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REACTIONS OF β-SUBSTITUTED AMINES—II

NUCLEOPHILIC DISPLACEMENT REACTIONS ON 3-CHLORO-1-ETHYLPIPERIDINE[1,2]

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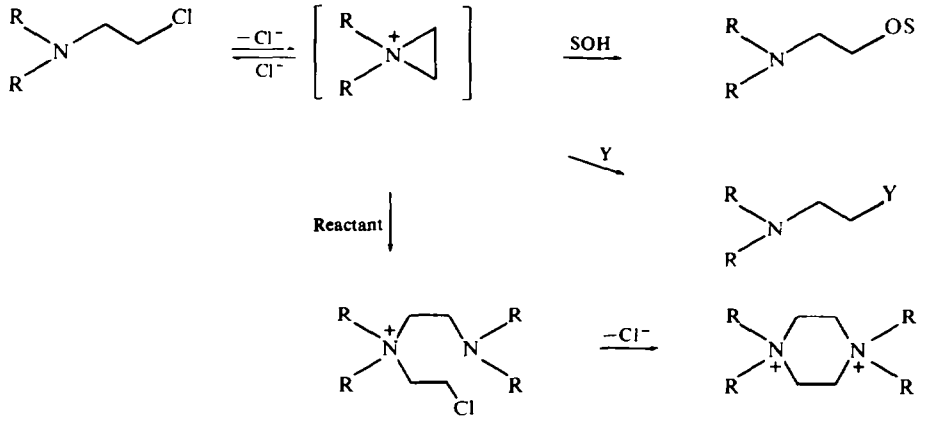
Abstract—Synthetic, kinetic and optical activity studies have established that 3-chloro-1-ethylpiperidine undergoes nucleophilic displacement reactions in solution by a two-step, neighboring group participation mechanism. Nitrogen displaces chloride internally, to give an ambident bicyclic aziridinium ion which then reacts with nucleophiles to give pyrrolidine and piperidine isomers. The aziridinium ion, 1-ethyl-1-azoniabicyclo[3.1.0]hexane perchlorate, has been synthesized separately.

MUCH work has been focused on the reactions of acyclic β-chloroethylamines.[4–7] Mechanistic studies by Cohen[8] and Bartlett[9] provide evidence for the following general mechanism for the reactions of tertiary, acyclic β-chloroethylamines:

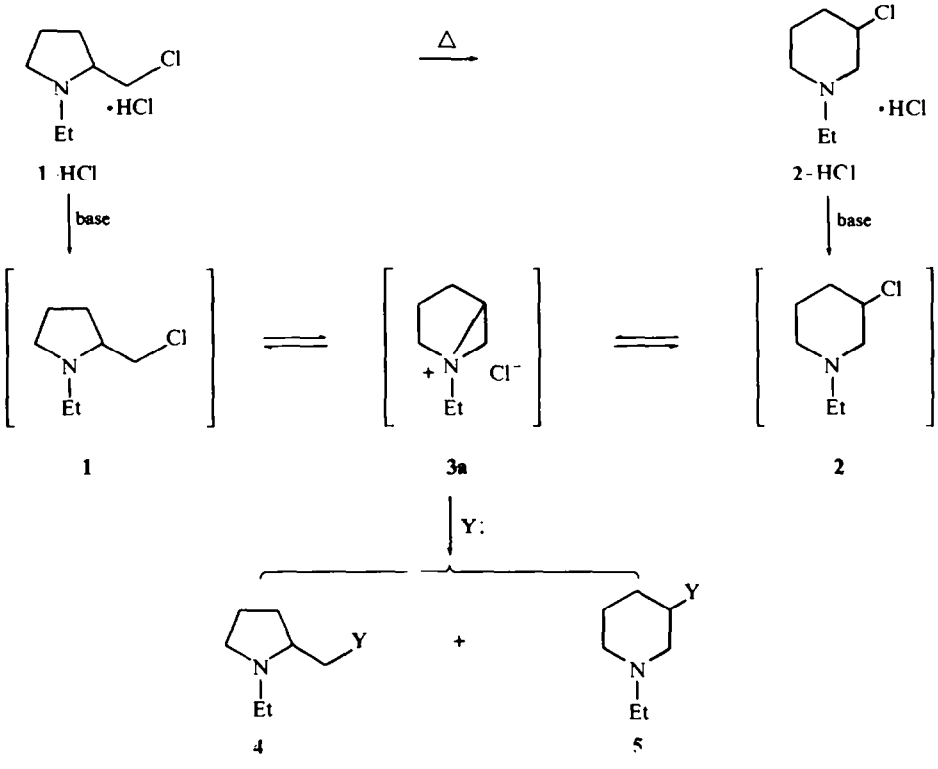


SCHEME 1

Initially, nucleophilic displacement of chloride by nitrogen gives an aziridinium ion which then can react with any nucleophile present. Back reaction with chloride regenerates the reactant; reaction with solvent (SOH) gives solvolysis products; reaction with other nucleophiles (Y) gives displacement products; and reaction with starting materials gives dimerization which usually proceeds to piperazinium ion formation. More recent studies of similar tertiary systems are consistent with this mechanism.[10–16]

Skeletally rearranged reactants and products are often observed in reactions of β-chloro amines,[4-7,17] due to ambident character of the intermediate aziridinium ions. Fuson[18] noted facile rearrangements of acyclic primary-chloro to secondary-chloro β-chloroethylamines,[19] and extended the rearrangement to the ring expansion of **1** to **2**, Scheme 2. Compound **1** rearranged so easily that it could not be isolated. A number of workers[20-25] have since observed ring-contracted and/or rearranged products from displacement reactions on 1-alkyl-3-chloropiperidine.

Beginning with the postulation of aziridinium ion **3a** by Fuson,[18] **3** has generally been accepted[26] as the intermediate in displacement or rearrangement reactions of **1** and **2**. However, only recently[2] has mechanistic evidence been presented to substantiate this. A detailed account of the synthetic, kinetic, and stereochemical evidence for the existence of the aziridinium ion, 1-ethyl-1-azoniabicyclo[3.1.0]hexane (**3**), is presented here.



