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The Synthesis and Conformational Analysis of Epimeric 17-Bromo-14β-androstan-16-ones[1]

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3β-Acetoxy-17β-bromo-5α,14β-androstan-16-one (VII) was synthesized by two different routes, namely from the Δ^{16}-ene (VIII) through the 16, 17-bromohydrin (IX) and from the 16-ketone (V) as shown in Chart 1. The epimeric 17α-bromo compound (X) was pre-pared from VII upon treatment with hydrobromic acid. On the basis of infrared, rotatory dispersion and circular dichroism spectral and polarographic data the nature of C-bromine bonds and the conformation of ring D with a ketone at C-16 have been discussed. A new method for synthesis of the 17α-hydroxy-16-ketone (IV) from the 17-ketone (I) is also described.

In the preceding papers the conformational analysis of ring D has been reported on the C/D-*cis* steroids.[3] With regard to the 14β-steroids, however, conformation of ring D having a ketone at C-16 has not yet been investigated. The present paper deals with the synthesis of the epimeric 17-bromo-16-ketones in 5α,14β-androstane series and conformation of ring D on the basis of their spectroscopic data.

An initial project was directed to the preparation of 5α,14β-androstan-16-one from the corresponding 17-ketone. Although several methods for the synthesis of 16-ketosteroids have already been proposed, the authors attempted to prepare the 17α-hydroxy-16-ketone with more ease through a different route. For this purpose 3β-acetoxy-5α,14β-androstan-17-one (I), derivable from dehydroepiandrosterone in several steps by the method of St. André, *et al.*,[4] was employed as a starting compound.

When I was stirred with potassium *tert*-butoxide at room temperature, oxidation occurred readily at C-16 to furnish the 16-hydroxy-Δ^{15}-17-ketone (IIa) in satisfactory yield. It is evident from ferric chloride test and spectroscopic data that the 16-oxygenated product exists in the diosphenol form[5] rather than in the diketo form. Treatment with benzyl chloride in the presence of potassium carbonate gave the 16-benzyloxy derivative (IIb), which on lithium aluminum hydride reduction was led to the 17-hydroxylic compound (III) without affecting any disturbance on the double bond. On brief exposure to mineral acid III underwent debenzylation yielding the 17α-hydroxy-16-ketone (IVa), the most stable ketol of four possible isomers,[6] in overall yield of 55% based upon the 17-ketone. Clemmensen reduction of the diacetate (IVb) in the manner as described in the previous paper[6] gave the 16-ketone (V).

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[1] This paper constitutes Part XLIII of the series entitled "Analytical Chemical Studies on Steroids"; Part XIII: T. Nambara, M. Numazawa, and S. Akiyama, *Chem. Pharm. Bull.* (Tokyo), **19**, 153 (1971).

[2] Location: *Aobayama, Sendai.*

[3] *a*) T. Nambara and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961); *b*) T. Nambara, H. Hosoda, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1266 (1968); *c*) T. Nambara, H. Hosoda, M. Usui, and J. Fishman, *ibid.*, **16**, 1802 (1968); *d*) T. Nambara, H. Hosoda, and M. Usui, *ibid.*, **17**, 375 (1969); *e*)T. Nambara, M. Usui, and H. Hosoda, *ibid.*, **17**, 1611 (1969).

[4] A.F.St. André, H. B. MacPhillamy, J. A. Nelson, A.C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

[5] Inspection of Dreiding model implies that C-ring of IIa would probably be in either boat or twist conformation.

[6] T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962).

Then V was treated with isopropenyl acetate and a catalytic amount of sulfuric acid according to the procedure of Gallagher and his co-workers.[7] Unfortunately the enol acetate (VI) could not be isolated in the crystalline state. However, the chromatographic behaviors and nuclear magnetic resonance (NMR) spectra indicated that the product was homogeneous and enolization took place preferentially toward C-17 rather than C-15. Subsequent halogenation with a calculated amount of bromine under non-enolizing condition gave the 17-bromo-16-ketone (VII) as a single product.

