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The Chemistry of Azetidines. I. Decomposition of Azetidinium Iodides

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The most convenient, general method for the preparation of tertiary azetidines involves catalytic reduction of the appropriate ethyl cyanoacetate, ring closure in dilute solution to the corresponding β-lactam, reduction of the β-lactam with lithium aluminum hydride, acylation of the secondary azetidine with an acyl halide, and reduction of the resulting amide to the desired alkyl azetidine (1) (Eq. 1). Although fairly good over-all yields are obtained in the preparation of multiply-substituted products, the effectiveness of the method, as with other methods of closure of four-membered rings, decreases markedly in the preparation of the simpler, monosubstituted azetidines.

In searching for more convenient methods of preparation of azetidines, the decomposition of azetidinium halides was investigated. If suitable decomposition systems could be found, advantage might be taken of the various simple methods of cyclic quaternization for the preparation of azetidine precursors (2,3).

To this end, the well-known Hoffmann decomposition of amine quaternary salts has been applied to the degradation of 1-(2-carbethoxyethyl)-1-methyl-3,3-di-*n*-pentylazetidinium iodide (III). Introduction of III into a vapor-phase chromatograph (v.p.c.) with a flash-heater temperature of 235° produced 2-*n*-pentyl-1-heptene (IV) in substantial yield and good purity. In the all-glass heated inlet (230°) of a mass spectrometer (m.s.), however, III furnished 1-methyl-3,3-di-*n*-pentylazetidine (V) as the principal product of thermal decomposition. Initial attempts to repeat the v.p.c. or m.s. experiments in the laboratory resulted in extensive decomposition, with little, if any, volatile product being formed.

In an attempt to duplicate the results obtained in the mass spectrometer heated-inlet system with the flash heater of the gas chromatograph, both of all-glass construction and maintained at essentially the same temperature, a series of possible catalysts was packed into the injection port of the chromatograph. Samples of III were introduced as solids or as methylene chloride solutions. With glass wool, quartz wool, 20- to 40-mesh Teflon, Teflon tubing, steel wool, 16% phosphoric acid on Celite 545, and 16% silver nitrate on Celite 545, IV was produced (with only trace amounts of V). With 16% sodium bicarbonate on Celite 545, however, approximately a 50:50 mixture of IV and V was formed, whereas, with 16% potassium hydroxide on Celite, only V resulted. In a distillation apparatus, V was prepared quantitatively by heating an intimate mixture of III and an equal weight of sodium bicarbonate or sodium carbonate; however, IV was obtained only in poor yield by mixing III with at least equal amounts of glass beads (180- to 200-mesh) and heating under vacuum (0.05-0.10 mm.), most of the III producing an intractable tar.

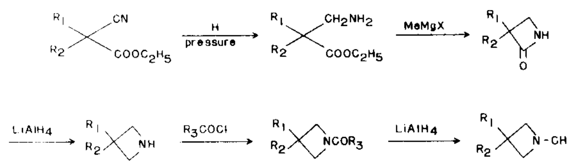
To elucidate further the difference in the v.p.c. and m.s. results, the hydroiodide salt of V was prepared and subjected to both decomposition systems. In the packed flash heater again, the basic medium

TABLE I

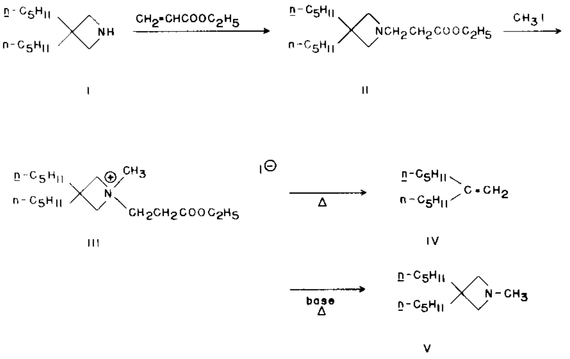
Decompositions in the Flash Heater of a Gas Chromatograph

Dec. Temp., °C	Flash-Heater Packing	Yield of IV,	Yield of V, % (a,b)
190	None	45	0
360	None	65	0
190	16% KOH on Celite 545	0	30
220	30% KOH on Celite 545	Trace	91
260	16% KOH on Celite 545	25	49
360	30% KOH on Celite 545	20	46

(a) Yields based on III. (b) A correction factor of 1.22 was applied to the v.p.c. area % to account for the difference in thermal response of *n*-undecane and V as determined from a comparison of the pure compounds.



