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Synthetic Studies by the Use of Carbonates. I. The Nucleophilic Substitution Reaction of Ethylene Carbonate with Amine Hydrohalides

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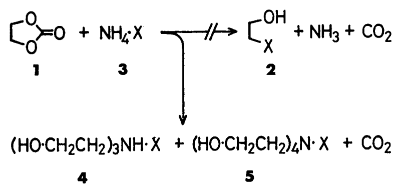
The reaction of ethylene carbonate with various amine hydrohalides gave the corresponding quaternary ammonium salts of *β*-hydroxyethylamines in good yields.

The nucleophilic substitution reactions of ethylene carbonate(**1**) with metal halides, such as potassium fluoride, lithium chloride, and sodium bromide, accompanied by the evolution of carbon dioxide gas, have been shown to give the corresponding ethylene halohydrins, and the reaction with potassium iodide has been shown to give ethylene oxide exclusively.[1] In view of these facts, the present authors attempted the reaction of **1** by ammonium halides and various amine hydrohalides. The results thus obtained will be described in this paper.

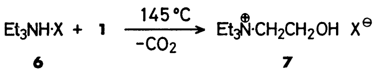
Results and Discussion

On the basis of the idea that the application of ammonium halides to the reaction of **1** in place of the above metal halides may bring about the formation of ethylene halohydrins(**2**), with a concomitant evolution of ammonia and carbon dioxide gas, ammonium bromide(**3**) was allowed to react with three moles of **1** at 145 °C. This reaction, however, afforded no ethylene bromohydrin, but only tri-(**4**) and tetra-*β*-hydroxyethylammonium bromides(**5**) in 54 and 45% (raw sirup) yields (Scheme 1). The structural assignment of **5** was accomplished by converting it into the corresponding perchlorate of the tetra-*O*-acetate.



Scheme 1

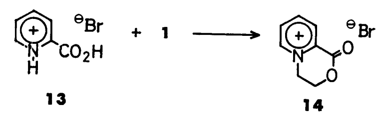
In addition, the reactions of an equimolar portion and two moles of **1** with **3** afforded **4** in 28 and 36% yields, besides the recovered **3** in 13 and 5% yields, respectively; no formation of *N*-mono-, -di-, and -tetra-*β*-hydroxyethylammonium bromides could be detected. Ammonium chloride and iodide also provided no halohydrin, but only unseparable mixtures of the corresponding tri- and tetra-*β*-hydroxyethylammonium halides, in reactions with **1**. Accordingly, such a comparative investigation of the reaction of **1** with these ammonium halides was abandoned. These results, however, led us to the assumptions regarding the reaction that halohydrins and ammonia are generated in the initial stage of the reaction, and that they react with each other successively to afford the products described above.



$$\underset{\mathbf{6}}{Et_3NH{\cdot}X} + 1 \xrightarrow[-CO_2]{145\,°C} \underset{\mathbf{7}}{Et_3\overset{\oplus}{N}{\cdot}CH_2CH_2OH\ X^{\ominus}}$$

Scheme 2

On the basis of these results, various amine hydrohalides were allowed to react with **1**, assuming that this reaction might be a general method for the preparation of *β*-hydroxyethylamine hydrohalides. Prior to the extention, the difference in the reactivity arising from the nature of halide ions was examined by heating an equimolar mixture of **1** and triethylamine hydrohalides (**6**) at 145 °C (Scheme 2). Volumes of the concomitantly-evolved gas were measured with a gas buret at room temperature under atmospheric pressure. In the cases of **6** (X=Br and I), the evolution of *ca.* 95% of the theoretical amount of carbon dioxide gas was observed within 1 hr; a steady state was thus obtained. In the case of **6**(X=Cl), on the other hand, the volume of evolved gas reached *ca.* 130% of the theoretical yield in the reaction with an equimolar **1**.[2] Such an unusual phenomenon may coincide with the exceedingly lowered yield (5%) of triethyl-*β*-hydroxyethylammonium halide(**7**) (X=Cl) in contrast with those of **7**(X=Br, 90%; X=I, 91% yield). In these experiments, the bromide (**7**, X=Br) was proved to be more easily crystallized from ethanol than the chloride and the iodide. Consequently, amine hydrobromides were used in the following experiments. The results thus obtained are summarized in Table 1, while the UV absorption spectral data of aromatic amine derivatives are listed in Table 2. The hydrobromides of tertiary amines, such as trimethylamine, pyridine, 2-(**8**), 4-aminopyridine(**9**), quinoline, 8-quinolinol, and nicotinamide(**10**), gave the corresponding mono-*β*-hydroxyethylammonium bromides in good yields. Moreover, the hydrobromides of primary and secondary amines, such as ethylamine, cyclohexylamine, and morpholine hydrobromides, afforded the corresponding mono-*β*-hydroxyethylammonium bromides selectively; this was in contrast with the corresponding free amines, which have well been known to afford the corresponding *β*-hydroxyethylcarbamates[3] selectively in reactions with **1**. The structural assignments of these products were accomplished on the basis of their UV and NMR spectral data. The structures of **11** and **12**, which were obtained from the reaction of **1** with **8**, and with **9**, were examined, since **8** and **9** have



