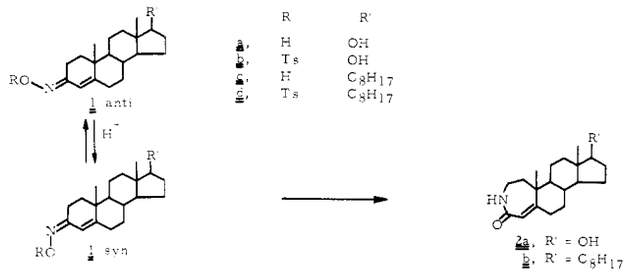
Communications

Regiospecific Beckmann Rearrangement of 3-Oxo-4-ene Steroid Oximes

Summary: Improved regiospecific Beckmann rearrangement of oxime *p*-toluenesulfonates of testosterone, cholestenone, 4-cholestene-3,6-dione, and 17,17-ethylenedioxy-19-hydroxy-4-androsten-3-one to afford 3-aza-*A*-homo steroids is described.

Sir: In the field of steroids, there is a serious drawback to using the Beckmann rearrangement and the Schmidt reaction in that they produce a mixture of both possible regioisomers.[1-3] Many Beckmann rearrangements of 3-oxo-4-ene steroid oximes (isomeric mixtures) have been carried out using thionyl chloride in nonpolar solvents with the yields of 3-aza lactams being slightly higher than might be expected from the percentage of syn isomer in the starting material.[4] Oximes which consist predominantly of the anti isomer seem to resist rearrangement under these reaction conditions.[5,6] Some other experimental approaches have been reported,[7-9] but none of them are entirely satisfactory. Our present paper deals with a new method which involves fast geometrical isomerization between syn and anti oxime *p*-toluenesulfonates in polar solvents and preferential rearrangement of the syn isomers to 3-aza lactams.

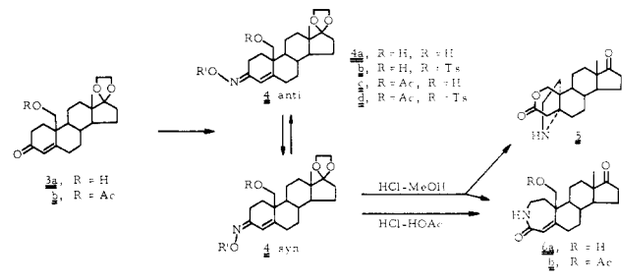
Testosterone oxime (**1a**) prepared in the usual manner consists of 33% syn isomer and 67% anti isomer.[10] The pure,



isolated isomers are stable in nonpolar solvents, but undergo rapid isomerization to the equilibrium mixture when exposed to polar solvents containing hydrogen chloride. When the oxime mixture was dissolved in chloroform containing 2 molar equiv of *p*-toluenesulfonyl chloride and treated with 15% sodium hydroxide solution, the hydroxyimino group was sulfonylated specifically while the 17-hydroxyl was not attacked. The ratio of geometrical isomers of **1b** was the same as that of starting oxime **1a.** This material was dissolved in methanol and then treated with concentrated hydrochloric acid at 50 °C for 30 min to give the 3-aza lactam **2a** in high yield, mp 293–295 °C (lit.[9] 282–285 °C). In one experiment where the pure geometrical isomers were used, we observed that the syn isomer rearranged smoothly at room temperature while the anti isomer required higher temperatures to complete the rearrangement, each isomer affording **2a** in 85–90% yields. These results clearly show the efficiency of the isomerization where the rate of vinyl migration of the anti isomer is very slow compared with alkyl migration of the syn isomer.

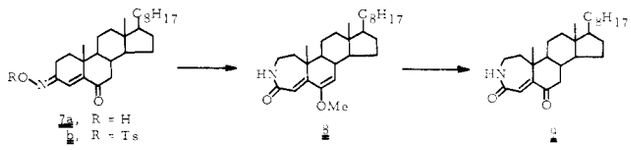
Almost the same results were obtained with the cholestenone oxime mixture **1c** (25% syn and 75% anti), which yielded **2b** in 87% yield, mp 251–253 °C (lit.[4e] 250–254 °C).

