Conformational Study of 3,4-Epiminopyrrolidines in Solution

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The NOE's of the pyrrolidine ring protons, H_A and H_B, on the phenyl ring protons of the N-substituent, H_D, were determined in 1-(*p*-methoxyphenyl)-3,4-epiminopyrrolidine (2), its N-benzyl derivative (1), and its N-acetate (12). Notable differences of NOE's observed in the latter two compounds suggested that the *p*-methoxyphenyl group is preferentially situated on the same side as the *cis*-fused aziridine ring in these compounds. Synthesis of some 3,4-epiminopyrrolidines was also reported in connection with this NOE study.

In a preceding paper,²⁾ we described the preparation of some 3,4-epiminopyrrolidine derivatives for biological examination, because this new heterocyclic skeleton constitutes one of the active principles in the anti-cancer antibiotics Mitomycins. In connection with this study, we also reported there that these compounds exhibited a characteristic common absorption pattern in their nuclear magnetic resonance (NMR) spectra and suggested that the N-substituent of these 3,4-epiminopyrrolidines does not substantially effect the conformation of this bicyclo[3.1.0]hexane skeleton. In addition to many useful technique in NMR spectroscopy, a study of internal nuclear Overhauser effect³⁾ (NOE) has recently been developed; from the NOE studies, it has been possible to determine experimentally which protons in conformationally rigid systems are situated proximate to each other. As a result, it was anticipated that this technique would provide us with further information regarding the conformational nature of the 3,4-epiminopyrrolidine system studied. This paper describes a spacial arrangement of the N-substituent of these bicyclic system deduced from NOE studies.

The NMR spectrum (100 MHz) of 1-(*p*-methoxyphenyl)-3,4-(N-benzylepimino)pyrrolidine (1), whose synthesis was presented in the previous paper,²⁾ is shown in Fig. 1. In addition to the methoxy methyl and benzyl methylene absorptions, a characteristic quartet absorption of an AB-like pattern with a coupling constant of 9.7 Hz are observed. As described previously,²⁾ this absorption is attributed to the non-equivalent 2,5-methylene protons of the pyrrolidine ring. Based on the estimated anisotropic shift observed in the NMR spectra of some analogs having an acyl substituted aziridine nitrogen atom, the sharp doublet absorption at a lower field centering at 3.34 ppm is assignable as H_A, which is located on the same side as the *cis*-fused aziridine ring. The other broad doublet absorption at 2.80 ppm with a half width of 4.1 Hz, which is partially coupled with the absorption (1.86 ppm) of the 3,4-annular protons, is due to the protons, H_B, on the back side.

The AA'BB'-pattern absorption corresponding to the *p*-methoxyphenyl ring protons falls at 6.33 ppm and 6.87 ppm. Irradiation⁴⁾ of the methoxy methyl absorption at 3.45 ppm increased the intensity of the lower-field signals, but no effect was observed with the higher ones. This indicates that the former signals are due to the proton situated adjacent to the

1) Location: Hiromachi, Shinagawa-ku, Tokyo.

2) S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **17**, 980 (1969).

3) F.A.D. Anet and A.J.R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965); R.H. Martin and J.C. Noulis, *Tetrahedron Letters*, **1968**, 2727 and references cited therein.

4) All the NOE's were determined without removal of oxygen in *ca.* 5% deuteriobenzene solution on a Varian HA-100 spectrometer.

Fig. 1. NMR Spectrum of 1-(*p*-Methoxyphenyl)-3,4-(*N*-benzylepimino)pyrrolidine (**1**) in C_6D_6 at 100 MHz

methoxyl group, H_B , and the latter ones are due to H_D . Alternatively, the signals of the aforementioned pyrrolidine protons, H_A , which is located on the same side as the aziridine ring, were saturated, affecting the absorption of H_D with *ca.* 12% increase in signal area, while saturation of the other ring protons absorption, H_B , resulted in a lesser effect on H_D with *ca.* 5% increase as shown in Fig. 2. This notable NOE is indicative of the preferential orientation of the *p*-methoxyphenyl substituent in a position close to the H_A ring protons, that is, the location of this group close to the aziridine ring as illustrated below. Presumably, this conformation of **1** may be ascribed to mutual repulsion of the electric dipoles produced by the unshared electron pairs of the nitrogen as discussed below. Moreover, irradiation of the benzyl methylene signal at 3.15 ppm results in a 10% increase for the 3,4-annular proton signal, H_C , at 1.86 ppm.

Fig. 2. NOE observed on the Spectrum of 1-(*p*-Methoxyphenyl)-3,4-(*N*-benzylepimino)pyrrolidine (**1**): (1) H_D with (Integral-I) and without Irradiation (Integral-N) at H_B ; (2) H_D with (Integral-I) and without Irradiation (Integral-N) at H_A

This interesting experimental observation prompted a NOE study of a 3,4-epiminopyrrolidine without aziridine *N*-substituent, because it was assumed that the unshared electrons of the aziridine nitrogen in this compound would not have any fixed arrangement and would not affect the location of the pyrrolidine *N*-substituent. For the preparation of 1-(*p*-methoxyphenyl)-3,4-epiminopyrrolidine (**2**), reductive cleavage of the *N*-benzyl group of **1** to yield directly **2** by hydrogenation was considered unfeasible, based on a preceding study;²⁾ therefore, the aziridine ring formation at the 3,4-position of 1-(*p*-methoxyphenyl)-3-pyrroline⁵⁾

5) J.J. Roberts and W.C.J. Ross, *J. Chem. Soc.*, 1952, 4288.

