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REACTIONS OF β-SUBSTITUTED AMINES—IV

KINETICS AND STEREOCHEMISTRY OF THE THERMAL TO (*R*)-3-CHLORO-1-ETHYLPIPERIDINE, AND THE STEREO-CHEMICAL COURSE OF THEIR REACTIONS WITH NUCLEOPHILES

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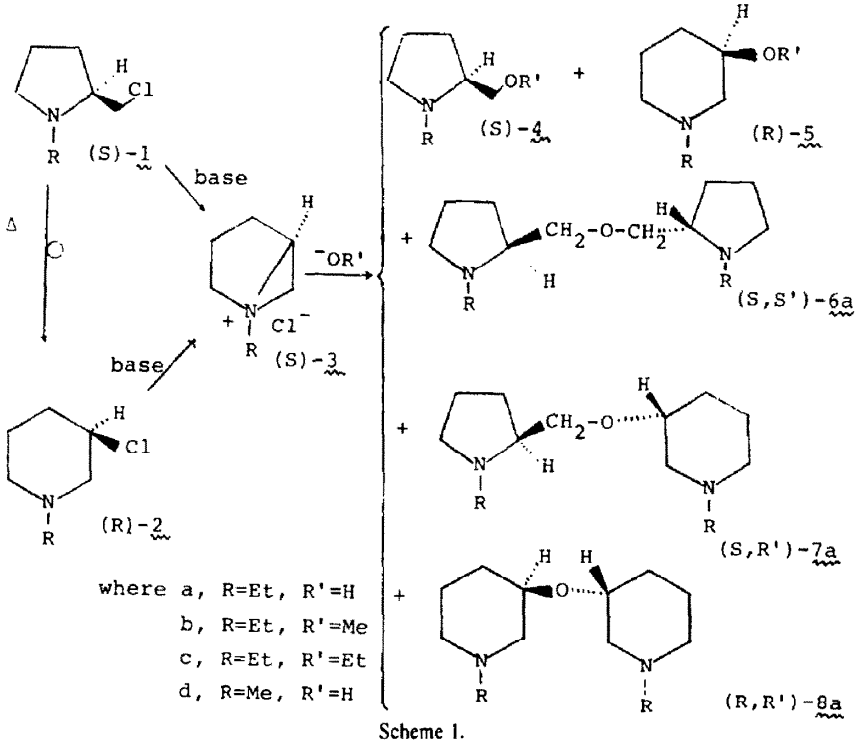
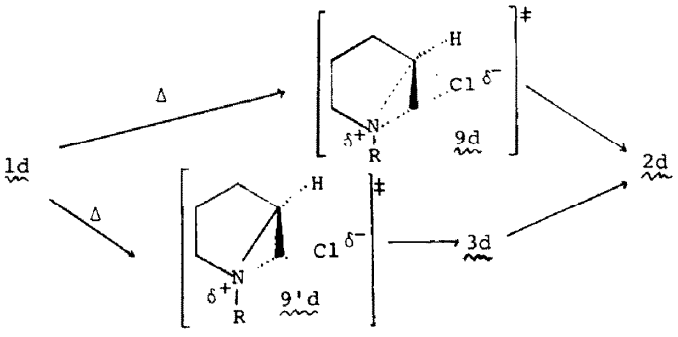
Abstract—The rate of the thermal rearrangement of (*S*)-2-chloromethyl-1-ethylpyrrolidine [(*S*)-**1a**] to (*R*)-3-chloro-1-ethylpiperidine [(*R*)-**2a**] has been examined at three temperatures in benzene by PMR and polarimetry. The rearrangement was shown to be completely stereospecific and to obey a simple first order rate law. The calculated E_a, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were 22 ± 2 kcal/mole (25°), 21 ± 2.5 kcal/mole (25°) and − 10 ± 2 e.u. (0°K) respectively. The effect of solvents having differing dielectric constants was also studied. A transition state **9'a** and an ion pair intermediate **3a** are suggested for the rearrangement. The stereochemical course of the reactions of (*S*)-**1a**, (*R*)-**2a** and (*S*)-**2a** with hydroxide and methoxide ions have been shown to be 100% stereospecific with an uncertainty of about 1%. The absolute configurations of all optically active reactants and products [(*S*)- and (*R*)-**4a**, (*S*)-**4b**, (*R*)- and (*S*)-**5a**, (*R*)-**5b**, (*S*, *S'*)-**6a**, (*S*, *R'*)-**7a** and (*R*, *R'*)-**8a**] were established by chemical correlations with known compounds or by ORD and chemical inference. The ring opening of both the primary and secondary aziridinium ion positions of 1-azonia-1-ethylbicyclo[3.1.0]hexane [(*S*)-**3a**] by nucleophiles proceeds entirely by S_N2 processes. The conversion of (*R*)-1-ethyl-3-hydroxypiperidine [(*R*)-**5a**] to (*S*)-**2a** · HCl with thionyl chloride in chloroform proceeds by inversion with 4.8% racemization, whereas the thermal rearrangement of (*S*)-**1a** to (*R*)-**2a** occurs with complete retention of absolute configuration.

The thermal rearrangement of 2-chloromethyl-1-ethylpyrrolidine (**1a**) to 3-chloro-1-ethylpiperidine (**2a**) first observed by Fuson and Zirkle[4] has been studied[1,5–8] (Scheme 1). The rearrangement of **1a** · HCl to **2a** · HCl by heating above the m.p. of **1a**·HCl is also well known.[1,4–8] We have reported previously[5–8] that this rearrangement of **1a** to **2a** and their reactions with nucleophiles had a stereospecificity of 98 ± 5%. The inaccuracy of these measurements left open the possibility that a portion of the reaction proceeded via a prior ring opening of the intermediate aziridinium ion **3a** to a secondary carbonium ion and subsequent reaction with a nucleophile to form the piperidine ring products **5** and **8**, as has been suggested by Leonard *et al.*[9] The thermal rearrangement of (*S*)-**1a** to (*R*)-**2a** was assumed to be stereospecific with retention of configuration, but the absolute configura-



Scheme 1.

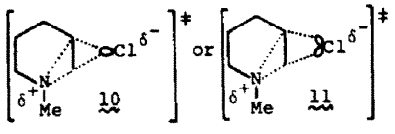


Scheme 2.

tion of the piperidines **2a**, **5a** and **5c** was undetermined.[5,6]

While Fuson and Zirkle[4] were unable to isolate **1a** from **1a**·HCl, Doyle *et al.*[10] successfully isolated **1d** from **1d**·HCl by treatment with cold sodium hydroxide. Doyle *et al.* also showed that **1d** was isomerized to 60% **2d** over a 2 hr period at 100° as a neat liquid, but rates of the rearrangement were not measured. They proposed the tricyclic transition state **9d** for the rearrangement as shown in Scheme 2.