In the case of 19-hydroxy analogue **4,** the reaction is somewhat more complex. The *p*-toluenesulfonate **4b,** prepared from oxime mixture **4a** (mp 208–210 °C; 25% syn and 75% anti), on treatment with hydrogen chloride in methanol at 50 °C for 2 h gave the amino lactone **5** in 65% yield, mp 171–172 °C, and the desired 3-aza lactam **6a** in 18% yield, mp 115–118 °C. The formation of **5** can be explained in terms of an intramolecular rearrangement induced by 19-hydroxyl participation. When the tosylate mixture **4d** was treated with 1% hy-



drogen chloride in acetic acid at 60 °C for 30 min, the acetoxy lactam **6b** was obtained in 85% yield, mp 202–203 °C. Hydrolysis of this compound in methanol with potassium hydroxide at room temperature gave the hydroxy lactam **6a** and acetylation of **6a** gave the acetoxy lactam **6b.** The hydroxy tosylate mixture **4b** gave similar results when the reaction was carried out in acetic acid; apparently acetylation of the 19-hydroxy group precedes the Beckmann rearrangement.

4-Cholestene-3,6-dione was also subjected to the specific rearrangement. Monooxime **7a,** prepared from the dione by



treatment with 1 molar equiv of hydroxylamine, consists predominantly of the anti isomer (100% after one recrystallization to remove a small amount of 6-oxime). It has been reported that this oxime did not undergo Beckmann rearrangement by the known method.[5] However, exposure of **7b** to methanol containing hydrochloric acid afforded only the 3-aza lactam enol ether **8** in 86% yield. Subsequent hydrolysis by hydrochloric acid in 2-propanol afforded 3-aza lactam **9** quantitatively, mp 211–214 °C (lit.[6] 213–215 °C).

These improved and simple procedures for the Beckmann rearrangement may afford a convenient method for the synthesis of salamander alkaloids,[3] especially cycloneosamandaridine.

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Supplementary Material Available: Experimental section describing rearrangement of **1a, 1c, 7a,** and **4b** (3 pages). Ordering information is given on any current masthead page.

References and Notes

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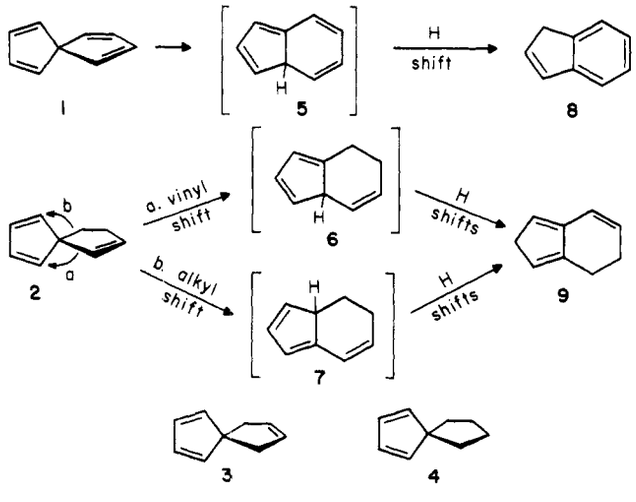
Rapid Vinyl Shifts in Spiro[4.4]polyenes: Verification of the Rate-Determining Step and the Identity of the Migrating Group.

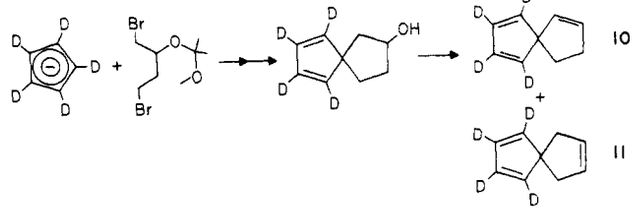
Summary: Pyrolysis studies of 1,2,3,4-tetradeuteriospiro[4.4]nona-1,3,6-triene (**10**) show that the 1,5-sigmatropic shift proceeds with negligible primary deuterium isotope effect, eliminating a rate-determining H shift in this multistep rearrangement. Pyrolysis of 1,2,3,4-tetramethylspiro[4.4]-nona-1,3,6-triene leads to specific vinyl migration, thereby establishing preferential vinyl as opposed to alkyl migration. The structure of the pyrolysis product was determined by an X-ray diffraction structure determination on a crystalline adduct with dimethyl 3,6-dicarboxy-1,2,4,5-tetraazabenzene; the adduct is the result of an unprecedented reaction of the tetrazine.

