3-Amino-5-Phenyl-1-(2-pyridyl)pyrrolidines. Synthesis and Stereochemistry.

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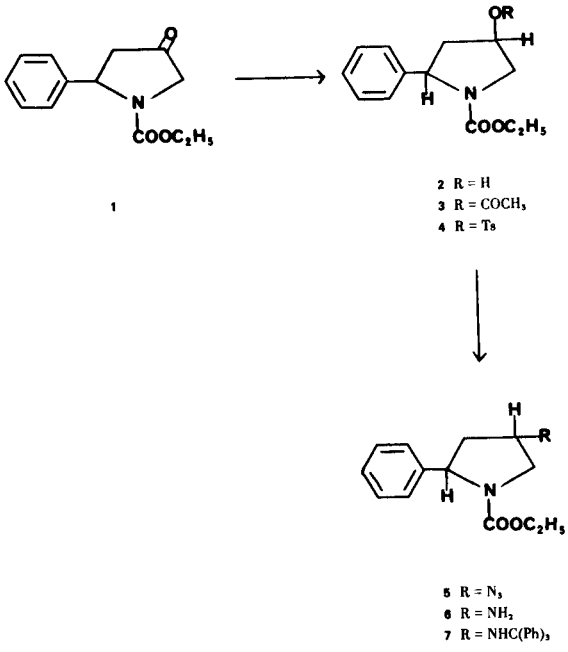
Stereoselective syntheses of *trans*- and *cis*-3-amino-5-phenyl-1-(2-pyridyl)pyrrolidine (**21** and **24**) are reported. Evidence for the relative stereochemistries of **21** and **24** was obtained by preparation of the bicyclic lactams *exo*- and *endo*- 7-phenyl-1,4-diazabicyclo[3.2.1.]octan-3-one (**16** and **19**) from precursors of **21** and **24**.

Substituted pyrrolidines have found utility in the investigation of the influence of steric and spatial relationships upon histamine antagonist activity (1-4). Thus, the title compounds (**21** and **24**) were prepared for possible use as intermediates in the synthesis of a series of conformationally restricted analogs of ethylenediamine histamine antagonists. In addition, since previous work in our laboratory (2) indicated that diastereomeric 1,5-diaryl-3-aminopyrrolidines exhibit specific characteristic differences in their nmr spectra which may be diagnostically useful, we wished to explore this possibility by synthesis and examination of the spectra of **21** and **24**.

The experimental approach involved preparation of the diastereomeric 3-triphenylmethylamino-5-phenylpyrrolidines (**8** and **13**), determination of their relative stereochemistries, and conversion of these intermediates to the title compounds. The departure point for the synthesis of **8** and **13** was 5-phenyl-1-carboethoxy-3-pyrrolidone (**1**) which was prepared as described by Wu and co-workers (5). Treatment of **1** with sodium borohydride produced the *cis*-alcohol **2** in an apparently stereospecific manner. Acetylation of **2** yielded an acetate (**3**) in which the methyl resonance appeared as a singlet at δ 1.78 in the nmr spectrum. In other experiments not reported here, diborane reduction of **1** followed by acetylation of the product afforded material which exhibited methyl singlets at δ 1.78 and δ 2.03 in the ratio of 82:18. Although diborane reduction of **1** proceeded with considerably less stereoselectivity than sodium borohydride reduction, both reactions appeared to have taken place preferentially from the same side of the ring. Examination of a Dreiding model of 1 indicates that if the *N*-carboethoxy group is held nearly in the plane of the pyrrolidine ring by resonance overlap between the ring nitrogen and the carbonyl group, the side of the ring which is *trans* to the 5-phenyl substituent is less sterically hindered than the face of the ring on which the phenyl group resides. This reasoning led to the assumption that hydride attack had taken place preferentially from the side of the ring *trans* to the phenyl group and that the alcohol **2** was the *cis*-diastereomer. In addition, the appearance of the acetoxy methyl resonance of **3** at δ 1.78 indicates that the aromatic π cloud of the *cis*-5-phenyl substituent exerts a shielding effect on the acetoxy methyl protons. Examination of a Dreiding model of **3** demonstrates the likelihood of such a shielding effect.

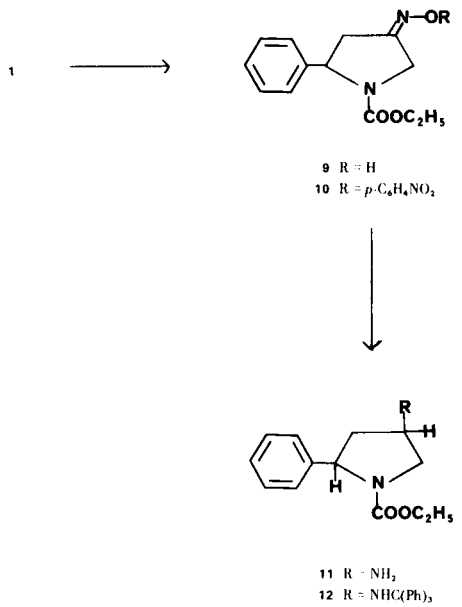
The alcohol **2** was transformed to the tosylate **4** which upon treatment with sodium azide underwent SN_2 displacement to yield the *trans*-azide 5. Reduction of **5** with sodium borohydride in refluxing 2-propanol provided the *trans*-amine **6** which was allowed to react with triphenylmethyl chloride to afford the *N*-trityl compound **7**. Hydrolysis of the sterically hindered *N*-carboethoxy

