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Anodic Oxidation of Amines. V.[1] Cyclic Voltammetry and Controlled Potential Electrolysis of Ephedrine and the Related Compounds in Aqueous Buffer Solution[1a]

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The anodic oxidations of ephedrine and several realted compounds have been studied in aqueous buffer solutions at a glassy-carbon electrode. The oxidation potentials of these alkanol amines are less positive than those of simple alkyl amines without β-hydroxy group. On controlled potential electrolysis, these compounds consume about two electrons per molecule, and substantially give 1-hydroxy-1-phenyl-2-propanone and the counterpart alkylamines. The relative amount of dealkylation from the amino-nitrogen is quite different from that predicted on the basis of the number of α-protons.

Keywords——aliphatic amines; anodic oxidation; ephedrine and the homologues; glassy-carbon electrode; dealkylation; 1-hydroxy-1-phenyl-2-propanone

Chemical and electrochemical oxidations of alkyl amines have been studied extensively by many groups of investigators,[3] and the dealkylation from amines has been stated to be governed essentially by the number and the acidity of α-protons and moreover by the ease of the second electron transfer from the intermediate neutral radical.[3g]

Among many α,β-amino alcohols having physiological interest, ephedrine and the series of the compound are relatively easily obtained, and the oxidation with alkaline ferricyanide and the metabolic products have already been reported.[4] We found in those papers that the oxidative bond fission between the α-carbon and amino-nitrogen occurs in some metabolic oxidation of several drugs and in the compounds having tertiarybutylamino group. In the latter case oxidative liberation of tertiary butyl group is impossible.

As a continuation of the previous works,[1,3f,3g] we report here the electrochemical oxidation of ephedrine and the related compounds.

Results

Cyclic Voltammetry of Ephedrine and the Related Compounds

In aqueous buffer solution, cyclic voltammetry of ephedrine showed two anodic waves between about pH 7 and pH 10 at a glassy-carbon electrode, but in acidic solution below pH 3, no wave was observed at all. When pH was raised up to 11.50, the second wave was merged

1) Part IV: H. Sayo and M. Masui, *Chem. Pharm. Bull.* (Tokyo), **24**, 2137 (1976); *a*) This paper was presented at 27th Annual Meeting of Kinki Branch, Pharmaceutical Society of Japan, Akashi, November 1977.

2) Location: *133-1, Yamada-kami, Suita-Shi, Osaka.*

3) *a*) P.J. Smith and C.K. Mann *J. Org. Chem.*, **34**, 1821 (1969); *b*) L.C. Portis, V.V. Bhat and C.K. Mann, *ibid.*, **35**, 2175 (1970); c) J.R. Lindsay Smith and D. Masher, *J. Chem. Soc. Perkin II*, **1976**, 47; *d*) J.R. Lindsay Smith and L.f. Mead, *ibid.*, **1973**, 206; *e*) J.R. Lindsay Smith and L.A. Mead, *ibid.*, **1976**, 1172; *f*) M. Masui, H. Sayo and Y. Thuda, *J. Chem Soc.* (*B*), **1968**, 973; *g*) M. Masui and H. Sayo, *ibid.*, **1971**, 1593.

4) *a*) S. Baba, A. Matsuda and Y. Nagase, *Yakugaku Zasshi*, **89**, 833 (1969); *b*) Y. Yamamoto, S. Higuchi, T. Fujiwara, S. Shimizu, K. Nishida and M. Uesaka, *Yakugaku Zasshi*, **97**, 244 (1977); *c*) A.H. Beckett and R. Achari, *J. Pharm. Pharmac.*, **29**, 645 (1977); *d*) E. Schmidt and G. Bumming, *Arch. Pharm.*, **247**, 141 (1909).

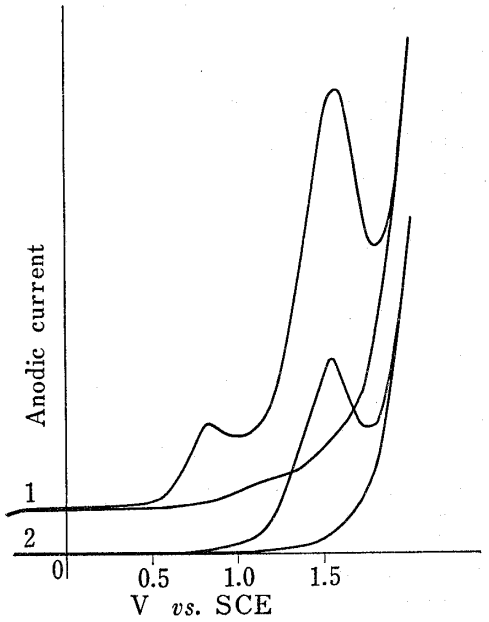
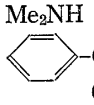


Fig. 1. Cyclic Voltammograms of Ephedrine (*ca.* 5 mM) and Phenylacetylcarbinol (*ca.* 2 mM) in Buffer Solution of pH 10 at Glassy-Carbon Electrode

Scan Rate is 0.05 V sec.$^{-1}$
1: ephedrine, 2: phenylacetylcarbinol.