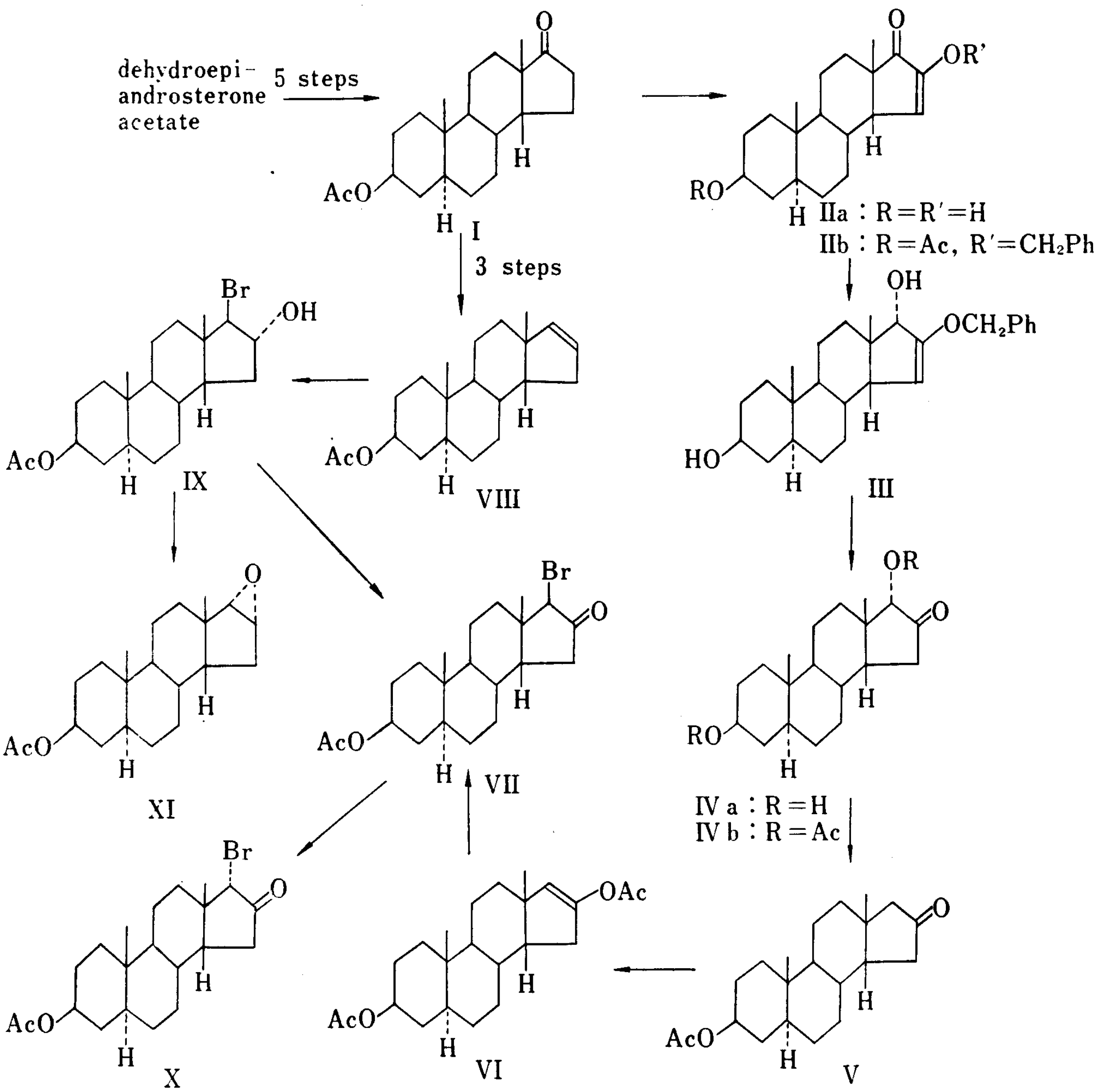

Chart 1

Since this synthetic route appeared to be of disadvantage with respect to the yield, the next project was focussed to the development of an alternative way through the 16,17-bromohydrin. Reaction of 5α,14β-androst-16-en-3β-ol acetate (VIII), prepared from the corresponding 17-ketone in three steps,[8] with hypobromous acid gave solely the 16,17-bromohydrin (IX) in satisfactory yield. The *trans*-bromohydrin structure was rationalized by the formation of the α-epoxide (XI), when IX was refluxed with methanolic potassium hydroxide and then acetylated in usual manner. Oxidation with chromium trioxide-pyridine

