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Syntheses of 3,4-Epoxy- and 3,4-Epimino-pyrrolidines[1]

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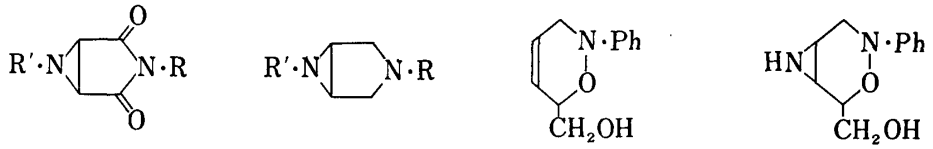
Some 3,4-epiminopyrrolidines were synthesized by two alternate methods. Lithium aluminum hydride reduction of N-(*p*-methoxyphenyl)-1-benzyl-2,3-aziridinedicarboximide (**6**) afforded 1-(*p*-methoxyphenyl)-3,4-(N-benzylepimino)pyrrolidine (**8**) in a low yield. Epoxidation of 1-benzoyl-Δ^3-pyrroline (**12**) with pertrifloroacetic acid gave 1-benzoyl-3,4-epoxypyrrolidine (**13**) which formed 1-benzoyl-*trans*-3-azido-4-mesyloxypyrrolidine (**15**) on successive treatment with sodium azide and mesyl chloride. **15** was converted into 1-benzyl-3,4-epiminopyrrolidine (**16**) on treatment with lithium aluminum hydride, or into 1-benzoyl-3,4-epiminopyrrolidine (**20**) with sodium borohydride and cobalt(II)-tris(α,α'-dipyridyl) bromide, respectively, in a fair yield. The nuclear magnetic resonance spectra of these compounds were evaluated.

Many derivatives of 2,4-dioxo-3,6-diazabicyclo[3.1.0]hexane (2,3-aziridinedicarboximide) (**1**) have been prepared and well characterized,[3,4] while synthesis of 3,6-diazabicyclo[3.1.0]hexane (3,4-epiminopyrrolidine) (**2**) having no oxygen function has apparently been left to be studied. This heterocyclic system is not only of chemical interest because of its potency as a synthetic intermediate, but also of pharmaceutical interest in cancer chemotherapy as one of the active principles of antitumor antibiotics, the Mitomycins. In a previous paper,[5] we reported the transformation of 2-phenyl-3,6-dihydro-1,2-oxazine-6β-methanol (**3**) into 2-phenyl-4β,5β-epiminotetrahydro-1,2-oxazine-6β-methanol (**4**) which would be convertible into some substituted 3,4-epiminopyrrolidine derivatives by hydrogenative fission of the N-O bond and subsequent recyclization of the resulting aminoalcohol into a pyrrolidine ring. We now wish to report more direct routes for the preparation of 3,4-epiminopyrrolidines.



1 2 3 4

Ph=C_6H_5

Chart 1

In consideration of the fact that succinimide can be converted into pyrrolidine, in a good yield, on reduction with lithium aluminum hydride,[6] it was first presumed that the most direct approach to 3,4-epiminopyrrolidine would be the lithium aluminum hydride reduction of 2,3-aziridinedicarboximide (**1**). The starting material was prepared by the procedure of Mustafa, *et al.*[3] in the following way: Cycloaddition reaction of N-(*p*-methoxyphenyl)maleimide with

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[1] A part of this work was presented as preliminary communications; S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 764 (1968); *idem*, *ibid.*, **16**, 1637 (1968).

[2] Location: *Hiromachi, Shinagawa-ku, Tokyo.*

[3] A. Mustafa, S.M.A.D. Zayed, and S. Hattab, *J. Am. Chem. Soc.*, **78**, 145 (1956).

[4] S.J. Davis and C.S. Rondestvedt, Jr., *Chem. Ind.* (London), 845 (1956); W.I. Awad, S.M.A.R. Omran, and G. Nagiel, *Tetrahedron*, **19**, 1591 (1963).

[5] S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **17**, 939 (1969).

[6] L.M. Rice, E.E. Reid, and C.H. Grogan, *J. Org. Chem.*, **19**, 884 (1954).

benzyl azide afforded N-(*p*-methoxyphenyl)-1-benzyl-Δ^2-1,2,3-triazolidine-4,5-dicarboximide (**5**), mp 161° (decomp.), in 80% yield. Pyrrolysis of **5** in Diglyme at an elevated temperature gave N-(*p*-methoxyphenyl)-1-benzyl-2,3-aziridinedicarboximide[7] (**6**), mp 137.5—139°, in 58% yield, along with a benzylaminomaleimide derivative (**7**), mp 115—116°. The aziridinedicarboximide (**6**) thereby obtained was treated with lithium aluminum hydride in ether to yield the desired 3,4-epiminopyrrolidine (**8**), mp 115—116°, but the yield was quite low (8.6%). Efforts to characterize the other reaction products gave disappointing results because of their higher unstability to ordinary chemical treatments. The structure of **8** was confirmed by elementary analysis and by means of infrared and nuclear magnetic resonance (NMR) spectrometry as will be described later.

