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A New Synthesis of Aziridines from β-Amino Alcohols with Triphenylphosphine Dibromide

Itaru OKADA, Kunihiro ICHIMURA and Rokuro SUDO

Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo

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The reaction of β-amino alcohols with triphenylphosphine dibromide was found to give the corresponding aziridines in good yields. The reaction opened a new route to the synthesis of aziridine compounds which seems to be more convenient than the Gabriel and Wenker methods. In the ring closure of ephedrine, a Walden inversion was observed. A possible mechanism is suggested.

Aziridine derivatives are usually prepared from β-amino alcohols by the Gabriel method or by the Wenker method,[1] but both methods are inconvenient because they involve two-step syntheses *via* β-amino hydrogen sulfates or β-haloamines.

In the present paper, a new one-step method is reported; by means of this method β-amino alcohols were rapidly converted to aziridines by using triphenylphosphine dibromide under mild reaction conditions.

Results and Discussion

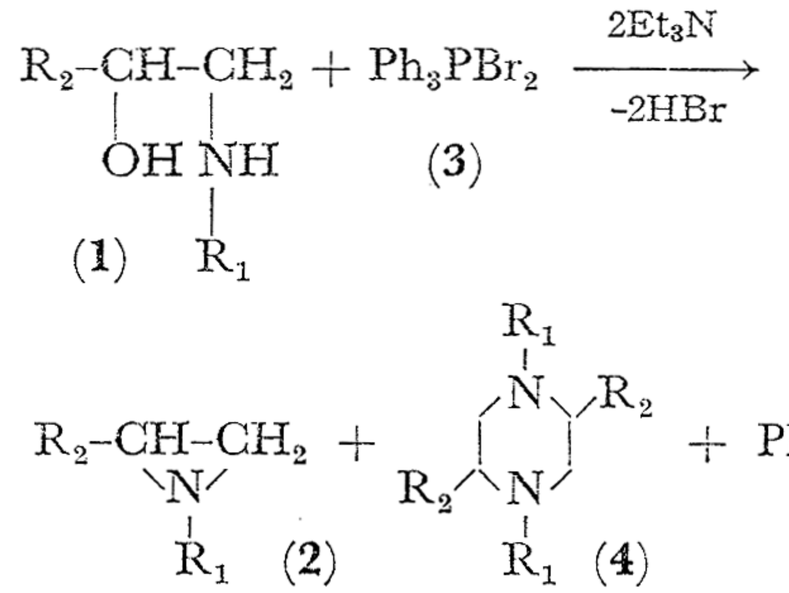
The amino alcohols (**1**) used were prepared by the reactions of amines with epoxides; the results are summarized in Table 1.

First, the reaction of β-amino alcohols (**1**) with phosphorus pentachloride in the presence of triethylamine was attempted, but the attempt to isolate aziridines (**2**) was unsuccessful.[2]

Triphenylphosphine dibromide (**3**), prepared by Horner and his co-workers, has a considerable advantage over phosphorus pentachloride in the preparation of alkyl and aryl halides from alcohols or phenols.[3]

By using this reagent (**3**), instead of phosphorus pentachloride, the expected aziridines (**2**) were readily obtained in good yields.

In the reaction of 1-phenyl-2-butylaminoethanol (**1a**) with triphenylphosphine dibromide (**3**) in the presence of two equivalents of triethylamine in dry acetonitrile at room temperature, 1-butyl-2-phenyl-aziridine (**2a**) was isolated in a 60% yield, along with 1,4-dibutyl-2,5-diphenylpiperazine (**4a**) as a by-product.