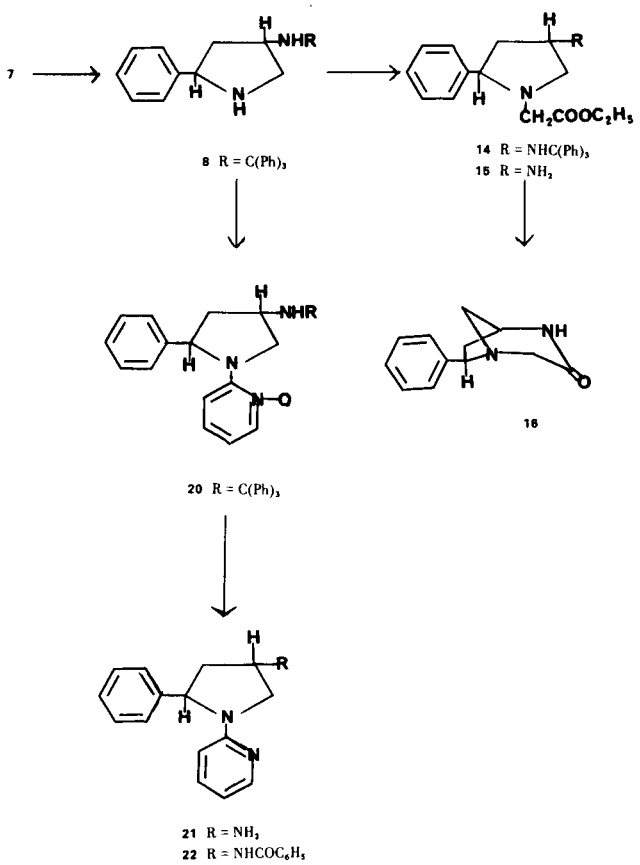


1

2 R = H
3 R = COCH₃
4 R = Ts

5 R = N₃
6 R = NH₂
7 R = NHC(Ph)₃



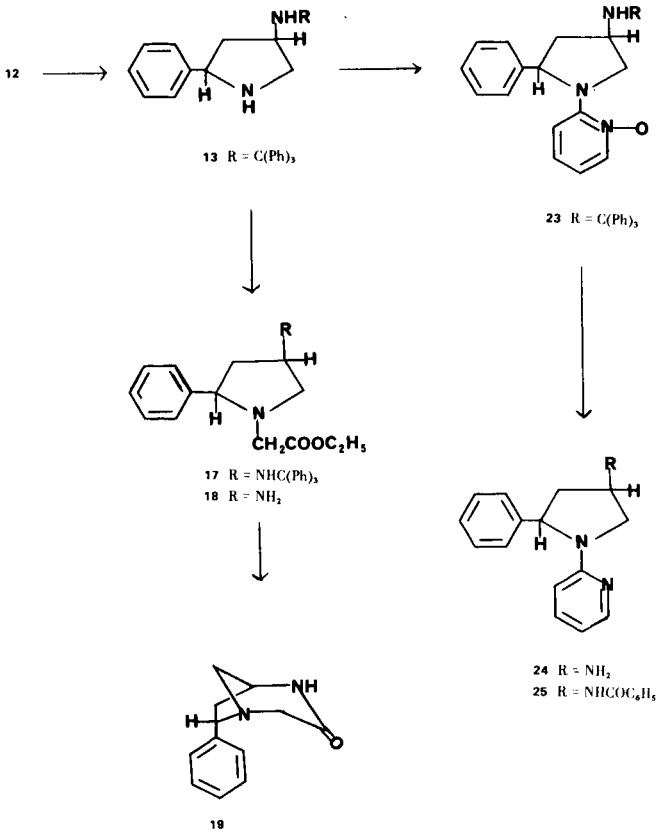


group was accomplished in 75% yield by refluxing **7** in concentrated potassium hydroxide-propanol for several days. Thus, the *trans*-isomer **8** was isolated as a crystalline solid.

The observation that both the borane and sodium borohydride reductions of **1** occurred preferentially from the same side of the ketone indicated that borane reduction of the oxime ester **10** might lead to selective formation of the *cis*-amine **11**. Thus, **1** was transformed in two steps to the oxime-*p*-nitrobenzoate **10** which upon treatment with borane (6,7) yielded predominantly the expected **11**. Acetylation of the product obtained by reduction of **10** gave a substance which exhibited two methyl singlets in the nmr spectrum at δ 2.40 and 2.33 in a ratio of 83:17. The conclusion that these two methyl resonances indicated the presence of two diastereomers was strengthened by the observation that the product of acetylation of **6** exhibited only a single methyl absorption band at δ 2.33. The similar chemical shifts observed for the acetamido methyl signals indicates that the methyl protons of the *cis*-acetamide do not experience the shielding effect of the 5-phenyl group which was observed with the acetate **3**. In other experiments it was observed that reduction of the oxime acetate of **1** with borane produced essentially identical results as reduction of the *para*-nitrobenzoate.

