**5-Bromo-5′-ethenyl-2,2′-bithiophene (10).** Sodium hydride (250 mg, 5.2 mmol) was washed with *n*-pentane to remove the oil. The flask was flushed with nitrogen, and DMSO (10 mL) was added. The mixture was heated at 75–80 °C until the evolution of hydrogen ceased. At 0 °C, methyltriphenylphosphonium bromide (1.9 g, 5.3 mmol) in DMSO (10 mL) was added. After 10 min, **5** (1.5 g, 5.5 mmol), dissolved in DMSO (10 mL), was added. The mixture was stirred at room temperature for 1 h. Then the mixture was poured in acidic water and extracted with $CHCl_3$. The organic layer was washed with brine and dried ($Na_2SO_4$). The removal of the solvent yielded a crude product that was chromatographed on $SiO_2$. The elution with *n*-hexane gave pure **10**: 1.2 g, 80%; $^1H$ NMR ($CDCl_3$) $\delta$ 7.3–6.0 (m, 5 H), 5.43 (dd, 1 H, $J_1$ = 18 Hz, $J_2$ = 1.5 Hz), 5.03 (dd, 1 H, $J_1$ = 10 Hz, $J_2$ = 1.5 Hz); IR (film) $\nu_{max}$ 1620, 1512, 1465, 1430, 1409, 1221, 1208, 1198, 975, 898, 787, 690 $cm^{-1}$; mass spectrum, *m/z* 272, 270. Anal. Calcd for $C_{10}H_7BrS_2$: C, 44.29; H, 2.6. Found: C, 44.4; H, 2.9.

**5-Ethenyl-5′-(1-propynyl)-2,2′-bithiophene (11).** **10** (1 g, 3.7 mmol), dissolved in benzene (9 mL), was treated with TEBAC (68 mg, 0.3 mmol), CuI (90 mg, 0.47 mmol), $Pd[P(Ph)_3]_4$ (345 mg, 0.3 mmol), propyne, and 2.5 N NaOH (14 mL), as described for **6**. The usual workup yielded a crude product that was chromatographed on $SiO_2$. Elution with *n*-hexane gave pure **11**: 0.72 g, 85%; $^1H$ NMR ($C_2D_6CO$) $\delta$ 7.3–6.0 (m, 5 H), 5.38 (dd, 1 H, $J_1$ = 16 Hz, $J_2$ = 1.5 Hz), 4.96 (dd, 1 H, $J_1$ = 10 Hz, $J_2$ = 1.5 Hz), 1.98 (s, 3 H); IR (film) $\nu_{max}$ 2240, 1622, 1468, 1450, 1431, 1380, 1230, 1210, 1200, 980, 900, 795, 775, 698 $cm^{-1}$; mass spectrum, *m/z* 230. Anal. Calcd for $C_{12}H_{10}S_2$: C, 67.79; H, 4.4. Found: C, 67.9; H, 4.7.

**5-[1-(4-Hydroxybut-1-ynyl)]-2,2′-bithiophene-5′-carbaldehyde (12).** **5** (1.1 g, 4 mmol), dissolved in benzene (14 mL), was treated with TEBAC (70 mg, 0.31 mmol), CuI (92 mg, 0.48 mmol), $Pd[P(Ph)_3]_4$ (348 mg, 0.3 mmol), 3-butyn-1-ol (6 mL), and 2.5 N NaOH (14 mL) as described for **7**. The usual workup furnished a crude product that was chromatographed on $SiO_2$. Elution with benzene–$Et_2O$ (2:1) gave pure **12**: 0.8 g, 76%; $^1H$ NMR ($CDCl_3$) $\delta$ 9.83 (s, 1 H), 7.64 (d, 1 H, $J$ = 4 Hz), 7.24 (d, 1 H, $J$ = 4 Hz), 7.15 (d, 1 H, $J$ = 4 Hz), 7.05 (d, 1 H, $J$ = 4 Hz), 3.82 (t, 2 H, $J$ = 7 Hz), 2.73 (d, 2 H, $J$ = 7 Hz), 2.33 (s, 1 H); IR ($CHCl_3$) $\nu_{max}$ 3600, 3420, 2230, 1670, 1460, 1440, 1385, 1100 $cm^{-1}$; mass spectrum, *m/z* 262. Anal. Calcd for $C_{13}H_{10}O_2S_2$: C, 52.52; H, 3.84. Found: C, 52.4; H, 3.9.

**5-[1-(4-Hydroxybut-1-ynyl)]-2,2′-bithiophene-5′-methanol (13).** **12** (800 mg, 3 mmol) was treated with $NaBH_4$ as described for **6**. The usual workup furnished pure **13**: 780 mg, 97%; oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.0 (m, 4 H), 6.85 (d, 1 H, $J$ = 4 Hz), 4.85 (s, 2 H), 3.84 (t, 2 H, $J$ = 7 Hz), 2.70 (t, 2 H, $J$ = 7 Hz), 2.35 (s, 1 H); IR ($CHCl_3$) $\nu_{max}$ 3600, 3420, 2230, 1450, 1385 $cm^{-1}$; mass spectrum, *m/z* 264. Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58. Found: C, 59.2; H, 4.3.

**5′-[(Isovaleryloxy)methyl]-5-[4-(isovaleryloxy)but-3-ynyl]-2,2′-bithiophene (14).** **13** (780 mg, 3 mmol), dissolved in dry pyridine (5 mL), was treated with isovaleryl chloride at 0 °C. After 0.5 h the mixture was poured in diluted HCl–ice and extracted with $Et_2O$. The neutral extracts were dried ($Na_2SO_4$). Removal of the solvent yielded a crude product that was chromatographed on $SiO_2$. Elution with *n*-hexane gave pure **13**: 900 mg, 71%; oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.0 (m, 4 H), 5.23 (s, 2 H), 4.18 (t, 4 H, $J$ = 7 Hz), 2.52 (t, 4 H, $J$ = 7 Hz), 2.21 (d, 4 H, $J$ = 7 Hz), 2.12 (m, 2 H), 0.98 (d, 12 H, $J$ = 6 Hz); IR ($CHCl_3$) $\nu_{max}$ 2220, 1740, 1190, 1170 $cm^{-1}$; mass spectrum, *m/z* 432.

**5-Methyl-2,2′-bithiophene-5′-carbaldehyde (16).** **3** (1 g, 4.2 mmol) was dissolved in acetonitrile (300 mL) in the presence of 2-methylthiophene (3 mL). The solution was outgassed with nitrogen for 1 h. The mixture was then irradiated in an immersion apparatus with a 500-W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket. After 3 h, the mixture was dissolved in chloroform and washed successively with 0.1 M $Na_2S_2O_3$ and then with brine. The organic phase was dried ($Na_2SO_4$), and the removal of the solvent yielded a crude product that was chromatographed on $SiO_2$. Elution with $CHCl_3$–*n*-hexane (3:2) gave pure **16** 0.6 g, 69%; mp 98–99 °C (lit.[27] mp 98–99 °C); $^1H$ NMR ($CCl_4$) $\delta$ 9.60 (s, 1 H), 7.57 (d, 1 H, $J$ = 4 Hz), 7.0 (m, 3 H), 2.10 (s, 3 H); IR (film) $\nu_{max}$ 1660, 1520, 1475, 1445, 1420, 1415, 1240, 1220, 1065, 1050 $cm^{-1}$; mass spectrum, *m/z* 208, 207. Anal. Calcd for $C_{10}H_8OS_2$: C, 57.66; H, 3.87. Found: C, 57.3; H, 4.0.

**5-Methyl-5′-[1-(buta-1,3-dienyl)]-2,2′-bithiophene (17).** Allyltriphenylphosphonium bromide (2.34 g, 6.1 mmol) was suspended in anhydrous $Et_2O$ (40 mL), and 1.2 N BuLi (5 mL) was added. The mixture was stirred for 2 h at room temperature. **16** (1.2 g, 5.8 mmol), dissolved in anhydrous THF (10 mL), was added. The mixture was stirred for 2 h and then filtered. The organic phase was diluted with $CHCl_3$, washed with diluted HCl and water, and dried ($Na_2SO_4$). Removal of the solvent yielded a crude product that was chroamtographed on $SiO_2$. Elution with *n*-hexane gave pure **17**: 0.82 g, 61%; mp unmeasurable; $^1H$ NMR ($CCl_4$) $\delta$ 7.0–6.0 (m, 5 H), 5.1 (m, 4 H), 2.38 (s, 3 H); IR ($CCl_4$) $\nu_{max}$ 1625, 1000, 940, 900 $cm^{-1}$; mass spectrum, *m/z* 232.

**Registry No.** **3**, 5370-19-4; **4**, 1003-09-4; **5**, 110046-60-1; **6**, 110046-61-2; **7**, 102054-38-6; **8**, 102054-37-5; **9**, 17257-07-7; **10**, 110046-62-3; **11**, 17257-06-6; **12**, 110046-63-4; **13**, 110046-64-5; **14**, 96853-77-9; **15**, 554-14-3; **16**, 32358-94-4; **17**, 93087-75-3; $CH_2$=$CHCH_2PPh_3Br$, 1560-54-9; $MePPh_3Br$, 1779-49-3; 2-thiophenecarboxaldehyde, 98-03-3; 2-thiophenemethanol, 636-72-6; 5-iodo-2-thiophenemethanol, 13781-27-6; propyne, 74-99-7; 3-butyn-1-ol, 927-74-2; isovaleryl chloride, 108-12-3; 5-(1-propyn-1-yl)-5′-(2,2-dibromoethenyl)-2,2′-bithiophene, 110046-65-6.

