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Studies on Azetidine Derivatives. II.[1] Reactions and Stereochemistry of 3-Substituted 1-Cyclohexyl-2-phenylazetidines[2]

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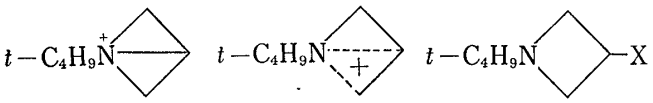
The stereochemical course of diastereomeric 1-cyclohexyl-2-phenyl-3-azetidinyl mesylates (IVa and Va) was investigated with nucleophilic reagents. The retention of the configuration in these reactions and ring contracted products in some cases of reactions of IVa were observed. The presence of 1-azabicyclobutonium ions (VII and VIII) as intermediates in these reactions has been proposed from these results.

The stereochemistry of 3-substituted azetidines obtained by nucleophilic reactions *via* IVa and Va was established by chemical evidence and nuclear magnetic resonance studies with a shift reagent, $Eu(DPM)_3$.

Recently, a conjecture to support the existence of a intermediary 1-heterobicyclobutonium ion in solvolysis reactions has received much interest in the chemistry of small heterocycles.[4] As for azetidines, 1-azabicyclobutonium ion (I) has been proposed in the solvolysis of 1-*t*-butyl-3-azetidinyl tosylate (IIIa)[5] and chloride (IIIb)[4] on the basis of the kinetics of reactions and products (IIIc and IIId). Furthermore, the possibility of a nonclassical type of 1-azabicyclobutonium ion (II) contributed to these reactions has also been proposed from inspection of reaction products.[4] But, no stereochemical discussion with regard to these reactions has so far been made.[6] It was expected that the deep insight might be obtained into the stereochemical course of these reactions. These prompted us to investigated reactions of diastereomeric 1-cyclohexyl-2-phenyl-3-azetidinyl mesylates[1] with nucleophilic reagents and the stereochemistry of the resulting 3-substituted 1-cyclohexyl-2-phenylazetidines.



I II

IIIa : X=OTs
IIIb : X=Cl
IIIc : X=CN
IIId : X=OMe

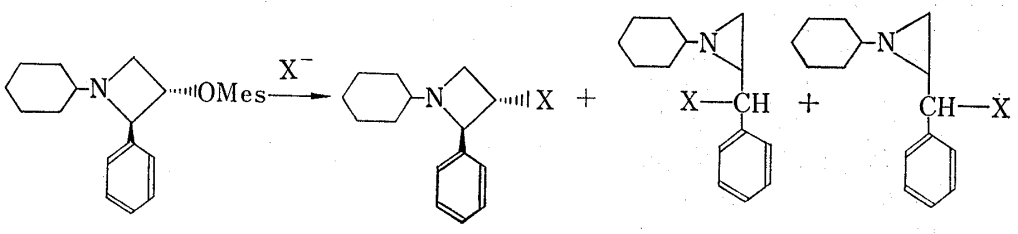
Ts=tosyl

Chart 1

Reactions with Nucleophiles

Hydrolysis of *trans*-1-cyclohexyl-2-phenyl-3-azetidinyl mesylate (IVa) with sodium hydroxide in 50% aqueous dioxane under reflux gave a mixture of *trans*-1-cyclohexyl-2-phenyl-

1) Part I: T. Okutani, T. Kaneko, and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **22**, 1490 (1974).
2) Presented in part at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Aug. 1971, Abstracts Paper, D-23-6.
3) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
4) V.T. Gaertner, *Tetrahedron Letters*, **1968**, 5919; *idem.*, *J. Org. Chem.*, **35**, 3952 (1970), and references cited therein.
5) *a*) J.A. Deyrup and C.L. Moyer, *Tetrahedron Letters*, **1968**, 6179; *b*) R.H. Higgins, F.M. Behlem, D.F. Eggli, J.H. Kreymborg, and N.H. Cromwell, *J. Org. Chem.*, **37**, 524 (1972).
6) After we had finished this investigation, a similar result with solvolysis of diastereomeric 1-*t*-butyl-2-methyl-3-azetidinyl tosylates has very recently been reported; R.H. Higgins and N.H. Cromwell, *J. Am. Chem. Soc.*, **95**, 120 (1973).



