Preparation of Optically Active Piperazines from Ethyl (*S*)-2-(2-Alkyl-1-aziridinyl)acetates

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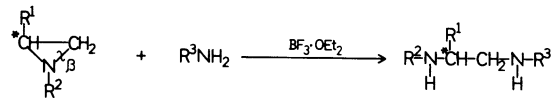
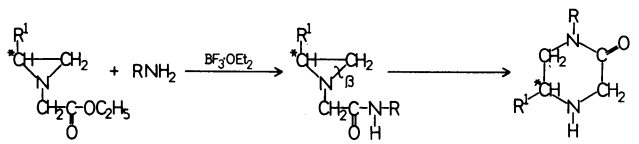
Synopsis. Reaction of ethyl (*S*)-2-(2-alkyl-1-aziridinyl) acetates with boron trifluoride etherate in a large excess of ethylamine or ammonia gives the corresponding optically active piperazines in good yields. These piperazines retain the configuration of the starting aziridines.

Optically active piperazine derivatives are usually prepared by dimerization of optically active aziridines,[1] by optical resolution of racemic piperazines,[2] or by cyclization of optically active amino acid derivatives,[3,4] but these processes are inconvenient because they involve complicated procedures. It was reported[5] that optically active aziridines react with amines under the catalytic action of boron trifluoride etherate ($BF_3 \cdot OEt_2$) to give optically active diamines:



R^1; C_2H_5, *i*-C_4H_9, R^2; H, C_2H_5, R^3; H, C_2H_5

The ring-opening reaction of an optically active aziridine (R^2=alkyl) with a nucleophilic reagent was found to proceed by β-cleavage (CH_2–N) to give the corresponding diamine retaining the configuration of the starting aziridine.[6,7] If ethyl (*S*)-2-(2-isobutyl-1-aziridinyl)acetate (**1**) is used in the above reaction, 3,6-diaza-1-ethoxy-4-isobutyl-1-octanone (R^1=*i*-C_4H_9, R^2=$CH_2COOC_2H_5$, R^3=C_2H_5) is expected to be produced. But the reaction of **1** with a large excess of ethylamine was found to give (*S*)-*N*-ethyl-2-(2-isobutyl-1-aziridinyl)acetamide (**2**) and (*S*)-1-ethyl-5-isobutyl-2-piperazinone (**3**) but no optically active diamines. In a similar procedure, optically active 2-(2-isobutyl-1-aziridinyl)acetamide (**4**) and 5-isobutyl-2-piperazinone (**5**) were prepared from **1** and ammonia:

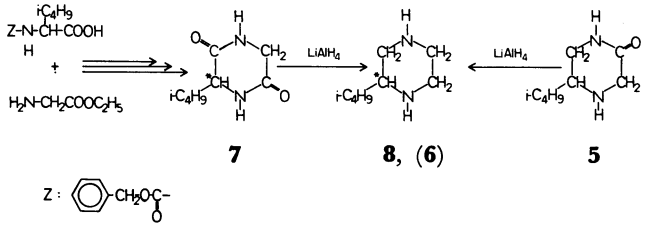


R^1=*i*-C_4H_9, **1**
R^1=C_2H_5, **9**

R^1=*i*-C_4H_9, R=C_2H_5, **2**
R^1=*i*-C_4H_9, R=H, **4**
R^1=R=C_2H_5, **10**

R^1=*i*-C_4H_9, R=C_2H_5, **3**
R^1=*i*-C_4H_9, R=H, **5**
R^1=R=C_2H_5, **11**

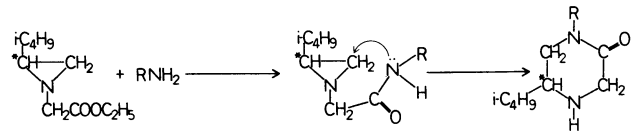
The configuration and structure of **5** were confirmed by direct comparison with an authentic sample. Optically active 2-isobutylpiperazine (**6**) was prepared by the reduction of **5** with lithium aluminium hydride ($LiAlH_4$). To determine the stereochemistry of **6**, (*S*)-2-isobutylpiperazine (**8**) was prepared by the reduction of (*S*)-3-isobutyl-2,5-piperazinedione (**7**)[3] with $LiAlH_4$:



7 **8**, (**6**) **5**

Z:

Compounds **6** and **8** showed identical ORD, CD, and IR spectra and retention times in GLC. **6**: ORD (MeOH) $[\Phi]_{205}$ +2790° and $[\Phi]_{220}$ +320°, in a positive simple dispersion curve; CD (MeOH) $[\theta]_{205}$ −350 and $[\theta]_{220}$ −110, in a negative simple dispersion curve; $[\alpha]_D^{15}$ +7.0° (*c* 2.33, EtOH); IR (neat) 3225 and 1520 cm^{-1}. **8**: ORD (MeOH) $[\Phi]_{205}$ +2850° and $[\Phi]_{220}$ +320°, in a positive simple dispersion curve; CD (MeOH) $[\theta]_{205}$ −360 and $[\theta]_{220}$ −110, in a negative simple dispersion curve; $[\alpha]_D^{15}$ +6.8° (*c* 1.07, EtOH); IR (neat) 3225 and 1520 cm^{-1}. In due course of these experiments, an effort was made in vain to determine the configuration and structure of piperadinones **3** and **5** since neither of these isomers was formed as expected. On the other hand, the reaction of **2** with $BF_3 \cdot OEt_2$ in a large excess of ethylamine was found to give **3** in a good yield. The fact that **2** and **4** gave optically active **3** and **5** with retained configuration, respectively, suggests occurrence of an intramolecular nucleophilic displacement of an intermediate acetamide derivative:



R; H, C_2H_5

Similarly, (*S*)-*N*-ethyl-2-(2-ethyl-1-aziridinyl)acetamide (**10**) and (*S*)-1,5-diethyl-2-piperazinone (**11**) were prepared from ethyl (*S*)-2-(2-ethyl-1-aziridinyl) acetate (**9**) and ethylamine.

Experimental

Materials. Ethylamine, ammonia, and $BF_3 \cdot OEt_2$ were commercial materials and were purified before use. (*S*)-2-Isobutylaziridine, with $[\alpha]_D^{25}$ −19.6° (*c* 2.02, EtOH) and bp 127—130 °C, was converted to **1**, with yield 89%, $[\alpha]_D^{25}$ +23.6° (*c* 2.63, EtOH), and 109—111 °C/17 mmHg (1 mmHg=133.322 Pa), by treating it with ethyl chloroacetate and triethylamine.[8] In a similar procedure, **9** was prepared by the reaction of (*S*)-2-ethylaziridine, with $[\alpha]_D^{25}$ −23.0° (*c* 1.54, EtOH) and bp 89—90 °C, with ethyl chloroacetate. **9**: yield 86%; bp 87—90 °C/18 mmHg; $[\alpha]_D^{25}$ +4.5° (*c* 1.02, MeOH).

Amide and Piperazine Derivatives. A large excess of ethylamine (5.4 g, 0.12 mol) and **1** (3.7 g, 0.02 mol) were placed in a stainless steel tube cooled in a Dry Ice-methanol bath, and $BF_3 \cdot OEt_2$ (0.4 cm³) was added to the mixture. The stainless steel tube was sealed and allowed to stand at 95—98 °C. After 72 h, the reaction mixture was dissolved in benzene and washed with 10% sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and the solution was distilled under reduced pressure. The product **3** (2.8 g, 76%) was obtained as colorless liquid: $[\alpha]_D^{25}$ +79.0° (*c* 0.61, EtOH); bp 106—107 °C/2 mmHg, ORD (MeOH) $[\Phi]_{300}$ +730°, $[\Phi]_{248}^{peak}$ +1880°, $[\Phi]_{243}^{trough}$ +1840°, and $[\Phi]_{220}$ +11800°, in a positive abnormal dispersion curve; CD (MeOH) $[\theta]_{223}^{trough}$ −3700 with crossover point 217 nm; IR (neat) 3275, 2940, 1635, 1496, 1465, 1430, 1304, 1213, 1164, and 791 cm⁻¹. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20%. Found: C, 64.87; H, 10.96; N, 15.19%.