(27) Skatteböl, L. *Acta Chem. Scand.* **1961**, *15*, 2047.

# Intramolecular Cyclization Products from Alkanolamines and Epichlorohydrin

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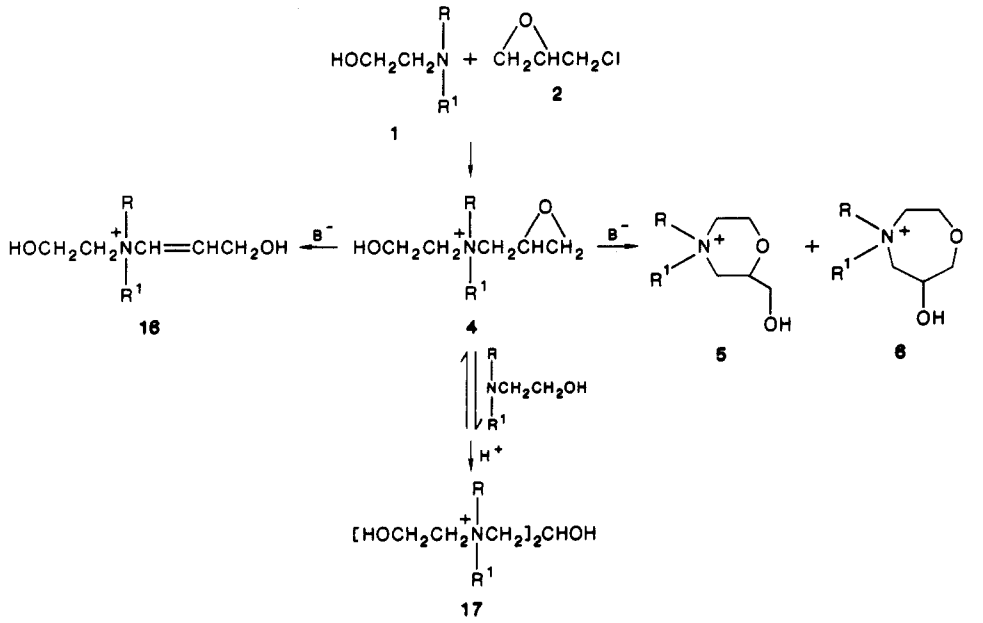
Tertiary (2-hydroxyethyl)dialkylamines reacted with epichlorohydrin to form mixtures containing equal amounts of 2-(hydroxymethyl)-4,4-dialkylmorpholinium chlorides and perhydro-6-hydroxy-4,4-dialkyl-1,4-oxazepinium chlorides. Secondary (2-hydroxyethyl)alkylamines gave a 9:1 ratio of the corresponding bases in agreement with the prediction of Baldwin's rules.

Reactions of amines with epichlorohydrin (**2**) are widely used in the manufacture of polyelectrolytes, modification of starch and fibers, and in epoxy resins. A detailed investigation of the reactions of tertiary alkanolamines with epichlorohydrin was undertaken because the NMR spectral properties of the product obtained from triethanolamine (TEA, **1c**) and epichlorohydrin did not agree with an authentic sample of the previously assigned structure,[1]

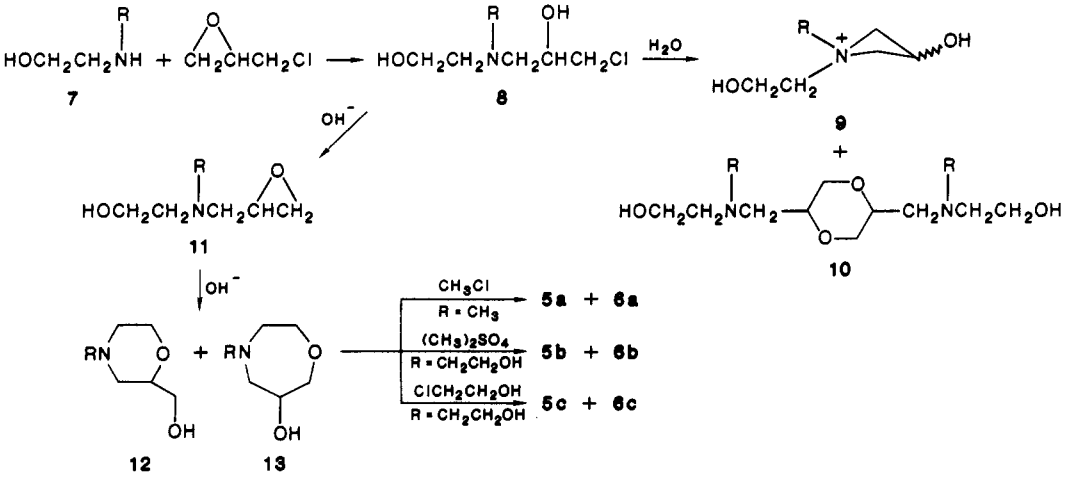
0022-3263/87/1952-5247$01.50/0 

**Scheme I. Tertiary Alkanolamines**[a]



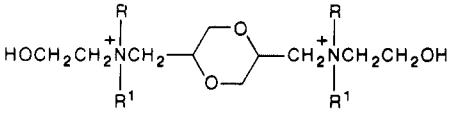
[a] a, R = R¹ = $CH_3$; b, R = $CH_3$, R¹ = $CH_2CH_2OH$; c, R = R¹ = $CH_2CH_2OH$.

**Scheme II. Secondary Alkanolamines**[a]



[a] a, R = $CH_3$; b, R = $CH_2CH_2OH$.

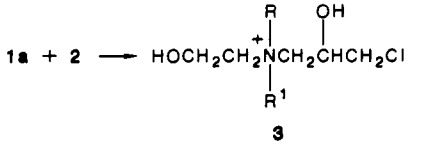
*trans*-(1,4-dioxane-2,5-diyldimethylene)bis[tris(2-hydroxyethyl)ammonium chloride] (**14c**). New products



**14a**, R = R¹ = $CH_3$
**b**, R = $CH_3$; R¹ = $CH_2CH_2OH$
**c**, R = R¹ = $CH_2CH_2OH$

obtained from tertiary (2-hydroxyethyl)amines were identified as 2-(hydroxymethyl)-4,4-dialkylmorpholinium chlorides **5** and perhydro-6-hydroxy-4,4-dialkyl-1,4-oxazepinium chlorides **6**, Scheme I. Compounds **5a** and **6a**, derived from dimethylethanolamine (DMEA, **1a**), were obtained in pure form by fractional crystallization. Identification of the components of the methyldiethanolamine (MDEA, **1b**) and TEA reactions was based on samples enriched by chromatography or obtained from alternative synthetic routes. Hydroxyl participation did not occur when the hydroxyl group was separated from nitrogen by three carbons.

The DMEA derivatives **5a** and **6a** were obtained by two routes. The tertiary amine hydrochloride route began with addition of epichlorohydrin to DMEA hydrochloride in water to form (3-chloro-2-hydroxypropyl)(2-hydroxyethyl)dimethylammonium chloride (**3a**).[2] On treatment



with base **3a** afforded (2,3-epoxypropyl)(2-hydroxyethyl)dimethylammonium chloride (**4a**). Compound **4a** underwent base-catalyzed intramolecular cyclization to

(1) McKelvey, J. B.; Benerito, R. R.; Ward, T. L. *Ind. Eng. Chem. Prod. Res. Dev.* **1967**, *6*, 115.

(2) Noguchi, J.; Sakota, N. U.S. Pat. 3 135 788, 1959; *Chem. Abstr.* **1964**, *61*, 5760c.

**Table I. $^{13}C$ NMR Spectral Data for Products Derived from DMEA (in ppm from external $Me_4Si$ in $D_2O$)**

| compd | assignments | | | | |
|---|---|---|---|---|---|
| | Me | CH | $CH_2N$ | 2-$CH_2O$[a] | 3-$CH_2$[b] |
| **4a** | 52.9 | 45.7 | 66.8, 68.3 | 56.2 | 46.3 |
| **16a** | 54.6 | 130.2, 135.7[c] | 59.9 | 57.2 | 69.9 |
| **5a** | 49.3, 49.5, 49.8[d] 58.7, 59.8, 59.2 | 72.4 | 63.1, 63.5[e] | 62.3[e] | 63.1[e] |
| **5a**(NaOD) | 49.6, 58.8 | 74.1 | 64.3 | 62.3 | 62.3 |
| **6a** | 56.3, 56.6, 56.8[d] | 67.5 | 70.1, 70.2 | 64.6 | 73.3 |
| **17a** | 54.5 | 63.4 | 68.3 | 57.0 | |
| **17a**(NaOD) | 54.3 | 64.3 | 68.9, 70.5 | 57.0 | |
| **14a** | 54.0 | 70.5 | 67.9 | 56.7 | 65.6 |
| **3a** | 54.3 | 66.9 | 68.3, 68.8 | 57.0 | 49.0 |
| **19a** | 53.9, 54.1, 54.3[d] | 67.8 | 68.1, 68.6, 68.8 | 57.1 | 65.4 |

[a] 2-$CH_2O$ means the C-2 of the 2-hydroxyethyl group and becomes C-6 in **5** and C-2 in **6**. [b] 3-$CH_2$ means the C-3 of epichlorohydrin which becomes the 2-hydroxymethyl carbon in **5**, C-7 in **6**, and C-2 in **14**. [c] Vinyl carbons. [d] C–N coupling. [e] Assignments may be interchanged within a row.

form a 1.2:1 mixture of **5a** and **6a**. The key to the structural assignments came from $^1H$ NMR spectra in DMSO-$d_6$[3] which indicated a primary hydroxyl in **5a** and a secondary hydroxyl in **6a**.