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[7] N.S. Leeds, D.K. Fukushima, and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

[8] T. Nambara and M. Yano, *Chem. Pharm. Bull.* (Tokyo), **13**, 1004 (1965).

complex under mild condition gave the α-bromoketone (VII), which proved to be identical with the above-mentioned halogenation product derived from the enol acetate. This result implies that the attack of a bromo cation from the less-hindered β-side of a molecule and subsequent *trans*-diaxial opening may result in formation of the 17β-bromo-16α-ol.

This bromoketone was readily epimerized to the 17α-bromo-16-ketone (X) upon exposure to hydrogen bromide in acetic acid. An equilibrated mixture consisted of 40% 17β and 60% 17α as judged by thin-layer chromatography (TLC). The desired 17α-epimer could be separated with success by fractional crystallization. The structural assignment was supported by the NMR spectra in which a siglet due to proton attached to carbon bearing halogen appeared at 5.73τ.

TABLE I. Spectral and Polarographic Data

Substance	IR		RD 1st extremum			CD			PG
	$\nu_{max}^{CCl_4}$ cm^{-1}	$\Delta\nu$	λ_{max}^{MeOH} mμ	$\Delta\lambda$	[φ]	λ_{max}^{MeOH} mμ	$\Delta\lambda$	[θ]	$E_{1/2}$ (*vs.* SCE) V
16-Ketone (V)	1743		313		+8650°	297		+10070	
17β-Bromo-16-ketone (VII)	1752	+ 9	334	+21	−4210°	310	+13	− 7590	−0.21
17α-Bromo-16-ketone (X)	1762	+19	322	+ 9	+9220°	299	+ 2	+11000	−0.68

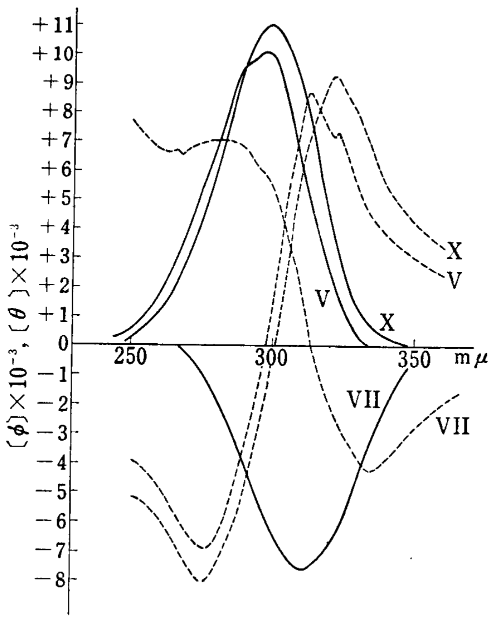

Fig. 1. Optical Rotatory Dispersion (----) and Circular Dichroism Curves (——) of V, VII and X in Methanol (at 20°)

The spectral data of two epimeric 17-bromo-16-ketones (VII, X) and the parent ketone (V) are collected in Table I. The shift value in the infrared (IR) absorption in X reflects the equatorial nature of the 17α-bond, while that in VII indicates the quasi-axial character of the 17β-bond. This finding is consistent with the previous result on the rotatory dispersion of the epimeric 17-acetoxy-16-ketones in 14β-series.⁹⁾

The wavelength shifts both in terms of the rotatory dispersion extremum and circular dichroism maximum accompanying introduction of halogen also support the conformational assignment of these 17-bromo-16-ketones. As illustrated in Fig. 1, the 17α-bromo derivative exhibits the positive Cotton effect with a somewhat larger amplitude than the parent ketone in contrast to the 17β-bromo compound with a negative sign. These results indicate that axial haloketone rule applicable to the α-halopentanones is also valid in 14β-steroidal ring D with a ketone at C-16.