They apparently did not favor an intermediate ion pair such as **9'd**→**3d** although the same intermediate (**3d**) was suggested for the reactions of **1d** or **2d** with nucleophiles. The chlorine atom of Doyle's proposed transition state **9d** could accomplish the desired 1,2-shift as a single orbital (**10**) or as two orbitals (**11**) as suggested by Craig:[11]



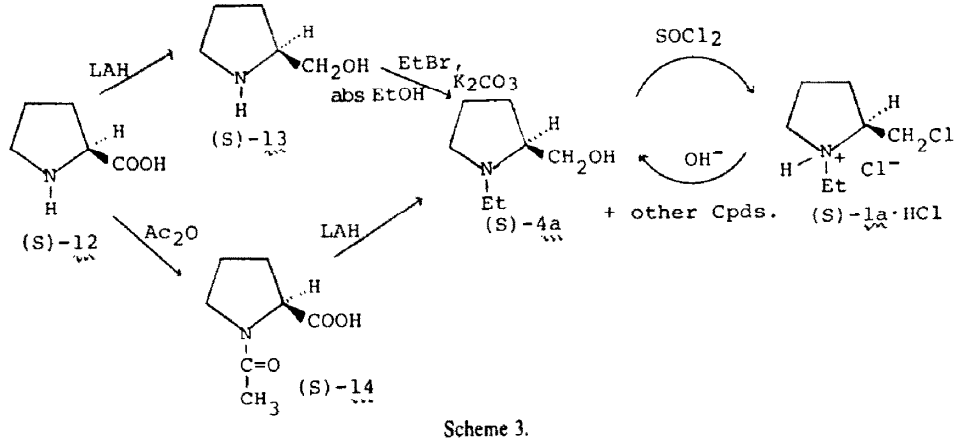
Any of these three representations (**9d**, **10** or **11**) for the transition state or an intermediate aziridinium ion pair (**9'**→**3**) would explain the retention of absolute stereochemistry that we report here.

Since our earlier reports,[5-7] we have discovered[1,8] three *bis*-β-aminoethers (**6a**, **7a** and **8a** in Scheme 1) as additional products of the reaction of **1a** or **2a** with hydroxide ion in water. We have also reported[11,12] that while **1a** is thermally isomerized to **2a** and the reactions of **1a** and **2a** follow clean first order kinetics to form the same intermediate aziridinium ion (**3a**), and **1a** proceeded directly to **3a** without prior isomerization to **2a**. The rate of loss of chloride ion from **1a**, which was four orders of magnitude faster than from **2a**, supported this conclusion. Since the product ratios changed drastically under near solvolytic conditions in 80% ethanol–water with no change in rate, a solvolysis mechanism was ruled out. Thus the high stereospecificity, the enhanced rate of the reaction of **2a** with hydroxide ion compared to cyclohexyl chloride, and the independence of the nucleophile used, supported a neighboring group participation mechanism ($S_Ni b$) in which **3a** is formed in the rate-determining step in all reactions of **1a** or **2a** with nucleophiles. Purification of all products was done very carefully because many 2-substituted methylpyrrolidine derivatives (except **4a**, **4b** and **4c**) thermally rearrange to the corresponding piperidine isomer.[6,7]

It has been found[11] that a stable cold benzene solution of **1a** can be prepared, thus making possible a complete kinetic study that could provide definitive information concerning the nature of this interesting rearrangement. This paper reports a detailed investigation of the absolute stereochemistries of both the reactants and all products as well as more accurate results (± 1%) on the stereospecificity of the reactions. In addition, the kinetics of the thermal rearrangement of (*S*)-**1a** to (*R*)-**2a** and the stereospecificity of the reactions of (*S*)-**4a** and (*R*)-**5a** with thionyl chloride to produce (*S*)-**1a**·HCl and (*S*)-**2a**·HCl respectively are reported.[13]

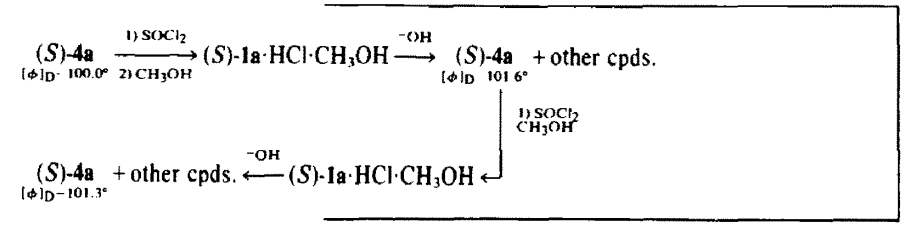
DISCUSSION AND RESULTS

L-Proline [(*S*)-**12**] was reduced with LAH[14] to (*S*)-2-hydroxymethylpyrrolidine [(*S*)-**13**], which was then ethylated to (*S*)-1-ethyl-2-hydroxymethylpyrrolidine [(*S*)-**4a**]. Alternately, (*S*)-**12** was acetylated to N-acetyl-L-proline [(*S*)-**14**] and reduced with LAH directly to (*S*)-**4a** (Scheme 3). While the absolute configuration of (*S*)-**4a**



Scheme 3.

can be assumed,[15] the optical purity is unknown because from batch to batch, a variable amount of racemization occurs during the acetylation[16] or reduction steps. Consequently, each sequence of reactions reported here was completed separately with a specific batch of **4a**. Reactions involving the pyrrolidine ring alcohol (*S*)-**4a** (shown below) are completely stereospecific within the experimental error (± 1%). This is proven by the fact that the



through 3.5 half life times and followed a perfect first order rate law.[12] These observations imply that an ion pair is formed in which Cl^- exchanges with any stronger nucleophile available in solution before attack by Cl^- can occur. In the present rearrangement, however, no other nucleophiles are present to exchange with Cl^- of the ion pair intermediate **3a**. Thus, either the more stable isomer **2a** results from attack by Cl^- on **3a** or the molecular rotation of the alcohol (*S*)-**4a** does not decrease after it has gone through the sequence ($CH_2OH \rightarrow CH_2 \rightarrow$ intermediate $\rightarrow CH_2OH$) twice.

The rate of rearrangement of **1a** in benzene was very slow at room temperature, with a half life of over 2 weeks. Addition of other solvents, however, had a marked influence on the rate as shown in Table 1. With a single solvent system, there is a direct relationship between the dielectric constant of the medium and the rate of the rearrangement. There is also a specific solvent effect, however, for when the solvent system is changed to 75/25 methylene chloride/benzene the rate is much greater, even through the dielectric constant is only 6.9 Debyes. In 75/25 chloroform/benzene (dielectric constant *ca* 4.0 Debyes) the rate is too rapid to measure by CW NMR at 30°. Hammer and Craig[12] found that the rearrangement of **1a** to **2a** in 80% aqueous ethanol (dielectric constant *ca* 34.1 Debyes) was slower than the rate of reaction of intermediate **3a** with base or solvent. Chloroform and methylene chloride are known[18] to solvate ions in organic solvents. This solvation may be more important in promoting the charge separation necessary to form **3a** than the dielectric constant of the medium. It is not possible to rank 80% aqueous ethanol in the above list of solvents because both solvolysis and nucleophilic displacement reactions are more rapid than the rearrangement in 80% ethanol. If rearrangement were competitive with the reaction of **1a** with base, the rate would become slower as the reaction proceeded. The rate of reaction of **1a** with base, however, remained constant reaction reverses to the less stable starting material **1a**. Moreover, the transition state **9'a** leading to the ion pair intermediate **3a**, and *not* the tricyclic transition state **9a** which was suggested by Doyle *et al.*,[10] is the reaction path best supported by these observations.