Compounds **5a** and **6a** were also prepared from the secondary alkanolamine methylethanolamine (MEA) (Scheme II). Epichlorohydrin was added to MEA at low temperature to give (3-chloro-2-hydroxypropyl)(2-hydroxyethyl)methylamine (**8a**). On treatment with base, the epoxide (**11a**) formed and cyclized to 2-(hydroxymethyl)-4-methylmorpholine (**12a**)[4] and perhydro-6-hydroxy-4-methyl-1,4-oxazepine (**13a**). Methylation of **12a** and **13a** with methyl chloride or dimethyl sulfate afforded **5a** and **6a**, 10:1, respectively. In the absence of base **8a** underwent intramolecular displacement of chlorine to form *cis*- and *trans*-1-(2-hydroxyethyl)-1-methyl-3-hydroxyazetidinium chloride (**9a**)[5] in 90% yield. Compound **10a** was a minor product formed from dimerization of **8a**.[6]

Additional pure compounds were prepared for comparison of NMR spectra and HPLC retention times. The DMEA analogue of McKelvey's compound, *trans*-(1,4-dioxane-2,5-diyldimethylene)bis[2-(hydroxyethyl)dimethylammonium chloride] (**14a**), was prepared from *trans*-bis(2,5-iodomethyl)-1,4-dioxane (**15**)[7] and DMEA. (2-Hydroxyethyl)(3-hydroxy-1-propenyl)dimethylammonium chloride (**16a**), the normal product of reactions of tertiary amines with epichlorohydrin,[8] was isolated by chromatography from a reaction in acetonitrile. (2-Hydroxytrimethylene)bis[(2-hydroxyethyl)dimethylammonium chloride] (**17a**) was prepared from DMEA and 1,3-dichloro-2-propanol (**18**) in water. (2-Hydroxyethyl)(2,3-dihydroxypropyl)dimethylammonium chloride (**19a**), which would be expected from hydrolysis of **4a**, was prepared by reaction of DMEA with glycidol (**20**) in water followed by neutralization with HCl.

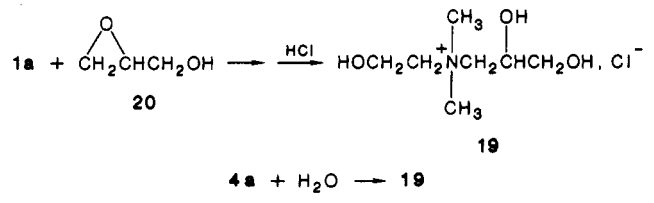



**Table II. Ion-Pair Chromatography Retention Times (min)**

| compd | system A | system B | compd | system A | system B |
|---|---|---|---|---|---|
| **1a** | 4.65 | 4.60 | **17b** | 6.04 | |
| **16a** | 4.74 | 5.59 | **10b** | 6.10 | |
| **5a** | 5.68 | 6.24 | **14b** | 7.03 | |
| **6a** | 4.85 | 6.99 | **3b** | | 7.82 |
| **17a** | 5.53 | | **19b** | | 4.22 |
| **14a** | 6.91 | | **1c** | 4.36 | 4.57 |
| **3a** | | 7.10 | **5c** | 4.51 | 5.05 |
| **9a** | 4.39 | | **6c** | 4.51 | 5.67 |
| **19a** | | 4.43 | **17c** | 5.85 | |
| **1b** | 4.45 | 4.58 | **14c** | 6.33 | |
| **16b** | 4.56 | 5.01 | **3c** | | 7.24 |
| **5b** | 4.75 | 5.75 | **19c** | | 4.08 |
| **6b** | 4.47 | 6.21, 6.39[a] | | | |

[a] Diastereoisomers.

Reactions of DMEA with epichlorohydrin were run under various conditions. Comparison of the $^{13}C$ NMR spectra (Table I) of the products established that **14a** was not a major component in any of the reaction mixtures.

Reaction mixtures were also analyzed by ion pair chromatography in order to determine if a small amount of **14a** was present and to determine the effect of solvent on the product distribution. The analysis required two solvent/column systems because refractive index detection prevented gradient elution. System A separated doubly charged compounds **17a**, **14a**, and occasionally higher oligomers (**21a**)[9] from singly charged compounds. System B separated all of the remaining compounds. Retention times are given in Table II. The product distributions are given in Table III and show that no **14a** was present. The major product in chloroform, acetone, and acetonitrile was **17a**. Compound **16a** was the major product in DMSO and a large component in acetonitrile. The cyclic products, **5a** and **6a**, dominated in water and alcohol. As expected, when the reaction in water was run more concentrated with a 10% excess of amine, the yield of **17a** and higher oligomers (42%) increased significantly. Addition of amine to a twofold excess of epichlorohydrin at 71 °C suppressed formation of **17a** and favored **16a**.

Extension of the study to MDEA and TEA required well-characterized standards. Reaction of diethanolamine (DEA) with epichlorohydrin[10] afforded compounds **12b** and **13b** (Scheme II). Methylation of **12b** and **13b** gave **5b** and **6b**. Reaction of **12b** and **13b** with 2-chloroethanol afforded **5c** and **6c**.

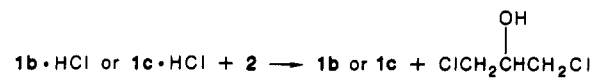
(3) Chapman, O. L.; King, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 1256.
(4) The 2-hydroxymethylmorpholine moiety is found in the antidepressant drug viloxazine: Brown, G. R.; Foubister, A. J.; White, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2577.
(5) Ross, J. H.; Baker, D.; Coscia, A. T. *J. Org. Chem.* **1964**, *29*, 824.
(6) Heywood, D. L.; Phillips, B. *J. Am. Chem. Soc.* **1958**, *80*, 1257.
(7) Summerbell, R. K.; Stephens, J. R. *J. Am. Chem. Soc.* **1954**, *76*, 6404.
(8) Burness, D. M. *J. Org. Chem.* **1963**, *29*, 1862.
(9) The quantity of higher oligomers was estimated from the material balance obtained from column chromatography.
(10) McKelvey, J. B.; Webre, B. G.; Benerito, R. R. *J. Org. Chem.* **1960**, *25*, 1424.

Table III. Comparison of Product Composition for the Reactions of Tertiary Alkanolamines with Epichlorohydrin

| substrate | solvent | percent composition[a] 1 | 19 | 16 | 5 | 6 | 17 | 21 |
|---|---|---|---|---|---|---|---|---|
| DMEA | chloroform[b] | 2.1 | | 21.3 | 6.5 | 11.8 | 54.7 | |
| DMEA | acetone[b] | | | 22.3 | 10.0 | 16.9 | 49.3 | |
| DMEA | acetonitrile[c] | | 1.4 | 38.9 | 2.3 | 4.5 | 49.9 | 1.5 |
| DMEA | DMSO[b] | | 5.2 | 73.8 | | 11.6 | 5.9 | |
| DMEA | water, dilute[b] | 0.4 | | | 28.9 | 38.1 | 28.7 | |
| DMEA | water, concentrated[d] | | 0.6 | 0.5 | 22.4 | 30.1 | 38.3 | 7.4 (42.0)[e] |
| DMEA | ethanol[b] | | | | 72.5[f] | | 27.5 | |
| DMEA | epichlorohydrin[g] | | 1.2 | 38.8 | 22.3 | 11.3 | 18.6 | 3.7 (12.5)[e] |
| DMEA·HCl | | | | | 49.2 | 42.1 | | |
| MDEA | | | | 4.5 | 28.4 | 46.6 | 18.0 | |
| MDEA | epichlorohydrin | | | 8.0 | 29.8 | 48.4 | 11.0 | |
| MDEA | 2-propanol | | | 22.4 | 34.3 | 41.8 | 16.0 | 21.0[e] |
| MDEA + 18 | | | 5.5 | | 31.9 | 42.7 | | |
| TEA | | | | | 33.5 | 37.0 | 4.7 | 24.0[e] |
| TEA[h] | | | | | 29.8 | 32.9 | 17.0 | 26.0[e] |
| TEA + 18 | | 7.7 | 6.0 | | 44.7 | 38.3 | | |

[a] Area percent by HPLC. [b] Concentration 1.47 mequiv/g. [c] Concentration 0.85 mequiv/g. [d] Concentration 3.98 mequiv/g with 10% excess 1a. [e] Column chromatography. [f] Only HPLC system A run, monoquaternary compounds not separated. [g] Mole ratio epichlorohydrin: 1a, 2:1. [h] $BF_3$ etherate, catalyst.

