Methyl 2-(*unsym*-Dimethylhydrazino)-1-cyclopentenecarboxylate (IIf).—This compound distilled at 72–73° (4 mm); $\lambda_{max}^{95\%\,EtOH}$ 291 mμ; $\nu_{max}^{CCl_4}$ 3250 (m, NH), 1653 cm^{-1} (s, chelated C=O); nmr (CCl_4) δ 1.81 (q, splitting = 7 cps 4-CH_2 in cyclopentene), 2.51 [s, $(CH_3)_2$], 3.60 (s, CH_3O). *Anal.* Calcd for $C_9H_{16}N_2O_2$: C, 58.66; H, 8.77; N, 15.21. Found: C, 58.75; H, 8.65; N, 15.22.

Cleavage of the Ring to Form Adipic Acid Diamides.—Methyl 2-cyclopentanonecarboxylate (Ia, 2.0 g, 0.014 mole) was placed in a flask, and a large excess (10 ml) of propylamine or isobutylamine was added. A white precipitate formed. The mixture was allowed to stand for 4 days and was then poured into hexane. The amide precipitated and was recrystallized from tetrahydrofuran. Identification of dipropyladipamide and diisobutyladipamide was positively established by analysis and comparison with amides prepared from adipic acid chloride.

N,N′-Dipropyladipamide.—This compound was obtained in 2% yield, mp 181°; ν_{max}^{mull} 3300 (NH), 1628 cm^{-1} (C=O). *Anal.* Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.29. Found: C, 63.02; H, 10.74; N, 12.21.

N,N′-Diisobutyladipamide.—This compound was obtained in 3% yield, mp 188°; ν_{max}^{mull} 3300 (NH), 1623 cm^{-1} (C=O); nmr (pyridine) δ 3.03 (t, J = 6.5 cps, CH_2N). *Anal.* Calcd for $C_{14}H_{28}N_2O_2$: C, 65.58; H, 11.01; N, 10.93. Found: C, 65.69; H, 10.85; N, 11.02.

Chromatographic Procedures.—The enamines were chromatographed on silica gel[13] using a 20% mixture of acetone dissolved in hexane. This system was effective for analysis using thin layer chromatography (tlc) or for separations using column chromatogaphy. Columns were packed dry and a water pump vacuum was used to assure even packing. An ultraviolet lamp was used for observing column fractionations since both ester and enamine fluoresced strongly.

On tlc plates the enamines gave light brown-purple colors when they were sprayed with methanolic ferric chloride. Amides were best detected by using bromine vapors. The relative rates of reaction as determined by tlc of the amines with methyl 2-cyclopentanonecarboxylate were as follows: benzylamine > propylamine > isobutylamine > isopropylamine > *t*-butylamine. The reaction may also be followed by means of nmr, infrared, and ultraviolet spectra.

Registry No.—Ia, 10472-13-6; Ib, 10472-14-7; Ic, 10472-15-8; Id, 10472-16-9; Ie, 10472-17-0; IIa, 10412-92-7; IIb, 10472-19-2; IIc, 10472-20-5; IId, 10472-21-6; IIe, 10472-22-7; IIf, 10472-23-8; methyl 2-cyclopentanonecarboxylate, 10472-24-9; ethyl 2-cyclopentanonecarboxylate, 611-10-9; N,N′-dipropyladipamide, 10263-96-4; N,N′-diisobutyladipamide, 10472-27-2.

Acknowledgment.—This research was supported by a National Science Foundation Research Grant (GB-3091) and by a National Science Foundation Undergraduate Research Grant (GE-6199). We are indebted to J. E. Keiser for his helpful suggestions and to J. G. Murphy for tlc analyses.

(13) Kieselgel, Camag, and Eastman Kodak silica gel coated plastic.

Investigation of the Claimed Synthesis of 1,1′-(Oxydiethylene)bisaziridine

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Manecke and Heller[1] claim to have synthesized 1,1′-(oxydiethylene)bisaziridine (I) by treating bis-2-chloroethyl ether with ethylenimine (Scheme I). They state that reaction of the presumed bisaziridine I with hydrobromic acid leads to the formation of 1,4-bis(2-{2-[(2-bromoethyl)amino]ethoxy}ethyl)piperazine tetrahydrobromide (II). They further claim that rigorous treatment of the bispiperazine II with hydriodic acid, followed by subsequent reaction with strong alkali, produces 1,4-piperazinediethanol (III), which they isolate as the known dipicrate.[2]