The kinetics of the rearrangement were studied in pure benzene at three temperatures so that the activation parameters could be determined. These data are shown in Table 2. The $\Delta S^{\ddagger}$ of −10 e.u. also suggests some change separation in the transition state lending further support for **9'a**. The rates of the rearrangement of (*S*)-**1a** to (*R*)-**2a** were found to be similar by both polarimetry and PMR. Therefore, the rearrangement was completely stereospecific, since the rate by polarimetry would be faster than the rate determined by PMR if racemization had occured. The rearrangement was observed through ten half lives (99.9%) and no racemization was seen in the polarimetric plot of $ln[(\alpha - \alpha_\infty/\alpha_0 - \alpha_\infty) \times 100]$ versus time, where α is the observed rotation.

A benzene solution of (*S*)-**1a**·HCl was prepared from (*S*)-**1a**·HCl. The PMR spectra of this solution before and after isomerization indicated that the solute was at least 99% (*S*)-**1a** and that no more than 1% contamination of (*R*)-**2a** was obtained. The contaminate was either trace amounts of **4a** or **1a**. Methylene chloride was added to speed up the thermal rearrangement. When this (*R*)-**2a** was reacted with aqueous hydroxide ion and the (*S*)-**4a** isolated from the five products, the molecular rotation of the product alcohol was identical, within experimental error, to that of the thermal isomerization of (*S*)-**1a** to

Table 1. Effect of solvent on the rate of rearrangement[a] of **1a** to **2a**

k (sec^{-1})[a,b]	relative rate	dielectric constant (Debyes)	solvent composition (v/v)
3.06×10^{-6}	1[c]	2.3	benzene[c]
$4.15 \pm 0.46 \times 10^{-5}$	14	18.1	50/50 nitrobenzene/benzene
$8.86 \pm 0.98 \times 10^{-5}$	29	26.0	75/25 nitrobenzene/benzene
$5.71 \pm 0.32 \times 10^{-4}$	187[d]	6.9	75/25 methylene chloride/benzene

a. at 30°C except as noted.

b. ± 2 standard deviations for a 95% confidence level

c. rate in benzene calculated at 30°C from data in Table 2.

d. rate at 36°C

Table 2. Kinetic data of the rearrangement of (*S*)-**1a** to (*R*)-**2a**[a]

T °C	k (sec^{-1})[b]	method of measurement
61.4°	$3.95 \pm 0.14 \times 10^{-5}$	pmr
60.2°	$3.77 \pm 0.02 \times 10^{-5}$	polarimetry
50.0°	$1.75 \pm 0.04 \times 10^{-5}$	polarimetry
39.4°	$6.15 \pm 0.10 \times 10^{-6}$	pmr
39.2°	$7.44 \pm 0.42 \times 10^{-6}$	polarimetry

Calculated Thermodynamic Parameters[b]

E_a = 22 ± 2 kcal/mole at 25°C

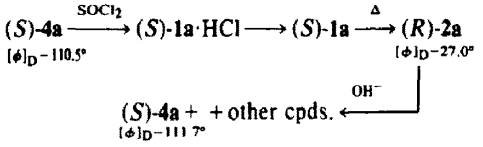
$\Delta H^{\ddagger}$ = 21 ± 2.5 kcal/mole at 25°C

$\Delta S^{\ddagger}$ = -10 ± 2 e.u. at 0°K

a. in pure benzene

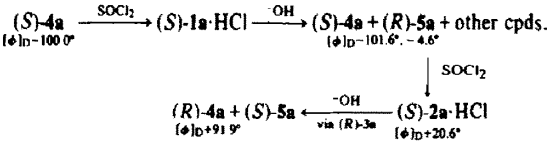
b. k ± 2 standard deviations for a 95% confidence level

(*R*)-**2a** and the reaction of (*R*)-**2a** with base is 100 ± 1% stereospecific:

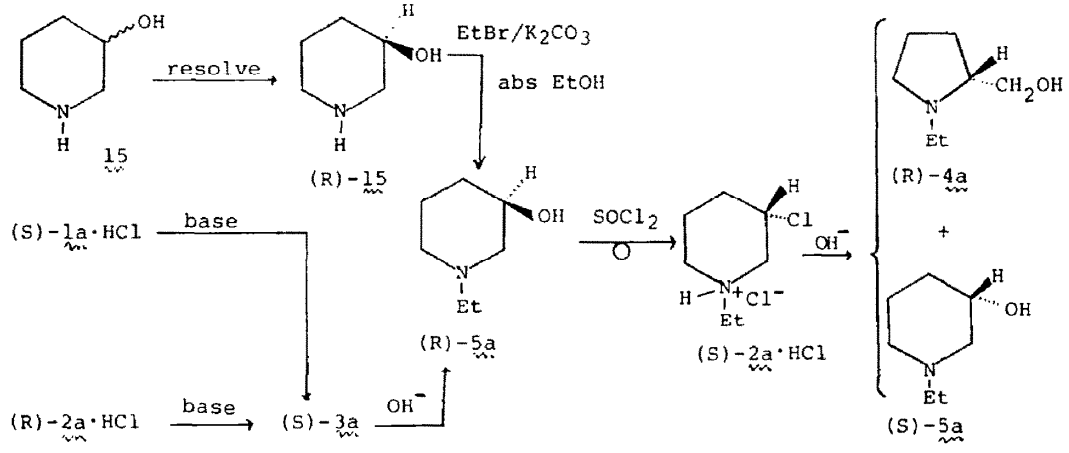


The absolute configuration of 1-ethyl-3-hydroxypiperidine (**5a**) from the reaction of (*S*)-**1a** or (*R*)-**2a** with aqueous hydroxide ion was demonstrated by synthesis (Scheme 4). Both (*R*)- and (*S*)-hydroxypiperidine, (*R*)-**15** and (*S*)-**15**, were prepared by resolution of racemic **15**.[18,19] The absolute configurations of **15** are known,[20] thus (*R*)-**15** was ethylated to (*R*)-**5a**. The glc retention times on two stationary phases,[1] the refractive index, and the PMR and IR spectra of this (*R*)-**5a** were the same as those of the (*R*)-**5a** recovered from the reaction of (*S*)-**1a** or (*R*)-**2a** with hydroxide ion. The ORD curves were nearly identical to the ORD curve of the synthetic (*R*)-**5a**, but shifted slightly in the positive direction. While the condition-sensitive ORD curves of (*R*)-**5a** (the free base) varied somewhat, the ORD curves of the hydrochlorides, (*R*)-**5a**·HCl, from both sources were identical.

The absolute configuration of (*R*)-**2a** was deduced by converting (*R*)-**5a** to (*S*)-**2a**·HCl by a route known to proceed with inversion of configuration.[21] The (*S*)-**2a** so produced had an ORD curve opposite to that of (*R*)-**2a** obtained from the thermal isomerization of (*S*)-**1a**:



The (*R*)-**4a** obtained had an ORD curve with the opposite sign and 90.5% intensity compared to the starting (*S*)-**4a**. The loss of optical activity is attributed to some racemization in the conversion of (*R*)-**5a** to (*S*)-**2a**·HCl with thionyl chloride, rather than racemization in the ring opening of the intermediate (*R*)-**3a** to form (*R*)-**4a** because the latter reaction had previously been shown to be 100% stereospecific. The $[\phi]_D$ expected for



Scheme 4.