IVa

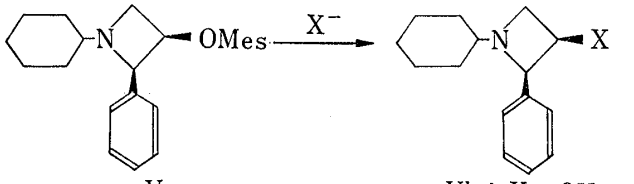
IVb : X=OH
IVc : X=OAc
IVd : X=OMe
IVe : X=CN
IVf : X=SMe
IVg : X=SC_6H_5

VIa : X=OH
VIb : X=OMe

VIa′ : X=OH
VIb′ : X=OMe

Chart 2 Mes=mesylate

azetidin-3-ol (IVb)[1] and *threo*- and *erythro*-1-cyclohexyl-2-(α-hydroxybenzyl)aziridines (VIa and VIa′) in 92% yield (products ratio, 1:1:1, on the basis of nuclear magnetic resonance (NMR) analysis of the crude product). The structures of these aziridines were confirmed by the reduction of 1-cyclohexyl-2-benzoylaziridine[7] with sodium borohydride. Acetolysis of IVa with potassium acetate in acetic acid at 65° yielded *trans*-3-acetoxy-1-cyclohexyl-2-phenylazetidine (IVc) in 36% yield and unidentified products (at least 3 products by TLC). The stereochemistry of IVc was confirmed by acetylation of IVb with acetic anhydride. Methanolysis of IVa with sodium methoxide in methanol under a refluxing temperature afforded a mixture of *trans*-1-cyclohexyl-3-methoxy-2-phenylazetidine (IVd) and *threo*- and *erythro*-1-cyclohexyl-2-(α-methoxybenzyl)aziridines (VIb and VIb′) in 99% yield (products ratio, 11:1:1, on the basis of NMR analysis of the crude product), and furthermore, solvolysis of IVa in methanol in the presence of triethylamine at 40° gave a mixture of IVd, VIb and VIb′ in 95% yield (products ratio, 1:4:5, on the basis of NMR analysis of the crude product). Treatment of IVa with potassium cyanide in methanol under a refluxing temperature afforded a mixture of *trans*-3-cyano-1-cyclohexyl-2-phenylazetidine (IVe), IVd, VIb and VIb′ in 87% yield (products ratio, 30:1:5:5, on the basis of the isolation of IVe and NMR analysis of a mixture of IVd, VIb and VIb′). Thioetheration of IVa with sodium methanethiolate and thiophenolate in ethanol under a refluxing temperature yield *trans*-3-methylthio- and 3-phenylthio-1-cyclohexyl-2-phenylazetidines (IVf and IVg) in 94% and 99% yields, respectively. In this case, no other compounds resulted as evidenced by NMR analysis of the crude products and by thin-layer chromatography (TLC). Furthermore, the *trans*-azetidinol (IVb) was treated with triphenylphosphine dibromide in the presence of triethylamine in acetonitrile[8] to give *trans*-3-bromo-1-cyclohexyl-2-phenylazetidine (IVh) in 47% yield. The stereochemistry of IVh was confirmed by conversion to IVe with potassium cyanide in methanol.



Va

Mes=mesylate

Vb : X=OH
Vc : X=OAc
Vd : X=OMe
Ve : X=CN
Vf : X=SMe
Vg : X=SC_6H_5

Chart 3

On the other hand, reactions of the *cis*-mesylate (Va) and the *cis*-azetidinol (Vb) were carried out under the same conditions as those in the case of the *trans*-mesylate (IVa). But, in this case, only *cis*-azetidine derivatives were obtained as follows: hydrolysis gave the *cis*-

7) N.H. Cromwell, N.G. Barker, R.A. Wankel, P.J. Vanderhorst, F.W. Olson, and J.H. Anglin, Jr., *J. Am. Chem. Soc.*, **73**, 1044 (1951).
8) J.P. Schaefer and D.S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).

azetidinol (Vb) in 97% yield, acetolysis gave the *cis*-acetate (Vc) in 92% yield, methanolysis with sodium methoxide and in the presence of triethylamine in methanol gave the *cis*-methyl ether (Vd) in 91% and 95% respectively, cyanation gave the *cis*-nitrile (Ve) and Vd in 84% and 11% respectively, thioetheration with methanethiolate and thiophenolate gave the *cis*-methyl thioether (Vf) and the *cis*-phenyl thioether (Vg) in 99% and 95% yields respectively, and bromination of Vb gave the *cis*-bromide in 74% yield.

It is noteworthy that in these reactions, the retention of the configuration is observed, and that the ring contracted products are obtained only in some cases of the reactions of the *trans*-mesylate and the products ratio of *threo*- and *erythro*-aziridines is approximately equal.

First order solvolytic rate constants were roughly determined in methanol in the presence of equivalent amounts of triethylamine according to the procedure described by Deyrup and Moyer.[5a] Values for IVa and Va were 2.2×10^{-5} sec^{-1} and 6.0×10^{-4} sec^{-1} at 40.0°, respectively.

