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ALKYL-2,3-EPOXYPROPYLAMINES

CYCLODIMERIZATION AND RELATED EIGHT-MEMBERED RING CLOSURES

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Abstract—An improved procedure yielded new alkyl-2,3-epoxypropylamines (**2**), ranging from very unstable (n-alkyl) to exceptionally stable (t-alkyl)types. Kinetics and other data relating to the stabilities of **2** are discussed.

Cyclodimerization of **2** gave 1,5-disubstituted-1,5-diazacycloöctane-3,7-diols (**4**). An alternative synthesis, which also yielded **4** with unlike substituents, employed diglycidylamines and primary amines. Conformational factors in these novel ring closures are discussed. Condensations of diglycidylamines with sulfide ion gave substituted 1-aza-5-thiacycloöctane-3,7-diols (**5**).

INTRODUCTION

IN THE course of research involving the additions of amines to epoxides, it was found that t-alkylamines[1] reacted readily with one equivalent of epichlorohydrin in methanol at 20–25°, and with a second equivalent only more slowly. Good yields of 1-t-alkylamino-3-chloro-2-propanols (**1**) were inferred. Dehydrohalogenation of **1** should provide novel t-alkyl-2,3-epoxypropylamines (**2**), of interest as intermediates and monomers. Since no stable compound bearing both the secondary or primary amine

$$RNH_2 \rightarrow \underset{\mathbf{1}}{RNHCH_2CHOHCH_2Cl} \rightarrow RNHCH_2\underset{\diagdown\,\diagup}{CH}CH_2 \quad (\mathbf{2})$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

2 (*a*, t-butyl; *b*, t-octyl)

and oxirane groupings has been reported[2,3] the stabilities of **2** were of special interest. Substitution with hindering t-alkyl groups has accomplished the stabilization of otherwise unstable structures.[4]

This paper[5] describes the synthesis and properties of **2**, including stability and

[1] N. Bortnick, L. S. Luskin, M. D. Hurwitz, W. E. Craig, L. J. Exner and J. Mirza, *J. Am. Chem. Soc.* **78**, 4039 (1956), found that t-octylamine and epichlorohydrin (water catalysis) gave only 1,3-di-t-octylamino-2-propanol. They obtained exclusively secondary amines from t-alkylamines and substituted ethylene oxides; however, see Ref. 3.

[2] Reviews and leading Refs: [a] F. Moller, in Houben-Weyl, *Methoden der Organische Chemie*, Edited by E. Müller, Band XI/I; pp. 323–326. Thieme, Stuttgart (1957); [b] A. M. Paquin, *Epoxydverbindungen und Epoxydharze* pp. 182–206, 250–254. Springer, Berlin (1958); [c] J. B. McKelvey, B. G. Webre and R. R. Benerito, *J. Org. Chem.* **25**, 1424 (1960); [d] J. B. McKelvey, B. G. Webre and E. Klein, *Ibid.* **24**, 614 (1959); [e] D. L. Heywood, U.S. Pat. 2,963,483, Dec. 6 (1960).

[3] A referee informed the writer that Messrs. L. S. Luskin and A. J. McFaull of the Rohm and Haas Company independently prepared **2a** and **2b** in 42% and 26% yields, respectively (water catalysis), and also t-butyldi-(2,3-epoxypropyl)amine in 28% yield similarly.

[4] For some recent examples, see: M. S. Newman, A. Arkell, and T. Fukunaga, *J. Am. Chem. Soc.* **82**, 2498 (1960), di-t-butylketene; A. K. Hoffman, A. M. Feldman, E. Gelblum, and W. G. Hodgson, *Ibid.* **86**, 639 (1964), di-t-butylnitroxide; H. E. Baumgarten, *Ibid.* **84**, 4975 (1962); J. C. Sheehan and I. Lengyel, *Ibid.* **86**, 1356 (1964), N-t-butylaziridinones.

[5] Preliminary report: V. R. Gaertner, *Tetrahedron Letters* No. 3. 141 (1964); also, U.S. Patent 3,236,837, Feb. 22 (1966).

related kinetics, a novel cyclodimerization of **2**, and related syntheses of eight-membered diheterocycles.

RESULTS AND DISCUSSION

Alkyl-2,3-epoxypropylamines (**2**). The controlled equimolar condensation of epichlorohydrin with t-alkylamines and isolation of crude unstable **1**, followed by prompt dehydrohalogenation, yielded **2**. Examples of pure **2** were the t-butyl (**2a**, 58% yield) and t-octyl (1,1,3,3-tetramethylbutyl, **2b**, 66%) amines. They were characterized by elemental analyses, including oxirane oxygen, and IR and NMR spectra.

These secondary glycidylamines were much more stable than previously described examples.[2] Refrigerated samples have been kept for months without measurable loss of oxirane content. Pure **2a** was unchanged for one month, and **2b**, at least two months. However, once it had begun, the loss of oxirane content occurred comparatively rapidly, suggesting that the reaction is autocatalytic and involves a hydrogen-bonded (by OH) transition state.[6] To characterize the self-reactivity of **2a**, the kinetics of initial dimerization in a swamping hydrogen-bonding solvent were determined. The initial rate of loss of oxirane content for **2a** in methanol at 25° was proportional to [**2a**],[2] as expected for the reaction,

$$2\,\mathbf{2a} \xrightarrow{k_2} \text{t-RNHCH}_2\text{CHOHCH}_2\text{NCH}_2\text{CHCH}_2$$

(t-R; O)

3a

The constant, k_2, was $7{\cdot}0 \times 10^{-6}$ l. mole^{-1} sec^{-1}, a value which may be compared to that for the similar addition of t-butylamine to epichlorohydrin, for which the value was found to be $2{\cdot}5 \times 10^{-5}$ l. mole^{-1} sec^{-1}. These rates are only an order of magnitude or so slower than those for ammonia-epoxide condensations.[7] The data are thus in agreement with the interpretation that such nucleophilic openings of epoxides involve long-bonded transition states in which steric effects are minimal and bond-breaking is more important than bond-making.[7] Therefore, the stabilities of **2** are attributed more to the absence of hydrogen-bonding catalysts than to steric hindrance around nitrogen, both factors being important.

The synthetic method was then applied to the preparation of known secondary glycidylamines. N-(2,3-Epoxypropyl)aniline[2c] was obtained in pure crystalline form (m.p. 29–30°) in this work, but remained unstable. Cyclohexyl-2,3-epoxypropylamine[2d] was easily prepared in 76% yield from the crystalline aminochloropropanol;[2d] it dimerized rapidly. The highly hindered 2-t-butyl-N-(2,3-epoxypropyl)6-methylaniline was also prepared and proved to be indefinitely stable under ambient conditions.

In view of the ease with which glycidylamines carrying secondary and tertiary alkyl groups were prepared, our attention was directed to the possibility of synthesizing the hitherto unknown n-alkyl type **2** (R = n-alkyl). We have very recently found that the latter compounds are not so inherently unstable as to preclude their isolation, as stated and implied.[2]

[6] I. T. Smith, *Polymer* **2**, 95 (1961), reviewed the evidence for this general mechanism of amine addition to epoxides.

[7] R. E. Parker and N. S. Isaacs, *Chem. Rev.* **59**, 737 (1959).

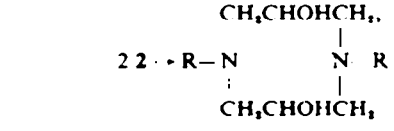
The ethyl, n-butyl, and n-octyl homologs were prepared in ascending yields (19, 32 and 77%, respectively), the last from a crystalline intermediate **1**. To obviate the isolation of unstable **1**, the reaction of amines with epichlorohydrin was carried out in dimethyl sulfoxide, which also promotes rapid complete dehydrohalogenation at ambient temperatures.[7a] These n-alkylglycidylamines indeed appeared to be less stable than previously known classes, losing on the average a few percent of their oxirane content in a day under ambient conditions.

Cyclodimerization of **2**. Since references to the polymerization of glycidylamines contained no characterization of the "polymers," we attempted to isolate the product, presumably $(—NCH_2CHOHCH_2—)_x$, from **2a**. However, neither the products from

the neat liquids nor those from solutions in methanol contained higher polymers.