(*S*)-**2a**·HCl is +24.5°, if the optical purity of the starting (*S*)-**4a** used in this experiment is corrected ($[\phi]_D$100.0/110.5°, therefore it should vary over all wavelengths by a factor of 0.908) from the previous experiment in which (*R*)-**2a**·HCl was prepared by the thermal rearrangement of (*S*)-**1a**·HCl. In fact, a point-by-point comparison of the expected (*S*)-**2a**·HCl rotation values with those of (*R*)-**2a**·HCl showed that the values were 90.4% as intense as expected, which is in excellent agreement with the 90.5% found for (*R*)-**4a** in this experiment. Thus the total inverse decrease in optical purity can be attributed to 4.8% [(100 − 90.4)/2] racemization in the thionyl chloride that led to the inversion of configuration of (*R*)-**5a** to (*S*)-**2a**·HCl.

Unfortunately, the (*S*)-**5a** obtained in this reaction could only be identified by glc retention time. Quantitative ORD could not be determined because the amount recovered by preparative glc was too small to remove the contamination traces of the glc stationary phase by molecular distillation. Qualitatively the ORD curve of (*S*)-**5a** was the same shape but opposite in sign to that of (*R*)-**5a**. In addition, when a few drops of HCl were added, a shift in the ORD curve was observed like that of (*R*)-**5a** to (*R*)-**5a**·HCl (Fig. 2) but in the opposite direction.

When the methanol crystallate of (*S*)-**1a**·HCl was inadvertently used in these studies, two additional peaks were found in the chromatograms. These were identified as (*S*)-1-ethyl-2-methoxymethylpyrrolidine [(*S*)-**4b**] and (*R*)-1-ethyl-3-methoxypiperidine[(*R*)-**5b**] by comparing their spectra with those of authentic samples.[1] The absolute configuration of the methoxy ethers was assigned on the basis of their ORD spectra and the now-demonstrated stereospecificity of the reaction. Since (*S*)-**4a** and (*S*)-**4b** have very similar ORD curves, they must have the same absolute configuration. The ORD curve of (*S*)-**4a** is consistent with the Cymerman–Craig rule,[22] which states in part, that the ORD curve of an amine chromophore with no other interfering chromophores is negative if the amino group has the same absolute configuration as the L-aminoacids.

The ORD spectra of **4** and **5** are interesting because both series have two possible chromophores, the $n \rightarrow \sigma^*$ transitions of the N and O nonbonded electrons. In **4** the nitrogen is adjacent to the asymmetric center, while in **5** the oxygen is adjacent. When both compounds are derived from the same source, the absolute stereochemistries of the asymmetric centers are the same. Thus it is now possible to assess the importance and sign of the two chromophores. For (*S*)-**4a** and (*R*)-**5a** in methanol, the nitrogen chromophore has a negative sign because the protonated (·HCl) spectra of both are more positive as shown in Figs. 1 and 2. While the oxygen chromophore in (*S*)-**4a** is also negative and approximately as intense, the oxygen chromophore in (*R*)-**5a** is positive and very much the dominant and shorter wavelength (higher energy) chromophore. The spectrum of (*R*)-**5a** in a non-polar solvent (isoöctane), however, is almost identical to those of (*R*)-**5b** and (*R*)-**5a**·HCl in methanol. Apparently only the oxygen $n \rightarrow \sigma^*$ transition is important, suggesting that (*R*)-**5a** in a non-polar solvent is a H-bonded dimer, making the oxygen chromophore similar to that of (*R*)-**5b**. The ORD spectrum of (*R*)-**5a** in 2% methanolic KOH (not shown) was also similar to that of (*R*)-**5b**, possibly due to the increased electron density on the oxygen caused by the presence of some (*R*)-**5a** alkoxide. It is also possible that there is a conformation change

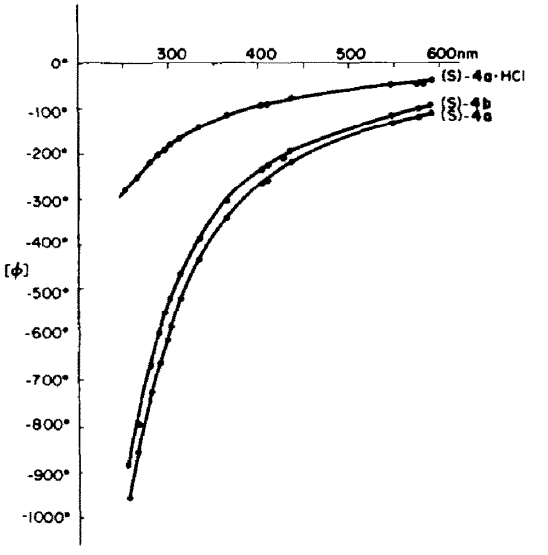


Fig. 1. ORD curves of (*S*)-**4a**, (*S*)-**4a**·HCl and (*S*)-**4b** in methanol.

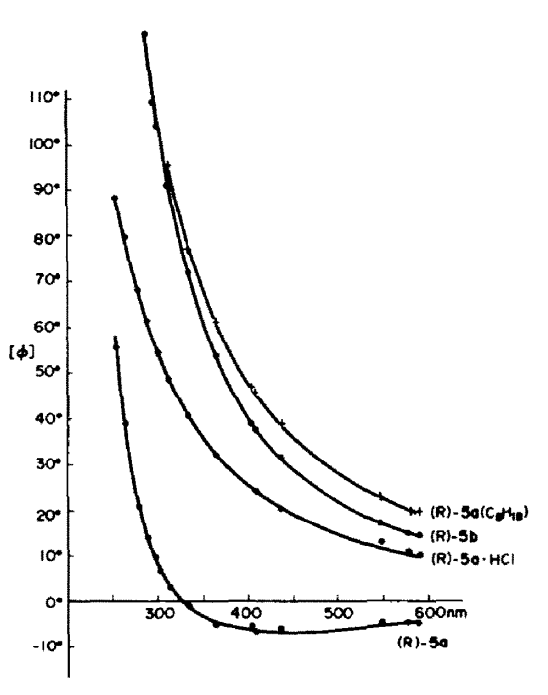
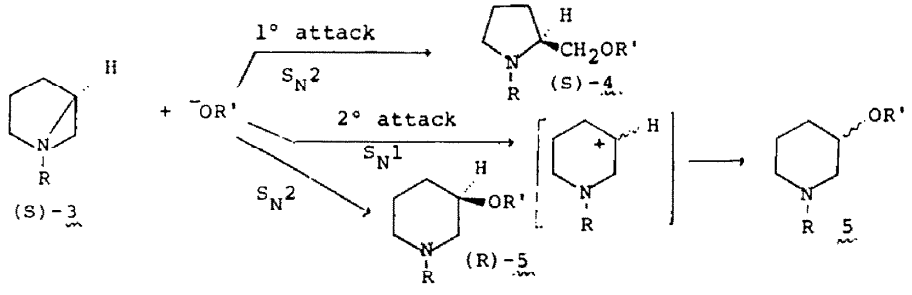


Fig. 2. ORD curves of (*R*)-**5a**, (*R*)-**5a**·HCl and (*R*)-**5b** in methanol, and (*R*)-**5a** in isoöctane.

of (*R*)-**5a** in methanol as has been demonstrated in 3-hydroxypiperidines[23,24] and could be the cause of the changes reported here. The pyrrolidines (*S*)-**2a** and (*S*)-**4b** have very similar negative ORD spectra and while (*S*)-**4a**·HCl is more positive, it still has a clear negative Cotton effect. Pyrrolidines are conformationally less flexible than the piperidines. This could account for the less pronounced changes in the ORD curves under varying conditions than was observed in the ORD curves of the piperidines. The similar behavior of the ORD curves of the methoxy ethers (*S*)-**4b** and (*R*)-**5b** to those of the alcohols (*S*)-**4a** and (*R*)-**5a**, as well as their intensities under the conditions detailed above, are taken as proof of both the absolute configuration and high degree of stereospecificity of their formation.