In contrast with DMEA·HCl, reaction of epichlorohydrin with MDEA·HCl or TEA·HCl resulted in formation of 1,3-dichloro-2-propanol (18) and free amine. However,

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the chlorohydrins **3b** and **3c** were obtained from reactions of the amines with a 5–6-fold excess of 1,3-dichloro-2-propanol. Treatment of the chlorohydrins with base gave **5b** and **6b** in a ratio of 1:1.33 and **5c** and **6c** in a ratio of 1:0.85, respectively.

Compounds **17b**, **17c**, **14b**, and **14c**, were prepared as described above for the DMEA analogues. A better route to **14c** involved reaction of DEA with **15** followed by reaction with 2-chloroethanol.

MDEA and TEA were less reactive than the dimethylalkanolamines because of decreased basicity and increased steric hindrance.[11] When equimolar amounts of MDEA and epichlorohydrin were mixed, an exothermic reaction occurred, leading to a solid mass. The exotherm became uncontrollable above 40 °C.[12] Addition of the amine to a twofold excess of epichlorohydrin at 71 °C resulted in the products separating as the reaction progressed. In 2-propanol at 71 °C, the product was homogeneous. The product distributions are given in Table III. Compound **14b** was not detected. The major products were perhydro-6-hydroxy-4-(2-hydroxyethyl)-4-methyl-1,4-oxazepinium chloride (**6b**) and 4-(2-hydroxyethyl)-4-methyl-2-(hydroxymethyl)morpholinium chloride (**5b**). A small amount of bis(2-hydroxyethyl)(3-hydroxy-1-propenyl)methylammonium chloride (**16b**) was confirmed by the presence of vinyl absorption in the NMR spectrum. (2-Hydroxytrimethylene)bis[bis(2-hydroxyethyl)methylammonium chloride] (**17b**) was also detected.

Mixing equimolar amounts of TEA and epichlorohydrin and heating to 42 °C for 24 h resulted in a solid mass. The product distributions are given in Table III. Compounds **16c** and **14c** were not detected. The components were perhydro-6-hydroxy-4,4-bis(2-hydroxyethyl)-1,4-oxazepinium chloride (**6c**), 4,4-bis(2-hydroxyethyl)-2-(hydroxymethyl)morpholinium chloride (**5c**), (2-hydroxytrimethylene)bis[tris(2-hydroxyethyl)ammonium chloride] (**17c**), and oligomeric material (**21c**). When the reaction was catalyzed by $BF_3$ etherate,[13] the amount of **17c** went up at the expense of **5c** and **6c**. The ratio of **5c** to **6c** remained close to 1:1.

When the hydroxyl group was separated from nitrogen by three methylene groups the intramolecular cyclization products were not observed. 3-(Dimethylamino)-1-propanol (**22**) reacted with epichlorohydrin in acetonitrile or without solvent to give a quantitative yield of (3-hydroxy-1-propenyl)(3-hydroxypropyl)dimethylammonium chloride (**23**). In water, (2,3-epoxypropyl)(3-hydroxypropyl)dimethylammonium chloride (**24**) was obtained. These results are directly analogous to those observed with trimethylamine.[5]

Base-catalyzed addition to epoxides usually occurs at the least substituted carbon atom,[14] which would result in formation of the seven-membered ring product. When intramolecular ring closures are involved, Baldwin's rules predict[15] products derived from exo modes, namely compounds containing six-membered rings. The first example was recently reported by Hibert and Zimmerman[16] who found that the reaction of the dipotassium salt of 1,2-dihydroxynaphthalene with epichlorohydrin gave a 60:40 mixture of six- and seven-membered ring systems. The secondary alkanolamines gave a 9:1 ratio of six- to seven-membered ring systems. In general, the tertiary alkanolamines favored seven- over six-membered ring systems. Some of the oxazepinium salts, seven-membered ring, may be formed by direct displacement of chloride at the 3-position rather than via the glycidylammonium salt **4**. DMEA gave a slight excess of the morpholine derivative by the amine hydrochloride route.

All of the products arise from base-catalyzed reactions of the glycidylammonium salt. The catalyst itself results from reaction of **4** with a second mole of amine to form the strong base **24**. As the basicity of the reaction mixture increases, epoxide ring opening of **4** by the 2-hydroxyethyl group[17] and carbanion formation compete with amine

(11) Partansky, A. M. In *Epoxy Resins*: Gould, R. F.; Ed.; American Chemical Society: Washington, DC, 1970; Advances in Chemistry Series 92, p 36.

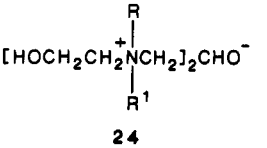
(12) Uncontrollable exotherms are often encountered in amine–epoxide reactions: Schechter, L.; Wynstra, J.; Kurkjy, R. P. *Ind. Eng. Chem.* **1956**, *48*, 94 and ref 1.

(13) Boron trifluoride etherate catalyzes alcohol–epoxide reactions but not amine–epoxide reactions, ref 11, p 31.

(14) Chitwood, H. C.; Freuse, B. T. *J. Am. Chem. Soc.* **1946**, *68*, 680.

(15) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(16) Hibert, M.; Zimmerman, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1432.



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addition. Hydroxylic solvents or substituents favor the intramolecular addition to form **5** and **6** while DMSO favors the rearrangement to **16**. Increased steric bulk also favors **5** and **6**. In aprotic solvents, **17** dominates because it separates from the solution.

**NMR Spectra.** $^{13}C$ NMR chemical shift data are given in Tables I and IV–VI. Some of the quaternary ammonium compounds had temperature-dependent chemical shifts which resulted in poor reproducibility[18] because they were heated by the decoupler. The spectra of some compounds were unexpectedly pH dependent.

The chemical shifts of carbon bound to oxygen and nitrogen occur in a small range with C–O downfield of C–N. The introduction of charged nitrogen caused the C–N lines to shift downfield of C–O. The methyl and methine carbons were assigned with certainty from coupled spectra. The remaining carbons all have the same multiplicity and frequently overlapped. Line broadening or splitting due to C–N coupling aided in making some assignments. The methyl groups of **5a** gave two sets of triplets separated by 10 ppm while **6a** had a single triplet in the $^{13}C$ NMR spectra.

The pH dependence[19] was most notable in compound **17a**. The secondary alcohol carbon at 63.4 ppm shifted to 64.3 ppm and the $CH_2N$ carbons at 68.3 ppm separated into two lines at 68.9 and 70.5 ppm in base. Similar changes were observed in the $^1H$ NMR spectrum. The methyl line at 3.36 became a doublet at 3.29 ppm, the $CH_2N$ multiplet at 3.70 split into two multiplets at 3.38 and 3.68 ppm, and the $CH_2OH$ multiplet shifted from 4.12 to 4.05 ppm. Smaller changes were observed for **5a**, **14b**, and choline chloride.

## Experimental Section

Melting points were determined with a Fisher-Johns melting point apparatus. All melting points are uncorrected. $^1H$ NMR spectra were measured with a Perkin-Elmer R-32 90-MHz spectrometer. The solvent was $D_2O$ containing 1% 3-(trimethylsilyl)propionic acid sodium salt as internal standard unless otherwise noted. Only significant $^1H$ NMR data is given. $^{13}C$ NMR spectra were measured with a JEOL FX 60-MHz spectrometer at ambient temperature in $D_2O$ using tetramethylsilane as an external standard, Tables I and IV–VI. Chemical shifts are accurate to ±1 ppm due to temperature instabilities associated with heating of the samples by the decoupler.

Total nitrogen was measured on a Carlo Erba nitrogen analyzer, Model 1106. Basic nitrogen and ionic chlorine were measured on Radiometer ABU-12 and ABU-80 automatic titrators. Total chlorine was measured after oxygen flask combustion. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

All commercial chemicals and reagents were used as received except for glycidol which was vacuum distilled just prior to use. Thin layer chromatography (TLC) was performed on 250-μm silica gel GHLF from Analtech, Newark, DE, using 10% ammonium hydroxide in methanol saturated with ammonium chloride. Flash chromatography[20] was performed with J. T. Baker 40-μm silica gel. The starting solvent was determined by dissolving the sample in methanol and adding ethyl acetate to just short of the cloud point. Sample loading was 1:10. Progress (100-mL fractions) was monitored by TLC. Oligomeric materials were slowly released from the column by 10% or 20% ammonium hydroxide in methanol saturated with ammonium chloride. Ammonium chloride was removed by ion exchange using Bio-Rad macroporous anion exchange resin AG MP-1, 20–50 mesh, in the hydroxide form. High performance liquid chromatography[21] (HPLC) in an ion-pairing mode was performed by using Waters 510 pumps with a 610 controller, Waters U6K injector, and ERMA RI detector ERC-7510. For solvent system A, an Alltech CN, 25 cm × 4.6 mm, 5-μm column was used at 40 °C. Solvent system A was $H_2O$/MeOH, 95:5, 0.02 M pentanesulfonic acid at pH 2.5 with $H_3PO_4$. With solvent system B, a Dupont, Zorbax CN, 25 cm × 4.6 mm, 5-μm column was used at 30 °C. Solvent system B was water containing 10 mM decanesulfonic acid sodium salt, 25 mM $H_3PO_4$, 165 mM NaBr and 25 mM $KH_2PO_4$. Flow rate was 1 mL/min. Retention times are given in Table II.