Repeated attempts to isolate the pure *cis*-amine **11** by chromatography or fractional crystallization of solid derivatives were unsuccessful. Therefore, the borane reduction product was treated directly with triphenylmethyl chloride in a manner similar to that employed in the preparation of **7**. However, attempts to purify the *N*-trityl derivative **12** by crystallization or column chromatography were also not successful and this material was subjected to aqueous potassium hydroxide-propanol hydrolysis. Work-up of this reaction mixture afforded the key intermediate **13**. Compound **13** was readily differentiated from the *trans*-diastereomer **8** by characteristic differences in the nmr spectra. In particular, the C-5 benzylic proton of **8** appeared as a three-peak multiplet centered at δ 4.13 while the corresponding C-5 proton of **13** appeared as a four-peak multiplet at 3.83.

In order to confirm the relative stereochemical designations of **8** and **13**, it was decided to convert these diastereomeric intermediates to the *N*-carboethoxymethyl esters **15** and **18**. This was accomplished by *N*-alkylation of **8** and **13** with ethyl bromoacetate to give **14** and **17** which were subsequently detritylated with 50% acetic acid. It was reasoned that the carboethoxymethyl groups of both **15** and **18** would reside preferentially in a configuration *trans* to the adjacent 5-phenyl substituent and therefore, compound **15** in which the ester and amino groups should be in a *cis* orientation might readily undergo cyclization to form the bicyclic lactam **16** (8). On the other hand, isomer **18**, in which these two functional groups would be expected to exist preferentially in a *trans*-orientation with respect to each other, should cyclize with considerably greater difficulty.



When **15** was heated at 175° for 66 hours in a stainless steel bomb, the expected lactam **16** was isolated in 60% yield as a crystalline solid. The nmr spectrum of **16** displayed a one proton multiplet at δ 4.33 which was assigned to the *endo*-C-7 proton and a one proton multiplet at δ 1.86 assigned to the *exo*-C-6 proton which is apparently shielded by the C-7 *exo*-phenyl group. Irradiation of the δ 1.86 multiplet resulted in the collapse of the δ 4.33 multiplet to a doublet (J = 7 Hz).

Treatment of **18** under the conditions described for the cyclization of **15** resulted in the isolation of bicyclic lactam **19** in 13% yield. The nmr spectrum of **19** exhibited a one proton multiplet at δ 4.58 which was assigned to the *exo*-C-7 proton and a two proton multiplet at δ 2.31. This latter band was assigned to the *endo*-C-6 proton and the *endo*-C-2 proton. Examination of a Dreiding stereomodel of **19** indicates that the *endo*-7-phenyl substituent is capable of exerting a shielding effect upon both of these protons.

These results confirm our assumptions regarding the relative ease of cyclization of **15** and **18** and provide further evidence for the stereochemical designations of **8** and **13**.

The diamines **8** and **13** underwent condensation with 2-chloropyridine *N*-oxide to afford **20** and **23** respectively. These *N*-oxide intermediates were treated with phosphorus trichloride and aqueous acid to form the desired amines **21** and **24**.

As indicated above, certain striking differences in the nmr spectra of the diastereomeric amines **21** and **24** are of interest. The C-4 methylene protons of the *trans*-isomer **21** appear as a multiplet ($W_{1/2}$ = 14 Hz) at δ 2.11 while the C-4 protons of **24** have distinctly different chemical shifts and appear as broad multiplets at δ 2.68 ($W_{1/2}$ = 29 Hz) and δ 1.85 ($W_{1/2}$ = 29 Hz). Apparently the conformation of pyrrolidine **24** places the C-4 protons in distinctly different chemical environments. It is reasonable to assume that the higher field C-4 proton in **24** is the one which is *cis* to the 5-phenyl substituent since the upfield absorption is probably due to the shielding effect of the adjacent aromatic ring. The C-4 proton absorption patterns seen in the spectra of **21** and **24** are similar to those observed in the spectra of *trans*- and *cis*-1,5-diphenyl-3-aminopyrrolidine (2) and they provide a useful means of identifying these diastereomeric 1,5-diaryl-3-aminopyrrolidines.

EXPERIMENTAL (9)

The ir spectra were recorded on Perkin-Elmer 237B and Perkin-Elmer infracord spectrophotometers. The nmr spectra were obtained using Varian A-60 D and Varian T-60 spectrometers; all compounds were dissolved in deuteriochloroform and tetramethylsilane was the internal reference standard. All ir and nmr spectra were consistent with the assigned structures. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

cis-3-Hydroxy-5-phenyl-1-carboethoxypyrrolidine (**2**).