(3) was undertaken in the following way. Following the method of Bobbit, *et al.*⁶⁾ treatment of *p*-anisidine with *cis*-1,4-dichloro-2-butene yielded the pyrroline derivative (3) in a fair yield. First, hydroxylation of 3 at the 3,4-position by potassium permanganate oxidation in acetone was attempted, but this resulted in formation of 1-(*p*-methoxyphenyl)pyrrole⁷⁾ (4) (*cf.* experimental). Alternatively, oxidation of 3 with osmium tetroxide in the presence of pyridine and decomposition of the resulting adduct with sodium sulfite afforded 3,4-dihydroxypyrrolidine (5), mp 159—160°, in 71% yield. Although no reliable data could be obtained from the NMR spectrum of 5, this product would be a *cis*-glycol considering the oxidation mode of the reagents used. Treatment of 5 with equivalent amount of tosyl chloride in pyridine gave a monotosylate (6), mp 148—150°, along with some starting material and a ditosylate (7), mp 146—147°, which could be separable by fractional recrystallization. The monotosylate (6) thereby obtained was treated with sodium azide in dimethylformamide affording *trans*-3-azido-4-hydroxypyrrolidine (8), mp 77—78.5°, whose isolation, however, was found to be very wasteful. Accordingly, the product was tosylated in pyridine without further purification, yielding *trans*-3-azido-4-tosyloxypyrrolidine (9), mp 101—102°, in a fair yield. As the main by-products of this reaction, the pyrrole derivative (4) and *trans*-3-azido-4-formyloxypyrrolidine (10), mp 80—82°, were isolated in small amounts. The latter compound (10) was hydrolyzed with base, giving *trans*-3-azido-4-hydroxyl derivative (8) in a good yield. Formation of these by-products would be due to further reaction of the azidotosylate (9). This was ascertained by direct conversion of 9 in to the pyrrole (4) on treatment with warm pyridine. In consideration of the literature,⁸⁾ a plausible route for the formation of the formate (10) would involve the displacement of the tosyloxy group of 9 by dimethylformamide, which may not have been completely removed during this procedure. Moreover, the retention of the configuration in the 4-position would be attributed to the neighbouring group participation of the pyrrolidine nitrogen atom *via* a possible intermediate (11) in this displacement reaction.

Lithium aluminum hydride reduction of the 3-azido-4-tosylate (9) afforded the desired 1-(*p*-methoxyphenyl)-3,4-epiminopyrrolidine (2), mp 103—110°, which was found to be unstable and partially decomposed during chromatographic purification on silica gel. Acetylation of the epimine (2) gave an acetate (12), mp 110—111°. Direct acetylation of the reduction product of 9, collection of the acetylepimine (12) and chromatography of the residual syrup afforded 3-acetamidopyrrolidine (13a), mp 164—166.5°. This suggested the presence of some 3-aminopyrrolidine derivative (13b) in the reduction product of 9. It is of interest to note the formation of 13b during this reduction. As the formed epimine (2) is insensitive to the further attack of the reagent and its conversion into 13b is unlikely, the formation of 13b would be illustrated analogously to the formation of the azidoformate (10) from 9: independent of the reduction of the azido group of 9 to an amine, the tosyloxy group of 9 would be initially removed under the participation of the pyrrolidine nitrogen atom and the resulting intermediate like 11 is converted into the pyrrolidine unsubstituted in the 4-position by subsequent attack of a hydride ion.

The NMR data of the epimine (2) and the acetylepimine (12) thus obtained are presented in Table I, indicating an analogous pattern to that of the benzylepimine (1). In the similar way, saturation of the corresponding H_A signals in the acetylepimine (12) results in a *ca.* 12% increase for H_D, whereas the increase in H_D by irradiation of H_B is negligible. This seems to parallel the case of the benzylepimine (1). On the other hand, irradiation of the H_A signals in the epimine (2) affects H_D with *ca.* 5% increase in signal area and that of the H_B signals with *ca.* 2% increase, indicating no marked difference of NOE. This fact suggests that the molecule of the epimine (2) without aziridine N-substituent has a versatile conforma-

6) J.M. Bobbit, L.H. Amundsen, and R.I. Steiner, *J. Org. Chem.*, **25**, 2230 (1960).

7) D.A. Shirly, B.H. Gross, and P.A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

8) F.C. Chang and R.T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

tion without specific orientation of the *p*-methoxyphenyl group. Based on the NOE study of these epimines, it may be concluded that their unshared electron pairs of aziridine nitrogen atom appreciably effects those of pyrrolidine nitrogen atom by a mutual repulsion of the electric dipoles and this interaction fixes the spacial arrangement of the nitrogen substituents. A NOE study on these 3,4-epiminopyrrolidine derivatives in some protonated form, which presumably would further substantiate this conclusion, was attempted, but without results, since these epimines were found to be sensitive to acids and no identifiable salt was isolable for the NOE study. Recently, much interest has been focussed on the stereochemistry of cyclic compounds having hetero atoms. However, there is no suitable example to be found in the literatures at present on the conformational interaction of nitrogen atoms located in the 1,4-position. The actual conformation of the six-membered ring, chair, boat or other form, in this bicyclic system still remains unsolved;⁹⁾ however, it may be acceptable to note that fusion of the aziridine ring to the pyrrolidine ring makes the latter's pseudorotation¹²⁾ fixed and forces the nitrogen atoms close to each other resulting in mutual interaction. Furthermore, it is of interest to note that natural mitomycins, whose configuration was determined by X-ray analysis¹³⁾ of the N-brosylate as illustrated in **14**, and whose bridgehead methoxy group is *trans* to the aziridine ring, has a sterically-favorable conformation under the same criterion applied to 3,4-epiminopyrrolidine herein.

Chart 3

Chart 4

- 9) In 1966, Trefonas and Sato¹⁰⁾ carried out a single crystal, three-dimensional X-ray study on the *p*-iodobenzenesulfonate of 3,4-epiminotetrahydrofuran:¹¹⁾ In this bicyclic compound, the aziridine ring is fused *cis* to the tetrahydrofuran ring with fusion angles of 112° and has the *p*-iodobenzenesulfonate group at an angle of 98.0°. Further, the bicyclic six-membered ring sits in the boat conformation with O-N distance of 2.65 Å as shown in the Chart. As already pointed out in the preceding paper,²⁾ the published NMR spectrum of this compound shows a sharp doublet absorption at a lower field and a broad doublet at a higher field corresponding to its 2,5-ring protons similar to the case of 3,4-epiminopyrrolidines, indicating that there is a common conformation between these bicyclo[3.1.0]-hexane systems where the hetero atom involved is oxygen or nitrogen. We are also attempting a X-ray analysis of some of 3,4-epiminopyrrolidines and this will be the subject of forthcoming papers.
- 10) L.M. Trefonas and T. Sato, *J. Heterocyclic Chem.*, **3**, 404 (1966).
- 11) P.E. Fanta and E.N. Walsh, *J. Org. Chem.*, **31**, 59 (1966).
- 12) "Conformational Analysis," ed. by E.L. Eliel, *et al.*, Interscience Publishers, John Wiley & Sons, Inc., New York, 1967, p. 200.
- 13) A. Tulinsky, *J. Am. Chem. Soc.*, **84**, 3188 (1962).

