Reactions of Aziridines. II. The Acid-Catalyzed Formation of 1,4-Dialkylpiperazines from 1-Alkylaziridines

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It has been demonstrated that hydrohalic acids in 2-propanone or 2-butanone will catalyze the conversion of certain 1-alkylaziridines to the corresponding 1,4-dialkylpiperazines in yields as high as 95%. The rates of piperazine formation were effected in the order HI > HBr > HCl. Perchloric acid and *p*-toluenesulfonic acid resulted in the formation of poly(1-alkylaziridines) rather than piperazines. The major products formed in a water solvent were poly(1-alkylaziridines) with 1,4-dialkylpiperazines being formed in maximum yields of 27% in the case of a hydriodic acid catalyst.

The formation of 1,1,4-trialkylpiperazinium halides from alkyl halides and 1-alkylaziridines was discussed in the first paper of this series.[1] The proposed mechanism involved the initial reaction of an alkylating agent with a 1-alkylaziridine to produce a 1,1-dialkylaziridinium salt which lead to the formation of either the piperazinium halide or a polymer. It was also demonstrated that the presence of a halide ion was necessary for piperazine formation. A further test of the proposed mechanism has now been carried out by replacing the alkylating agents with acids under the same conditions as previously reported. In the presence of acids the expected products would be either polymer or 1,4-dialkyl piperazines and their acid salts.

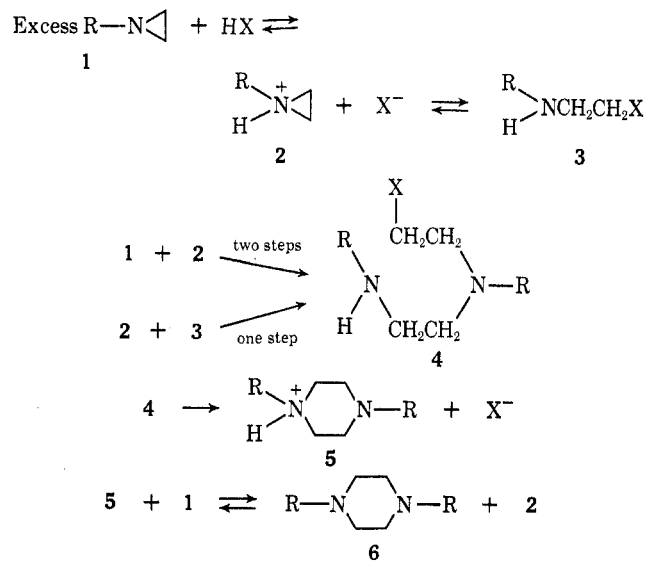
From a consideration of the data in Table I it is apparent that halogen acids are required (reactions 1–6, 9, 10, 11) for piperazine formation and that the order of catalyst effectiveness is HI > HBr ≫ HCl. Replacement of the halides by ions of low nucleophilicity such as perchlorate (reaction 7) and *p*-toluenesulfonate (reaction 8) resulted in polymer formation. The effect of solvent polarity on product distribution can be ascertained by comparing the yields of 1,4-diethylpiperazine in acetone (reactions 1, 6) with those achieved in acetone–water mixtures (reactions 11, 12). It is apparent that a solvent of low polarity and solvating power favors piperazine formation. The general results concerning the effects of anions and solvent polarity are in complete agreement with those results reported for alkylating agents.[1]

A predictable difference between alkylating agents and acids was noted when it was found that several moles of 1,4-diethylpiperazine were produced for each equivalent of hydrohalic acid charged thereby demonstrating that the acids were functioning as catalyst. Thus the formation of 1,4-dialkylpiperazines using an acid catalyst can best be formulated according to Scheme I.

Through a series of steps the monomer **1** is ultimately converted to **4** which cyclizes to form the 1,4-dialkylpiperizinium halide (**5**). The transfer of a proton from **5** to **1** results in the formation of the 1,4-dialkylpiperazine (**6**) plus **2** which completes the catalyst cycle. It is worth noting that as the reaction progresses the position of the equilibrium **5** + **1** ⇄ **6** + **2** will favor **5** at the expense of **2**. Thus the rate of conversion and the total conversion achievable within some practical time limit will be dependent on the initial monomer to acid catalyst ratio (reactions 1–4).

In order to further demonstrate that halide ions are

SCHEME I



involved in the product determining step of piperazine formation, a series of rate measurements was made and is depicted by the adjoining graph. It is evident that the rate of diethylpiperazine formation is dependent on the particular halide ion involved, $I^- > Br^- > Cl^-$, and that the reaction rate closely approaches zero at low aziridine conversions in the case of hydrochloric acid catalyst. The perchloric acid curve depicts a typical acid catalyzed polymerization, *i.e.*, a very rapid consumption of monomer followed by an equally rapid cessation of the reaction (Figure 1).

