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Anodic Oxidation of Amines. VI.[1] Revised Reaction Scheme for the Oxidation of Ephedrine

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The anodic oxidation of ephedrine was reexamined in aqueous buffer solution at pH 10. Cleavage of the (α)C-(β)C bond occurs predominantly in the initial chemical process to give benzaldehyde, rather than the usual C–N bond fission such as that observed in the simple aliphatic amines. A revised scheme for the anodic oxidation is proposed.

Keywords——ephedrine; anodic oxidation; glassy-carbon electrode; (α)C–(β)C bond fission; benzaldehyde

We have previously studied the anodic oxidation of ephedrine and related compounds in aqueous buffer solution at a glassy-carbon electrode,[1] and found that the effects of the hydroxy group on the first oxidation potential and the relative amounts of the oxidation products, that is, those of dealkylation of the alkylamine moiety, were extremely complex. However, based on the reaction scheme proposed for the anodic oxidation of simple aliphatic amines,[3] a tentative scheme was suggested for the oxidation.

Among many papers reporting chemical and electrochemical oxidation of α,β-alkanolamines, several have described the production of carbonyl compounds as the final products *via* (α)carbon(β)carbon fission[4] instead of C–N bond fission.[5] Similar C–C bond fission to produce carbonyl compounds is usually observed in the oxidation of 1,2-glycols.[6]

Taking the reported results into consideration, we reexamined the anodic oxidation of ephedrine and found an error in the previous study.[1] The main product was previously identified as phenylacetylcarbinol by comparison of its cyclic voltammogram and behavior on high performance liquid chromatography (HPLC) and TLC with those of an authentic sample and by similar comparison of the 2,4-dinitrophenylhydrazones. However, further study has now shown this product to be benzaldehyde. The oxidation scheme is, therefore, revised in this paper.

Results and Discussion

When the electrolyzed solution was analyzed by gas-liquid chromatography (GLC) instead of high performance liquid chromatography (HPLC) and TLC, a peak corresponding to benzaldehyde rather than phenylacetylcarbinol was observed. The identity of this material as benzaldehyde was confirmed by the elemental analysis data for the 2,4-dinitrophenylhydrazone.

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[2] Location: *133-1, Yamada-Kami, Suita-shi, Osaka.*

[3] H. Sayo and M. Masui, *J. Chem. Soc.* (*B*), **1971**, 1593.

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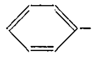
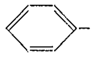
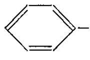
Table I. Anodic Oxidation Products of Ephedrine in Buffer Solution of pH 10 at a Glassy-Carbon Electrode

$E_{app.}$[a]	n[b]	Products	Yield (%)[c]
1.04	2.29—2.66	 -CHO	65
		 -COOH	12
		MeCHO	68
		$MeNH_2$	87
		HCHO	12
		 -CH-CHNH$_2$ OH Me	9[d]

[a] V *vs*. SCE.
[b] Coulombs passed per mole of the starting material.
[c] mol per cent yield on the basis of the starting material.
[d] Cited from Part. V.[1]

The results are shown in the Table. The coulometric n value tended to increase as the duration of electrolysis was increased.

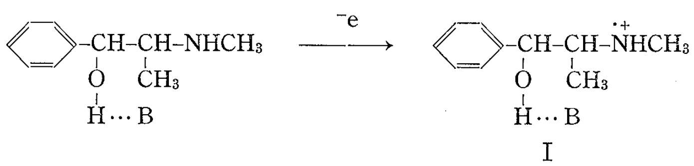
The error in the previous paper was a result of the experimental procedure used to identify the compound. Phenylacetylcarbinol shows essentially the same behavior as benzaldehyde under the conditions employed. Phenylacetylcarbinol also seemed to be a reasonable product, based on the oxidation mechanisms of simple aliphatic amines.

Phenylacetylcarbinol was converted into benzaldehyde on exposure to air in the alkaline aqueous buffer solution with mechanical stirring, but the amount formed in the time required for the electrolysis (usually less than five hours) was rather small. This observation and the n value (2.2—2.6) suggest that almost all of the benzaldehyde was produced directly during the electrolysis of ephedrine.

