

Reactions of Ethylenimines XI. Ring Opening of
R(+)-2-Ethylaziridine in Acidic Aqueous Solution and with S(+)-Cysteine (1)

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In an earlier report (2) it was suggested that the ring opening of unsymmetrical aziridines with water in the presence of acids was primarily of an S_N2 character at the primary carbon and primarily of an S_N1 character at a tertiary carbon. The intermediate case containing a secondary carbon in the ring was not so clear cut. By using optically active 2-ethylaziridine, hydrolysis in aqueous acids has now been shown to involve a Walden inversion at C2 (96% with the most favorable conditions) to product II and retention of configuration (98% optical purity) to product III (Chart I). Along with previous kinetic work and the determination of thermodynamic parameters (2), this suggests that hydrolytic reactions at both primary and secondary carbons in aziridines may be controlled to give exclusively aminoalcohols resulting from S_N2 type opening.

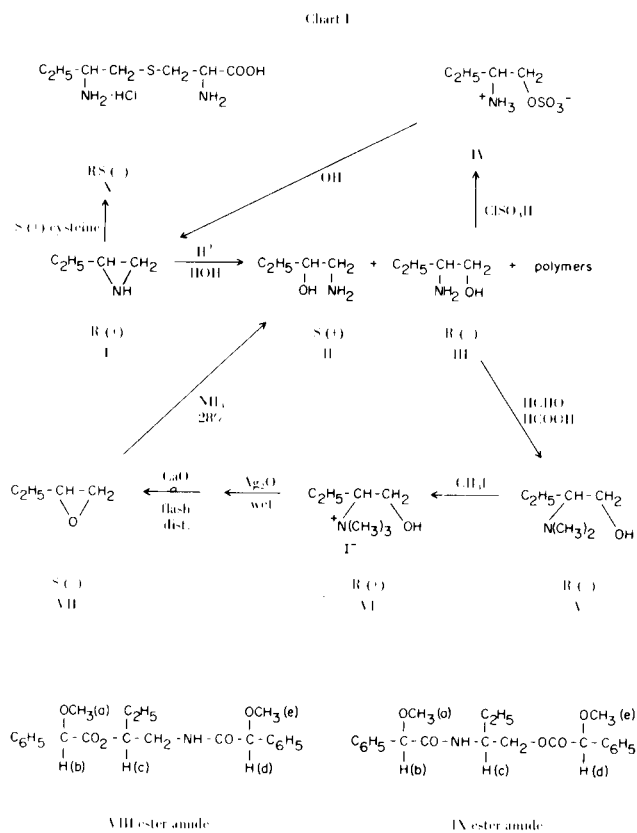
The most favorable conditions just mentioned are an excess of perchloric acid (2 moles or greater) at 30° for 554 hours in 1.6 *M* solution. With less acid (perchloric or sulfuric) and with a weaker acid (90% acetic acid, for example (3)) racemization at the secondary carbon accompanies the hydrolytic Walden inversion, suggesting the interposition of a carbonium ion (S_N1) in the reaction.

The optically active R(+)-2-ethylaziridine was obtained from R(-)-2-amino-1-butanol (4,5) by reaction with chlorosulfonic acid to give IV, followed by base (Chart I). The aziridine thus obtained (I) had a higher optical rotation than that obtained by the Wenker method (6). The optical rotation of R(+)-2-ethylaziridine depends on the solvent and in aqueous solution, rather markedly on the concentration (Table I).

TABLE I

Optical Rotation of R(+)-2-Ethylaziridine

Solvent	Conc. (g./100 ml.)	$[\alpha]_D^{25}$	Remarks
Methanol	7.63	+23.82°	Chlorosulfonic acid prep.
Methanol	7.63	+22.08°	Wenker method
Water	8.50	+20.25°	
Water	17.0	+18.13°	
Water	34.0	+13.24°	
Water	68.0	+10.98°	
Neat		+17.14°	Ref. 5, $[\alpha]_D^{18} = 17.57^\circ$



The composition of the hydrolysis products of 2-ethylaziridine depends on the amount of acid used in the catalysis. Results (Table II) show that yields of aminoalcohols increase as the ratio of acid to aziridine increases while polymers (including piperazines (7) and dimers) predominate with molar and less than molar amounts of acid (8).