Compounds (4, 5)	Nucleophile (Y)	Substituent (−Y)
a	OH^-	—OH
b	$PhCH_2NH_2$	$—NHCH_2Ph$
c	$(PhCH_2)_2NH$	$—N(CH_2Ph)_2$
d	CN^-	—CN
e	OAc^-	—OAc

SCHEME 2

RESULTS AND DISCUSSION

Products from reactions of 3-chloro-1-ethylpiperidine (2). The reaction of 2 with nucleophiles has been found[21–25] to involve displacement of chloride by the nucleophiles, with partial or total ring contraction, to give 5- and 6-membered ring products (Scheme 2). Several reactions were performed to clarify earlier work. With refluxing 10% aqueous sodium hydroxide, 2 gave, after distillation, a mixture of amino alcohols (**4a** and **5a**), in a ratio of 68:32 and a total yield of 65%. (The pot residue contained dimer ethers, whose structures and stereochemistries will be published separately.[22]) Either isomer could be distilled without rearrangement, and the products were stable under the reaction conditions. The 68:32 product ratio is essentially the same as that obtained by Paul and Tchelitcheff.[23]

The reaction of 2 with excess benzylamine,[24] dibenzylamine, and sodium cyanide[20,23] gave exclusively the ring-contracted products, **4b**, **4c**, and **4d**, in 80%, 70%, and 68% yields respectively. The reaction of 2 with acetate gave differing product ratios, depending upon reaction conditions. Refluxing 2 with sodium acetate in acetic anhydride (139°) for 6 hr gave a mixture of acetate esters (4e and 5e) in a ratio of 20:80 (reported,[23] 17:83) as measured by PMR spectra of the crude product. The reaction was repeated at 90° for 8 hr. The corresponding PMR-determined product ratio was 75:25 (**4e**:**5e**). Heating the latter mixture at 106–107° for 1 day left the ratio unchanged; however, elevating the temperature to 126–127° for 6 days produced a slow rearrangement of **4e** to **5e**. The preponderance of **5e** in the reaction at 139° is apparently due to rearrangement of the predominant initial product, **4e**. This is further indicated by the finding of Paul[23] that **4a** reacts with refluxing acetic anhydride to give the same product ratio of 4e to **5e** as that found from the reaction of 2 with sodium acetate in refluxing acetic anhydride. No rearrangement was encountered in synthesizing **5e** by refluxing **5a** in acetic anhydride. From the above reactions it is evident that strong nucleophiles (CN^-, amines) give only 5-membered ring products; whereas, weaker nucleophiles (OH^-, OAc^-) give mixtures of 5- and 6-membered ring products.

Kinetics of aziridinium ion formation. If aziridinium ion formation (first step in Scheme 2) is rate determining and reversibility is slight, then the rate of appearance of chloride should be first order and independent of the type or concentration of nucleophile involved in the second step. Table 1 shows the results for the rate of chloride ion formation from 2 in 80 vol % aqueous ethanol upon addition of different nucleophiles. The solutions contained 1 M sodium perchlorate, to keep the ionic strength constant. For 2 with excess sodium hydroxide, a plot of the logarithm of chloride ion concentration versus time gave a straight line through two to three half-lives, and there was no significant change in the order or value of the rate observed when other nucleophiles were substituted for hydroxide. This confirmed the first-order nature of the reaction.

Nitrogen participation cannot occur when the nitrogen is protonated. At moderate or low pH, the rate of reaction becomes a function of the pH. In excess base, solvent protonation of 2 would not be a problem. When anionic nucleophiles are used, solvent protonation of 2 might occur, but this should not be significant in 80% aqueous ethanol. With neutral nucleophiles or under solvolytic conditions, the second step in the reaction of 2 would release one mole of hydrogen ions, which could be neutralized by the reactant, by the products, or by the excess nucleophile.

TABLE 1. RATE CONSTANTS FOR THE REACTION OF 2 IN THE PRESENCE OF NUCLEOPHILES[a]

Nucleophile	10^4k (sec^{-1})
Chloroacetate	1·74 ± 0·13
Hydroxide	1·74 ± 0·04
Formate	1·76 ± 0·04
Azide	1·78 ± 0·05
Cyclohexylamine	1·80 ± 0·05
Acetate	1·85 ± 0·05
β-Phenylcyclopentylglycolate	1·85 ± 0·04
Benzylamine	1·85 ± 0·04
2-Methylindole	1·90 ± 0·04
Aniline	1·93 ± 0·05
Methoxide	1·98 ± 0·06
p-Bromoaniline	2·03 ± 0·07
Tosylate	2·04 ± 0·05
Thiosulfate	2·14 ± 0·05

[a] Run at 45° in 80 vol % aqueous ethanol containing 1·0 M sodium perchlorate. The concentrations of nucleophile and 2 were 0·25 M and 0·01 M respectively.

Table 2 shows the pK_a's in water for some amines of interest. While these values can not be applied directly to the aqueous ethanol used for kinetics, β-amino alcohols and other products should be significantly more basic than the reactant. Hence, until the overall reaction of 2 with neutral nucleophiles or solvent neared completion, protonation of 2 by liberated acid should not seriously affect first-order plots. In studying the effect of nucleophiles upon the rates of chloride ion formation from 2, no large departures from linear first-order plots were noted which could be attributed to protonation of 2 by products. If these nucleophiles reacted with 2 in a rate-determining S_N2 step, then going from tosylate to thiosulfate should cause a rate difference

TABLE 2. AQUEOUS pK_a VALUES FOR SOME β-SUBSTITUTED AMINES

Compound	pK_a in water	Temp (°C)
1-Ethyl-2-hydroxymethylpyrrolidine (**4a**)	9·5	21
1-Alkyl-3-hydroxypiperidine compounds		
R = Methyl (**8a**)	9·2	21
Ethyl (**5a**)	9·3	21
n-Propyl (**8b**)	9·4	21
i-Propyl (**8c**)	9·7	21
n-Butyl (**8d**)	9·6	21
1-Alkyl-3-chloropiperidine compounds		
R = Methyl (**9a**)	8·1	23
Ethyl (**2**)	8·3	23
n-Propyl (**9b**)	8·4	23
i-Propyl (**9c**)	8·6	23
n-Butyl (**9d**)	8·6	23

spanning many orders of magnitude. The total variation in rates is around 20% for all nucleophiles (1.9×10^{-4} sec^{-1} ± 10%), ruling out any significant S_N2 process and establishing this as a first-order mechanism. In light of possible protonation interferences and the estimated experimental error of ±5%, the values of the rate of reaction of the various nucleophiles with **2** are not considered worthy of further discussion.

The nucleophiles added (Table 1) are not necessarily the ones operative in solution. For example, adding sodium hydroxide to 80% aqueous ethanol would give hydroxide and alkoxide as nucleophiles. Reactions with non-nucleophilic reagents such as tosylate salts are probably solvolytic. This is indicated by the work of Hammer[27] and Cox,[28] who found β-tosyloxy amines to be more reactive towards nucleophilic displacement than β-chloro amines.

Anchimeric assistance. In order to distinguish between a first-order ionization process and first-order neighboring group participation in the formation of chloride from **2**, a comparison to a carbocyclic analog was sought. Since the precise deaza analog, 3-ethylcyclohexyl chloride exists in theoretically troublesome *cis* and *trans* isomers, cyclohexyl chloride was chosen for the comparison. The reaction of cyclohexyl chloride in 80% aqueous ethanol was first or *pseudo* first order, with a rate of 3×10^{-6} sec^{-1}.