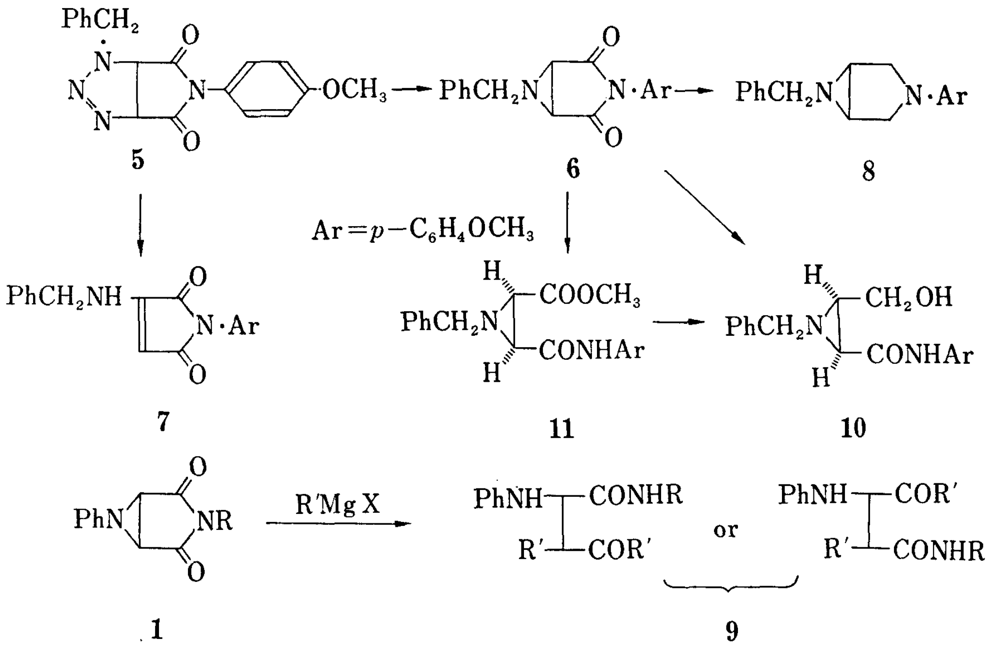

Chart 2

In general, Grignard reagent[8] or lithium aluminum hydride[9] normally attacks a carbonyl function elsewhere in the molecule of aziridine derivatives without affecting the aziridine ring, while it was reported that N-phenylaziridinedicarboximide (**1**: R=aromatic substituent) was treated with Grignard reagent to give **9** with the aziridine ring opened.[10] In consideration of this fact, it was presumed that lithium aluminum hydride also damages the aziridine ring of **6**, which decreases the yield of **8**.

Reduction of **6** with sodium borohydride in boron trifluoride etherate[11] in place of lithium aluminum hydride was attempted in expectation of a higher yield of **8**. However, the treatment of **6** with this reagent only gave a small amount of **8** and mainly afforded 1-benzyl-*cis*-2-*p*-methoxyphenylcarbamoyl-3-hydroxymethylaziridine (**10**). The infrared spectrum of **10** exhibited a broad OH and NH absorption at 3100 cm^{-1} and secondary amide absorptions at 1693 and 1550 cm^{-1}. The NMR spectrometry revealed its structure and, especially, the

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[7] The benzyl group of **6** could not be detached from the nitrogen by shaking in hydrogen atmosphere with palladium-charcoal in alcohol. *cf.* M.A. Stolberg, J.J. O'Nell, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **75**, 5045 (1953). Hydrogenation of **6** over platinum in acetic acid afforded N-(*p*-methoxyphenyl) succinimide, mp 163—164°, along with an unidentified product, mp 125—127°.

[8] N.H. Cromwell, *J. Am. Chem. Soc.*, **69**, 258 (1947); N.H. Cromwell, J.H. Anglin, F.W. Olsen, and N.G. Barker, *ibid.*, **70**, 2803 (1951).

