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THE CHEMISTRY OF HINDERED SYSTEMS: THE STEREOSPECIFIC REARRANGEMENT OF A TRANS AZACYCLOHEPTANE-4,5-DIOL

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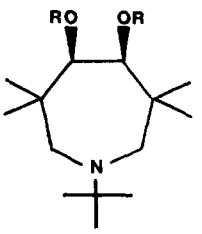
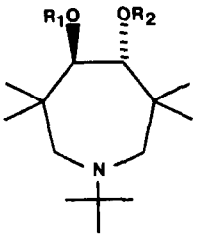
As part of our synthetic work on hindered amines as potential anticancer agents[1], we wished to derivatize cis (meso) and trans (d,l)[2] diols 1 and 2 as their respective diacetates 3 and 4. While diol 1 was readily converted to its diacetate 3 in near quantitative yield upon treatment with refluxing acetic acid-acetic anhydride for 3 hours, diol 2 was converted instead to a sin-

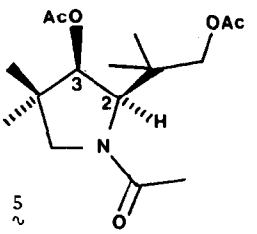


1, R=H
3, R=Ac



2, $R_1=R_2=H$
4, $R_1=R_2=Ac$
7, $R_1=H, R_2=Ac$

gle product which displayed no tert-butyl singlet in its ^1H NMR spectra but rather showed four singlets (3H each) near 1.0 δ and three singlets (3H each) near 2.0 δ. This unexpected product was identified by its spectra as ring contracted amide 5 (ir($CHCl_3$)1730 and 1648 cm^{-1}; mass spectrum m/e 313 (M^+)). The ^{13}C NMR spectra of 5 showed that only one diastereomer was present. The 6 Hz coupling constant observed for the vicinal protons at C-2 and C-3, which occur as doublets at 4.24 and 5.25 δ respectively, indicated a cis relationship[3] for these protons and the large downfield shift observed for the C-2 proton in 5 relative to the equivalent proton in amine 6 (see below) indicated an E conformation for the amide group as shown.



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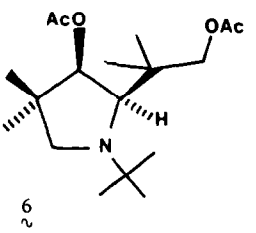

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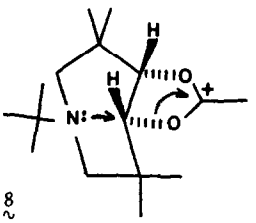
In order to better understand this unusual reaction, a series of experiments were carried out in order to identify the rearranging species. When diol 2 was heated at 80° or 140° for 1 hour in acetic acid, no reaction was observed and trans diol was recovered in high yield. Unlike diol 2, trans-monoacetate 7 (mp 65-66°), which was synthesized independently by treating 2 with one equivalent of acetic anhydride in pyridine at 25° and purified by column chromatography, was converted to amine 6 in 60% yield when heated in acetic acid at 80-90° for 1 hour. When 2 was heated in various mixtures of acetic acid-acetic anhydride for 1 hour at 80-90°, however, variable mixtures of desired trans-diacetate 2 (mp 79-82°) and ring contracted amine 6 were isolated, the latter usually being the major product. Only small amounts of amide 5 were isolated under these mild conditions. Amines 2, 7, and 6 were all converted to amide 5, however, when heated for several hr (> 140°) in acetic acid-acetic anhydride. The fact that seven membered ring amides were not obtained from these reactions tends to indicate that the loss of the tert-butyl group occurs only after rearrangement to the five membered ring.

A rationale which is consistent with the data presented for these transformations, including stereochemistry, involves formation of monoacetate 7 from 2 and its subsequent loss of water with backside participation by the acetate carbonyl group to give cis oxonium ion 8.



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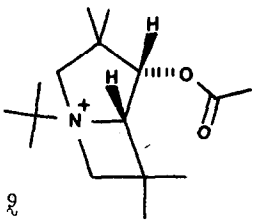

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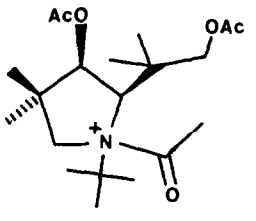

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Intramolecular opening of the cyclic oxonium ion by nitrogen would lead to a four membered ring intermediate 9 which would be expected to solvolyze to 6 in acetic acid.

Finally, formation of amide 5 from amine 6 is believed to involve loss of isobutylene from acylammonium ion 10 which is formed at the higher reaction temperatures.

Further studies on the scope and mechanism of this type of doubly anchimerically assisted stereospecific rearrangement are in progress.

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References

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