It has already been established that of two epimeric α-bromooxosteroids the thermodynamically less stable epimer is polarographically reducible with more ease than the more stable one.¹⁰⁾ Diagnosis by this criteria tells us that with these 17-bromo-16-ketones the nature of C-bromine bonds is in qualitative agreement with the magnitude of the half-wave potential.

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9) C. Djerassi, J. Fishman, and T. Nambara, *Experientia*, **17**, 565 (1961).
10) S. Goya, H. Hosoda, T. Kudo, C. Anzo, and T. Nambara, *Yakugaku Zasshi*, **89**, 336 (1969).

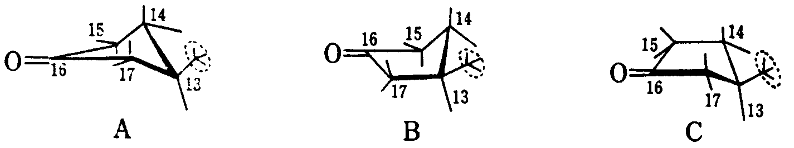

Fig. 2. Conformation of Ring D in 14β-Androstan-16-one

All these spectroscopic evidences together would support the half-chair (A) or the β-envelope conformation (B) for ring D in the 17β-bromo compound and the half-chair (A) or the α-envelope conformation (C) in the 17α-epimer.

Experimental[11]

3β,16-Dihydroxy-5α,14β-androst-15-en-17-one (IIa)——To a solution of *tert*-BuOK prepared from K (200 mg) and *tert*-BuOH (10 ml) was added a solution of 3β-acetoxy-5α,14β-androstan-17-one (I) (200 mg) in *tert*-BuOH (10 ml) and the resulting solution was stirred at room temperature for 30 hr. The reaction mixture was neutralized with dil. HCl and evaporated under reduced pressure. The residue thus obtained was extracted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crystalline product obtained was recrystallized from aq. acetone to give IIa (170 mg) as colorless needles. mp 187—188° (lit. mp 190—191°).[12] UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε): 259 (6900). $FeCl_3$ test showed a brown color.

3β-Acetoxy-16-benzyloxy-5α, 14β-androst-15-en-17-one (IIb)——To a solution of IIa (165 mg) in EtOH (15 ml) were added anhydrous K_2CO_3 (450 mg) and $PhCH_2Cl$ (0.25 ml) and refluxed for 13 hr. The resulting solution was diluted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily residue (*ca.* 200 mg) obtained was chromatographed on Al_2O_3 (5 g). Elution with benzene–ether (1:1) afforded the semicrystalline product (190 mg). Usual treatment with pyridine and Ac_2O followed by recrystallization from MeOH gave IIb (180 mg) as colorless plates. mp 126—128°. $[\alpha]_D^{21}$ +145.5° (c= 0.11). *Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 76.77; H, 8.36. NMR (5% solution in CCl_4) τ: 9.28 (3H, s, 19-H), 9.00 (3H, s, 18-H), 8.08 (3H, s, 3β-$OCOCH_3$), 5.40 (1H, m, 3α-H), 5.06 (2H, s, -OCH_2Ph), 3.83 (1H, d, J=3 cps 15-H), 2.74 (5H, s, -$OCH_2C_6H_5$).

3β, 17α-Dihydroxy-5α, 14β-androstan-16-one (IVa)——To a solution of IIb (180 mg) in ether (20 ml) was added $LiAlH_4$ (300 mg) at -10° and allowed to stand for 1 hr. After decomposition of the excess reagent with moistened ether, the reaction mixture was acidified with 10% H_2SO_4. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave 16-benzyloxy-5α, 14β-androst-15-ene-3β, 17α-diol (III) (135 mg) as colorless oil. A solution of III dissolved in MeOH (10 ml)-6N H_2SO_4 (0.4 ml) was allowed to stand at room temperature for 30 min. The resulting solution was neutralized with 5% $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with AcOEt, washed with H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crystalline product obtained was submitted to preparative TLC using benzene–ether (1:3) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.25) with acetone and recrystallization of the eluate from acetone–hexane gave IVa (100 mg) as colorless leaflets. mp 168—170° (lit. mp 168—171°).[6] 3,17-Diacetate (IVb): mp 190—192° (lit. mp 194—197°).[6] Mixed melting point on admixture with the authentic sample showed no depression and IR spectra of two samples were entirely identical in every respect.

