The Isolation of a Bicyclic Aziridinium Ion Intermediate

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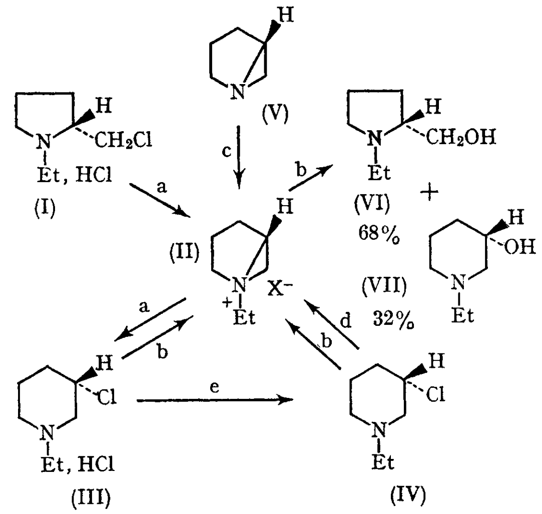
THE molecular rearrangement of 2-chloromethyl-*N*-ethylpyrrolidine hydrochloride (I) to 3-chloro-*N*-ethylpiperidine hydrochloride (III)[1] and the similar reaction of 3-chloro-*N*-ethylpiperidine (IV) and its hydrochloride salt (III) with various nucleophiles[2] to give various mixtures of substituted 2-methylenepyrrolidines (VI, general case) and 3-piperidines (VII, general case) have been considered to proceed *via* an intermediate bicyclic aziridinium ion (II; X = Cl).[3,4]



a, heat; b, NaOH; c, $EtClO_4$; d, $AgClO_4$; e, HCO_3^-.

We now wish to report the isolation of this intermediate (II) as the perchlorate salt, as well as its synthesis by an independent method. The reaction of 1-azabicyclo[3,1,0]hexane (V)[5] in dry ether with ethyl perchlorate in absolute ethanol yields a semi-solid, which on extraction with methylene chloride gave a ^1H n.m.r. spectrum similar to the ^1H n.m.r. spectrum (Figure 1) of the oil obtained from the reaction of 3-chloro-*N*-ethylpiperidine (IV) with silver perchlorate in dry acetone.

The chemical shifts of the ethyl group methyl and methylene protons in (II; $X = ClO_4$) are substantially downfield (1·40 and 3·40 p.p.m., respectively) from the chemical shifts of the corresponding protons in 3-chloro-*N*-ethylpiperidine (IV) (1·00 and 2·40 p.p.m., respectively). When the acetone impurity peak is subtracted, the integration ratios for the groups of peaks at 2·8—4·2, 1·6—2·8, and 1·2—1·6 p.p.m. indicate 7H : 4H : 3H, which is expected for structure (II). In addition, the infrared spectrum of (II) does not show absorption maxima assignable to $>C=\overset{+}{N}<$ of $R_3\overset{+}{N}H$, which would be present for some possible alternative structures but not for (II). These spectral data are consistent with the proposed structure for the intermediate ion (II) and is in agreement with the data of similar compounds reported by Leonard.[6] Further, the reaction of (II; $X = ClO_4$) with 10% aqueous sodium hydroxide for five hours gave the same product ratio, 68% of (VI) and 32% of (VII), as was found for the reaction of (III) or (IV) under identical conditions. It has also been reported[5b] that the reaction of 1-azabicyclo[3,1,0]hexane (V) with two moles of methyl iodide gave the methiodide salt of 3-iodo-*N*-methylpiperidine.

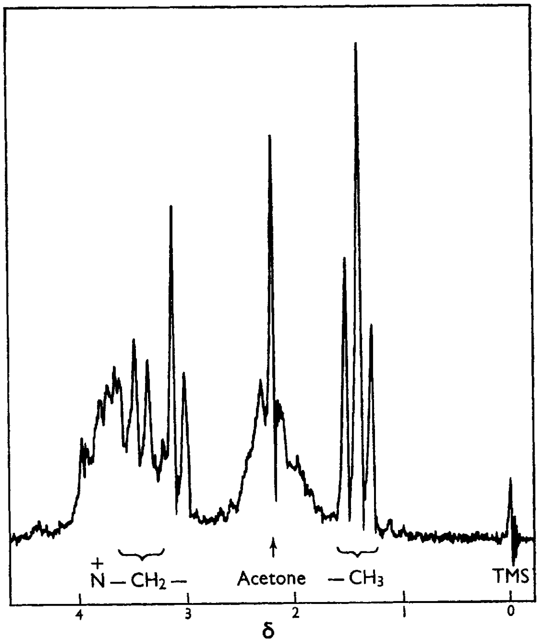


FIGURE. 60 *Mc./sec.* ^1H-*n.m.r. spectrum of* (*II*; $X = ClO_4$) *in methylene chloride* (*an impurity acetone peak is located at* 2·20 *p.p.m.* δ). *Chemical shift scale is p.p.m.* (δ) *relative to tetramethylsilane* (*TMS*) *as an internal standard.*

Preliminary kinetic results have shown that the reaction of (IV) with fourteen nucleophiles is of the first order, is independent of the nucleophiles, and shows a substantially increased rate, $>10^4$, relative to the rate observed for cyclohexyl chloride with hydroxide ion. A stereochemical study[4] has shown that reaction of (IV) with nucleophiles proceeds with 100% optical purity [retention of configuration for (IV) → (VII) and inversion of configuration for (IV) → (VI)].

A complete kinetic study as well as a complete stereochemical study for the mechanism of this reaction is under way and will be reported as a separate account.

(*Received, November 7th*, 1966; *Com.* 860.)

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[1] R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, 1948, **70**, 2760.

[2] (*a*) R. H. Reitsema, *J. Amer. Chem. Soc.*, 1949, **71**, 2041; (*b*) E. G. Brain, F. P. Doyl, and M. D. Mehta, *J. Chem. Soc.*, 1961, 633, and references therein; (*c*) E. M. Fry, *J. Org. Chem.*, 1965, **30**, 2058.

[3] The bicyclic azetidinium ion intermediate for *N*-methyl-2-(β-chloroethyl)pyrrolidine has been isolated previously (*cf.*, A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, 1964, **47**, 745).

[4] C. F. Hammer and S. R. Heller, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1965, p. 65S.

[5] (*a*) P. Gassman, private communication; (*b*) A. L. Logothetis, *J. Amer. Chem. Soc.*, 1965, **87**, 749; (*c*) R. Buyle, *Chem. and Ind.*, 1966, 195.

[6] For a review of Leonard's work and a discussion of the n.m.r. and i.r. spectra of these compounds, see N. J. Leonard, *Rec. Chem. Progr.*, 1965, **26**, 211.