As was previously noted,[1] not all 1-alkylaziridines will form the corresponding piperazines even under the most favorable conditions. The ethylaziridine, 1-*n*-butyl aziridine, 1-phenethylaziridine, and 1-allylaziridine were all converted to the corresponding piperazines in good yields with hydriodic acid and sodium iodide in acetone. However, 1-(2-hydroxyethyl)aziridine and 1-cyanoethylaziridine did not form piperazines even in the presence of the added sodium iodide.

Further consideration of the data in Table I revealed that all of the aziridine converted is not forming 1,4-diethylpiperazine. Runs 1–4 demonstrate that higher acid–aziridine ratios result in lower yields, or alternatively, that higher conversions of aziridines result in lower yields of 1,4-diethylpiperazine. Runs 1 and 5 were completely devolatilized to determine if the loss in product was due to polymer formation. The residues were subjected to infrared analysis and were

(1) C. R. Dick, *J. Org. Chem.*, **32**, 72 (1967).

TABLE I

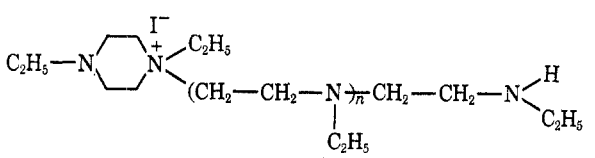
REACTION OF 1-ETHYLAZIRIDINE WITH ACIDS IN ACETONE

Run no.	Acid, equiv/equiv aziridine	Aziridine conversion, %[a]	Diethylpiperazine %[b] yield by glpc	Diethylpiperazine %[b] yield by ir	Nonvolatile residue, g	Piperazine rings in residue, %[c]
1	HI, 0.116	96	73	76	1.75	52
2	HI, 0.058	81	87	90		
3	HI, 0.035	65	93	95		
4	HI, 0.012	28	93	93		
5	HBr, 0.116	78	80	83	1.4	23
6	HCl, 0.116	31	48	48	1.0	<1.0
7	$HClO_4$, 0.116	77	0	<0.4	3.3[d]	<1.0
8	*p*-Toluenesulfonic, 0.116	79	0	<0.4	3.5[d]	<1.0
9	HI, 0.116, plus 0.006 mol of NaI	98	81	83		
10	HCl, 0.116, plus 0.006 mol of NaI	97	72	76		
11	HI, 0.116, 50% water–acetone	99+	27			
12	HCl, 0.116, 50% water–acetone	97	<1		3.1[d]	

[a] 24-hr reaction time. [b] After stirring reaction solution with excess potassium carbonate to ensure all acid was neutralized; yields calculated on basis of converted aziridine. [c] 1,1,4-Triethylpiperazinium bromine used infrared standard. [d] Poly(1-ethylaziridine).

found to contain significant quantities of nonvolatile monoquaternary piperazines.

In order to prepare a large quantity of the piperazine containing residue, reaction 1 was repeated on a larger scale from which 27.6 g of residue were isolated. This residue was separated into a 21-g diethyl ether insoluble fraction I which contained all of the piperazine moieties and a 5.2-g fraction II which was poly(1-ethylaziridine), completely free of piperazine rings as determined by infrared analysis. In addition to the aforementioned monoquaternary piperazines, the infrared spectra of fraction I was also found to contain bands characteristic of a significant concentration of acyclic, secondary amino nitrogen. Based on the infrared data, elemental analysis, molecular weight determination, and secondary and primary amine analysis, it was concluded that fraction I was a mixture of quaternary piperazines best represented by structure 7. For an M_n of 380, the average value of n is 0.7.



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The formation of a quaternary nitrogen demonstrates the existence of an acid catalyst consuming reaction; therefore, reaction 1 was repeated and allowed to stand for 7 days at which time no further reaction could be detected by glpc. Additional 1-ethylaziridine was then added to the reaction mixture and the concentration of 1,4-diethylpiperazine was noted to increase approximately 50% thereby demonstrating that these reactions seem to stop at high conversions not only because of quaternary piperazine formation but due to amine salt formation other than the aziridinium salts (2).

Experimental Section[2]

Preparation of 1,4-Diethylpiperazine (Table I).—A series of four-ounce bottles containing 100.0 ml of 0.52 *M* 1-ethylaziridine in acetone or acetone–water were placed in a 25.0° bath. Sodium iodide (0.77 g, 0.006 mol) was added to the appropriate bottles. The indicated amount of acid was added as a 6.0 *N* aqueous solution to each bottle which was shaken and returned to the bath. After 24 hr, 15 g of anhydrous potassium carbonate was added in order to neutralize the acid and the bottles were shaken for 4 hr. After allowing the solids to settle, the contents of each bottle were analyzed for 1,4-diethylpiperazine and unconverted 1-ethylaziridine by standard glpc and infrared techniques.