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Chart 5

Chart 6

Next, we would like to discuss the synthesis of other 3,4-epiminopyrrolidines carried out in connection with this NOE study. We pursued the method of Scheiner¹⁴) in order to prepare an epiminopyrrolidine with an N-phenyl substituent at the aziridine nitrogen: treatment of 3-pyrroline with *p*-bromophenyl azide gave a triazoline (**15**) whose photodecomposition was effected in a quartz tube by a Hanovia UV-lamp, giving 3,4-(*p*-bromophenylepimino)-pyrrolidine (**16a**): however, the yield of **16a** expected from the literature¹⁴) could not be obtained (*cf.* experimental). Other synthetic approach to **16a** or its analog was also attempted, but without result. Acetylation of **16a** afforded an acetate (**16b**), mp 163—163.5°. As is shown in Table I, the NMR signals of **16a** due to its 2,5-methylene protons appear as an analogous AB-like pattern, while those of the acetate (**16b**) as a couple of the same patterns, which suggests that the protons in the 2-position have different chemical shifts from those in the 5-position, probably, owing to an anisotropic effect of the neighbouring N-acetyl group.

Synthesis of 3,4-epiminopyrrolidines with an N-alkyl substituent was conducted by our previous method²) as follows: acetylation of 3-pyrroline gave 1-acetyl-3-pyrroline (**17a**), mp 57—61°, whose oxidation with pertrifluoroacetic acid afforded 1-acetyl-3,4-epoxypyrrolidine (**18a**), mp 61—63°. Treatment of **18a** with sodium azide in dimethylformamide gave *trans*-3-azido-4-hydroxypyrrolidine (**19a**) as a syrup, whose tosylation in pyridine afforded a tosylate (**20a**), mp 88—90°. Lithium aluminum hydride reduction **20a** yielded 1-ethyl-3,4-epiminopyrrolidine (**21a**), which could not be purified successfully by distillation, giving an unidentified polymeric substance; therefore, **21a** was characterized as its oxalate,¹⁵) mp 130—160° (decomp.). Treatment of the crude **21a** with phenyl isocyanate afforded a phenylurea derivative (**21b**), mp 148—150°. Alternatively, the *trans*-3-azido-4-tosyloxy derivative (**20a**) was converted into a deuterated analog (**21c**) on treatment with lithium aluminum deuteride, which formed also a deuterated phenylurea (**21d**), mp 148.5—150°. The NOE study of **21d** was also carried out, since it was of interest to know how the size of pyrrolidine N-substituent affects the NOE of the 2,5-methylene protons. However, irradiation of the methyl signals of **21d** at 0.75 ppm resulted in a negligible increase in both H_A and H_B signals.

On the other hand, we wanted to prepare 3,4-epiminopyrrolidine (**21e**) without an N-substituent as follows: 3-pyrroline was converted into its N-carbobenzyloxy derivative (**17b**), whose peracid oxidation yielded a syrupy 3,4-epoxide (**18b**) in a good yield. Treatment of **18b** with sodium azide afforded *trans*-3-azido-4-hydroxypyrrolidine (**19b**), mp 68—68.5°, which formed a mesylate (**20b**), mp 81—84°. Following the method of Ponsold,^{2,16}) treatment of **20b** with sodium borohydride and cobalt-(II)-tris(α,α' -dipyridyl) bromide gave 1-carbobenzyloxy-3,4-epiminopyrrolidine (**21f**) in 70% yield. Removal of the N-protecting group from **21f** by hydrogenation on palladium-charcoal was attempted; however, the reduction product was found to be unstable, giving polymerized material with coloring on standing in solution, on concentration, or purification by distillation. The product formed

14) P. Scheiner, *Tetrahedron*, **24**, 2757 (1968).

15) Satisfactory analytical samples could not be obtained.

16) K. Ponsold, *J. Pract. Chem.*, **36**, 148 (1967).

an oxalate, mp 155° (decomp.) which, however, did not give a satisfactory analysis or spectral data. The 1-carbobenzyloxy derivative (**21f**) formed a benzoate (**21g**), mp 86—89°, an acetate (**21h**), mp 62—64°, and a syrupy methoxycarbonyl derivative (**21i**). Removal of the 1-protecting group in these derivatives was also attempted; however, the benzoate (**21g**) resisted

Chart 7

TABLE I. NMR Data of 3,4-Epiminopyrrolidines

No.	R ₁	R ₂	H _A (sharp doublet ppm)	H _B (broad doublet ppm)	H _C (broad singlet ppm)	J _{AB} (Hz)
1	CH ₂ C ₆ H ₅	<i>p</i> -CH ₃ O-C ₆ H ₄	3.61	3.14	2.47	10 ^{a)}
2	H	<i>p</i> -CH ₃ O-C ₆ H ₄	3.56	3.06	2.53	9.5 ^{b)}
			3.18	2.62	2.18	9.5 ^{c)}
12	COCH ₃	<i>p</i> -CH ₃ O-C ₆ H ₄	3.85	3.02	3.26	10.5 ^{d)}
			3.80	3.00	3.14	10.0 ^{b)}
			3.50	2.40	2.57	10.5 ^{c)}
16a	<i>p</i> -Br-C ₆ H ₄	H	3.20	2.75	2.86	12.7 ^{d)}
16b	<i>p</i> -Br-C ₆ H ₄	COCH ₃	3.87, 4.07	3.57, 3.42	3.03	11.13 ^{d)}
21a	H	CH ₂ CH ₃	3.72	3.27	3.15	12.5 ^{e)}
21b	CONHC ₆ H ₅	CH ₂ CH ₃	3.35	2.31	3.16	10.5 ^{d)}
			3.25	2.24	3.00	10.0 ^{b)}
			3.12	1.80	2.65	10.3 ^{c)}
21f	H	COOCH ₂ C ₆ H ₅	3.72	3.93	2.63	11.5 ^{d)}
21g	COC ₆ H ₅	COOCH ₂ C ₆ H ₅	4.01	3.38	3.37	12.7 ^{d)}
21h	COCH ₃	COOCH ₂ C ₆ H ₅	4.02	3.32	3.20	11.9 ^{d)}
21i	COOC ₂ H ₅	COOCH ₂ C ₆ H ₅	4.10	3.33	3.12	11.8 ^{d)}
21j	H	CH ₃	4.15	3.80	3.87	13.1 ^{e)}
21k	COOC ₂ H ₅	COCH ₃	3.99	3.30	3.21	12.3 ^{d)}

