

quentially with 2 M sodium hydroxide, 2 M hydrochloric acid, and water, then dried, and filtered prior to injection. In several instances, the α -naphthamides of amines used in this study were isolated and shown to have properties corresponding to reported literature values. Most of the amines used in this study are well-known and were from commercial sources or from prior studies. Asymmetric syntheses of some of the amines employed have been reported by Meyers and Fuentes.⁶

Acknowledgment. This work has been supported in part by the National Science Foundation. We are grateful to Hoffman-La Roche, Inc. and Merrell Dow Pharmaceuticals, Inc. for several of the amines used in this study.

Registry No. 1, 74927-72-3; (\pm)-2 (R = Me; n = 0), 79171-53-2; (R)-2 (R = Me; n = 0) *N*- α -naphthoyl derivative, 90132-84-6; (S)-2 (R = Me; n = 0) *N*- α -naphthoyl derivative, 90132-85-7; (\pm)-2 (R = Bu; n = 0), 90132-74-4; (R)-2 (R = Bu; n = 0) *N*- α -naphthoyl derivative, 90132-86-8; (S)-2 (R = Bu; n = 0) *N*- α -naphthoyl derivative, 90132-87-9; (\pm)-2 (R = Me; n = 1), 3000-79-1; (R)-2 (R = Me; n = 1) *N*- α -naphthoyl derivative, 90132-88-0; (S)-2 (R = Me; n = 1) *N*- α -naphthoyl derivative, 90132-89-1; (\pm)-2 (R = Et; n = 1), 78738-37-1; (R)-2 (R = Et; n = 1) *N*- α -naphthoyl derivative, 90132-90-4; (S)-2 (R = Et; n = 1) *N*- α -naphthoyl derivative, 90132-91-5; (\pm)-2 (R = Pr; n = 1), 3238-60-6; (R)-2 (R = Pr; n = 1) *N*- α -naphthoyl derivative, 90132-92-6; (S)-2 (R = Pr; n = 1) *N*- α -naphthoyl derivative, 90132-93-7; (\pm)-2 (R = Bu; n = 1), 68144-45-6; (R)-2 (R = Bu; n = 1) *N*- α -naphthoyl derivative, 90132-94-8; (S)-2 (R = Bu; n = 1) *N*- α -naphthoyl derivative, 90132-95-9; (\pm)-2 (R = (CH₂)₄CH₃; n = 1), 90132-75-5; (R)-2 (R = (CH₂)₄CH₃; n = 1) *N*- α -naphthoyl derivative, 90132-96-0; (S)-2 (R = (CH₂)₄CH₃; n = 1) *N*- α -naphthoyl derivative, 90132-97-1; (\pm)-2 (R = Ph; n = 1), 90192-86-2; (R)-2 (R = Ph; n = 1) *N*- α -naphthoyl derivative, 90132-98-2; (S)-2 (R = Ph; n = 1) *N*- α -naphthoyl derivative, 90132-99-3; (\pm)-2 (R = CH₂CH(c-C₆H₁₁)₂; n = 1), 35193-73-8; (R)-2 (R = CH₂CH(c-C₆H₁₁)₂; n = 1) *N*- α -naphthoyl derivative, 90133-00-9; (S)-2 (R = CH₂CH(c-C₆H₁₁)₂; n = 1) *N*- α -naphthoyl derivative, 90133-01-0; (\pm)-3 (R = Me; Y = H; n = 1), 90192-87-3; (R)-3 (R = Me; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-02-1; (S)-3 (R = Me; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-03-2; (\pm)-3 (R = Bu; Y = H; n = 1), 90192-88-4; (R)-3 (R = Bu; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-04-3; (S)-3 (R = Bu; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-05-4; (\pm)-3 (R = *i*-Bu; Y = H; n = 1), 90192-89-5; (R)-3 (R = *i*-Bu; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-06-5; (S)-3 (R = *i*-Bu; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-07-6; (\pm)-3 (R = Bz; Y = H; n = 1), 90132-76-6; (R)-3 (R = Bz; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-08-7; (S)-3 (R = Bz; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-09-8; (\pm)-3 (R = Ph(CH₂)₂; Y = H; n = 1), 90192-90-8; (R)-3 (R = Ph(CH₂)₂; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-10-1; (S)-3 (R = Ph(CH₂)₂; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-11-2; (\pm)-3 (R = Me; Y = 4,5-(OMe)₂; n = 1), 38520-68-2; (R)-3 (R = Me; Y = 4,5-(OMe)₂; n = 1) *N*- α -naphthoyl derivative, 90192-91-9; (\pm)-3 (R = Me; Y = H; n = 0), 90132-77-7; (R)-3 (R = Me; Y = H; n = 0) *N*- α -naphthoyl derivative, 90133-12-3; (S)-3 (R = Me; Y = H; n = 0) *N*- α -naphthoyl derivative, 90133-13-4; (\pm)-3 (R = Et; Y = H; n = 0), 90132-78-8; (R)-3 (R = Et; Y = H; n = 0) *N*- α -naphthoyl derivative, 90133-14-5; (S)-3 (R = Et; Y = H; n = 0) *N*- α -naphthoyl derivative, 90133-15-6; (\pm)-4 (R = Me; Y = H; n = 1), 74497-74-8; (R)-4 (R = Me; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-16-7; (S)-4 (R = Me; Y = H; n = 1) *N*- α -naphthoyl derivative, 90133-17-8; (\pm)-5 (R = *p*-CH₃OC₆H₄CH₂), 57849-23-7; (R)-5 (R = *p*-CH₃OC₆H₄CH₂) *N*- α -naphthoyl derivative, 90133-18-9; (S)-5 (R = *p*-CH₃OC₆H₄CH₂) *N*- α -naphthoyl derivative, 90133-19-0; (\pm)-6, 90147-60-7; (\pm)-7, 90132-79-9; (\pm)-8, 90132-80-2; (\pm)-9 (isomer 1), 90132-81-3; (\pm)-9 (isomer 2), 90132-82-4; (\pm)-10, 90132-83-5; (S)-3 (R = Me; Y = 4,5-(OMe)₂; n = 1) *N*- α -naphthoyl derivative, 90192-92-0.