The absolute configuration of the three *bis*-β-amino-ethers, 2,2'-*bis*-(1-ethyl-2-pyrrolidinomethyl) ether (**6a**), 3-(1'-ethyl-2'-pyrrolidinomethoxy)-1-ethylpiperidine (**7a**), and 3,3'-*bis*-1-ethyl-3-piperidinyl ether (**8a**) were assigned on the basis of their origin, the now-demonstrated stereospecificity of the reaction, and their optical activity. It has been shown that the ethers arise from the reaction of intermediate **3a** with the anions of the alcohols **4a** and **5a** formed from the reaction of the intermediate **3a** with hydroxide ion.[1] Thus one of the pyrrolidine moieties in **6a** and one of the piperidine moieties in **8a** must have the same configuration as **4a** and **5a** respectively. Therefore the absolute configurations of the second pyrrolidine moiety in **6a** and second piperidine moiety in **8a** must have the same configuration as (*S*)-**4a** and (*R*)-**5a** respectively. If not, **6a** and **8a** would be *meso* and be optically inactive. Thus, the symmetric ethers are (*S, S'*)-**6a** and (*R, R'*)-**8a** respectively. Similarly, **7a** has been assigned (*S, R'*)-**7a** because of its high optical activity. (*S, S'*)-**6a** has an observed molecular rotation ($[\phi]_D$ of −190°, −196° and −185° from three reactions) that is twice the molecular rotation of the methoxy ether (*S*)-**4b**. This simple additivity would be expected if the two asymmetric centers in (*S, S'*)-**6a** did not interact. While the molecular rotation of (*S, R'*)-**7a** ($[\phi]_D$ −116°) is higher than the sum of the molecular rotations of methoxy ethers (*S*)-**4b** and (*R*)-**5b**, an asymmetric interaction could be expected here because the optical centers are closer together. In (*R, R'*)-**8a** ($[\phi]_D$ −24·) the oxygen chromophore is adjacent to both asymmetric centers, hence additivity would not be expected. In addition, significant changes in the conformational equilibrium of the piperidine ring systems of **7a** and **8a** are to be expected relative to the conformational equilibrium of **5b**. As in the case of the methoxy ethers (*S*)-**4b** and (*R*)-**5b**, the high optical activity is taken as indicative of high stereospecificity in the formation of (*S, S'*)-**6a**, (*S, R'*)-**7a** and (*R, R'*)-**8a**.

Now that we have proven the absolute configurations of all the products and the 100% stereospecificity of the reaction mechanism[6,7,11] we can now comment on the ring opening of secondary positions of aziridinium ion. Leonard *et al.*[9] have suggested that ring opening reactions of aziridinium ions can be described as S_N1-like or S_N2-like. They have assumed that the ring opening at a primary (unsubstituted) position must involve an S_N2 attack by the nucleophile, but that attack at a secondary (or tertiary) position occurs via an S_N1 like mechanism (see Scheme 5, as applied to our example):



Scheme 5.

If this suggestion were correct for this reaction, then no optical activity would have been observed in (*R*)-**5a** or (*R*)-**5b**. Based on this work, we can conclude that *none* of the ring opening of this secondary aziridinium ion proceeds via an S_N1-like mechanism. When either (*S*)-**4a** or (*R*)-**5a** were cycled through the reaction twice via the chlorides, the only racemization that occurred was due to the formation of (*S*)-**2a**·HCl from (*R*)-**5a** in the thionyl chloride step and not from racemization in the ring opening steps. Further work on a tertiary case is in progress.

CONCLUSIONS

The thermal rearrangement of **1a** and **2a** follows first order kinetics and is 100% stereospecific. The data presented support a transition state having some charge separation such as **9'a**, and the probable formation of an ion pair intermediate like **3a**, which is suggested by the specific solvent effects. It has been proven that the reactions of **1a** or **2a** with hydroxide and methoxide ions are 100% stereospecific with an uncertainty of 1%. The absolute stereochemistries of the reactants and all products have also been established. The ring opening of the intermediate aziridinium ion **3a** with nucleophiles at both the primary and secondary positions proceeds only by an S_N2 mechanism. This is a necessary condition of the mechanism previously proposed[1,5,7] for this reaction and is, therefore, final confirmation of the mechanism. The only meaningful ORD data of these compounds must be obtained on the salts where intramolecular H-bonding and resulting conformational changes are not important. Using the information presented here, it is now possible to synthesize either the (*R*)- or (*S*)-series of 2-substituted-methylpyrrolidines or 3-substituted-piperidines with ease. Variable racemization, however, occurs in the reduction step of the L-prolines, and the reaction of **5a** with thionyl chloride proceeds with inversion and 4.8% racemization.

EXPERIMENTAL

(*S*)-**13**, was prepared by the reduction of (*S*)-**12**, with LAH.[25] B.p. 70–73°(5 mm) [lit. b.p.[6] 69–72°(2 mm), b.p.[26] 100–105°(9 mm) and b.p.[27] 105–110°(10 mm)]; $[\phi]_D$ +2.9°, +3.9° and +0.9° for three batches[28] [lit.[6] $[\phi]_D$ +10° and +1° and[25] +3°]. $[\phi]_D$ of (*S*)-**13**·HCl +23 ± 1° [lit.[26] $[\phi]_D$ +21.8° for the oxalate]; η_D^{20} 1.4878.

(S)-1-*ethyl*-2-*hydroxymethylpyrrolidine*[(S)-**4a**]

By ethylation of (S)-**13** *with ethyl bromide*[7]. (*S*)-**13** (18.9 g) gave (*S*)-**4a** (10.8 g, 47%), η_D^{20} 1.4720, $[\phi]_D$ −106.7°.

By reduction of N-*acetyl*-L-*proline* [(S)-**14**]. (*S*)-**14** was prepared by acetylation of L-proline.[29] $[\alpha]_D$ −115°, m.p. 84–90° [lit.[16] $[\alpha]_D$ −106°, m.p. 81–82° for the monohydrate]. LAH (25 g, 0.66 mole) was suspended in ether (2 L) under flowing N_2, vented through a condenser and stirred mechanically. The mixture was cooled in an ice bath and (*S*)-**14** (31.0 g, 0.197 mole) was

added in small portions over a 2 hr period. The suspension was refluxed for 4 days, with continued N_2 and stirring. The mixture was cooled and diatomaceous earth (250 g) was added. Water (100 ml) and MeOH (100 ml) were successively added slowly. The slurry was suction filtered and the filter cake was extracted with boiling MeOH (2 × 100 ml), which was filtered and combined with the ether filtrate. The combined filtrate was evaporated under reduced pressure at 45° until an aqueous slurry remained. The slurry was extracted with benzene (4 × 25 ml) and most of the benzene evaporated through a column containing glass beads to a height of 5 cm. The residual liquid containing 25 to 50% benzene was purified by glc.[1] Pure (*S*)-**4a** was collected (15.0 g, 0.116 mole, 58%), $[\phi]_D$ − 101.6°, − 110.4° and − 100.0° for three batches[14] [lit.[7] $[\phi]_D$ − 96° and − 105°]; η_D^{20} 1.4720, 1.4718, and 1.4720 [lit.[7] η_D^{27} 1.4660 and $^{30}\eta_D^{25}$ 1.4662 (racemic)].