13 **14**

Scheme 3

TABLE 1. NUCLEOPHILIC SUBSTITUTION REACTION OF ETHYLENE CARBONATE WITH VARIOUS AMINE HYDROBROMIDES[a]

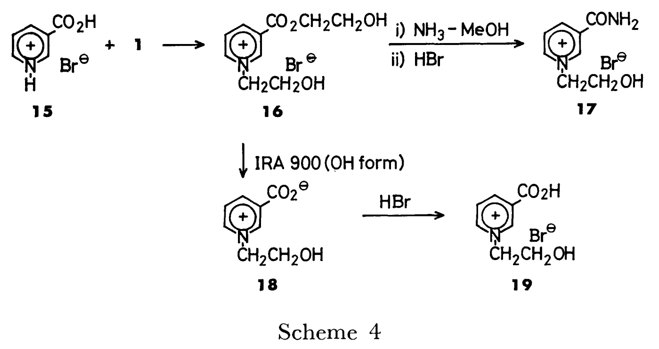
Hydrobromide of	Molar ratio, **1**/Salt	Reaction temp., °C	Period, min	Product[b]	
				Mp, °C[c] (bp/mmHg)	Yield, %
Ethylamine	1.1	140—150	60	(148/15)[d]	32
Cyclohexylamine	1.1	150	60	124—126	70
Morpholine	1.1	155—160	90	(61—63/0.5)[d]	60
Trimethylamine	1.1	140—145	40	230	74
Pyridine	1.5	140—145	50	104—105	81
2-Aminopyridine	1.1	130—135	85	129—131.5	79
4-Aminopyridine	1.1	140—145	70	130—131	99
Quinoline	2.0	145	25	139—139.5	71
8-Quinolinol	2.5	145	45	182.5—183.5	71
Nicotinamide	2.5	155	20	153—154	100
Picolinic acid	2.0	150	15	225	61
Nicotinic acid	5.0	150	40	90—91	87

a) All the reactions were carried out by the use of 10 mmol of the hydrobromides. b) Products are β-hydroxyethylammonium bromides. c) All the melting points are uncorrected. d) These compounds were isolated as free amines.

TABLE 2. ULTRAVIOLET ABSORPTION SPECTRAL DATA OF *N*-β-HYDROXYETHYLAMMONIUM BROMIDES[a]

Bromide	λ_{max}, nm[b]		$\lambda_{shoulder}$, nm[b]	
N-β-Hydroxyethylpyridinium	260 (4500)		254 (3400),	266 (3400)
$N_{(1)}$-β-Hydroxyethyl-2-aminopyridinium (**11**)[d]	232 (7700),	302 (5700)	251 (220)	
$N_{(1)}$-β-Hydroxyethyl-4-aminopyridinium (**12**)	269 (21000)		—	
N-β-Hydroxyethylquinolinium	316 (12500),	236[d] (54000)	258[c] (280)	
N-β-Hydroxyethyl-8-quinolinolium	256 (35400),	363 (150)	275 (2950)	
$N_{(1)}$-β-Hydroxyethylpicolinolactononium (**14**)	265 (7700)		259 (6550),	271 (6900)
$N_{(1)}$-β-Hydroxyethylnicotinamidium (**17**)	265 (3800)		259 (3100),	272 (3200)
$N_{(1)}$-β-Hydroxyethylnicotinate (**18**)[e]	265 (4300)		258 (3400),	272 (3900)
$N_{(1)}$-β-Hydroxyethylnicotinium (**19**)	266 (3800)		260 (3150),	272 (3200)

a) All the spectra were taken in distilled water. b) Numbers in parentheses are molar extinction coefficient (ε). c) The data are of the minimum absorption. d) In the vicinity of this peak, fine structures were observed at 235, 235.5, 237, and 238.5 nm. d) *cf.* Gol'farb, O. N. Setkina, and Y. L. Danyushevskii, *Zh. Obshch. Khim.*, **18**, 124 (1948); *Chem. Abstr.*, **38**, 4137 (1949). e) This is not bromide but inner salt.