The temperature dependence of the reaction of **2** was determined under the same conditions of solvent and nucleophile (Table 3), the activation parameters were determined (E_a = 25·1 ± 1 Kcal/mol and $\Delta H^{\ddagger}$ = 24·5 ± 1 Kcal/mol; $\Delta F^{\ddagger}$ = 26·0 ± 1 Kcal/mol and $\Delta S^{\ddagger}$ = − 7 ± 5 eu/mol at 25°), and the rate of reaction of **2** at 80·5° (1.65×10^{-2} sec^{-1}) was then calculated. At 80·5°, **2** reacts 3·7 orders of magnitude faster than cyclohexyl chloride. This anchimeric assistance rules out solvolytic mechanisms for the reaction of **2** and clearly points to the participation of nitrogen in the rate-determining step.

TABLE 3. TEMPERATURE VARIATION OF THE RATE CONSTANT FOR THE REACTION OF 2 WITH SODIUM HYDROXIDE[a]

Temp (°C)	k(sec^{-1})
25·0	$1.25 \pm 0.07 \times 10^{-5}$
45·0	$1.75 \pm 0.03 \times 10^{-4}$
60·0	$1.45 \pm 0.06 \times 10^{-3}$
80·5	1.65×10^{-2} (calculated)

[a] Run in 80 vol % aqueous ethanol containing 1·0 M sodium perchlorate and 0·25 M sodium hydroxide.

The effect of ionic strength and solvent polarity. Both an increase in solvent polarity and an increase in ionic strength should enhance the reaction rate of **2** by preferentially stabilizing the aziridinium ion. The effects of various solvents upon aziridinium ion formation are shown in Table 4. Increasing solvent polarity does indeed give significant rate enhancement.

The solvent parameters of Kosower[29] (Z values), shown in Table 4, are for the corresponding solvent without sodium perchlorate. While this salt would increase

the Z values for all of the solvents listed, it is unlikely that it would change the order of solvent polarity.

Table 5 shows the effects of increasing ionic strength upon the rate of chloride ion formation from **2**. Going from no added sodium perchlorate to 2M sodium perchlorate,

TABLE 4. RATE CONSTANTS FOR THE REACTION OF **2** WITH SODIUM HYDROXIDE IN VARIOUS SOLVENTS[a]

Solvent[b]	10^5k (sec^{-1})	Z[c]
Water	6·50 ± 0·15	94·6
70% Ethanol	1·65 ± 0·1	86·4
90% Methanol	1·37 ± 0·08	85·8
80% Ethanol	1·25 ± 0·07	84·8
95% Ethanol	0·72 ± 0·05	81·2
90% Acetone	0·51 ± 0·03	76·6

[a] Containing 1·0 M sodium perchlorate, and sodium hydroxide; temp 25°.

[b] Percentages are by volume.

[c] Z values [29] are for solvent system with no salt added.

the rate increases by a factor of nearly 3 in 80% ethanol. Although the true ionic strengths for the solutions would be somewhat less than ideal, due to high salt concentrations and low solvent polarity, this would not affect our qualitative conclusion that the increase in rate with increasing solvent polarity and ionic strength supports a reaction mechanism involving an aziridinium ion.

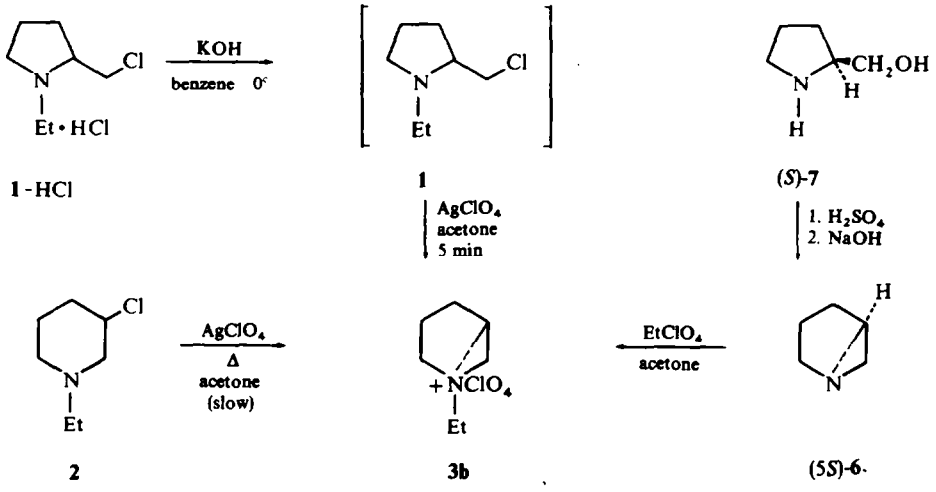
TABLE 5. RATE CONSTANTS FOR THE REACTION OF **2** WITH SODIUM HYDROXIDE AT DIFFERING IONIC STRENGTHS[a]

Sodium perchlorate (M)	10^4k (sec^{-1})	μ[b]
0·0	0·86 ± 0·1	~0·1
0·1	1·20 ± 0·04	~0·2
0·5	1·61 ± 0·07	~0·6
1·0	1·74 ± 0·04	~1·1
2·0	2·35 ± 0·07	~2·1

[a] Run at 45·0° in 80 vol % aqueous ethanol containing sodium hydroxide.

[b] Ionic strength, assuming complete dissociation of the sodium perchlorate.

Synthesis of the aziridinium ion intermediate (**3b**). Three approaches were taken (Scheme 3) to prepare **3b**. 1-Azabicyclo[3,1,0]hexane,[30–32] (5S)-**6**, was prepared from (*S*)-**7** by the method of Gassman[32] and reacted in dry ether with a solution of ethyl perchlorate in absolute ethanol, giving a semisolid product which was extracted with methylene chloride. The optically active extract, (5*S*)-**3b**, exhibited the



SCHEME 3

same PMR spectrum as that for **3b** from the treatment of **2** with silver perchlorate in refluxing anhyd. acetone or from the addition of a solution of silver perchlorate in acetone to an ice-cold solution of **1** in benzene.* The latter reaction, which is complete within 5 min, appears to be the method of choice for preparing **3b**.

The identification of **3b** rests on its PMR[2] and IR spectra and on its reactivity (in typical aziridinium ion fashion) with sodium thiosulfate and sodium hydroxide. (The compound was too unstable and difficult to purify to get an elemental analysis.) The broad IR spectrum of **3b** showed perchlorate bands but no significant absorptions for $C{=}N^+$ or R_3N^+-H, ruling out all reasonable alternative structures.