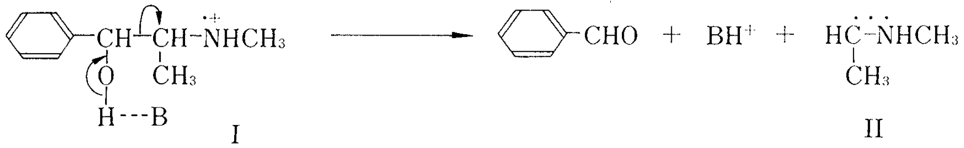
The crude 2,4-dinitrophenylhydrazones prepared by treating the electrolysis solution with 2,4-dinitrophenylhydrazine showed several GLC peaks which coincided with those for the hydrazones of crotonaldehyde, cinnamaldehyde and acrolein in addition to those of benzaldehyde, acetaldehyde and formaldehyde. This indicates that the recoveries of benzaldehyde, acetaldehyde and formaldehyde from the solution after the electrolysis are reduced by side reactions among the aldehydes during prolonged electrolysis under basic conditions (pH 10).

Benzoic acid and formaldehyde were produced when benzaldehyde (*ca*. 10^{-2} M) and methylamine (*ca*. 5×10^{-3} M) were subjected to electrolysis in the buffer solution at the potential used for the electrolysis of ephedrine, and the amounts increased with time up to about 30% and 15%, respectively, at fifteen hours. Benzaldehyde and methylamine, however, were less easily oxidized by air to benzoic acid and formaldehyde, respectively, when no current was passed.

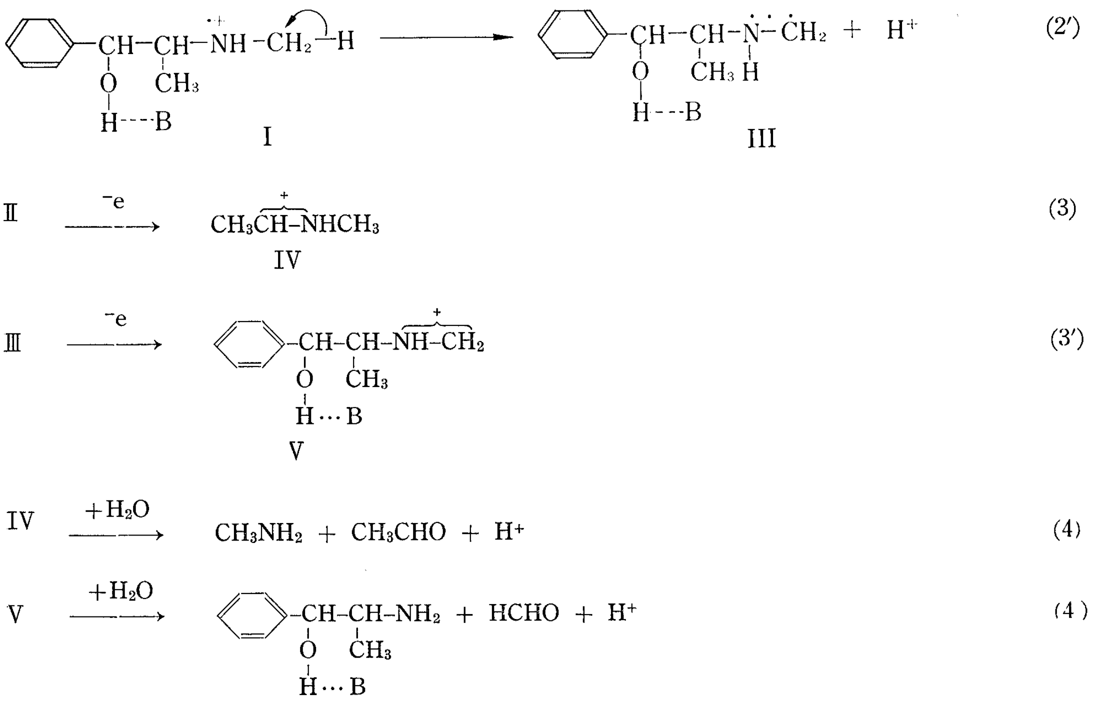
The reaction scheme proposed in the previous paper, therefore, must be altered as follows.



(1)



(2)



B : base

The oxidation is considered to be initiated by electron transfer from the amino-nitrogen to form the cation radical (I) as described in the previous work.[1] The product distribution shows that the total rate of steps (2), (3) and (4) is much faster than that of steps (2′), (3′) and (4′). The main effect of the hydroxy group on the reaction is, therefore, considered to be intermolecular hydrogen bonding to base molecules in the solution. This induces net negative charge on the oxygen atom, which makes the oxidation potential less positive, and also promotes cleavage of the (α)C-(β)C bond to produce a stable aldehyde, BH^+ and a radical (II) (eq. (2)) in preference to deprotonation from the methyl carbon (eq. (2′)). Since deprotonation from oxygen is usually much faster than that from carbon,[7] these considerations seem reasonable.