Sodium borohydride (16.04 g., 0.42 mole) was added in small portions to a solution of 19.70 g. (0.08 mole) of 5-phenyl-1-carboethoxy-3-pyrrolidone (**1**) in 300 ml. of 95% ethanol. The mixture was stirred at room temperature for 24 hours, cooled in an ice bath and adjusted to *p*H 4 by dropwise addition of 25% acetic acid. The *p*H was then converted to 8 by dropwise addition of 10% sodium hydroxide and the ethanol was removed *in vacuo*. The aqueous residue was extracted with three 200 ml. portions of chloroform, washed (water), dried (magnesium sulfate), and evaporated to afford **2** as a golden oil (19.56 g., 98%). Tlc on alumina sheets using 3 solvent systems [(chloroform); (chloroform-ethanol, 99:1); benzene-methanol, 95:5)] indicated the presence of a single product. Ir (liquid film) 3300 cm^{-1} (OH); nmr: δ 7.29 (s, C_6H_5); 4.93 (m, C-5H); 3.26-4.58 (m, OCH_2, C-2 methylene, C-3 H); 2.55 (m, C-4 H); 1.91 (m, C-4 H); 2.66 (s, broad, OH); 1.06 (t, broadened, CH_3). The alcohol (**2**) was used without further purification.

cis-3-Acetoxy-5-phenyl-1-carboethoxypyrrolidine (**3**).

To a solution of the alcohol (**2**) (0.50 g., 0.002 mole) in 5 ml. of pyridine was added 5 ml. of acetic anhydride in one portion. The solution was allowed to stand at room temperature in a stoppered flask for 24 hours. It was then poured with stirring into cold, dilute sodium carbonate and extracted with three 50 ml. portions of dichloromethane. The combined extracts were washed

with 5% hydrochloric acid and water and dried (magnesium sulfate). Evaporation afforded 0.51 g. (87%) of **3** as a golden oil; nmr: δ 7.28 (s, C_6H_5); 5.16 (m, C-5H, C-3H); 3.91 (m, OCH_2, C-2 methylene); approx. 2.36 (broad m, C-4 methylene); 1.78 (s, $OCOCH_3$); 1.11 (t, broadened, CH_3). An analytically pure sample of **3** was obtained by preparative tlc on alumina (chloroform) and extraction with dichloromethane.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.08; H, 6.79; N, 5.18.

O-p-Toluenesulfonyl-*cis*-3-hydroxy-5-phenyl-1-carboethoxypyrrolidine (**4**).

The alcohol **2** (5.01 g., 0.02 mole) was dissolved in 43 ml. of pyridine and cooled in an ice-salt bath. *p*-Toluenesulfonyl chloride (8.12 g., 0.043 mole) was added in one portion and the mixture was stirred at 0° until solution was complete. The reaction mixture was refrigerated 66 hours in a stoppered flask, poured onto ice with vigorous stirring and filtered. The solid product was washed with water and petroleum ether (b.p. 30-60°), dissolved in chloroform and dried (magnesium sulfate). Evaporation afforded **4** as a pink oil which was crystallized from chloroform-cyclohexane to yield 6.76 g. (82%) of the tosylate as a white solid, m.p. 124-126°.

Anal. Calcd. for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.80; H, 6.02; N, 3.83.

trans-3-Azido-5-phenyl-1-carboethoxypyrrolidine (**5**).

To a solution of **4** (12.19 g., 0.03 mole) in dimethylformamide (125 ml.) was added a solution of sodium azide (2.60 g., 0.04 mole) in water (6 ml.). The solution was heated under a nitrogen atmosphere for 5 hours at 75°, cooled to room temperature and poured onto 1250 ml. of saturated sodium chloride and 125 g. of ice. The mixture was extracted with two 274 ml. portions of ether, solid sodium chloride was added to the aqueous mixture and the extraction was repeated. The combined ether extracts were washed twice with 275 ml. portions of saturated sodium chloride, dried (magnesium sulfate) and evaporated *in vacuo* to yield 8.02 g. (98%) of **5** as a nearly colorless oil which was used without further purification; ir (liquid film) 2100 cm^{-1} (N_3).

trans-3-Amino-5-phenyl-1-carboethoxypyrrolidine (**6**).

To the azide (**5**) (8.02 g., 0.031 mole) dissolved in 65 ml. of 2-propanol was added sodium borohydride (4.69 g., 0.124 mole). The resulting mixture was heated under reflux for 48 hours, cooled in an ice bath and treated with dilute acetic acid. Evaporation of the 2-propanol *in vacuo* afforded a clear colorless solution which was cooled in an ice bath and made basic (*p*H 11) by addition of 5% sodium hydroxide. Solid sodium chloride was added and the mixture was extracted with three 500 ml. portions of ether. The combined ether extracts were washed (saturated sodium chloride), dried (magnesium sulfate) and evaporated to afford 7.58 g. of a nearly colorless oil. The oil was dissolved in a minimal volume of 5% hydrochloric acid, washed with two portions of ether, cooled in an ice bath and made basic (*p*H 11) with 10% sodium hydroxide. After the basic mixture was saturated with solid sodium chloride, it was extracted with three 150 ml. portions of ether which were combined, washed (saturated sodium chloride) and dried (magnesium sulfate). Evaporation *in vacuo* afforded 6.00 g. (83%) of **6** as a colorless oil. Nmr: δ 7.26 (narrow m, C_6H_5); 5.05 (m, C-5H); 4.41-3.06 (m, OCH_2, C-2 methylene, C-3H); 2.06 (m, $W_{1/2}$ = 14 Hz, C-4 methylene); 1.55 (NH_2); 1.06 (m, CH_3).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.27; H, 7.52; N, 11.81.