(1)



(2)

furnished V, and a neutral medium (quartz, glass wool) furnished IV. In the m.s. heated inlet, as in the decomposition of III, the major product was V.

The essential difference in the v.p.c. and m.s. decompositions appears to be the removal of hydrogen iodide from the decomposition site before a secondary thermal decomposition can occur. This is accomplished in the heated inlet of the mass spectrometer by virtue of the vacuum (10^{-2} to 10^{-3} mm.) and the extremely small sample size (1 mg. or less), whereas in the v.p.c. flash heater or in a gross sample, base is necessary to take up the hydrogen iodide.

Vapor-phase chromatographic results suggest V hydroiodide as a possible intermediate in the decomposition of III to IV. In the mass spectrometer heated inlet, however, considerably less IV is obtained from the decomposition of V hydroiodide than from III, indicating a reaction path from III to IV not involving V hydroiodide.

The foregoing results indicate that azetidine quaternary salts with a good leaving group such as carbethoxyethyl may be useful intermediates for the preparation of a variety of *N*-substituted azetidines.

EXPERIMENTAL

(1) Preparation of Intermediates.

3,3-Di-*n*-pentylazetidine (I) was prepared by the method of Testa, *et al.*, (4,5) in 86% yield (b.p. 97°/0.38 mm., n_D^{25} 1.4529).

Anal. Calcd. for $C_{13}H_{27}N$: C, 79.2; H, 13.8. Found: C, 79.2; H, 13.6.

1-(2-Carbethoxy)-3,3-di-*n*-pentylazetidine (II) was prepared in 86% yield (b.p. 94-100°/0.010 mm.) by refluxing a solution of I in excess ethyl acrylate for 2 hours, stripping off the unreacted ethyl acrylate and distilling the residue.

Anal. Calcd. for $C_{18}H_{35}NO_2$: C, 72.4; H, 12.0; N, 4.7. Found: C, 72.7; H, 11.9; N, 4.7.

1-(2-Carbethoxyethyl)-1-methyl-3,3-di-*n*-pentylazetidinium iodide (III) (m.p. 171.5°) precipitated in 96% yield from an ethereal solution of II and an equal weight of methyl iodide, upon standing overnight at room temperature.

Anal. Calcd. for $C_{19}H_{38}INO_2$: C, 51.9; H, 8.7; I, 28.9; N, 3.2. Found: C, 51.8; H, 8.7; I, 29.2; N, 3.2.

(2) Thermal Decomposition of III.

Decomposition of III in the flash heater of a gas chromatograph is summarized in Table I. Solutions of III in methylene chloride were injected into the center of the flash heater of a nonpolar column, and the various decomposition products were trapped for instrumental identification after chromatographing isothermally at 213° or 250°. Yield data were obtained by comparing the areas on the chromatograms for the decomposition products and a measured amount of *n*-undecane. By assuming that hydrocarbons IV and *n*-undecane have the same thermal response, and applying a correction factor obtained by direct comparison of measured amounts of V and *n*-undecane, reliable yield data can be obtained, even with small experiments.

Preparative decompositions were carried out in a standard Claisen-type distillation apparatus under full pump vacuum (pressures varied from 0.2 mm. to 1.0 mm., depending on the rate of decomposition), as illustrated by the following examples:

A 1.0-gram sample of III was intimately mixed with 1.0 gram of sodium bicarbonate or sodium carbonate and the mixture heated slowly to 190° over a 1-hour period. 1-Methyl-3,3-di-*n*-pentylazetidine (V) was collected continuously during the decomposition, furnishing 0.50 gram of 95% v.p.c. purity material (100% yield).

Anal. for HI salt. Calcd. for $C_{14}H_{30}IN$: C, 49.6; H, 8.9; I, 37.4; N, 4.1. Found: C, 48.8; H, 8.7; I, 37.7; N, 4.1. M.P. 96.5-98°.

A 0.50-gram sample of III was intimately mixed with 1.0 gram of acid-washed glass beads and heated at 175-200° under vacuum. A small yield of IV distilled off, with no V detectable by gas chromatography.

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