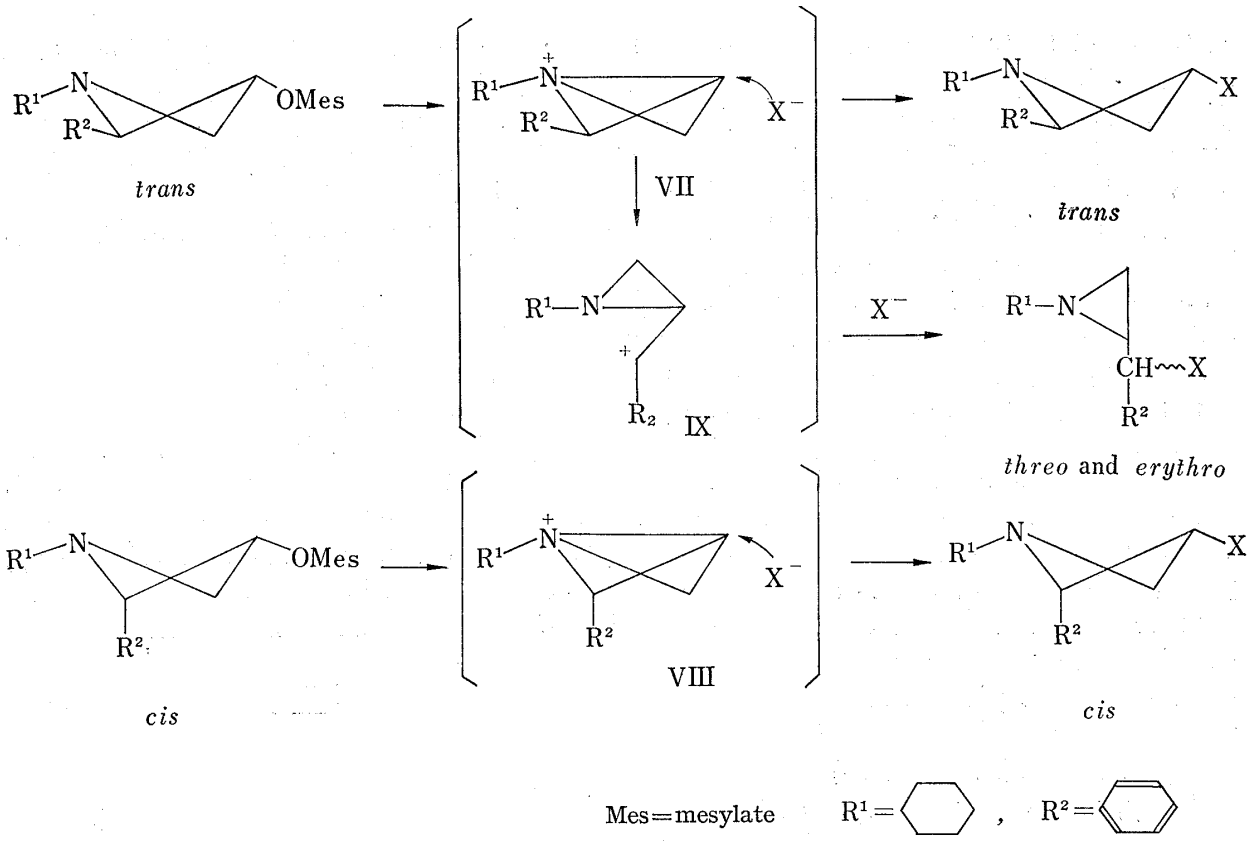


Chart 4

These results clearly indicate that the intermediary fomration of bridged ions, 1-azabicyclobutonium ions (VII and VIII), are present in these reactions, and that in this case[4] the ring contracted products are formed by N_1–C_4 bond cleavage in VII, followed by S_N1 reactions *via* IX (Chart 4). The difference in reactivity of the diastereomeric mesylate, *i.e.*, the ring contracted products are obtained from the *trans*-isomer (IVa) and not from the *cis*-isomer (Va), appeares to be due to the difference in the steric hindrance of two bicyclobutonium ions from inspection of the molecular model and the rate retardation of IVa (relative to Va), and the bicyclobutonium ion VII from IVa might be less stable due to the nonbonded interaction of substituents at the 1- and 2-positions.[9,10] These results with nucleophilic substitution

9) It has been pointed out that the nonbonded 1, 2 interaction of substituents play an important role in the reactivity and the conformational stability of azetidines.[6]

10) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, Chapter 6.

reactions of the diastereomeric mesylates are good agreement with those of hydrolysis of diastereomeric 1-*t*-butyl-2-methyl-3-azetidinyl tosylates except the formation of the ring contracted products observed in the present case.[6]

Stereochemistry

In a previous paper,[11] we reported the configurational assignment of diastereomeric azetidinols (IVb and Vb) with a shift reagent, $Eu(DPM)_3$, in NMR studies.[12] More recently, these results have been supported by spectroscopic studies with regard to the configurational analysis of 1-alkyl-2-methylazetidin-3-ols.[13] Further evidence on the stereochemistry of the present series of diastereomeric azetidines by the chemical procedure and the application of the shift reagent will be described.

