"Abnormal" Intramolecular Basic Aziridine Opening; Six- and Seven-Membered Diheterocycles

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Sir:

We wish to report that basic aziridine intermediates carrying amine or thiol nucleophiles cyclized *in situ* to form mixtures of seven- and six-membered diheterocycles, involving "normal" and "abnormal" openings, respectively. The first authentic "abnormal" openings by thiols are described. Comparative oxirane reactions were investigated.

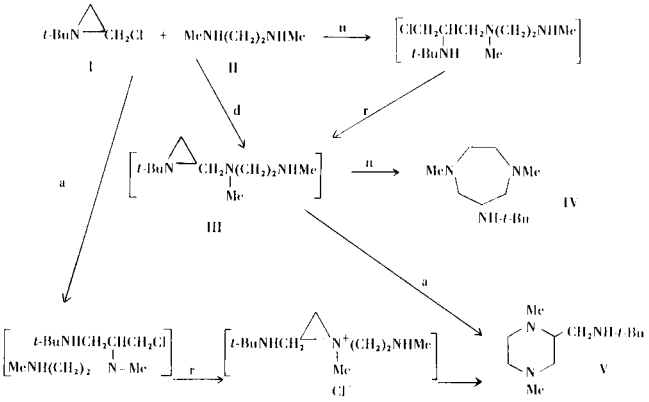
Recently we showed that 3-10% of "abnormal" isomers were formed (along with the "normal" product) in simple amine cleavages of certain basic aziridines (1). Preliminary evidence favored a monolithic S_N2 mechanism rather than the dual S_N1-S_N2 processes usually accepted for activated or tertiary aziridines and weaker nucleophiles (2). Independently, Clapp and co-workers presented stereochemical data supporting the S_N2 mechanism of acidic hydrolysis at both primary and secondary carbons of basic aziridines (3).

To extend these studies to cyclizations, the general preference for six-membered ring formation was pitted against the strong tendency of basic aziridines to yield "normal" products, which in these cases were seven-membered diheterocycles.

Formation of diheterocycles by intramolecular nucleophilic aziridine opening is little known and cyclization by double aziridine cleavage is apparently novel. Ring expansions of activated 2-acylaziridine phenylhydrazones have been described (4), but product rings other than five-membered and studies of basic aziridines are lacking. In the oxirane series, cyclizations of intermediates from epihalohydrins or dihalohydrins with glycols were claimed to yield only the "abnormal" 1,4-dioxanes (5). An unusual example of double "normal" oxirane cleavage with seven-membered ring formation is the synthesis of 6-hydroxy-1,4-dithiacycloheptane (X) from dihalohydrins and 1,2-ethanedithiol, which Fuson and Speziale termed "anomalous" (6). Dimerizations of monoglycidylamines and double additions of amines or sulfide ion to diglycidylamines gave "normal" eight-membered diheterocycles (7). "Abnormal" thiol cleavage seems not to have been described for any small heterocycle.

The reactions of 1-*t*-butyl-2-chloromethylaziridine (I) with excess simple nucleophiles were earlier shown to involve direct displacement (d), "normal" (n) and "abnormal" (a) ring cleavage, and recyclization (r)- reopening in which n and a were indistinguishable (8). A vicinal dinucleophile, *e.g.*, N,N′-dimethylethylenediamine (II), opens the major possibilities shown in the Chart; the products are the seven-membered (IV) and the six-membered (V) dinitrogen heterocycles. Since "normal" intermolecular opening predominates (1), the ratio, IV:V, will be determined almost entirely by the ratio of "normal" to "abnormal" opening of the key intermediate aziridine (III).

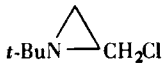
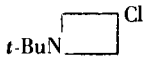
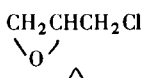
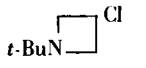
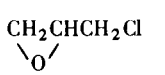
CHART



The mixture from complete reaction of I with II (9) was fractionated and shown by gas chromatography (gc) to contain two isomers in a ratio of 14:86. They were characterized by usual methods (10). The major product, 2-(*t*-butylaminomethyl)-1,4-dimethylpiperazine (V), exhibited two 3-proton singlets (τ 7.77, 7.74) due to nonequivalent *N*-methyl groups, while the symmetrical 6-*t*-butylamino-1,4-dimethyl-1,4-diazacycloheptane (IV) showed a single methyl peak (τ 7.67, 6 H). Clearly, "abnormal" opening of III to give the six-membered V predominated over "normal" cleavage ot the seven-membered ring product (IV), reversing the ratio observed for intermolecular opening (1).

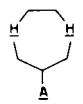
TABLE

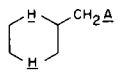
Diheterocycles by Small-Ring Opening

Nucleophile	Electrophile	Products Ratio (a)		Yield (c)
1. $MeNH(CH_2)_2NHMe$		IV:V (9)	14:86	63
2. $MeNH(CH_2)_2NHMe$		IV:V (9)	2:98	67
3. $MeNH(CH_2)_2NHMe$		VI:VII (11)	67:33	14
4. $HS(CH_2)_2SH$		VIII:IX (12)	51:49 (b)	29
5. $HS(CH_2)_2SH$		VIII:IX (12)	34:66 (b)	25
6. $HS(CH_2)_2SH$		X (6,13)	>98:2	10

(a) In area percent, except (b) in mole percent. (c) Not optimized.