3β-Acetoxy-5α, 14β-androstan-16-one (V)——Prepared from IVb by reduction with Zn dust in AcOH according to the method previously reported. mp 142—144° (lit. mp 147—149°).[6]

5α, 14β-Androst-16-ene-3β, 16-diol Diacetate (VI)——To a solution of V (100 mg) in isopropenyl acetate (5 ml) was added 10 drops of the catalyst solution (isopropenyl acetate (1 ml) and conc. H_2SO_4 (0.04 ml)) and refluxed for 4 hr. The reaction mixture was concentrated to one-half of its volume by slow distillation over 1 hr. An additional 2 ml of isopropenyl acetate containing 5 drops of catalyst solution was added and the solution was again concentrated to *ca.* 2 ml over another 1 hr. The resulting solution was diluted with ether and washed with cold 5% $NaHCO_3$, H_2O and dried over anhydrous Na_2SO_4. After usual work-up an oily residue obtained was dissolved in hexane and filtered through Al_2O_3 (5 g). Upon concen-

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11) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were determined in $CHCl_3$ solution unless otherwise specified. IR spectra were obtained on carefully calibrated Hitachi Model 621 spectrophotometer. Optical rotatory dispersion and circular dichroism measurements were carried out on JASCO Model ORD/UV-5 recorder. NMR spectra were run on Hitachi Model H-60 spectrometer at 60 Mcps using $(CH_3)_4Si$ as an internal standard. For preparative TLC silica gel H (E. Merck AG) was used as an adsorbent.

12) A.C.Campbell, W. Lawrie, and J. McLean, *J. Chem. Soc.* (*C*), **1969**, 554.

tration of the filtrate an oily product, which showed a single spot on TLC (*Rf* 0.40 hexane–AcOEt (8:1)), was obtained. NMR (5% solution in $CDCl_3$) τ: 9.20 (3H, s, 19-H), 8.90 (3H, s, 18-H), 7.98 (3H, s, 3β-$OCOCH_3$), 7.89 (3H, s, 16-$OCOCH_3$), 5.35 (1H, m, 3α-H), 4.68 (1H, s, 17-H).

3β-Acetoxy-17β-bromo-5α, 14β-androstan-16-one (VII)——i) To a solution of IX (50 mg) in pyridine (1 ml) was added CrO_3–pyridine complex[13] (0.5 ml) and allowed to stand at room temperature for 5 hr. The reaction mixture was diluted with ether and washed with 10% AcOH, 10% Na_2CO_3 and H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crystalline product obtained was recrystallized from EtOH to give VII (45 mg) as colorless plates. mp 144—145°. $[\alpha]_D^{25}$ -37.5° (c=0.60). *Anal.* Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59. Found: C, 61.04; H, 7.83. NMR (5% solution in CCl_4) τ: 9.16 (3H, s, 19-H), 8.77 (3H, s, 18-H), 8.06 (3H, s, 3β-$OCOCH_3$), 6.32 (1H, s, 17α-H), 5.40 (1H, m, 3α-H).

ii) To a stirred solution of VI (37 mg) in CCl_4 (10 ml) containing anhydrous K_2CO_3 (35 mg) was added dropwise a solution of the calculated amount of Br_2 in CCl_4 at 0°. The resulting solution was washed with 10% $NaHSO_3$ and H_2O and dried over anhydrous Na_2SO_4. After usual work-up the crystalline product obtained was recrystallized from EtOH to give VII (10 mg) as colorless plates. mp 145—147°. Mixed melting point on admixture with the sample obtained in i) showed no depression and IR spectra of two samples were entirely identical in every respect.