a) cf. ref. 2; b) CCl₄ solution, 100 MHz; c) deuteriobenzene solution, 100 MHz;
 d) CDCl₃ solution, 60 MHz; e) D₂O solution as an oxalate, 60 MHz

to hydrogenation and no reaction occurred.¹⁷⁾ Treatment of **21g** with lithium in liquid ammonia was also attempted, but without result, giving a complex mixture. Although the hydrogenation of the acetate (**21h**) was smoothly carried out, the product easily polymerized and no identifiable product could be isolated from it. Hydrogenation of the methoxycarbonyl compound (**21i**) yielded a N-free pyrrolidine which was characterized as its acetate (**21j**). On the other hand, direct lithium aluminum hydride reduction of the 1-carbobenzyloxy compound (**21f**) yielded 1-methyl-3,4-epiminopyrrolidine (**21k**), which formed an oxalate, mp 155° (decomp.).¹⁵⁾ The NMR data of these 3,4-epiminopyrrolidine derivatives are presented in Table I. Some of these compounds were tested biologically with no notable pharmaceutical activity being observed.

Experimental

Melting points are not corrected. IR spectra were determined on a Perkin-Elmer Model 221 or Perkin-Elmer Infracord and NMR spectra on a Varian A-60 or HA-100 spectrometer. Removal of solvent *in vacuo* was accomplished with a rotating flash evaporator at 20–30 mmHg and usually at 35–50°. Plates for thin-layer chromatography were prepared with Silica Gel G (E. Merck AG) and visualization of spots was effected by spraying iodine or a solution of NH_4VO_3 in 50% H_2SO_4 , followed by heating. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad; sh., shoulder.

Potassium Permanganate Oxidation of 1-(*p*-Methoxyphenyl)-3-pyrroline (3)—A solution of 790 mg of KMnO_4 in 10 ml of H_2O was added dropwise to a stirred solution of 876 mg of **3** in 50 ml of acetone over a period of 3 hr with ice-cooling. Then the mixture was further stirred for 1 hr at room temperature and filtered. After the filtrate was concentrated *in vacuo*, the resulting crystals were collected and washed with EtOH, yielding 640 mg of 1-(*p*-methoxyphenyl)pyrrole (**4**) as leaflets, mp 108–111.5°. Recrystallization from EtOH gave leaflets, mp 110–111.5° (reported mp, 112–113°.⁷⁾) IR $\nu_{\text{max}}^{\text{NaJol}}$ cm^{-1} : 1523, 1461, 1260, 1247, 1029, 828, 722. NMR (60 MHz, CDCl_3) δ ppm: 3.82 (3H, s), 6.31 (2H, t, $J=2.1$ Hz), 6.99 (2H, t, $J=2.1$ Hz), 6.92 (2H, d, $J=9.0$ Hz). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{ON}$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.88; H, 6.33; N, 7.97.

cis-1-(*p*-Methoxyphenyl)-3,4-dihydroxypyrrolidine (5)—To a stirred solution of 690 mg of **3** and 0.6 ml of pyridine in 20 ml of ether was added dropwise a solution of 1.0 g of OsO_4 in 15 ml of ether with ice-cooling and the resulting mixture was stirred further at room temperature for 2 hr. The solid thus obtained was collected (2.19 g) and suspended in a solution of 10 g of Na_2SO_3 in 65 ml of 40% aq. EtOH. The mixture was refluxed for 3.5 hr with stirring and filtered. The filtrate was concentrated *in vacuo* to 40 ml and allowed to stand. The resulting crystals were collected and washed with H_2O and EtOH successively. Thus, 250 mg of **5**, mp 158–159°, were obtained. In addition, the combined filtrate and washings left as above was extracted three times with CHCl_3 and the extract was dried (Na_2SO_4). Evaporation of the solvent *in vacuo* left 410 mg of a crystalline mass which was recrystallized from EtOH to 330 mg of **5** as leaflets, mp 159–160°. Total yield was 580 mg (71%). IR $\nu_{\text{max}}^{\text{NaJol}}$ cm^{-1} : 3360, 1520. NMR (60 MHz, $\text{Me}_2\text{SO}-d_6$) δ ppm: 3.04 (2H, dd, $J=9.3$, 4.6 Hz), 3.39 (2H, dd, $J=9.3$, 5.6 Hz), 3.67 (3H, s), 4.15 (2H, m), 4.72 (2H, d, $J=4$ Hz), 6.61 (4H, A_2B_2 -pattern absorption). Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{N}$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.96; H, 7.17; N, 6.68.

cis-1-(*p*-Methoxyphenyl)-3-hydroxy-4-tosyloxy- (6) and -3,4-ditosyloxypyrrolidine (7)—To a solution of 1.48 g of **5** in 35 ml of pyridine was added in portions 1.54 g of TsCl with cooling and stirring and the mixture was allowed to stand at room temperature overnight. After being concentrated *in vacuo* to 1/3 volume, the mixture was diluted with ice-water and extracted with CHCl_3 . The extract was dried (Na_2SO_4) and evaporated *in vacuo* to dryness, leaving 3.12 g of a dark brown crystalline residue which was dissolved in 4 ml of CHCl_3 with warming. On standing at room temperature, the solution gave a mixture of **6** and unchanged **5** (1.31 g) as powder which was collected and recrystallized fractionally, yielding 927 mg of **6** as leaflets, mp 148–150°, along with 224 mg of the starting material (**5**). IR $\nu_{\text{max}}^{\text{NaJol}}$ cm^{-1} : 3520, 1520, 1368, 1174. NMR (60 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$) δ ppm: 2.45 (3H, s), 2.9–3.7 (4H, m), 3.74 (3H, s), 4.46 (1H, q, $J \approx 5$ Hz), 4.99 (1H, q, $J \approx 5$ Hz), 6.62 (4H, A_2B_2 -pattern absorption), 7.60 (4H, A_2B_2 -pattern absorption). Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{O}_5\text{NS}$: C, 59.49; H, 5.82; N, 3.82. Found: C, 59.51; H, 5.88; N, 3.97.