The products from **2a** were largely volatile below 200°/1 mm. Two crystalline dimers were isolated, the higher melting (**4a**, 124–125°) isomer being easily separated in up to 23% yield, and the lower (**4b**, 69–72°) proving very difficult to purify or isolate quantitatively. Analytical data, molecular weights, infrared and NMR spectra indicated **4** were diaminodiols.

The NMR spectrum of **4a** provided a conclusive proof of structure. The ratio of t-butyl:methylene:methine:hydroxyl protons was 18:8:2:2. Both **4a** and its crystalline diacetate exhibited only 8 methylene peaks recognizable as the AB part of ABX system (Fig. 1). This region closely resembled the methylene spectrum of 3,3,4,4,5,5-hexadeuteriocyclohexanol, shown by Anet[8] to agree with theoretical analysis for an $(AB)_2X$ system. Since Anet's calculations indicated that this spectrum corresponded to predominantly equatorial (*e*) hydroxyls and acetoxyls, it is clear that **4a** has a *double* $(AB)_2X$ system with *e,e* hydroxyls (*e,e* t-butyls are assumed). The data prove that both $—CH_2CHOHCH_2—$ groups in **4a** have identical symmetrical average conformations, and that **4a** is 1,5-di-t-butyl-1,5-diazacycloöctane-3,7-diol. Examina-



tion of the Stuart-Briegleb models suggested that **4a** is the *trans* diol, with a twisted ring and a centre of symmetry. X-Ray powder diffraction studies,[9] confirmed by single crystal analysis, supported the *trans* (but not the *cis*) structure for **4a**.[10]

[7a] V. R. Gaertner, U.S. Patent 2,965,652, Dec. 20 (1960).

[8] F. A. L. Anet, *J. Am. Chem. Soc.* **84**, 1053 (1962). The writer is indebted to Prof. Anet for pointing out the bearing of his work on the present case.

[9] Dr. Emile D. Pierron and Mr. Hector Yepez determined and interpreted the data.

[10] R. Kolinski, H. Piotrowska and T. Urbanski, *J. Chem. Soc.* 2319 (1958), showed by dipole moment studies that both the *cis* and *trans* isomers of 3,7-diethyl-3,7-dinitro-1,5-diazacycloöctane have the "crown" conformation and stabilization in this form was attributed to N···H···N and N—H—O···N hydrogen-bonding. The present assignments for **4a** (*trans*) and **4b** (*cis*) are in agreement with the earlier less conclusive analysis.[8] Formation of both isomers, *trans* from a molecule of *d*-**2a** and one of *l*-**2a** and *cis* from two of either *d*-**2a** or *l*-**2a**, is expected, barring conformational selectivity in cyclization *vs.* polymerization of **3**. However, satisfactory X-ray analysis could not be obtained for **4b**, and the structure remains tentative.

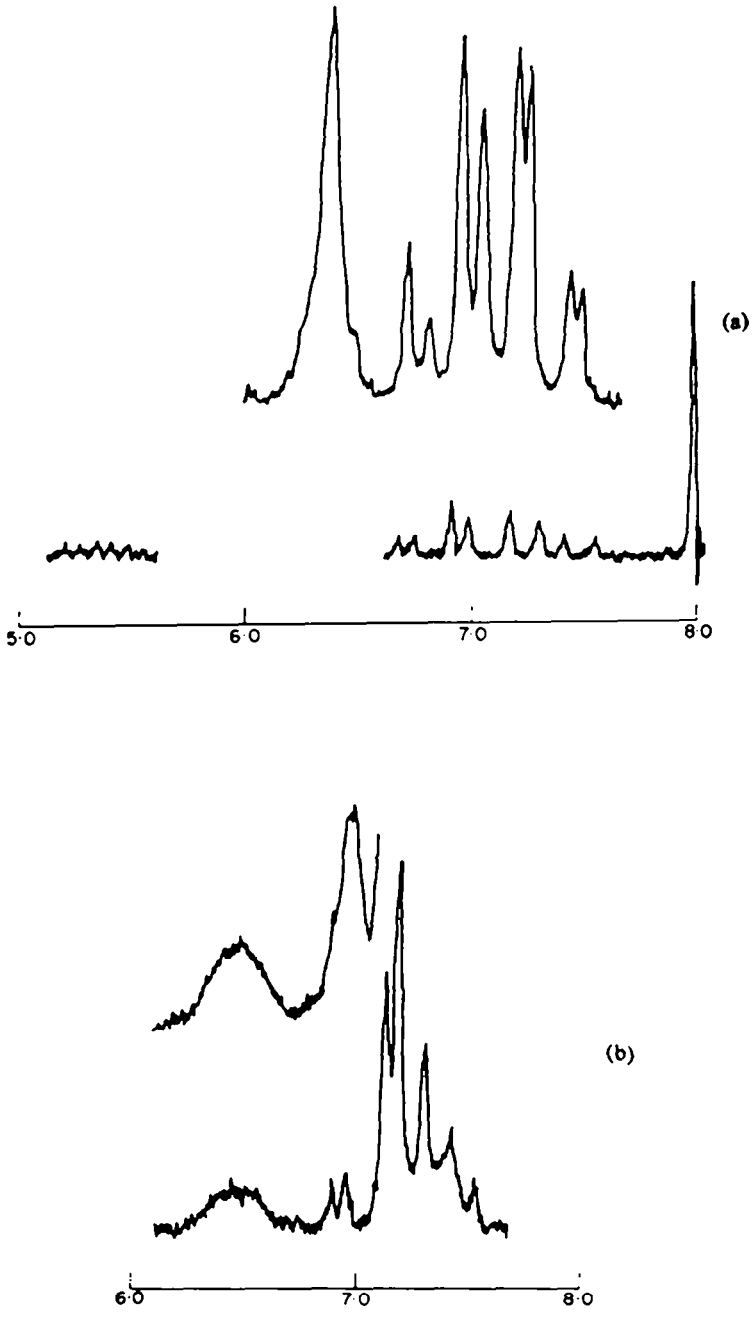
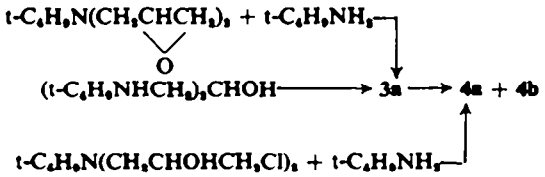


FIG. 1. NMR spectra in deuteriochloroform. a. Upper, **4a**, 25% w/v. Lower, **4a** diacetate. b. Lower, **4b**, 13% w/v. Upper, **4b**, the same solution before dilution, 25% w/v, at the same amplification.

That **4** were 1,5-diazacycloöctane-3,7-diols was finally supported by three alternative syntheses. The first two methods had in common the intermediate **3a**.



In the second, crude **3a** was prepared by equimolar reaction of the diaminopropanol with epichlorohydrin, followed by dehydrohalogenation. The third method is the most conclusive as a proof of structure, direct displacement of halide from 1,2- and 2,1-chlorohydrins by amines having been shown to occur without epoxide intermediacy.[11] Formation of medium rings typically occurs in vanishingly small yields.[12] Specifically, direct cyclization to form 1,5-diazacycloöctanes is limited to the formation in low yields of 3,7-dialkyl-3,7-dinitro derivatives from 1-nitroalkanes, formaldehyde and ammonia,[10] the reduction cyclization of cyanoethylated amines,[13] and cyclialkylations of sulfonamides, e.g., 1,3-di-*p*-toluenesulfonamidopropane with 1,3-dibromopropane,[14] however, only the latter method and reductive cleavages of the N—N bond of bicyclic hydrazines[15] appear to be of preparative value in the 1,5-diazacycloöctane series. A single example of the closure of a smaller ring related to the present cases was the formation of a pyrrolidine-3,4-diol from *p*-aminosalicyclic acid and butadiene dioxide.[16]

The above cyclodimerization of glycidylamines proved to be general. Thus **2b** yielded di-t-octyldiazacycloöctanediol (**4c**); N-(2,3-epoxypropyl)aniline gave the 1,5-diphenyl analog (**4d**, 17% yield), also obtained in 25% yield from aniline and N,N-di-(2,3-epoxypropyl)aniline.