We have repeated the work of Manecke and Heller and have isolated products which have the same melting points and elemental analyses as were cited by them for compounds I and II. Instrumental analyses and an alternate method of synthesis revealed that the presumed compound I was really 4-[2-(1-aziridinyl)-ethyl]morpholine (IV). The synthesis of IV by the two methods shown in Scheme II was accompanied in each case with the production of a small amount of 4-(2-methoxyethyl)morpholine (V). The presumed compound II was found to be 4-[2-(2-bromoethyl)aminoethyl]morpholine dihydrobromide (VI). Treatment of IV with hydrobromic acid should not affect the morpholine ring; a normal opening of the aziridine ring should be expected.[3]

Samples of IV, prepared by the two different methods, had identical nmr spectra and gave the known derivative 2-[(2-morpholinoethyl)amino]ethanethiol dihydrochloride (VII) upon treatment with hydrogen sulfide and subsequently with hydrochloric acid.[4]

The treatment of the haloethylamine VI with hydriodic acid, under the vigorous conditions cited by Manecke and Heller, could easily lead to the formation of 1,4-piperazinediethanol (III).

That morpholine derivatives can result from the treatment of bis-2-chloroethyl ether with amines is not surprising. Farrar[5] has reported his inability to form 1,1′-(oxydiethylene)bishydrazine by treating bis-2-chloroethyl ether with hydrazine. Instead, his major reaction product was 4-aminomorpholine. Rappaport[6] and Cerkovnikov and Stern[7] have reported the synthesis of 4-phenylmorpholine from aniline and bis-2-chloroethyl ether. Cerkovnikov, *et al.*,[8] also has reported that treatment of benzylamine with the bis-halo ether resulted in 4-benzylmorpholine.

An alternate approach to the bisaziridine I, involving reaction of the tosylate of 1-(2-hydroxyethyl)aziridine with the alkoxide of the same amino alcohol, was investigated. The reaction product gave evidence of being the desired compound [nmr studies of the crude reaction product (Figure 1), together with the quantitative recovery of the expected by-products, sodium *p*-toluenesulfonate and sodium chloride]. Unfortunately, the product has repeatedly undergone violent decomposition soon after removal of the reaction solvent. Attempts to prepare stable derivatives of this product have been unsuccessful.

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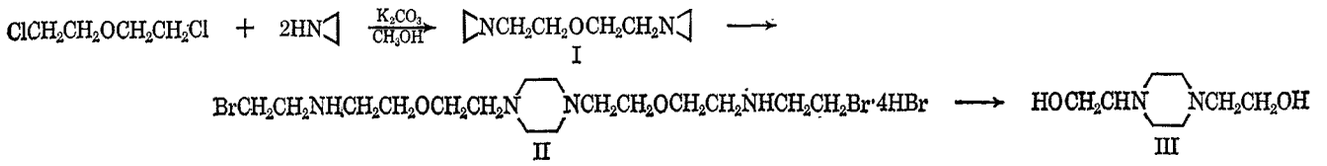
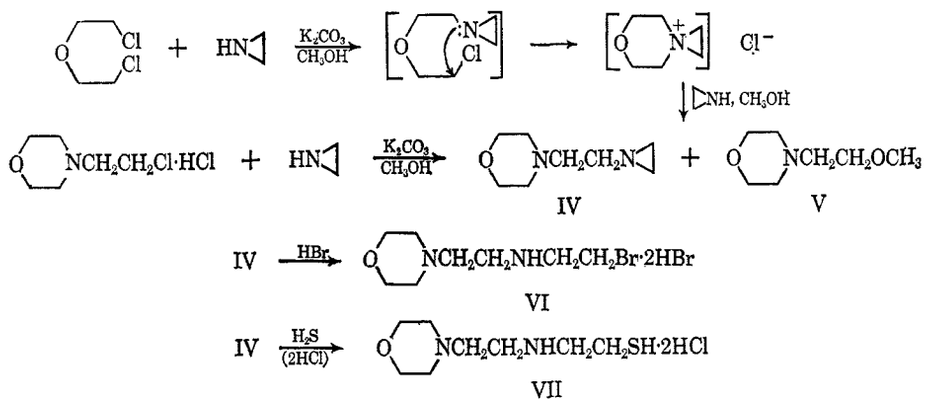
SCHEME I



SCHEME II



Experimental Section

The infrared spectra were determined on Perkin-Elmer Model 21 and Model 137 infrared spectrophotometers with sodium chloride optics.

Proton magnetic resonance spectra were obtained on a Varian A-60 spectrometer. All chemical shifts are reported in parts per million (ppm) on the δ scale. Tetramethylsilane (TMS) was used as a 0 reference with chloroform-*d* and acetone-d_6, while sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used with deuterium oxide solutions.

