** proceeded slowly, that of **1** did not proceed at all even after 3 days.

Table I. UV and NMR Spectra of 1 and 2

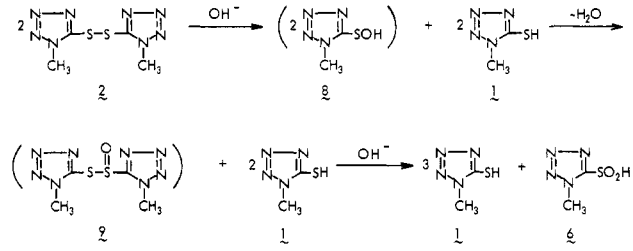
compd	1	1[a]	1	2
		UV		
solv	0.1 N H_2SO_4	H_2O[b]	CH_3CN	0.1 N H_2SO_4
λ_{max}, nm	241.0	223.5	246.0	210[c]
ε	14 000	11 800	14 200	11 000
		NMR[d]		
solv	0.1 N DCl	D_2O[e]	$CDCl_3$	$CDCl_3$
^{1}H NMR, δ				
NCH_3	3.88	3.84	3.933	4.189
^{13}C NMR, δ				
NCH_3	34.7	34.2	34.1	35.0
ring	164.1	165.5	164.2	151.1

[a] N-Anion. [b] A phosphate buffer solution (pH 7.0). [c] End absorption. [d] Me_4Si or DSS was used as an internal reference. [e] Added with $NaHCO_3$ (pH 9.5).

Scheme I



Scheme II



Decomposition of 2 in Aqueous Solution. Gradual decomposition of compound **2** ($\tau_{1/2}$ ca. 40 h at 25 °C) in dilute sulfuric acid (pH 1.25) and formation of **1** were indicated by the change of the ultraviolet absorption intensities at 210 and 241 nm. At pH 7.39, however, **2** decomposed very rapidly, and formation of 3 mol of **1** from 2 mol of **2** was suggested from the UV maxima at 223.5 nm ($\epsilon^{1\%}$ = 1540) at pH 7.39 and 241.0 nm ($\epsilon^{1\%}$ = 1810) at pH 1.41.[5] Acid-quenching experiments with 30-s intervals revealed that the decomposition went to completion within the first 30 s at 25 °C. Polarographic measurements also revealed that **2** decomposed gradually at pH 1.80 and rapidly at pH 7.01, showing an oxidation wave corre-

(1) (a) Lipsky, J. J. *Lancet* **1983**, II (8343), 192. (b) Lipsky, J. J. *Ibid.* **1983**, II (8350), 624. (c) Wold, J. S.; Buening, M. K.; Hanasono, G. K. *Ibid.* **1983**, II (8346), 408. (d) Lipsky, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 2893. (e) See also: Uchida, K.; Ishigami, T.; Komeno, T. *Jpn. J. Pharmacol.*, in press.

(2) Bartels-Keith, J. R.; Burgess, M. T.; Stevenson, J. M. *J. Org. Chem.* **1977**, *42*, 3725.

(3) Estimated from the value (ca. 0.01 V) observed at pH 1.80 with a shift of –0.06 V/pH.

(4) Dubbos, D. In "Electrochemical Data"; Elsevier Science Publishing: New York, 1975.

(5) Analysis by ^{1}H NMR measurement suggested that 1.00 mol of **2** produced 1.67 mol of **1** and 0.33 mol of **7** (after 430 min at 37 °C) via an unstable intermediate.

0022-3263/85/1950-2794$01.50/0