**(3-Chloro-2-hydroxypropyl)(2-hydroxyethyl)dimethylammonium Chloride (3a).** Epichlorohydrin (5.2 g, 0.056 mol) was added to DMEA·HCl (7.0 g, 0.056 mol) in water (8.6 g) and the reaction mixture was stirred vigorously for 3 h at room temperature. Removal of solvent in vacuo left 12.4 g of **3a**: $^1H$ NMR ($D_2O$) δ 3.34 (s, 6 H, $CH_3$).

**(2,3-Epoxypropyl)(2-hydroxyethyl)dimethylammonium Chloride (4a).** Potassium hydroxide (3.3 g, 0.05 mol) was dissolved in 30 mL of absolute EtOH and added to **3a** (13.1 g, 0.06 mol). Potassium chloride precipitation began immediately. After 1 h, the reaction mixture was neutralized with concentrated HCl and filtered. Removal of solvent in vacuo left 11.0 g. Crystallization of 8.8 g from absolute EtOH afforded 4.6 g of **4a**: mp 112.5–114 °C; $^1H$ NMR ($D_2O$) δ 2.88 (m, 1 H, H-3), 3.15 (t, 1 H, H-3), 3.36 (s, 6 H, $CH_3$), 3.62–3.80 (m, 4 H, $OCH_2CH_2N$), 4.01–4.24 (m, 3 H, $-CHCH_2-$).

**2-(Hydroxymethyl)-4,4-dimethylmorpholinium Chloride (5a) and Perhydro-6-hydroxy-4,4-dimethyl-1,4-oxazepinium Chloride (6a).** (2,3-Epoxypropyl)(2-hydroxyethyl)dimethylammonium chloride (**4a**) (5.0 g, 0.028 mol) was dissolved in dry EtOH (50 mL) and sodium ethoxide in ethanol (13 mL of 0.32 M, 0.0042 mol) was added. After 16 h at room temperature, crystals separated (1.3 g) and were identified as 2-(hydroxymethyl)-4,4-dimethylmorpholinium chloride (**5a**). Recrystallization from EtOH afforded pure material: mp 225.5–227.5 °C; $^1H$ NMR ($D_2O$) δ 3.35 (s, 6 H, $CH_3$); $^1H$ NMR (DMSO-$d_6$) OH, triplet. Anal. Calcd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.89; Cl, 19.52; N, 7.71. Found: C, 46.13; H, 8.78; Cl, 19.41; N, 7.57.

Fractional crystallization of the filtrate afforded 0.4 g of perhydro-6-hydroxy-4,4-dimethyl-1,4-oxazepinium chloride (**6a**). Recrystallization from EtOH afforded pure material (195.7 mg): mp 248–249.5 °C dec; $^1H$ NMR ($D_2O$) δ 3.30 (s, 3 H, Me), 3.41 (s, 3 H, Me); $^1H$ NMR (DMSO-$d_6$) OH, doublet. Anal. Calcd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.89; Cl, 19.52; N, 7.71. Found: C, 46.17; H, 8.74; Cl, 19.41; N, 7.67.

**(2-Hydroxytrimethylene)bis[(2-hydroxyethyl)dimethylammonium chloride] (17a).** DMEA (26.7 g, 0.30 mol), 1,3-dichloro-2-propanol (19.4 g, 0.15 mol), and water (30.0 g) were combined and heated at 85–87 °C for 18 h. The reaction mixture was neutralized with Rexyn 101 $H^+$, filtered, and freeze-dried to a syrup. Ethanol was added and removed in vacuo until crystallization began. An analytical sample of **17a** was obtained from absolute ethanol: mp 149.5–150.5 °C; $^1H$ NMR ($D_2O$) δ 3.37 (s, 12 H, $CH_3$), 3.62–3.82 (m, 8 H, $CH_2N$), 4.16 (m, 4 H, $CH_2O$), 5.05 (m, 1 H, CHOH); $^1H$ NMR (NaOD) δ 3.40 (s and m, 16 H, $CH_2N$ and $CH_3$), 3.50–3.85 (m, 4 H, $CH_2O$), CHOH was obscured by $H_2O$ resonance. Anal. Calcd for $C_{11}H_{28}Cl_2N_2O_3$: C, 43.00; H, 9.19; Cl, 23.08; N, 9.12. Found: C, 43.07; H, 8.86; Cl, 22.83; N, 9.13.

***trans*-(1,4-Dioxane-2,5-diyldimethylene)bis[(2-hydroxyethyl)dimethylammonium iodide] (14a).** *trans*-2,5-Bis(iodomethyl)-1,4-dioxane[7] (0.50 g, 0.0015 mol) and DMEA (2.0 g, 0.022 mol) were combined and heated on a steam bath for 90 min. The reaction temperature reached 85 °C and the mixture was inho-

(17) In the absence of strong base, ring opening by nitrogen always dominates.

(18) Axelson, D. E.; Blake, S. L. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 2507.

(19) Hoagland et al. (Hoagland, P. D.; Pfeffer, P. E.; Valentine, K. M. *Carohydr. Res.* **1979**, *74*, 135) observed similar pH-dependent chemical shifts and changes in multiplicities in the $^{13}C$ NMR spectra of *N*-alkyl-(1-deoxylactitol-1-yl)amines and the corresponding quaternary ammonium salts.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(21) Retention times and capacity factors decreased with time because of low pH and adsorption of polyquaternary compounds.

**Table IV. $^{13}C$ NMR Spectral Data for Products Derived from MDEA (in ppm from external $Me_4Si$ in $D_2O$)**

| compd | assignments | | | | | |
|---|---|---|---|---|---|---|
| | Me | CH | $CH_2N$ | 2-$CH_2O$[a] | 3-$CH_2$[b] | *exo*-2-$CH_2OH$[c] |
| **5b** | 46.6, 56.6 | 71.8 | 61.3, 61.5,[d] 71.8[e] | 62.8[d] | 62.5[d] | 56.5 |
| **6b** | 54.2, 54.0, 53.7[f] | 67.4 | 67.5, 68.9[d] | 64.5[d] | 73.4[d] | 56.8 |
| **17b** | 52.1 | 63.1 | 66.6 | | | 56.7 |
| **14b** | 51.8 | 70.3 | 64.0, 66.2 | | 67.9 | 56.6 |
| **14b**(NaOD) | 52.1 | | 64.2, 67.5, 67.7 | | 68.4 | 52.0 |
| **3b** | 51.8 | 66.9 | 66.2, 66.4 | | 48.7 | 56.5 |

[a,b] Same as in Table I. [c] Assigned to C-2 of the hydroxyethyl group. [d] Assignments may be interchanged within a row. [e] Assigned to the exocyclic $CH_2N$. [f] C–N coupling.

**Table V. $^{13}C$ NMR Spectral Data for Products Derived from TEA (in ppm from external $Me_4Si$ in $D_2O$)**

| compd | assignments | | | | |
|---|---|---|---|---|---|
| | CH | $CH_2N$ | 2-$CH_2O$[a] | 3-$CH_2$[b] | *exo*-2-$CH_2OH$[c] |
| **5c** | 71.5 | 62.8, 68.1[d] | 60.1[d] | 61.4[d] | 56.4, 57.6 |
| **6c** | 67.4 | 66.2[d] | 64.6[d] | 73.6 | 56.8 |
| **17c** | 62.9 | 63.8 | | | 56.3 |
| **14c** | 70.3 | 63.6, 61.7 | | 67.8 | 56.5 |
| **3c** | 63.5 | 64.4, 66.1 | | 48.9 | 56.3 |

[a,b] Same as footnotes in Table II, respectively. [c] Assigned to C-2 of the hydroxyethyl group. [d] Assignments may be interchanged within a row.

mogeneous. The solids were collected with suction and washed with benzene. The material weighed 0.67 g (88%), mp 253–255 °C dec. An analytical sample of **14a** was obtained by crystallization from water: mp 265–267 °C dec; $^1H$ NMR ($D_2O$) $\delta$ 3.31 (s, 12 H, $CH_3$). Anal. Calcd for $C_{14}H_{32}I_2N_2O_4$: C, 30.78; H, 5.90; I, 46.46; N, 5.13. Found: C, 30.98; H, 5.97; I. 46.68; N, 5.10.

**(2-Hydroxyethyl)(2,3-dihydroxypropyl)dimethylammonium Chloride (19a).** Glycidol (1.19 g, 0.015 mol, freshly distilled) was added to DMEA (1.3 g, 0.015 mol) in water (5.0 g) in an ice bath. The reaction mixture was stirred overnight and allowed to warm to room temperature. The reaction mixture was neutralized with HCl and concentrated in vacuo to a syrup: $^1H$ NMR ($D_2O$) $\delta$ 3.30 (s, 6 H, $CH_3$).

