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Oxidative Bond Fission of β-Alkanolamines by Chlorine Dioxide and the Effect of an Oxymethylene Group at the β-Carbon on the Reaction

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Oxidative bond fission of β-alkanolamines, $R^1R^2C(OH)CR^3_2NHR^4$ (group A amines) and R^5-O-$CH_2CH(OH)$-CH_2NHR^6 (group B amines) by chlorine dioxide was studied in buffer solution of pH 10, and the results were compared with those obtained by electrochemical oxidation of group A amines. No significant difference was found between the two groups of amines, and the fission mainly occurred at the C–N rather than the (α)C–(β)C bond except in the case of the amine in which R^1=phenyl. Chlorine dioxide oxidation, in general, caused more C–N bond fission than electrochemical oxidation did, and the reason for this is discussed.

Keywords——chlorine dioxide; oxidation; β-alkanolamine; β-blocker; cyclic voltammetry; bond fission

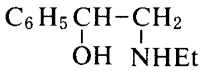
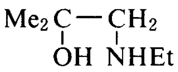
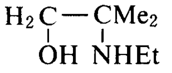
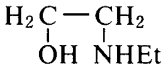
Oxidative bond fission of β-alkanolamines, $R^1R^2C(OH)CR^3R^4NR^5R^6$, where R^1—R^4 are hydrogen atoms, alkyl or phenyl groups (group A amines) and R^5, R^6 are hydrogen or alkyl groups, was studied in the previous paper by using electrochemical methods,[1] and it was found that these amines are mostly cleaved through the (α)C–(β)C bond when at least one of the R groups is phenyl, nearly half cleaved through this bond when R is alkyl, and only about a tenth cleaved through this bond when R^1—R^4 are all hydrogen. Among β-adrenergic blocking agents there are several amines having the structure R^1-O-CH_2-$CH(OH)$-$CH_2NR^2R^3$ (group B amines). This structure has both a β-alkanolamine and an adjacent glycol moiety in the molecule. Hence, it is of interest to investigate the relative rates of oxidative bond cleavages of the amines. Electrochemical oxidation was first applied but heavy filming of the carbon electrode during the oxidation of most of the group B amines made this approach impossible. Chlorine dioxide was therefore used as an oxidant in the present work, since Mann *et al.* had reported that electrochemical oxidation of amines and chemical oxidation by chlorine dioxide are similar, though they did not describe the relative amounts of the oxidation products.[2] Some preliminary tests using hypochlorite and chlorine dioxide in aqueous alkaline media indicated that the use of the latter reagent gave satisfactory results.

As regards the oxidative bond fission, some difference was found between the electrochemical oxidation and chemical oxidation by chlorine dioxide, and the effect of an oxymethylene group at the β-carbon on the bond fission is probably the reason for the fact that the fission occurs mainly at the C–N bond rather than at the (α)C–(β)C bond in the chemical oxidation.

Results

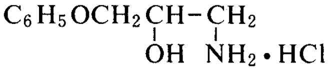
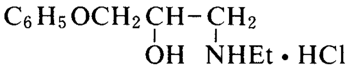
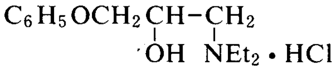
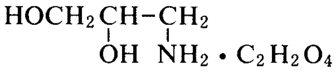
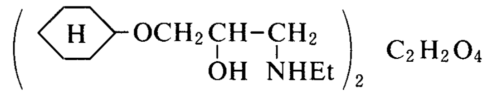
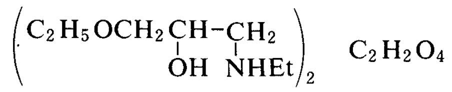
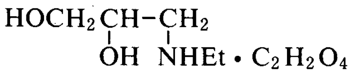
The oxidation was carried out at pH 10, because the anodic oxidation reported in the previous paper was performed at the same pH and the products of the oxidation did not consume chlorine dioxide, ClO_2^- or ClO_3^- under the conditions used.[3] On the reaction of **1** with two mole equivalents of chlorine dioxide, known to be a one-electron oxidant, at room temperature for up to one hour, the absorption of chlorine dioxide (380 nm) disappeared and the absorbance of benzaldehyde (250 nm) reached a maximum. Hence, one hour was thought to