Metabolites of the Pulmonate *Siphonaria lessoni*

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The pulmonates are air-breathing gastropod molluscs found in the high intertidal region. Previous studies of pulmonates of the genus *Siphonaria* have reported the isolation of antimicrobial metabolites having "polypropionate" carbon skeletons. The major metabolites of *S. diemenensis* from southeastern Australia are diemenensin-A (1) and diemenensin-B (2).¹ *Siphonaria pectinata* from Florida contained pectinatone (3).² We now report the isolation and characterization of norpectinatone (4) and *E* and *Z* isomers of a related furanone, 5 and 6, from the Chilean pulmonate *Siphonaria lessoni* (Chart I).

The pulmonate *Siphonaria lessoni* was collected intertidally at Dichato, Cocholgue, and the Bio-Bio River mouth, all near Concepcion, Chile. Each collection was stored separately in acetone. The acetone extracts of the three samples were identical by chromatographic and ¹H NMR analyses. The combined extracts were fractionated by medium-pressure silica chromatography, and the "polypropionate" fraction was further purified by precipitation of the sterols from acetonitrile. The acetonitrile-soluble material was separated by LC on Partisil by using ether as eluant to obtain two "polypropionate" fractions that comprised norpectinatone (4) and a 1:1 mixture of *E* and *Z* furanones 5 and 6. The geometrical isomers could not be separated by HPLC.

Norpectinatone (4), [α]_D +49.2° (*c* 2.5, CHCl₃), was isolated as an oil. The similarity between norpectinatone (4) and pectinatone (3) was obvious from the spectral data. The high-resolution mass measurement (*m/z* 320.2367) defined the molecular formula as C₂₀H₃₂O₃. A major fragment ion at *m/z* 207 was caused by allylic cleavage resulting in the loss of a C₈H₁₇ fragment. The ultraviolet spectrum [300 nm (ϵ 7600), 232 nm (ϵ 13 100)] was similar to that reported for pectinatone (3) [301 nm (ϵ 5063)].² The ¹³C NMR spectrum contained signals at δ 165.9 (s), 165.5 (s), 159.2 (s), 106.5 (s), and 98.7 (s) for the pyrone carbons and at δ 126.1 (s) and 142.8 (d) for the olefinic carbons. These data indicated the presence of a 5-(2-alkyl-1-methylvinyl)pyrone, similar in structure to pectinatone (3) but lacking one methylene group in the alkyl chain. The ¹H NMR spectrum contained one terminal methyl signal at δ 0.81 (t, 3 H, *J* = 7 Hz) and three secondary methyl signals at δ 0.86 (d, 6 H, *J* = 6 Hz) and 0.99 (d, 3 H, *J* = 6.5 Hz) with the latter signal coupled to an allylic proton signal at δ 2.65 (m). The major differences between the ¹³C NMR spectra of the pectinatone (3) and norpectinatone (4) can be ascribed to the replacement of a terminal propyl group [δ 14.3 (q), 19.9 (t), and 39.2 (t)] by an ethyl group [δ 11.2 (q) and 29.3 (t)].³