**(2-Hydroxyethyl)(3-hydroxy-1-propenyl)dimethylammonium Chloride (16a).** Epichlorohydrin (18.5 g, 0.20 mol) and acetonitrile (40.0 g) were combined and heated to 48 °C. DMEA (8.9 g, 0.10 mol) was added at 48–86 °C over 15 min. Phase separation began almost immediately. The reaction mixture was heated for an additional hour at 67–70 °C. Methanol (9 mL) was then added to give a homogeneous solution. The reaction mixture was concentrated in vacuo to remove excess epichlorohydrin. Methanol (18.1 g) was added to the residue. A 2.0-g sample was diluted to 10 mL with water. The pH was 10.13. The MeOH solution was diluted with AcOEt (23.6 g) and chromatographed on 200 g of flash silica gel in the same solvent. Fractions 1–7 were blank. Fraction 8, 1.2 g, was a mixture of **1a** and **16a**. Fractions 9, 2.2 g, and 10, 1.2 g, were **16a**: $^1H$ NMR ($D_2O$) $\delta$ 3.22 (s, 6 H, $CH_3$), 3.45–3.68 (m, 2 H, $CH_2N$), 3.70–3.95 (m, 2 H, 2-$CH_2OH$), 4.14 (m, 2 H, 3-$CH_2OH$), 6.24 (br, 2 H, vinyl). Anal. Calcd for $C_7H_{16}ClNO_2 \cdot (0.25CH_3OH)$: C, 45.91; H, 9.03; Cl, 18.69; N, 7.38. Found: C, 45.70; H, 8.80; Cl, 18.49; N, 7.21.

**Solvent Dependence of Reaction of DMEA with Epichlorohydrin.** DMEA (7.0 g, 0.080 mol) was added to epichlorohydrin (7.4 g, 0.080 mol) and 40 g of solvent. The reaction mixture was heated. If the reaction mixture became inhomogeneous, the phases were separated and concentrated in vacuo. The residues were dissolved in water. The pH was measured and adjusted to pH 4–5. The product compositions were measured by HPLC and are given in Table III.

**2-(Hydroxymethyl)-4-methylmorpholine (12a) and Perhydro-6-hydroxy-4-methyl-1,4-oxazepine (13a).** Epichlorohydrin (27.7 g, 0.30 mol) was added to MEA (22.5 g, 0.30 mol) in water (22.5 g) at 25–34 °C over 25 min. The reaction mixture was stirred for an additional hour at 13 °C to give (3-chloro-2-hydroxypropyl)(2-hydroxyethyl)methylamine (**8a**): $^1H$ NMR ($CDCl_3$) $\delta$ 2.34 (s, 3 H, $CH_3$). Sodium hydroxide (24 mL of 50%, 0.30 mol) was added over 20 min keeping the temperature below 35 °C. The reaction mixture was stirred for an additional 30 min and then filtered to remove NaCl. The NaCl was washed with ethanol and a portion of the combined filtrate was distilled in vacuo. The first three fractions, 10.9 g, 15.9 g, and 12 g, contained traces of amines and distilled below 30 °C/0.3 mm. Fraction 4 (9.4 g) distilled at 67–74 °C/0.2 mm and fraction 5 (6.0 g) distilled at 79–89 °C/0.2 mm. Fractions 4 and 5 contained two components, **12a** and **13a**. The distillation residue weighed 20.2 g. The methyl groups of **12a** and **13a** were at 2.29 and 2.40 ppm ($D_2O$), respectively, in the $^1H$ NMR spectrum. Redistillation of fraction 5 afforded a 90% pure sample of **12a**, bp 62–64 °C/0.2 mm.

**2-(Hydroxymethyl)-4,4-dimethylmorpholinium Chloride (5a).** Compounds **12a** and **13a** (6.5 g, 0.050 mol) were dissolved in water (30.0 g) in a pressure bottle fitted with a septum. Methyl chloride (4.9 g, 0.097 mol) was charged and the mixture was heated at 78 °C for 18 h. The pressure was released and the contents were evaporated in vacuo to 7.9 g. Crystallization from absolute EtOH afforded 3.7 g of **5a**, mp 227–229 °C. The filtrate contained a 1:1 mixture of **5a** and **6a** ($^{13}C$ NMR).

**Dimethyl Sulfate Methylation of 12a. 2-(Hydroxymethyl)-4,4-dimethylmorpholinium Methosulfate (5a).** Compound **12a** (0.5 g, 0.0038 mol) in $D_2O$ (1.2 g) was cooled in an ice bath and dimethyl sulfate (0.5 g, 0.0040 mol) was added. The mixture was shaken vigorously and allowed to warm to room temperature. After 80 min, the pH was neutral. The product was **5a** methosulfate.

**Dimethyl Sulfate Methylation of a 1:1 Mixture of 12a and 13a. 2-(Hydroxymethyl)-4,4-dimethylmorpholinium Methosulfate (5a) and Perhydro-6-hydroxy-4,4-dimethyl-1,4-oxazepinium Methosulfate (6a).** The procedure was the same as above.

**Reaction of Triethanolamine with Epichlorohydrin.** TEA (37.3 g, 0.25 mol) and epichlorohydrin (23.1 g, 0.25 mol) were combined and heated in a water bath at 40–45 °C for 22 h. The mixture became too viscous to stir. Methanol (25 mL) was added and the mixture was heated for an additional 6 h. Anal. Calcd

**Table VI. $^{13}C$ NMR Spectral Data for Products Derived from Secondary Amines (in ppm from external $Me_4Si$ in $D_2O$)**

| compd | assignments | | | | | |
|---|---|---|---|---|---|---|
| | Me | CH | $CH_2N$ | 2-$CH_2O$[a] | 3-$CH_2$[b] | *exo*-2-$CH_2OH$[c] |
| **12a** | 46.1 | 77.1 | 54.6, 56.4 | 67.0 | 63.6 | |
| **13a** | 47.4 | 70.0 | 60.6 | 71.8[d] | 75.5[d] | |
| **16a** | 51.3, 52.8 | 59.8, 60.4 | 66.1, 67.7[e] | | 75.2[f] | 57.1 |
| **12b** | | 77.0 | 53.6, 55.4, 59.2[d] | 67.0 | 63.8 | 60.5[d] |
| **13b** | | 70.3 | 58.2,[f] 59.9[d] | 71.7 | 75.4 | 61.4[d] |
| **10b** | | 74.7 | 56.3, 57.4 | | 70.2 | 60.1 |

[a,b] Same as in Table I. [c] Assigned to C-2 of the hydroxyethyl group. [d] Assignments may be interchanged within a row. [e] Assigned to exocyclic $CH_2N$. [f] Assigned to C-2 and C-4 of the azetidinium ring.

for $C_9H_{20}ClNO_4$: N, 5.80; Cl, 14.67. Found: N, 5.49; Cl, 13.72; basic nitrogen 0.33; ionic chlorine, 14.40; HPLC (A and B) 33.5% **5c**, 37.0% **6c**, 4.7% **17c** and 14.88% **21c**. A portion (6.0 g) was chromatographed on 100 g of silica gel in MeOH. Fraction 2, 0.6 g, and fraction 3, 2.4 g, represented 60% of the total. Fractions 4–12 contained 0.5 g, 10% of the total. Fraction 2 was mostly **5c**. HPLC analysis (A) indicated the following compositions: fraction 2, **5c** and **6c** (93%), **17c** (5%), higher oligomers **21c** (2%); fraction 3, **5c** and **6c** (78%), **17c** (6.8%), higher oligomers **21c** (14%); and fractions 4–12, **5c** and **6c** (20%), **4c** (2%), and higher oligomers **21c** (78%).

**Boron Trifluoride Etherate Catalyzed Reaction of Triethanolamine with Epichlorohydrin.** Boron trifluoride etherate (1.8 g, 0.013 mol) was added to TEA (37.3 g, 0.25 mol). The reaction mixture became semisolid and the temperature rose to 33 °C. Epichlorohydrin (23.1 g, 0.25 mol) was added and the reaction mixture (clear and fluid) was heated at 40–50 °C for 10 h. Methanol (24 g) added to the viscous mixture. Anal. Calcd for $C_9H_{20}ClNO_4$; N, 5.80; Cl, 14.67. Found: N, 5.79; Cl, 13.79; basic nitrogen, 0.36; ionic chlorine, 13.79. HPLC (A) gave **5c** and **6c** (64%) and **17c** (17%). Flash chromatography gave 26% oligomers.

***cis*- and *trans*-1-(2-Hydroxyethyl)-1-methyl-3-hydroxyazetidinium Chloride (9a).** MEA (15.0 g, 0.20 mol) was dissolved in water (33.5 g) and cooled to 10 °C. Epichlorohydrin (18.5 g, 0.20 mol) was added at 10–46 °C over 80 min. The resulting solution was stirred overnight at room temperature. HPLC analysis indicated 88.7% **9a** and 11.3% **10a**. Spectra of **9a**: $^1H$ NMR ($D_2O$) $\delta$ 3.29 and 3.39 (s, 3 H ratio 1:2, $NCH_3$), 3.70 (m, 2 H, $NCH_2CH_2OH$), 4.10 (m, 2 H, $CH_2OH$), and 4.15–5.30 (m, 5 H, azetidinium ring).

Analysis for total and ionic chlorine gave 2.93 and 2.20 mequiv/g, respectively, calculated 2.99 mequiv/g. Sodium hydroxide titration gave 0.51 mequiv/g of basic nitrogen. The total nitrogen was 3.14 mequiv/g, calculated 2.99 mequiv/g. These values correspond to 83.6% **9a** and 16.2% **10a**.

