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STEREOCHEMISTRY OF [1,3]ALKYL SIGMATROPIC SHIFT FROM NITROGEN TO CARBON AND ITS REVERSE IN CERTAIN NITROGEN HETEROCYCLES

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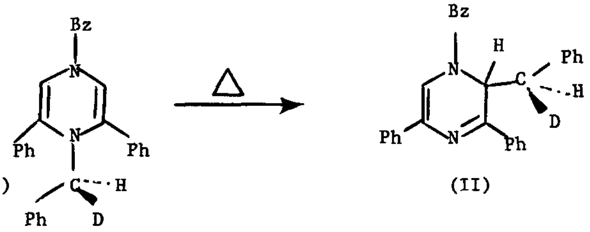
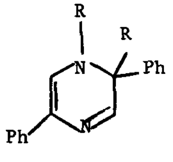
1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine (I) undergoes a stereospecific thermally induced suprafacial [1,3] sigmatropic benzyl shift with inversion of configuration to give the corresponding 1,2-dihydropyrazine (II).[1] In view of the sensitivity of [1,3] sigmatropic shifts to molecular environment [2] it was of interest to examine the stereochemistry of the corresponding rearrangement in 1,4-dihydro-2,5-diphenylpyrazines (III).[3] We report that the sequence of reactions between chiral 1,2-dihydropyrazines and dimethyl acetylenedicarboxylate [4] permits the establishment of the stereochemistry of [1,3] alkyl sigmatropic shifts in both directions (N→C and C→N). The method is illustrated in schemes 1 and 2. For the case of (IV) = (-)(R)-amphetamine,[5] (VIIIa) [with one [1,3] sigmatropic shift during its formation] upon thermolysis affords pyrrole (S)-(XIa) (100% yield) (required retention of configuration at position 1 of VIIa) and amide (S)-(XV) (100% yield) (82% overall retention for two successive [1,3] sigmatropic shifts) during preparation. reaction with dimethyl acetylenedicarboxylate and subsequent cleavage). The comparable result from (+)(S)-amphetamine corresponds to 82.5% overall retention in the double [1,3] sigmatropic shift.

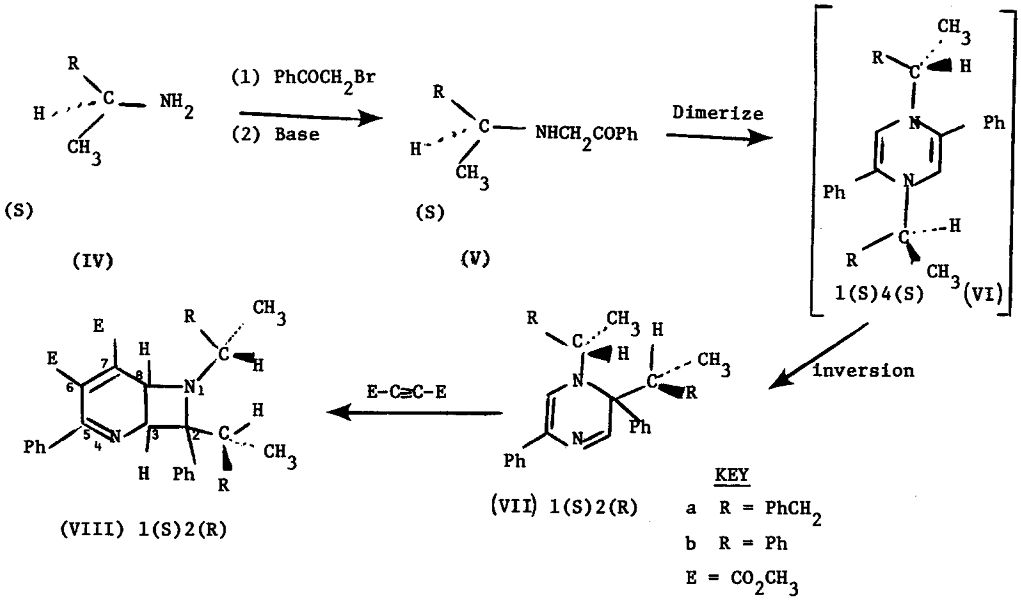
(I)



(II)



(III)



SCHEME 1

To decide between the possible allowed double suprafacial inversion or disallowed double suprafacial retention, key experiments were performed with chiral α-methylbenzylamines. In this instance (VIIIb) upon thermolysis afforded products (Xb) and (XIb) corresponding to the direct cleavage of (IX) and permitting the establishment of the stereochemistry of a single [1,3] alkyl shift (See Scheme 2). The stereochemical results are summarized in the table.