TABLE I. Products of ClO_2 Oxidation and Anodic Oxidation of Group A Amines

	Compds.	Products	Yield, %[a] Mean (Limit)	
			ClO_2 Oxi.	Anodic Oxi.[b]
1	 $C_6H_5\underset{OH}{CH}-\underset{NHEt}{CH_2}$	C_6H_5CHO	98 (5)	75 (5)
		HCHO	79 (6)	67 (2)
		NH_2Et	91 (4)	79 (6)
		MeCHO	13 (4)	10 (2)
2	 $Me_2\underset{OH}{C}-\underset{NHEt}{CH_2}$	Me_2CO	5 (0.1)	43 (5)
		HCHO	17 (1)	18 (2)
		NH_2Et	65 (4)	35 (3)
		MeCHO	28 (0.2)	34 (9)
3	 $H_2\underset{OH}{C}-\underset{NHEt}{CMe_2}$	HCHO	12 (3)	50 (1)
		Me_2CO	7 (3)	66 (3)
		NH_2Et	6 (0.2)	44 (2)
		MeCHO	92 (4)	26 (3)
4	 $H_2\underset{OH}{C}-\underset{NHEt}{CH_2}$	HCHO	5 (0.3)	14 (2)
		NH_2Et	43 (1)	43 (1)
		MeCHO	65 (2)	44 (4)

a) Determined based on chlorine dioxide.
b) M.Masui, Y.Kamada, E.Sasaki and S,Ozaki, *Chem. Pharm. Bull.*, **30**, 1234 (1982).

TABLE II. Cyclic Voltammetric Data for Group B Amines at pH 10

	Compds.	E_p[a]
	 $C_6H_5OCH_2\underset{OH}{CH}-\underset{NH_2\cdot HCl}{CH_2}$	1.36
5	 $C_6H_5OCH_2\underset{OH}{CH}-\underset{NHEt\cdot HCl}{CH_2}$	0.93
	 $C_6H_5OCH_2\underset{OH}{CH}-\underset{NEt_2\cdot HCl}{CH_2}$	0.70
	 $HOCH_2\underset{OH}{CH}-\underset{NH_2\cdot C_2H_2O_4}{CH_2}$	1.54
6		1.00
7	 $\left(C_2H_5OCH_2\underset{OH}{CH}-\underset{NHEt}{CH_2}\right)_2 C_2H_2O_4$	0.95
8	 $HOCH_2\underset{OH}{CH}-\underset{NHEt\cdot C_2H_2O_4}{CH_2}$	1.02

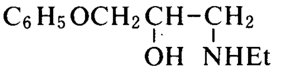
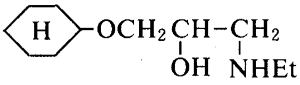
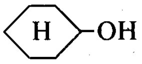
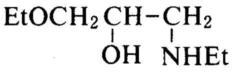
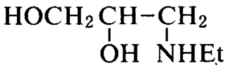
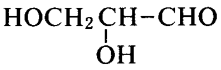
a) Values are V *vs.* SCE measured with 5 mM amines at a sweep rate of 50 mV/s.

be sufficient for the oxidation under these conditions, which were also applied for the other amines. The estimation of products was performed after reaction for one hour. The results for group A amines having no oxymethylene group on the β-carbon are shown in Table I together with the results of anodic oxidation.

In the case of amines (**1**) and (**4**),the relative rates of bond fissions seem to be quite similar for both oxidation methods, that is, one phenyl group at the β-carbon makes the (α)C–(β)C bond fission predominant, whereas when R^1—R^4 are all hydrogen atoms, C–N bond fission is predominant. In the cases of amines (**2**) and (**3**), in contrast the amount of acetone produced by (α)C–(β)C bond cleavage is very small in chlorine dioxide oxidation. With amine (**2**), the amount of ethylamine is larger for the chlorine dioxide oxidation, though the amount of formaldehyde is similar, and with amine (**3**), the amounts of formaldehyde, acetone and ethylamine are less than 10% in the oxidation by chlorine dioxide, while that of acetaldehyde is almost 90%. The results indicate that the relative rate of (α)C–(β)C bond cleavage is smaller in the chlorine dioxide oxidation than in the anodic oxidation, except in the case of amine (**1**), which has a phenyl group at the β-carbon. In particular, the chlorine dioxide oxidation mainly cleaves the N–C bond of the ethylamino group in amine (**3**), whereas the anodic oxidation mostly cleaves the (α)C–(β)C bond. The results are different from those reported by Dennis *et al.*4) They reported that C–C bond scission was the oxidative reaction path for the chlorine dioxide oxidation of β-amino and β-hydroxy amines, though they did not carry out exact estimation of all the products of the oxidation.