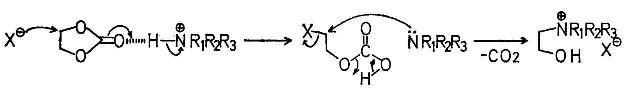


Scheme 4

two potential sites susceptible to the β-hydroxyethylation. Compound **11** was identified with the product of the reaction of **8** with ethylene bromohydrin,[4] and an apparent difference (*ca.* 4.5 Hz) between the $\equiv\overset{+}{N}$–CH_2– NMR signals of **11** (δ 4.32 ppm) and $N_{(1)}$-β-hydroxyethyl-2-aminopyridinium chloride[5] (δ 3.57 ppm) in their chemical shifts was observed. The esterification of **11** with acetic anhydride–trifluoroboron diethyl etherate afforded the corresponding mono-*O*-acetate. Thus, the structure of **11** was identified as $N_{(1)}$-β-hydroxyethyl-2-aminopyridinium bromide. The structure of **12**($\equiv\overset{+}{N}$–CH_2– NMR signal: δ 4.32 ppm) was similarly concluded to be $N_{(1)}$-β-hydroxyethyl-4-aminopyridinium bromide. On the other hand, picolinic acid hydrobromide(**13**) and nicotinic acid hydrobromide(**15**) gave $N_{(1)}$-β-hydroxyethylpicolinolactononium bromide(**14**) [IR 1735 cm^{-1} (six-membered lactone)] and β-hydroxyethyl $N_{(1)}$-β-hydroxyethylnicotinium bromide(**16**) respectively. The treatment of **16** with methanolic ammonia, followed by treatment with aqueous hydrobromic acid, gave $N_{(1)}$-β-hydroxyethylnicotiamidium bromide(**17**), which was identical with the product from the reaction of **1** with **10**; its treatment with Amberlite IRA-900 (OH form) and then with aqueous hydrobromic acid gave $N_{(1)}$-β-hydroxyethylnicotinium bromide(**19**) *via* the zwitter ion, *i.e.*, $N_{(1)}$-β-hydroxyethylnicotinate(**18**).

It can thus be stated, in view of the above results, that this reaction is synthetically advantageous from the following standpoints: 1) The corresponding mono-*N*-β-hydroxyethylated ammonium halides can be prepared in a fairly good yield without regard to whether the amine is aliphatic or aromatic, in contrast with the reactions of **1** with free amines.[3] 2) The process of the reaction can easily be checked by measuring the volume of the carbon dioxide gas evolved in the course of the reaction; this is easier than the procedures involving the reaction of free amines with ethylene halohydrins or those with ethylene oxide in the presence of hydrogen halides or perchloric acid.[6]

The reaction can be assumed to proceed *via* a two-step mechanism; *i.e.*, the first step may be induced by the nucleophilic attack of the halide ion on the methylene carbon atom of **1** to afford an ethylene halohydrin, accompanied by the evolution of carbon dioxide gas; subsequently the resultant amine may attack the methylene carbon, to which the halogen atom is linked, to afford mono-*N*-β-hydroxyethylated ammonium halide, as is shown in Scheme 5.[7]



Scheme 5

Experimental

All the melting points are uncorrected. The IR spectra were determined in potassium bromide disks or neat liquid on a Hitachi EPI-S2 spectrophotometer. The NMR spectra were taken with a Varian T-60 spectrometer, in deuterium oxide as the solvent; the chemical shifts were recorded in δ values relative to sodium 2,2-dimethyl-2-silapentanesulfonate (DSS) as the internal standard, unless otherwise noticed.