Separations were done by preparative glc on a Hewlett-Packard Model 776 Prepmaster Jr. chromatograph, as previously described.[1] Liquid fractions were further purified by molecular distillation before physical measurements were made. Thermal stability of (*S*)-**4a** was demonstrated by passing a sample ($[\phi]_D$ − 110.4°) through the preparative glc, collecting and reinjecting for a total of five passes ($[\phi]_D$ − 110.5° after fifth pass).

IR and PMR spectra were identical to known racemic samples concomitantly determined.[1]

(R)- *and* (S)-3-*Hydroxypiperidine*[(R)- *and* (S)-**15**].[18,19] Racemic **15** (Aldrich Chemical Co., 10.1 g, 0.10 mole) in acetone (400 ml) was mixed with *d*-camphor-10-sulfonic acid (Aldrich Chemical Co., 30.2 g, 0.13 mole) in acetone (400 ml). The solution was stored in a freezer for 5–10 days, until crystal growth ceased. The crystals were collected by filtration and air dried, m.p. 134–134.5° [lit.[18] m.p. 131–135°]. Then the crystals were dissolved in 4N H_2SO_4 (25 ml) and extracted with $CHCl_3$ (5 × 10 ml). The aqueous soln was made strongly basic with 50% NaOH (carefully!) and extracted with $CHCl_3$ (5 × 10 ml). The $CHCl_3$ soln was dried over $MgSO_4$, filtered and evaporated through a column containing about 5 cm height glass beads. A little ether was added to the oily residue and the white crystals, which formed on standing at room temp., were filtered and dried: m.p. 80–85°, $[\phi]_D$ + 8.9° [lit.[18] $[\phi]_D$ − 3.0° and[19] − 1.6° and[20] − 7.5° for the other enantiomer].

(R)-1-*Ethyl*-3-*hydroxypiperidine* [(R)-**5a**]. To (*R*)-**15** (2.01 g, 0.02 mole) in abs. EtOH (100 ml), EtBr (2.15 g, 0.02 mole) in abs. EtOH (60 ml) was added dropwise at 40°. After addition was complete, heating and stirring was continued for 24 hr. The soln was neutralized to the congo-red end point with HCl and the alcohol evaporated. The aqueous slurry was made strongly basic with 50% NaOH and mixed with diatomaceous earth (10 g), packed in a 25 × 200 mm chromatographic tube and eluted with ether (250 ml). The ether was dried over $MgSO_4$, filtered and evaporated through a column containing glass beads to a height of 5 cm. Crystals of (*R*)-**15** (440 mg, 22% recovery) were filtered and washed with a little ether. Most of the ether was evaporated and the oily residue was purified by preparative glc on the column previously described.[1] Yield of pure (*R*)-**5a** was 550 mg (27% based on unrecovered (*R*)-**15**); η_D^{20} 1.4973, $[\phi]_D$ − 1.6° and (*R*)-**5a**·HCl, $[\phi]_D$ + 9 ± 1° [lit.[4] η_D^{23} 1.4744].

(S)-2-*Chloromethyl*-1-*ethylpyrrolidine hydrochloride* [(S)-**1a**·HCl] was prepared from (*S*)-**4a** as previously reported:[4] m.p. 210–210.5° [lit.[4] m.p. 193.5–194°]; $[\phi]_D$ − 31.4°, − 30.4°, − 22.5° and − 25.5° for 4 batches.[31] The MeOH solvate (*S*)-**1a**·HCl·CH_3OH was prepared as previously reported.[1]

(R)-3-*Chloro*-1-*ethylpiperidine* [(R)-**5a**] was prepared from (*S*)-**1a** by thermal isomerization. (*S*)-**1a**·HCl was layered with benzene, 50% NaOH added and shaken vigorously.[11] The benzene layer was separated and dried over $MgSO_4$, filtered, CH_2Cl_2 added and refluxed. The isomerization was followed by PMR by observing the Me triplet (1.05 ppm δ) of (*S*)-**1a** decrease as the methyl triplet (0.95 ppm δ) of (*R*)-**2a** increased. The solvents were removed and (*R*)-**2a** distilled; η_D^{20} 1.4708 [lit.[4] η_D^{20} 1.4674 and[6] 1.4646]. (*R*)-**2a**·HCl: m.p. 213–214.5° [lit.[4] 193–194°], $[\phi]_D$ − 27.0°.[31]

(S)-3-*Chloro*-1-*ethylpiperidine hydrochloride* [(S)-**2a**·HCl]. To (*R*)-**5a** (2.38 g, 0.018 mole) in $CHCl_3$ (50 ml) stirred in a 3-neck round bottomed flask cooled in an ice bath, $SOCl_2$ (4.8 g, 0.04 mole) in $CHCl_3$ (10 ml) was slowly added dropwise. The ice bath was replaced with a heating mantle and the soln was refluxed for 2 hr with stirring. The solvent was removed under reduced pressure and the residue was decolorized by refluxing with charcoal in MeOH five times. Evaporation of the MeOH yielded white crystals, which were shown to contain about 50 : 50 (*R*)-**5a**·HCl and (*S*)-**2a**·HCl from the IR spectrum. Recrystallization from isopropanol three times gave pure (*S*)-**2a**·HCl (470 mg, m.p. 213–214.5° and $[\phi]_D$ + 20.6°.[31] The IR spectra of (*S*)-**2a**·HCl and racemic **2a**·HCl (Aldrich Chemical Co.) as KBr disks concomitantly determined were identical.

Reactions of (*S*)-**1a**·HCl, (*S*)-**1a**·HCl·CH_3OH, (*R*)-**2a** and (*S*)-**2a** · HCl with 25% aq NaOH were performed as previously described.[1] The optically active products were separated by preparative glc and purified by molecular distillation as described above.[1]

Kinetics of the thermal rearrangement of (S)-**1a** *to* (R)-**2a**

Stock benzene solutions of (*S*)-**1a**. (*S*)-**1a**·HCl (usually 200 mg) was placed in a 3 ml test tube. Benzene (1.0 ml) and 50% aq NaOH (about 0.2 ml) were added and rapidly shaken. The benzene layer was carefully pipetted into a second 3 ml test tube containing anhyd $MgSO_4$ (about 100 mg) and was shaken vigorously. The benzene soln was filtered into a 5 mm. NMR tube or polarimeter cell. No attempt was made to determine the final concentration because it was shown that the rate was constant when starting with 60–200 mg (*S*)-**1a**·HCl. It was also shown that the solute prepared as described above was at least 99% (*S*)-**1a**. A benzene soln of **1a** has a "musty" odor not observed for **2a** either neat or in benzene soln.