Related cyclizations. The synthesis of **4** bearing unlike N-substituents was accomplished by similar methods. "Mixed" dimerizations of two glycidylamines—**2a** and N-glycidylaniline—produced only a trace of 1-t-butyl-5-phenyl-1,5-diazacycloöctane-3,7-diol (**4e**), along with **4a** and **4d**. However, the condensations of N,N-di-(2,3-epoxypropyl)aniline with t-butylamine and of t-butyl-di-(2,3-epoxypropyl)amine with aniline gave **4e** in 24% and 28% yields, respectively, results which establish the structure conclusively. The generality[17] of the method was demonstrated with the

[11] T. Colclough, J. I. Cunneen and C. G. Moore, *Tetrahedron* **15**, 187 (1961).

[12] Review: E. L. Eliel, in "*Steric Effects in Organic Chemistry* (Edited by M. S. Newman) pp. 116–117. Wiley, New York (1956).

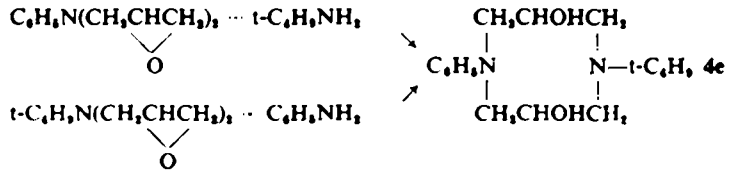
[13] I. N. Nazarov and G. A. Shvekhgeimer, *Zh. Obsch. Khim.* **24**, 163 (1954); *Chem. Abstr.* **49**, 3034 (1955). A. P. Terent'ev, A. N. Kost and K. I. Chursina, *Zh. Obsch. Khim.* **21**, 268 (1951); *Chem. Abstr.* **45**, 7008 (1951).

[14] J. Hernandez-Mora, *Diss. Abs.* **20**, 2032 (1959); W. Marckwald, *Ber. Dtsch. Chem. Ges.* **31**, 3265 (1898). Very recently, toluenesulfonamide and epichlorohydrin were shown by W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.* **31**, 277 (1966), to give the ditoluenesulfonamide of the parent 1,5-diazacycloöctane-3,7-diol.

[15] E. I. Buhle, A. M. Moore and F. Y. Wiselogle, *J. Am. Chem. Soc.* **65**, 29 (1943); H. Stetter and H. Spangenberger, *Chem. Ber.* **91**, 1982 (1958); C. Grob and O. Schier, U.S. Pat. 3,093,631 (1963).

[16] H. Hopff and H. Spänig, Brit. Pat. 896,047, 1953, *via* Ref. 2*b*, p. 128.

[17] D. M. Burness and H. O. Bayer, *J. Org. Chem.* **28**, 2283 (1963), however, observed no cyclizations in similar additions of amines and hydrogen sulfide to mono- and diglycidylamines and -ammonium salts under somewhat different conditions.



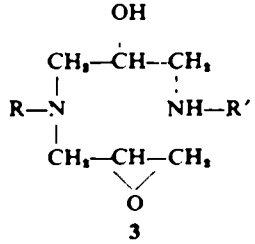
corresponding n-butylamines in place of the t-butyl isomers. The reaction involving aniline (1·5% yield of **4f**) as the primary amine was markedly inferior to that with n-butylamine (24%).

Factors affecting cyclization. In addition to the above cases in which pure compounds were isolated, a series of other reactions was carried out between pairs of primary amines and diglycidylamines. Although distillation of the crude products gave in each case a fraction which analyzed correctly for a diaminodiol, no additional pure compounds have been isolated. The Table summarizes the results of all runs, *r* being the ratio of the diaminodiol fraction to higher condensation products. Clearly cyclization is favoured most importantly by larger steric requirements of both R and

$RN(CH_2CHCH_2)_2$ (O)	$R'NH_2$	*r*	Product (yield)
t-butyl	t-butyl	16+	**4a** (28%), **4b**
t-butyl	n-butyl	4–	—
t-butyl	phenyl	2·6	**4e** (28%)
phenyl	n-butyl	1·7	**4f** (24%)
n-butyl	n-butyl	1·5	
n-butyl	phenyl	1·1	**4f** (1·5%)
n-butyl	methyl	0·6	—

R′. It is favoured secondly by increased nucleophilicity of the primary amine. The exact nature of the interaction between these factors cannot be specified, lacking complete characterization of the isomeric products.

These unpredictably facile syntheses of eight-membered diheterocycles are rationalized by considering the intermediate **3**, which may either cyclize or react intermolecularly. A bulky R serves to assure the proximity of the reacting groupings, as



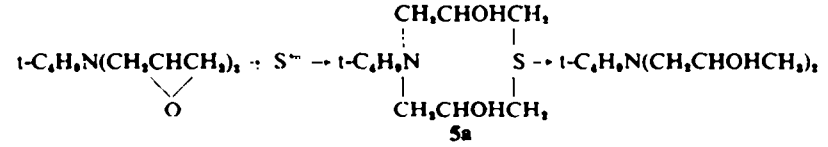
3

in the "*gem*-dimethyl effect."[18] Conformational principles do not predict that a *pseudo*-cyclic transition state will be favoured unless solvation of both the hydroxyl and the oxirane oxygens is assumed to stabilize these groups *trans* to the tertiary nitrogen. Indeed, methanol was very effective in promoting cyclization, acting also as a hydrogen-bonding catalyst. A bulky R′ probably hinders intermolecular reaction more than it does cyclization.

[18] G. S. Hammond, in Ref. 12, p. 462.

In a model **3a**, the spherical transition state conformation in which nitrogen approaches backside to the terminal oxirane carbon seemed to be favoured by these factors. If solvation is importantly involved, higher temperatures might be expected to decrease the effect and result in less dimer formation. Heating the usual concentrated reaction mixtures did greatly diminish yields of **4a**. Further, when dimerized **2a** (i.e., mainly **3a**) was added very slowly to much boiling methanol, a lower yield of **4a** resulted. Attempts to obtain definitive kinetic evidence on this point met with analytical difficulties.

1-*Substituted*-1-*aza*-5-*thiacycloöctanediols* (**5**). A related reaction was the addition of sodium sulfide to t-butyldiglycidylamine. The novel structure of the product, **5a**, was apparent from the identity (VPC, IR) of the product of desulfurization of **5a** with t-butyldi-(2-hydroxypropyl)amine obtained from t-butylamine and propylene oxide.



5a

An attempted alternative synthesis from di-(2,3-epoxypropyl) sulfide and t-butylamine gave no detectable **5a**, the absence of a steric orienting effect being decisive here.

The formation of **5a** exhibited an interesting variation of yield with technique and temperature. In contrast with the parallel diazacycloöctanediol synthesis, the reaction was very rapid. The yield was lowered by cooling below 25° and augmented by heating to 40°. Further, a high dilution method consisting of simultaneous addition of the separate reactants to methanol at 40° gave 50% yield. In this rapid closure, solvation may be less important than the statistical effect of dilution favouring intramolecular reaction.

The formation of **5** was also general. Cyclohexyldiglycidylamine gave a good yield (48%) of the corresponding **5**. A hindered aniline (2,6-dimethyl, 27%) was predictably superior as a starting material to aniline itself (14%) or to *o*-anisidine (11%).

Synthetic utility. An example of the use of these compounds, **4a** and **5a**, was the conversion of the diols to 1,5-diaza- and 1-aza-5-thia-3,7-dichlorocycloöctane (di)hydrochloride by thionyl chloride. Interestingly, one t-butyl group of **4a** was lost under mild conditions in this reaction. These intermediates, which are at once 2-halo alkyl sulfides and amines, should undergo a variety of substitutions.