In a similar procedure, **2** was prepared by the reaction of **1** with ethylamine at room temperature for 24 h. From the crude mixture (**2** and **3**), **2** was obtained by a fractional distillation: yield 54%; bp 78—80 °C/1 mmHg, $[\alpha]_D^{20}$ +31.9° (*c* 1.40, EtOH); ORD (MeOH) $[\Phi]_{300}$ +110° and $[\Phi]_{215}$ +2250°, in a positive simple dispersion curve; CD (MeOH) $[\theta]_{210}^{trough}$ −1350; IR (neat) 3300, 3050, 2960, 1650, 1535, 1332, 1293, 1251, 1168, and 828 cm⁻¹. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20%. Found: C, 64.68; H, 10.95; N, 15.33%. Compounds **4** and **5** were prepared from **1** and ammonia in similar procedures. Each product was purified by column chromatography (developing solvent MeOH/acetone) on silica gel. **4**: yield 58%; mp 78—81 °C; $[\alpha]_D^{20}$ +42.1° (*c* 0.27, MeOH); ORD (MeOH) $[\Phi]_{300}$ +570° and $[\Phi]_{215}$ +1580°, in a positive simple dispersion curve; CD (MeOH) $[\theta]_{216}^{trough}$ −650 with crossover point 205 nm; IR (KBr) 3390, 3180, 3045, 2950, 1630, 1463, 1412, 1396, 1327, 1234, 1170, 867, 782, and 705 cm⁻¹. **5**: yield 42%; mp 77—79 °C, $[\alpha]_D^{20}$ +80.9° (*c* 0.21, MeOH); ORD (MeOH) $[\Phi]_{300}$ +430°, $[\Phi]_{263}^{peak}$ +810°, $[\Phi]_{242}^{trough}$ +680°, and $[\Phi]_{220}$ +9800°, in a positive abnormal dispersion curve; CD (MeOH) $[\theta]_{221}^{trough}$ −5650 with crossover point 214 nm; IR (KBr) 3210, 2945, 1692, 1653, 1493, 1462, 1365, 1117, 916, 830, and 786 cm⁻¹. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93%. Found: C, 61.08; H, 10.34; N, 18.01%.

Compounds **10** and **11** were prepared from **9** and ethylamine. **10**: yield 65%; bp 88—89 °C/4 mmHg; $[\alpha]_D^{20}$ +11.2° (*c* 0.91, EtOH); ORD (MeOH) $[\Phi]_{300}$ +70° and $[\Phi]_{215}$ +1340°, in a positive simple dispersion curve; CD (MeOH) $[\theta]_{213}^{trough}$ −790; IR (neat) 3375, 3048, 2960, 1652, 1534, 1375, 1295, 1253, 1168, and 828 cm⁻¹. **11**: yield 70%, bp 104—105 °C/3 mmHg; $[\alpha]_D^{20}$ +82.8° (*c* 1.44, EtOH); ORD (MeOH) $[\Phi]_{300}$ +450°, $[\Phi]_{247}^{peak}$ +1150°, $[\Phi]_{243}^{trough}$ +1100°, and $[\Phi]_{220}$ +7200°, in a positive abnormal dispersion curve; CD (MeOH) $[\theta]_{223}^{trough}$ −2250 with crossover point 215 nm; IR (neat) 3290, 2965, 1637, 1496, 1458, 1430, 1305, 1215, 1171, 830, and 791 cm⁻¹. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93%. Found: C, 61.03; H, 10.39; N, 18.16%.

Reduction of 7. A solution of **7** (1.7 g, 0.01 mol) in 25 cm³ of diethyl ether was added to a diethyl ether solution (25 cm³) of $LiAlH_4$ (0.43 g, 0.011 mol) at 0 °C. The mixture was stirred for 48 h and the reaction was terminated by adding water. The organic layer was dried over anhydrous magnesium sulfate and the solution was concentrated under reduced pressure. The product **8** was purified by sublimation: yield 64%; mp 85—87 °C (hygroscopic); $[\alpha]_D^{15}$ +6.8° (*c* 1.07, EtOH).

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