(Eq. 1)

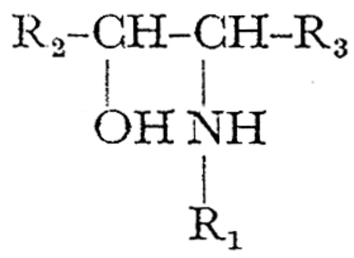
(**a**) $R_1=n\text{-}C_4H_9$, $R_2=C_6H_5$
(**b**) $R_1=t\text{-}C_4H_9$, $R_2=C_6H_5$
(**c**) $R_1=C_6H_{11}$, $R_2=C_6H_5$
(**d**) $R_1=C_6H_5CH_2$, $R_2=C_6H_5$
(**e**) $R_1=C_6H_{11}$, $R_2=CH_3$
(**f**) $R_1=C_6H_5CH_2$, $R_2=CH_3$
(**g**) $R_1=C_6H_5CH_2$, $R_2=C_2H_5$

1) P. E. Fanta, "Heterocyclic Compounds with Three- and Four-Membered Rings," Part I, ed. by A. Weissberger, Interscience Publishers, Inc., New York, N. Y. (1964), p. 524.

2) Deyrup and Moyer reported that the reaction of β-amino alcohols with thionyl chloride in the presence of triethylamine gave not the expected aziridines but 2-oxo-1,2,3-oxathiazolidines.[5]

3) a) L. Horner, H. Oediger and H. Hoffmann, *Ann.*, **626**, 26 (1959); b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y. (1967), p. 1247—1249.

Table 1. Amino alcohols



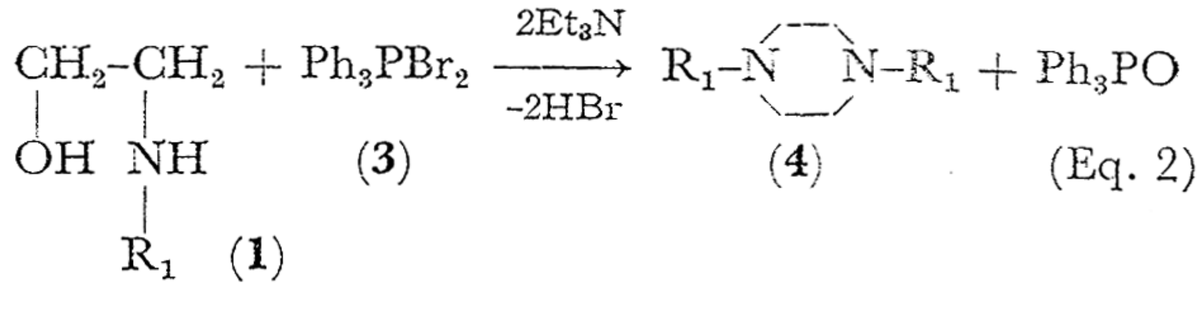
Compound	R_2	R_1	R_3	Mp, °C or Bp, °C/mmHg	Yield, %
1a	C_6H_5	*n*-C_4H_9	H	58—59[c,d]	62
1b	C_6H_5	*t*-C_4H_9	H	86—89[c,e]	81
1c	C_6H_5	C_6H_{11}	H	90—91.5[c]	78
1d	C_6H_5	$C_6H_5CH_2$	H	100—102[f]	68
1e	CH_3	C_6H_{11}	H	46—48[c]	75
1f	CH_3	$C_6H_5CH_2$	H	117.5—119.5/1.5	48
1g	C_2H_5	$C_6H_5CH_2$	H	126/2	61
1h	H	C_6H_{11}	H	91/1.5[h]	64
1i	H	$C_6H_5CH_2$	H	119—121/2[i]	50
1j	C_6H_5	CH_3	CH_3[a]	116—118[j]	42
1k	C_6H_5	CH_3	CH_3[b]	217—218[k]	

Compound	Formula	Elemental analysis					
		Calcd, %			Found, %		
		C	H	N	C	H	N
1c	$C_{14}H_{21}NO$	76.66	9.65	6.39	76.67	9.68	6.40
1d	$C_{15}H_{17}NO$	79.26	7.54	6.16	78.93	7.27	6.15
1e	$C_9H_{19}NO$	68.74	12.18	8.91	68.65	11.89	8.76
1g	$C_{11}H_{17}NO$	73.70	9.56	7.81	73.41	9.50	7.81

a) D(+)-*threo*- and L(−)-*erythro*-Ephedrine mixture.
b) L(−)-*erythro*-Ephedrine hydrochloride, commercial product.
c) Recrystallized from *n*-hexane.
d) Lit, mp 58—59°C, bp 164—179°C/18 mmHg.[4]
e) Lit, mp 86—87°C.[5]
f) Recrystallized from a benzene - *n*-hexane mixture.
g) Lit, bp 93—95°C/0.2 mmHg.[6]
h) Lit, bp 87—89°C/1 mmHg.[7]
i) Lit, bp 112—114°C/1 mmHg.[7]
j) Recrystallized from acetonitrile. Lit, mp 118°C.[8]
k) Lit, mp 216°C.[8]