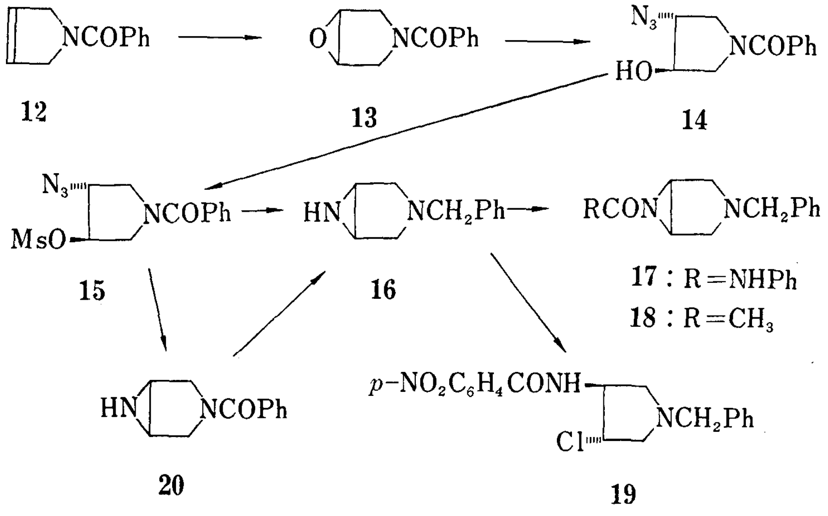
[9] R.v. Capeller, R. Griot, M. Haring, and T. Wagner-Jauregg, *Helv. Chim. Acta*, **40**, 1652 (1957).

[10] W.J. Awad, F.G. Badder, M.A. Omara, and S.M.A.R. Omran, *J. Chem. Soc.*, **1956**, 2040.

[11] G.R. Pettit, U.R. Ghatak, B. Green, T.R. Kasturi, and D.M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

coupling constant (J=7.0 cps) between the C-H protons of the aziridine ring indicated a *cis*-orientation of the substituents in the 2- and 3-positions.[12] Supposedly, formation of **10** is similar to the recent observation on the reduction of glutarimides or barbiturates with sodium borohydride.[13] **10** was also obtained by lithium aluminum hydride reduction of methyl 1-benzyl-*cis*-2-(*p*-methoxyphenylcarbamoyl)aziridine-3-carboxylate (**11**) which was prepared by the hydrolysis of **6** with a base, followed by treatment of the resulting acid, mp 171° (decomp.), with diazomethane. In order to obtain the epiminopyrrolidine by recyclization of **10**, tosylation of **10** was attempted, but without success, only producing a deeply colored complex reaction mixture, from which no simple product was separated.

The second approach was based on the stepwise synthesis of an aziridine ring on a pyrrolidine system in the following way. 1-Benzoyl-Δ^3-pyrroline[14] (**12**) was found to be inert to ordinary peracetic acid or anhydrous peracetic acid[15] but was successfully oxidized with pertrifluoroacetic acid in the presence of disodium hydrogen phosphate[16] in dichloroethane, yielding 1-benzoyl-3,4-epoxypyrrolidine (**13**), mp 66—68°, quantitatively. The NMR spectrum of **13** was not characterized well, but indicated the absence of the 3,4-vinyl protons. Treatment of **13** with sodium azide gave a syrupy azidoalcohol (**14**) whose infrared spectrum showed an azide absorption at 2090 cm^{-1}, along with a hydroxyl absorption at 3350 cm^{-1}. **14** formed a syrupy azidomesylate (**15**) on treatment with mesyl chloride in pyridine. Lithium aluminum hydride reduction of **15** in ether afforded the desired 1-benzyl-3,4-epiminopyrrolidine (**16**), bp 106—107° (0.7 mmHg), with accompanying reduction of the N-benzoyl group to N-benzyl group. The yield of **16** from **12** was 68%. 3,4-Epiminopyrrolidine (**16**) thus obtained was characterized as its crystalline phenylurea derivative (**17**), mp 168.5—169°. Acetylation of **16** with acetic anhydride or benzoylation with benzoic anhydride gave the corresponding acetate (**18**) or benzoate, respectively, as a syrup, while benzoylation of **16** with *p*-nitrobenzoyl chloride in pyridine afforded 1-benzyl-*trans*-3-chloro-4-(*p*-nitrobenzamido)pyrrolidine (**19**), mp 134.5—135°, with the aziridine ring opened.[17]



Ph=C_6H_5 Ms=CH_3SO_3

Chart 3

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[12] S.L. Manatt, D.D. Elleman, and S.J. Brois, *J. Am. Chem. Soc.*, **87**, 2220 (1965); A.E. Pohland, R.C. Badger, and N.H. Cromwell, *Tetrahedron Letters*, **1965**, 4369.