*Reaction of Ethylene Carbonate(**1**) with Ammonium Bromide (**3**).* A mixture of **1**(2.7 g, 30 mmol) and **3**(0.9 g, 10 mmol) was heated at 145 °C for *ca.* 1.5 hr until the evolution of carbon dioxide gas has ceased. After the mixture had cooled to room temperature, acetone(30 ml) was added to the mixture. The resultant crystals were filtered and recrystallized from ethanol to give triethanolaminehydrobromide[tri-β-(hydroxyethyl)ammonium bromide](**4**) (2.3 g, 54% yield). Mp 187—189 °C. Found: C, 31.44; H, 6.82; N, 6.18%. Calcd for $C_6H_{16}O_3NBr$: C, 31.31; H, 7.00; N, 6.08%. NMR: δ 3.50 (6H, $-\mathbf{CH_2}-\overset{+}{N}\equiv$) and 3.99 (6H, $-\mathbf{CH_2}-O-$) ppm.

The evaporation of the above filtrate *in vacuo* gave the raw sirup of tetra-β-hydroxyethylammonium bromide(1.1 g, 45% yield). The sirup(2.7 g, *ca.* 10 mmol) was then treated with 1 M sodium ethoxide solution(10 ml), and the mixture was concentrated *in vacuo* to dryness. The residue was treated with anhydrous ethanol(10 ml), and the resultant crystals of sodium bromide were removed by filtration. The solution was neutralized with a 60% aqueous perchloric acid solution and then concentrated *in vacuo* to afford a sirup(1.9 g); this sirup was treated with acetic anhydride(8 ml) in the presence of trifluoroboron diethyl etherate(5 drops) at room temperature and then stirred with methanol(50 ml) for 2 hr, with evaporations *in vacuo* repeated 3 times after the addition of each 20-ml portion of benzene-ethanol(1 : 1 v/v), to give a sirup. The sirup was crystallized in a refrigerator, and the crude crystals were recrystallized from ethanol to give tetra-β-acetoxyethylammonium perchlorate. Mp 103.5—105.5 °C. Found: C, 41.87; H, 6.07; N, 3.21%. Calcd for $C_{16}H_{28}O_{12}NCl$: C, 41.60; H, 6.11; N, 3.03%. NMR(DMSO-d_6, DSS): δ 2.10(12H, -OAc), 4.00(8H, $-\mathbf{CH_2}-\overset{+}{N}\equiv$) and 4.60 (8H, $-\mathbf{CH_2}-O-$) ppm.

On the utilization of an equimolar amount and 2 mol of **1** to **3**, tetra-β-hydroxyethylammonium bromide was not obtained, but tri-β-hydroxyethylammonium bromide was obtained in 28 and 36% yields respectively. Moreover, 13 and 5% recoveries of **3** were observed in these two cases.

*Reaction of **1** with Triethylamine Hydrohalides(**6**). The Measurement of the Velocity of Carbon Dioxide Gas Evolution.* The The reaction vessel used for the measurements was a three-necked, 100-ml, round-bottomed flask fitted with an air-tight stirrer and an Allihn condenser. The top of the condenser was attached to a gas buret. The flask, containing **1**(1.76 g, 20 mmol) and triethylamine hydrohalides (**6**)(20 mmol), was immersed in a constant-temperature bath held at 145±0.2 °C. For the isolation of the products, the reaction mixtures were treated with dried acetone(50 ml); the resulting crystals were filtered and recrystallized from ethanol to give the corresponding triethyl-β-hydroxyethylammonium halides.

The Chloride was obtained as an equimolar mixture with triethylamine hydrochloride; its yield was calculated as 5% by means of the NMR spectrum of the mixture. NMR: δ 1.28 (9H, 3Me), 3.29(6H, $CH_3-\mathbf{CH_2}-\overset{+}{N}\equiv$), and 3.38(2H, $HOCH_2-\mathbf{CH_2}-\overset{+}{N}\equiv$), and 3.94(2H, $-O-\mathbf{CH_2}-$) ppm.

The Bromide: Mp>230 °C. Found: C, 42.74; H, 8.82; N, 6.46%. Calcd for $C_8H_{20}ONBr$: C, 42.48; H, 8.82; N, 6.19%. NMR: δ 1.27(9H, 3Me), 3.29(6H, $CH_3-\mathbf{CH_2}-\overset{+}{N}\equiv$), 3.38(2H, $HOCH_2-\mathbf{CH_2}-\overset{+}{N}\equiv$), and 3.94(2H, $-\mathbf{CH_2}-O-$) ppm.