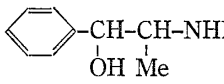
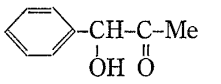
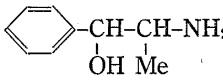
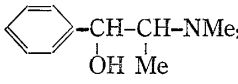
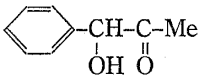
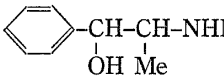
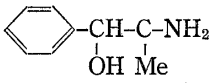
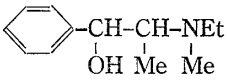
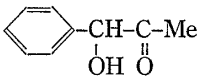
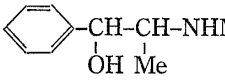
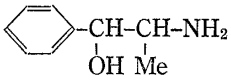
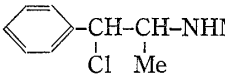
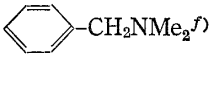
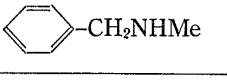
in the background current. The voltammograms of ephedrine and its oxidation product, 1-hydroxy-1-phenyl-2-propanone (phenylacetylcarbinol), are shown in Fig. 1. Voltammetry of ephedrine and the related compounds were performed mainly at pH 10, since the most distinct wave was developed at pH 10. The peak potentials of those compounds together with those of their oxidation products at pH 10 are shown in Table I. Two or three irreversible waves were generally observed at a scanning rate of 0.20—0.017 sec.$^{-1}$ The peak potentials of the first wave of 2-amino-1-hydroxy-1-phenylpropane (norephedrine), ephedrine and N-methyl and N-ethylephedrines indicate that these amines are in general more susceptible to electrochemical oxidation than the corresponding primary, secondary and tertiary alkyl amines without β-hydroxy group. 2-Methylamino-1-phenylpropane (methamphetamine) showed an anodic wave at nearly the same potential as that of simple secondary alkyl amines, but 1-chloro-2-methylamino-1-phenylpropane showed an anodic wave at a very positive potential.

Table I. Cyclic Voltammetric Data of Ephedrine and the Related Compounds in Buffer Solution of pH 10 at Glassy-Carbon Electrode

Compds.	E_{p1}[a]	E_{p2}[a]	E_{p3}[a]
	0.83	1.55	
$MeNH_2$	1.48		
	1.30	1.80	
	1.57		
	0.51	1.53	
Me_2NH	1.00	1.45	
	0.45	1.47	1.67
MeNHEt	1.00	1.46	
	1.47		
	1.05		
$HOCH_2CH_2NMe_2$	0.67[b]		
	0.64[b,c]		

a) V *vs.* SCE.
b) Half-peak potential at pH 12, quoted from Part II.[3g]
c) Contains 1% dioxane.

Table II. Anodic Oxidation Products of Ephedrine and the Related Compounds in Buffer Solution of pH 10 at Glassy-Carbon Electrode

compds.	$E_{app.}$[a]	n[b]	Products	Yield (%)[c]
	1.00	1.97—2.21		‡[d]
			$MeNH_2$	91
			HCHO	4
				9
	0.60	1.80—2.26		‡[d]
			Me_2NH	97
				0.30—0.44
			HCHO	2.8
			$MeNH_2$	Trace
				Trace
	0.55	1.88—2.05		‡[d]
			MeNHEt	99
			HCHO	4.4
				0.5 —2.86
			$EtNH_2$	0.15
			$MeNH_2$	0.19—1.68
				Trace
	1.50	0.09[e]	$MeNH_2$	5.9
			HCHO	0.9
$HOCH_2CH_2NMe_2$[f]	0.68	0.34[g]	HCHO	80[h]
			Me_2NH	13[h]
			$HOCH_2CH_2NHMe$	77[h]
	0.70	0.24[g]	HCHO	62[h]
			Me_2NH	39[h]
				48[h]

a) V *vs.* SCE.
b) Coulombs passed per mole of the starting amine.
c) mol per cent yield on the basis of the starting amine, average of five experiments.
d) In several runs, the yield was apparently over 100%, probably because the authentic sample, phenylacetylcarbinol was easily degraded on standing after purification.
e) Electrolysis was interrupted at the point where *ca.* 5% of the starting amine was consumed (see results section.)
f) Electrolysis at pH 12, quoted from Part II.[3g]
g) Electrolysis was interrupted at the point where formation of a primary amine was still negligible.
h) mol per mol electrolysed, %.