[13] Y. Kondo and B. Witkop, *J. Org. Chem.*, 33, 206 (1968), and its preceding papers.

[14] F. Anderlini, *Ber.*, **22**, 2512 (1889).

[15] B. Philips, P.S. Starcher, and B.D. Ash, *J. Org. Chem.*, **23**, 1823 (1958).

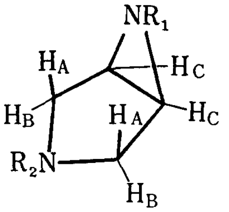
[16] W.D. Emmons and G.B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955) and its preceding papers.

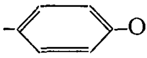
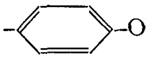
[17] K. Ponsold and D. Klemm, *Chem. Ber.*, **99**, 1502 (1966).

In 1967, Ponsold reported that, treatment of α-azidotosylate with sodium borohydride and cobalt (II)-tris (α,α′-dipyridyl) bromide successfully converted it into an aziridine without any damage to other ester or amide function.[18] Following the Ponsold's method, treatment of the azidomesylate (**15**) with this reagent in ethanol yielded 1-benzoyl-3,4-epiminopyrrolidine (**20**), mp 98.5—100°, in a fair yield. **20** was converted into **16** on further reduction with lithium aluminum hydride. The product was identified as its phenylurea (**17**) by mixed melting point test and infrared spectrometry.

The NMR data of the epiminopyrrolidines synthesized here are presented in Table I. The NMR spectrum of 1-benzyl-3,4-epiminopyrrolidine N-acetate (**18**), shown in Fig. 1, exhibited a pair of doublet absorptions at 3.23 and 2.28 ppm, and a broad singlet absorption at 3.01 ppm. The former doublets would be due to the methylene protons (HA and HB) adjacent to the pyrrolidine nitrogen, and the latter broad singlet to the C–H protons (Hc)

TABLE I. NMR Data of 3,4-Epiminopyrrolidines in $CDCl_3$



Compound	R_1	R_2	HA (sharp doublet, ppm)	HB (broad doublet, ppm)	Hc (broad singlet, ppm)	J_{AB} (cps)	Half width of HB, Hc (cps)
8	$-CH_2Ph$	--OMe	3.61	3.14	2.47	10	4.0
	$-CH_2Ph$	--OMe	(3.34	2.80	1.86	9.7	4.1)[a]
16	$-H$	$-CH_2Ph$	3.07	2.31	2.39	9.5	2.5
17	$-CONHPh$	$-CH_2Ph$	3.34	2.41	3.09	10.5	2.5
18	$-COCH_3$	$-CH_2Ph$	3.23	2.28	3.01	10.5	2.2

[a] The data were taken on a Varian HA-100 spectrometer in deuteriobenzene.

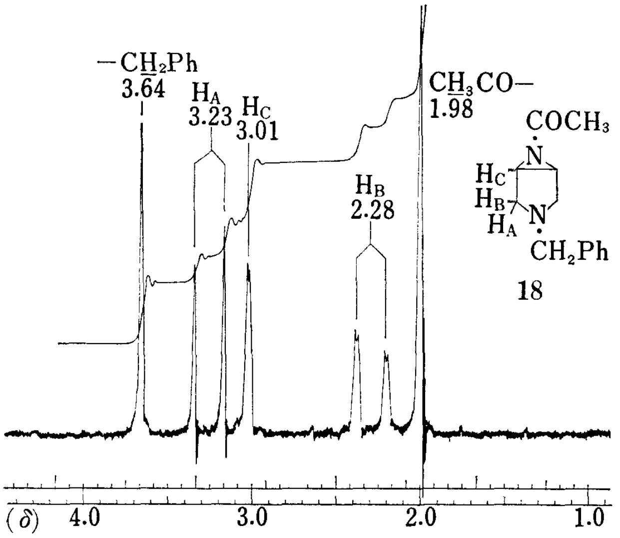


Fig. 1. NMR Spectrum of 1-Benzyl-3,4-epimino-pyrrolidine N-Acetate (**18**) in $CDCl_3$