Treatment of IVe with sodium methoxide in dimethyl sufoxide (DMSO) at 100° for 2 hr, followed by hydration yielded an amide, while the same amide was obtained from Ve under the same condition. The amide was treated with triphenylphosphine dibromide in the presence of triethylamine in acetonitrile[14] to afford the nitrile which was identical with IVe (Chart 5). The amide obtained from IVe and Ve, therefore, was *trans*-1-cyclohexyl-2-phenylazetidine-3-carboxamide (IVi) since the *trans*-azetidine is thermodynamically more stable than the *cis*-one.[15] Furthermore, only *trans*-3-benzoyl-1-cyclohexyl-2-phenylazetidine (IVj)[16] was obtained by the reaction of IVe and Ve with phenylmagnesium bromide. These facts together with the aformentioned results of the reactions of the mesylates concluded that a series of the azetidines derived from IVa are the *trans*- and the others are the *cis*-isomers except IVi and IVj. Similarly the bromides, IVh and Vh, derived from IVb and Vb are the *trans*- and the *cis*-isomer, respectively.

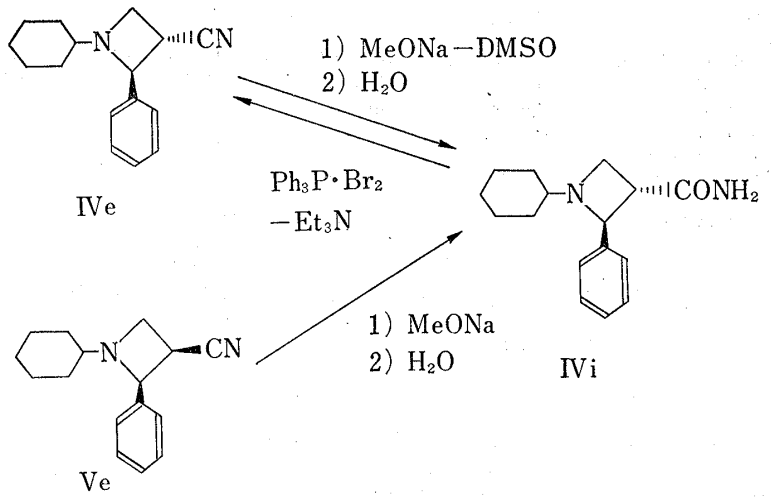
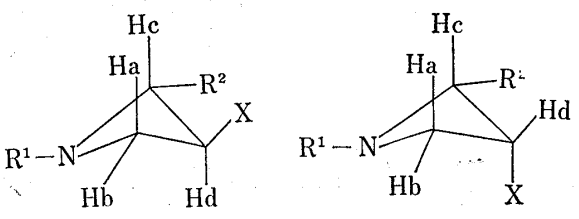


Chart 5

As for the configurational assignment with the shift reagent, it was expected that the signal of the proton Hc of the *trans*-isomer would be more shifted than that of the *cis*-isomer from inspection of the molecular model since the proton of the *trans*-isomer is located closer to the metal than that of the *cis*-isomer.[9]

11) T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Letters*, **1971**, 1115.
12) J.K.M. Sanders, S.W. Hanson, and D.H. Williams, *J. Am. Chem. Soc.*, **94**, 5325 (1972), and references cited therein.
13) R.H. Higgins and N.H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1059 (1971).
14) L. Horner, H. Oediger, and H. Hoffmann, *Ann.*, **626**, 26 (1959).
15) J.-L. Imbach, E. Doomes, R.P. Rebman, and N.H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).
16) E. Doomes and N.H. Cromwell, *J. Org. Chem.*, **34**, 310 (1969).