The CHCl_3 filtrate from the mixture of **5** and **6** was diluted with warm EtOH and allowed to stand, giving a mixture of **6** and **7**. Fractional recrystallization from EtOH afforded 300 mg of **7** as leaflets, mp 146–147°, along with a second crop of **6** (269 mg). IR $\nu_{\text{max}}^{\text{NaJol}}$ cm^{-1} : 1516, 1365, 1178. NMR (60 MHz, CDCl_3) δ ppm: 2.45 (6H, s), 3.49 (4H, d), 3.73 (3H, s), 4.98 (2H, m), 6.57 (4H, A_2B_2 -pattern absorption), 7.55

17) 1-Benzyl-3,4-epiminopyrrolidine²⁾ or its N-benzoate was also found to resist to hydrogenation over palladium-charcoal or platinum.

(8H, A_2B_2 -pattern absorption). *Anal.* Calcd. for $C_{25}H_{27}O_7NS_2$: C, 58.01; H, 5.26; N, 2.71. Found: C, 57.79; H, 5.32; N, 2.72.

trans-1-(p-Methoxyphenyl)-3-azido-4-hydroxy- (8), -3-azido-4-tosyloxy- (9), and -3-azido-4-formyloxy-pyrrolidine (10)—A mixture of 2.06 g of **6**, 3 g of NaN_3 , and 30 ml of dimethylformamide was warmed on a steam bath at 75° for 6.5 hr with stirring. After cooling, the mixture was diluted with H_2O and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to dryness, leaving 1.32 g of a brown syrup which deposited 19 mg of **8** as powder, mp 77—78.5°, on trituration with hexane-ether and standing. The product revealed one spot on thin-layer chromatogram, except for a spot corresponding to a small amount of dimethylformamide. IR ν_{max}^{Nujol} cm^{-1} : 3430, 2100, 1513. NMR (60 MHz, $CDCl_3 + D_2O$) δ ppm: 3.0—3.8 (4H, m), 3.74 (3H, s), 3.99 (1H, ddd, $J=5.7, 3.5, 3.5$ Hz), 4.31 (1H, ddd, $J=5.0, 3.5, 3.5$ Hz), 6.66 (4H, A_2B_2 -pattern absorption).

The mother liquor left by removal of **8** as above was concentrated *in vacuo* to dryness, leaving 1.24 g of a syrup which was dissolved in 15 ml of pyridine. To the solution was added 1.7 g of TsCl and the mixture was allowed to stand at room temperature for 1 day. Then, the mixture was diluted with ice-water and extracted twice with benzene. The extract was dried (Na_2SO_4) and evaporated *in vacuo*, giving 1.79 g of a red syrup which gave 746 mg of **9** as prisms, mp 98—100°, on trituration with EtOH containing a small amount of benzene. Recrystallization from EtOH gave the analytical sample as fine needles, mp 101—102°. IR ν_{max}^{Nujol} cm^{-1} : 2070, 1364, 1173. NMR (60 MHz, $CDCl_3$) δ ppm: 2.47 (3H, s), 3.1—3.9 (4H, m), 3.75 (3H, s), 4.22 (1H, ddd, $J=5.5, 3.5, 3.5$ Hz), 4.91 (1H, ddd, $J=5.5, 3.5, 3.5$ Hz), 6.66 (4H, A_2B_2 -pattern absorption), 7.61 (4H, A_2B_2 -pattern absorption). *Anal.* Calcd. for $C_{18}H_{20}O_4N_4S$: C, 55.65; H, 5.19; N, 14.43. Found: C, 55.45; H, 5.23; N, 14.90.

The mother liquors from the isolation of **9** were combined and evaporated *in vacuo*, leaving 0.90 g of a syrup whose infrared spectrum indicated the presence of untosylated compounds. Consequently, the syrup was redissolved in 6 ml of pyridine and tosylated with 1 g of TsCl. After standing overnight, the mixture was treated as described above, giving 1.07 g of a syrup which was chromatographed over 20 g of silica gel. Elution with benzene followed by evaporation of the solvent gave 180 mg of 1-(p-methoxyphenyl)pyrrole (**4**), mp 108—110°. Successive elution with benzene-ether (30:1, v/v) followed by removal of the solvent and recrystallization of the residue from benzene-EtOH yielded 236 mg of **9**. Further elution with the same solvent followed by removal of the solvent gave a crystalline mass which was recrystallized from EtOH to give 155 mg of **10**, mp 80—82°. IR ν_{max}^{Nujol} cm^{-1} : 2080, 1727, 1520. NMR (60 MHz, $CDCl_3$) δ ppm: 3.60 (3H, s), 3.15—3.95 (4H, m), 4.09 (1H, ddd, $J=3, 1.5, 1.5$ Hz), 5.15 (1H, ddd, $J=3, 1.5, 1.5$ Hz), 6.63 (4H, A_2B_2 -pattern absorption), 8.01 (1H, s). *Anal.* Calcd. for $C_{12}H_{14}O_3N_4$: C, 54.95; H, 5.38; N, 21.37. Found: C, 55.20; H, 5.55; N, 21.26.

The formate (**10**) (58 mg) was dissolved in a mixture of 50 mg of KOH, 1 ml of tetrahydrofuran, and 0.5 ml of H_2O and the mixture was stirred for 30 min at room temperature. The mixture was extracted with $CHCl_3$ and the extract was washed with H_2O . Drying of the extract followed by evaporation *in vacuo* gave 52 mg of a crystalline mass, mp 75.5—77.5°. Recrystallization from benzene gave the analytical sample of **8** as powder, mp 77—78.5°. *Anal.* Calcd. for $C_{11}H_{14}O_2N_4$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.30; H, 6.07; N, 23.60.