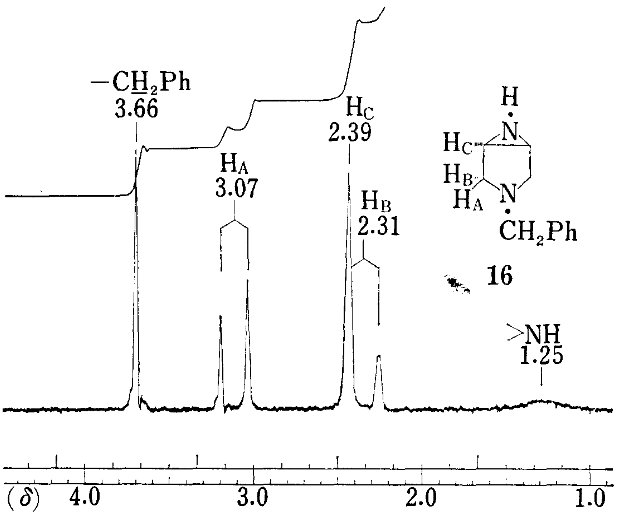


Fig. 2. NMR Spectrum of 1-Benzyl-3,4-epimino-pyrrolidine (**16**) in $CDCl_3$

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[18] K. Ponsold, *J. Prakt. Chem.*, **36**, 148 (1967).

of the aziridine ring for the following reasons. The methylene protons (H_A and H_B) of the pyrrolidine ring would not be equivalent owing to the fusion of the three-membered ring; hence the absorption pattern of these protons would apparently be of the AB-type, if the coupling constants (J_{AC} and J_{BC}) are very small. The two doublet absorptions of **18** at 3.23 and 2.28 ppm with $J_{AB}=10.5$ cps reflect this coupling mode of H_A and H_B. In addition, comparison of the NMR spectrum of 1-benzyl-3,4-epiminopyrrolidine (**16**), shown in Fig. 2, with that of its acetate (**18**) shows that the doublet absorption at 2.31 ppm is not affected by substitution of the aziridine nitrogen, while the other at 3.07 ppm shifts to a further low field by 0.16 ppm. A similar phenomenon was observed on comparison of the chemical shifts of **16** with that of its phenylurea derivative (**17**) as shown in Table 1. This phenomenon would be ascribed to the anisotropic deshielding by the neighboring N-substitution; hence, the doublet absorption appearing at a lower field corresponds to H_A, which is located on the same side as the aziridine ring, and the doublet at a higher field to H_B. The broad singlet peak at 2.39 ppm would be due to the C–H protons (H_C) of the aziridine ring. Further, it was also observed that the H_A absorption is a sharp doublet, while the H_B and H_C absorptions are broad with fine splitting shown in Table I as their half width. This fact suggests a mutual coupling between H_B and H_C, probably along with further coupling with the corresponding protons of the methylene and methine on the other side, indicating a spin-coupled system of $A_2B_2C_2$.

As will be seen from Table I, the NMR spectrum of **8** exhibited an analogous pattern, suggesting that the N-substituent does not give a substantial effection with the conformation of this bicyclo[3.1.0]hexane skeleton. In addition, it is interesting to note that the NMR spectrum of 3,4-epiminotetrahydrofuran[19] or some of 3-oxabicyclo[3.1.0]hexane derivatives[20] found in literatures shows a sharp doublet absorption at a lower field and a broad doublet at a higher field similar to that of these epiminopyrrolidines, indicating that there is a common pattern of conformation between these bicyclo[3.1.0]hexane system, whether some hetero-atoms are involved or not. Additional observations by NMR analysis of these epiminopyrrolidine will be discussed in relation to their conformation in a forthcoming paper.

Experimental

Melting points are not corrected. Infrared spectra were determined on a Perkin-Elmer Model 221 or a Perkin-Elmer Infracord (Model 137), and NMR spectra usually on a Varian A-60 spectrometer. The removal of solvent *in vacuo* was accomplished by a rotating flash evaporator at 20—30 mmHg and usually at 35—50°.

N-(*p*-Methoxyphenyl)-1-benzyl-Δ^2-1,2,3-triazolidine-4,5-dicarboximide (5)——A solution of 35.0 g (0.172 mole) of N-(*p*-methoxyphenyl)maleimide,[21] and 26.4 g (0.198 mole) of benzyl azide[22] in 50 ml of dioxane was warmed on a steam bath for 1 hr. Crystals (45.5 g, 80%), mp 158—160° (decomp.), formed in the cooled reaction mixture were collected and recrystallized from AcOEt, giving **5** as needles of mp 161° (decomp.). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1725, 1759 (weak). NMR (CDCl$_3$) δ ppm: 3.79 (3H, singlet), 4.18 (1H, doublet, $J=11$ cps), 5.48 (1H, doublet, $J=11$ cps), 4.73 (1H, doublet, $J=15.3$ cps), 5.48 (1H, doublet, $J=15.3$ cps), 6.8—7.3 (4H, multiplet), 7.34 (5H, singlet). *Anal.* Calcd. for $C_{18}H_{16}O_3N_4$: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.14; H, 4.95; N, 16.90.