Gas chromatographic data were obtained on a Wilkens Model 350 Aerograph using 6-ft columns of 10% SE-30 on 60–80 mesh Diatoport-S. Helium was used as carrier gas.

4-[2-(1-Aziridinyl)ethyl]morpholine (IV). A. From Bis-2-chloroethyl Ethyl Ether.—A reaction flask was charged with 200 ml of methanol, anhydrous potassium carbonate (140 g, 1 mole), and freshly distilled ethylenimine (86 g, 2 moles). This mixture was stirred and heated to reflux. Bis-2-chloroethyl ether (71.5 g, 0.5 mole) was added dropwise over 2 hr. Refluxing was continued for an additional 3 hr. Inorganic solids were removed by filtration, and solvent was removed under reduced pressure. The residual, straw-colored oil was distilled under reduced pressure. A 37-g forerun was taken over the following range: 51.5–67.5° (6 mm) and then 65–70.5° (4 mm). This forerun consisted mainly of recovered unreacted bis-2-chloroethyl ether contaminated with about 14% (determined by vpc) of 4-(2-methoxyethyl)morpholine (V). The product was then obtained as a colorless liquid in about 95% purity (vpc): 21.8 g (28%), bp 72–76° (4 mm), n^{25}D 1.4717. There remained in the still pot a considerable amount of undistillable solid residue. The product was redistilled to achieve a purity of >99% (vpc): bp 77–78.5° (4 mm), n^{25}D 1.4725.

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9. Found: C, 61.4; H, 10.4; N, 17.8.

B. From 4-(2-Chloroethyl)morpholine Hydrochloride.—A flask was charged with 200 ml of methanol, anhydrous potassium carbonate (140 g, 1 mole), and ethylenimine (43.1 g, 1.0 mole). The mixture was heated to reflux. From a heated dropping funnel was added a warm solution of 4-(2-chloroethyl)morpholine hydrochloride (93.0 g, 0.5 mole) in 250 ml of methanol over 2 hr. The mixture was refluxed for an additional 3 hr. Inorganic solids were removed by filtration, and solvent was removed under reduced pressure. The straw-colored residue was distilled to give a series of distillation cuts of bp 35–47° (0.4 mm) to 45° (0.25 mm). The initial cuts totaled 19.1 g and were assayed by vpc to show a net composition of 9.2 g of 4-(2-methoxyethyl)morpholine (V) and 9.9 g of 4-[2-(1-aziridinyl)ethyl]morpholine (IV). The latter cuts totaled 22.7 g and exhibited a net composition (vpc) of 1.8 g of the methoxymorpholine derivative and 20.9 of the desired morpholine–aziridine derivative.

The initial cuts were combined and redistilled to give pure (vpc) V: bp 31–32° (0.5 mm) [lit.[9] bp 104–105.8° (44 mm)], n^{25}D 1.4498. The latter series of cuts were combined and redistilled to give pure IV; bp 47–48° (0.5 mm), n^{25}D 1.4726.

Anal. Calcd for $C_7H_{15}NO_2$ (V): C, 57.9; H, 10.4; N, 9.6. Found: C, 58.2; H, 10.6; N, 10.0.

Compound V as isolated from this reaction was identical with V isolated by vpc from the above-described reaction between bis-2-chloroethyl ether and ethylenimine. Their infrared spectra and vpc retention times were identical.

Anal. Calcd for $C_8H_{16}N_2O$ (IV): C, 61.5; H, 10.3; N, 17.9. Found: C, 61.3; H, 10.5; N, 17.6.

The nmr spectrum of IV in $CDCl_3$ (Figure 1) shows multiplets at 1.10 and 1.72 ppm characteristic of the aziridine ring. Apparent triplets at 3.70 and 2.47 ppm represent methylene groups adjacent to O and N, respectively, in the morpholine ring. An overlapping multiplet at approximately 2.5 ppm accounts for the remaining two methylenes between the rings. Area intensity ratios of these methylene fragments are 2:2:8:4 and are in agreement with the above assignments.

The desired compound I would be expected to show the same multiplicity of peaks as well as approximately the same chemical shifts; however, intensity ratios of the methylene fragments should all be equal, *i.e.*, in the ratio 4:4:4:4. The unstable reaction product obtained from the reaction between the tosylate of 1-(2-hydroxyethyl)azirdine and the alkoxide of the same amino alcohol gave an nmr spectrum (Figure 1) which did meet all of these requirements.