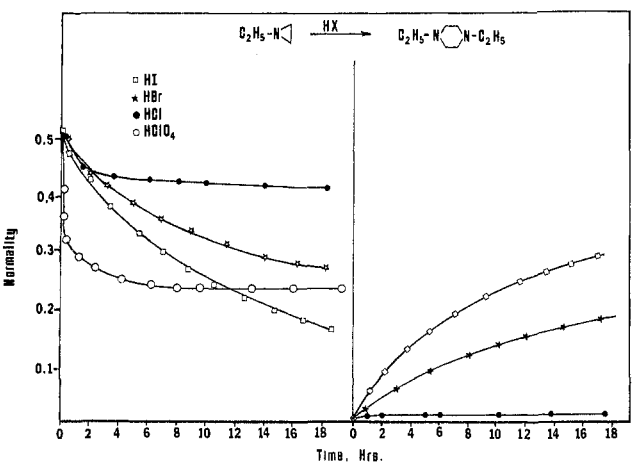

Figure 1.—Rate of acid-catalyzed formation of 1,4-diethylpiperazine.

The glpc column was 9 ft × 0.25 in. stainless steel packed with 15% Carbowax 20M plus 5% potassium hydroxide on 60–80 mesh Chromosorb W. For infrared analysis, the band at 955 cm^{-1} was used for diethylpiperazine and at 730 cm^{-1} for 1-ethylaziridine. The data is reported in Table I.

Preparation and Identification of Residue from Hydriodic Acid Catalyzed Reactions.—To a well-stirred mixture of 1425 ml of acetone and 80 g (1.11 mol) of 1-ethylaziridine maintained at 25–30° was added dropwise (1 hr) 30 ml of concentrated hydriodic acid. The mixture was stirred an additional 3 hr at 25–30°, was transferred to a stoppered bottle, and was stored in the dark. After 5 days, 150 g of anhydrous potassium carbonate was added and the mixture was stirred for 12 hr. The solution was filtered and devolatilized in a rotary evaporator. The residue was taken up in 100 ml of tetrahydrofuran, filtered to remove traces of potassium carbonate, and again devolatilized. The product, 27.6 g, was shown to be free of 1,4-diethylpiperazine by glpc analysis.

The product was fractionated by dissolving in 300 ml of tetrahydrofuran and adding three 40-ml aliquots of diethyl ether. After each addition a gummy phase separated which was removed. The three fractions and the mother liquor were freed of solvent. Product isolated from the mother liquor, 5.2 g, was shown to be poly(1-ethylaziridine) by comparison of its infrared spectra with that of an authentic sample. Fractions 1, 2, and 3

(2) All melting points are uncorrected. Infrared spectra were taken on a Beckman IR-9. Glpc data were taken on an F & M 810.

were combined, 21 g, since they had nearly identical infrared spectra. The spectra of the composite indicated the presence of high concentrations of a 1,1,4-trisubstituted piperazinium salt (1210–1220 cm^{-1}), $(-CH_2-)_3N$ (1060, 2860 cm^{-1}) characteristic of poly(1-ethylaziridine), and $(-CH_2-)_2NH$ (1110, 2810 cm^{-1}). Since poly(1-ethylaziridine) is soluble in diethyl ether, the composite was thoroughly washed with ether and dried, and its spectra remained unchanged. The ether washed was found to contain no polymer. Analysis of the residue is reported below.

Anal. Found: N, 12.85; C, 42.20; H, 8.78; I, 33.19; >NH, 3.4; $-NH_2$, <0.1; mol wt, 340 (ebulliometrically in 2-butanone) [Calcd: mol wt, 383 (based on iodide), 378 (based on secondary amine)].

Procedure for Rate Determinations.—Into a 100-ml volumetric flask were weighed 2.00 g of phenetole and 3.70 g of 1-ethylaziridine. The flasks were filled with 2-butanone and placed in a 25.0° water bath. To each flask was added 0.50 ml of 6.0 *N* acid and the contents were thoroughly mixed. At predetermined time intervals the reaction mixtures were analyzed by standard glpc techniques using the phenetole as an internal standard. The glpc column previously mentioned was used for these analyses. All runs were made in duplicate.

Preparation of 1,4-Disubstituted Piperazines for Glpc and Infrared Standards.—The diethyl-, di-*n*-butyl-, and diallylpiperazines were prepared by mixing 0.12 mol of the corresponding aziridine and 10 g (0.078 mol) of sodium iodide in 150 ml of 2-butanone followed by the addition of 3.2 g of concentrated hydriodic acid. After remaining at room temperature (24–26°) for 48 hr, the mixtures were shaken for 4 hr with 50 g potassium carbonate and filtered, and the solvent was removed by distillation at atmospheric pressure. The piperazines were isolated from the distillation residues by preparative scale glpc using the aforementioned Carbowax column.