Further evidence that **3b** is an intermediate was obtained by reacting **3b** with 10% aqueous sodium hydroxide under the same conditions used for the preparative reaction of **2** with sodium hydroxide. The crude reaction product from **3b** gave the same PMR spectrum as that from **2**, indicating formation of the same types and amounts of products.

Kinetics of the reaction of aziridinium ion **3b**. The reaction of aziridinium ions with solvent or other nucleophiles could occur by either of two mechanisms.[5b] They could react directly with nucleophiles in bimolecular (S_N2-type) processes or they

TABLE 6. RATE CONSTANTS FOR THE REACTION OF **3b** WITH NUCLEOPHILES[a]

Nucleophile	$10^3 k_{observed}$ (l. mole^{-1} sec^{-1})
Hydroxide	5·9 ± 0·5
Chloride	3·1 ± 0·3
Acetate	1·9 ± 0·2

[a] Run at 25·0° in 50 vol % aqueous acetone containing 1·0 M sodium perchlorate.

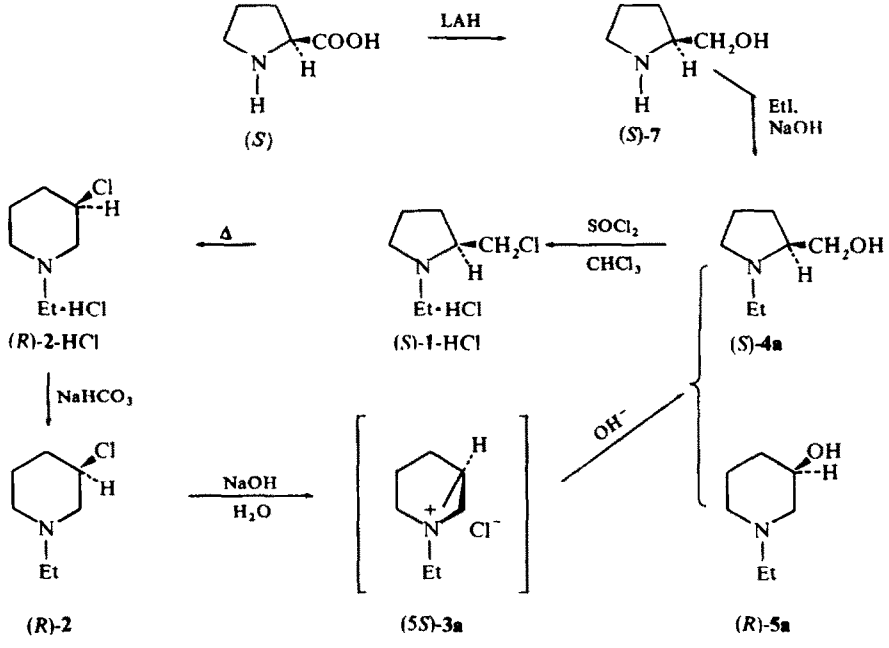
* Further evidence establishing the existence of **1** in benzene solutions will be presented in a later paper

could undergo reversible ring opening to β-amino carbonium ions which could then react by S_N1 types of processes. Kinetic and stereochemical tests can be used to study these two possibilities.

The kinetics of the reaction of **3b** with three nucleophiles were determined, using the well-known procedure[14, 33, 34] of quenching unreacted aziridinium ion with sodium thiosulfate and then back titrating with iodine. The partially purified **3b** was prepared by the reaction of **2** with silver perchlorate. The rate of the reaction of **3b** with three nucleophiles (Table 6) was found to be dependent on the type of nucleophile and to follow second order kinetics. These rates are the unseparated total rates for all reactions in which the aziridinium ion is destroyed.

The uncertainty in the rates of the reaction of **3b** should be noted. This is due to the impure nature of the isolated **3b** (*circa* 95%), to the rapidity of the reaction of **3b** with strong nucleophiles, and to difficulties inherent in the sodium thiosulfate-iodine analysis. The error is estimated at ±10%, and may in addition, contain a component of solvolysis for the reactions involving chloride and acetate. Fortunately, only the demonstrated second order character and dependence on nucleophile type is important in establishing the bimolecularity of the reaction.

Stereochemical study. An optical study concerning the reactions of **2** is shown in Scheme 4. A correction of the stereochemistry shown in Part I of this series[2] should be noted.



SCHEME 4

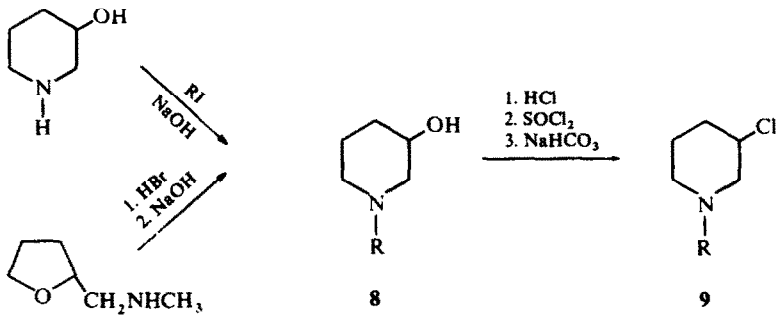
Alkylation of (*S*)-7[32] with ethyl iodide gave (*S*)-**4a**, which was treated with thionyl chloride in chloroform to give (*S*)-1-HCl, which was rearranged to 2-HCl (optically active) upon heating. The ring expansion was expected from the results of Fuson.[18] The optically active free base (**2**) was then isolated from the hydrochloride salt and

refluxed with 10% aqueous sodium hydroxide. Upon work up and spinning band column distillation, two optically active amino alcohols were isolated, **4a** and **5a**. As compared to the original (*S*)-**4a**, the optical purity of **4a** after completing the cycle (Scheme 4) was 98 ± 5%. We suspect that there was no racemization in the formation of **5a**, but this can not be proved since the molar rotation and absolute configuration of **5a** are not known. The essentially total retention of configuration in going from (*S*)-**4a** to **2** and then back to (*S*)-**4a** establishes the optical integrity of each step in the cycle.

In view of the reaction kinetics, anchimeric assistance, and the lack of racemization in the reaction of **2** with sodium hydroxide, **2** must react by a participation mechanism *via* an intermediate aziridinium ion. By working backwards from the product (*S*)-**4a** in the stereochemical cycle (Scheme 4), one can infer the stereochemistry of each compound involved. Formation of (*S*)-**4a** from **3a** would involve displacement of nitrogen from the methylene group of the aziridinium ring by hydroxide. Since the chiral carbon atom is not involved, the stereochemistry of **3** would be 5*S*. Going from **2** to (5*S*)-**3a** *via* the participation mechanism would not involve the chiral carbon atom, indicating an *R* configuration for **2** and **2**-HCl. In the thermal ring expansion of (*S*)-**1**-HCl to **2**-HCl, it was implied[18] but not proved that neighboring group participation by nitrogen was involved. If we now propose that rearrangement of (*S*)-**1**-HCl to **2**-HCl proceeds by dissociation of the salt, aziridinium ion formation, S_N2-type attack of chloride at the methine carbon of the aziridinium ring (inversion of configuration), and then reprotonation by hydrogen chloride, the double inversion in going from (*S*)-**4a** to (*R*)-**2** and back to (*S*)-**4a** will be explained.

