Azabicyclic Urethane Rearrangements. I. A Novel Route to Substituted Azabicyclo[3.2.1]oct-2-enes.

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Although a number of general synthetic routes to 6-azabicyclo[3.2.1]octanes 1 have been developed, $^{1-3}$ none is particularly well-suited for the synthesis of derivatives with a substituent on the two-membered bridge adjacent to nitrogen. We here describe a novel synthetic route from readily available⁴ 2-azabicyclo[2.2.2]oct-5-ene 2 to the 7-azabicyclo-[3.2.1]oct-2-ene ring system 3, and an extension of this reaction to the synthesis of 6-aryl derivatives $\frac{4-5}{2}$.



In a typical run a solution of N-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene $\frac{2a}{\sqrt{2}}$ (1.8 g) and toluene sulfonic acid monohydrate (1.9 g) was refluxed in benzene (100 ml) containing water (500 mg) to effect rearrangement to $\frac{3}{2}$.⁵ After three hours, workup and distillation afforded 450 mg (25%) of an oil, bp 64-65° (0.15 mm). Preparative vpc (5m, 2% XF1150 on 60/80 Chrom W, 135°) afforded $\frac{2a}{2}$ (4%, RT 11 min) and $\frac{3}{2}$ (96%, RT 13 min). Chemical shifts and major coupling constants of $\frac{3}{2}$ (δ , CDCl₃) are: 6.02 (H₂), 5.54 (H₃, J_{2,3} = 9.2 Hz), 4.24 (H₁, J_{1,2} = 6 Hz), 4.08 (OCH₂), 3.55 (H_{6x}, J_{5,6x} = 5.5 Hz), 3.21 (H_{6n}, J_{6x,6n} = 11 Hz), 2.57 (H₅), 2.50 and 2.06 (H₄ and H₄; ; J_{4,4}, = 20 Hz, J_{4,4}, with H_{2,3,5} of 2-3 Hz), 1.76 (H_{7,8}), 1.22 (Me).



Similarly, separate solutions of either 83:17 or 90:10 <u>exo-endo</u> mixtures of 3-phenyl-Ncarbethoxy-2-azabicyclo[2.2,2]oct-5-ene 2b afforded diphenylmethane (10%), small amounts of urethane and benzylurethane, and 18-25% yields of an oil, bp 130° (0.3 mm), which was separated by vpc (vide supra, 190°) into 2b (10-15%, RT 15 min), and a mixture of stereoisomers 4 (25-30%), RT 17 min) and 5 (55-65%, RT 20 min). Chemical shifts and major coupling constants for the <u>endo-phenyl</u> isomer 4 (6, acetone-d₆) are: 7.20-7.24 (Ph), 6.08 (H₂), 5.40 (H₃, $J_{2,3} = 9.0$ Hz), 5.06 (H_{6x}, doublet, $J_{5,6} = 5.7$ Hz), 4.44 (H₁, $J_{1,2} = 6.0$ Hz), 3.92 (OCH₂), 2.72 (H₅), 2.5-1.9 (H_{4,4},), 2.06 (H₈, $J_{1,8} = 4.0$ Hz), 1.88 (H₇, $J_{7,8} = 11$ Hz), 0.88 or 1.2 (CH₃). For the <u>exo-phenyl</u> isomer 5 the shift parameters are: 7.20-7.24 (Ph), 6.24 (H₂), 5.52 (H₃, $J_{2,3} = 9.0$ Hz) 4.68 (H_{6n}, singlet), 4.30 (H₁, $J_{1,2} = 5.5$ Hz), 3.92 (OCH₂), 2.48 (H₅), 2.50-1.90 (H_{4,4},), 2.18 (H₈, $J_{1,8} = 4.5$ Hz), 1.60 (H₇, $J_{7,8} = 11$ Hz), 0.88 or 1.2 (CH₃).

The stereochemical assignment and determination of isomer ratios follow from the resonance for H_{6n} of the <u>exo</u>-phenyl isomer 5, which because of the 90° dihedral angle with the adjacent bridgehead hydrogen appears only as a singlet, whereas in the <u>exo</u>-phenyl isomer 4, H_{6x} couples to the bridgehead hydrogen and appears as a doublet, $J_{6n,5} = 5.7$ Hz). Reactions were generally terminated when most of the starting olefin 2b had rearranged. Longer reaction times led to decreasing amounts of 2b, but also to disappearance of 4 and 5 via degradation to urethane, diphenylmethane, and unidentified polymeric material. When reaction was 50% complete, recovered 2b was not epimerized, indicating epimerization of phenyl does not precede isomerization. Variations in the relative amounts of 4 and 5 are an apparent result of moderate sensitivity to minor differences in reagent concentrations and reaction times. The observed reaction products are consistent with a mechanism for rearrangement of $\frac{2b}{2b}$ (<u>exo-Ph</u>) shown in Scheme I. Initial protonation of the urethane results in ring-opening to cyclohexenyl cation §. In the presence of water, the cyclohexenyl cation § can isomerize to χ by a path involving proton loss and reprotonation.⁷ Allylic cation intermediate χ can be attacked by urethane nitrogen at either of two positions to give <u>endo-phenyl</u> adduct 4 (path a) or <u>exo-phenyl</u> adduct 5 (path b). Since the same intermediate χ will derive from the <u>endo-</u> phenyl isomer of χ , this mechanism accounts for the observation that product stereochemistry shows no apparent relationship to the stereochemistry of starting olefin χ . In addition, it can be readily shown that cyclohexenyl cation § is a rational precursor for the formation of benzylurethane, urethane, and diphenylmethane (Scheme II).





2177



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