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# SYNTHESIS APPLICATIONS OF AZA-COPE REARRANGEMENTS. STEREOCONTROLLED SYNTHESIS OF CYCLOHEPTA[b]PYRROLIDINES[1]

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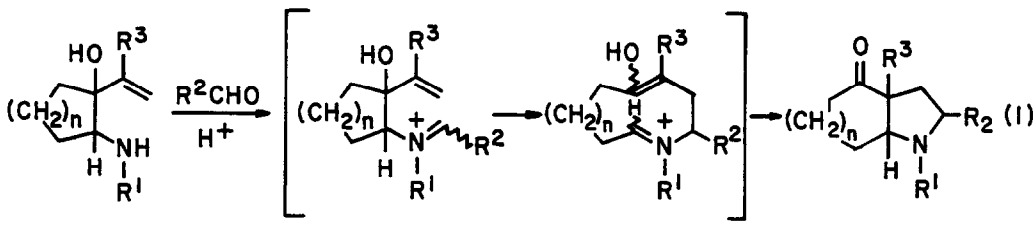
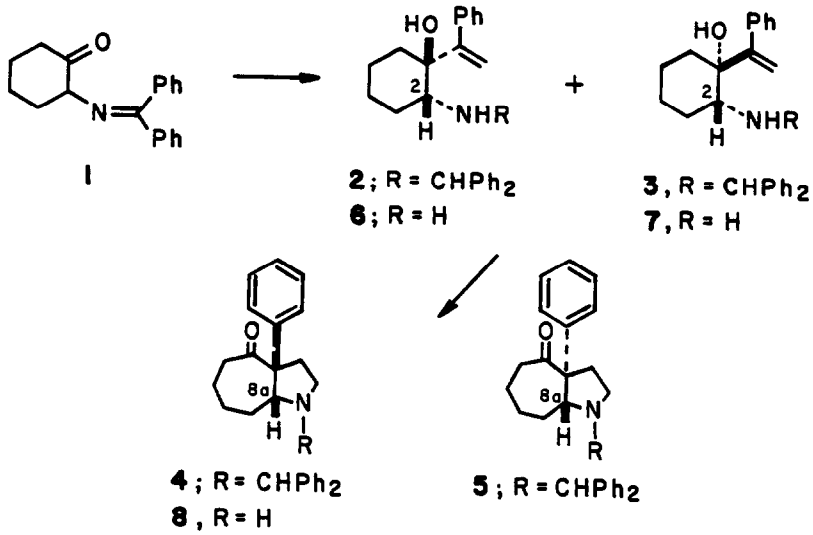
Summary: Both cis- and trans-3a-aryl-4-oxo-decahydrocyclohepta[b]pyrroles can be prepared in stereocontrolled fashions by the reaction of 2-amino-1-(1-phenylvinyl)cyclohexanols with formaldehyde and acid.

Recent papers from our laboratory have described the use of "Mannich-directed" cationic aza-Cope rearrangements for the preparation of octahydroindolones by an unusual ring-enlarging pyrrolidine annulation reaction (eq 1, n=1).[1,2] In this Letter, we report that the analogous rearrangement of cyclohexanols provides a convenient entry to cyclohepta[b]pyrrolidines (eq 1, n=2). This ring system,[3] although not common, is found in several natural products, for example, the antihypertensive alkaloid gelsemine.[4] We moreover report that the ring-fusion stereochemistry of the 3a-aryl-4-oxo-decahydrocyclohepta[b]pyrroles




prepared in this fashion can be rationally controlled by substituent and solvent effects.

The annulation reaction was initially explored with cyclohexanols 2 and 3, which were prepared as summarized in the Scheme. Addition of (1-phenylvinyl)-lithium[2] to iminocyclohexanone 1[5] (-78°C, THF), followed by reduction of this crude product with $NaCNBH_3$ in acidic methanol gave an 8:1 mixture of 2 and 3 (70% yield). Chromatography on silica gel gave pure samples of the crystalline major isomer 2[7] (50% yield; mp 78°C; $^1H$ NMR δ2.67 broad s, $C_2$-H) and the oily minor isomer 3[7] (2-10% yield; $^1H$ NMR δ 2.69, dd, J=10.7 and 4.4 Hz, $C_2$-H).