The peak potential and wave form of the second wave of ephedrine closely resembled that of phenylacetylcarbinol much better than that of methylamine. The second wave of N-methyl and N-ethylephedrines also did not coincide with the oxidation wave of dimethylamine and methylethylamine, respectively, but with that of phenylacetylcarbinol, though the secondary amines are the major oxidation product from both compounds (Table II). The voltammetric waves for methylamine, dimethylamine and methylethylamine in aqueous buffer solution are rather ill defined and drawn out over appreciable potential range, while phenylacetylcarbinol shows a sharp peak. 1-Chloro-2-methylamino-1-phenyl-propane and methamphetamine did not show a second wave, because filming on the electrode surface owing to the oxidation products at the first wave prevented the development of the second wave (see next section).

Product obtained on Controlled Potential Electrolysis

Controlled potential electrolyses were carried out at about pH 10 and about 0.1—0.15 V more positive potentials than the first peak potentials using a glassy-carbon plate electrode. Since the electrolytic current of the electrolysis carried out at the potential near the first peak did not fall to the background current even on prolonged electrolysis, the little higher potential was used. The electrolytic current, under the above condition, decreased exponentially with time and fell to the background value. The results of the electrolysis are shown in Table II.

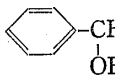
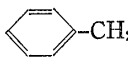
Ephedrine and ephedrine analogues were oxidized through two-electron oxidation and predominantly yielded phenylacetylcarbinol and the counterpart alkyl amines. In contrast with the results of anodic oxidation of aliphatic tertiary amines,[3g] only a very little demethylation was observed. In exhaustive electrolyses, further oxidation of the primary oxidation products was considered to occur, because the same matter was observed in the case of aliphatic tertiary amines.[3g] In the present study, however, the further oxidation was observed to occur much less extent than that observed in the previous case, probably because the potentiometer used has much better response than the older one and the potentials applied for the electrolysis of the starting amines are at least 0.40 V less positive than those of the major oxidation products.

Electrolysis of 1-chloro-2-methylamino-1-phenylpropane was interrupted at the point where about five per cent of the starting amine was consumed, since this amine caused heavy filming on the glassy-carbon electrode on electrolysis. Preparative electrolysis of methamphetamine was essentially impossible because of much heavier filming on the electrode than that observed on the above compound.

Products from Oxidation with Potassium Hexacyanoferrate (III)

As the large scale electrolysis of methamphetamine was impossible, the oxidation of methamphetamine together with ephedrine was carried out with alkaline potassium hexacy-

Table III. Yields[a] of Products from the Oxidation of Ephedrine and Methamphetamine by Potassium Hexacyanoferrate(III); 1.02×10^{-2} M—$K_3Fe(CN)_6$, *ca.* 2×10^{-2} M—Amine, 2 M—KOH in 30% Aqueous Methanol

