

SYNTHESIS AND CYCLODIMERIZATION OF STABLE 1-t-ALKYLAMINO-2,3-
EPOXYPROPANES; RELATED STERICALLY PROMOTED
EIGHT-MEMBERED RING CLOSURES

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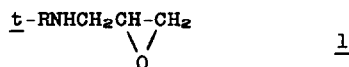
We wish to describe exceptionally stable new secondary amino epoxides, their cyclodimerization to diazacyclo^ooctanediols, and novel related eight-membered ring closures which may be generally useful.

Although several adequately characterized secondary amino epoxides have been described (1), none was appreciably stable under ambient conditions.

Equimolar reaction of t-alkylamines with epichlorohydrin¹ (2), either reactant being present in 25-100% excess in methanol at 20-25°C, followed by expeditious isolation and dehydrohalogenation with alkali (both below 35°) of the crude 1-t-alkylamino-3-chloro-2-propanols, provided 1-t-alkylamino-2,3-epoxypropanes, 1, in good yields; 1a, t-butyl, mobile colorless liquid, b.p. 54-55°/10 mm., n_D^{25} 1.4307, 58% yield based on t-butylamine; 1b, t-octyl

¹Aliquots were titrated with anhydrous hydrogen bromide in acetic acid (3); when the decrease in oxirane content corresponded to 95-105% of that predicted for equimolar reaction (2-3 days), the mixture was concentrated in vacuo to remove solvent and excess reactant. Dehydrohalogenation with 40-50% aqueous alkali was completed by drying the product over alkali pellets; residual alkali, which caused partial polymerization during distillation, was removed by charcoal.

(1,1,3,3-tetramethylbutyl), b.p. 65-66°/1 mm., n_D^{25} 1.4492, 66% yield based on epichlorohydrin².

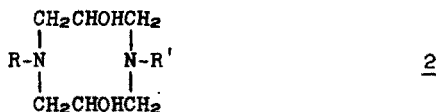


These secondary glycidylamines, 1 were far more stable than the previously described examples (1). When atmospheric moisture was carefully excluded, the pure compounds could be kept at room temperature for some time without measurable change. Water or alcohols catalyzed the disappearance of oxirane content. In methanol at 25.0°C the second order constant for the initial dimerization of 1a was 7.0×10^{-6} l. mole⁻¹ sec.⁻¹. This rate is remarkably only 3.5-fold slower than the initial reaction of the less hindered primary t-butylamine with epichlorohydrin ($k_2 = 2.5 \times 10^{-5}$ l. mole⁻¹ sec.⁻¹, 25.0°C, 96/4 v/v methanol/water). Clearly the stability of 1 was attributable more to the absence of hydrogen-bonding catalysts than to the steric effect.

Although earlier workers (1) have stated or implied that secondary glycidylamines homopolymerized, 1 either neat or in methanol gave largely distillable dimers. After two months in methanol at 20-25° less than 10% of the original weight of 1a was not volatile up to 220°/1 mm. The two major products isolated from the distillate by crystallization from heptane and then from 30-60° petroleum ether, m.p. 124-125° (23% yield) and m.p. 69-72° (incompletely separated from unidentified oils), were 1,5-di-t-butyl-1,5-diazacyclooctane-3,7-diols, 2a. Evidence for the structure, in addition to the analytical and spectral

²Satisfactory elemental analyses, including oxirane contents (3), and consistent n.m.r. and infrared spectra were obtained for new compounds.

data² and osmometric molecular weights, included three alternative



syntheses:³ condensation of t-butyl-bis-(2,3-epoxypropyl)amine(2) with t-butylamine; consecutive equimolar addition of 1,3-di-t-butylamino-2-propanol to epichlorohydrin, dehydrohalogenation, and cyclization; and condensation of impure t-butyl-bis-(3-chloro-2-hydroxypropyl)amine with t-butylamine at 140° in the absence of solvent, conditions which were shown (4) to result in direct displacement of halide from 1,2- and 2,1-chlorohydrins by piperidine and not to involve the epoxide.