Polarimetric measurements. Rotations were measured at 546 nm with a Perkin–Elmer Model 141 automatic digital polarimeter. The jacketed cells were 1.0 dm long. Between measurements, the cell and hoses were kept in a thermostated box. The box was insulated with polystyrene foam and had glass coils in the walls, bottom and top through which water from a thermostated bath (± 0.02°) was circulated, an arrangement that eliminated small variations in cell temperature due to heat losses from hoses.

PMR measurements. The central peak heights of the Me triplets of the N-Et groups of **1a** and **2a** at 1.1 and 1.0 ppm δ, respectively, were measured on a Varian A-60 NMR Spectrometer. The sum of the peak heights was determined and the percent of **1a** and **2a** calculated. An average of nine measurements was calculated for each kinetic point. Since the A-60 instrument used did not have a variable temp. probe, a time correction was made for the period the sample spent in the probe. This time correction was calculated using the approximation that the rates doubled for every 10° rise in temp. This approximation proved to be nearly correct for the observed rearrangement. The NMR tube was thermostated between measurements by direct immersion in a constant temp. bath (± 0.02°).

Solvent effects study. The effect of different solvent mixtures was determined by PMR, but with only five measurements made per point at probe temp. The probe temp. was 30° during the runs using the nitrobenzene/benzene solvent mixtures, but was 36° during the runs using methylene chloride/benzene solvent mixture. In the latter solvent system, the rate of rearrangement was so rapid that only one determination per point could be made. The poor standard deviation of this rate calculation shown in Table 1 reflects this difficulty.

Calculations. Rates were calculated from the slope of a least squares fitted line through the points of a plot of $\ln[(\alpha - \alpha_\infty/\alpha_0 - \alpha_\infty) \times 100]$ vs time for the polarimetric determinations and ln(%**1a**) vs time for the PMR determinations. The activation parameters E_a, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated using standard procedures.[32]

Rotatory dispersion data. While the cause was not established, the ORD data previously reported[6,7] for (*S*)-**1a**·HCl and (*R*)-**2a**·HCl are most certainly incorrect. The rotations determined here for four samples of (*S*)-**1a**·HCl and a sample each of (*R*)- and (*S*)-**2a**·HCl, each independently prepared, strongly suggest that the present values are correct.[31] Since all of the optically

active compounds used in this study have their origin in (*S*)-**4a** (except one sample of (*R*)-**5a**, (*S*)-**14** and the precursors of (*S*)-**4a**), and the problem of racemization during the reduction with LAH has already been noted,[14] rotatory dispersion data are given only for the highest values determined. The optical rotations were measured at the sodium D line (589.3 nm) and most of the major mercury emission lines between 580 and 254 nm in a 1.0 dm or 2.0 cm thermostated cell at 25° with a Perkin–Elmer Model 141 M automatic digital polarimeter. Errors for each measurement are given for the first and last value quoted and are the same in between unless otherwise indicated.

(*S*)-**1a**·HCl, $c = 2.1$ in MeOH. $[\phi]_{589} - 31.4° \pm 0.4°$, $[\phi]_{580} - 33.9°$, $[\phi]_{546} - 37.2°$, $[\phi]_{436} - 59.9°$, $[\phi]_{404} - 70.1°$, $[\phi]_{365} - 88.8°$, $[\phi]_{334} - 107.3°$, $[\phi]_{313} - 125.2°$, $[\phi]_{302} - 136.9°$, $[\phi]_{289} - 151.1°$, $[\phi]_{280} - 163.7°$, $[\phi]_{265} - 186.7°$, $[\phi]_{254} - 202.8 \pm 0.4°$.

(*R*)-**2a**·HCl, 3.1 in MeOH. $[\phi]_{589} - 27.0° + 0.3°$, $[\phi]_{577} - 27.1°$, $[\phi]_{546} - 30.7°$, $[\phi]_{436} - 51.8°$, $[\phi]_{404} - 62.3°$, $[\phi]_{365} - 80.8° \pm 0.3°$, $[\phi]_{313} - 123° \pm 1.5°$, $[\phi]_{289} - 156°$, $[\phi]_{265} - 207°$, $[\phi]_{254} - 230° \pm 1.5°$.

(*S*)-**2a**·HCl, $c = 4.7$ in MeOH. $[\phi]_{589} + 20.6° \pm 0.2°$, $[\phi]_{577} + 22.3°$, $[\phi]_{546} + 25.5°$, $[\phi]_{436} + 43.3°$, $[\phi]_{408} + 51.7° \pm 0.2°$, $[\phi]_{404} + 53° \pm 1°$, $[\phi]_{365} + 67° \pm 1°$.

(*S*)-**4a**, $c = 1.9$ in MeOH, $[\phi]_{589} - 110.4° \pm 0.3°$, $[\phi]_{577} - 115.6°$, $[\phi]_{546} - 130.1°$, $[\phi]_{436} - 220.6°$, $[\phi]_{408} - 259.5°$, $[\phi]_{404} - 265.0°$, $[\phi]_{365} - 344.1°$, $[\phi]_{334} - 435.3°$, $[\phi]_{313} - 522.9°$, $[\phi]_{302} - 580.7°$ $[\phi]_{297} - 612.9°$, $[\phi]_{289} - 660.1°$, $[\phi]_{280} - 724.8°$, $[\phi]_{265} - 854.3°$, $[\phi]_{254} - 958.7° \pm 0.3°$.

(*S*)-**4a**·HCl, $c = 1.2$ in MeOH, $[\phi]_{589} - 39.8° \pm 0.4°$, $[\phi]_{580} - 42.2°$, $[\phi]_{577} - 42.8°$, $[\phi]_{546} - 47.5°$, $[\phi]_{436} - 79.6°$, $[\phi]_{408} - 89.3°$, $[\phi]_{404} - 90.3°$, $[\phi]_{365} - 116.0°$, $[\phi]_{334} - 140.1°$, $[\phi]_{313} - 164.3°$, $[\phi]_{302} - 179.3°$, $[\phi]_{297} - 190.4°$, $[\phi]_{289} - 199.9°$, $[\phi]_{280} - 217.5°$, $[\phi]_{265} - 250.9°$, $[\phi]_{254} - 276.4° \pm 0.4°$.

(*R*)-**4a**, $c = 1.9$ in MeOH, $[\phi]_{589} + 91.9° \pm 0.3°$, $[\phi]_{577} + 96.5°$, $[\phi]_{546} + 109.1°$, $[\phi]_{436} + 184.8°$, $[\phi]_{404} + 221.7° \pm 0.3°$, $[\phi]_{365} + 289° \pm 1.6°$, $[\phi]_{313} + 440°$, $[\phi]_{297} + 516°$, $[\phi]_{280} + 608°$, $[\phi]_{254} + 698° \pm 1.6°$.

(*S*)-**4b**, $c = 2.6$ in MeOH, $[\phi]_{589} - 95.2° \pm 0.3°$, $[\phi]_{577} - 99.9° \pm 0.3°$, $[\phi]_{546} - 114° \pm 1.4°$, $[\phi]_{436} - 195°$, $[\phi]_{408} - 228°$, $[\phi]_{404} - 233°$, $[\phi]_{365} - 304°$, $[\phi]_{334} - 388°$, $[\phi]_{313} - 467°$, $[\phi]_{302} - 519°$, $[\phi]_{297} - 551°$, $[\phi]_{289} - 598°$, $[\phi]_{280} - 663°$, $[\phi]_{265} - 793°$, $[\phi]_{254} - 884° \pm 1.4°$.