IV V

$R^1=C_6H_{11}$, $R^2=C_6H_5$

Chart 6

The normal NMR spectra of diastereomeric azetidines obtained in the present paper are summarized in Table I and Table II. The paramagnetic shifts of the azetidines in which functional groups can be coordinated with europium complex are summarized in Table III. The NMR spectra of the nitriles and the thioethers were almost unaffected by the addition of the shift reagent.[17] With respect to the proton Hc, all the signals of the *trans*-isomers which

Table I. Chemical Shifts of *trans*-1-Cyclohexyl-2-phenylazetidines (IV)

Compd.	Proton (Hz)[a]					Coupling constant (Hz)			
	a	b	c	d	CH_3	ab	ad	bd	cd
IVa	294 t	376 t	399 d	449 q	281 s	−6.8	7.0	6.6	6.0
IVb	266 t	368 t	371 d	400 q	—	−8.0	7.7	5.8	5.8
IVc	273 t	383 t	394 d	472 q	199 s	−6.8	6.7	5.8	7.0
IVd	269m	[b]	385 d	[b]	322 s	[c]	[c]	[c]	5.0
IVe[d]	306	367 t	419 d	287	—	−5.9	8.9	7.3	7.9
IVf	278dd	372 t	389 d	311 q	202 s	−8.5	6.2	7.0	7.2
IVg	281dd	381 t	388 d	350 q	—	−8.0	6.5	6.5	7.5
IVh	311m	[e]	418 d	[e]	—	[c]	[c]	6.2	5.9
IVi[d]	312dd	352 t	415 d	283 q	—	−6.6	8.7	7.4	7.7
IVj[f]	316m	374	438 d	*ca.* 388	—	−7.3	[c]	[c]	[c]

a) Downfield shift from TMS, internal standard, with respect to a 100 MHz field in $CDCl_3$. The proton assignment was confirmed by the decoupling and with $Eu(DPM)_3$. the multiplicity: s=singlet, d=doublet, dd=doublet of doublet, t=triplet, q=quartet and m=multiplet
b) 354—375 (2H, m)
c) could not be determined
d) The NMR spectrum of this compound was simulated by computer with parameters given.
e) 386—416 (2H, m)
f) Chemical shifts of Ha and Hb were determined by the deuteration of Hd.[14]

Table II. Chemical Shifts of *cis*-1-Cyclohexyl-2-phenylazetidines (V)

Compd.	Proton (Hz)[a]					Coupling constant (Hz)			
	a	b	c	d	CH_3	ab	ad	bd	cd
Va	328 q	364dt	435bd	527td	220 s	−9.4	5.8	1.2	6.0
Vb	311 q	335[b]dt	413 d	419 t	—	−7.9	5.5	1.4	6.2
Vc	320 q	347dt	429bd	530td	168 s	−9.2	5.7	1.4	5.9
Vd	302 q	340dt	412bd	395td	285 s	−8.2	5.7	1.3	5.4
Ve	310 q	356dd	426 d	333td	—	−6.9	7.8	2.0	7.2
Vf	[c]	[c]	433 d	353m	160 s	[d]	[d]	[d]	6.3
Vg	[e]	[e]	448 d	408m	—	[d]	[d]	[d]	7.2
Vh	[f]	[f]	435bd	463td	—	−8.9	5.9	1.8	6.8
Vi[g]	303 t	409dd	460 d	432m	—	−6.9	7.1	2.8	9.0

a) Downfield shift from TMS, internal standard, with respect to a 100 MHz field in $CDCl_3$. The proton assignment was confirmed by the decoupling and with Eu $(DPM)_3$. the multiplicity: s=singlet, d=doublet, bd=broad doublet, dd=doublet of doublet, t=triplet, td=triplet of doublet, m=multiplet
b) This value was erroneously reported in the previous paper.[9]
c) 318—324 (2H, m)
d) could not be determined
e) 333—340 (2H, m)
f) *ca.* 358 (2H, m)
g) prepared according to the literature[14]

17) J.K.M. Sanders and D.H. Williams, *J. Am. Chem. Soc.*, 93, 641 (1971).

Table III. Paramagnetic Shifts of IV and V with $Eu(DMP)_3$

Compd.	Molar ratio[a]	Proton (Hz)			
		a	b	c	d
IVa	6	19	15	14	30
IVb	6	161	97	177	241
IVc	6	54	36	35	90
IVd	sat.[b]	97	[c]	95	[c]
IVj	6	34	18	39	31
Va	6	7	12	7	36
Vb	6	80	142	101	264
Vc	6	15	38	30	102
Vd	sat.[b]	18	44	21	58
Vj	6	10	35	12	22

a) Compd./$Eu(DPM)_3$
b) saturated with $Eu(DPM)_3$
c) Could not be determined.

can be coordinated with the metal were shifted more strongly than those of the *cis*-isomers (Table III). These results with the shift reagent are identical with those of the aforedescribed chemical procedure.

Experimental

All melting points were recorded on a micro hot stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi Model 215 spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrophotometer using TMS as internal standard.

Preparation of Materials——The preparation of *trans*- and *cis*-1-cyclohexyl-2-phenyl-3-azetidinyl mesylates (IVa and Va) was described in the previous paper.[1] *trans*- and *cis*-1-Cyclohexyl-2-phenyl-3-benzoylazetidines (IVj and Vj) were prepared according to the literature,[16] IVj, mp 96—97° (lit. mp 96—97°), Vj, mp 86—87° (lit. mp 102—103°).