The sample of **8** was identified with that obtained earlier by infrared spectrometry and also gave the tosylate (**9**) quantitatively on treatment with TsCl in pyridine.

1-(p-Methoxyphenyl)-3,4-epimino- (2), -3,4-acetylepimino- (12) and -3-acetamido-pyrrolidine (13a)—To a ice-cold solution of 743 mg of **9** in 50 ml of ether was added in portions 250 mg of $LiAlH_4$ and the mixture was stirred for 3 hr with cooling. Excess of the reagent was decomposed by a careful addition of EtOH containing a small amount of H_2O and the solid was filtered. The filtrate was diluted with H_2O and extracted with benzene. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to dryness. The residual pale yellow syrup (343 mg) revealed two spots on a thin-layer chromatogram. The syrup (200 mg) was placed on 5 g of alumina with benzene and chromatographed.¹⁸⁾ Elution with 3% (v/v) ether-benzene followed by removal of the solvent gave 66 mg of **2**, mp 103—110°, as powder. IR ν_{max}^{Nujol} cm^{-1} : 1514, 1463, 1377, 1242, 1036, 816. NMR¹⁹⁾ (100 MHz, CCl_4) δ pm: 3.66 (3H, s), 6.51 (4H, A_2B_2 -pattern absorption).

On the other hand, the crude reaction product (143 mg) was acetylated with Ac_2O -pyridine in a usual manner and the product (143 mg) was chromatographed over 5 g of silica gel. Fractions eluted with benzene-hexane (1:1, v/v) were evaporated to give 50 mg of **12** which was recrystallized from EtOH to afford needles, mp 110—111°. IR ν_{max}^{Nujol} cm^{-1} : 1671, 1516. NMR¹⁹⁾ (60 MHz, CCl_4) δ ppm: 1.90 (3H, s), 3.66 (3H, s), 6.53 (4H, m). *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.82; H, 6.96; N, 11.80.

Further elution with 2% (v/v) MeOH- $CHCl_3$ and evaporation of the solvent gave a crystalline mass which was recrystallized from benzene-EtOH to yield 15 mg of **13a** as leaflets, mp 164—166.5°. IR ν_{max}^{Nujol}

18) Use of silica gel for the chromatography of the epimine (**2**) resulted in partial decomposition.

19) NMR data not listed in Table I are presented.

cm^{-1} : 3250, 3060, 1641, 1551, 1513. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.70; N, 11.80.

3,4-(*p*-Bromophenylepimino)pyrrolidine (16a) and Its Acetate (16b)—Following the procedure of Scheiner,¹⁴ a solution of 3 g of the triazoline (15) in 180 ml of tetrahydrofuran in a quartz tube was irradiated with a Hanovia high pressure mercury lamp (450 W) with cooling and stirring. After irradiation for 2 hr, the mixture was filtered and the crystals obtained were recrystallized from MeOH to yield 200 mg of a hydrobromide of 16a as prisms, mp 162–163°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2760, 1569, 1490, 1378, 1253, 822. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{Br} \cdot \text{HBr}$: C, 37.64; H, 3.78; N, 8.75; Br, 49.97. Found: C, 37.79; H, 3.92; N, 8.67; Br, 49.66.

The hydrobromide was treated with dil. aq. Na_2CO_3 , giving 16b, mp 114–115°, as prisms (from hexane). On the other hand, the filtrate left by collection of the hydrobromide was evaporated *in vacuo* and the residue was extracted with hexane several times. The combined extracts was evaporated *in vacuo*, leaving 800 mg of the crude 16a, which was recrystallized from hexane, giving 300 mg of 16a, mp 114–115° (reported mp,¹⁴ 115–116°). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1584, 1486, 1460, 1381, 1257, 1167, 824, 803. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 1.55 (1H, br. s); 7.10 (4H, A_2B_2 -pattern absorption). *Anal.* Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{Br}$: C, 50.22; H, 4.64; N, 11.72; Br, 33.41. Found: C, 50.42; H, 4.82; N, 11.76; Br, 33.25.

Treatment of 16a with Ac_2O in pyridine gave an acetate (16b), mp 163–163.5°, as needles (from benzene). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1642, 1444, 1255, 1005, 842. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 1.96 (3H, s), 7.12 (4H, A_2B_2 -pattern absorption). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{13}\text{ON}_2\text{Br}$: C, 51.26; H, 4.66; N, 9.96. Found: C, 51.79; H, 4.70; N, 10.02.

1-Acetyl-3-pyrroline (17a)—To a stirred suspension of 45 g of K_2CO_3 in a solution of 20.3 g of 3-pyrroline in 80 ml of benzene was added dropwise a mixture of 36 g of Ac_2O and 20 ml of benzene. An exothermic reaction occurred and the mixture was kept at 80° for 2 hr. The cooled solution was filtered and the solid was washed with benzene. The combined filtrate and washings was evaporated *in vacuo*, leaving a crystalline mass which was recrystallized from hexane–benzene to give 18.0 g (55%) of 17a as hygroscopic prisms, mp 56–61°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1648, 1624. NMR (60 MHz, CDCl_3) δ ppm: 2.09 (3H, s), 4.27 (4H, s), 5.87 (2H, br.). *Anal.* Calcd. for $\text{C}_6\text{H}_9\text{ON}$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.68; H, 8.03; N, 12.62.

1-Acetyl-3,4-epoxypyrrolidine (18a)—To a cooled and stirred mixture of 6.9 g of 17a, 62 g of Na_2CO_3 (solid), and 85 ml of dichloromethane was added over a period of 30 min a pertrifluoroacetic acid solution prepared from 30 ml of 90% H_2O_2 , 18 ml of trifluoroacetic anhydride in 12 ml of dichloromethane. After being further stirred for 1.5 hr with cooling, the solid was filtered. To the cooled filtrate was added 25 g of K_2CO_3 and the resulting mixture was stirred for 1.5 hr with cooling. After filtration, the solvent was evaporated *in vacuo* to dryness, leaving 3.27 g (41%) of the crude 18a. Recrystallization from benzene–hexane gave analytical sample of 18a as hygroscopic prisms, mp 61–63°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1644. NMR (60 MHz, CDCl_3) δ ppm: 2.01 (3H, s), 3.33 (1H, br. d, $J=13.5$ Hz), 3.55 (1H, br. d, $J=11.7$ Hz), 3.75 (2H, br. s), 3.77 (1H, d, $J=11.7$ Hz), 3.96 (1H, d, $J=13.5$ Hz). *Anal.* Calcd. for $\text{C}_6\text{H}_9\text{O}_2\text{N}$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.25; H, 7.13; N, 10.91.