The nmr of V in $CDCl_3$ exhibits multiplets at 3.72 and 2.48 ppm representing methylenes adjacent to O and N, respectively, in the morpholine ring. Triplets occur at 3.54 and 2.57 ppm corresponding to the methylenes adjacent to the O and N. The remaining singlet at 3.35 ppm is due to the methoxyl group. The proton count was in agreement with the above assignments.

4-[2-(2-Bromoethyl)aminoethyl]morpholine Dihydrobromide (VI).—4-[2-(1-Aziridinyl)ethyl]morpholine (IV, as obtained from bis-2-chloroethyl ether, 3.3 g, 0.021 mole) was dissolved in 6 ml of water. The solution was cooled in an ice water bath, and to it was slowly added 75 ml of 48% hydrobromic acid. The resulting solution was stirred at room temperature for 30 min. Excess hydrobromic acid was removed under reduced pressure. The orange residue rapidly solidified. This solid was triturated with ethanol and collected to give 8.0 g (95%) of pale buff powder, mp 192–195° dec. This crude solid was recrystallized from ethanol to give small, colorless needles, mp 195–197° dec.

Anal. Calcd for $C_8H_{19}Br_3N_2O$: C, 24.1; H, 4.8; Br, 60.1; N, 7.0. Found: C, 24.2; H, 5.0; Br, 59.7; N, 7.0.

The nmr of VI was determined in D_2O. The morpholine ring showed triplets at 4.07 and 3.52 ppm for the methylenes adjacent to the O and N atoms, respectively. The remaining methylene groups absorb at 3.70 and 3.74 ppm. The singlet at 4.69 ppm accounts for the three exchangeable amine hydrobromide protons. Integration gave intensity ratios of 4:4:8:3.

(9) J. P. Mason and S. Malkiel, *J. Am. Chem. Soc.*, **62**, 1448 (1940).

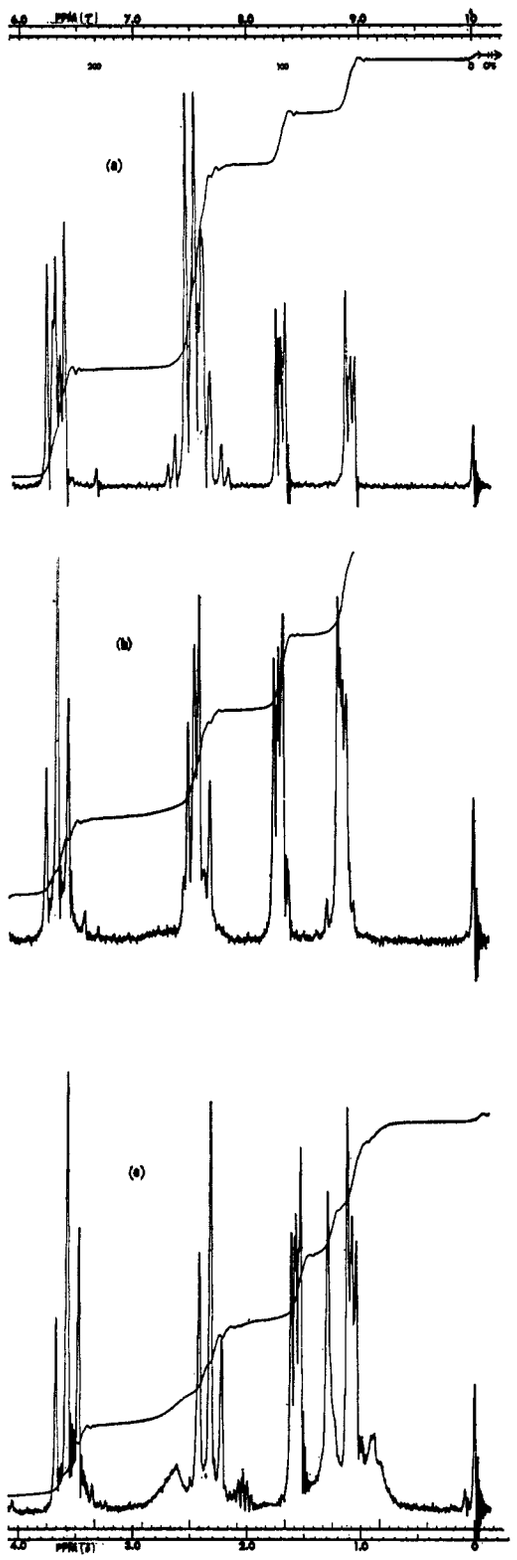


Figure 1.—Partial nmr spectra of (a) 4-[2-(1-aziridinyl)ethyl]-morpholine (IV), determined in $CDCl_3$; (b) crude 1,1′-(oxydiethylene)bisaziridine (I), free of mineral oil but contaminated with unconverted tosylate (peak at 2.45 ppm), determined in $CDCl_3$; (c) crude I, contaminated with mineral oil (peaks at 0.9 and 1.3 ppm) and an unidentified impurity peak (2.6 ppm), determined in CD_3COCD_3. Spectra b and c were obtained from the products of two reactions; in the former case mineral oil was removed from the sodium hydride dispersion prior to reaction with 1-(2-hydroxyethyl)aziridine.