Acetylation of **6** with acetyl chloride in pyridine-benzene afforded the acetamide as a yellow oil. A single methyl resonance appeared in the nmr spectrum at δ 2.33.

trans-3-Triphenylmethylamino-5-phenyl-1-carboethoxypyrrolidine (**7**).

The amide (**6**) (16.84 g. 0.072 mole) and triethylamine (14.55 g., 0.14 mole) were dissolved in 216 ml. of chloroform at room temperature. Triphenylmethyl chloride (20.00 g., 0.072 mole) was added in several portions and the solution was stirred for 48 hours, washed with water, dried (magnesium sulfate) and evaporated *in vacuo* to afford 38.00 g. of viscous residue. Trituration of the residue with ether gave 13.50 g. of white solid, m.p. 145-148°. Repeating the trituration afforded two more crops of white solid product (6.00 g., m.p. 144-146° and 2.05 g., m.p. 140-142°) for a total yield of 21.55 g. (63%). An analytically pure sample was prepared by recrystallization from ether, m.p. 149-151°.

Anal. Calcd. for $C_{32}H_{32}N_2O_2$: C, 80.64; H, 6.77; N, 5.88. Found: C, 80.52; H, 6.56; H, 5.96.

trans-3-Triphenylmethylamino-5-phenylpyrrolidine (**8**).

A mixture of **7** (9.50 g., 0.02 mole), 10 *N* potassium hydroxide (9.5 ml.), solid potassium hydroxide (4.75 g.) and 1-propanol (19 ml.) was stirred under reflux for 6 days, cooled to room temperature and extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and dried (magnesium sulfate). Evaporation *in vacuo* afforded 8.05 g. of a viscous residue which upon trituration with petroleum ether (b.p. 60-70°) containing a small percentage of ether yielded 6.10 g. (75%) of **8** as a white solid, m.p. 126-128°. Recrystallization from pentane gave analytically pure **8**, m.p. 128-129°; nmr: δ 7.33 (m, 4 C_6H_5); 4.13 (m, C-5H); 3.50-2.16 (m, C-2 methylene, C-3H); 1.85 (s, 2 NH); 1.56 (m, $W_{1/2}$ = 16 Hz, C-4 methylene).

Anal. Calcd. for $C_{29}H_{28}N_2$: C, 86.09; H, 6.97; N, 6.92. Found: C, 85.81; H, 7.25; N, 6.76.

trans-3-Triphenylmethylamino-5-phenyl-1-carboethoxymethylpyrrolidine (**14**).

Sodium carbonate (1.02 g., 0.01 mole) was added to a solution of ethyl bromoacetate (3.30 g., 0.02 mole) in 70 ml. of dry benzene and the mixture was warmed to near the reflux temperature. A solution of 6.31 g. (0.015 mole) of **8** in 33 ml. of dry benzene was added dropwise and the resulting mixture was stirred under reflux for 48 hours, cooled to room temperature and diluted with 10% sodium bicarbonate. The benzene layer was separated, washed with water and saturated sodium chloride, and dried (magnesium sulfate). Evaporation afforded a viscous residue which upon trituration with petroleum ether (b.p. 60-70°) afforded 5.70 g. (75%) of **14**, m.p. 100-103°. Analytically pure **14** (m.p. 104°) was obtained by recrystallization from petroleum ether (b.p. 60-70°).

Anal. Calcd. for $C_{33}H_{34}N_2O_2$: C, 80.78; H, 6.98; N, 5.71. Found: C, 81.07; H, 6.90; N, 5.76.

trans-3-Amino-5-phenyl-1-carboethoxymethylpyrrolidine (**15**).

A solution of **14** (5.70 g., 0.0119 mole) in 30 ml. of 50% acetic acid was heated on a steam bath for 30 minutes, cooled to room temperature and filtered to remove triphenylcarbinol. The filtrate was diluted with ethanol and thoroughly evaporated to a solid mass which upon trituration with ether formed 2.77 g. of a white precipitate (m.p. 115-117°) which was collected by filtration. This solid was dissolved in 35 ml. of chloroform and stirred for 30 minutes with 5 ml. of 10% sodium carbonate. The layers

were separated and the aqueous portion was extracted with chloroform. The chloroform extracts were combined, dried (sodium sulfate), and evaporated *in vacuo*. Addition of a small amount of ether to the residue resulted in precipitation of 0.03 g. of white solid which was discarded. Evaporation of ether afforded 1.80 g. (61%) of **15** as a red oil which was used without further purification; ir (liquid film) 1735 cm^{-1}; nmr: δ 7.30 (C_6H_5); 4.33-3.50 (m, OCH_2, C-2 methylene, C-5H); 3.21 (d, NCH_2CO); 2.63-1.78 (m, C-3H, C-4 methylene); 1.80 (s, NH_2); 1.20 (t, CH_3).

exo-7-Phenyl-1,4-diazabicyclo[3.2.1]octan-3-one (**16**).