The Walden inversion at C2 was nearly complete (96%) in 2 *M* perchloric acid for the formation of 1-amino-2-butanol but was accompanied by some racemization with less concentrated acid (Table II). Retention of configuration in the formation of 2-amino-1-butanol was also complete (98%) under the same conditions.

TABLE II

Percentage Composition and Optical Rotations of Hydrolysis Products of R(+)-2-Ethylaziridine

Products	H ₂ SO ₄ (0.5 M) %	$[\alpha]_{\text{D}}^{25}$	HClO ₄ (1.0 M) %	$[\alpha]_{\text{D}}^{25}$	HClO ₄ (2.0 M) %	$[\alpha]_{\text{D}}^{25}$	HClO ₄ (a) (3.0 M) %
S(+)-1-Amino-2-butanol	9.6	+5.57° (c, 1.2)	9.3	+5.80° (c, 0.98)	13.7	+6.23° (c, 0.94)	22.
R(-)-2-Amino-1-butanol	30.8	-7.92° (c, 1.6)	39.9	-8.92° (c, 4.97)	47.9	-9.92° (c, 3.28)	61.
Piperazines, dimers (volatile)	12.1		19.9		27.6		
Polymers (residue)	47.8		31.1		11.1		17. (b)

(a) Results from Ref. 2. (b) Includes piperazines, dimers, and polymers.

The separation of the two aminoalcohols by fractional distillation (2) was found to be unreliable on a small scale. The results in Table II were made feasible by the discovery that the two aminoalcohols, volatile piperazines, and dimers were readily separated on a 30-foot Free Fatty Acid Phase (FFAP) gas chromatography column supported on Chromosorb W.

Unfortunately we were unable to resolve racemic II into optical isomers and hence the absolute configuration of II, obtained from R(+)-2-ethylaziridine in the hydrolysis reaction, was determined by an independent synthesis (Chart 1). The reaction series with configurations are given on the assumption that only the formation of VII involves a Walden inversion.

R(-)-2-Amino-1-butanol was methylated with formaldehyde and formic acid by a standard procedure (9) to give R(-) V. No racemization occurred in this step since the *d*- α -bromcamphor- π -sulfonate salt of R(-) V had the same rotation (within experimental error) of the salt resolved by the same reagent from *dl* V. Compound R(-) V was methylated with methyl iodide to give VI and converted to the quaternary hydroxide with wet silver oxide. The inverted epoxide (10) S(-) VII was obtained by dropping the wet quaternary hydroxide onto hot calcium oxide in a flash distillation. Finally the S(+)-1-amino-2-butanol (81% optically pure) was obtained from S(-) VII with retention of configuration by reaction with aqueous ammonia.

The optical purity of the final product II in the synthesis was determined by application of nmr spectroscopy using the *O*-methylmandelic acid derivative (IX) in a method recently exploited by Raban and Mislow (11). Preliminary work was done on the *O*-methylmandelic acid ester-amide derivatives of *dl* and R(-)-2-amino-1-butanol (VIII). Since racemic and pure optically active isomers

were known, chemical shifts for the protons VIIa,b,c,d,e were identifiable. This preliminary work allowed identification of the protons IXa,b,c,d,e in the closely related isomer IX. Integration of the areas under the methoxy peaks in the 3.17-3.39 δ region was not reliable because of the interference of the proton IXc. Even though CH peaks of IXb,d were smaller, they were usable. Finally integration of the CH peaks at δ 4.45 and δ 4.68 were selected to calculate percentages of S(+)- and R(-) II present from the reaction of S(-) VII with aqueous ammonia. The result was 9.7% of R(-) II and 90.3% of S(+)-II. Thus, the optical purity of S(+)-1-amino-2-butanol obtained in the route V \rightarrow VI \rightarrow VII \rightarrow II was 80.6%. The optical rotation of the mixture was $[\alpha]_{\text{D}}^{25} = +5.67^{\circ}$ (c, 1.92, methanol) and hence optically pure S(+)-1-amino-2-butanol would have a rotation, $[\alpha]_{\text{D}}^{25} = +6.90^{\circ}$.

Thiophenol (12) and benzoic acid (13) open unsymmetrical aziridines at the primary carbon. Cysteine reacts with aziridine itself to form a new C-S bond (14,15). However, the three functional groups, SH, COOH, and NH₂, in the same molecule (cysteine, for example) have not been allowed to react with an unsymmetrical aziridine.