This optical circle can not establish whether the reaction of (5*S*)-**3a** with base to give (*S*)-**4a** occurred *via* direct displacement or by way of an amino carbonium ion, since the chiral carbon atom is not involved. The latter mechanism, however, seems unlikely due to the high-energy nature of primary carbonium ions. Also, such an ion might be expected to rearrange rapidly *via* carbon participation to give an unobserved predominance of 6-membered ring products which could contain significant amounts of material resulting from rearrangement of iminium ions.[5b] Since the optical purity of **5a** is not known, one can not rule out some carbonium character in the reaction of (5*S*)-**3a** with hydroxide at the methine carbon to give **5a**. If an achiral secondary carbonium ion is involved, however, it cannot be formed reversibly, since this would racemize (5*S*)-**3a**, which would result in racemized (*S*)-**4a**. Irreversible formation of a secondary carbonium ion followed by base or solvent capture to give **5a** does not seem as likely as S_N2-type attack by hydroxide. The *R* configuration is being assigned tentatively to optically active **5a**, based on the likelihood it is formed from (5*S*)-**3a** by an S_N2-type mechanism.

Kinetics of 1-*alkyl*-3-*chloropiperidines*. Some β-chloro amines closely related to **2** were also investigated. The effectiveness of nitrogen in displacing the β-chloro group should be related to the availability of its lone pair of electrons and to any steric destabilization of the aziridinium ion by the substituent on the nitrogen atom, as compared to the 1-alkyl-3-chloropiperidine precurser. Compound **8a** was prepared from N-methyltetrahydrofurfurylamine by a method similar to that of Biel[35] (Scheme 5). The other 3-hydroxypiperidines (**8b-8d**) were prepared by direct alkylation of 3-hydroxypiperidine with the corresponding alkyl iodides and sodium hydroxide. The 1-alkyl-3-hydroxypiperidines (**8**) were converted to the corresponding β-chloro



a: R = Me; b: R = *n*-Pr; c: R = *i*-Pr; d: R = *n*-Bu

SCHEME 5

amine hydrochlorides (**9**·HCl) by treatment in chloroform first with hydrogen chloride gas and then with thionyl chloride. The β-chloro amine hydrochlorides were then converted to the free bases (**9**).

Table 7 shows the effect of 1-alkyl substitution of 3-chloropiperidine on the rate of aziridinium ion formation. It might be suggested that competing inductive and steric factors are responsible for this order; however the trend does not appear sufficiently clear to merit detailed analysis.

TABLE 7. RATE CONSTANTS FOR THE REACTION OF 1-ALKYL-3-CHLORO-PIPERIDINES WITH SODIUM HYDROXIDE[a]

Alkyl substituent	$10^5 k$ (sec^{-1})
Methyl (**9a**)	3·75 ± 0·14
Ethyl (**2**)	17·5 ± 0·40
n-Propyl (**9b**)	4·81 ± 0·17
i-Propyl (**9c**)	8·65 ± 0·23
n-Butyl (**9d**)	6·48 ± 0·25

[a] Run at 45·0° in 80 vol % aqueous ethanol containing 1·0 M sodium perchlorate and sodium hydroxide.

CONCLUSION

Synthetic, kinetic and stereochemical evidence have confirmed that **2** reacts with nucleophiles *via* a two-step neighboring group participation mechanism involving the intervention of a bicyclic aziridinium ion intermediate (**3**), formed by the initial rate-determining displacement of chloride by nitrogen *via* an "internal backside nucleophilic substitution" ($S_Ni b$) mechanism. The second step involves the attack of available nucleophiles on **3**, probably by an S_N2-type of displacement, to give 5- and 6-membered ring products.

EXPERIMENTAL

M.ps are corrected. B.ps are uncorrected. PMR spectra were recorded on a Varian Associates A-60 spectrometer. Chemical shifts (δ) are relative to TMS as an internal standard. IR spectra were obtained on a Perkin–Elmer Model 521 grating infrared spectrophotometer. Chemical analyses were performed by Organic Microanalyses. Montreal. Canada. or on a Perkin–Elmer Model 240 elemental analyzer. All pK_a values were obtained on a Metrohm Potentiograph Model E336A. Commercial cyclohexyl chloride was distilled.

3-Chloro-1-ethylpiperidine (**2**). Excess solid $NaHCO_3$ was slowly added to a vigorously stirred aqueous soln (200 ml) of **2**-HCl (100 g. 0·53 mol) overlayed with ether (300 ml). The ether layer was separated. dried ($MgSO_4$). and the ether removed *in vacuo*. The residue was vacuum distilled. and **2** (46 g. 48%) collected at 39–40° (2 mm); η_D^{27} 1·4646 [lit.[18] b.p. 74–76° (20 mm). η_D^{20} 1·4678].

Reaction of **2** *with sodium hydroxide.* A mixture of **2** (14·7 g. 0·010 mol) in 10% aq NaOH (100 ml) was refluxed for 5 hr. cooled in ice. and the β-hydroxy amines extracted with ether (10 × 50 ml). The ether extracts were dried ($MgSO_4$) and the ether removed *in vacuo*. The residue was vacuum distilled on a 90 cm spinning band column, yielding **4a** [4·3 g, 0·034 mol. b.p. 90–91° (30 mm), η_D^{27} 1·4662] and **5a** [2·3 g, 0·017 mol. b.p. 106–108° (30 mm), η_D^{27} 1·4756] in an overall yield of 51% [reported for **4a**[36] b.p. 82–84° (24 mm), η_D^{25} 1·4662. and reported for **5a**[37] b.p. 97–98° (21 mm). η_D^{23} 1·4743]. Continuous ether extraction for three days improved yields to over 65%.

Reaction of **2** *with benzylamine.* A soln of benzylamine (11 g. 0·10 mol) and **2** (14·7 g. 0·10 mol) in water (30 ml) was heated for 2 days at 65–70°. After cooling. the semi-solid mixture was dissolved in water (50 ml) and overlayed with ether (300 ml). Excess $NaHCO_3$ was added to the mixture. and. after vigorous shaking. the ether was decanted and the remaining aqueous layer extracted with ether (2 × 50 ml). The combined ether extracts were dried ($MgSO_4$) and the ether removed *in vacuo*. The residue was vacuum distilled. giving **4b**: 17 g; 80%; b.p. 110–112° (0·1 mm) [lit.[24] b.p. 126° (0·5 mm)].