The Iodide: Mp>230 °C. Found: C, 33.68; H, 7.26; N, 5.03%. Calcd for $C_8H_{20}ONI\cdot 1/2H_2O$: C, 34.05; H, 7.14; N, 4.96%. NMR: δ 1.28(9H, 3Me), 3.40(6H, $CH_3-\mathbf{CH_2}-\overset{+}{N}\equiv$), 3.37(2H, $HOCH_2-\mathbf{CH_2}-\overset{+}{N}\equiv$), and 3.98(2H, $-\mathbf{CH_2}-O-$) ppm.

*Reaction of **1** with Ethylamine Hydrobromide.* Compound **1**(2.7 g, 30 mmol) and ethylamine hydrobromide(3.7 g, 30 mmol) were heated together for 1 hr at 155—160 °C to evolve carbon dioxide gas almost quantitatively. After cooling, the mixture was treated with acetone(30 ml); the resulting crystals were then filtered and recrystallized from ethanol–acetone to give ethyl-β-hydroxyethylammonium bromide(1.7 g, 32% yield). Mp 40—45 °C(hygroscopic). Found: C, 28.34; H, 7.15; N, 8.13%. Calcd for $C_4H_{12}ONBr$: C, 28.25; H, 7.11; N, 8.23%. NMR: δ 1.32(3H, Me), 3.08(2H, $-\mathbf{CH_2}-\overset{+}{N}\equiv$), 3.35(2H, $HOCH_2-\mathbf{CH_2}-\overset{+}{N}\equiv$), and 3.90(2H, $-\mathbf{CH_2}-O-$) ppm. The concentration of the mother liquor of the recrystallization gave a sirup(2.0 g) which was deduced to be a carbamate from its IR spectrum (1688 cm^{-1}).

*Reaction of **1** with Cyclohexylamine Hydrobromide.* The reaction of **1**(2.0 g, 22 mmol) with cyclohexylamine hydrobromide(3.6 g, 20 mmol) was carried out in a manner similar to that described above to give cyclohexyl-β-hydroxyethylammonium bromide(3.1 g; 70% yield). Mp 124—126 °C. Found: C, 43.09; H, 9.93; N, 6.5%. Calcd for $C_8H_{18}ONBr$: C, 42.87; H, 9.99; N, 6.25%. NMR: δ 1.2—2.1 (10H, m, ring proton), 3.21(2H, $HOCH_2$-$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), and 3.88 (2H, -$\mathbf{CH}_2$-O-) ppm.

*Reaction of **1** with Morpholine Hydrobromide.* Compound **1**(4.8 g, 55 mmol) and morpholine hydrobromide(8.4 g, 50 mmol) were heated together at 155—160 °C for about 1.5 hr. After cooling, ethanol(50 ml) was added to the mixture, and the resulting mixture was treated with a 1 M methanolic sodium methoxide solution to remove the hydrobromic acid. The solvent was vaporated *in vacuo*, and the residue was treated with acetone(80 ml) to remove the sodium bromide by filtration. After the evaporation of the solvent *in vacuo*, the resultant sirup was distilled to give *N*-β-hydroxyethylmorpholine(4.1 g, 61% yield). Bp 61—63 °C/ 0.5 mmHg. Found: C, 54.64; H, 9.93; N, 10.69%. Calcd for $C_6H_{13}O_2N$: C, 54.94; H, 9.99; N, 10.68%. NMR-($CDCl_3$-TMS): δ 2.51—2.56(6H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$) and 3.67-(6H, -$\mathbf{CH}_2$-O-) ppm.

*Reaction of **1** with Pyridine Hydrobromide.* Compound **1**(2.7 g, 30 mmol) and pyridine hydrobromide(3.3 g, 20 mmol) were heated together for 50 min at 140—145 °C. After cooling, ethanol(40 ml) was added to the mixture, it was treated with active charcoal, and acetone(50 ml) was added. The resulting crystals were filtered and found to be pure enough for elemental analysis. The yield of *N*-β-hydroxyethylpyridinium bromide was 3.3 g(81%). Mp 104—105 °C. Found: C, 40.81; H, 4.91; N, 6.41%. Calcd for $C_7H_{10}ONBr$: C, 41.19; H, 4.94; N, 6.86%. NMR: δ 4.17 (2H, -$\mathbf{CH}_2$-O-), 4.86(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), 8.23(2H, H_β), 8.70 (1H, H_γ), and 9.00(2H, H_α) ppm. UV: $\lambda^{H_2O}_{max}$ 260 nm(ε 4500) and $\lambda^{H_2O}_{shoulder}$ 254 and 266 nm(ε 3400 and 3400 respectively).