Similarly 1-*t*-butyl-3-chloroazetidine (8) and II yielded only IV and V as final 1:1 products and IV again undoubtedly formed by "normal" opening of aziridine III. The actual result (IV:V::2:98) confirms that direct displacement of chloride (which leads only to V) competed strongly with initial ring opening (8).





	B	A	
IV	NMe	NH-*t*-Bu	V
VI	NMe	OH	VII
VIII	S	NH-*t*-Bu	IX
X	S	OH	

1,2-Ethanedithiol and epichlorohydrin were also studied. The 1:1 products were VI and VII from II and epichlorohydrin (11), VIII and IX from I and ethanedithiol (12), and only X (6, 13) from the latter and epichlorohydrin. The data appear in the Table.

The structures of amines VIII and IX were correlated with the known seven-membered alcohol X by treating the crude *O*-mesylate (an unstable liquid, prepared by the method (8) involved in the synthesis of I) of X with *t*-butylamine to yield (58%) the pure amine IX. Ring contraction was to be expected, in view of the similar outcome in conversion of X to the chloride (6).

The present results establish that basic aziridines may cleave largely to "abnormal" isomers, presumably due to the entropy effect, there being no reason to expect a change in mechanism. Aziridine intermediates underwent "abnormal" opening to greater extents than did oxiranes, and the same was true for the secondary amine nucleophile compared to the mercaptide anion. That order suggests that the stronger electrophile, oxirane, and nucleophile, mercaptide, lead to the "tighter" S_N2 transition state complex in which polarizability effects act more importantly to favor "normal" opening.

REFERENCES

(1) V. R. Gaertner, *J. Heterocyclic Chem.*, **8**, 177 (1971). However, methyl mercaptan and 1-*t*-butyl-2-methylaziridine gave only the "normal" product, as have published thiol cleavages (2, p. 236). The terms "normal" (at a primary ring carbon atom) and "abnormal" (at a secondary ring carbon atom) are used here in the usual sense (2) and reflect the rarity of "abnormal" products from basic aziridines with strong nucleophiles.

(2) Review: O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y. 1969, pp. 230-240.

(3) H. W. Wenghoefer, K. T. Lee, R. M. Srivastava, G. Srimannarayana, and L. B. Clapp, *J. Heterocyclic Chem.*, 7, 1407 (1970).

(4) Ref. 2, p. 240.

(5) C. Moureu, *Ann. Chim. Phys.*, 18, 76 (1899); A. Fourneau, *J. Pharm. Chim.*, 1, 55 (1910); French Patent 770,485, Sept. 14, 1934; U. S. Patent 2,366,661, Jan. 2, 1945; M. S. Kharasch and

W. Nudenberg, *J. Org. Chem.*, 8, 189 (1943).

(6) R. C. Fuson and A. J. Speziale, *J. Am. Chem. Soc.*, 71, 823 (1949); *ibid.*, 71, 1582 (1949).

(7) V. R. Gaertner, *Tetrahedron*, 23, 2123 (1967).

(8) V. R. Gaertner, *J. Org. Chem.*, 35, 3952 (1970).

(9) A solution of 0.020 mole of both reactants in 10 ml. of acetonitrile was heated in a 25-ml. stainless steel bomb at 110°. Gc indicated disappearance of the electrophile after 1-3 days; no more than traces of possible intermediates were detected in any run. From I and II were obtained IV and V; b.p. 66-71° at 1 mm.; gc, column C (8), 170°. The ratio was nearly unchanged by added sodium carbonate in acetonitrile (14:86, 63%), or by reaction in methanol (11:89, 42%) or neat (11:89, 46%).

(10) Consistent elemental analyses, osmometric molecular weights (both by Galbraith Laboratories, Knoxville, Tenn.) and integrated pmr spectra in chloroform-*d* were obtained for all products. Detailed methods have been described (1,8). The *t*-butyl singlets for VI and VIII appeared at higher field than those for VII and IX (12), and the ring multiplets were simpler and more symmetrical for the seven-membered series, which usually crystallized (VIII, X). These data and the number of *N*-methyl singlets provided unequivocal structural assignments.

(11) Equimolar reaction in methanol at 20° overnight was followed by slow addition (cooling) of 25% aqueous sodium hydroxide and stirring overnight. The product, b.p. 43-55° at 0.2 mm. (gc, column C (8), 170°), contained VI (lower boiling, single 6-H *N*-methyl peak) and VII (two 3-H singlets, complex ring multiplet).

(12) Gc separation was incomplete. The mixture of VIII and IX, b.p. 84-86° at 0.2 mm., was analyzed by integration of the expanded *t*-butyl peaks. Dissolution in pentane at 20° and slow cooling to -20° yielded VIII, m.p. 67-68°; *t*-butyl singlet at τ 8.96, multiplet with major line at 7.10. The liquid IX has the *t*-butyl singlet at 8.95 and a complex ring multiplet with three sharp lines.

(13) M.p. 64.5-65.5°, found and literature (6). No isomer could be detected in our crude product by gc or pmr, even after conversion to the trimethylsilyl ether.