17β-Bromo-5α, 14β-androstane-3β, 16α-diol 3-Acetate (IX)——To a solution of 5α, 14β-androst-16-en-3β-lo acetate[8] (VIII) (154 mg) in dioxane (10 ml) containing 0.5N $HClO_4$ (0.5 ml) was added N-bromoacetamide (200 mg) and stirred at room temperature for 15 min. After addition of $NaHSO_3$ solution the reaction mixture was diluted with ether, washed with 5% $NaHCO_3$ and H_2O and dried over anhydrous Na_2SO_4. On usual work-up the crystalline product obtained was recrystallized from acetone-hexane to give IX (200 mg) as colorless needles. mp 144—145°. $[\alpha]_D^{21}$ +10.0° (c=0.10). *Anal.* Calcd. for $C_{21}H_{33}O_3Br$: C, 61.01; H, 8.05. Found: C, 60.71; H, 8.10. NMR (5% solution in CCl_4) τ: 9.21 (3H, s, 19-H), 8.90 (3H, s, 18-H), 8.06 (3H, s, 3β-$OCOCH_3$), 6.17 (1H, s, 17α-H), 5.2—5.8 (2H, 3α-H and 16β-H).

Transformation of IX into 16α, 17α-Epoxy-5α, 14β-androstan-3β-ol Acetate (XI)——To a solution of IX (20mg) in MeOH (2 ml) was added 5% KOH (0.5 ml) and refluxed for 2 hr. The reaction mixture was diluted with ether, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crystalline product, which in turn was treated with pyridine and Ac_2O. After usual work-up the crude product obtained was recrystallized from MeOH to give XI (5 mg) as colorless needles. mp 119—120°. Mixed melting point on admixture with the authentic sample [3a] showd no depression.

3β-Acetoxy-17α-bromo-5α, 14β-androstan-16-one (X)——To a solution of VII (110 mg) in glacial AcOH (3 ml) was added AcOH saturated with HBr (0.2 ml) and allowed to stand at room temperature for 24 hr. The resulting solution was poured onto ice-water and the precipitate was collected by filtration and washed with H_2O. Fractional crystallization from MeOH gave X (20 mg) as colorless needles. mp 199—200°. $[\alpha]_D^{20}$+109.1° (c=0.22). *Anal.* Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59. Found: C, 61.09; H, 7.76. NMR (5% solution in $CDCl_3$) τ: 9.17 (3H, s, 19-H), 8.81 (3H, s, 18-H), 8.01 (3H, s, 3β-$OCOCH_3$), 5.73 (1H, s, 17β-H), 5.40 (1H, m, 3α-H). Concentration of the mother liquor gave the crystalline product. Upon repeated recrystallization from MeOH VII (8 mg) was recovered as colorless plates. mp 142—143°. The mother liquors were combined and then submitted to preparative TLC using benzene–ether (10:1) as developing solvent. Elution of the adsorbent corresponding to the spots (*Rf* 0.56, 0.63) gave X (13 mg) and VII (16 mg), respectively.

Polarography——Polarographic reductions were run by Yanagimoto Model PA-102 polarograph equipped with a capillary of the following characteristics: m=1.115 mg/sec, t=3.34 sec at a mercury height of 63.4 cm. An electrolysis solution was prepared by weighing the sample into a 10 ml volumetric flask, dissolving it in iso-PrOH (*ca.* 5 ml) and adding the acetate buffer (pH 6.0) (2 ml). The solution was then made up to 10 ml with additional iso-PrOH. The sample solution thus prepared was deaerated by bubbling N_2 gas and then polarographed at 25 ± 0.2°. Half-wave potential was expressed in volt *vs.* the saturated calomel electrode.

Acknowledgement The authors are indebted to Hitachi, Ltd. for IR spectral measurement and to all the staffs of central analytical laboratory of this Institute for elemental analyses and spectral measurements.

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13) G.I. Poos, G.E. Arth, R.E. Beyler, and L.H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).