OPTICAL ACTIVITY OF PRODUCTS [6] FROM REACTION OF CHIRAL 1,2-DIHYDROPYRAZINES AND DIMETHYL ACETYLENEDICARBOXYLATE $[\alpha]_D^{25}$ (PhH)

General Structure	Chiral Amine			
	(−)(R)(IVa)[5]	(+)(S)(IVa)	(S)(−)(IVb)[8]	(R)(+)(IVb)
(VII)	-105.6	+108.8	-76.4	+72.8
(VIII)	-70.7	+ 74.3	-85.40	+88.9
(XI)[a]	- 77.8	+75.6	-57.25	+57.80
(XI)[b]	-	-	-59.80	—
(XV)[a]	+6.55(82%)[d]	- 6.85 (82.5%)[d]	-54.30[c]	+53.80[c]
(XV)[b]	+7.9	- 8.45	-55.5	+55.60
(X)			-21.85[e]	+20.95[e]
(X)			-22.40[f]	

a. Product from thermolysis

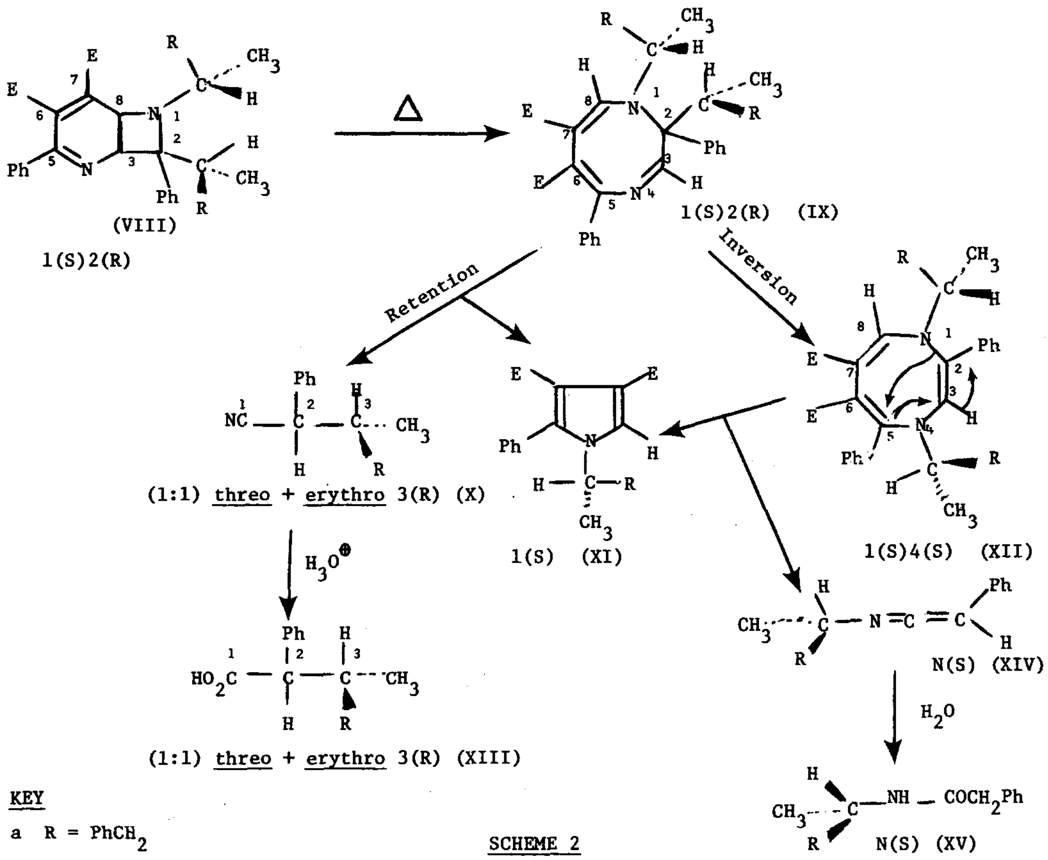
b. Authentic synthetic sample

c. Isolated in 2-3% yield

d. % overall retention

e. *erythro* diastereomer

f. Value in presence of scavenger nBuSH



KEY
a R = $PhCH_2$
b R = Ph
E = CO_2CH_3

SCHEME 2

The configuration of the known erythro (R)(-) 2,3-diphenylbutyronitrile ($[\alpha]_D^{26}$ - 24°, PhH) has been correlated with that of (R)(+) α-phenethyl chloride, by S_N2 inversion [7], which in turn has been correlated with both (R)(+) glyceraldehyde [8] and (S)(-) α-methylbenzylamine.[8] The purified erythro diastereomer m.p. 135° from (Xb) ($[\alpha]_D^{25}$ - 21.85, PhH), therefore corresponds to 91.3% overall inversion (i.e. a single inversion in the step (VIb) to (VIIb) and retention in the step (IXb) to (Xb). It follows that formation of (XV) in 82% overall retention corresponds to two successive N→C (VIa to VIIa) and C→N (IXa to XIIa) allowed suprafacial [1,3] sigmatropic shifts. The analogous [1,3] sigmatropic shift (I) to (II) exhibits a 12 ± 6% contribution from the radical dissociation recombination mechanism [1] which may account for the loss of 18% activity observed here. In fact thermolysis of (VIIIb) at a higher temperature produced some 2,3-diphenylbutane from α-methylbenzyl coupling in addition to (X) and (XIb). The present system should allow further insight into the general question of orbital symmetry [2] or least motion control [2d] in [1,3] shifts. To this end we are examining substituent electronic effects on the stereochemistry of these migrations induced both thermally and photochemically.[10]

References and Notes

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10. An alternative mechanism suggested by a referee for formation of (VIII) from (III) involving prior reversible formation of the symmetrical 1,4-dihydropyrazine, which then adds the acetylenic ester with subsequent valence tautomerism, [1,3] sigmatropic (N→C) shift and Cope rearrangement, may be ruled out since 6-d-(III) gives rise to selectively 8-labelled (VIII) only.[4] The symmetrical 1,4-dihydropyrazine would have given rise to label scrambling at the 3 and 8 positions of (VIII) and also in the cycloreversion products (XI) and (XIV).