Sir: Migratory aptitudes in 1,5-sigmatropic shifts are presently not well understood. Examples suggest that sp^2-hybridized carbon migrates at an especially high rate compared to similar saturated carbon substituents.[1-3] This is particularly dramatic in rearrangements of 1,1-disubstituted cyclopentadiene derivatives.[1,2] We were first attracted to the question after observing high rates of unimolecular rearrangement for spiro[4.4]nonatetraene (**1**) and spiro[4.4]nona-1,3,6-triene (**2**) compared to spiro[4.4]nona-1,3,7-triene (**3**) and spiro[4.4]-nona-1,3-diene (**4**).[2] Using a picture in which the transition state for carbon shift in compounds **1-4** resembles a carbon unit migrating around a cyclopentadienyl radical, we[2] and others[1] have proposed that the rate enhancement ($\sim 10^4$ for **1**, 10^3 for **2**) is due to π^* (LUMO) of a migrating vinyl substituent interacting with the HOMO for the cyclopentadienyl unit.



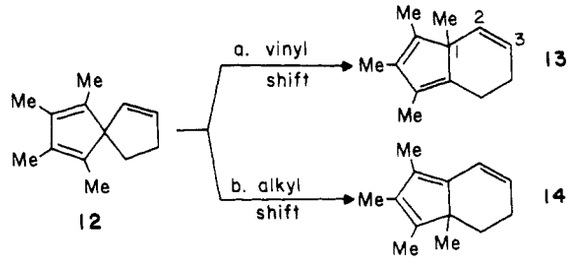
Experimental support of this mechanism has been lacking, however, due to the fact that the expected first products (**5**, **6**) from rearrangement of **1** and **2** have not been observed or trapped; presumably, they rearrange rapidly via 1,5-hydrogen shifts to the more stable (observed) isomers, **8** and **9**. This allows at least two alternate explanations for the high reactivity of **1** and **2**. First, it might be that the carbon shift (**1** → **5** and **2** → **6**) is fast and reversible and then the hydrogen shift is rate determining.[4] Second, it might be that the presence of a vinyl group facilitates the migration of the geminal substituent (vinyl for **1**, alkyl for **2**). With **2**, a vinyl shift would give **6** and a "vinyl-assisted" alkyl shift would give **7**; both products could reasonably produce the observed product, **9**, via hydrogen shifts. In the present work, we have focused on rearrangement of **2** and established that: (1) the hydrogen shift is *not* rate determining; and (2) the vinyl substituent *is* the migrating group.

Since deuterium isotope effects for 1,5-hydrogen shifts in substituted cyclopentadienes fall in the range k_H/k_D = 4.5-7.7,[5] a rate-determining hydrogen shift in the rearrangement of **2** would mean a substantially slower rate of rearrangement for the deuterium-labeled analogue **10**. Our synthesis[2] of **2** is not readily amenable to the preparation of **10**, so we developed a new approach via the reaction[7] of the cyclopentadienyl anion (perdeuterio[8]) with 1,4-dibromo-2-(1-methyl-1-methoxyethoxy)butane.[9] The initial adduct was converted (a. thionyl chloride; b. potassium *tert*-butoxide) to a mixture of 1,2,3,4-tetradeuteriospiro[4.4]nonatriene isomers **10** and **11** (92-93% deuterium incorporation by ^{1}H NMR analysis). The isomers were separated by GLC and



subjected to gas-phase pyrolysis, as described before.[2] The isomers **2** and **3** were pyrolyzed in a precisely parallel way. Comparing rearrangement of **2** and **10** at 95.7 °C showed k_H/k_D = 1.0 ± 0.1 (average of five runs). Comparing rearrangement of **3** and **11** at 158.2 °C showed k_H/k_D = 1.1 ± 0.2 (average of three runs). Therefore, the rate-determining step for rearrangement of **2** and **3** is not the hydrogen shift.

To support the idea that the vinyl group in **2** is migrating preferentially, we studied reactions of 1,2,3,4-tetramethylspiro[4.4]nona-1,3,6-triene (**12**). This analogue of **2**, prepared according to the method of Criegee,[10] can undergo either vinyl migration (to give **13**) or alkyl migration (to give **14**); isomerization via 1,5-hydrogen shift is not available, and the corresponding 1,5-methyl shift (in **13** or **14**) is expected to have a substantially higher activation barrier, perhaps 45 kcal/mol.[11]



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