We report that R(+)-2-ethylaziridine reacts with S(+)-cysteine to give one product, X, isolated in 80% yield as the monohydrochloride. Under the same conditions S(-)-cysteine does not react at all with the same aziridine.

In view of the use of ethylenimine to block mercapto groups in the study of protein structure (16a) and for other biological purposes (16b), it appeared useful to determine the path of the reaction with the optically active aziridine. Desulfurization of X with Raney nickel in ethanol established its structure. Both C-S bonds were cleaved. R(+)-*sec*-butylamine hydrochloride was isolated in 58% yield, optically pure. 2,4-Dinitrophenylalanine was isolated to show that alanine was the other cleavage pro-

duct. Since R(-)*sec*-butylamine has been related to R(+)*glyceraldehyde* (17), R(+)*2-ethylaziridine* (18) and R(-)*2-amino-1-butanol* all have the same absolute configuration.

The *sec*-butylamine was obtained with an aged (6 months) sample of Raney nickel catalyst in ethanol. When freshly prepared Mazingo catalyst was used in ethanol, a mixture of *N*-ethyl-*sec*-butylamine and *sec*-butylamine (9:1) was obtained.

EXPERIMENTAL

IR spectra were taken using a Perkin-Elmer Model 337 Grating Spectrophotometer. The NMR spectra were determined with a Varian A-60A spectrometer and peak positions are reported in δ units relative to TMS as internal standard. In NMR data the symbols are m, multiplet and s, singlet.

R(+)-2-Ethylaziridine (I).

Resolved 2-amino-1-butanol was obtained from the *d*-tartrate salt and had an optical rotation: $[\alpha]_{\text{D}}^{25} = -10.15^{\circ}$ (neat) while the literature (5) reports $[\alpha]_{\text{D}}^{22} = -10.00^{\circ}$ (c, 2, ethanol).

Eighty-nine g. (one mole) of R(-)-2-amino-1-butanol (III) in 400 ml. of carbon tetrachloride at 0° was treated dropwise with 116.5 g. (one mole) of chlorosulfonic acid over 45 minutes, holding the temperature below 5°. The tacky mixture was stirred overnight and then 150 ml. of water was added during the stirring until the aminoalkyl sulfate (IV) dissolved. The sulfate was converted to R(+)-2-ethylaziridine by treatment with concentrated base in the Wenker synthesis (6), yield 34 g., 48%, b.p. 89.0-90.9°.

Hydrolysis of R(+)-2-Ethylaziridine.

The hydrolysis reactions were carried out as previously described (2) in 50 ml. of solution (approximately 1.6 *M* in acid when a total of 0.0845 mole of perchloric acid was used with 3.0 g. (0.0423 mole) aziridine) at 30 ± 0.5° for 554 hours. The hydrolysis products were treated with solid potassium hydroxide until the solution was saturated. The upper layer was extracted with four portions of 50 ml. of ether and dried over anhydrous magnesium sulfate. The ether was removed and the hydrolysis products were transferred by vacuum to a 5 ml. ground glass collecting flask. A sample was then chromatographed on a column prepared as follows.

Chromosorb W (45/60 mesh, Johns-Manville Products Corp.) was washed repeatedly with 1 *M* potassium hydroxide solution. The basic Chrom W was then dried at 100° and 50 g. of it was added to 150 ml. of methylene chloride in which 2.2 g. (5%) of FFAP (Wilkens Instrument and Research, Inc.) was dissolved. The methylene chloride was slowly removed on a rotary evaporator and the dry product was transferred to a 30-foot (0.25 in. diam.) column of aluminum tubing. The column was baked at 200° for 3 days before use in separating the two aminoalcohols and the volatile polymers from residual polymers. Retention times for 1-amino-2-butanol and 2-amino-1-butanol were verified by authentic samples on the column. The optical rotations of the aminoalcohols are recorded in Table II. The two compounds were also identified by IR and NMR spectra. The absence of unreacted aziridine in the volatile fraction was determined by a thiosulfate analysis (19).

R(-)-2-Dimethylamino-1-butanol (V).