A solution of **15** (0.52 g., 0.002 mole) in 15 ml. of 1,2-dimethoxyethane was heated at 175° for 66 hours in a 45 ml. stainless steel bomb. The resulting clear orange solution was evaporated to dryness *in vacuo* and treated with ethyl acetate. Filtration provided 0.186 g. of **16** (m.p. 183-184°). Evaporation of the ethyl acetate followed by treatment of the residue with ether afforded a second crop (0.057 g.) of **16**, m.p. 179-181°, total yield, 0.243 g. (60%). Recrystallization from ethyl acetate gave analytically pure **16**, m.p. 184°; ir (potassium bromide): 1650 cm^{-1} (lactam); nmr: δ 7.76 (NH); 7.33 (s, C_6H_5); 4.33 (m, C-7H); 4.16-2.51 (m, exo C-6H, C-5H, C-2 methylene, C-8 methylene); 1.86 (m, exo C-6H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.97; N, 13.85. Found: C, 71.21; H, 6.87; N, 13.77.

trans-3-Triphenylmethylamino-5-phenyl-1-(1-oxido-2-pyridyl)pyrrolidine (**20**).

A mixture of sodium carbonate (0.70 g., 0.006 mole) and 2-chloropyridine *N*-oxide hydrochloride (0.83 g., 0.005 mole) in 95% ethanol (35 ml.) was stirred at room temperature for 15 minutes followed by addition of **8** (2.02 g., 0.005 mole). After stirring at reflux temperature for 48 hours, the mixture was cooled to room temperature, filtered, and the solids were washed with ethanol and chloroform. The combined filtrates were evaporated *in vacuo*, taken up in chloroform and filtered. Evaporation of the filtrate and treatment of the residue with ethyl acetate afforded **20** (1.15 g., 46%) after standing in the cold. Recrystallization from ethyl acetate-methanol gave pure **20**, m.p. 220°.

Anal. Calcd. for $C_{34}H_{31}N_3O$: C, 82.06; H, 6.28; N, 8.44. Found: C, 81.64; H, 6.41; N, 8.36.

trans-3-Amino-5-phenyl-1-(2-pyridyl)pyrrolidine (**21**).

To a cold solution of **20** (3.70 g., 0.0074 mole) in 37 ml. of chloroform was added 7.5 ml. of phosphorus trichloride. The solution was heated on a steam bath for 90 minutes, cooled to room temperature, diluted with water (56 ml.), and stirred for 15 minutes. The chloroform layer was separated, extracted with water and the combined aqueous portions were cooled in an ice bath and made basic (*p*H 11) with 10 *N* potassium hydroxide. The basic mixture was extracted with chloroform, dried (magnesium sulfate) and evaporated to afford **21** (1.45 g., 81%) as a viscous oil which solidified upon standing in the cold, m.p. 81-83°; nmr: δ 5.93-8.18 (m, C_6H_5, C_5H_4N); 4.96 (m, C-5 H); 3.28-4.20 (m, C-2 methylene, C-3 H); 2.11 (m, $W_{1/2}$ = 14 Hz, C-4 methylene); 1.50 (s, NH_2). A sample of **21** was converted to the benzamide **22** for elemental analysis.

trans-3-Benzamido-5-phenyl-1-(2-pyridyl)pyrrolidine (**22**).

To the amine **21** (0.24 g., 0.001 mole) in chloroform (10 ml.) was added benzoyl chloride (0.28 g., 0.002 mole) and 30 ml. of 5% sodium hydroxide. After the mixture was stirred at room temperature for 30 minutes and allowed to stand without stirring for 4 hours, the layers were separated and the aqueous layer was extracted with chloroform. The combined chloroform solution was dried (magnesium sulfate) and evaporated to afford a residue which was triturated with ether and filtered to give **22** (0.32 g., 90%) as a white solid, m.p. 189-190°. Recrystallization from cyclohexane-ethyl acetate afforded analytically pure **22**, m.p. 192-193°.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 76.92; H, 6.13; N, 12.07.

5-Phenyl-1-carboethoxy-3-pyrrolidone Oxime (**9**).

The ketone **1** (7.00 g., 0.03 mole) in 70 ml. of ethanol was added to a solution of hydroxylamine hydrochloride (17.5 g., 0.25 mole) in 4% sodium hydroxide (175 ml.). The reaction mixture was heated at reflux for 15 minutes on a steam bath, cooled in an ice bath, and extracted with chloroform. The chloroform extracts were combined, washed (water), dried (magnesium sulfate), and evaporated *in vacuo* to afford 7.5 g. (100%) of **9** as a yellow oil which was used without further purification.