2-[(2-Morpholinoethyl)amino]ethanethiol Dihydrochloride (VII). A. From IV as Derived from Bis-2-chloroethyl Ether.—4-[2-(1-Aziridinyl)ethyl]morpholine (IV, 6.1 g, 0.04 mole) was poured into a precooled solution of hydrogen sulfide (7 g) in 50 ml of methanol (−75°). The stirred reaction mixture was maintained at −60° for 20 min, then allowed to slowly warm to room temperature. Excess hydrogen sulfide and solvent were removed under reduced pressure leaving 6.8 g of a pale violet liquid. The crude free base was dissolved in 25 ml of water, and the solution was acidified with 6 *N* hydrochloric acid. After concentrating to dryness under reduced pressure, a quantitative yield of the solid dihydrochloride was obtained. This solid was recrystallized from methanol to provide 6.5 g (62%) of coarse, colorless needles, mp 186–188° (lit.[4] mp 185–188°).

B. From IV as Derived from 4-(2-Chloroethyl)morpholine Hydrochloride.—The reaction was carried out in the same manner as described under A above. The following amounts of reagents were employed: IV (10.0 g, 0.064 mole), hydrogen sulfide (8 g, in 50 ml of methanol). There was obtained 13.1 g (78%) of pure dihydrochloride, mp 185–187°. No depression was observed when a mixture melting point was taken with the dihydrochloride obtained from IV as derived from bis-2-chloroethyl ether. Infrared and nmr spectra of these two derivatives were identical.

Anal. Calcd for $C_8H_{20}Cl_2N_2OS$: C, 36.5; H, 7.6; Cl, 26.9; N, 10.6; S, 12.2. Found for VIIa: C, 36.5; H, 7.7; Cl, 26.7; N, 10.6; S, 12.1. Found for VIIb: C, 36.5; H, 7.9; Cl, 26.9; N, 10.6; S, 11.8.

Reaction of the Tosylate of 1-(2-Hydroxyethyl)aziridine with the Alkoxide of the Same Amino Alcohol.—1-(2-Hydroxyethyl)-aziridine (43.6 g, 0.50 mole) was added dropwise over 30 min to a suspension of sodium hydride (21.7 g, of a 58% mineral oil dispersion, 0.525 mole) in 1.5 l. of dry ether. [Prewashing of the sodium hydride–mineral oil dispersion with petroleum ether (bp 30–60°) was an effective means of removing the mineral oil, which interfered with subsequent nmr study of the crude reaction product.] The resulting white slurry was stirred at room temperature for 3 hr, then cooled to −10° (Dry Ice–methanol bath). A solution of *p*-toluenesulfonyl chloride (47.7 g, 0.25 mole) was added over 2 hr at −10°. The mixture was left overnight at room temperature. Sodium chloride and the sodium salt of *p*-toluenesulfonic acid, which had deposited quantitatively, were removed by filtration.

Small aliquots of the ethereal filtrate were evaporated under reduced pressure to provide samples of the crude liquid product (pronounced musty odor), which were used for nmr study. The spectra had to be obtained rapidly, since within minutes after solvent removal the liquid residues decomposed violently. Several runs were made using an excess of the alkoxide to ensure basicity of the reaction mixture. Results were always the same—product decomposition soon after solvent removal.

Registry No.—IV, 10580-47-9; V, 10220-23-2; VI 10562-13-7; VII, 10588-76-8; 1,1′-(oxydiethylene)bisaziridine, 10580-48-0.

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Amide Derivatives of 1,2,3,4,7,7-Hexachloro-3-hydroxy-5-sulfotricyclo[2.2.1.$0^{2,6}$]heptane Sultone

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1,2,3,4,7,7-Hexachloro-3-hydroxy-5-sulfotricyclo-[2.2.1.$0^{2,6}$]heptane sultone (I) is easily prepared by the homoallylic addition of sulfur trioxide to 1,2,3,4,7,7-