**4-(2-Hydroxyethyl)-2-(hydroxymethyl)morpholine (12b) and Perhydro-6-hydroxy-4-(2-hydroxyethyl)-1,4-oxazepine (13b).** Epichlorohydrin (67.1 g, 0.725 mol) was added to DEA, (75.0 g, 0.714 mol) at 24–38 °C over 50 min. The reaction mixture was stirred at 27–31 °C for an additional 3.5 h and then diluted with 2-propanol (60 mL). Potassium hydroxide (47.0 g, 0.714 mol) was dissolved in 2-propanol (300 mL) and cooled to 28 °C. The amine solution was added keeping the temperature below 28 °C. The mixture was stirred for 3 h and filtered and the filtrate was concentrated in vacuo to 120.5 g. Vacuum distillation of 119.2 g afforded 82.0 g (71.3%) of **12b** and **13b**: bp 142–145 °C/0.15 mm. Redistillation afforded **12b**: bp 127 °C/0.05 mm. Anal. Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.27; H, 9.41; N, 8.88.

**Reaction of 12b and 13b with 2-Chloroethanol. 4,4-Bis(2-hydroxyethyl)-2-(hydroxymethyl)morpholinium Chloride (5c) and Perhydro-4,4-bis(2-hydroxyethyl)-6-hydroxy-1,4-oxazepinium Chloride (6c).** 4-(2-Hydroxyethyl)-2-(hydroxymethyl)morpholine (**12b**) (70%), perhydro-6-hydroxy-4-(2-hydroxyethyl)-1,4-oxazepine (**13b**) (30%) (30.4 g, 0.189 mol), 2-chloroethanol (26.7 g, 0.332 mol), ethanol (17.0 g), and potassium iodide (0.19 g, 0.011 mol) were combined and refluxed for 2 days. Removal of excess 2-chloroethanol and solvent in vacuo left **5c**, **6c**, and a small amount of the HCl salt of **12b**.

**4-(2-Hydroxyethyl)-2-(hydroxymethyl)-4-methylmorpholinium Methosulfate (5b).** 4-(2-Hydroxyethyl)-2-(hydroxymethyl)morpholine (**12b**) (2.7 g, 0.017 mol) was dissolved in MeOH (10 mL) at 5 °C and dimethyl sulfate (2.1 g, 0.017 mol) was added. The reaction mixture was allowed to warm to 25 °C over 2.5 h. The solvent was removed in vacuo to give an oil, **5b**. Compound **5b**-methosulate was ion exchanged to **5b**-chloride.

**(2-Hydroxytrimethylene)bis[tris(2-hydroxyethyl)ammonium chloride] (17c).** TEA (36.5 g, 0.245 mol), 1,3-dichloro-2-propanol (15.8 g, 0.122 mol), and potassium iodide (0.3 g, 0.0010 mol) were combined and heated at 100–132 °C for 7 h. Ethanol (150 mL) was added and the mixture was heated to achieve a homogeneous solution. On cooling, phase separation occurred. The EtOH-soluble material was decanted and concentrated in vacuo, and the residue was triturated a second time with EtOH. The ethanol-soluble portion (18.7 g) was diluted with MeOH to a total of 67.0 g and 33.5 g was chromatographed on 100 g of silica gel in MeOH. Fractions 3 and 4, 6.0 and 1.3 g, respectively, were identified as **17c**: $^1H$ NMR ($D_2O$) $\delta$ 3.50 (broad d, 4 H, $CH_2CHOH$), 3.97 (m, 12 H, $CH_2N$), 4.10 (m, 12 H, $CH_2OH$), and 5.08 (m, 1 H, CHOH). Anal. Calcd for $C_{15}H_{36}Cl_2N_2O_7 \cdot CH_3OH$: C, 41.83; H, 8.77; Cl, 15.32; N, 6.09. Found: C, 41.40; H, 8.38; Cl, 15.66; N, 6.41.

**1,4-[Dioxane-2,5-diylbis(methylenenitrilo)]-*trans*-2,2′,2″,2‴-tetraethanol (10b).** *trans*-2,5-Bis(iodomethyl)-1,4-dioxane[7] (5.5 g, 0.015 mol) and DEA (6.3 g, 0.060 mol) were combined and heated in an oil bath at 100–122 °C for 2 h and then at 67 °C for 15 h. Methanol and $Na_2CO_3$ (3.2 g, 0.030 mol) were added and the mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated in vacuo. Crystallization of the residue from MeOH/AcOEt afforded 3.7 g (77%) of **10b**. An analytical sample was obtained from AcOEt: mp 75–76.5 °C; $^1H$ NMR ($D_2O$) 2.61 (d, 4 H, $CHCH_2N$), 2.76 (t, 8 H, $NCH_2CH_2OH$), 3.36–4.10 (m, 14 H, $CH_2O$, CHO). Anal. Calcd for $C_{14}H_{30}N_2O_6$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.17; H, 9.60; M, 8.54.

***trans*-(1,4-Dioxane-2,5-diylmethylene)bis[tris(2-hydroxyethyl)ammonium chloride] (14c).** 2-Chloroethanol (6.0 g, 0.075 mol), **10b** (2.7 g, 0.0084 mol), and potassium iodide (32.7 mg, 0.0002 mol) were combined and heated on a steam bath for 7 days. Excess 2-chloroethanol was removed in vacuo and the residue was crystallized from a mixture of EtOH and MeOH: **14c**, 2.5 g. An analytical sample was obtained from MeOH, mp 213.5–215 °C. Anal. Calcd for $C_{18}H_{40}Cl_2N_2O_8$: C, 44.72; H, 8.34, Cl, 14.07; N, 5.80. Found: C, 44.38; H, 7.95; Cl, 14.45, N, 5.69.

**Synthesis of 14c from *trans*-2,5-Bis(iodomethyl)-1,4-dioxane and Triethanolamine.** TEA (10.0 g, 0.067 mol) and *trans*-2,5-bis(iodomethyl)-1,4-dioxane[7] (6.8 g, 0.020 mol) were combined and heated at 100 °C for 4 days. Addition of methylene chloride/MeOH caused a crystalline solid to separate, 2.0 g (18%), identified as the hydriodide salt of TEA. TLC indicated that the reaction mixture contained TEA·HI and **14c**. Chromatography on 150 g of silica gel afforded 6.9 g of TEA and TEA·HI and 2.4 g of mixtures of TEA with **14c**. Methanol saturated with $NH_4Cl$ released additional mixed fractions and finally single component fractions of **14c** contaminated with $NH_4Cl$. The later were ion exchanged to remove $NH_4Cl$, leaving 0.5 g of **14c** identical with that from the above reaction.

**(2-Hydroxytrimethylene)bis[bis(2-hydroxyethyl)methylammonium chloride] (17b).** MDEA (23.8 g, 0.20 mol), 1,3-dichloro-2-propanol (12.9 g, 0.10 mol), and water were combined and heated at 70–77 °C for 17 h. Water was removed in vacuo and ethanol was added and removed in vacuo several times. The residue was crystallized from MeOH, mp 83.5–85 °C: $^1H$ NMR ($D_2O$) $\delta$ 3.36 (s, 3 H, $CH_3N$). Anal. Calcd for $C_{13}H_{32}Cl_2N_2O_5$: C, 42.51; H, 8.78; Cl, 19.30; N, 7.63. Found: C, 42.60; H, 8.60; Cl, 19.22; N, 7.61.

***trans*-(1,4-Dioxane-2,5-diyldimethylene)bis[bis(2-hydroxyethyl)methylammonium iodide] (14b).** MDEA (10.0 g, 0.084 mol) and *trans*-2,5-bis(iodomethyl)-1,4-dioxane[7] (3.4 g, 0.01 mol) were combined and heated in an oil bath at 101 °C with mechanical stirring for 7 h. The reaction mixture was heterogeneous throughout. Methanol was added to the cooled reaction mixture and the solid, 4.6 g (80.1%), was collected with suction. A 2.0-g sample was recrystallized from water/methanol, mp 223–225 °C: $^1H$ NMR ($D_2O$) $\delta$ 3.29 (s, 6 H, $CH_3N$). Anal. Calcd for $C_{16}H_{36}I_2N_2O_6$: C, 31.70; H, 5.99; N, 4.62; I. 41.86. Found: C, 31.92; H, 5.58; I, 42.39; N, 4.71.

**Reaction of Methyldiethanolamine with Epichlorohydrin, Neat.** MDEA (35.8 g, 0.30 mol) and epichlorohydrin (27.8 g, 0.30 mol) were combined at room temperature. A mild exotherm developed after 25 min. The reaction mixture was maintained at 25–40 °C with intermittent cooling for 3 h. It became too thick to stir. Methanol (10 g) was added and the temperature was maintained at 32 °C for 2.5 h and then at room temperature overnight. The reaction mixture was heated to 79 °C over 45 min. A 6.7-g sample was chromatographed on 100 g of silica gel in 1:1 AcOEt/MeOH. Fraction 4, 0.3 g, contained **1b**; fraction 5, 1.0 g, **6b**; fraction 6, 0.7 g, mixture of **5b** and **6b**; fractions 7–9, 0.5 g, **17b**; fractions 10–28, 1.4 g, **21b**. $^{13}C$ NMR ($D_2O$): $\delta$ 51.9 ($CH_3$), 56.6 ($CH_2OH$), 63.0, 66.5 (large and broad, $CH_2N$), 73.2 and 74.3 ($CH_2O$). HPLC (A) analysis indicated 4.5% **16b**, 75% **5b** and

**6b**, and 18% **17b**. HPLC (B) analysis indicated 37.9% **5b** and 62.1% **6b**. Anal. Calcd for $C_8H_{18}ClNO_3$: Cl, 16.75; N, 6.62. Found: Cl, 16.33; N, 6.50; ionic chlorine, 13.68; basic nitrogen, 0.8.