EXPERIMENTAL[19]

General procedures. The reactions of amines with epichlorohydrin or other epoxides were carried out by mixing the reactants at once in reagent MeOH and maintaining the mixture in the range 20–30°,

[19] Some composite experiments are reported to conserve space. M.ps and b.ps are not corrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. IR spectra were determined on the Beckman IR-4 or IR-5, using neat liquids or mulls of solids in both Nujol and hexachlorobutadiene. The wavelengths are in microns and the letters indicate: i—intense, 60% absorption or more; m—medium, 30–60%; b—broad; s—shoulder. Statements of sample identity indicate that mixture m.ps were not depressed and that IR spectra were essentially superimposable. The NMR spectra were determined mainly on the Varian A-60, using the neat liquids or solutions of solids in $CDCl_3$ with internal TMS reference. *Tau* values are listed; integration of peaks was employed routinely in the assignments, which are thus consistent as given. The careful determination of critical spectra by Mr. Donald G. Bauer is gratefully acknowledged, as is the coöperation of other Research Center colleagues too numerous to name.

nominally 25°, with cooling as necessary. Aliquots were titrated periodically with 0·4–0·7 1N HBr (anhyd) in glacial AcOH to the crystal violet end-point.[90] The disappearance of oxirane was expressed as "90% of 1:1 reaction", for example, indicating that 90% of the limiting reagent had reacted. Although exactly stoichiometric ratios of reactants can be used, secondary reactions became important after a few days.[91] When the desired extent of reaction had been attained, the solvent and excess reagent were rapidly removed at reduced press below 35° with efficient stirring to minimize side reactions. The crude aminochloropropanols were satisfactory for further work, but deteriorated[91] at room temp. They were stored in a deep-freeze at −20°. The apparent neutralization equivs (N.E.) as measured by the Durbetaki method characterized the products and measured changes, since both free amine and oxirane groupings react quantitatively. The free amine content could be measured also by titration with perchloric acid in AcOH; the oxirane in glycidylamines did not consume this reagent. The oxirane oxygen contents were calculated from the difference between these analyses. These methods were also used to measure rates of dimerization and extents of reaction of glycidylamines with other reactants. The presence of oxirane can easily be detected by rapid Durbetaki titration to an end-point which fades.

Synthesis of t-alkyl-2,3-epoxypropylamines (2)

t-Butyl-2,3-epoxypropylamine (**2a**). t-Butylamine (vesicant; 109 g: 1·5 moles) in 105 g reagent MeOH (cooling) was treated at once with 92·5 g (1·0 mole) epichlorohydrin and allowed to react for 46 hr at 20–25° (101% of 1:1 reaction). The crude aminochloropropanol had N.E. 174; calc., 165·6. A solid was removed by dissolution in ether and filtration; the resulting oil, 146·3 g, had N.E. 157. The solid was 1,3-di-t-butylamino-2-propanol hydrochloride, from which the free amine, m.p. 59–61°, was isolated (see below).

Dehydrohalogenation of 145·8 g of impure oil in 100 ml ether with 100 g 50% KOHaq below 25° was followed by separation and extraction with ether. Drying of the extracts over successive portions of KOH pellets, filtration through a charcoal bed, and aspiration of the solvent below 20° left 105·1 g light yellow oil. Charcoal treatment removed traces of alkali which catalyzed polymerization. These operations were all accomplished within a few hr, and the oil was stored at −20° or distilled immediately. Rapid distillation of 104 g of the oil in a modified Claisen flask at 11 mm, principally at 57°, gave 75·1 g, n_D^{25} 1·4304–1·4307, a conversion of 59% based on epichlorohydrin. Careful refractionation in a 1-ft glass helices-packed column gave no change in the constants.

t-Butyl-2,3-epoxypropylamine was a mobile colorless liquid, fuming slightly in air, with an odor resembling that of t-butylamine. (Found: C, 64·91; H, 11·64; N, 10·78; O (oxirane), 12·47. $C_7H_{15}NO$ requires: C, 65·1; H, 11·7; N, 10·8; O, 12·4%.) IR: 3·25 ms, 3·34 i, 6·71 m, 6·80 ms, 6·86 ms, 7·15 m, 7·28 i, 7·91 ms, 8·07 i, 8·87 m, 9·02 m, 9·71 mb, 10·10 mb, 10·79 m, 11·69 i, 11·89 ms, 11·99 m, 12·4 mb, 12·9 mb, 13·7 mb, 15·03 mb. NMR: CH_3, 8·98 covering the major line of the NH triplet (?) with satellites at 8·57 and 9·43; CH_3, 9 lines, 7·25–7·65; OCH, 7·10, multiplet.

In the first distillation, 7·0 g of t-butyldi-2,3-epoxypropylamine (see below), b.p. 72–76°/11 mm, n_D^{25} 1·4542, and 16·5 g of viscous amber residue were also obtained.

2,3-*Epoxypropyl-t-octylamine* (**2b**). t-Octylamine (1,1,3,3-tetramethylbutylamine), 97·0 g. (0·75 mole), in 201·3 g MeOH was treated with 92·5 g epichlorohydrin at 20–25° for 66 hr, when 100% of 1:1 reaction had occurred. After removal of the volatiles below 30°/5 mm, 169·8 g of a turbid oil remained; N.E., 222 (calc., 222).

The oil (111 g) was promptly dehydrohalogenated as usual. The crude product (80·7 g) was rapidly distilled in part, 72·6 g giving 55·4 g mobile oil with a mild amine odor, n_D^{25} 1·4496–1·4517, b.p. 65–73°/0·6–0·7 mm. The yield based on the starting amine corresponded to 66%. A higher boiling fraction (9·3 g) and small residue (2·0 g) were not investigated.

A portion of the product was refractionated, the 65–67°/1 mm cut having n_D^{25} 1·4492. (Found: C, 71·19, 70·99; H, 12·57, 12·71; N, 7·28, 7·55; O (oxirane), 8·50, 8·77, 8·71. $C_{11}H_{23}NO$ requires: C, 71·3; H, 12·5; N, 7·6; O, 8·6%). IR: 3·24 ms, 3·34 i, 3·40 is, 6·71 i, 7·12 ms, 7·18 i, 7·27 i, 7·37 ms, 7·96 ms, 8·08 i, 8·61 mb, 8·26 ms, 8·94 ms, 9·10 m, 10·80 m, 11·74 i, 12·00 i, 12·15 mb, 13·17 mb, 13·40 mb, 13·85 mb, 15·02 mb. NMR: terminal CH_3 (and NH major line), 9·03; internal CH_3, 8·94; CH_3 of the octyl group, 8·60; glycidyl CH_2, 7·3–7·7 (7 resolved lines); OCH, 7·13, multiplet

[90] A. J. Durbetaki, *Analyt. Chem.* **28**, 2000 (1956).

[91] These reactions are to be described elsewhere.

t-Dodecyl-2,3-epoxypropylamines. A commercial mixture of t-dodecylamines (Primene 81-R, Rohm and Haas Co., 57·0 g) was condensed with 120% excess epichlorohydrin in MeOH (97% of 1:1 reaction in 50 hr). The crude aminochloropropanol, in part, (56·5 g), 30 ml DMSO, and excess NaOH gave by usual methods a mixture of glycidylamines, b.p. 105–127°/1 mm, n_D^{25} 1·4560–1·4668. The 110–115° cut was analyzed. (Found: C, 74·41; H, 13·10; O (oxirane), 6·77. $C_{15}H_{31}NO$ requires: C, 74·5, H, 12·9; O, 6·62%.)

n-Alkyl-2,3-epoxypropylamines. n-Butylamine (36·5 g, 0·5 mole) in 70 g of DMSO was treated at once with 46·3 g epichlorohydrin and cooled slightly to maintain the temp at 25–30°. After 20 hr titration of an aliquot indicated 90% completion of the condensation. Half of the mixture (0·25 mole, 76·4 g) was cooled below 20° while 100 g 20% NaOHaq was added in portions during 10 min. Dilution with 100 ml water and extraction with ether were carried out rapidly. The extracts were dried over KOH pellets briefly, treated with several grams of charcoal and filtered through a bed of filter aid and charcoal. The filtrate was aspirated below 20° in a rotating evaporator. The residual oil was immediately distilled at 1 mm using a 42–52° water bath and an ice-cooled receiver. The yield of nearly pure *n-butyl-2,3-epoxypropylamine* was 10·0 g (32%). Redistillation was carried out similarly through a 6-inch Vigreux column at 2 mm from a 55–60° bath; b.p. 42–43°; n_D^{25} 1·4353 (Found: C, 64·98; H, 11·57; N, 11·02; O (oxirane), 12·2. $C_7H_{15}NO$ requires: C, 65·1; H, 11·7; N, 10·8; O, 12·4%.) A sample stored in a screwcap vial at ambient conditions lost 3·6% of the oxirane content in a day, 20% in two days.