2a was identified by elemental analysis and by means of a study of the NMR spectrum, and its IR spectrum shows neither NH or OH stretching vibrational absorption bands (3280, 1300 cm^{-1}). The structure of **4a** was established by the results of elemental analysis and by a comparison of its infrared spectrum with that of the authentic sample prepared by a procedure similar to that used in a previous paper.[9] A variety of 1,2-disubstituted aziridine derivatives (**2b**—**2g**) were prepared from β-amino alcohols (**1b**—**1g**) in the same way. The results are summarized in Table 2.

The application of this procedure to the synthesis of 1-monosubstituted aziridines was unsuccessful; in the case of 2-cyclohexyl-(**1h**) and 2-benzylaminoethanol (**1i**), the products isolated were only the



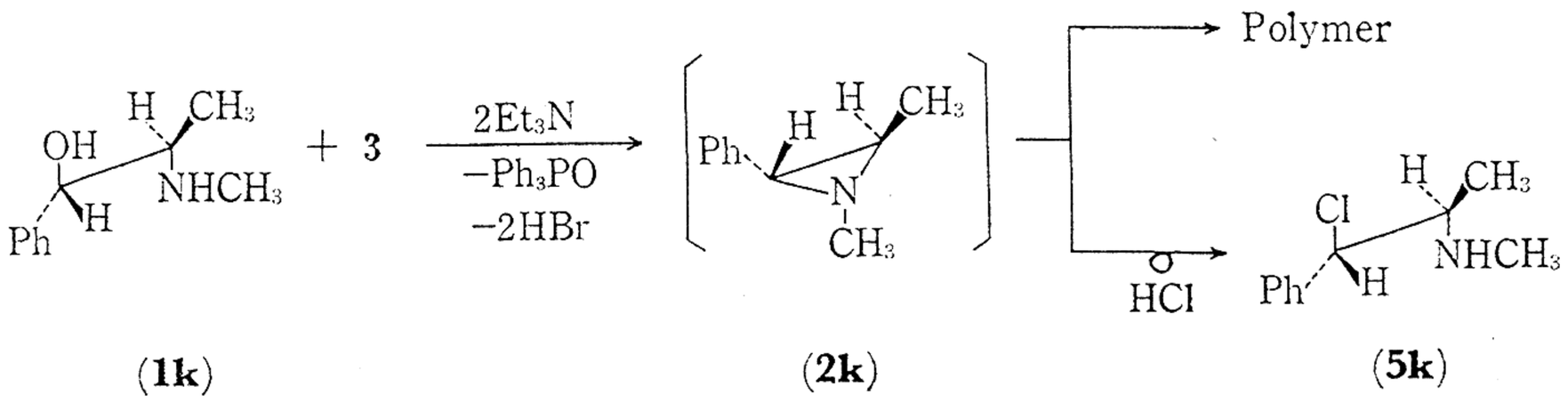
(Eq. 2)

(**h**) $R_1=C_6H_{11}$ (**i**) $R_1=C_6H_5CH_2$

4) W. S. Emerson, *J. Amer. Chem. Soc.*, **67**, 516 (1945).
5) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).
6) M. A. Stolberg, J. O'Neill and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **75**, 5045 (1953).
7) A. T. Bottini and J. D. Roberts, *ibid.*, **80**, 5203 (1958).
8) K. Tanaka, *Yakugaku Zasshi*, **70**, 220 (1950).
9) I. Okada, N. Itoh and R. Sudo, This Bulletin, **42**, 547 (1969).