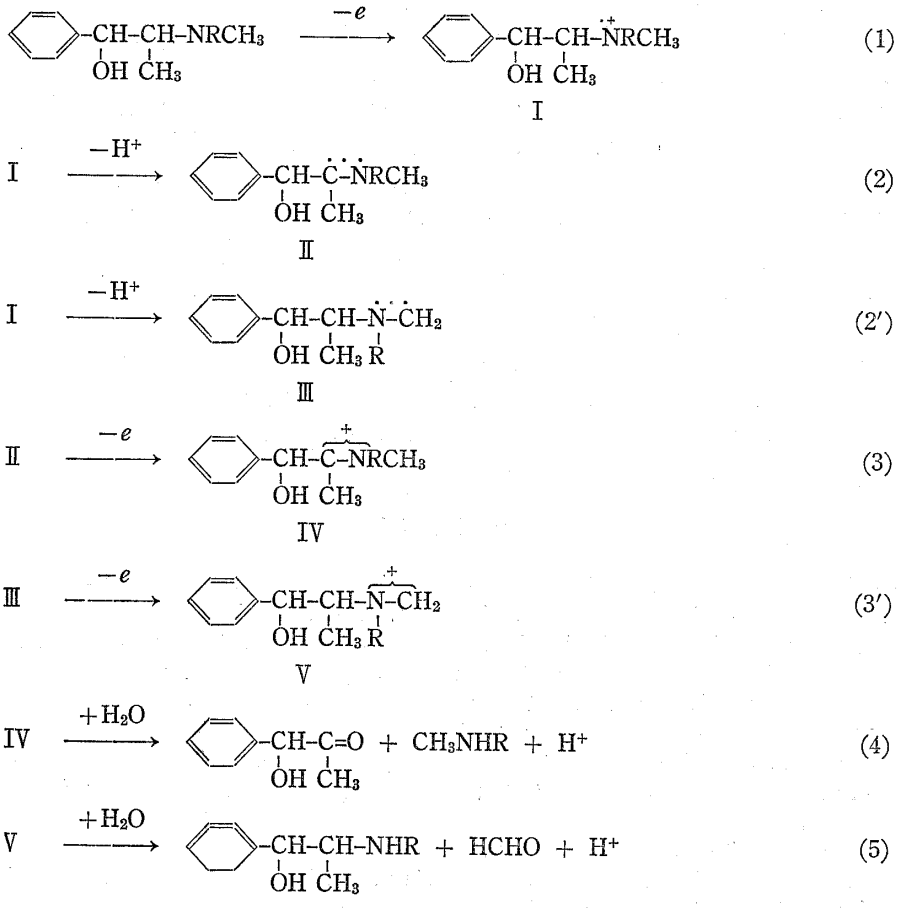
Amines	Products[a]	
	HCHO	$MeNH_2$
	8.5—11	95
	24 —35	76

a) mol per cent based on oxidant, average of three experiments.

anoferrate (III) in 30% aqueous methanol[1d] to examine the effect of β-hydroxy group on the relative amount of products. As shown in Table III. the ratio of methylamine to formaldehyde in the case of ephedrine is about 9:1, while in the case of methamphetamine this ratio is reduced to about 3:1.

Discussion

From the product analysis and the n value of about two, the similar reaction scheme as that proposed for the electrochemical oxidation of aliphatic tertiary amines[3g] is suggested for anodic oxidation of ephedrine and its analogues.



It is most probable to consider that the oxidation is initiated by an electron transfer from the amino-nitrogen to form aminium cation radical (I), because (i) observed potentials for the first peak are rather less but close to those of the corresponding aliphatic amines, (ii) no oxidation wave is developed in acidic solution owing to the protonation of the nitrogen, and (iii) the differences in potentials of the first anodic peaks among norephedrine, ephedrine and N-methyl or N-ethylephedrine are similar to those observed in aliphatic primary, secondary and tertiary amines without β-hydroxy group. If the amino-nitrogen forms an intramolecular hydrogen bond with the β-hydroxy group, the potential of the first wave should be more positive than that of the corresponding aliphatic amines without β-hydroxy group, but the observed values are less positive. The hydroxy group, therefore, looks like acting as electron donator to the amino-nitrogen in step (I).

In the studies on the oxidation of unsimmetrically substituted aliphatic tertiary amines, the relative amounts for dealkylation have been claimed to be governed mainly by the number and the acidity of α-protons, and also affected by the ease of the second electron transfer.[3g] The product distribution found in the present work is, however, far from the value predicted

on the basis of the number of α-protons, suggesting that the total rate of steps (2) and (3) is much faster than that of steps (2′) and (3′). Thus the loss of the alkyl group from the nitrogen is not governed by the number of α-protons, but by the other factors, that is, the acidity of α-protons, the ease of the second electron transfer from (II) and (III), or the stability of cations (IV) and (V). In 2-dimethylaminoethanol and N,N-dimethylbenzylamine, such large discrepancies from simple alkyl tertiary amines as above were not observed.[3g]

To explain the less positive potentials for the first wave of those compounds than those of the amine without hydroxy group and the relative amount of the dealkylation, the contribution of the hydroxy group must be considered together with that of the phenyl group. The hydroxy group at the benzyl carbon is hardly ionized at pH 10, therefore, the through bond inductive effect of free hydroxy group should work as electron withdrawing as chlorine atom does, and thus the dealkylation ratio can be understood qualitatively, but the observed oxidation potential is against the above effect. If a through-space interaction between the alcohol oxygen and the aminium-nitrogen can stabilize aminium cation (I),[3e] the oxidation potential in step (1) should be lower, and the electron-withdrawing effect of free hydroxy group make deprotonation step (2) more predominant than (2′). At present, we can not say what sort of through-space interaction is possible in those cases. Considering further the results of the similar anodic oxidation reported for 2-dimethylaminoethanol and N,N-dimethylbenzylamine,[3g] in which the first wave potentials are more positive and the percentage of demethylation was larger than those for ephedrine and the analogues, and also those observed in the oxidation of 1-chloro-2-methylamino-1-phenylpropane and methamphetamine in the present work, the effect of the phenyl group on the carbon atom bonded with hydroxy group looks like assisting or rather multiplying the effect of the hydroxy group.