Ethylamine (13·6 g, 0·3 mole) was condensed similarly with epichlorohydrin in DMSO; 99% completion in 24 hr. Rapid dehydrohalogenation and isolation, followed by distillation from a 20° bath into a Dry Ice-cooled receiver yielded 5·9 g (19% yield) of rather pure material. Redistillation was carried out at 15 mm from a 44–48° bath into an ice-cooled receiver; b.p. 37°; n_D^{25} 1·4304. The product was *2,3-epoxypropylethylamine.* (Found: C, 58·61; H, 10·87; N, 13·01; O (oxirane), 16·0. $C_5H_{11}NO$ requires: C, 59·3; H, 11·0; N, 13·8; O, 15·8%.) In a day at ambient conditions, it lost 86% of the oxirane content.

n-Octylamine, 51·7 g, 0·4 mole, was condensed with 74 g epichlorohydrin in 250 ml Skellysolve F at 20–25°. After 10 hr (75% of 1:1) the soln was cooled to 0° and the flocculent solid removed by filtration. By repeated refrigeration overnight of the mother liquors and rinsings, a total of 53·7 g (61% yield) was isolated; m.p. 44–46°. Recrystallization of the unstable *3-chloro-1-n-octylamino-2-propanol* from the same solvent without heating gave fairly pure needles; m.p. 45·5–46·5°. (Found: Cl, 15·80; N, 7·14. $C_{11}H_{24}ClNO$ requires Cl, 16·0; N, 6·3%.) The compound, 16·7 g, was dehydrohalogenated (DMSO) as usual, and isolated rapidly; 10·7 g (77% yield); b.p. 85–86°/1 mm; n_D^{25} 1·4454. *2,3-Epoxypropyl-n-octylamine* solidified and remelted at −11 to −8°. (Found: C, 71·36; H, 12·62; N, 7·67; O, 8·00. $C_{11}H_{23}NO$ requires: C, 71·3; H, 12·5; N, 7·6; O, 8·6%.) It lost 3·5% of the oxirane content in 2 days, 22% in 3 days.

Cyclohexyl-2,3-epoxypropylamine (**2d**). The pure crystalline N-(3-chloro-2-hydroxypropyl)-cyclohexylamine was prepared as described[14]. Although these authors (who implied about 40% yield) experienced loss by polymerization during distillation when sodium silicate was the dehydrohalogenation reagent, the use of the alkali (DMSO) and charcoal method described herein for **2a**, **2b**, etc., gave a smoothly distillable crude product. The yield on the 0·1 mole scale was 76%; b.p. 59°/0·7 mm; colorless mobile liquid; n_D^{25} 1·4762. The purity was satisfactory. (Found: N, 8·80; O, 9·72. Calc. for $C_9H_{17}NO$: N, 8·9; O, 10·3%.) The compound was essentially unchanged after a day without special precautions (2·6% oxirane loss) but was 27% dimerized after 5 days.

t-Butyl-di-(2,3-epoxypropyl)amine[9]. t-Butylamine (73·1 g, 1·0 mole) was condensed with 191 g (2·06 moles) of epichlorohydrin in 102 g MeOH as usual, 72 hr being required for 81% of 2:1 reaction. Concentration to 50°/25 mm left 241·7 g of an oil, which was treated with 50 ml. DMSO, and 200 g 40% NaOHaq, then dried and treated with charcoal. After a forerun (13·6 g) of impure **2a**, 77·1 g (42%) of the diglycidylamine was collected; b.p. 87–88°/1·0 mm; n_D^{25} 1·4634. Lower yields resulted with higher degrees of reaction. (Found: C, 64·62; H, 10·56; N, 8·03; O (xirane), 17·8. $C_{10}H_{19}NO_2$ requires: C, 64·8; H, 10·4; N, 7·6; O, 17·3%.)

Di-(2,3-epoxypropyl)t-octylamine. t-Octylamine and epichlorohydrin (1:2 molar ratio) were condensed as usual (7 days, 86% of 1:2). Dehydrohalogenation (DMSO), rapid distillation, and refractionation, gave 7% yield of mobile colorless oil; b.p. 104–106°/0·5 mm; n_D^{25} 1·4712. The 105° cut was analyzed; other cuts contained slightly lower oxirane percentages. (Found: C, 71·15; H, 10·95; N, 5·83; O (oxirane), 12·8. $C_{16}H_{31}NO_2$ requires: C, 69·7; H, 11·3; N, 5·8; O, 13·3%.)

N-(2,3-Epoxypropyl)aniline[24]. Aniline (1·0 mole, 100% excess) was condensed with epichlorohydrin by the above methods (43 hr, 94% of 1:1,). The crude anilinochloropropanol, after removal of most of the excess aniline up to 55°/1 mm, was dehydrohalogenated as usual, and the oily crude product crystallized when stored overnight at −20°; m.p. 10–15°.

A portion was distilled rapidly in a short-path flask; the 111–116°/1–2 mm cut, 52% yield based on epichlorohydrin, was analyzed; n_D^{25} 1·5698 (supercooled liquid). (Found: O (oxirane), 10·9. Calc. for $C_9H_{11}NO$: O, 10·7%.) It solidified upon being cooled and seeded; crystals freed of oil on a clay plate melted at 29–30°, but they could not be recrystallized satisfactorily. After collection of this cut, the contents of the pot apparently underwent polymerization exothermically (caution!), a tendency noted previously.[24] The product lost oxirane content rapidly at room temp, but was stable at −20° for several months. One sample lost only 1·2% of the oxirane content in a day at room temp (supercooled liquid).

2-t-Butyl-N-(2,3-epoxypropyl)6-methylaniline. 2-t-Butyl-6-methylaniline required seven months to react (101% of 1:1) with 20% excess epichlorohydrin in MeOH. The crude anilinochloropropanol had N.E. 253 (calc. 256); n_D^{25} 1·5361. Dehydrohalogenation, using DMSO, gave the title compound, b.p. 124°/0·8 mm. (mainly); n_D^{25} 1·5316–1·5313; 57% yield. (Found: C, 76·82, 76·79; H, 9·59, 9·64; N, 6·50, 6·41; O (oxirane), 7·30, 7·44. $C_{14}H_{21}NO$ requires: C, 77·0; H, 9·7; N, 6·4; O, 7·3%.)

It was unchanged after several months at room conditions without special precautions and had lost only 19% of the oxirane content after 50 days in 28% solution in MeOH.

Dimerization of 1-amino-2,3-epoxypropanes

Kinetics. Satisfactory second-order constants were obtained at 25·0°, after numerous unsuccessful attempts, only with freshly distilled **2a**. Older samples showed an unexplained induction period. All runs were made in bottled reagent MeOH; nitrogen sparging had no effect.

The constant was calculated from the usual equation, $k_2 = x/[ta(a - x)]$, x being based upon twice the loss in oxirane concentration in time t, as measured by Durbetaki titration. A 25% loss in titer corresponded to 50% loss of oxirane and to 100% dimerization; conc solns (at least 2M) were used and the 1 ml pipet used for aliquots was calibrated and used on a "to contain" basis. The titration of aliquots to a stable blue-green end-point became increasingly slow during the course of a run and at least 15 min was finally necessary for complete reaction. The Durbetaki reagent was stored in an automatic buret protected from moisture and standardized before every run against 0·5N AcONa–AcOH. Not more than 5% MeOH or 1% water in AcOH was allowable for sharp end-points. In MeOH, a typical run with **2a** gave values of k_2 of 6·97(±0·17) × 10^{-4} l. $mole^{-1}$ sec^{-1} through at least 33% "dimerization."