Reaction of **2** *with dibenzylamine.* The procedure was identical to the preceding reaction. Compound **4c** (24 g. 70%) was collected at 180–185° (0·1 mm). (Found: C. 82·31; H. 8·78; N. 8·96. Calcd. for $C_{19}H_{28}N_2$: C. 81·81; H. 9·09; N. 9·09%).

Reaction of **2** *with sodium cyanide.* A soln of **2** (14·7 g. 0·10 mol) and NaCN (6·4 g. 0·13 mol) in 80 vol % aqueous EtOH (50 ml) was refluxed for 2 hr. After cooling. 95% EtOH (50 ml) was added and the mixture filtered. The remaining EtOH was removed from the filtrate *in vacuo* and the residue extracted with ether (3 × 25 ml). The combined ether extracts were dried ($MgSO_4$) and the ether removed *in vacuo*. The residue was vacuum distilled, giving **4d**; 9·5 g; 68%; b.p. 98–100° (10 mm); η_D^{25} 1·4608 [lit.[23] b.p. 108–108·6° (20 mm), η_D^{21} 1·4626].

Reaction of **2** *with sodium acetate.* A soln of **2** (14·7 g, 0·10 mol) in Ac_2O (25 ml) was slowly added to a soln of NaOAc (16·4 g. 0·20 mol) in Ac_2O (50 ml). and the mixture refluxed for 6 hr. A PMR spectrum of the product showed a mixture of **4e** and **5e** in a ratio of *circa* 20:80. Upon heating the same materials at 90° for 8 hr. a PMR spectrum showed **4e** and **5e** in a ratio of 75:25. Then heating the latter mixture at 106–107° for one day produced no change in the ratio; however. continued heating at 126–127° for 6 days caused a slow isomerization of **4e** to **5e** ($T_{1/2} \simeq 60$ hr). Heating a 50:50 mixture of **4e** to **5e** for one day at 90° caused no change in composition. as measured by PMR.

3-Acetoxy-1-ethylpiperidine (**5e**). A soln of **5a** (10·2 g. 0·080 mol) in Ac_2O (112 g. 1·2 mol) was refluxed overnight. cooled, and made basic with 50% aq NaOH. The aqueous layer was extracted with ether (5 × 50 ml). the combined ether extracts dried ($MgSO_4$). and the ether removed *in vacuo*. The residue was vacuum distilled. giving **5e**: 7·8 g; 59%; b.p. 93–95° (10 mm): η_D^{25} 1·4504 [lit.[23] b.p. 100·4–101·6° (20 mm); $\eta_D^{22.5}$ 1·4518].

1-Ethyl-1-azoniabicyclo[3.1.0]*hexane perchlorate* (**3b**)

Method 1. from **2**. A soln of **2** (14·8 g. 0·10 mol) in dry acetone (50 ml) was added to a soln of anhydrous silver perchlorate (21 g. 0·10 mol) in dry acetone (100 ml). The mixture was refluxed overnight. the AgCl removed by filtration. and the acetone evaporated *in vacuo*. The remaining light brown oil was dissolved in dry CH_2Cl_2 and filtered. The CH_2Cl_2 was then removed *in vacuo*. giving a yellow oil. which was identified as **3b** by PMR[2] and IR spectra.

2-Chloromethyl-1-ethylpyrrolidine hydrochloride (**1**-HCl). To a solution of **4a** (5·0 g. 0·039 mol) in EtOH free $CHCl_3$ (15 ml) was slowly added a soln of $SOCl_2$ (9·7 g. 0·089 mol) in $CHCl_3$ (5 ml). while stirring and cooling in an ice bath. Then. the mixture was refluxed for 2 hr. cooled. and concentrated to dryness *in vacuo*. The residue was decolourized twice (Nuchar C-190 N) from water and recrystallized from acetone-EtOH. giving **1**-HCl as very fine needles: 3·6 g; 51%; m.p. 197–198° [lit.[18] m.p. 193·5–194°].

1-Ethyl-1-azoniabicyclo[3.1.0]*hexane perchlorate* (**3b**)

Method 2. from **1**-HCl. A soln of **1**-HCl (2·0 g, 0·010 mol) in water (2 ml) was overlayed with benzene (25 ml), cooled to 0°, and made basic with 50% aq NaOH (1 ml) and then anhyd K_2CO_3 (3 g). After vigorously swirling, the benzene layer was decanted and the residue further extracted with benzene (2 × 10 ml). The combined benzene extracts were dried (K_2CO_3) and then filtered into a stirred soln of silver perchlorate (2·3 g, 0·010 mol) in acetone (25 ml). The mixture was then stirred for 5 min, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* below 40°, giving a clear syrup: 1·9 g; 82%. The PMR spectrum of this product (CH_2Cl_2) was the same as that for **3b** prepared by Method 1, except that a small benzene impurity peak, but less acetone, was present.

3-Iodo-1-methylpiperidine methiodide. Excess MeI was added to a soln of freshly distilled (5*S*)-**6**[32] (5 g, 0·060 mol) in dry ether (20 ml). The ether was removed *in vacuo* and the residue recrystallized from EtOAc: m.p. 208–212° [lit.[30] m.p. 210–215° (dec)].

(5*S*)-*1-Ethyl-1-azoniabicyclo*[3.1.0]*hexane perchlorate* [(5*S*)-**3b**]

Method 3. from (5*S*)-**6**. A soln of ethyl perchlorate (1·3 g, 0·010 mol, freshly prepared from EtI and silver perchlorate in abs EtOH) in EtOH was added to a soln of freshly distilled (5*S*)-**6**[32] (0·80 g, 0·010 mol) in dry ether (25 ml) and the combined solns evaporated to dryness *in vacuo*, yielding a white paste. Extraction of (5*S*)-**3b** with dry CH_2Cl_2 and concentration *in vacuo* gave a clear oil whose PMR spectrum was the same as that obtained for **3b** by Methods 1 and 2.

When reacted with 10% aq NaOH for 5 hr, samples from both Methods 1 and 3 gave the same ratios of products (determined by PMR) as did **2**. The IR spectrum of the mixture showed only O–H and C–H absorptions in the 3000 cm^{-1} region and above and no other significant peaks down to 1500 cm^{-1}.

(*S*)-*2-Chloromethylpyrrolidine hydrochloride.* A soln of (*S*)-**7**[32] (10 g, 0·10 mol) in dry $CHCl_3$ (50 ml) was saturated with HCl gas, and then a soln of $SOCl_2$ (14 g, 0·20 mol) in dry $CHCl_3$ (50 ml) was added (with ice-cooling) over a period of 1 hr. Afterwards, the soln was allowed to attain room temp, and the $CHCl_3$ removed *in vacuo*. The residue was decolourized 4 times (charcoal) in MeOH and recrystallized from EtOH, giving (*S*)-2-chloromethylpyrrolidine hydrochloride: 8·3 g; 56%; m.p. 143–144° [lit. m.p.[38] 141–142° and m.p.[31] 145°].