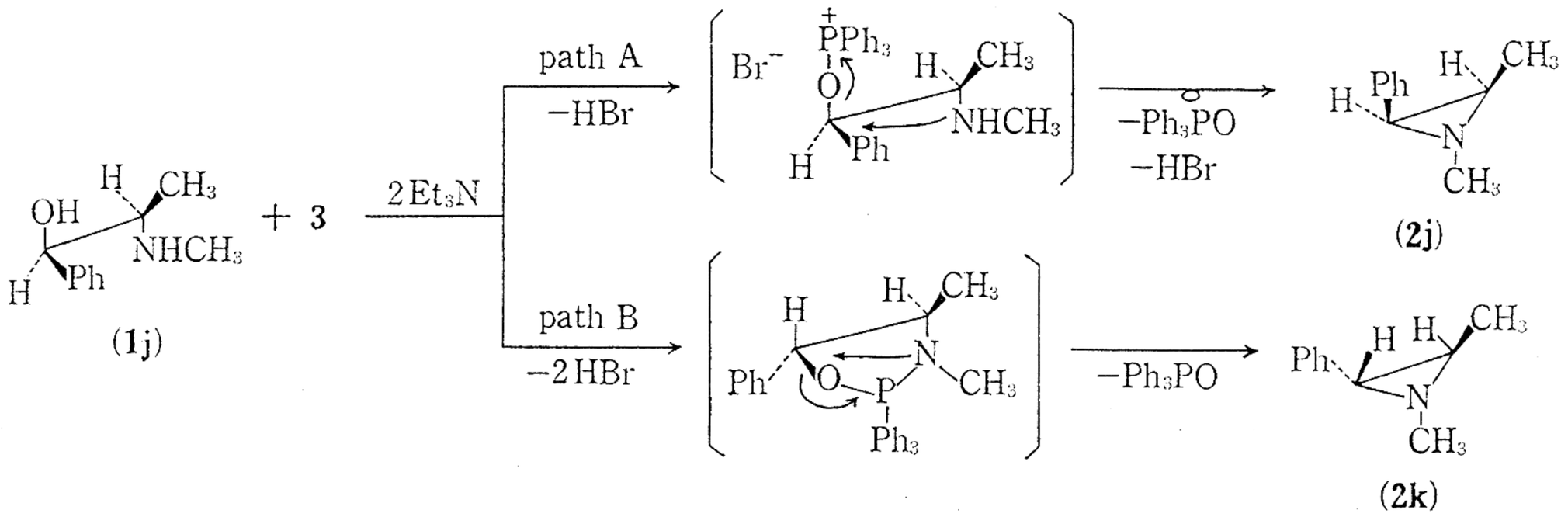
corresponding 1,4-disubstituted piperazines (**4h** and **4i**), which were identified by means of their melting points and their infrared spectra.

The stereochemical study of this ring-closure reaction (Eq. 1) was performed in the reaction of D(+)-*threo*-(**1j**) and L(−)-*erythro*-ephedrine (**1k**) with triphenylphosphine dibromide (**3**). In the case of *threo*-ephedrine (**1j**), L(−)-*cis*-1,2-dimethyl-3-phenylaziridine (**2j**) was prepared in a 74% yield. Although an analytically-pure sample was not



(**1k**) (**2k**) (**5k**)