The addition of some water to the MeOH gave interesting results. Data from a typical run in 96/4 v/v methanol/water were: a, 2·473M

t, hr	$k_2 \times 10^4$	"Dimerization", %
2·00	(3·60)	—
2·75	3·94	7·9
5·25	4·28	14·9
8·25	5·97	27·3
13·0	6·78	39·4
22·5	17·5	69·7

Graphical extrapolation gave an "initial k_2" of about 3·5 × 10^{-4}. Clearly the data show a trend away from second order toward lower order with the inclusion of water. This is rationalized qualitatively by the assumption that in the reaction sequence, 2A → B → C, the first step to give the open dimer (**3a**) occurs in methanol almost exclusively in the early part of the reaction. However, added water slows this step somewhat and accelerates the second step, ring closure to C. This general sequence has been described theoretically,[25] but the data for a test were not obtainable, due to the analytical difficulties.

For the addition of t-butylamine to epichlorohydrin, both 2·010M, at 25·0° in 96/4 v/v MeOH/water, k_2 was found to be 2·46(±0·10) × 10^{-4} l. $mole^{-1}$ sec^{-1}, measured similarly, through at least

[25] J.-Y. Chien, *J. Am. Chem. Soc.* **70**, 2256 (1948).

58% reaction. Attempts to determine the rate of dimerization of 2,3-epoxypropyl-t-octylamine were invalidated by an induction period.

Isolation of 1,5-*di-t-butyl*-1,5-*diazacyclooctane*-3,7-*diols* (**4a**, **4b**)

A soln of 6·5 g t-butylglycidylamine, **2a**, in 50 g MeOH was kept at room temp after initial cooling to maintain it at 25°. Aliquots were analyzed periodically; after two months no further detectable change occurred. Removal of the solvent left 5·4 g residual oil, which crystallized from hexane to yield 0·92 g colorless prisms; m.p. 123–124·5°. A second crop of 0·24 g was isolated from the liquors by crystallization from low boiling petroleum ether (Skellysolve F), the total yield of isolated solid being 23%, corrected for sampling. A purified sample (AcOEt–hexane) of **4a** melted at 124–125°. (Found: C, 65·17; H, 11·90; N, 10·98; mol. wt., 260 (osmometric in acetonitrile); N.E., 129, 130. $C_{14}H_{30}N_2O_2$ requires: C, 65·1; H, 11·7; N, 10·8%; mol. wt., 259; N.E., 129·5.) IR: 2·90 i, 3·13 mb, 3·36 i, 3·42 i, 3·53 i, 6·71 i, 6·87 i, 7·08 i, 7·18 i, 7·34 i, 7·41 ms, 7·67 m, 7·72 m, 7·83 ms, 7·90 i, 8·00 m, 8·18 i, 8·38 ib, 8·59 m, 8·79 m, 8·98 i, 9·37 i, 9·48 m, 9·75 m, 9·79 m, 9·94 m, 10·20 i, 10·68 m, 11·31 i, 12·46 m, 13·04 ms, 13·21 mb, 15·04 mb. NMR: (25% in $CDCl_3$). Shown in Fig. 1, except the $(CH_3)_3C$, 8·93. At 14% the OH peak shifted to 6·29 but did not split, and the spectrum was otherwise identical.

X-Ray powder diffraction (filtered Cu K_α, 40 KV, 20 mA) was used[9] to determine the crystallographic data for the 124–125° diol: monoclinic with space group $P2_1/m$-C^2_{2h}; unit cell, a_0 = 10·416 Å, b_0 = 17·335 Å, c_0 = 8·607 Å, β = 95°, 54; volume, 1546·8 Å (4 molecules); density: Calc., 1·091; Found: (float-and-sink), 1·109. A model with *trans* equatorial OH groups was in agreement with the space volume and space group data. The data were confirmed by single crystal analysis. Satisfactory data could not be obtained for the following 69–72° isomer, apparently due to the presence of impurities. IR studies on progressively diluted solutions of **4a** and **4b** in CCl_4 did not conclusively demonstrate whether either isomer exhibited intramolecular hydrogen-bonding.

In the above run, the liquors contained a lower melting solid (**4b**). Rapid distillation gave 3·45 g distillate up to 200°/1 mm (metal bath temp), leaving 0·4 g amber residue, which began to decompose above 220°. From the distillate an impure solid (m.p. 60–67°) was obtained by crystallization from pet. ether (b.p. 30–60°). This solid, **4b**, combined samples, was further purified by recrystallization but the best melting range of **4b** was 69–72°. Mixture m.ps with added **4a** were greatly depressed. (Found: C, 64·99; H, 11·41; N, 10·61; N.E., 128. $C_{14}H_{30}N_2O_2$ requires: C, 65·1; H, 11·7; N, 10·8%; N.E. 129·5.) IR: (supercooled mixture with Nujol) 2·95 m, 3·38 i, 6·72 m, 7·17 m, 7·32 i, 7·91 m, 8·18 m, 8·34 i, 8·58 m, 9·1 mb, 9·5 ib, 9·8 ib, 10·37 m, 12·52 mb. NMR: (25% in $CDCl_3$) similar to Fig. 1; $(CH_3)_3C$, 8·96. The same soln was diluted to 13% and repeated with the resultant splitting of the OH peak shown in Fig. 1.

Attempts to separate the reaction mixture more quantitatively, by column chromatography on neutral alumina, or by gas chromatography on several packings and capillaries, were unsuccessful. Some indications of at least 5 components were obtained in the latter work, despite incomplete resolution. Trimethylsilylation was also tried unsuccessfully. Fruitless attempts to improve the yield of either crystalline product included addition of water after dimerization was complete, which accelerated the reaction but resulted in more residual gums and isomeric mixtures. Attempted cyclization at high dilution in boiling methanol also was ineffective.

The 125° dimer, **4a**, was also isolated in 15% conversion from an impure sample of **2a** which had been stored without precautions against atmospheric moisture at room conditions for 45 days.

Alternative syntheses of **4a** *and* **4b**

1. A soln of 18·5 g of t-butyldi-(2,3-epoxypropyl)amine in 101 g MeOH was cooled at 20–25° and treated with 7·3 g t-butylamine. After 29 days the crude product yielded 7·4 g (28%), m.p. 124–125°, identical (IR and mixture m.p.) with **4a**. The liquors were distilled and the second fraction (7·4 g, of the total 13·8 g, b.p. 180–215/1–2 mm) recrystallized twice from hexane: Skellysolve F, first at about 8° and then at 20°, to yield 1·1 g, m.p. 67–69°, identical with **4b**.

2. The crude 1:2 adduct of t-butylamine and epichlorohydrin (25·8 g) was mixed with 7·3 g t-butylamine (exothermic) in a 100 ml stainless steel bomb, which was partially evacuated, sealed and heated rapidly to 100°, and more slowly to 140°, then maintained at 140° for 18 hr. The cooled bomb was vented (small press, odor of isobutylene) and the resinous contents dissolved in water and ether, made just alkaline, rapidly separated and distilled below 1 mm. The distillate, 8·2 g, yielded

0·70 g, m.p. 122–123·5°, of **4a**. No conclusive evidence for the presence of **4b** could be obtained from the infrared spectra of fractions which oiled out of usual solvents.

3. 1,3-*Di-t-butylamino-2-propanol* was prepared in good yield by condensation of t-butylamine with epichlorohydrin (2:1) in the presence of excess aqueous alkali at 55–60°. The viscous distillate, b.p. 91–93° (mainly); 2 mm., solidified and was recrystallized from hexane; m.p. 60–61°: (Found: C, 65·11, 64·88; H, 13·10, 12·77; N, 13·81, 13·78; N.E., 99·5. $C_{11}H_{26}N_2O$ requires; C, 65·2; H, 13·0; N, 13·9%; N.E. 101·2.)

The diaminopropanol (10·1 g) was treated with 20 mole% excess epichlorohydrin in MeOH; after 5 days at 20–25°, titration indicated 92% of 1:1 condensation had occurred and the solvent was aspirated below 30° leaving 13·3 g viscous crude aminochloropropanol. An ethereal soln of 12·8 g of this oil was promptly dehydrohalogenated with KOH pellets, filtered with charcoal, and the solvent again replaced with MeOH (30 g). After 33 days at 20–25°, 1·48 g **4a** was isolated; m.p. 122–124°.