R(-)-2-Amino-1-butanol was methylated with formaldehyde

and formic acid by the standard method (9) in 57% yield, b.p. 62-65° (20mm.), $[\alpha]_{\text{D}}^{22} = -11.54^{\circ}$ (c, 14.43, methanol); nmr spectrum, δ 0.89 (m, 3), 1.40 (m, 2), 2.28 (s, 6), 2.36 (m, 1), 3.43 (d, 2), 4.29 (s, 1); ir spectrum (sodium chloride) 3410, 1042 cm^{-1} .

The *d*- α -bromcamphor- π -sulfonate salt of the R(-)-2-dimethylamino-1-butanol was prepared by evaporating a water solution of the ammonium salt of the resolving agent. Ammonia was lost as the evaporation proceeded. The oily residue was recrystallized twice from wet ethyl acetate to give a salt of constant optical rotation, $[\alpha]_{\text{D}}^{22} = +64.3^{\circ}$ (c, 2.3, methanol), m.p. 130-131°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{30}\text{BrNO}_5\text{S}$: C, 44.86; H, 7.06; N, 3.27. Found: C, 44.78; H, 6.92; N, 3.28.

Racemic 2-dimethylamino-1-butanol was resolved with the same reagent after thirteen recrystallizations from wet ethyl acetate to a compound with the same melting point and comparable optical rotation, $[\alpha]_{\text{D}}^{22} = +62.3^{\circ}$. Aminoalcohol recovered from this salt had the same rotation as that given above.

R(+)-2-(1-Hydroxybutyl)trimethylammonium Iodide (VI).

The methyl iodide salt of R(-)-2-dimethylamino-1-butanol was obtained in 80% yield, m.p. 240.0-242.0°, recrystallized from ethanol-ether, mildly hygroscopic. Optical rotation, $[\alpha]_{\text{D}}^{22} = 1.99^{\circ}$ (c, 15, methanol); nmr spectrum (deuterium oxide) δ 1.05 (m, 3), 1.84 (m, 2), 3.14 (m, 1), 3.18 (m, 9), 4.09 (m, 2), 4.52 (s, 1); ir spectrum (potassium bromide) 3400, 3050, 1490 cm^{-1} . The racemic iodide gave a m.p. 227-229° and the same nmr spectrum.

Anal. Calcd. for $\text{C}_7\text{H}_{18}\text{INO}$: C, 32.42; H, 6.94; N, 5.40. Found: C, 32.44; H, 6.96; N, 5.55.

S(-)-1,2-Epoxybutane (VII).

Thirty-nine g. (0.15 mole) of R(+)-2-(1-hydroxybutyl)trimethylammonium iodide was ground in a ball mill with a slurry of wet silver oxide prepared from 77.7 g. (0.3 mole) of silver nitrate (20) for 36 hours. Evaporation of the filtrate from this reaction mixture gave a viscous liquid, 27.6 g., (126%) of the hydroxide which was used directly in the next step.

The viscous hydroxide (4.2 g.) was dropped onto hot calcium oxide powder and the distillate was collected over anhydrous magnesium sulfate at 0°. The 1,2-epoxybutane (0.6 g.) was immediately chromatographed on an 8 ft. (0.25 in.) column of 20% XF-1150 silicone fluid (Wilkens Instrument and Research, Inc.) on Chrom P-90. An authentic sample of racemic epoxide was used to determine the retention time. The S(-)-1,2-epoxybutane was collected and an optical rotation taken at once: $[\alpha]_{\text{D}}^{22} = -9.29^{\circ}$ (c, 5.3, methanol). The compound racemized on standing, losing 30% of its rotation in 3 days; nmr spectrum (neat) δ 1.11 (m, 3), 1.56 (m, 2), 2.58 (m, 3). A trace of trimethylamine in the sample gave a singlet at δ 2.12.

S(+)-1-Amino-2-butanol (II).

The S(-)-1,2-epoxybutane from 14 g. of crude 2-(1-hydroxybutyl)trimethylammonium hydroxide was immediately allowed to react with 300 ml. of 28% ammonia for one day. Workup as described by Kitchen and Pollard (21) and gas chromatographic separation as before gave S(+)-1-amino-2-butanol in 10% yield (Table II); nmr spectrum (deuterium oxide) δ 0.88 (m, 3), 1.45 (m, 2), 2.62 (m, 2), 3.50 (m, 1), 4.54 (s, 3).