*Reaction of **1** with Hydrobromides of Trimethylamine, 2-(**8**), 4-Aminopyridine(**9**), Quinoline, 8-Quinolinol, and Nicotinamide (**10**).* These reactions were carried out in almost the same way as has been described in the preceding reactions.

N-*β-Hydroxyethyltrimethylammonium Bromide*: The crystals resulting from the addition of acetone to the ethanolic solution of the resulting reaction mixture were recrystallized from ethanol to give a product(4.1 g, 74% yield). Mp >230 °C. Found: C, 32.71; H, 7.76; N, 7.64%. Calcd for $C_5H_{13}ONBr$: C, 32.62; H, 7.66; N, 7.61%. NMR: δ 3.25(8H, 3Me), 3.53(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), and 4.05(2H, -$\mathbf{CH}_2$-O-) ppm.

$N_{(1)}$-*β-Hydroxyethyl-2-aminopyridinium Bromide* (**11**): The crystals obtained in the way described in the preceding experiment were recrystallized from ethanol to give the product(1.8 g; 79% yield). Mp 129—131.5 °C. Found: C, 38.48; H, 5.36; N, 13.10%. Calcd for $C_7H_{11}ON_2Br$: C, 38.37; H, 5.06; N, 12.78%. NMR: δ 4.05(2H, -$\mathbf{CH}_2$-O-), 4.32(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), and 6.8—8.1(4H, m, ring protons) ppm. UV: $\lambda^{H_2O}_{max}$ 232 and 302 nm (ε 7700 and 5700 respectively), and $\lambda^{H_2O}_{min}$ 251 nm (ε 220).

$N_{(1)}$-*β-Hydroxyethyl-4-aminopyridinium Bromide* (**12**); The crystals obtained in the same way were recrystallized from ethanol to give a product(2.3 g; 99% yield). Mp 130—131 °C. Found: C, 38.60; H, 4.78; N, 13.10%. Calcd for $C_7H_{11}ON_2Br$: C, 38.37; H, 5.06; N, 12.78%. NMR: δ 4.00(2H, -$\mathbf{CH}_2$-O-), 4.32(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), 6.92(2H, H_β), and 8.06(2H, H_α) ppm. UV: $\lambda^{H_2O}_{max}$ 269 nm (ε 21000).

*Acetylation of **11** and **12**:* Compounds **11** and **12**(920 mg, 4 mmol) were treated with acetic anhydride(3 ml) and trifluoroboron diethyl etherate(3 drops) respectively at room temperature overnight. After the addition of methanol (50 ml), the mixture was stirred for 3 hr at room temperature and the solvent was evaporated *in vacuo* to dryness. The resultant crystals were recrystallized from ethanol to give colorless crystals.

$N_{(1)}$-*β-Acetoxyethyl-2-aminopyridinium Bromide*: Yield, 1.14 g(81%). Mp 164—166 °C. Found: C, 41.55; H, 5.18; N, 10.58%. Calcd for $C_9H_{13}O_2N_2Br$: C, 41.45; H, 5.02; N, 10.73%. NMR: δ 2.17(3H, -OAc), 4.61(2H, -$\mathbf{CH}_2$-OAc), 4.70(2H, -$\mathbf{CH}_2$-$\overset{+}{N}_{(1)}\equiv$), 6.9—8.1(4H, m, ring protons) ppm.

$N_{(1)}$-*β-Acetoxyethyl-4-aminopyridinium Bromide*: Yield, 0.63 g(67%). Mp 208—209 °C. Found: C, 41.41; H, 4.91; N, 10.87%. Calcd for $C_8H_{13}O_2N_2Br$: C, 41.45; H, 5.02; N, 10.73%. NMR: δ 2.30(3H, -OAc), 4.03(2H, -$\mathbf{CH}_2$-OAc), 4.58(2H, -$\mathbf{CH}_2$-$N_{(1)}\equiv$), 8.10(2H, H_β), and 8.60(2H, H_α) ppm.

N-*β-Hydroxyethylquinolinium Bromide.* The crystals obtained in the same way as in the reaction of **1** with pyridinium bromide were recrystallized from acetonitrile–acetone to give a product(2.24 g; 71% yield). Mp 139—139.5 °C. Found: C, 51.30; H, 4.52; N, 5.31%. NMR: δ 4.38(2H, -$\mathbf{CH}_2$-O-), 5.38(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), 7.9—8.7(5H, m, ring protons), 9.28(1H, H-4), and 9.59(1H, H-2) ppm. UV: $\lambda^{H_2O}_{max}$ 236 and 316 nm(ε 54000 and 12500 respectively) and $\lambda^{H_2O}_{min}$ 258 nm(ε 280).