Derivatives. The dimer, **4a**, in pyridine was acetylated with Ac_2O; sublimation and recrystallization from light petroleum ether gave the *diacetate*; m.p. 59·5–60·5°. The important portion of the NMR spectra is shown in Fig. 1; $(CH_3)_3C$, 8·96. (Found: C, 62·99; H, 10·00; N, 8·36. $C_{18}H_{34}N_2O_4$ requires: C, 63·1; H, 10·0; N, 8·18.)

The *monoöxalate* salt was prepared from an ethereal soln of **4a** by addition of saturated ethereal oxalic acid and recrystallized from MeOH–ether; m.p. 206–207·5° (dec). Samples prepared from **4a** by the above syntheses showed no depression. (Found: C, 58·36; H, 7·64; N, 7·58. $C_{16}H_{32}N_2O_6$ requires: C, 58·7; H, 7·66; N, 7·60%.)

Dimerization of 2,3-*epoxypropyl-t-octylamine* (**2b**). An analytically pure sample (1·26 g) of **2b**, after 16 months at ambient conditions in a screwcap vial, slowly became turbid and viscous. Pet. ether (30–60°) was added and crystals separated upon refrigeration; 0·13 g; m.p. 122–124°. A purified sample melted at 123·5–124·5°. This dimer is **4c**. (Found: C, 71·70; H, 12·61; N, 7·50. $C_{22}H_{46}N_2O_2$ requires: C, 71·3; H, 12·5; N, 7·6%.) IR: 2·96 m, 3·46 i, 3·54 i, 6·85 i, 7·27 m, 7·33 ms, 7·70 m, 8·07 m, 8·20 ms, 9·41 mb, 9·70 m, 9·92 m. NMR: (25%) $(CH_3)_3C$, 9·04; $-(CH_2)_3CN$, 8·80; isolated CH_2, 8·57; ring CH_2 as a very broad major peak, with max, 7·18, and 3 shoulders, 7·31, 7·13, 7·07, with incipient splitting barely evident at each of the 4 values; O*H*, 6·98 (broad); OC*H*, about 6·45, multiplet. The similarly to the spectrum of **4a** suggests that **4a** and **4c** have closely similar conformations. No other crystalline product could be isolated from either the above liquors or attempted dimerization in MeOH.

Dimer (**4d**) *of* N-(2,3-*epoxypropyl*)*aniline*. A soln of 7·5 g of the freshly distilled compound in 50 g MeOH was kept at 20–25°. After 6 days crystals separated. After a month filtration gave 1·4 g (19%) of **4d** as white rhombs; m.p. 208–213°. Recrystallization from AcOEt gave pure **4d**; m.p. 212–213°. No other crystalline compound could be isolated.

This compound was also obtained similarly from aniline and N,N-di-(2,3-epoxypropyl)aniline after 24 days (28% yield; m.p. 202–210°). Recrystallized, m.p. 212–213°, it was identical with the above sample. (Found: 71·97; H, 7·23; N, 9·11; mol. wt., 352, 357 (osmometric, acetonitrile), $C_{18}H_{22}N_2O_2$ requires: C, 72·4; H, 7·42; N, 9·39%; mol. wt., 298.) IR: 2·99 i, 3·35 i, 6·19 i, 6·33 i, 6·58 i, 6·73 i, 6·93 m, 7·20 i, 7·31 m, 7·52 m, 7·84 i, 7·92 is, 8·17 m, 9·44 i, 9·69 i, 10·00 mb, 11·04 m, 11·35 m, 13·51 i, 14·51 i, 15·02 m. This compound was not soluble enough in $CDCl_3$ for reliable NMR characterization.

Co-dimerization of N-(2,3-*epoxypropyl*)*aniline and t-butyl*-2,3-*epoxypropylamine*. An equimolar soln of 7·5 g of the former amine and 6·5 g of **2a** in 50 g MeOH at 20–25° after 48 days, during which seeds of the diphenyl dimer, **4d**, were added, was filtered to give 0·21 g of **4d**; m.p. 210·5–212·5°.

The first liquors were concentrated to near-dryness, dissolved in two volumes of AcOEt, diluted with hexane and seeded with mixed diol (**4e**, described below), giving 0·19 g of **4e**; m.p. 154–155·5°.

The second liquors were again concentrated to dryness and extracted with 3 portions of hot hexane; the extracts yielded 2·3 g of a gum, of which 1·5 g flash-distilled at 1 mm. The distillate was dissolved in 9:1 hexane: AcOEt and seeded. The solvent was slowly allowed to evaporate and finally deposited a single large platelet (55 mg), m.p. 120·2–122°, of **4a**. The low yields of dimers were due, largely, to formation of by-products of higher mol. wts.

Reactions of diglycidylamines with primary amines. A series of these reactions was carried out by methods described above. Two pairs of complementary reactants gave crystalline products.

1-*t-Butyl*-5-*phenyl*-1,5-*diazacycloöctane*-3,7-*diol* (**4e**). The condensation of aniline (9·3 g) and t-butyldi-(2,3-epoxypropyl)amine (18·5 g) in 101 g MeOH for 18 days, followed by flash-distillation

and crystallization, gave 8·0 g (29%) of an impure product; m.p. 140–150°, raised to 157–158° by purification.

Similarly, N,N-di-(2,3-epoxypropyl)aniline and t-butylamine gave 25% yield of nearly pure material, m.p. 154–157°, also raised to 157–158°, identical with the above sample. (Found: C, 68·76; H, 9·45; N, 9·69; mol. wt., 251 (osmometric, acetonitrile). $C_{16}H_{26}N_2O_3$ requires: C, 69·0; H, 9·4; N, 10·1%; mol. wt. 278.) IR: 3·00 ib, 3·27 m, 3·37 i, 3·43 i, 3·43 i, 6·09 ms, 6·21 i, 6·33 i, 6·58 i, 6·68 is, 6·72 i, 6·83 m, 6·99 m, 7·13 i, 6·18 is, 7·28 i, 7·32 is, 7·36 is, 7·54 ms, 7·58 m, 7·69 i, 7·80 i, 7·94 is, 8·00 is, 8·06 i, 8·17 ms, 8·33 i, 8·55 m, 9·48 i, 9·53 is, 9·60 i, 9·72 i, 9·96 i, 11·13 m, 11·40 i, 11·56 ms, 13·30 i, 13·40 i, 14·39 i, 15·07 mb, 15·58 mb. NMR: (low solubility, major lines only) $(CH_3)_3C$, 9·02; CH_2, 7·95, 7·15, 7·10, 7·04; 6·41, 6·34; C_6H_5, 3·33–2·62 (10 lines).

1-n-Butyl-5-phenyl-1,5-diazacyclooctane-3,7-diol. From n-butylamine and N,N-di-(2,3-epoxypropyl)aniline (20 days, 24%) by distillation and crystallization from MeOH, this compound melted at 127–129°. Recrystallization from EtOH–hexane gave m.p. 133–134°.

Alternatively, aniline and *n*-butyldi-(2,3-epoxypropyl)amine gave the compound (8 days, 1·5%); m.p. 128–132°, raised to 132–133°. (Found: C, 68·94; H, 8·98; N, 9·93. $C_{16}H_{26}N_2O_3$ requires: C, 69·0; H, 9·4; N, 10·1%.) IR: 2·96 i, 3·23 i, 3·27 m (doublet), 3·34 is, 3·38 i, 3·45 is, 3·50 ms, 6·21 i, 6·34 i, 6·58 i, 6·78 m, 6·91 m, 7·19 i, 7·31 m, 7·67 i, 7·73 m (doublet), 7·90 m, 7·97 i, 8·13 i, 8·30 i, 8·43 m, 8·64 m, 8·95 m, 9·36 m, 9·68 i, 9·78 i, 10·11 i, 10·32 mb, 11·04 m, 11·50 m, 13·41 i, 14·35 i, 15·02 mb, 15·10 mb. NMR: (low solubility, major lines only). n-C_4H_9, 9·1–8·4; CH_2, 7·84, 7·23, 7·16; 6·46, 6·37; C_6H_5, 3·33–2·63 (10 lines).