1-Acetyl-trans-3-azido-4-hydroxypyrrolidine (19a)—A mixture of 3.27 g of the crude 18a, 5.4 g of NaN_3 , 1.6 g of NH_4Cl , 50 ml of dimethylformamide, and 8 ml of H_2O was kept at 100–110° for 6 hr with stirring. The cooled mixture was diluted with CHCl_3 and filtered. The filtrate was concentrated *in vacuo* and diluted with CHCl_3 . The resulting solid was filtered off and the filtrate was evaporated *in vacuo* to dryness, leaving 4.77 g of 19a as an orange syrup which contained a small amount of dimethylformamide. The syrup revealed one spot on thin-layer chromatogram except for a spot corresponding to dimethylformamide. Attempted distillation of this syrup at 160° (0.2 mmHg, bath temp.) resulted in a decomposition with gas evolution. IR $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 3330, 2100, 1630. NMR (60 MHz, CDCl_3) δ ppm: 2.06 (3H, s); 3.3–3.9 (4H, m), 4.03 (1H, m), 4.30 (1H, m), 4.95 (1H, br., OH).

1-Acetyl-trans-3-azido-4-tosyloxypyrrolidine (20a)—To an ice-cold solution of 4.28 g of the crude 19a in 40 ml of pyridine was added 5.0 g of TsCl and the mixture was allowed to stand for 1 day. Further, to the mixture was added 1.5 g of TsCl and, after standing for an additional day, the mixture was concentrated *in vacuo* to half a volume, diluted with ice-water and extracted with CHCl_3 . The extract was dried (Na_2SO_4) and evaporated *in vacuo* to dryness, leaving 6.63 g of a dark brown syrup which was chromatographed over 40 g of silica gel. Fractions eluted with benzene–ether (1:1, v/v) followed by evaporation of the solvent afforded 2.4 g of a crystalline residue which was recrystallized from benzene–ether to 1.91 g of 20a as prisms, mp 88–90°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2100, 1650, 1371, 1172. NMR (60 MHz, CDCl_3) δ ppm: 1.98 and 2.03 (3H, s, ca. 1:1), 2.48 (3H, s), 3.3–4.5 (5H, m), 4.81 (1H, m), 7.57 (4H, A_2B_2 -pattern absorption). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{N}_4\text{S}$: C, 48.14; H, 4.97; N, 17.28. Found: C, 47.95; H, 5.15; N, 17.00.

1-Ethyl-3,4-epiminopyrrolidine (21a) and Its Phenylurea Derivative (21b)—To a stirred solution of 616 mg of 20a in a mixture of 8 ml of tetrahydrofuran and 20 ml of ether was added in portions 200 mg of LiAlH_4 with ice-cooling, and the mixture was further stirred for 4 hr with cooling. After decomposition of excess of the reagent by addition of a minimum amount of H_2O , the mixture was filtered and the solid was washed with ether. The combined filtrate and washings was dried (Na_2SO_4) and diluted with ether to 50 ml. To 25 ml of this solution was added a solution of 150 mg of oxalic acid in 10 ml of ether, depositing 142 mg of an oxalate of 21a as powder, mp 130–160° (decomp.). NMR¹⁹ (60 MHz, D_2O) δ ppm: 1.31 (3H, t, $J=7.3$ Hz), 3.61 (2H, q, $J=7.3$ Hz).

To the remaining solution of **21a** (25 ml) was added 300 mg of phenyl isocyanate with cooling. The mixture was stood for 1 hr and extracted with cold dil. HCl. The HCl layer was made basic with dil. Na_2CO_3 and extracted with ether. The ether extract was dried and evaporated *in vacuo* to leave 130 mg of a crystalline mass which was recrystallized from benzene-hexane to 102 mg of **21b** as fine needles, mp 148–150°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3260, 1658. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 1.00 (3H, t, $J=7$ Hz), 2.51 (2H, q, $J=7$ Hz), 6.8–7.6 (6H, m). Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{ON}_3$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.45; H, 7.53; N, 18.14.

Analogously, treatment of **20a** with LiAlD_4 and successive treatment of the deuterio derivative (**21c**) with phenyl isocyanate afforded a deuterated phenyl urea derivative (**21d**) as needles, mp 148.5–150°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3260, 2170, 2040, 1658. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 1.00 (3H, br. s), 6.8–7.6 (6H, m).

1-Carbobenzyloxy-3-pyrroline (17b)—To a cooled suspension of 10 g of NaHCO_3 (solid) in a solution of 10 g of 3-pyrroline in 100 ml of benzene was added dropwise 27.2 g of carbobenzyloxy chloride over a period of 30 min with stirring and the mixture was stirred for 1 hr with cooling and further for 30 min at room temperature. Then the mixture was poured into ice-water and extracted with CHCl_3 . The extract was dried (Na_2SO_4) and evaporated, leaving 25 g of a colorless syrup which was distilled to give 16.3 g (56%) of **17b**, bp 133–137° (0.6 mmHg). IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1710, 1420, 1360, 1327, 1110.

1-Carbobenzyloxy-3,4-epoxypyrrolidine (18b)—A pertrifluoroacetic acid solution (prepared by the addition of 26 ml of trifluoroacetic anhydride to a cooled mixture of 4.9 ml of 90% H_2O_2 and 20 ml of dichloroethane) was added dropwise into a suspension of 80 g of Na_2HPO_4 in a solution of 14.3 g of **17b** in 160 ml of dichloroethane at 0° over a period of 1 hr and the mixture was stirred at room temperature for 2 hr. Then, the mixture was poured into ice-water and the resulting mixture stood for 1 hr. The organic layer was collected and the aq. layer was extracted with CHCl_3 . The combined organic layer and extract was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* left 14.6 g (95%) of the crude **18b** as a colorless syrup. Analytical sample was prepared by distillation, bp 156–157° (0.3 mmHg, bath temp.). IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1708, 1430, 1327, 1105, 846. Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_3\text{N}$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.00; H, 6.05; N, 6.35.