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**2**; R = $CHPh_2$
**6**; R = H

**3**, R = $CHPh_2$
**7**, R = H

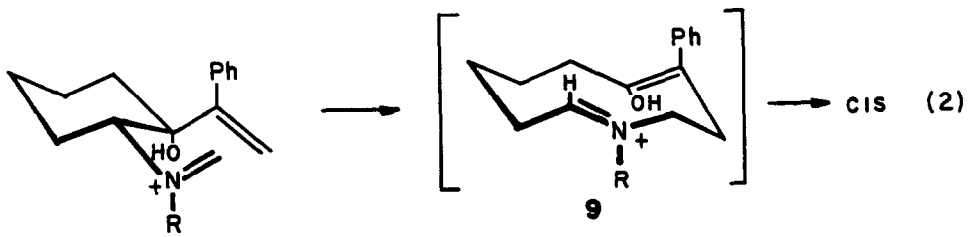
**4**; R = $CHPh_2$
**8**, R = H

**5**; R = $CHPh_2$

Stereochemical assignments followed from the clean axial nature of the $C_2$-H of 3, and by analogy with the cyclopentanol series[2] where preferential addition of lithium reagents from the side of the imine substituent had been established crystallographically.[8] Reaction of 3 with paraformaldehyde (1.0 equiv) and d-10-camphorsulfonic acid (0.9 equiv) in refluxing benzene for 22 h gave the crystalline cis-cycloheptapyrrolidine 4[7] (mp 122°C; IR 1706 $cm^{-1}$; $^1H$ NMR δ 4.78, s, C<u>H</u>$Ph_2$; 3.56, d, J=10.3 Hz, $C_{8a}$-H)[9] in >95% yield. The structure and stereochemistry of 4 were confirmed by single-crystal x-ray analysis.[10] Under identical conditions, cyclohexanol 2 rearranged to give a 3.5:1 mixture (94%) of trans-cycloheptapyrrolidine 5[11] (isolated in 41% yield after two recrystallizations, mp 135°C; IR 1696 $cm^{-1}$; $^1H$ NMR δ 5.28, s, C<u>H</u>$Ph_2$; 2.80, dd, J = 3.8 and 10.4 Hz, $C_{8a}$-H) and 4 respectively. The ratio of cis and trans cycloheptapyrrolidines formed from 2 at 80°C varied greatly with solvent:[12] 4:5 (solvent) - 1:1 (THF), 13:1 ($CH_3NO_2$), 24:1 (DMF), >30:1 (DMSO). Control experiments in benzene and DMSO established that the isomer ratios produced in these solvents reflected kinetic control in the rearrangement step. Rearrangement of 2 in DMSO at 80°C afforded crystalline cis-cycloheptapyrrolidine 4 in 75% yield.

The rearrangement was also examined with cyclohexanols 6 and 7, which were prepared (6:1 ratio and 65% yield) by sequential treatment of 1 with (1-phenylvinyl)lithium[2] and aqueous oxalic acid. Separation on silica gel gave pure samples of 6[7] (36% yield; mp 103°C; $^1H$ NMR δ 2.9, m, $C_{8a}$-H) and 7[7] (7% yield; mp 120°C; $^1H$ NMR δ 2.94, dd, J = 4.9 and 10.5 Hz, $C_{8a}$-H). In contrast to secondary amines 2 and 3, both 6 and 7 rearranged cleanly in refluxing benzene (>90% yield; 1.0 equiv paraformaldehyde, 0.9 equiv $RSO_3H$) to the cis-fused bicyclic 8. Cycloheptapyrrolidine 8[7] showed a characteristic doublet at δ 3.89 (J = 9.9 Hz, $C_{8a}$-H) in the 250 MHz $^1H$ NMR spectrum and could be prepared from cis-4 by hydrogenolysis (Pd/C, cyclohexene).

Cope rearrangements of both cis- and trans-1,2-divinylcyclohexanes are known to occur preferentially via chair transition states.[13,14] The formation of only the cis-fused cycloheptapyrrolidine from the reaction of both 3 and 7 with formaldehyde and acid is consistent[15] with a chair pericyclic process (eq 2) and the intermediacy of the trans,trans-1,5-azacyclodecadiene 9. The rearrangement