(*R*)-**5a**·HCl, $c = 2.9$ in MeOH, $[\phi]_{589} + 10.2° \pm 0.3°$, $[\phi]_{577} + 10.7°$, $[\phi]_{546} + 12.8°$, $[\phi]_{436} + 20.5°$, $[\phi]_{408} + 24.1°$, $[\phi]_{365} + 32.1°$, $[\phi]_{334} + 40.4°$, $[\phi]_{313} + 48.4°$, $[\phi]_{302} + 54.2°$, $[\phi]_{289} + 61.2°$, $[\phi]_{280} + 67.8°$, $[\phi]_{265} + 79.6°$, $[\phi]_{254} + 87.9° \pm 0.3°$.

(*R*)-**5a**·HCl, synthesized from resolved (*R*)-**15**, $c = 2.5$ in MeOH, $[\phi]_{589} + 9° \pm 1.7°$, $[\phi]_{577} + 9°$, $[\phi]_{546} + 13°$, $[\phi]_{404} + 27°$, $[\phi]_{365} + 33°$, $[\phi]_{334} + 39°$, $[\phi]_{297} + 56°$, $[\phi]_{254} + 89° \pm 1.7°$

(*R*)-**5a**, $c = 2.3$ in MeOH, $[\phi]_{589} - 4.6° \pm 0.3°$, $[\phi]_{577} - 4.5°$, $[\phi]_{546} - 4.8°$, $[\phi]_{436} - 6.4°$, $[\phi]_{408} - 6.4°$, $[\phi]_{404} - 5.6°$, $[\phi]_{365} - 4.9°$, $[\phi]_{334} - 1.0°$, $[\phi]_{313} + 3.0°$, $[\phi]_{302} + 6.7°$, $[\phi]_{297} + 9.7°$, $[\phi]_{289} + 13.9°$, $[\phi]_{280} + 20.9°$, $[\phi]_{265} + 38.8°$, $[\phi]_{254} + 55.6° \pm 0.3°$.

(*R*)-**5a**, $c = 2.6$ in 2,2,4-trimethylpentane (isoöctane), $[\phi]_{589} + 19.8° \pm 0.2°$, $[\phi]_{580} + 20.3°$, $[\phi]_{546} + 23.1°$, $[\phi]_{436} + 38.9°$, $[\phi]_{408} + 45.7°$, $[\phi]_{404} + 46.9° \pm 0.2°$, $[\phi]_{365} + 61° \pm 1.7°$, $[\phi]_{334} + 77°$, $[\phi]_{313} + 91°$, $[\phi]_{302} + 102° \pm 1.7°$.

(*R*)-**5b**, $c = 1.8$ in MeOH, $[\phi]_{589} + 14.5° \pm 0.7°$, $[\phi]_{577} + 15.0°$, $[\phi]_{546} + 17.3°$, $[\phi]_{436} + 31.7°$, $[\phi]_{408} + 37.8°$, $[\phi]_{404} + 38.9°$, $[\phi]_{365} + 53.7° \pm 0.7°$, $[\phi]_{334} + 72° \pm 2°$, $[\phi]_{313} + 91°$, $[\phi]_{302} + 104°$, $[\phi]_{297} + 109°$, $[\phi]_{289} + 124°$, $[\phi]_{280} + 139°$, $[\phi]_{265} + 185°$, $[\phi]_{254} + 216° \pm 2°$.

(*S,S'*)-**6a**, $c = 1.8$ in MeOH, $[\phi]_{589} - 196.3° \pm 0.7°$, $[\phi]_{580} - 204.9°$, $[\phi]_{577} - 207.1°$, $[\phi]_{546} - 233.7°$, $[\phi]_{436} - 401.1°$, $[\phi]_{408} - 473.4°$, $[\phi]_{404} - 481.7°$, $[\phi]_{365} - 634.4° \pm 0.7°$, $[\phi]_{334} - 815° \pm 3°$, $[\phi]_{302} - 1099°$, $[\phi]_{297} - 1177° \pm 3°$.

(*S,R'*)-**7a**, $c = 1.5$ in MeOH, $[\phi]_{589} - 116° \pm 1°$, $[\phi]_{580} - 119°$, $[\phi]_{577} - 121°$, $[\phi]_{546} - 138°$, $[\phi]_{436} - 231°$, $[\phi]_{408} - 271° \pm 1°$, $[\phi]_{404} - 280° \pm 4°$, $[\phi]_{365} - 371° \pm 4°$.

(*R,R'*)-**8a**, $c = 0.6$ in MeOH, $[\phi]_{589} - 24°$, $[\phi]_{580} - 41°$, $[\phi]_{577} - 48°$, $[\phi]_{546} - 55°$, $[\phi]_{436} - 80°$, $[\phi]_{408} - 83°$, $[\phi]_{404} - 99°$, $[\phi]_{365} - 121°$.

(*S*)-**13**, $c = 5.47$ in MeOH, $[\phi]_{589} + 3.9° \pm 0.1°$, $[\phi]_{580} + 4.0°$, $[\phi]_{546} + 4.4°$, $[\phi]_{436} + 5.2°$, $[\phi]_{404} + 5.0°$, $[\phi]_{365} + 3.3°$, $[\phi]_{334} - 0.3°$, $[\phi]_{302} - 10.7°$, $[\phi]_{297} - 13.9°$, $[\phi]_{265} - 27.4°$, $[\phi]_{254} - 48.9° \pm 0.1°$.

(*S*)-**13**·HCl, $c = 3.1$ in MeOH, $[\phi]_{589} + 23° \pm 1°$, $[\phi]_{577} + 24°$, $[\phi]_{546} + 27°$, $[\phi]_{436} + 44°$, $[\phi]_{404} + 50°$, $[\phi]_{365} + 64°$, $[\phi]_{334} + 79°$, $[\phi]_{313} + 92°$, $[\phi]_{302} + 102°$, $[\phi]_{289} + 115°$, $[\phi]_{280} + 123°$, $[\phi]_{265} + 144°$, $[\phi]_{254} + 159° \pm 1°$.

(*S*)-**14**, $c = 0.9$ in MeOH, $[\phi]_{589} - 131° \pm 1°$, $[\phi]_{577} - 136°$, $[\phi]_{546} - 154°$, $[\phi]_{436} - 266°$, $[\phi]_{404} - 326°$, $[\phi]_{365} - 432°$, $[\phi]_{334} - 568°$, $[\phi]_{313} - 703°$, $[\phi]_{302} - 800°$, $[\phi]_{297} - 860°$, $[\phi]_{289} - 946°$, $[\phi]_{280} - 1077°$, $[\phi]_{265} - 1390° \pm 1°$.

(*R*)-**15**, $c = 1.1$ in MeOH, $[\phi]_{589} + 8.9° \pm 0.5°$, $[\phi]_{577} + 10.0°$ $[\phi]_{546} + 11.6°$, $[\phi]_{436} + 18.8°$, $[\phi]_{408} + 21.6°$, $[\phi]_{404} + 22.1°$, $[\phi]_{365} + 30.7° \pm 0.5°$, $[\phi]_{334} + 45° \pm 2.3°$, $[\phi]_{313} + 60° \pm 2.3°$.

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