***threo*- and *erythro*-1-Cyclohexyl-2-(α-hydroxybenzyl)aziridines (VIa, and VIa′)**——To a stirred solution of 1-cyclohexyl-2-benzoylaziridine[7] (3000 mg) in MeOH (100 ml) was added $NaBH_4$ (500 mg) under ice-cooling and allowed to stir for 30 min at room temperature. After evaporation of the solvent, the residue was diluted with water and extracted with ether, and then the organic layer was dried over $MgSO_4$. The solvent was evaporated to give crude crystals, which were fractionally recrystallized from *n*-hexane to afford VIa (819 mg) and VIa′ (380 mg). VIa, mp 129—130°. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.11; H, 9.08; N, 6.01. NMR ($CDCl_3$) δ ppm: 0.89—*ca.* 2.20 (11H, m), 1.23 (1H, d, J=6 Hz), 1.65—1.78 (1H, m), 1.88 (1H, d, J=3 Hz), 3.43 (1H, broad s, OH), 4.67 (1H, d, J=3 Hz), 7.20—7.45 (5H, m). VIa′, mp 130—131°. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.61; H, 9.15; N, 6.02. NMR ($CDCl_3$) δ ppm: 0.95—2.05 (11H, m), 1.36 (1H, d, J=6.5 Hz), 1.61—1.77 (1H, m), 1.83 (1H, d, J=3 Hz), 3.68 (1H, broad s, OH), 4.30 (1H, broad t), 7.20—7.44 (5H, m). The stereochemistry of VIa and VIa′ was determined by NMR spectra.[18]

Hydrolysis——a) To a solution of NaOH (2000 mg) in 50% aq. dioxane was added IVa (1000 mg) and the mixture was heated under reflux for 1.5 hr. After evaporation of the solvent under reduced pressure, the residue was diluted with water and extracted with ether, and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a crystalline residue (730 mg), which was roughly fractionated by column chromatography on silica gel (100 g, benzene: AcOEt=8: 2), followed by recrystallization from *n*-hexane to yield IVb (30 mg), mp 138—140°, VIa (60 mg), mp 130—131°, and VIa′ (165 mg), mp 126—128°.

b) Va (200 mg) was treated with NaOH (400 mg) in 50% aq. dioxane (10 ml) as described in a). After drying over $MgSO_4$, the organic solvent was evaporated to give Vb (147 mg), mp 100—102°.

Acetylation of Diastereomeric Azetidinols (IVb and Vb)——a) A solution of IVb (1000 mg) in acetic anhydride (5 ml) was allowed to stand overnight, and then the resulting solution was poured into ice water and extracted with ether. The extract was washed with a saturated $NaHCO_3$ solution, followed by water and dried over $MgSO_4$. Evaporation of the solvent gave IVc (1080 mg), mp 72—73.5° (from pet. ether). *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.51; H, 8.47; N, 5.12. IR ν_{max}^{KBr} cm^{-1}: 1752, 1239.

18) J.A. Deyrup and C.L. Moyer, *J. Org. Chem.*, **35**, 3424 (1970).

b) A solution of Vb (150 mg) in acetic anhydride (1 ml) was treated as described in a) to give Vc (150 mg), colorless liquid. *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.50; H, 8.51; N, 5.15. IR ν_{max}^{KBr} cm^{-1}: 1753, 1246.

Acetolysis——a) A mixture of IVa (250 mg) and AcOK (1000 mg) in AcOH (5 ml) was warmed at 65° for 7 hr. After evaporation of the solvent under reduced pressure below 50°, the residue was diluted with water and extracted with ether. The organic solvent was washed with a saturated $NaHCO_3$ solution, followed by water and dried over $MgSO_4$. Evaporation of the solvent afforded colorless oily residue (247 mg), to which pet. ether was added and the precipitate was collected to give IVc (98 mg), mp 72—73.5° (from pet. ether).

b) In the same experiment as described in a) except that IV was replaced with Va, a series of treatment gave Vc (215 mg), colorless liquid.