(*S*)-*1-Ethyl-2-hydroxymethylpyrrolidine* [(*S*)-**4a**]. A soln of EtI (33 g, 0·20 mol) in abs EtOH (50 ml) was slowly added to an ice-cooled soln of (*S*)-**7**[32] (20 g, 0·20 mol) containing powdered anhyd K_2CO_3 (30 g) in abs EtOH (50 ml). The mixture was refluxed for 18 hr, cooled and filtered. The filtrate was then acidified with conc HCl and concentrated to dryness *in vacuo*. The residue was dissolved in water (50 ml), saturated with KOH, and extracted with ether (7 × 50 ml). The combined ether extracts were concentrated to 100 ml *in vacuo*, dried ($MgSO_4$), and the ether removed *in vacuo*. The residue was vacuum distilled and (*S*)-**4a** (19 g, 75%) collected at 80–82° (20 mm). η_D^{27} 1·4660 [reported[36] for racemic **4a**, b.p. 82–84° (24 mm), η_D^{25} 1·4662].

(*S*)-*2-Chloromethyl-1-ethylpyrrolidine hydrochloride* [(*S*)-**1**-HCl]. The same procedure was used as that for **1**-HCl. From (*S*)-**4a** (20 g, 0·15 mol) was obtained 14·7 g (53%) of (*S*)-**1**-HCl: m.p. 194–196°.

(*R*)-*3-Chloro-1-ethylpiperidine* [(*R*)-**2**]. Compound (*S*)-**1**-HCl was heated at the m.p. for several minutes and then worked up as for the preparation of **2**. The same results were obtained.

Reaction of (*R*)-**2** *with sodium hydroxide.* This was performed by the same method and the results were the same as for the reaction of **2** with NaOH. The optical consequences are reported in the section on ORD data.

3-Hydroxy-1-methylpiperidine (**8a**). HBr gas (160 g, 2·0 mol) was slowly passed into a warmed (100–110°) soln of N-methyltetrahydrofurfurylamine (127 g, 1·0 mol) in glacial AcOH (72 g, 1·2 mol). The soln was then cooled below 25°, and very slowly neutralized with 50% aq KOH. Additional KOH (500 g in 400 ml water) was slowly added, and the soln distilled until aliquots of distillate no longer gave an oily layer when saturated with KOH. The distillate was then extracted with ether (4 × 250 ml), and the combined ether extracts concentrated to 250 ml *in vacuo*, dried ($MgSO_4$), and the ether removed *in vacuo*. The residue was vacuum distilled, giving **8a**: 95 g; 74%; b.p. 78–80° (14 mm); η_D^{27} 1·4741 [lit.[35] b.p. 80–82° (15 mm), lit.[39] b.p. 79° (15 mm), η_D^{16} 1·4695].

3-Chloro-1-methylpiperidine (**9a**). A soln of **8a** (34 g, 0·30 mol) in dry $CHCl_3$ (100 ml) was saturated with HCl gas, and then a soln of $SOCl_2$ (44 g, 0·40 mol) in dry $CHCl_3$ (100 ml) was slowly added. The mixture was refluxed for 3 hr, cooled, and the $CHCl_3$ removed *in vacuo*. The residue was dissolved in water (75 ml), overlayed with ether (200 ml), and excess solid $NaHCO_3$ added. After vigorous stirring, the ether layer was separated, dried ($MgSO_4$), and the ether removed *in vacuo*. The residue was vacuum distilled, and **9a** (18 g, 45%) collected at 49–50° (15 mm). η_D^{27} 1·4705 [lit.[20] b.p. 52–53° (16–17 mm), η_D^{20} 1·4677].

3-Hydroxy-1-n-propylpiperidine (**8b**). The procedure was the same as that for (*S*)-**4a**. Compound **8b**

was obtained in 74% yield from 3-hydroxypiperidine and n-propyl iodide: b.p. 117–120° (25 mm); η_D^{27} 1·4635 [lit.[39] b.p. 76–77° (5 mm). η_D^{15} 1·4589].

3-Chloro-1-n-propylpiperidine (**9b**). The procedure was identical to that for **9a**. Compound **9b** was prepared in 56% yield from **8b**: b.p. 55–57° (1 mm); η_D^{27} 1·4628 [lit.[40] b.p. 55–56° (7 mm). η_D^{23} 1·4651].

The picrate of **9b** was also prepared. m.p. 164–166°. (Found: C, 42·92; H, 4·77; N, 14·24. Calcd. for $C_{14}H_{19}ClN_4O_7$: C, 43·04; H, 4·88; N, 14·34%).

3-Hydroxy-1-i-propylpiperidine (**8c**). The procedure was the same as that for (*S*)-**4a**. Compound **8c** was obtained in 68% yield from 3-hydroxypiperidine and i-propyl iodide: b.p. 96–98° (13 mm); η_D^{27} 1·4771 [lit.[41] b.p. 99–100° (17 mm)].

3-Chloro-1-i-propylpiperidine (**9c**). The procedure was the same as that for **9a**. Compound **9c** was prepared in 32% yield from **8c**: b.p. 56–59° (3 mm); η_D^{26} 1·4673.

The picrate of **9c** was also prepared. m.p. 157–159°. (Found: C, 42·89; H, 4·98; N, 14·28. Calcd. for $C_{14}H_{19}ClN_4O_7$: C, 43·04; N, 4·88; N, 14·34%).

1-n-Butyl-3-hydroxypiperidine (**8d**). The procedure was identical to that for (*S*)-**4a**. Compound **8d** was obtained in 70% yield from 3-hydroxypiperidine and n-BuI: b.p. 98–100° (4 mm); η_D^{22} 1·4707 [lit.[42] b.p. 104–107° (12 mm). η_D^{20} 1·4712].

1-n-Butyl-3-chloropiperidine (**9d**). The procedure was identical to that for **9a**. Compound **9d** was prepared in 43% yield from **8d**: b.p. 67–70° (3 mm); η_D^{22} 1·4645 [lit.[43] b.p. 102–104° (29 mm). η_D^{22} 1·4644].

Kinetics. Kinetics were run in a Magni-Whirl MR-3220-A constant temp water bath (±0·1° control) from the Blue M Electric Co. Organic nucleophiles were checked for purity by determining their refractive indices and PMR spectra. Inorganic nucleophiles were Fisher Scientific Co. or J. T. Baker Chemical Co. reagents, and were used without further purification.

