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CYCLIZATION OF 1-ALKYLAMINO-3-HALO-2-ALKANOLS TO 1-ALKYL-3-AZETIDINOLS

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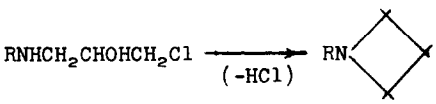
We describe here a simple two-step synthesis of 1-alkyl-3-azetidinols, whereby this new series becomes the most readily prepared class of azetidines. The method points to a general conversion of complex primary amines to 3-azetidinols, as well as providing an entree into the 3-substituted azetidines. The four-membered trimethyleneimine ring is considered to be the most difficultly closed of the simple nitrogen heterocycles (1).

The unstable intermediates, 1-alkylamino-3-chloro-2-propanols (1), obtained from primary amines and epichlorohydrin (2), spontaneously cyclized to 1-alkyl-3-azetidinol (2) hydrochlorides.



1 2

a. cyclohexyl
b. t-butyl
c. 1,1,3,3-tetramethylbutyl
d. 2-propyl
e. neopentyl

In favorable cases, pure crystalline 1 were isolated and cyclized in good yields. Thus, 1-chloro-3-cyclohexylamino-2-propanol (1a, 3), 19.2 g. in 20 g. of DMSO, heated at 40° six days, the partially crystallized mixture treated with aqueous alkali and extracted with ether, and the solid crystallized from hexane, gave 1-cyclohexyl-3-azetidinol (2a, mp 79-80°; 55% yield).

1-t-Butylamino-3-chloro-2-propanol (1b, isolated by rapid distillation of crude 1b (2) in up to 53% yield; crystallized from hexane, mp 42-43°), heated either neat or in DMSO at 50°, gave either 62% or 54% yield, respectively, of 1-t-butyl-3-azetidinol (2b; mp 45-46°; hygroscopic), also isolated from the still residue of 1b. Similarly, from 1,1,3,3-tetramethylbutylamine, neat distilled 1c, although not obtained in pure form (mp 27-30°), was cyclized at 50-60° to 2c (mp 52-53°) in up to 68% yield.

Since attempted purification of 1 often leads to extensive decomposition, the isolations were obviated by condensation of the primary amine with equimolar epichlorohydrin at 20-25° in DMSO or methanol for one or more days (2), followed by closure of 1 in situ, usually at 40-50° for 5-10 days. After extraction, vacuum distillation of the crude 2 expedited crystallization.

By this method, 1-t-butyl-(2b), 1-(1,1,3,3-tetramethylbutyl)-(2c), 1-isopropyl (2d, mp 57-58°), and 1-neopentyl-3-azetidinols (2e, bp 55-56°/0.3 mm) were prepared, 2b, 2c, and 2e in 20-35% yields. Epibromohydrin also served, without advantage, in the preparations of 2a, 2b, and 2c. From 3-bromo-1,2-epoxybutane and t-butylamine was synthesized 1-t-butyl-2-methyl-3-azetidinol (bp 65-68°/0.7 mm, two dl pairs from which one, mp 83-84°, crystallized).

The nmr spectra of 2* - of which the simplest was that of 2b-

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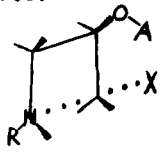
* Measured on approx. 50% w/w solutions in $CDCl_3$ with internal TMS; tau values are listed. The other 2 had closely related spectra as did the acetate ester of 2c (no OH; acetate, 7.98, 3 H). All 2 exhibited broad hydrogen-bonded hydroxyl absorption in the infrared at 3.0μ (neat, supercooled melts). Elemental analyses, amine neutralization equivalents, molecular weights, and other data also supported the structural assignments.

were consistent only with the 3-azetidinol structures. The spectrum for 2b exhibited triplets (6.68, 6.93, 2 H each, J = 6.5, by first order analysis), for the two H_α and the two H_β of the ring methylenes; a one-proton multiplet (5.59) for the hydrogen alpha to the hydroxyl group (3.19, 1 H); and the t-butyl singlet (9.03, 9 H).

The facility of these cyclizations, compared to those of other γ-haloalkylamines (1), was further studied by "blocking" the hydroxyl group. Selective acetylation (acetic anhydride, 0-5°, ether) yielded the 1b ester, which in DMSO (5 days, 50°) gave an ester mixture containing 30% of 2b acetate. The acetate of 1c, however, closed sluggishly and gave only 14% of 2c acetate.

Consideration of the transition state for cyclization (3, 4), with eclipsed RNH-,-CH_2X groups, suggests that a bulky R favors closure (1,4) mainly by suppressing intermolecular reactions. From the resistance of 1c acetate to cyclization, it appears that a very large R, when combined with a sizable A, retards cyclization by favoring the trans over the gauche RNH-, (OA)CH_2X conformations, reducing the average linearity in the reacting triad, N...C...X, required for closure. These cyclizations involve displacement of halide from vic-halohydrins by amino nitrogen without the intermediacy of the epoxide. The failure of glycidylamines to cyclize directly (2) is rationalized in terms of the non-linearity of the grouping N...C...O in the analogous transition state.



The synthesis and chemistry of this novel class (5) are under continuing study.

References.

(1) See, for a review, J. A. Moore, in A. Weissberger, ed., Heterocyclic Compounds with Three- and Four-Membered Rings, Part Two, Interscience Publ., New York, 1964, pp 885-977. Functionally ring-substituted azetidines have been rare.

(2) V. R. Gaertner, Tetrahedron Letters, No. 3, 141 (1964), and references therein. Note also that 1 with alkalies gave 2,3-epoxypropylamines, thus ruling out the alkaline Gabriel conditions of the azetidine synthesis from γ-haloamines (1). The glycidylamines did not cyclize directly (vide infra) but dimerized; the dimers cyclized to 1,5-diazacyclooctanediols.

Messrs. L. S. Luskin and A. J. McFaull of the Rohm and Haas Co. (see ref. 2 of the above Letter) independently isolated and distilled liquid 1b. They also isolated an oil, bp 90°/0.3 - 112°/1.2, from crude 1c with alkali. From analytical and infrared data ("bonded hydroxyl (or NH)"), they speculated that the oil was "either a 2-hydroxymethylazirane or the 3-hydroxyazetidine", but they did not plan to pursue these preliminary findings.

(3) J. B. McKelvey, B. G. Webre, and E. Klein, J. Org. Chem., 24, 614 (1959).

(4) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, ibid., 26, 138 (1961), discussed, generally, conformational factors in cyclizations to form azetidines.

(5) R. A. Clasen and S. Searles, Jr., Chem. Comm., No. 10, 289 (1966), recently described the photochemical cyclization of phenacylamines to 3-phenyl-3-azetidinols.