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RING-OPENING ALKYLATIONS AND EQUILIBRIA INVOLVING 1,1-DIETHYL-3-SUBSTITUTED-AZETIDINIUM CATIONS

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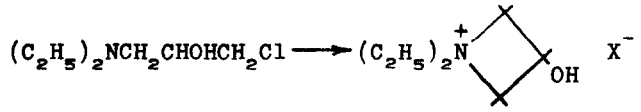
We have found that a monocyclic azetidinium salt alkylates a variety of nucleophiles, reacting with ring scission to relieve strain present in the four-membered cycle. Related equilibria reveal a "cater-cornered" 1,3 steric effect.

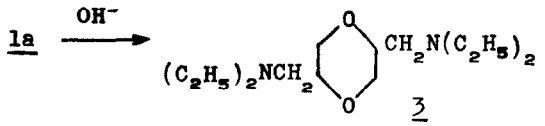
Although the more highly strained aziridines and, especially, quaternary aziridinium salts (1) are powerful alkylating agents, certain complex azetidinium compounds have only recently been shown to act in this manner and the examples involved bicyclic (2) or tricyclic (3) systems with bridgehead quaternary members, leaving unsettled the question of the reactivity of the simpler monocycles (4). The parent azetidines lack alkylating properties (5). The only report concerning a monocyclic azetidinium salt listed the failure of 1,1-diethylazetidinium salts to react with cysteine under mild physiological conditions (6).

Our interest in the spontaneous cyclization of 1-alkylamino-3-chloro-2-propanols to 1-alkyl-3-azetidinol hydrochlorides (7) led to a study of 1,1-diethyl-3-hydroxyazetidinium salts (1). This cycle also forms spontaneously from 1-diethylamino-3-chloro-2-propanol (2) and the chloride (1a) is apparently stable (8, mp 154-155°). The structure (1a) assigned by Rothstein and



2 1a. Cl^- 1b. ClO_4^-

Binovic (8) has been controversial. In view of the conversion of 1a by alkali to a dioxane (3, 8) compounds such as 1a were considered subsequently (9) to be simply 3 dihydrochlorides.



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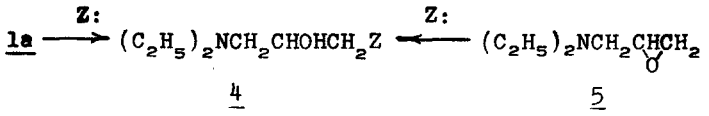
However, recent physical evidence (10) supported the original structure. In the present work, structure 1 is established unequivocally and the transformation of 1a to 3 - the only reaction of 1 which has been reported - is rationalized.

The alkylation of good nucleophiles (Z:) by 1 is general Thus 1a reacted smoothly with sodium methoxide (CH_3OH, 65°, 75% yield), sodium t-butylmercaptide (H_2O, 100°, 83%), diethylamine (H_2O, 100°, 95%), N-methylaniline (CH_3OH, 100°, 99%), sodium phenoxide (H_2O, 100°, 90%), and potassium cyanide (H_2O, 50°, 74%) to give compounds of type 4.≠ That the structures



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were in fact those expected of ring opening (and that structure 1a is correct) was evident from their identity≠≠ with the products obtained from diethylglycidylamine (5) and the same reagents by usual methods. These reactions of 1a gave 4 containing no detectable isomers.

≠ Yields and conditions were not optimized; excess Z: (2:1) was usually employed in a small stainless steel bomb.

≠≠ Confirmed by both infrared and nmr spectra, and by usual analytical and physical data.

Indeed, the formation of 1a from 2 proved to be reversible, an example of alkylation of halide ions (11). From 1a at 140-150°/1 mm, 2 distilled in very pure form (mp 1-3°) and at least 95% yield. By titration of 1a with silver perchlorate (12) in acetonitrile (AN), or with the nitrate in water, the chlorine was completely ionic, and 1a is stable in these solvents at 25°. No 2 was detected although a trace (< 0.5%) is probably present. When a 1.00 M AN solution of either 1a or pure 2 was heated at 60°, the final concentrations were: 0.83 M 1a, 0.17 M 2. Thus the system, 1a⇌2, constituted a reversible equilibrium with $K_{eq}^{60°}$ = 0.25 in AN. The cyclization of 2 in AN followed first order kinetics with $k_1^{25.0°}$ = 2.65 (± 0.03)X 10^{-5} sec^{-1}, through at least 40% reaction.