1-Carbobenzyloxy-trans-3-azido-4-hydroxypyrrolidine (19b)—A mixture of 13.6 g of **18b**, 5.0 g of NH_4Cl , 25 g of NaN_3 , 150 ml of dimethylformamide, and 18 ml of H_2O was heated on a steam bath for 3 hr. The mixture was diluted with H_2O and extracted three times with CHCl_3 . The extract was dried (Na_2SO_4) and evaporated *in vacuo* to dryness, leaving 13.1 g of the crude **19b** as a red syrup which crystallized on standing. Recrystallization from benzene gave **19b** as colorless prisms, mp 68–68.5°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3400, 2100, 1670, 1455, 1115. Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3\text{N}_4$: C, 54.95; H, 5.38; N, 21.37. Found: C, 55.35; H, 5.36; N, 21.32.

1-Carbobenzyloxy-trans-3-azido-4-mesyloxypyrrolidine (20b)—To an ice-cold solution of 13.8 g of **19b** in 30 ml of pyridine was added slowly 6.85 g of MsCl and the mixture left standing at room temperature overnight. Then the mixture was poured into ice-water and extracted twice with benzene. The extract was successively washed with cold dil. HCl and H_2O and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* left 12.5 g of a red syrup which crystallized on standing. Recrystallization from MeOH gave **20b** as fine needles, mp 81–84°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2150, 1704, 1423, 1366, 1348, 1171, 1100. Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_5\text{N}_4\text{S}$: C, 45.88; H, 4.73; N, 16.45; S, 9.40. Found: C, 45.96; H, 5.06; N, 16.50; S, 8.89.

1-Carbobenzyloxy-3,4-epiminopyrrolidine (21f) and Its N-Derivatives (21g–i)—A solution of 6 g of **20b** in 60 ml of EtOH was added to a solution of 0.9 g of CoBr_2 and 2.16 g of α, α' -dipyridyl in 300 ml of EtOH. To the mixture thereby obtained was added 3.0 g of NaBH_4 in small portions with cooling and stirring and the mixture was allowed to stand at room temperature for 2 hr. After concentration at room temperature under a reduced pressure to half volume, the mixture was diluted with 400 ml of H_2O and extracted twice with CHCl_3 . After drying, the extract was evaporated *in vacuo*, leaving a brown syrup which was distilled or chromatographed over silica gel to yield 2.7 g (70%) of **21f** as a colorless syrup, bp 140–150° (0.2 mmHg, bath temp.). IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 3300, 1705, 1429, 1108. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 0.74 (1H, br. s) 5.07 (2H, s) 7.30 (5H, s). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{N}_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.10; H, 6.69; N, 12.04.

Treatment of **21f** with benzoic anhydride in pyridine gave a benzoate (**21g**) as needles, mp 86–89° (from MeOH-hexane). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1695, 1660. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 5.11 (2H, s), 7.32 (5H, s), 7.2–8.0 (5H, m). Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.65; H, 5.69; N, 8.75.

Treatment of **21f** with Ac_2O in pyridine gave an acetate (**21h**) as prisms, mp 62–64° (from ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1705 (sh.), 1690. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 2.08 (3H, s), 5.11 (2H, s), 7.34 (5H, s). Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_3\text{N}_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.32; N, 10.74.

Treatment of **21f** with ethyl chloroformate in CHCl_3 in the presence of triethylamine gave an ethylcarbamate (**21i**) as a colorless syrup. Analytical sample was obtained by purification on silica gel chromatogram. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1720 (br.), 1427, 1310, 1220, 1187, 1118. NMR¹⁹ (60 MHz, CDCl_3) δ ppm: 1.18 (3H, t, $J=7$ Hz), 4.03 (2H, q, $J=7$ Hz), 5.09 (2H, s), 7.34 (5H, s). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{N}_2$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.99; H, 6.44; N, 9.75.

1-Methyl-3,4-epiminopyrrolidine (21j)—A solution of 3.0 g of **21f** in 20 ml of tetrahydrofuran was added dropwise to a stirred suspension of 1.8 g of LiAlH_4 in 40 ml of tetrahydrofuran with cooling. The mixture was stirred for 1 hr at room temperature and then for 2 hr with reflux. After cooling, the mixture was diluted with 60 ml of ether and the careful addition of 5 ml of H_2O decomposed the excess of the reagent. After stirred for 30 min, the mixture was filtered and the filtrate was concentrated to 2/3 the original volume with Vigreux column. Addition of an ethereal solution of 1 g of oxalic acid to the mixture thus obtained yielded 1.2 g of an oxalate of **21j** as plates, mp $171\text{--}173^\circ$ (decomp.) with softening at $124\text{--}126^\circ$. The sample was recrystallized from 80% EtOH, but did not give a satisfactory analysis. NMR^{10} (60 MHz, D_2O) δ ppm: 3.08 (3H, s).

1-Acetyl-3,4-(ethoxycarbonylepimino)pyrrolidine (21k)—A solution of 941 mg of **21h** in 10 ml of MeOH was hydrogenated over 340 mg of Pd-C in a slow stream of H_2 for 5 hr. After filtration, the mixture was almost evaporated *in vacuo* and the residue was dissolved in 5 ml of benzene. After 300 mg of Ac_2O was added, the mixture stood for 1 day and poured into ice-water. The organic layer was collected and the aq. layer was extracted with CHCl_3 . The combined organic layer and extracts was dried and evaporated *in vacuo*, leaving 523 mg of a syrup which was distilled to yield 60 mg of **21k** as a colorless syrup, bp 115° (3 mmHg, bath temp.). IR $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 1705, 1437, 1382, 1337, 1119. NMR^{10} (60 MHz, CDCl_3) δ ppm: 1.24 (3H, t, $J=7$ Hz), 2.09 (3H, s), 4.12 (2H, q, $J=7$ Hz). *Anal.* Calcd. for $\text{C}_9\text{H}_{14}\text{O}_3\text{N}_2$: C, 54.53; H, 7.12; N, 14.13. Found: C, 53.76; H, 7.26; N, 13.74.