O-(*p*-Nitrobenzoyl)-5-phenyl-1-carboethoxy-3-pyrrolidone Oxime (**10**).

To a cold solution of **9** (6.73 g., 0.027 mole) in 70 ml. of ether was added *p*-nitrobenzoyl chloride (5.03 g., 0.027 mole) in 40 ml. of ether. The mixture was stirred for 5 minutes, evaporated *in vacuo* and the residue was dissolved in dichloromethane (200 ml.). The dichloromethane solution was washed with three 200 ml. portions of 5% sodium bicarbonate and water, and was dried (magnesium sulfate). After evaporation *in vacuo*, the yellow residue was dissolved in hot ethanol, filtered and cooled. The product was collected as a white solid (5.86 g., 54%), m.p. 157-159°. In some experiments, a fraction melting at 146° was was collected which apparently was the other isomer of the oxime ester. Both isomers gave satisfactory nmr spectra and elemental analyses.

Found: C, 60.60; H, 4.58; N, 10.63.

Borane Reduction of **10**.

To a cold solution of **10** (9.25 g., 0.023 mole) in 100 ml. of anhydrous THF was added dropwise 233 ml. of a 1 *M* solution of borane in THF. The solution was stirred 20 hours at room temperature, cooled in an ice bath and made acidic by dropwise addition of 233 ml. of 5% hydrochloric acid. THF was evaporated *in vacuo*, the aqueous residue was washed with two 300 ml. portions of ether, filtered, cooled, and made basic (*p*H 11) with 20% sodium hydroxide. Excess solid sodium chloride was added and the mixture was extracted with three 250 ml. portions of ether which were combined, washed with saturated sodium chloride, dried (magnesium sulfate) and evaporated to yield 4.33 g. (98%) of a colorless oil which was used directly in the next reaction. The nmr spectrum of this material gave the expected integration and contained a two proton band at δ 1.40 which disappeared upon treatment with deuterium oxide.

Treatment of the crude reduction product with acetyl chloride in pyridine-benzene gave the *cis*- and *trans*-acetamides as a golden oil which exhibited CH_3 bands in the nmr spectrum at δ 2.40 and δ 2.33 in a ratio of 83:17.

Treatment of the crude reduction product with benzoyl chloride in pyridine-benzene afforded a benzamide which was recrystallized from cyclohexane-ethyl acetate, m.p. 167-168°.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.11; H, 6.64; N, 8.29.

cis-3-Triphenylmethylamino-5-phenylpyrrolidine (**13**).

To a solution of the above described borane reduction product (4.50 g., 0.019 mole) and triethylamine (3.89 g., 0.38 mole) in 60 ml. of chloroform was added triphenylmethyl chloride (5.38 g. 0.019 mole) in several portions. The solution was stirred at room temperature for 24 hours followed by 24 hours under gentle reflux. After cooling to room temperature, the solution was washed with several portions of water, dried (magnesium sulfate), and evaporated to afford 8.75 g. of a yellow viscous residue. The residue was dissolved in 1-propanol (18 ml.) to which was added 10 *N* potassium hydroxide (9 ml.) and solid potassium hydroxide (4.4 g.). The mixture was stirred under reflux for 7 days, cooled to room temperature, diluted with water, and extracted with ether. The ether extracts were washed with saturated sodium chloride, dried (magnesium sulfate), and evaporated *in vacuo* to afford a viscous residue which upon treatment with boiling ether yielded **13** (2.30 g., 30% for two steps) as a crystalline solid m.p. 132-134; nmr: δ 7.30 (m, 4 C_6H_5); 3.83 (m, C-5 H); 3.28 (C-3 H); 2.83-0.90 (m, C-2 methylene, C-4 methylene); 1.85 (s, 2 NH). Recrystallization from ether gave analytically pure **13**, m.p. 136°.

Anal. Calcd. for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.93. Found: C, 85.90; H, 6.91; N, 6.86.

cis-3-Triphenylmethylamino-5-phenyl-1-carboethoxymethylpyrrolidine (**17**).

Sodium carbonate (1.05 g., 0.01 mole) was added to a solution of ethyl bromacetate (3.50 g., 0.021 mole) in 75 ml. of dry benzene and the mixture was warmed to near the reflux temperature. A solution of **13** (6.65 g., 0.016 mole) in 35 ml. of benzene was added dropwise and the resulting mixture was stirred under reflux for 48 hours, cooled to room temperature, and diluted with 10% sodium bicarbonate. The benzene layer was separated, washed with water and saturated sodium chloride and dried (magnesium sulfate). Evaporation *in vacuo* afforded a dark viscous residue which was treated with 600 ml. of boiling petroleum ether (b.p. 60-70°) and decanted. The solution was evaporated and the residue was taken up in ethanol. After standing in the cold, **17** (3.80 g., 48%) was collected as a white solid, m.p. 104-106°. Recrystallization from ethanol afforded analytically pure **17**, m.p. 108-109°.