Methanolysis with Sodium Methoxide——a) To a solution of MeOH (10 ml), in which was dissolved with Na (100 mg), was added IVa (618 mg) and the mixture was heated under reflux for 2 hr. After evaporation of the solvent, the residue was diluted with water and extracted with ether, and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent yielded colorless liquid (484 mg). The oily substance was fractionated by column chromatography on silica gel (50 g, benzene: AcOEt=9: 1) to give IVd (362 mg), VIb (26 mg) and VIb′ (29 mg). IVd, colorless liquid. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.59; H, 9.46; N, 6.01. VIb, colorless liquid. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.39; H, 9.30; N, 5.93. NMR ($CDCl_3$) δ ppm: 0.90—*ca.* 1.95 (11H, m), 1.15 (1H, d of t, J=6 Hz, J=1 Hz, J=1 Hz), 1.41—*ca.* 1.67 (2H, m), 3.28 (3H, s), 3.71 (1H, d of t, J=7 Hz, J=1 Hz, J=1 Hz), 7.27 (5H, s). VIb′, colorless liquid. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.53; H, 9.56; N, 5.81. NMR ($CDCl_3$) δ ppm: 0.75—*ca.* 1.85 (11H, m), 1.33 (1H, d, J=6.5 Hz), 1.54 (1H, t of d), 1.86 (1H, d, J=3.5 Hz), 3.18 (3H, s), 7.30 (5H, m). The stereochemistry of VIb and VIb′ was determined by NMR spectra in which absorption pattern of the aziridine ring protons are similar to those of VIa and VIa′.

b) To a solution of MeOH (5 ml), in which was dissolved with Na (50 mg), was added Va (309 mg) and the mixture was heated under reflux for 30 min. After the reaction mixture was treated as described in a), evaporation of the solvent gave an oily residue, to which a small amount of pet. ether was added was allowed to stand at room temperature until crystals formed. The crystals were collected to give Vd (223 mg), mp 49—51° (from pet. ether).

Methanolysis in the Presence of Triethylamine——A mixture of IVa (618 mg) and triethylamine (210 mg) in MeOH (20 ml) was allowed to stir at 40° for 20 hr. After evaporation of the solvent, the residue was diluted with water and extracted with ether and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent afford an oily residue (467 mg), which was fractionated by column chromatography on silica gel (50 g, benzene: AcOEt=9: 1) to give the unreacted IVa (34 mg), IVd (14 mg), VIb (133 mg) and VIb′ (199 mg).

b) A mixture of Va (309 mg) and triethylamine (105 mg) in MeOH (10 ml) was heated at 40° for 7 hr and the reaction mixture was treated as described in a). Evaporation of the solvent yielded Vd (233 mg), mp 49—51° (from pet. ether).

Reaction with Potassium Cyanide——a) A mixture of IVa (927 mg) and KCN (500 mg) in MeOH (30 ml) was heated under reflux for 8 hr. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with ether and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave an oily residue (720 mg) which was fractionated by column chromatography on silica gel (80 g, benzene: AcOEt=19: 1) to afford IVe (417 mg) and 187 mg of a mixture of IVd, VIb and VIb′. IVe, mp 89—90° (from *n*-hexane). *Anal.* Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.65. Found: C, 79.80; H, 8.40; N, 11.51. IR ν_{max}^{KBr} cm^{-1}: 2240.

b) A mixture of Va (500 mg) and KCN (250 mg) in MeOH (15 ml) was heated under reflux for 1 hr and then the mixture was treated as described in a). An oily residue was fractionated by column chromatography on silica gel (20 g, benzene) to give Vd (42 mg) and Ve (328 mg). Ve, mp 123.5—124° (from *n*-hexane). *Anal.* Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.65. Found: C, 80.06; H, 8.25; N, 11.83. IR ν_{max}^{KBr} cm^{-1}: 2240.

c) A solution of IVh (176 mg) and KCN (400 mg) in MeOH (10 ml) was stirred at room temperature for 8 hr and the mixture was concentrated to dryness. The residue was diluted with water and extracted with ether and then the organic layer was dried over $MgSO_4$. After evaporation of the solvent, an oily residue was fractionated by column chromatography on silica gel (10 g, benzene: AcOEt=19: 1) to give IVe (81 mg, 56%), mp 86—88°, and 18 mg of an oily mixture of IVd, VIb and VIb′.

d) A solution of Vh (239 mg) and KCN (500 mg) in MeOH (12 ml) was stirred at room temperature for 5 hr and the resulting solution was treated as described in a) to give a crystalline residue, which was purified by column chromatography on silica gel (1 g, benzene) to yield Ve (162 mg, 83%), mp 123.5—125°.

Methylthioetheration——a) To a solution of methanethiol (200 mg) in EtOH (12 ml), in which was dissolved Na (55 mg), was added IVa (370 mg) and the mixture was heated under reflux for 1 hr. After evaporation of the solvent, the residue to which water was added was extracted with ether and the extract was dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was purified by column

chromatography on silica gel (5 g, benzene) to yield IVf (292 mg), colorless liquid. *Anal.* Calcd. for $C_{16}H_{23}NS$: C, 73.51; H, 8.86; N, 5.35. Found: C, 73.56; H, 8.79; N, 5.63.

b) To a solution of methanethiol (160 mg) in EtOH (10 ml), in which was dissolved Na (45 mg), was added Va (300 mg) and the mixture was treated as described in a) to give Vf (240 mg), colorless liquid. *Anal.* Calcd. for $C_{16}H_{23}NS$: C, 73.51; H, 8.86; N, 5.35. Found: C, 73.73; H, 8.94; N, 5.56.