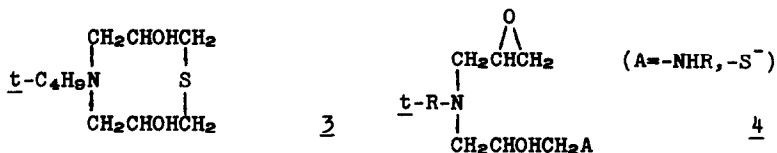
The different behaviors of the hydroxyl n.m.r. peaks upon dilution suggested that the higher and lower melting diols are trans and cis isomers, respectively. Thus in 25% solution in deuteriochloroform, the higher melting diol gave a broad peak ($\tau=6.14$), which shifted as expected ($\tau=6.29$) in 14% solution but did not resolve. The lower-melting compound had a broad peak ($\tau=6.98$) at 25%, which both shifted and resolved cleanly into two equal peaks ($\tau=6.89, 6.94$) at 14%. Examination of the Stuart-Briegleb models indicates that the trans diol has a preferred conformation (twisted ring) with equivalent equatorial hydroxyls. The cis model has several similar conformational isomers, in none of which are the hydroxyls equivalent. These tentative assignments are consistent with physical properties, also.

³Statements of the identity of two samples were supported by both undepressed mixture melting points and essentially superimposable infrared spectra.

Another example of cyclodimerization of 1-amino-2,3-epoxypropanes indicated that the reaction is not limited to highly hindered starting materials. 1-Anilino-2,3-epoxypropane gave the diphenyl analog, 2c, m.p. 212-213°, in 17% yield, alternatively obtained from aniline and N,N-di-2,3-epoxypropylaniline (25% yield). An equimolar mixture of 1a and 1-anilino-2,3-epoxypropane gave, in addition to 2a and 2c, a trace of 1-t-butyl-5-phenyl-1,5-diazacyclooctane-3,7-diol, 2d, m.p. 158-159°.

The above reaction of a primary amine with a diglycidylamine was also general and provided 2 carrying two different substituents. Complementary reactant pairs yielded a single 2, unequivocally proving the structure. Thus either aniline and t-butyl-bis(2,3-epoxypropyl)amine or t-butylamine and N,N-bis-(2,3-epoxypropyl)-aniline gave 2d (28% and 24% yields, respectively). Similarly, from the two appropriate pairs, 2e (R=n-butyl, R'=phenyl), m.p. 133-134°, was prepared. In these cases only one pure crystalline compound, probably the trans isomer, was isolated.

A similar eight-membered ring closure involving an intermediate mercaptide occurred in the rapid exothermic reaction of sodium sulfide with t-butyl-bis-(2,3-epoxypropyl)amine; 1-t-butyl-1-aza-5-thiacyclooctane-2,3-diol, 3, m.p. 94.5-95°, resulted in 27% yield. The structure was established by hydrogenolysis with Raney nickel catalyst to t-butyl-bis-(2-hydroxypropyl)amine (v.p.c. isolation), identical (infrared) with the product prepared from t-butylamine with excess propylene oxide (63% yield, b.p. 85°/0.6 mm., n_D^{25} 1.4558).



These cyclizations are rationalized by a sterically favored conformer of solvated intermediate of type 4 which both promotes ring formation and inhibits polymerization. This interpretation and additional supporting evidence will be discussed later, along with details.

These unusually simple closures of otherwise difficult obtainable eight-membered saturated heterocyclic rings (5) in comparatively good yields and with concomitant formation of reactive hydroxyl groups beta to the hetero atoms will likely apply to rings of other sizes. The results further suggest broad investigation of ring closures involving a variety of oxirane-opening reactions.

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References.

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

Recently we learned that Messrs. Leo S. Luskin and Albert J. McFaul of the Rohm and Haas Company independently prepared compounds 1a and 1b by the water-catalyzed reaction, in 42% and 26% yields, respectively. Similarly they prepared N-t-butyl-bis-(2,3-epoxypropyl)amine in 28% yield; our method (footnote 1) using the 1:2 mole ratio gave this compound (b.p. 88°/1 mm., n_D^{25} 1.4634) in up to 42% yield.

- (3) A. J. Durbetaki, Anal. Chem., 28, 2000 (1956).
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- (5) Review: E. L. Eliel, in M. S. Newman, ed., "Steric Effects in Organic Chemistry," Wiley, New York, 1956, pp. 116-117.