Anal. Calcd for 1,4-diethylpiperazine: N, 19.72. Found: 19.82; $n^{25}D$ 1.4530 (lit.[3] 1.4520).

Anal. Calcd for 1,4-di-*n*-butylpiperazine: N, 14.1. Found: 19.82; $n^{25}D$ 1.4540 (lit.[3] 1.4542).

Anal. Calcd for 1,4-diallylpiperazine: N, 16.87. Found: 16.68; $n^{25}D$ 1.4754 (lit.[4] 1.4761).

The preparation of 1,4-diphenethylpiperazine was the same as above; however the product was isolated by devolatalizing the filtered reaction mixture, washing the residue with water to remove the soluble salts, and recrystallizing the crude product from an acetone–water mixture, mp 79.5–80.5°.

Anal. Calcd: N, 9.52. Found: 9.44.

Attempted Preparation of 1,4-Disubstituted Piperazines Other Than 1,4-Diethylpiperazine.—Using the preceeding procedure, 1-cyanoethylaziridine, 1-(2-hydroxyethylaziridine), 1-allylaziridine, 1-phenethylaziridine, and 1-*n*-butylarizidine were treated with hydriodic acid and sodium iodide in 2-butanone at 25°. After filtering the reaction mixtures in order to remove the potassium salts, the concentrations of the reacted aziridines and of the corresponding piperazines were determined by infrared analysis. The conversions of the aziridines were 99+% in each case.

Anal. % yield for 1,4-substituted piperazine: 1,4-bis(cyanoethyl), <1.0; 1,4-bis(2-hydroxyethyl), <10; 1,4-diallyl, 46; 1,4-diphenethyl, 73; 1,4-di-*n*-butyl, 83.

Registry No.—1-Ethylaziridine, 1072-45-3; 1-*n*-butylaziridine, 1120-85-0; 1-phenethylaziridine, 3164-46-3; 1-allylaziridine, 5536-99-2.

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(3) J. I. G. Cadogan, *J. Chem. Soc.*, 2971 (1955).

(4) G. B. Butler, and R. L. Bunch, *J. Amer. Chem. Soc.*, **71**, 3120 (1949).

Reactions of Nucleophiles with 1-*tert*-Butyl-3-chloroazetidine and 1-*tert*-Butyl-2-chloromethylaziridine[1]

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These small heterocycles, **1** and **2**, are exceptionally unreactive β-aminoalkyl chlorides. With nucleophiles under vigorous conditions **1** and **2** reacted by simple displacement (mercaptides, alkoxides, and uncatalyzed amines), partial (hydrolysis) or complete (cyanide) ring expansion of **2** to form azetidines, or ring cleavage, recyclization, and reopening (acetic acid, acid-catalyzed amines). Isomerization, **1** ⇄ **2**, occurred with mechanistic duality. Equilibria involving the 1-*tert*-butylazabicyclobutonium and 1-*tert*-butyl-2-aziridinylcarbinyl cations are proposed. Cyclization of β-aminoalkyl mesylates was a versatile route to aziridines carrying functional groups.

A problem of current interest in the chemistry of small heterocycles concerns the nature of nucleophilic substitution of azetidines bearing exophiles in the 3 position. A possible intermediate is the simple carbonium ion (I). The formal relationship of I to the

I II III IV

cyclobutyl–cyclopropylcarbinyl nonclassical cation system[2] suggested a parallel investigation of aziridinylcarbinyl derivatives, perhaps leading to cation II. Nitrogen participation in either case would lead to the strained quaternary 1-azabicyclobutonium ion (III), while the possibility of nonclassical hybridization implies intermediates such as IV.

We recently presented preliminary evidence to support nitrogen assistance in the ionization of the chlorides corresponding to ions I and II (R, *tert*-Bu) and suggested that a common intermediate (such as III alone) could not rationalize the results.[1] Independently Deyrup and Moyer proposed III as an intermediate in solvolysis of the tosylate of 1-*tert*-butyl-3-azetidinol, but they considered unclear the mechanism by which the aziridinylcarbinyl tosylate reacted.[3] The present paper concerns expanded evi-

(1) Preliminary account: V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968). Presented in part at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968; Abstracts, ORGN 1.

(2) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959). Review: R. Breslow, in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 233–294. J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **90**, 4303 (1968), gave a recent summary. See, however, R. E. Davis and A. Ohno, *Tetrahedron*, 2063 (1968), for the view that cyclobutyl cation is classical.

(3) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968). We are grateful to Professor Deyrup for initiating an exchange of results with the writer.