**Reaction of MDEA with Excess Epichlorohydrin.** Epichlorohydrin (55.6 g, 0.60 mol) was heated to 71 °C and MDEA (35.8 g, 0.30 mol) was added over 2.25 h at 71–90 °C. The reaction mixture contained two phases. Water and methylene chloride were added and the aqueous phase was separated and concentrated in vacuo to 73.9 g. Flash chromatography gave 26% oligomers. Anal. Calcd for $C_8H_{18}ClNO_3$: Cl, 16.75; N, 6.62. Found: Cl, 16.50; N, 6.89; ionic chlorine, 17.45; basic nitrogen, 0.013.

**Reaction of MDEA with Epichlorohydrin in 2-Propanol.** Epichlorohydrin (23.1 g, 0.25 mol) and 2-propanol were combined and heated to 71 °C. MDEA (29.8 g, 0.25 mol) was added over 2.3 h at 71–84 °C. The reaction mixture was heated at 82 °C for an additional 45 min. Water (40 mL) was added. The reaction mixture contained two layers. The organic layer was separated by extraction with methylene chloride (0.8 g residue). The aqueous layer weighed 93.7 g. Anal. Calcd for $C_8H_{18}ClNO_3$: Cl, 16.75; N, 6.62. Found: Cl, 15.81; N, 7.14; ionic chlorine, 15.44; basic nitrogen, 0.05.

A portion was freeze-dried and 5.5 g was chromatographed in MeOH on 100 g of silica gel. Fraction 3, 2.4 g; fraction 4, 1.3 g; fraction 5, 0.3 g, fractions 6 and 7, 0.4 g, were obtained representing 80% of the material. HPLC (A) analysis on fraction 5 indicated 76% higher oligomers.

**(3-Hydroxy-1-propenyl)(3-hydroxypropyl)dimethylammonium Chloride (23).** 3-(Dimethylamino)-1-propanol (0.53 g, 0.0051 mol), epichlorohydrin (0.47 g, 0.0051 mol), and acetonitrile (4.0 g) were combined at room temperature. A crystalline solid separated after 24 h. After 9 days, the solid was collected with suction, 1.0 g. Recrystallization from EtOH–$Et_2O$ afforded an analytical sample, mp 123.5–125.0 °C: $^{13}C$ NMR ($D_2O$) $\delta$ 26.9 ($CH_2$), 53.5 ($CH_3$), 59.3, 59.7, 77.2 ($CH_2N$, $CH_2O$), 130.4 (CH), 135.0 (NCH); HPLC (B) $t_R$ 6.57 min. Anal. Calcd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27; Cl, 18.21; N, 7.16. Found: C, 48.94; H, 9.40; Cl, 17.97; N, 7.16.

**Reaction of 3-(Dimethylamino)-1-propanol with Epichlorohydrin, Neat.** 3-(Dimethylamino)-1-propanol (41.3 g, 0.4 mol) was added to epichlorohydrin (37.0 g, 0.40 mol) at 29–38 °C. After addition of 31.7 g (1 h) the temperature reached 65 °C and an uncontrollable exotherm heated the mixture to 126 °C. The remainder was added at 39–47 °C over 10 min. After 4 h at room temperature, a portion (21.4 g) was dissolved in water (10 g). The pH was 10.6. Analysis on the reaction mixture: HPLC (B) $t_R$ 5.36 min (2.0%), 6.47 min (98%) (**23**).

**Reaction of 3-(Dimethylamino)-1-propanol with Epichlorohydrin in Water.** Epichlorohydrin (9.3 g, 0.10 mol) and water (39.0 g) were combined (immiscible). 3-(Dimethylamino)-1-propanol (10.3 g, 0.10 mol) was added at 28–46 °C over 1 h. After 4 h, the pH of the solution (12.1) was adjusted to 5 with concentrated HCl (0.7 g, 0.007 mol). $^1H$ NMR and $^{13}C$ NMR identified the product as (2,3-epoxypropyl)(3-hydroxypropyl)-dimethylammonium chloride (**24**): $^{13}C$ NMR ($D_2O$) 25.5 ($CH_2$), 45.2 (C-2), 45.7 (C-3), 51.6 ($CH_3$), 58.4 ($CH_2OH$), 63.0 and 66.7 ($CH_2N$).

**(3-Chloro-2-hydroxypropyl)bis(2-hydroxyethyl)methylammonium Chloride (3b).** MDEA (11.9 g, 0.10 mol) and 1,3-dichloro-2-propanol (64.0 g, 0.50 mol) were combined and heated at 90–95 °C for 23 h. The reaction mixture was extracted with water (50 mL). The aqueous layer was freeze-dried to a syrup which was dissolved in absolute ethanol and concentrated in vacuo to 16.4 g of **3b**: $^1H$ NMR ($D_2O$) $\delta$ 3.35 (s, 3 H, $CH_3N$). Absolute ethanol was added to give a total weight of 55.3 g. HPLC (B) $t_R$ 4.22 min (10.3%) **19b**, 4.79 min (5.6%) **1b**·HCl, 6.62 min (82.7%) **3b**, and 7.82 min (1.4%).

**Reaction of 3b with Potassium Hydroxide.** Potassium hydroxide (2.8 g, 0.050 mol) was dissolved in ethanol (15 g) and added to an ethanol solution of **3b** (42.2 g, 0.066 mol) at room temperature. Potassium chloride precipitated immediately. The reaction mixture was filtered to remove salt and the pH was adjusted to 6 with concentrated HCl (0.9 g, 0.009 mol). The filtrate was concentrated in vacuo to 9.6 g: HPLC (B) (5.5%) **19b**, (31.9%) **5b**, (42.7%) **6b**, (7.7%), **3b**.

**(3-Chloro-2-hydroxypropyl)tris(2-hydroxyethyl)ammonium Chloride (3c).** TEA (14.9 g, 0.10 mol) and 1,3-dichloro-2-propanol (62.1 g, 0.48 mol) were combined and heated at 96 °C for 23 h. The reaction mixture contained a solid which was removed by filtration, 6.6 g (36%), and identified as TEA·HCl. The filtrate was extracted with 50 mL of water and the aqueous layer was freeze-dried to give 15.1 g of **3c**. Ethanol was added to the residue to give 53.3 g: HPLC (B) (5.5%) **19c**, (6.7%) **1c**·HCl, (9.3%) **5c**, (14.3%) **6c**, and (64.7%) **3c**.

**Reaction of 3c with Potassium Hydroxide.** Potassium hydroxide (2.5 g, 0.045 mol) was added to a solution of **3c** in ethanol (43.4 g, 0.057 mol) at room temperature. After 5 h, the solution was filtered to remove potassium chloride and the pH of the filtrate was adjusted to 6 with concentrated HCl (2.5 g, 0.025 mol). The filtrate was concentrated in vacuo to 10.1 g: HPLC (B) $t_R$ (6.0%) **19c**, (7.7%) **1c**·HCl, (44.7%) **5c**, (38.3%) **6c**.

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**Registry No.** **1a**·HCl, 2498-25-1; **1b**·HCl, 54060-15-0; **1c**·HCl, 637-39-8; **3a**·$Cl^-$, 84434-68-4; **3b**·$Cl^-$, 110529-20-9; **3c**·$Cl^-$, 66786-97-8; **4a**·$Cl^-$, 110528-91-1; **5a**·$Cl^-$, 110528-92-2; **5a**·$CH_3OSO_3^-$, 110529-00-5; **5b**·$Cl^-$, 110529-15-2; **5b**·$CH_3OSO_3^-$, 110529-11-8; **5c**·$CL^-$, 110529-03-8; **6a**·$Cl^-$, 110528-93-3; **6a**·$CH_3OSO_3^-$, 110529-02-7; **6b**·$Cl^-$, 110529-16-3; **6c**·$Cl^-$, 110529-04-9; **8a**, 63125-83-7; *cis*-**9a**·$Cl^-$, 110529-06-1; *trans*-**9a**·$Cl^-$, 110529-07-2; **10a**, 110529-08-3; *trans*-**10b**, 110587-24-1; **12a**, 40987-46-0; **12b**, 99669-14-4; **13a**, 110528-98-8; **13b**, 110529-09-4; **14a**·$2I^-$, 110528-95-5; *trans*-**14b**·$2I^-$, 110529-14-1; *trans*-**14c**·$2Cl^-$, 110529-12-9; **16a**·$Cl^-$, 110528-97-7; **16b**·$Cl^-$, 110529-17-4; **17a**·$2Cl^-$, 110528-94-4; **17b**·$2Cl^-$, 110529-13-0; **17c**·$2Cl^-$, 110529-05-0; **19a**·$Cl^-$, 110528-96-6; **19b**·$Cl^-$, 110529-21-0; **19c**·$Cl^-$, 109232-32-8; **23**·$Cl^-$, 110529-18-5; **24**·$Cl^-$, 110529-19-6; DMEA, 108-01-0; MEA, 109-83-1; TEA, 102-71-6; DEA, 111-42-2; MDEA, 105-59-9; epichlorohydrin, 106-89-8; 1,3-dichloro-2-propanol, 96-23-1; glycidol, 556-52-5; 2-chloroethanol, 107-07-3; 3-(dimethylamino)-1-propanol, 3179-63-3; *trans*-2,5-bis(iodomethyl)-1,4-dioxane, 56127-59-4.