Condensation of diglycidlyamines with sodium sulfide[23]

1-t-Butyl-1-aza-5-thiacyclooctane-3,7-diol (**5a**). The best yield (52%, crude) was obtained by dilute simultaneous addition at 40° in MeOH as described below, lower yields being obtained similarly at 25° (44%), 0–5° (48%, very impure), and Dry Ice temp (39%, but much of the reaction occurred as the bath was allowed to warm slowly). Rapid combination of the reactants in MeOH at 25° gave a 27% yield exothermically.

In the best run, 9·25 g of t-butyldi-2,3-epoxypropylamine diluted to 66·6 ml with MeOH was added during 2 hr proportionally and simultaneously with 66·6 ml of 0·75M $Na_2S{\cdot}9H_2O$ in MeOH (standardized against the Durbetaki Reagent) to 200 ml MeOH stirred and heated at 40°. After being heated another 30 min and standing overnight, the mixture was concentrated *in vacuo*, extracted with ether, and the extracts dried and distilled. The major cut, 7·2 g, b.p. 150–162°/1 mm, was crystallized from AcOEt–ligroin, giving 5·6 g (52%); m.p. 80–86°. No other solid could be isolated.

Repeated recrystallization gave white needles; m.p. 94·5–95°. (Found: C, 54·78; H, 10·01; N, 7·01; S, 14·93; N.E., 215. $C_{10}H_{21}NO_2S$ requires: C, 54·7; H, 9·7; N, 6·4%.; S, 14·6; N.E., 219.) IR: 3·05 i, 3·33 m, 7·26 m, 7·64 m, 7·73 m, 8·14 mb, 8·78 m, 9·80 i, 10·03 ms, 13·37 mb, 15·03 mb. NMR: (11%) $(CH_3)_3C$, 8·94; CH_2 and OH, 6·9–7·6 (8 lines, including a "doublet," 7·00); OC*H*, 6·05, multiplet.

The compound was resistant to desulfurization by Raney Ni catalyst in aqueous EtOH, but reacted after adding several portions of excess fresh catalyst and raising the temp by slow (16 hr) distillation of the EtOH. From 3·7 g of **5a** was obtained only 0·7 g of colorless oil, b.p. approximately 75–100°/1 mm, n_D^{25} 1·4557, along with a small forerun and residue.

From t-butylamine and 2·8 molar equivs of propylene oxide in MeOH at 20–25° was isolated after 7 days a 27% yield of impure 1-t-butylamino-2-propanol, b.p. 53–58°/0·6 mm, n_D^{25} 1·4341, and a 63% yield of the 1:2 adduct, b.p. 85°/0·6 mm, n_D^{25} 1·4558. The latter was analyzed. (Found: C, 63·10, 63·17; H, 12·53, 12·51; N, 7·38, 7·42; N.E., 185. Anal. Calc. for $C_{10}H_{23}NO_2$: C, 63·4; H, 12·6; N, 7·40%; N.E., 185.)

Both the desulfurized product and the adduct were subjected to gas chromatography at 225° on a 2-ft. Oronite-on-Celite column. The former contained 3 volatile impurities, not identified, and a main peak which was resolved and collected in a cold trap at the exit port. The adduct contained a minor volatile impurity and a major peak with the same retention time as the first sample, also collected. The major components from both samples can only be *t-butylaminodi-2-propanol*, as also shown by their IR spectra (neat) which were virtually superimposable: 2·98 ib, 3·38 i, 3·42 is, 6·77 m,

[23] These reactions were conducted mainly by Mr. Wendell E. Rhine, who also prepared many of the intermediates.

6·85 mb, 7·07 m, 7·17 m, 7·31 i, 7·46 m, 7·81 mb, 8·20 ms, 8·31 m, 8·81 ib, 9·21 mb, 9·41 m, 9·88 m, 10·64 m, 11·09 m, 11·87 m, 12·07 m, 13·64 mb, 15·04 mb.

Other 1-*substituted* 1-*aza*-5-*thiacycloöctane*-3,7-*diols* (**5**)

A series of similar reactions were carried out[25] by dilute simultaneous addition at 0–5° (*b*, *c*) or 25° (*d*, *e*). Yields may not be optimum. The cystalline products, with main-crop m.p., crude yield, solvent, m.p. of purified sample and analytical data are listed; several other reaction mixtures yielded only impure oils or gums.

b. 1-*Cyclohexyl*-1-*aza*-5-*thiacycloöctane*-3,7-*diol*. 130–135°, 48%, wet MeOH, 135–136·5°: (Found: C, 58·70; 9·56; N, 5·81; S, 13·29. $C_{13}H_{25}NO_2S$ requires: C, 58·8; H, 9·44; N, 5·71%; S, 13·05.)

c. 1-*Phenyl*-1-*aza*-5-*thiacycloöctane*-3,7-*diol*, 146–155°, 14%, AcOEt–ligroin, 165–166°. (Found: C, 60·39; H, 7·24; N, 5·91; S, 13·53. $C_{13}H_{17}NO_2S$ requires: C, 60·2; H, 7·16; N, 5·85%; S, 13·40.)

d. 1-(2,6-*Dimethylphenyl*)1-*aza*-5-*thiacycloöctane*-3,7-*diol*, 181–183°, 27%, AcOEt–MeOH, 183–184°. (Found: C, 62·75; H, 7·72; N, 5·17; S, 11·82. $C_{15}H_{21}NO_2S$ requires: C, 62·9; H, 7·90; N, 5·23%; S, 12·0.)

e. 1-(2-*Methoxyphenyl*)1-*aza*-5-*thiacycloöctane*-3,7-*diol*, 149–151°, 11%, MeOH–AcOEt, 151–152·5°. (Found: C, 57·87; H, 7·04; N, 5·18; S, 11·77. $C_{13}H_{19}NO_3S$ requires: C, 58·0; H, 7·10; N, 5·20%; S, 11·9%.)

1-*t*-*Butyl*-3,7-*dichloro*-1-*aza*-5-*thiacycloöctane hydrochloride*

The diol, **5a**, 2·19 g, was added in small portions to 10 ml $SOCl_2$, protected from moist air and cooled and stirred in an ice-bath. As the bath melted and warmed, the solid dissolved and the soln evolved gases. The soln was heated slowly to reflux during 2 hr. Skellysolve F was then added slowly to the cooled mixture, separating a lower layer which crystallized.

The solid was dissolved in warm Chf, decolorized and precipitated with ether, giving 2·45 g (84%); m.p. 212–213° (dec). After repurification, the compound had m.p. 213–214° (dec, sample placed in 200° bath). (Found: C, 40·97; H, 6·79; Cl, 36·35; S, 10·79. $C_{10}H_{20}Cl_2NS$ requires: C, 41·0; H, 6·9; Cl, 36·3; S, 11·0%.) NMR: (in D_2O, external TMS) $(CH_3)_3C$, 8·00; CH_2 and $ClCH$, 5·3–6·4 (7 lines, two major at 5·59 and 5·64).

1-*t*-*Butyl*-3,7-*dichloro*-1,5-*diazacycloöctane dihydrochloride*

A soln of 3·6 g of **4a** in 20 ml chf was treated with anhyd HCl, giving 2 layers. With cooling below 15°, 3·6 g of reagent $SOCl_2$ in 10 ml chf was added. The mixture became homogeneous slowly and was allowed to warm to ambient temp, with slow gas evolution. Addition of 10·0 ml of $SOCl_2$, standing overnight, and finally heating to 60–64°, was followed by aspiration. The powdery solid residue was rinsed with warm chf; 4·0 g (78%); it decomposed without melting at 210–215°. The product was slightly water soluble, but could not be recrystallized from usual solvent pairs. It was purified by Soxhlet extraction with chf. Analysis indicated that one t-butyl group had been lost and this was confirmed by the NMR integration. (Found: C, 38·23, 37·97; H, 6·86, 6·89; Cl, 45·71; N, 8·62. $C_{10}H_{22}Cl_4N_2$ requires: C, 38·4; H, 7·1; Cl, 45·4; N, 9·0%.) NMR: (in D_2O, external TMS) $(CH_3)_3C$, 7·99; CH_2 and $ClCH$, 5·2–6·3 (major peak, 5·44).