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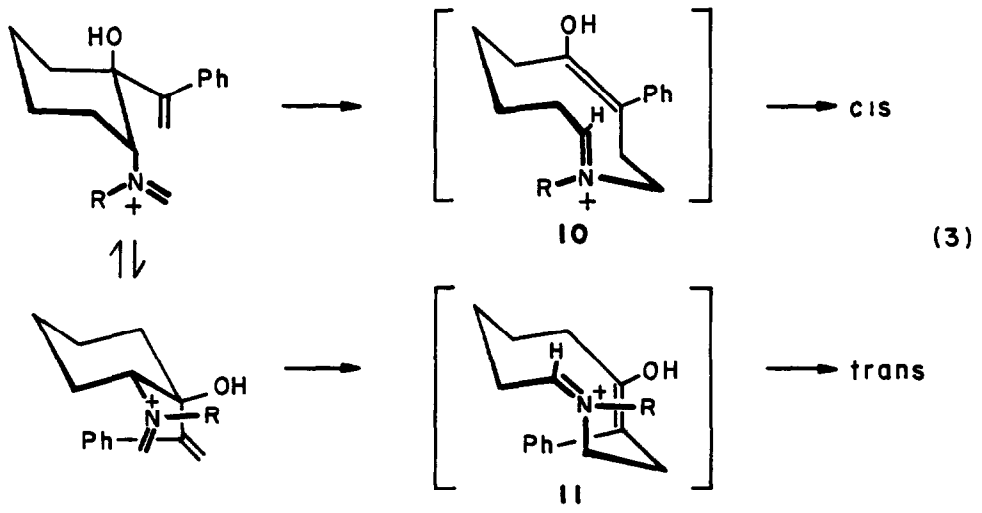
of iminium ions derived from cyclohexanols 2 and 6, which have cis-oriented amine and vinyl groups, is more complex, since two chair pericyclic transition states are possible (eq 3). The formation of only the cis-cycloheptapyrrolidine 8 from reaction of 6 is consistent[15] with the intermediacy of the cis,trans-1,5-azacyclodecadiene 10. This event is reasonable, since rearrangement in the alternate chair sense thrusts the bulky phenyl group under the cyclohexane ring. When the nitrogen substituent is the diphenylmethyl group, the two chair processes are more nearly balanced in energy, since destabilizing steric interactions with the Ph or $CHPh_2$ group are expected in either transition state. The preferential formation of the cis product from the rearrangement of 2 in DMSO may be rationalized by an effective increase in size of the OH group in DMSO,[16] and a resulting increase in the quasi 1,3-diaxial interaction of this group with the bulky R-substituent in the transition state leading to 11.



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References and Notes:

1. Part 8 in the series: For part 7, see preceding paper.

2. Overman, L.E.; Mendelson, L.T. J. Am. Chem. Soc. 1981, 103, 5579.

3. For syntheses of the parent ring system see: Prelog, V.; Geyer, U. Helv. Chim. Acta 1945, 28, 576. Ayerest, G.G.; Schofield, K. J. Chem. Soc. 1960, 3445.

4. Cf. Glasby, J.S. "Encyclopedia of the Alkaloids," Plenum: New York, 1975; Vol. 1, p 621.

5. mp 76-77°C. Prepared from trans-2-aminocyclohexanol by reaction with benzophenone (pTSOH catalyst) followed by Swern[6] oxidation.

6. Mancuso, A.J.; Huang, S.; Swern, D. J. Org. Chem. 1978, 43, 2480.

7. New compounds showed IR, 250 MHz $^{1}H$ NMR, 63 MHz $^{13}C$ NMR, and mass spectra consistent with their assigned structures, and had correct molecular compositions by high resolution mass spectral or combustion analysis.

8. Mendelson, L.T. Ph.D. Thesis, University of California, Irvine, 1981.

9. The doublet observed for this hydrogen$_{10}$ is consistent with the cycloheptane conformation found in the solid state.

10. For a single crystal of monoclinic symmetry, $P2_1/n$, with a = 16.514 (7), b = 16.410 (4), c = 17.563 (6) A, 2345 non-zero reflections were collected to 2θ (Mo) = 45°. R = 0.96 after final refinement with phenyl rings treated as rigid groups. Details will be published in a subsequent full account.

11. This sample contained ~ 10% of the cis-isomer 4.

12. Determined by integration of the $CHPh_2$ singlets at δ 4.85 and 5.28 in the 250 MHz $^{1}H$ NMR spectrum of crude reaction products.

13. Cf. Grob, C.A.; Link, H.; Scheiss, P.W. Helv. Chim. Acta 1963, 51, 483. Heimbach, P. Angew. Chem. Int. Ed. Engl. 1964, 3, 702.

14. Many related examples in the sesquiterpene area are summarized in: Rhoads, S.J., Raulins, N.R. Org. React. 1975, 22, 1.

15. This conclusion assumes that irreversible Mannich ring closure of an azacyclodecadiene would be more rapid than any loss of stereochemical integrity of this intermediate. All the results obtained to date are consistent with this view.

16. Cf. Gordon, J.; Ford, R.A. "The Chemist's Companion" John Wiley and Sons: New York; 1972; p 157.

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