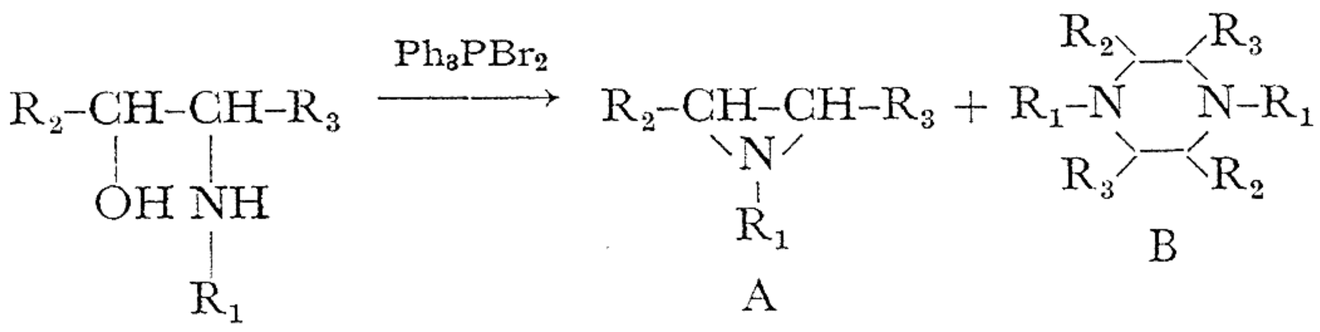
Scheme 1



(**1j**) (**2j**) (**2k**)

Scheme 2

TABLE 2. REACTION OF β-AMINO ALCOHOLS WITH TRIPHENYLPHOSPHINE DIBROMIDE



Compound	R_2	R_1	R_3	Product	Bp, °C/mmHg or Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2a	C_6H_5	*n*-C_4H_9	H	A	80—81/1	60	$C_{12}H_{17}N$	82.23	9.78	7.99	82.13	9.52	8.26
4a				B	109.5—110.5[b]	12	$C_{24}H_{34}N_2$	82.23	9.78	7.99	82.16	9.51	8.18
2b	C_6H_5	*t*-C_4H_9	H	A	120/20[c]	66	$C_{12}H_{17}N$	82.23	9.78	7.99	82.22	9.95	7.87
4b				B	109—110[b]	9	$C_{24}H_{34}N_2$	82.23	9.78	7.99	82.61	9.96	8.14
2c	C_6H_5	C_6H_{11}	H	A	155—156/16	50	$C_{14}H_{19}N$	83.53	9.51	6.96	83.77	9.21	6.62
2d	C_6H_5	$C_6H_5CH_2$	H	A	138—139/1	54	$C_{15}H_{15}N$	86.08	7.22	6.69	85.83	6.98	6.85
2e	CH_3	C_6H_{11}	H	A	58—59/12	11	$C_9H_{17}N$	77.63	12.31	10.06	77.89	11.91	9.88
2f	CH_3	$C_6H_5CH_2$	H	A	57—58/1.5[d]	51	$C_{10}H_{13}N$	81.58	8.90	9.52	81.20	8.75	9.56
2g	C_2H_5	$C_6H_5CH_2$	H	A	102/13	51	$C_{11}H_{15}N$	81.93	9.37	8.69	81.56	8.99	8.62
4h	H	C_6H_{11}	H	B	117—118[b,e]	44	$C_{16}H_{30}N_2$	76.74	12.08	11.19	76.66	11.81	10.98
4i	H	$C_6H_5CH_2$	H	B	90—91[f,g]	28	$C_{18}H_{22}N_2$	81.16	8.33	10.52	81.01	8.70	10.35
2j	C_6H_5	CH_3	CH_3	A[a]	82/14[h]	74[h]							

a) See Experimental.
b) Recrystallized from acetonitrile.
c) Lit, bp 50°C/0.1 mmHg.[5]
d) Lit, bp 58°C/2 mmHg.[6]
e) Lit, mp 118°C[10]
f) Recrystallized from ethanol.
g) Lit, mp 92°C.[11]
h) Lit, 72°C/7 mmHg.[8]

10) C. N. Ionescu, *et al.*, *Acad. Rep. Populare Romine, Sutdii Cercetari Chim.*, **5**, No. 1, 7–15 (1957); *Chem. Abstr.*, **52**, 398i (1958).

11) Heilbron, "Dictionary of Organic Compounds," ed. by A. H. Cook and E. R. H. Jones, Oxford University Press, New York, N. Y. (1953), p. 216.