Work along this line is in progress.

Experimental

Reagents——Japanese pharmacopoeia grade *l*-ephedrine hydrochloride, *d,l*-N-methylephedrine and methamphetamine were used without further purification. N-Etyhlephedrine was prepared by ethylation of ephedrine hydrochloride with ethyl iodide in benzene containing potassium carbonate. The reaction was carried out in a sealde stainless tube at 100° for 20 hr. The crude N-ethylephedrine was purified by column chromatography on a silica gel. N-Etyhlephedrine hydrochloride was recrystallized from ethanol-ethyl acetate (mp 175—178°). Phenylacetylcarbinol[5] and 1-chloro-2-methylamino-1-phenylpropane[6] were prepared according to the literatures. The infrared (IR) spectrum of phenylacetylcarbinol displayed strong absorption in chloroform at 3450 cm^{-1} (HO), 1715 cm^{-1} (C=O) and at 1360 cm^{-1} ($COCH_3$). On cyclic voltammetry at pH 10, phenylacetylcarbinol showed a single anodic wave (Table I, Fig. 1). Ethylmethylamine was prepared and purified by the standard method.[7]

Cyclic Voltammetry——Cyclic votammetry was carried out with the same apparatus and the procedures as described previously,[8] except for the cleaning procedures of the working electrode. After each run the working electrode was rinsed with and subjected to electrical pretreatment, *i.e.*, twice voltage sweep fron *ca.* −0.1 to *ca.* 1.50V. Measurements were made at 25±0.05° in a carbonate buffer solution (0.1M Na_2CO_3-$NaHCO_3$) with the amines of *ca.* 5 mM.

Controlled Potentiac Electrolysis——Eledtrolyses were performed with the same apparatus as described previously.[8] The quantity of electricity consumed in the electrolysis was calculated by integration from the current-time curve. The anode compartment was separated by an agar plug and frittered flass disk. The electrolysis was carried out with the amine concentration of *ca.* 10 mM in a buffer solution of pH 10 with mechanical stirring.

Oxidation of Ephedrine and Methamphetamine by Potassium Hexacyanoferrate (III)——Oxidations were carried out at 80° in a sealed glass tube by mixing 30% aqueous methanolic solutions of 2M poatssium hydroxide and 10.7 mM potassium hexacyanoferrate (IIII) with about two-fold molar excess of the amine. The reaction mixture was cooled to room temperature when the mixture became colourless, and the aliquot was used for the analysis of methylamine and formaldehyde.

5) K. Kaji, *Yakugaku Zasshi*, **77**, 855 (1957).
6) K. Tanaka, *Yakugaku Zasshi*, **70**, 212 (1950).
7) H.E. Baumgarten, "Organic Syntheses," Col. Vol. V, John Wiley and Sons, Inc., New York, 1973, p. 758.
8) H. Sayo and M. Masui, *J. Chem. Soc. Perkin II*, **1973**, 1640.

Products Analysis:——a) Amines: The secondary and the primary amines obtained on electrolyses were analysed as their sulphonamides.[9] Methylamine obtained on oxidation by potassium hexacyanoferrate (III) was estimated by gas–liquid chromatography. Stainless steel columns (2 m × 3 mm) packed with P.E.G. 20M (Nishio Kogyl Co.,) were used at 80° in a JEOL JGC-750 20K gas chromatograph.

(b) Other Products: Phenylacetylcarbinol was identified by thin–layer chrolmatography (TLC) as 2,4-dinitrophenylhydrazone. Quantitative determination of the carbinol was carried out by a Waters high speed liquid chromatograph Model 6000 equipped with spectrophtometric detector (JASCO UVIDEC-1). Analyses were performed on a column packed with BONDAPAK C_{18}. Eluent was 12% aqeous methanol and the wavelength of the spectrometer was adjusted to its absorption maximum, 248 nm

Formaldehyde was determined by the method of Tannenbaum and Brickler.[10]

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9) *a*) W.R. Gray and B.S. Hatrley, *Biochem. J.*, **89**, 59 (1963); *b*)N. Seiler and M. Weichmann, *Z. Anal. Chem.*, **220**, 109 (1966).

10) M. Tannenbaum and C.E. Bricker, *Anal. Chem.*, **23**, 354 (1951).