R(-)-Methoxymandelic Acid Ester-Amide of R(-)-2-Amino-1-butanol (VIII).

Methoxymandelic acid was resolved by means of *l*-ephedrine using the published procedure (22), $[\alpha]_{\text{D}}^{25} = -163^{\circ}$ (c, 1.5, water).

The ester-amide of R(-)-2-amino-1-butanol was obtained from the optically active methoxymandelic acid through the acid chloride (23) in low yield, 18%, after recrystallization from methanol-water, m.p. 82-84°; ir spectrum (potassium bromide) 3320, 1740, 1660, 1530, 1450 cm⁻¹. The band at 1740 cm⁻¹ was a doublet in the derivative made from racemic 2-amino-1-butanol; nmr spectrum (deuteriochloroform) δ 0.77 (m, 3, CH₃-CH₂), 1.30 (m, 2, CH₃CH₂), 3.33 and 3.50 (s, 6, from VIIIa and e), 3.80 (m, 4, OCH₂ + NH + VIIIc), 4.45 (s, 1) and 4.88 (s, 1, VIIIb and d), 7.42 (m, 10). In the derivative, m.p. 71-73°, made from racemic 2-amino-1-butanol, four singlets appeared for the methoxy groups VIIIa and e at δ 3.31, 3.36, 3.39, and 3.47. The peaks for VIIIb and d appeared at δ 4.53, 4.61, 4.72, and 4.85.

Anal. Calcd. for C₂₂H₂₇NO₅: N, 3.63. Found: N, 3.77.

R(-)Methoxymandelic Acid Ester-Amide of S(+)-1-Amino-2-butanol (IX).

The R(-)methoxymandelic acid ester-amide of S(+)-1-amino-2-butanol was made in the same manner as just described for the isomeric compound but the product did not crystallize. The workup described by Jacobus, *et al.* (23) gave a pure compound, however, as determined by ir and nmr spectra; ir spectrum (deuteriochloroform) 3340, 1760, 1680, 1525, 1460 cm⁻¹; nmr spectrum (deuteriochloroform) δ 0.85 (m, 3, CH₃-CH₂), 1.42 (m, 2, CH₃CH₂), 2.96 (m, 1, IXc), 3.37 and 3.42 (s, 6, from IXa and e), 4.68 and 4.81 (s, 2, IXb and d), 4.75 (m, 2, CH₂N), 7.49 (m, 10). One proton, NH, was a broad peak centered at δ 3.74 integrating for 3H, probably due to some water in the oily product.

In the corresponding derivative made from racemic 1-amino-2-butanol, four singlets appeared for the methoxy groups IXa and e at δ 3.17, 3.28, 3.37, and 3.39. The peaks for IXb and d appeared at δ 4.47, 4.66, 4.76, and 4.80.

The peaks at δ 4.68 and 4.81 in the derivative of S(-)-1-amino-2-butanol and the peaks at δ 4.45 and 4.88 in the derivative of R(-)-2-amino-1-butanol were used to determine the content of the mixture of the two aminoalcohols obtained in the hydrolysis of R(+)-2-ethylaziridine previously described. Finally the peaks at 4.45 δ and 4.68 δ were settled on as being the most accurate for integration to determine percentage composition.

RS(-)- β -(2-Aminobutylthio)alanine Hydrochloride (X).

Four g. (0.035 mole) of S(+)-cysteine, $[\alpha]_D^{26} = +7.6^\circ$ (c, 12, 1 N hydrochloric acid) was dissolved in 50 ml. of degassed distilled water and filtered into a two-necked flask. Nitrogen gas was passed into the flask to remove air and then 2.45 g. (0.035 mole) of R(+)-2-ethylaziridine $[\alpha]_D^{22} = +17.14^\circ$ (neat) in 15 ml. of degassed water was added dropwise over 15 minutes with stirring. The reaction was allowed to continue for 12 hours at room temperature and then unreacted aziridine was removed by bubbling dry nitrogen through the solution. Solvent was removed at room temperature by vacuum (using a rotatory evaporator) to about 1/4 the original volume. Acidification with concentrated hydrochloric acid to pH 6 and addition of 500 ml. of acetone precipitated the diaminoacid. Recrystallization from ethanol-water yielded 6.2 g. (79%) of RS(-)- β -(2-aminobutylthio)alanine hydrochloride, m.p. 209-210° dec., $[\alpha]_D^{22} = -41.40^\circ$ (c, 8.1, water); ir spectrum, NH₃⁺, 2030, 1610 cm⁻¹; nmr spectrum (10% deuterium oxide, W/V) δ 1.0 (t, CH₃), 1.46-1.98 (q, CH₂), 2.8-3.7 (m, 5, CH₂-S-CH₂ + CHNH₂), 4.0 (t, CH, deshielded by NH₃⁺ and COO⁻), 4.7 (s, 6, 2NH₃⁺).