The results observed for the anodic oxidation of ephedrine are better explained by revised reaction scheme than by that proposed previously. Further work is in progress to confirm the reaction process and to clarify the effects of other factors on the reaction.

Experimental

Reagents——1-Ephedrine hydrochloride, benzaldehyde, acetaldehyde and phenylacetylcarbinol were obtained in the manner described in the previous paper.[1] Reagent grade crotonaldehyde, cinnamaldehyde and acrolein were used without further purification.

Apparatus and Procedures——Cyclic voltammetry and controlled potential electrolysis were performed with the apparatus and procedures described in the previous paper.[1] The quantity of electricity consumed during electrolysis was measured with a Hokuto Denko HF-102 coulombmeter.

Products Analysis——a) Amines: Methylamine and norephedrine were analyzed as their sulfonamides in the manner described previously.[1]

b) Aldehydes: Formaldehyde was determined by the method described previously.[1] Acetaldehyde was determined by means of the iodoform reaction.[8] Benzaldehyde was estimated by gas chromatography. A stainless steel column (2 m × 3 mm) packed with P.E.G. 20 M (Nishio Kogyo Co.) was used at 170° in a JEOL JGC-750 20 K gas chromatograph. Benzaldehyde was also identified as its 2,4-dinitrophenylhydrazone; *i.e.*, a solution after electrolysis was acidified with 5N HCl and extracted with ether, then the ether was

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7) J. Hine, "Physical Organic Chemistry," International Student Edition, McGraw-Hill Book Co. Inc., Kogakusha Co., Tokyo, 1962, p. 112 and p. 236.

8) S.D. Nogare, T.O. Norris and John Michell, Jr., *Anal. Chem.*, **23**, 1473 (1951).

evaporated off under reduced pressure. Next, 10 ml of ethanol and an excess of 2,4-dinitrophenylhydrazine in 2N HCl were added to the residure. The amorphous crystalline product was recrystallized from ethanol–DMF. mp 242—243° *Anal.* Calcd for $C_{13}H_{10}N_4O_4$: C, 54.55; H, 3.52; N, 19.58. Found: C, 54.44; H, 3.38; N, 19.48. No mixed melting point depression was observed. The IR spectrum of the crystalline product was identical with that of an authentic sample.

2,4-Dinitrophenylhydrazones of crotonaldehyde, cinnamaldehyde and acrolein were identified by GLC using a column packed with silicone SF-96[9] and using a column packed with P.E.G. 20M, maintained at 250° and 160°, respectively.

c) Benzoic Acid: The IR spectrum of the product extracted from the electrolyzed solution with ether after addition of concentrated hydrochloric acid and 2,4-dinitrophenylhydrazine, and purified by sublimation, was identical with that of an authentic sample. The amount of the acid in the electrolyzed solution was estimated using i) the spectrophotometric method of Tamura[10] and ii) HPLC (Waters Associates Inc., model 6000, and Nihon Bunko UVIDEC-1). In HPLC, the solution (20 μl) was analyzed on a column packed with BONDAPAK C_{18} using 20% aqueous methanol as an eluent. The absorption maximum of benzoic acid at 223 nm was used for estimation.

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Syntheses of Two Microbial Metabolites, 5-Chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin and 8-Hydroxy-6-methoxy-3-methylisocoumarin[1]

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The racemate of 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (I), a fungal metabolite of *Periconia macrospinosa*, was synthesized from 6-chloro-3,5-dimethoxyhomophthalic acid (III) *via* compounds IV, VI, VII and VIII. Catalytic hydrogenation of V resulted in dechlorination, yielding 6-methoxy-8-hydroxy3-methylisocoumarin (II), another natural product from *Streptomyces mobaraensis*.

Keywords——fungal metabolite; *Periconia macrospinosa*; chloroisocoumarin; chloro-3,4-dihydroisocoumarin; 3,4-dihydro-8-hydroxyisocoumarin; *Streptomyces mobaraensis*

In 1969, Giles and Turner isolated a chlorine-containing metabolite from a fungus, *Periconia macrospinosa*, and identified it as 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin(I).[3] We have recently reported that oosponol(8-hydroxy-4-ω-hydroxyacetylisocoumarin) and oospolactone (8-hydroxy-3,4-dimethylisocoumarin), isolated by us from a wood-rotting basidiomycete, *Gloeophyllum sepiarium*, have antifungal activities[4,5] Later

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[1] This work was presented at the 99 th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August 1979, p. 308.

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