Kinetic data were obtained for the β-chloro amines by following the rate of formation of chloride using the general procedure of Bartlett,[9] with the following modifications: Chloride ion concentration was determined potentiometrically, using a silver-silver chloride combination electrode[44] and an automatic differential titrator apparatus.[45] which produced a voltage proportional to the second derivative of the plain potentiometric titration curve, and recorded the results on a strip-chart. A constant flow rate of silver ions (0·1000 N $AgNO_3$) was obtained from a Mariott bottle.[46]

For each kinetic run at 25·0, 45·0, or 62·0°, approximately 0·01 to 0·03 mol (generally 0·02 mol) of the nucleophile or the sodium salt of the nucleophile was dissolved in the appropriate solvent. About 0·01 mol of the appropriate β-chloro amine was also dissolved in the appropriate solvent, and the two solutions were then combined in a 50 or 100 ml volumetric flask and diluted to volume. The volumetric flask was shaken vigorously and the soln quickly poured into a round-bottom flask, immersed in the constant temp bath. The soln was continuously mechanically stirred. Aliquots of 5 or 10 ml were removed at various times and quickly poured into a separatory funnel containing benzene (10 ml) and distilled water (10 ml). The funnel was thoroughly shaken and the aqueous layer drained into a 30 ml beaker containing 70% perchloric acid (3 ml). This soln was then stirred and potentiometrically titrated with $AgNO_3$. Before each series of titrations, aliquots of standard 0·1000 N NaCl were titrated quantitatively to standardise the apparatus. All nucleophiles and solvents were run as blanks, and were found to contain no detectable chloride.

For kinetic runs at 80·5° (cycloalkyl chlorides), the kinetic solns were prepared exactly as described previously, poured into a buret, and 5·00 ml aliquots placed in 7 ml Pyrex ampoules and sealed. The ampoules were placed in the water bath simultaneously and removed individually at appropriate time intervals, cooled quickly with running water, cut open, and poured into a separatory funnel containing distilled water (7 ml) and benzene (10 ml). The ampoules were then rinsed with distilled water (3 × 1 ml). The combined aqueous extracts were analyzed as previously described.

Attempts were made to run all reactions through two to three half lives. From 8 to 17 points were taken for each kinetic run and two or more runs were performed for each set of conditions. The rate constant, half life, and error analysis (average deviation) were determined from the raw data of each run by a computer program for the calculation of kinetic data following first-order kinetics.[47] The program, which averaged the instantaneous rate constants for each of the points of a given run, was written in Fortran II and run on an IBM 1620-II computer.

The kinetics of the second step of the reaction were determined at 25° by following the disappearance of **3b** in a manner similar to that used by previous workers.[34] A solution of **3b** in 50 vol % aqueous acetone containing 1·0 M sodium perchlorate, and a soln of an equimolar amount (±10%) of the appropriate nucleophile in the same solvent, were quickly poured into a 100 ml volumetric flask, diluted to volume, and transferred to a flask in the constant temp bath. At appropriate time intervals, 10 ml aliquots were removed

and quenched with excess $Na_2S_2O_3$. Then a 25 ml aliquot of 1 M AcOH-NaOAc buffer (pH 4·65) was added. After 3 hrs unreacted thiosulfate was titrated with a 0·1000 N I_2 soln to a starch end point. Second order rate constants were computed in the usual manner.

Optical rotatory dispersion data. ORD spectra were obtained on a Cary 60 or a Jasco ORD-CD Model 5 spectropolarimeter (water. except where noted) in 1 cm cells. and are reported in terms of molecular rotation. $[\phi]$. The cell compartment temp was 26–28°. The accuracy is estimated at ±5%.

(*S*)-L-*Proline*: $[\phi]_D$ −90°. $[\phi]_{300}$ −542°. $[\phi]_{220}$ −1660°. $[\phi]_{210}$ −3220°. $[\phi]_{202}$ −4650° (trough). $[\phi]_{195}$ −3740° [lit.[48] $[\phi]_D$ −99° (water)]. This was the commercial material used for synthesizing (*S*)-7.

(*S*)-7:[32] $[\phi]_D$ +10°. $[\phi]_{525}$ 0°. $[\phi]_{400}$ −7°. $[\phi]_{390}$ +16°. $[\phi]_{230}$ +316°. $[\phi]_{220}$ +502°. [lit.[49] $[\phi^{18}]_D$ +1°].

(*S*)-*Pyrrolidine-2-methylsulfuric acid*:[32] $[\phi]_D$ +442°. $[\phi]_{300}$ +2280°. $[\phi]_{200}$ +6500°. $[\phi]_{190}$ +7400°.

(5*S*)-**6**:[32] Freshly distilled (5*S*)-**6** was diluted in dry ether. A qualitative scan from 600 to 250 nm gave a plain negative curve. [lit.[32] $[\phi]^{28}_D$ −16°].

(5*S*)-**3b**: A qualitative curve of (5*S*)-**3b** in dry MeOH from 600 to 240 nm gave a plain negative curve.

3-*Iodo*-1-*methylpiperidine methiodide* (MeOH): $[\phi]_D$ −89°. $[\phi]_{400}$ −465°. $[\phi]_{300}$ −1190°. $[\phi]_{250}$ −2240°.

(*S*)-**4a**: $[\phi]_D$ −105°, $[\phi]_{400}$ −640°, $[\phi]_{250}$ −1210°, $[\phi]_{230}$ −1610°, $[\phi]_{200}$ −4650°, $[\phi]_{190}$ −4100°.

(*S*)-2-*Chloromethylpyrrolidine hydrochloride*: $[\phi]_D$ +78°. $[\phi]_{300}$ +355°. $[\phi]_{200}$ +1280°. $[\phi]_{195}$ +1400°.

(*S*)-**4a** (from reaction of (*R*)-**2** with NaOH. going through the ring expansion and ring contraction cycle): $[\phi]_D$ −96°. $[\phi]_{400}$ −258°. $[\phi]_{350}$ −405°. $[\phi]_{300}$ −655°. $[\phi]_{250}$ −1140°. $[\phi]_{230}$ −1630°. The percentage difference in rotation (initial (*S*)-**4a** *versus* (*S*)-**4a** from ring expansion and ring contraction), calculated at each wavelength reported for the latter, gave an average loss of rotation of 2 ± 5%.

(*S*)-**5a** (from reaction of (R)-**2** with NaOH): $[\phi]_D$ −102°. $[\phi]_{350}$ −435°. $[\phi]_{300}$ −800°. $[\phi]_{250}$ −1160°.

(*S*)-**1**-*HCl*: $[\phi]_D$ −143°. $[\phi]_{400}$ −190°. $[\phi]_{300}$ −255°. $[\phi]_{200}$ −605°.

(*R*)-**2**-*HCl*: $[\phi]_D$ +50°. $[\phi]_{540}$ 0°. $[\phi]_{400}$ −145°. $[\phi]_{300}$ −590°. $[\phi]_{210}$ −1500°.

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