obtained, the structure was confirmed by a comparison of its NMR spectrum with that of the authentic sample reported in the literature.[10] The $[\alpha]_D^{23} -134°$ (EtOH), of the product (**2j**) indicates the occurrence of Walden inversion during the ring closure. On the other hand, in the reaction of *erythro*-ephedrine (**1k**) with **3**, the expected D(+)-*trans*-1,2-dimethyl-3-phenylaziridine (**2k**) was not isolated, and only a polymeric material was obtained. Taguchi and Kojima observed an analogous polymerization of the *trans*-isomer (**2k**) in the application of the Wenker synthesis to *erythro*-ephedrine (**1k**).[12] It seems probable that the *trans*-isomer (**2k**) is easily polymerized during the isolation. Therefore, immediately after the reaction was over, hydrogen chloride gas was introduced into the reaction mixture. The product isolated was the expected L(−)-*erythro*-1-chloro-1-phenyl-2-methylaminopropane hydrochloride (**5k**), which would suggest the formation of **2k**. Although the melting point of this product, 186—188°C, was slightly lower than the literature value,[8] 198°C, $[\alpha]_D^{23} -68.6°$ (EtOH), the infrared spectrum supported the structure.

On the basis of the results described above, in the cases of both *threo*- (**1j**) and *erythro*-ephedrine (**1k**), a Walden inversion should occur in the ring-closure process. This fact supports the idea of the 1,2-*trans*-elimination in path A postulated in Scheme 2; the five-membered ring intermediate shown in path B, which should afford a *cis*-isomer, can thus be eliminated.

Experimental

The acetonitrile used was distilled from phosphorus pentoxide and dried over calcium hydride. The triethylamine was distilled and dried over sodium. All the melting points and boiling points are uncorrected.

β-Amino Alcohols (1). These compounds were prepared by the methods of Emerson,[4] Stolberg,[6] and Bottini;[7] their physical constants are summarized in Table 1.

1-Butyl-2-phenylaziridine (2a). The general procedure for the reaction of β-amino alcohols (**1**) with triphenylphosphine dibromide (**3**) was as follows. To a solution of **3**, prepared from 10.48 g (0.04 mol) of triphenylphosphine in 100 m*l* of acetonitrile and 6.40 g (0.04 mol) of bromine in 40 m*l* of acetonitrile, 7.72 g (0.04 mol) of **1a** was added under ice cooling. A solution of 8.08 g (0.08 mol) of triethylamine in 10 m*l* of acetonitrile was then stirred, drop by drop, into the above mixture. After this mixture had stood overnight at room temperature, the precipitated triethylamine hydrobromide was filtered off (8.90 g, 62%). The filtrate was concentrated by rotary evaporation. The residue was extracted several times with *n*-hexane, and the extract was concentrated by rotary evaporation to about 5 m*l*. The triphenylphosphine oxide thus separated was removed by filtration, and the filtrate was further concentrated. The yellow residue (5.90 g) was distilled to give **2a**; bp 88—89.5°C/2 mmHg. Yield, 4.15 g (60%). The analytical sample was obtained by redistillation as a colorless liquid; bp 80—81°C/1 mmHg. IR (NaCl): 3030, 2920, 1600, 1495, 1450, 1205, 1080, 1025, 740, 720, and 690 cm^{-1}; NMR ($CDCl_3$): τ 2.8 (5H, singlet) due to aromatic protons, τ 7.5—7.9 (3H, multiplet) due to >N–C<u>H</u>$_2$–C<u>H</u>$_2$– and C_6H_5–C<u>H</u>, τ 8.1—9.0 (6H, multiplet) due to C_6H_5–CH–C<u>H</u>$_2$ and CH_3–C<u>H</u>$_2$–C<u>H</u>$_2$–, and τ 9.1 (3H, triplet) due to –CH_3. The oily, brown distillation residue was treated with a small quantity of ethanol to give 1,4-dibutyl-2,5-diphenylpiperazine (**4a**) as needle crystals. Yield, 0.85 g (12%). Recrystallization from acetonitrile afforded colorless needles; mp 109.5—110.5°C. Benzene and water were added to the residue resulting from *n*-hexane extraction. The organic layer was concentrated to give 10.60 g (96%) of triphenylphosphine oxide. The evaporation of the aqueous layer afforded 5.90 g (41%) of triethylamine hydrobromide. The total yield of this compound was 93%.

D(+)-*threo*-Ephedrine (1j). This compound was prepared from L(−)-*erythro*-ephedrine hydrochloride (**1k**) by the procedure of Tanaka.[8] The ratio of D(+)-*threo*- to L(−)-*erythro*-ephedrine in the product was 65 : 35.