Only cyclic voltammetry was successful for the electrochemical study of group B amines. The results of preliminary tests on the variation of the peak height and potential with pH of the solution and the values in Table II show that the oxidation of group B amines also occurs at the amino nitrogen.

TABLE III. Products of Chlorine Dioxide Oxidation of Group B Amines

	Compds.	Products	Yield, %a) Mean (Limit)
5	 $C_6H_5OCH_2\underset{OH}{CH}-\underset{NHEt}{CH_2}$	HCHO	3 (0.2)
		NH_2Et	49 (2)
		$C_6H_5OCH_2CHO$	Not detected
		MeCHO	50 (6)
		C_6H_5OH	30 (0.2)
6		HCHO	5 (0.2)
		NH_2Et	54 (1)
		MeCHO	55 (1)
			18 (1)
7	 $EtOCH_2\underset{OH}{CH}-\underset{NHEt}{CH_2}$	HCHO	4 (0.4)
		NH_2Et	55 (1)
		MeCHO	53 (1)
		EtOH	Trace
8	 $HOCH_2\underset{OH}{CH}-\underset{NHEt}{CH_2}$	HCHO	2 (0.1), 7 (3)b)
		NH_2Et	56 (2), 33 (2)b)
		$HOCH_2CHO$	Not detected
		MeCHO	53 (4), 42 (8)b)
		 $HOCH_2\underset{OH}{CH}-CHO$	Trace

a) Determined based on chlorine dioxide.
b) Yield from anodic oxidation.

Though the reason is not clear, very heavy filming of the electrode during oxidation completely prevented further electrochemical study of group B amines except for amine (**8**). Chlorine dioxide, therefore, was used in this oxidation study. The results are shown in Table III.

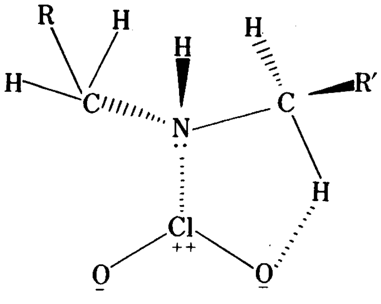
With the amines (**5**—**8**), the most common and distinct feature is that the amount of formaldehyde derived from the C–C bond fission is quite small, and the total amount of products from C–N bond fission, acetaldehyde and ethylamine, is almost quantitative. Even a phenoxymethylene group on the β-carbon (amine **5**) only slightly affects the oxidative fission around the amino group. About 30% phenol was obtained in the oxidation of amine (**5**). Without electrolysis, **5** did not produce any phenol on standing for at least 72 h in the buffer solution of pH 10.

Neither 2-hydroxyethanal from amine (**8**) nor 2-phenoxyethanal from amine (**5**) was detected in the solution after electrolysis. Isolation of glyceraldehyde from the oxidation of amine (**8**) was the only successful case of detection of hydroxyaldehyde production. Controlled potential electrolysis of group B amines was successful only for amine (**8**), and the result is rather similar to that of the chlorine dioxide oxidation.