N-(*p*-Methoxyphenyl)-1-benzyl-2,3-aziridinedicarboximide (6)——A solution of 4.98 g of **5** in 30 ml of diglyme was warmed gradually in an oil bath with stirring. At about 150° or so, the generation of N_2 started and the mixture was kept at about 160° for 3 hr with stirring. The cooled mixture was poured into 150 ml of cold water and extracted with 70 ml of AcOEt. The extract was washed twice with 70 ml each of H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* left an orange crystalline syrup (6.51 g), which gave 3.70 g of crystals on digestion with 10 ml of EtOH. Recrystallization of the collected crystals twice from EtOH afforded 2.64 g (58%) of **6** as colorless leaflets, mp 137.5—139°. IR

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[19] P.E. Fanta and E.N. Walsh, *J. Org. Chem.*, 31, 59 (1966).

[20] T. Shono, A. Oku, T. Morikawa, M. Kimura, and R. Oda, *Bull. Chem. Soc. Japan*, 38, 940 (1965).

[21] W.R. Roderick, *J. Am. Chem. Soc.*, 79, 710 (1957).

[22] T. Curtius and G. Ehrhart, *Chem. Ber.*, 55, 1565 (1922).

ν_{max}^{Nujol} cm^{-1}: 1723, 1785 (weak). NMR ($CDCl_3$) δ ppm: 3.09 (2H, singlet), 3.69 (2H, singlet), 3.78 (3H, singlet), 7.04 (4H, AA'BB'-pattern multiplet), 7.34 (5H, singlet). *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.45, H, 5.21; N, 9.07.

The combined mother liquor of the recrystallization was concentrated and the resulting crystals were recrystallized from EtOH to 0.70 g (15%) of benzylamino-N-(*p*-methoxyphenyl)maleimide (**7**) as yellow needles of mp 115—116°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1710, 1640. UV λ_{max}^{EtOH} mμ(ε): 233 (24,900), 280 (8,100), 365 (2,100). NMR ($CDCl_3$) δ ppm: 3.80 (3H, singlet), 4.37 (2H, doublet), 4.98 (1H, singlet), 5.91 (1H, broad), 7.10 (4H, AA'BB'-pattern multiplet), 7.33 (5H, singlet). *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.62; H, 5.20; N, 8.87.

1-(*p*-Methoxyphenyl)-3,4-(N-benzylepimino)pyrrolidine (8)——To a solution of 1.41 g of **6** in 30 ml of tetrahydrofuran, 0.40 g of $LiAlH_4$ was added in small portions with stirring and cooling. The mixture was refluxed for 6 hr. After decomposition of the excess of the reagent by careful addition of H_2O, the mixture was filtered. The solid was washed successively with EtOH and $CHCl_3$. The combined filtrate and washings was concentrated *in vacuo* and extracted with $CHCl_3$. The extract was evaporated *in vacuo* to leave 1.33 g of a brown syrup, which was chromatographed on 25 g of silicagel. Removal of the solvent from the fractions eluted with benzene containing increasing gradient of 10—25% (v/v) of ether gave 180 mg of a crystalline residue which was recrystallized from EtOH to give 82 mg (8.6%) of **8** as leaflets of mp 115—116°. The infrared spectrum showed no absorption of NH, OH, or C=O. *Anal.* Calcd. for $C_{18}H_{20}ON_2$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.93; H, 7.29; N, 9.95.

1-Benzyl-*cis*-2-(*p*-methoxyphenylcarbamoyl)aziridine-3-carboxylic Acid and Its Methyl Ester (11)——A mixture of a solution of 506 mg of **6** in 7 ml of tetrahydrofuran and a solution of 300 mg of Na_2CO_3 in 2 ml of H_2O was refluxed for 4 hr. Neutralization of the cooled mixture with AcOH and standing in a refrigerator afforded 496 mg (93%) of crystals, mp 166° (decomp.), which were recrystallized from MeOH giving 1-benzyl-*cis*-2-(*p*-methoxyphenylcarbamoyl)aziridine-3-carboxylic acid as leaflets, mp 171° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3350, 2500, 1740, 1693, 1549. UV λ_{max}^{EtOH}: 257.5 mμ (ε 14,200). *Anal.* Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.80; H, 5.58; N, 8.85.