Anal. Calcd. for $C_{33}H_{34}N_2O_2$: C, 80.78; H, 6.99; N, 5.71. Found: C, 80.51; H, 6.72; N, 5.96.

cis-3-Amino-5-phenyl-1-carboethoxymethylpyrrolidine (**18**).

A solution of **17** (2.75 g., 0.0057 mole) in 50% acetic acid (20 ml.) was heated on a steam bath for 30 minutes, cooled to room temperature and filtered. The filtrate was diluted with ethanol and thoroughly evaporated *in vacuo* to yield a brown oil which was taken up in chloroform (35 ml.) and stirred for 15 minutes with 5 ml. of 10% sodium carbonate. The chloroform layer was separated, dried (sodium sulfate), and evaporated to yield **18** (1.40 g., 97%) which was used without further purification; ir (liquid film) 1735 cm^{-1}; the nmr spectrum gave the expected integration: δ 7.31 (m, C_6H_5); 4.05 (q, OCH_2); 1.91 (s, NH_2); 1.18 (t, CH_3); the remainder of the spectrum consisted of complex, overlapping multiplets.

endo-7-Phenyl-1,4-diazabicyclo[3.2.1]octan-3-one (**19**).

A solution of **18** (0.52 g., 0.002 mole) in 1,2-dimethoxyethane (15 ml.) was heated at 175° for 66 hours in a 45 ml. stainless steel bomb. The resulting clear, brown solution was evaporated *in vacuo* and the residue was treated with benzene containing a small portion of ether. The resulting precipitate (0.052 g., 13%) m.p. 225°, was recrystallized from benzene to give **19**, m.p. 225°; ir (potassium bromide) 1640 cm^{-1} (lactam); nmr: δ 7.40 (s, C_6H_5 over broad NH); 4.58 (m, exo C-7 H); 4.16-2.66 (m, exo C-2 H, C-5 H, exo C-6 H, C-8 methylene); 2.31 (m, endo C-2H, endo C-6 H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.44; H, 6.73; N, 13.69.

cis-3-Triphenylmethylamino-5-phenyl-1-(1-oxido-2-pyridyl)pyrrolidine (**23**).

A mixture of sodium carbonate (0.69 g., 0.006 mole) and 2-chloropyridine *N*-oxide hydrochloride (0.83 g., 0.006 mole) in 35 ml. of 95% ethanol was stirred at room temperature for 15 minutes followed by addition of 2.02 g. (0.005 mole) of **13**. After stirring under reflux for 48 hours, the mixture was cooled to room temperature, filtered and the solids were washed with ethanol and chloroform. The combined filtrates were evaporated *in vacuo* and the residue was crystallized from ethyl acetate to yield 23 (1.0 g., 40%) m.p. 243-246°. Recrystallization from ethyl acetate gave analytically pure **23**, m.p. 245°.

Anal. Calcd. for $C_{34}H_{31}N_3O$: C, 82.06; H, 6.28; N, 8.44. Found: C, 81.96; H, 6.50; N, 8.32.

cis-3-Amino-5-phenyl-1-(2-pyridyl)pyrrolidine (**24**).

To a cold solution of **23** (2.55 g., 0.005 mole) in chloroform (25 ml.) was added 5 ml. of phosphorus trichloride. The solution was heated on a steam bath for 90 minutes, cooled and diluted with water (38 ml.). After stirring for 15 minutes, the layers were separated and the chloroform was extracted with water. The aqueous portions were combined, cooled in an ice bath, made basic (*p*H 11) with 10 *N* potassium hydroxide and extracted (chloroform). The chloroform extract was dried (magnesium sulfate) and evaporated to yield 0.95 g. of an oil which was taken up in 10% hydrochloric acid (25 ml.). The acidic mixture was filtered, extracted with ether, cooled in ice and adjusted to *p*H 11 with 10 *N* potassium hydroxide. The basic mixture was saturated with solid sodium chloride and extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and dried (magnesium sulfate). Evaporation *in vacuo* afforded **24** (0.48 g., 40%) as a white solid, m.p. 87-89°; nmr: δ 8.20-5.96 (m, C_6H_5, C_5H_4N); 4.80 (m, C-5H); 4.15 (m, C-3H); 3.56 (m, C-2 methylene); 2.68 (m, C-4 H); 1.85 (m, C-4H); 1.38 (broad, NH_2). A sample of **24** was converted to the benzamide **25** for elemental analysis.

cis-3-Benzamido-5-phenyl-1-(2-pyridyl)pyrrolidine (**25**).

To the amine **24** (0.12 g., 0.0005 mole) in 5 ml. chloroform was added benzoyl chloride (0.14 g., 0.001 mole) and 15 ml. of 5% sodium hydroxide. After the mixture had been stirred at room temperature for 30 minutes and allowed to stand for 4 hours, the layers were separated and the aqueous layer was extracted with chloroform. The combined chloroform solution was dried (magnesium sulfate) and evaporated to afford a residue which was triturated with ether and filtered to afford **25** (0.15 g., 86%), m.p. 212-214°. Recrystallization from ethyl acetate gave analytically pure **25**, m.p. 221°.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 76.95; H, 6.11; N, 12.53.

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