Discussion

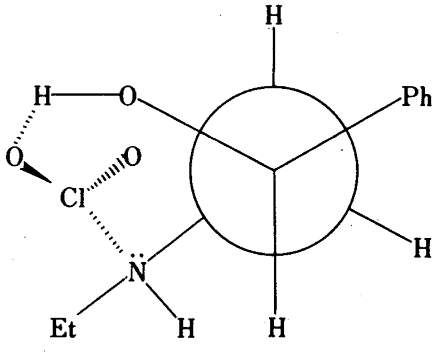
Both anodic and chlorine dioxide oxidations mainly cleave β-alkanolamine at the (α)C–(β)C bond when a phenyl group is present on the β-carbon, but with the other β-alkanolamines the oxidaton by chlorine dioxide causes much less (α)C–(β)C bond cleavage. Though a fair amount of α-hydroxyaldehyde, $Me_2C(OH)$–CHO and $CH_2(OH)$–CHO, must be produced from **2** and **4** , respectively, and the aldehydes could not be detected, the total amount of ethylamine and acetaldehyde indicates that the main reaction is C–N bond cleavage in the oxidation by chlorine dioxide. In the case of amine (**3**) too, the C–N bond between the nitrogen and the α-carbon without hydrogen is not cleaved directly$^{5)}$ and oxidative fission occurs mostly at the C–N bond between the nitrogen and the ethyl group. In amine (**5**), the effect of phenyl group is greatly weakened by the insersion of an oxymethylene group between the phenyl and the β-carbon, and in terms of the oxidative bond fission, amine (**5**) resembles the other amines having no phenyl group on the β-carbon, except for the formation of a fair amount of phenol. The amount of products shown in Table III and the experimental conditions suggest that the phenol must be derived from the decomposition of the primary oxidation product, probaby 2-hydroxy-3-phenoxypropanal. The origin of alcohols formed from (**6**) and (**7**) may be similar.

As regards oxidative bond fission, therefore, many β-adrenergic blocking agents having an aryloxymethylene group on the β-carbon to the amino nitrogen may well undergo C–N bond fission predominantly, rather than the C–C fragmentation observed for ephedrine and other similar amines.



I

Fig. 1



II

Fig. 2

To explain why the chemical oxidation by chlorine dioxide results in cleavage of the C–N bond rather than that of the C–C bond which is generally observed in electrochemical oxidation of β-alkanolamines, the molecular geometries I (Fig. 1) and II (Fig. 2) must be considered.

When the chlorine atom of chlorine dioxide approaches the nitrogen to be oxidized, one of the oxygens of chlorine dioxide is also close to the hydrogen on the α-carbon to the nitrogen (see Fig. 1), because the bond lengths of N–C and Cl–O are both nearly 1.5 Å,[6a)] and the oxygen acts as a good proton acceptor. When a phenyl group is present on the β-carbon to the amino nitrogen, a conformer such as that as shown in II is predominant (Fig. 2),[6b)] and in this case, proton abstraction from the hydroxy group will be considerable. In electrochemical oxidation, geometry such as I is not present, and the proton acceptor is a water molecule near the amine, so the probability of deprotonation or liberation of carbocation is mainly governed by the acidity and the number of α-protons, or the stability of hydroxycarbocation, $[R^1R^2C(OH)]^+$.[1,5)]

If the supposed hydroxyaldehydes produced in the oxidation of group B amines are oxidized or decomposed to give resinous products in the course of the experiments, this would explain the heavy filming of the electrode surface in the electrochemical oxidation and the failure to detect them in the solution after chlorine dioxide oxidation. The validity of this assumption has yet to be tested experimentally.