In contrast, 2 acetate ester cyclized very sluggishly (neat: <5%, 11 days/60°; 2 M in AN, <8%, 3 days/60°). When 1 M 1a was acetylated (acetic anhydride in AN, 3 days/25°) partial ring scission occurred. The solution contained 48% 1a acetate and about 52% 2 acetate; the latter was the only non-ionic product formed.

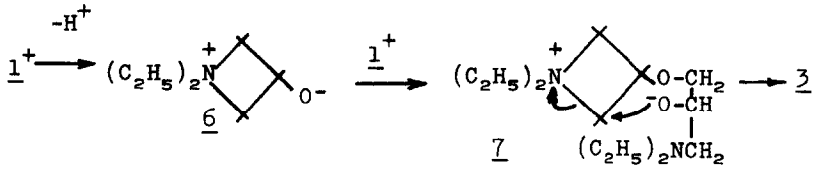
These data established that the 1,1-diethyl-3-hydroxy-azetidinium cation is more stable than is the corresponding 3-acetate ester, each with respect to its open precursor. Examination of the models suggests that in the cycles themselves, and in the transition states for cyclization/scission, there is steric interference between an N-alkyl group and a large substituent in the 3 position, i.e., a ring destabilizing "cater-cornered" 1,3 steric effect. This hypothesis is an extension to reversible reactions of a recently described effect in irreversible cyclizations to form 1-alkyl-3-azetidinols (7).

The question as to whether opening to 2, and dehydrohalo-

genation of 2 to 5, accounts for the alkylations of 1a was answered negatively, using the perchlorate, 1b (mp 181-183°). With excess sodium methoxide (CH_3OH, 60°) 1b gave the corresponding 4 (74%). Clearly, however, there is no reason to expect chloride to compete effectively for 1 with the better nucleophiles.

In the reactions of both 1a and 1b with methoxide a higher-boiling by-product (7% and 5%, respectively) was identified as 3, also obtained from 1b and aqueous potassium hydroxide (16%). The latter finding militates against an earlier explanation (9) for the formation of 3 which did not involve 1a as an intermediate.

We suggest that 3 is formed by two consecutive azetidinium alkylations:



A good base converts 1 cation to 1 zwitterion (6) which - as an alkoxide - is alkylated by a second 1 cation to give zwitterion 7; 7 then undergoes intramolecular alkylation to give 3.

Alkylations of good nucleophiles by 1 are undoubtedly S_N2 in type, as are similar reactions of aziridinium cations (1). However, in contrast to the facile methanolysis at 65° of the latter (considered S_N1, 1), 1b at 100°/6 hrs. gave only 2% of the 4. Also, Leonard (1) and his students have shown that halides add rapidly to aziridinium cations; accordingly, β-halo amines do not cyclize appreciably but require the assistance of poorly nucleophilic silver salts to form isolable yields of the cyclic salts.

In summary, this simple four-membered azetidinium monocycle exhibits the minimum ring strain which promotes S_N2 (and not S_N1)

alkylative ring scission but still allows complete spontaneous cyclization of the halo amine intermediate, subject to the 1, 3 steric effect. The resulting moderate reactivity of azetidinium salts implies that they may be selective alkylating agents. A continuing study of the formation and reactions of 1 and related cations will be reported in detail later.

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12. The writer gratefully acknowledges the kindness of Prof. N. J. Leonard and D. A. Durand in supplying unpublished directions for the closure of a γ-chloroalkylamine to an azetidine with this reagent. In the present work, potentiometric titrimetry (glass/silver electrodes) easily determined 1a (instantaneous) in the presence of 2 (slow) in AN; 1a acetate ester was determined similarly, 2 acetate being unreactive.