N-*β-Hydroxyethyl-8-quinolinolium Bromide.* The crystals obtained as in the above cases were recrystallized from ethanol–acetone to give a product(3.90 g; 73% yield). Mp 182.5—183.5 °C. Found: C, 48.99; H, 4.54; N, 5.26%. Calcd for $C_{11}H_{12}O_2NBr$: C, 48.90; H, 4.48; N, 5.19%. NMR: δ 4.30(2H, -$\mathbf{CH}_2$-O-), 5.53(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), 7.4—8.2(4H, m, ring protons), 9.03(1H, H-4), and 9.15(1H, H-2) ppm. UV: $\lambda^{H_2O}_{max}$ 256 nm(ε 35400), $\lambda^{H_2O}_{shoulder}$ 275 nm(ε 2950), and $\lambda^{H_2O}_{min}$ 363 nm(ε 150).

$N_{(1)}$-*β-Hydroxyethylnicotinamidium Bromide* (**17**). The crystal obtained in the same way as above were recrystallized from ethanol to give a product(4.9 g; 100% yield). Mp 153—154 °C. Found: C, 38.78; H, 4.40; N, 11.60%. Calcd for $C_8H_{11}O_2N_2Br$: C, 39.04; H, 4.10; N, 11.40%. NMR: δ 4.17(2H, -$\mathbf{CH}_2$-O-), 4.90(2H, -$\mathbf{CH}_2$-$\overset{+}{N}\equiv$), 8.30(1H, H-5), 9.00(1H, H-6), and 9.39(1H, H-2) ppm. UV: $\lambda^{H_2O}_{max}$ 265 nm(ε 3800), $\lambda^{H_2O}_{shoulder}$ 259 and 272 nm(ε 3100 and 3200 respectively).

*Reaction of **1** with Picolinic Acid Hydrobromide (**13**).* Compound **1**(1.8 g, 20 mmol) and picolinic acid hydrobromide (2.04 g, 20 mmol) were heated together at 152 °C for 40 min, after which the mixture was treated with acetone–ethanol (1 : 3 v/v, 100 ml). The filtration of the resultant yellow granular crystals gave *N*-β-hydroxyethylpicolinolactononium bromide(2.8 g; 61% yield), which was analytically pure enough. Mp 225 °C. Found: C, 42.06; H, 3.68; N, 6.20%. Calcd for $C_8H_8NO_2Br$: C, 41.77; H, 3.50; N, 6.09%. NMR: δ 5.15(4H, -$\mathbf{CH}_2$-), 8.3—9.0 (3H, ring protons), and 9.15(1H, H-6) ppm. IR: 1735 cm^{-1} (six-membered lactone). UV: $\lambda^{H_2O}_{max}$ 265 nm (ε 7700), $\lambda^{H_2O}_{shoulder}$ 259 and 272 nm (ε 3100 and 3200 respectively).

*Reaction of **1** with Nicotinic Acid Hydrobromide (**15**).* Compound **1**(8.8 g, 100 ml) and nicotinic acid hydrobromide (**15**)(4.2 g, 20 mmol) were heated together at 150 °C for 40 min. The resultant red-brown sirup was treated with dioxane-ethanol(1 : 1 v/v, 80 ml) to give colorless crystals of β-hydroxyethyl *N*-β-hydroxyethylnicotinatonium bromide (**16**) (5.07 g, 87% yield). Found: C, 40.97; H, 5.21;

N, 4.69%. Calcd for $C_{10}H_{14}O_4NBr$: C, 41.40; H, 4.83; N, 4.80%. NMR: δ 4.00 and 4.14(2H and 2H respectively, $-CH_2OH$), 4.60(2H, $-CH_2-O-CO-$), 4.88(2H, $-CH_2-\overset{+}{N}\equiv$), 8.29(1H, H-5), 9.11(1H, H-2) ppm.