This acid formed a syrupy methyl ester quantitatively by treatment with CH_2N_2. IR $\nu_{max}^{liq.}$ cm^{-1}: 3360, 1747, 1682. NMR (C_6D_6) δ ppm: 2.46 (2H, AB-pattern quartet, J=7.2 cps), 3.17 (2H, AB-pattern quartet, J=14 cps), 3.14 (3H, singlet), 3.29 (3H, singlet), 7.19 (5H, multiplet), 7.21 (4H, AA'BB'-pattern multiplet), 8.65 (1H, broad).

1-Benzyl-*cis*-2-(*p*-methoxyphenylcarbamoyl)-3-hydroxymethylaziridine (10)——(i) To a solution of 308 mg of **11** in 5 ml of ether 60 mg of $LiAlH_4$ was added with cooling and stirring, and then the mixture was stirred for 3 hr at room temperature. After decomposition of the excess of the reagent by adding H_2O carefully, the mixture was filtered. The filtrate was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*. Recrystallization of the residual crystals from ether–MeOH gave 92 mg (33%) of **10** as needles of mp 94.5—96°. IR ν_{max}^{Nujol} cm^{-1}: 3100 (broad), 1693, 1550. NMR (C_6D_6) δ ppm: 1.03 (1H, doublet of triplets, J=7 and 5.5 cps), 1.33 (1H, doublet, J=7 cps), 3.20 (2H, singlet), 3.32 (3H, singlet), 3.68 (2H, doublet, J=5.5 cps), 7.11 (4H, AA'BB'-pattern multiplet), 7.21 (5H, singlet), 8.41 (1H, broad singlet). *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.67. Found: C, 69.63; H, 6.57; N, 8.72.

(ii) To a cooled solution of 1.03 g (0.0033 mole) of **6** in 10 ml of BF_3–etherate was added dropwise a solution of 520 mg (0.013 mole) of $NaBH_4$ in 10 ml of Diglyme with stirring. The mixture was further stirred for 1 hr with cooling and then heated to reflux with stirring. After refluxing for 3 hr, the cooled mixture was poured into H_2O and the resulting solid was collected by filtration. The filtrate was washed with benzene, basified with Na_2CO_3 solution, and extracted with benzene. The extract was washed with H_2O, dried and evaporated *in vacuo*, leaving 100 mg of a crystalline mass. Recrystallization from EtOH gave 10 mg of the epiminopyrrolidine (**8**).

The collected solid was treated with conc. NaOH solution and the separated oil was extracted with benzene. The extract was dried and evaporated *in vacuo*, leaving a syrup, which crystallized on standing overnight in a refrigerator. After being washed with ether the crystals of mp 95—97° (200 mg) were recrystallized from benzene–ether to **10** of mp 95.5—96°.

These products of **8** and **10** were identified with the corresponding samples obtained before by mixed mp and infrared spectrometry.

1-Benzoyl-3,4-epoxypyrrolidine (13)——A pertrifluoroacetic acid solution,[16] prepared by the addition of 3.5 ml of trifluoroacetic anhydride to a cooled solution of 0.58 ml of 90% H_2O_2 in 2.5 ml of dichloroethane, was added dropwise into a suspension of 12 g of Na_2HPO_4 in a solution of 2 g of 1-benzoyl-Δ^3-pyrroline (**12**) in 15 ml of dichloroethane at 0° during 30 min. The mixture was stirred at 0° for 1 hr and then at room temperature for 1 hr. Then the mixture was poured into ice–water and the resulting solution was stood for 1 hr. The organic layer was separated and the aqueous layer was extracted several times with $CHCl_3$. The combined organic layer and extracts was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* left 2.23 g of the crude **13** as a syrup which crystallized on standing. Recrystallization from AcOEt gave **13** as prisms, mp 66—68°, bp 160° (0.4 mmHg, bath temp.). IR ν_{max}^{Nujol}: 1617 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.89; H, 5.77; N, 7.21.