L(−)-*cis*-1,2-Dimethyl-3-phenylaziridine (2j). **2j** was prepared in a manner analogous to that described for the preparation of **2a**. Bp 82°C/14 mmHg. Yield, 74% $[\alpha]_D^{23}$ −134° (EtOH). (Lit, $[\alpha]_D^{11}$ −127°, EtOH). NMR ($CDCl_3$): τ 2.75 (5H, singlet) due to aromatic protons, τ 7.55 (3H, singlet) due to >N–CH_3, τ 7.65 (1H, doublet) due to C_6H_5–C<u>H</u>, τ 8.4 (1H, quintet) due to –C<u>H</u>CH_3, and τ 9.15 (3H, doublet) due to –CH–C<u>H</u>$_3$. IR (NaCl): 2950, 1600, 1500, 1460, 1400, 1120, 730, and 700 cm^{-1}.

Reaction of L(−)-*erythro*-Ephedrine Hydrochloride (1k) with Triphenylphosphine Dibromide (3). 4.03 g (0.02 mol) of **1k** was added, under ice cooling, to a solution of **3** which had been prepared from 5.24 g (0.02 mol) of triphenylphosphine in 25 m*l* of acetonitrile and 3.20 g (0.02 mol) of bromine in 10 m*l* of acetonitrile. A solution of 6.06 g (0.06 mol) of triethylamine in 10 m*l* of acetonitrile was then stirred, drop by drop, into the mixture. After 0.5 hr, the triethylamine hydrobromide and hydrochloride thus precipitated were filtered off (7.50 g, 75%). This filtrate was treated with water or hydrogen chloride.

a) Treatment with Water. The filtrate was concentrated by rotary evaporation. The residue was treated with water, and the insoluble product was collected by filtration, washed with ethanol, and dried (1.30 g); mp 270—290°C. This compound could not be recrystallized from normal solvents. IR (KBr): 2950, 1600, 1490, 1450, 1025, 750, and 700 cm^{-1}.

b) Treatment with Hydrogen Chloride. Hydrogen chloride was introduced into the filtrate. The mixture was concentrated by rotary evaporation, and the residue was treated with 40 m*l* of benzene and 40 m*l* of water. The evaporation of the organic layer afforded 5.00 g (89%) of triphenylphosphine oxide. The aqueous layer was concentrated to give 2.90 g of L(−)-*erythro*-1-chloro-1-phenyl-2-methylaminopropane hydrochloride (**5k**). Recrystallization from ethanol gave colorless plates; mp

12) S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, **42**, 5113 (1966).
13) T. Taguchi and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **7**, 103 (1959).

186—188°C, $[\alpha]_D^{23}$ −68.6° (EtOH). (Lit, $[\alpha]_D^{11}$ −65°, EtOH).[8] IR (KBr): 2950, 2750, 2400, 1600, 1450, 1400, 850, 760, and 700 cm^{-1}.

Found: C, 50.11; H, 6.24; N, 5.96%. Calcd for $C_{10}H_{15}NCl_2 \cdot H_2O$: C, 50.42; H, 6.30; N, 5.88%.

1,4-Dibutyl-2,5-diphenylpiperazine (4a). A mixture of 1.75 g (0.01 mol) of **2a**, a catalytic amount of aluminum chloride, and 20 m*l* of methanol was refluxed for 7 hr. The solvent was then evaporated, and the residue was treated with a slight excess of potassium hydroxide and water. The solution was then extracted several times by ether. The ether layer was dried over anhydrous potassium carbonate and evaporated. The crude product, 1.20 g (69%), was recrystallized from acetonitrile to give colorless needles; mp 109.5—110.5°C. IR (KBr): 2950, 2800, 1600, 1490, 1450, 1140, 1110, 750, and 700 cm^{-1}.

Found: C, 82.29; H, 9.59; N, 8.06%. Calcd for $C_{24}H_{34}N_2$: C, 82.23; H, 9.78; N, 7.99%.