Treatment of ***16*** *with Methanolic Ammonia.* Compound **16**(290 mg) was treated with methanolic ammonia saturated at 0 °C(50 ml) in a stoppered flask in a refrigerator overnight. The subsequent evaporation of the solvent *in vacuo* gave orange scaly crystals (290 mg); the residue was dissolved in ethanol (30 ml) followed by treatment with 10% aqueous hydrobromic acid, with the pH adjusted at about 5. After the evaporation of the solvent *in vacuo*, the residue was dissolved in ethanol (30 ml), treated with active charcoal, and then filtered. To the filtrate, we added *n*-hexane until the turbidity was noticed; the mixture was then allowed to stand in a refrigerator. The resultant scaly crystals were filtered to afford $N_{(1)}$-β-hydroxyethylnicotinamidium bromide(250 mg; 100% yield). Mp 153—154 °C. The product was identified with **17** by examining the mixed melting point.

Treatment of ***16*** *with Amberlite IRA-900.* Compound **16** (1.0 g) was treated with Amberlite IRA-900(OH form, 20 ml) in methanol(100 ml) under stirring overnight; the resin was then filtered and the solvent was evaporated to about 30 ml to give pale yellow crystals of $N_{(1)}$-β-hydroxyethylnicotinate (**18**) (0.4 g, 72% yield). Mp 230—231 °C. Found: C, 57.58; H, 5.87; N, 8.68%. Calcd for $C_8H_9O_2N$: C, 57.48; H, 5.43; N, 8.38%. NMR δ 4.19(2H, $-CH_2-O-$), 4.80(2H, $-CH_2-\overset{+}{N}\equiv$), 8.14(1H, H-5), 8.90(1H, H-4), and 9.19(1H, H-2) ppm.

Treatment of ***18*** *with Aqueous Hydrobromic Acid.* Compound **18**(167 mg) was dissolved in methanol (30 ml); the mixture was treated with 10% aqueous hydrobromic acid, with the pH adjusted at about 5 by the use of a pH test paper. After the evaporation of the solvent, the residue was recrystallized from ethanol to give $N_{(1)}$-β-hydroxyethylnicotinium bromide (**19**) (140 mg, 57% yield). Mp 107—109 °C. Found: C, 38.44; H, 3.94; N, 5.87%. Calcd for $C_8H_{10}O_3NBr$: C, 38.73; H, 4.06; N, 5.64%. NMR: δ 4.16(2H, $-CH_2-O-$), 4.89(2H, $-CH_2-\overset{+}{N}\equiv$), 8.29(1H, H-5), 9.10(1H, H-4), 9.12(1H, H-6), and 9.47(1H, H-2) ppm. UV: $\lambda_{max}^{H_2O}$ 266 nm(ε 3800) and $\lambda_{shoulder}^{H_2O}$ 260 and 272 nm(ε 3150 and 3200 respectively).

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References

1) E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, **1966**, 899.

2) The unusual increment in gas evolution may be due to ethylene oxide, which was formed by triethylamine-catalyzed elimination reaction of hydrogen chloride from resulting ethylene chlorohydrin. Actually, ethylene oxide was detected as the bisulfate addition compound when the evolved gas was passed into a sodium bisulfate solution [W. M. Lauer and A. Hill, *J. Amer. Chem. Soc.*, **58**, 1873 (1936)]. In addition, the elimination reaction was followed by heating triethylamine and ethylene chlorohydrin at refluxing point, giving **7** (33%) and triethyamine hydrochloride (20%).

3) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. Chim. Soc. Fr.*, **1954**, 1142; R. Delaby, A. Sekira, P. Chabrier, and P. Piganial, *ibid.*, **1951**, 392.

4) It is well known that alkylation reaction takes place on the ring nitrogen of aminopyridine in the reaction with alkyl halides. *Cf.* A. E. Tschitschibabin and E. D. Ossertrowa, *Chem. Ber.*, **58**, 1708 (1925).

5) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949); The δ values of $-CH_2-\overset{+}{N}\equiv$ NMR signals are little affected by the variation of the counteranion of alkyl ammonium halides as observed in the series of *N*-β-hydroxyethylammonium halides(See the experimental part).

6) A. M. Eastham, *J. Chem. Soc.*, **1956**, 1936; A. M. Eastham, B. deB. Darwent, and P. E. Beanbien, *Can. J. Chem.*, **29**, 575 (1951); A. M. Eastham and B. deB. Darwent, *ibid.*, **29**, 585 (1951); T. Yamamoto, S. Tsunoda, and T. Nanba, *Yukagaku*, **11**, 298, 369, 464 (1962),

7) Kinetic study of this reaction is now in progress in our laboratory, and will be reported elsewhere.