1-Benzyl-3,4-epiminopyrrolidine (16)——(i) A mixture of 2.23 g of the crude **13**, 0.75 g of NH_4Cl, 4 g of NaN_3, 30 ml of dimethylformamide, and 3.6 ml of H_2O was warmed on a steam bath for 5 hr. The mixture was diluted with H_2O and extracted four times with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*, leaving 2.70 g of **14** as a syrup which revealed one spot on thin-layer chromatogram. The azide (**14**) thus obtained was dissolved in 25 ml of dry pyridine and 2.60 g of mesyl chloride was added to the solution. After the mixture was warmed on a steam bath for 1 hr, the cooled mixture was poured into H_2O and extracted three times with benzene. After drying, the extract was evaporated to dryness *in vacuo* and left 3.14 g of an azidomesylate (**15**). Without further purification, **15** was dissolved in 160 ml of dry ether and the resulting solution was added dropwise into 50 ml of ether containing 1.5 g of $LiAlH_4$, during 30 min with stirring and cooling. The mixture was further stirred for 1 hr with cooling and for 1 hr at room temperature. After decomposition of excess of the reagent by adding AcOEt, the mixture was diluted with H_2O, and ether layer was separated. After drying over anhyd. Na_2SO_4, ether was evaporated *in vacuo* and the residue distilled, yielding 1.36 g (68% from **12**) of **16** as a colorless oil, bp 110° (0.6 mmHg, bath temp.). IR $\nu_{max}^{liq.}$ cm^{-1}: 3270, 2890, 2790. *Anal.* Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.46; H, 8.09; N, 16.06.

Acetylation of **16** with Ac_2O gave an acetate (**18**) as a colorless oil, bp 140—150° (0.2 mmHg, bath temp.) IR $\nu_{max}^{liq.}$ cm^{-1}: 1690. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.23; H, 7.58; N, 13.07.

Treatment of **16** with phenyl isocyanate in ether gave its phenylurea derivative (**17**) as needles (from EtOH), mp 168.5—169°. IR ν_{max}^{Nujol} cm^{-1}: 3310, 1666, 1540. *Anal.* Calcd. for $C_{18}H_{19}ON_3$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.54; H, 6.45; N, 14.17.

(ii) To a stirred suspension of 0.1 g of $LiAlH_4$ in 5 ml of ether was added dropwise a solution of 122 mg of **20** in 5 ml of ether and the mixture was stirred at room temperature for 1 hr. Working up in the usual manner, 101 mg of **16** was obtained and identified with the sample, obtained as above, by thin-layer chromatography and infrared spectrometry. Further, its phenylurea was prepared and identified by mixed mp and infrared spectrometry.

1-Benzyl-*trans*-3-chloro-4-(*p*-nitrobenzamido)pyrrolidine (19)——A solution of 168 mg of **16** and 300 mg of *p*-nitrobenzoyl chloride in 3 ml of pyridine was allowed to stand overnight at room temperature. Then the mixture was poured into ice-water and extracted twice with benzene. After drying, the extract was evaporated *in vacuo*, leaving 320 mg of a crystalline mass which was recrystallized twice from MeOH to 143 mg of **19**, fine yellow needles, mp 134.5—135°. IR ν_{max}^{Nujol} cm^{-1}: 3280, 3080, 1646, 1603, 1560, 1520. NMR ($CDCl_3$) δ ppm: 2.65 (1H, doublet of doublets, $J=10.7$ and 5.0 cps, H_A of $-CH_AH_B-\overset{|}{N}-CH_CH_D-$), 2.79 ($H_C$, doublet of doublets, $J=10$ and 3.3 cps), 3.07 (H_D, doublet of doublets, $J=10$ and 5.7 cps), 3.47 (H_B, doublet of doublets, $J=10.7$ and 6.5 cps), 3.73 (2H, singlet), 4.25 (1H, multiplet), 4.68 (1H, multiplet), 6.85 (1H, broad), 7.34 (5H, singlet), 8.12 (4H, AA'BB'-pattern multiplet). *Anal.* Calcd. for $C_{18}H_{18}O_3N_3Cl$: C, 60.08; H, 5.04; N, 11.68. Found: C, 59.83; H, 4.94; N, 11.66.

1-Benzoyl-3,4-epiminopyrrolidine (20)——The azidomesylate (**15**) (1.53 g), prepared by the procedure described for **16**, was dissolved in 10 ml of EtOH and the solution was added to a solution of 0.26 g of $CoBr_2$ and 0.62 g of α,α'-dipyridyl in 100 ml of EtOH. To this mixture was added 0.93 g of $NaBH_4$ in small portions, with cooling and stirring, and the resulting mixture was allowed to stand at room temperature for 1 hr. The mixture was concentrated at room temperature under a reduced pressure to one-half its original volume and diluted with 150 ml of H_2O. After removal of dipyridyl by washing with 50 ml of benzene, the mixture was extracted with three 60 ml portions of $CHCl_3$. The extract was dried and evaporated to dryness *in vacuo*, leaving 940 mg of a syrup which crystallized on standing. Recrystallization of the collected crystals from AcOEt gave **20** (480 mg) as prisms, mp 98.5—100°. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1624. *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.42; N, 14.95.

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