Phenylthioetheration——a) To a solution of thiophenol (420 mg) in EtOH (20 ml), in which was dissolved Na (85 mg), was added IVa (390 mg) and the mixture was heated under reflux for 1 hr. After evaporation of the solvent under reduced pressure, the residue was treated with aqueous 2N NaOH and extracted with ether and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, to which a small amount of pet. ether was added was crystallized to give IVg (406 mg), mp 57—59° (from pet. ether). *Anal.* Calcd. for $C_{21}H_{25}NS$: C, 77.97; H, 7.79; N, 4.33. Found: C, 77.94; H, 8.02; N, 4.33.

b) To a solution of thiophenol (320 mg) in EtOH (15 ml), in which was dissolved with Na (61 mg), was added Va (280 mg) and the mixture was treated as described in a) to give Vg (291 mg), mp 131—132° (from *n*-hexane). *Anal.* Calcd. for $C_{21}H_{25}NS$: C, 77.97; H, 7.79; N, 4.33. Found: C, 77.85; H, 7.69; N, 4.25.

Bromination of Azetidinols (IVb and Vb) a) To a stirred solution of triphenylphosphine dibromide, prepared from triphenylphosphine (262 mg) and bromine (160 mg), in dry acetonitrile (5 ml) was added IVb (231 mg) and triethylamine (205 mg). The mixture was stirred at room temperature for 1 hr and then heated under reflux for 30 min. After evaporation of the solvent *in vacuo*, the residue was diluted with water and extracted with ether and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (7 g, benzene: AcOEt=19: 1) to give IVh (160 mg), light yellow liquid. *Anal.* Calcd. for $C_{15}H_{20}NBr$: C, 61.23; H, 6.85; N, 4.76. Found: C, 61.35; H, 6.72; N, 4.81.

b) In the same experiment as described in a) except that IVb was replaced with Vb, a series of the treatment gave Vh (326 mg), colorless liquid. *Anal.* Calcd. for $C_{15}H_{20}NBr$: C, 61.23; H, 6.85; N, 4.76. Found: C, 61.65; H, 7.14; N, 4.62.

***trans*-1-Cyclohexyl-2-phenylazetidine-3-carboxamide (IVi)**——a) To a stirred molecular sieve dried DMSO (2 ml), in which was dissolved with NaH (25 mg), were added MeOH (66 mg) and IVe (100 mg) and the mixture was heated at 100° for 2 hr and with exclusion of moisture. After cooled to room temperature, the reaction mixture was diluted with water and extracted with ether and then the organic layer was dried over $MgSO_4$. Evaporation of the solvent yielded IVi (90 mg, 84%), mp 139—141° (from *n*-hexane). *Anal.* Calcd. for $C_{16}H_{22}ON$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.32; H, 8.62; N, 10.58. IR ν_{max}^{KBr} cm^{-1}: 3480—3150, 1683, 1658.

b) In the same experiments as described in a) except that IVe was replaced with Ve, a series of the treatment gave IVi (98 mg, 91%), mp 140—142°.

Conversion of the *trans*-Amide (IVi) to the *trans*-Nitrile (IVe)——To a stirred solution of triphenylphosphine dibromide, prepared from triphenylphosphine (136 mg) and bromide (82 mg), in dry acetonitrile (5 ml) were added triethylamine (105 mg) and IVi (135 mg) and the mixture was allowed to stir at room temperature for 1 hr. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (7 g, benzene: AcOEt=9: 1) to yield IVe (105 mg, 84%), mp 88—90° (from *n*-hexane).

***trans*-1-Cyclohexyl-2-phenyl-3-benzoylazetidine (IVj)**——a) To a stirred solution of IVe (180 mg) in dry ether (30 ml), was added dropwise phenylmagnesium bromide (347 mg) in ether (10 ml) under ice-cooling and with exclusion of moisture. The reaction mixture was heated under reflux for 2 hr and allowed to stand at room temperature overnight. To the mixture was added a saturated NH_4Cl solution and the organic layer was separated, dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (18 g, benzene: AcOEt=19: 1) to give IVj (55 mg, 22%), mp 95—96° (from MeOH).

b) In the same experiment as described in a) except that IVe was replaced with Ve, a series of the treatment gave IVj (104 mg, 44%), mp 96—97° (from MeOH).

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