Anal. Calcd. for C₇H₁₇ClN₂O₂S: C, 36.75; H, 7.49; N, 12.25; Cl, 15.50. Found: C, 36.69; H, 7.42; N, 12.30; Cl, 15.41.

The same compound was obtained by treating 1-chloro-2-aminobutane hydrochloride (24) with cysteine in the presence of aqueous potassium hydroxide but this does not constitute a proof of structure since the aziridine is an intermediate.

Desulfurization of RS(-)- β -(2-Aminobutylthio)alanine Hydrochloride.

RS(-)- β -(2-Aminobutylthio)alanine hydrochloride (1.97 g., 8.6 mmoles) in 20 ml. of water was treated with 3.3 ml. of suspended Mozingo (25) catalyst (Raney nickel W-2) in 150 ml. of ethanol (25,26). After standing one hour the reaction mixture was slowly brought to reflux for two hours. After cooling, 3 g. of sodium hydroxide was added and the alcohol and amine were distilled. Addition of 1.2 g. (8.9 mmoles) of phenylisothiocyanate gave 1.1 g. of a mixture of two thioureas, estimated by nmr spectra to be 20% phenylthiourea of *sec*-butylamine and 80% phenylthiourea of *N*-ethyl-*sec*-butylamine. Repeated recrystallization from ethanol-water and sublimation (77°/0.05 mm) gave an analytical sample of the latter, m.p. 103-104°.

Anal. Calcd. for C₁₃H₂₀N₂S: C, 66.05; H, 8.53; N, 11.85. Found: C, 66.36; H, 8.45; N, 11.89.

The nmr spectrum confirmed the structure (deuteriochloroform, 5% W/V) δ 0.66-1.9 (complex, 11, 3CH₃ + CH₂), 3.53 (q, CH₂N), 5.21 (1, CH-N<, quartet but each band of the quartet was further split into a diffused triplet), 6.88-7.56 (doublet at 7.28) (m, 5 aromatic + 1NH). The NH proton was moved downfield to 8.56 (δ) (broad signal) by addition of a drop of pyridine to the nmr tube.

The phenylthiourea of *sec*-butylamine, prepared from an authentic sample of the amine, m.p. 102-104°, gave the following nmr spectrum (deuteriochloroform, 5% W/V) δ 0.9 (t, 3, CH₃), 1.18 (d, 3, CH₃), 1.46 (q, 2, CH₂), 4.43 (q, 1, CH-N, quartet but each band of the quartet was further split into a diffused triplet), 4.13 (br, 1, NH), 8.05 (br, 1, other NH), 7.0-7.66 (m, 5, doublet at 7.33).

With an aged sample of Mozingo catalyst, only *sec*-butylamine, (58%) was isolated after the procedure described above was used to obtain the amine. Hydrogen chloride converted the alcohol distillate to R(+)-*sec*-butylamine hydrochloride, m.p. 149-150°, $[\alpha]_D^{22} = +0.88^\circ$ (c, 1.6, H₂O). Lit. (27) $[\alpha]_D^{20} = +0.96$ to 1.05 at various concentrations in water. The compound is hygroscopic.

The *sec*-butylamine hydrochloride was identified by comparison of the nmr spectrum of an authentic sample.

In a separate reaction between racemic 2-ethylaziridine and S(+)-cysteine, the product X was desulfurized with Raney nickel and alanine was identified through a 65% yield of 2,4-dinitrophenylalanine, using 2,4-dinitrofluorobenzene, m.p. 179-181° (28).

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Received July 9, 1970

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Revised November 7, 1970