Experimental

Reagents——Group A (**1**—**4**) were prepared by the procedures previously reported.[1)] The HCl salt of **5** was prepared by the reaction of glycidyl phenyl ether with ethylamine.[7)] mp 119—120°C (lit.[8)] 126°C). (*Anal.* Calcd for $C_{11}H_{18}ClNO_2$: C, 57.0; H, 7.83; Cl, 15.3; N, 6.04. Found: C, 56.8; H, 7.94; Cl, 15.2; N, 6.11). The oxalates of **6**, **7** and **8** were prepared by ethylaminolysis of 1-chloro-3-cyclohexyloxy-2-propanol, 1-chloro-3-ethoxy-2-propanol and glycidol,[9)] respectively. 1-Chloro-3-cyclohexyloxy-2-propanol and 1-chloro-3-ethoxy-2-propanol[10)] were prepared by reaction of epichlorohydrin with cyclohexanol and ethanol, respectively. Glycidol was purchased from Aldrich Chemical Co. The oxalate of **6**, mp 167—172°C ($C_{24}H_{48}N_2O_8$ requires C, 58.5; H, 9.82; N, 5.69. Found: C, 58.3; H, 10.00; N, 5.73). The oxalate of **7**, mp 106—108°C ($C_{16}H_{36}N_2O_8$ requires C, 50.0; H, 9,44; N, 7.29. Found: C, 49.7; H, 9.69; N, 7.26). δ(DMSO-d_6) 1.10 (6H, m, 2x–CH_3), 2.94 (4H, m, 2x–NH–$C\underline{H}_2$–), 3.35 (4H, m, –CH_2OCH_2–), 3.95 (1H, br, $\geqslant$CH), 7.92 (4H, s, –OH, $>\overset{+}{N}H\cdot C_2H_2O_4$). The oxalate of **8**, mp 124—127°C ($C_7H_{15}NO_6$ requires C, 40.2; H, 7.23; N, 6.70. Found: C, 39.9; H, 7.24; N, 6.73). δ (DMSO-d_6) 1.21 (3H, t, $J=6$ Hz, –CH_3), 2.90 (4H, m, 2x–$N\underline{H}$–CH_2–), 3.36 (2H, m, HO–$C\underline{H}_2$–), 3.75 (1H, br, $\geqslant$CH), 7.69 (5H, s, 2×–OH, $>\overset{+}{N}H\cdot C_2H_2O_4$). Phenoxyacetaldehyde was prepared by lead tetraacetate oxidation of α-glyceryl phenyl ether,[11)] which was obtained by the reaction of phenol with glycerol α-monochlorohydrin. bp 65°C (3 mmHg) [lit.[12)] 94°C (6 mmHg)] (*Anal.* Calcd for $C_8H_8O_2$; C, 70.6; H, 5.92. Found: C, 70.3; H, 5.90).

Apparatus and Procedures——a) Chlorine Dioxide Oxidition: Chlorine dioxide aqueous solution was prepared by the method of Chitani[13)] and stored under refrigeration. The concentration was determined from the absorbancy at 380 nm prior to use.[14)] Oxidations were carried out by adding ClO_2 (5×10^{-5} mol) in 4—10 ml of water to 5 ml of 0.1 M carbonate buffer containing 5×10^{-5} mol of amines at room temperature. Products analysis was performed on the reaction mixture when it had been allowed to stand for about 1 h after disappearence of the yellow color of ClO_2.

b) Cyclic Voltammetry and Controlled Potential Electrolysis: Cyclic voltammetry and controlled potential electrolysis were performd with the same apparatus and procedures as 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) Ethylamine was converted into ethylcarbamate by the method of Gejvall,[15)] and the latter was determined by gas liquid chromatography (GLC) (with ethylbenzoate as an internal standard) using a stainless steel column (2 m×3 mmϕ) packed with PEG 20M (Nishio Kogyo Co.) and maintained at 150°C.

b) Aldehydes: Benzaldehyde and formaldehyde were determined by the method described in the previous paper.[1)] Acetadehyde was determined by GLC, (with ethanol as an internal standard) using a stainless steel column (2 m×3 mmϕ) packed with Ethofat 60/25 (Shimadzu Co.) and maintained at 50°C.

c) Other Products: Acetone was determined by GLC (with ethanol as an internal standard) using a stainless steel column (2 m×3 mmϕ) packed with Ethofat 60/25 (Shimadzu Co.) and maintained at 40°C. Phenol was determined by high performance liquid chromatography (HPLC) (Waters Model 6000) with a spectrophotometric detector (JASCO UVIDEC-1) set at 224 nm, using a Radial-PAK A (Waters Associates, Inc.,) and 35% (v/v) aqueous methanol as an eluent. Cyclohexanol was determined by GLC (with methylbenzoate as an internal standard) using a stainless steel column (2 m×3 mmϕ) packed with Tenax GC (Gasukuro Kogyo) and maintained at 190°C. Ethanol was identified by GLC using a column packed with Ethofat 60/25 and a column packed with Gaskuropak (Gasukuro Kogyō), maintained 100 and 200°C, respectively.

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