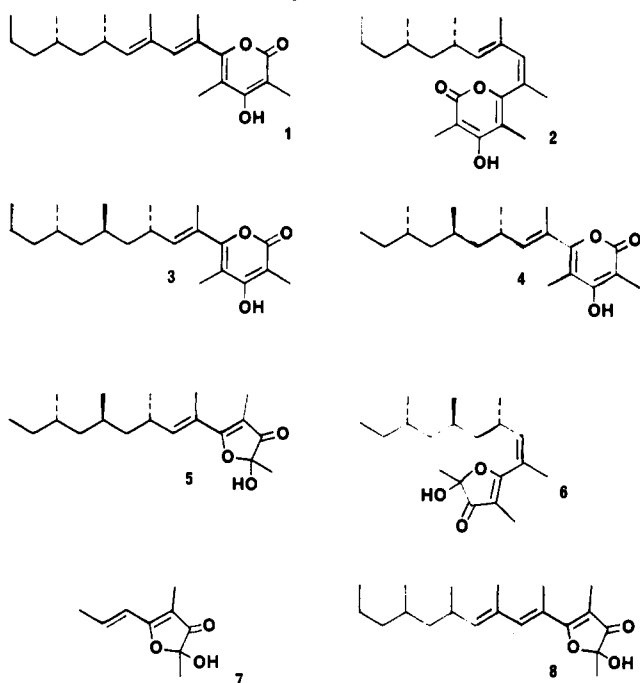
Ozonolysis of norpectinatone (4) followed by oxidation of the ozonide gave 2,4,6-trimethyloctanoic acid, [α]_D +39° that was transformed into methyl 2,4,6-trimethyloctanoate, [α]_D +46°, by using ethereal diazomethane solution. We have tentatively assigned the absolute stereochemistry as 2*S*,4*R*,6*S*, similar to that of pectinatone (3), on the fol-

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(3) Calculated ¹³C NMR shifts for the terminal ethyl group are δ 10.9 and 29.8 (Lindeman-Adams Rules).

Chart I



lowing basis. The optical rotations of four isomers of methyl 2,4,6-trimethylnonanoate have been measured⁴ [$2R,4R,6R = -23^\circ$; $2R,4S,6R = -35^\circ$; $2S,4S,6R = +2^\circ$; $2S,4R,6R = +9^\circ$] and are consistent with the report by Odham⁵ that, for a trimethyldecanoate series, "the largest optical rotations are given by optically active centers...at position 2 and in the antieiso position which rotate in the same direction". Thus a large positive rotation in the trimethyldecanoate and trimethylnonanoate series, and by inference in the trimethyloctanoate series, should be associated with a $2S,6S$ isomer. Since methyl (2*R*,4*R*,6*R*)-trimethyloctanoate has a rotation of -30° ,⁶ larger in magnitude than that of the corresponding homologue, we predict that the isomer with a rotation of $+46^\circ$ should have the $2S,4R,6S$ geometry.

The furanones 5 and 6 could not be separated by HPLC although the presence of two isomers could easily be deduced from the presence of two olefinic signals at δ 6.09 (d, 0.5 H, $J = 10$ Hz) and 6.13 (d, 0.5 H, $J = 10$ Hz) in the ^1H NMR spectrum. The mass spectrum of the mixture was compatible with two isomers having the molecular formula $\text{C}_{19}\text{H}_{32}\text{O}_3$. The ^{13}C NMR spectrum of the mixture of furanones 5 and 6 contained signals at δ 203.6 (s), 182.0/181.8 (s), 106.2 (s), and 101.3 (s) assigned to the carbons of the 2-hydroxy-2,3-dihydrofuran-3-one ring. The infrared bands at 3400 and 1680 cm^{-1} and the UV absorptions at 308 nm (ϵ 8300) and 243 (ϵ 4900) are similar to data reported for 2,3-dihydro-2-hydroxy-2,4-dimethyl-5-*trans*-propenylfuran-3-one (7).⁵ The ^1H NMR spectrum contained methyl signals at δ 1.54 (3 H), 1.82 (3 H), and 1.97 (3 H), each of which appeared as a doublet with separations between the peaks of δ 0.005, 0.006, and 0.011, respectively. We assign these duplicate signals to the presence of two geometrical isomers. We considered other possible causes for the doubling of the ^1H NMR signals: a mixture of isomers at C-2, restricted rotation about the 5,6 bond, and a mixture of isomers at C-8. The latter possibility was easily eliminated since ozonolysis of the

mixture of furanones 5 and 6 gave a single acid, (2*S*,4*R*,6*S*)-trimethyloctanoic acid, identical in all respects, including optical rotation, with the acid obtained previously. The ^1H NMR spectrum does not change at elevated temperatures, suggesting that restricted rotation is unlikely. A mixture of isomers at C-2 is unlikely to cause the maximum shift difference for the olefinic proton at C-7, particularly since the intervening ring is planar. The only satisfactory explanation of all the slight differences in spectral data is a mixture of geometrical isomers. The major support for this proposal is found in the ^{13}C NMR spectrum where the signal at δ 13.4 (q) is very small while a signal at δ 20.4 (q) is much larger than its neighbors. We have assigned the signal at δ 13.4 (q) to the methyl group at C-6 of the *E* isomer and the signal at δ 20.4 (q) to a composite of the C-6 methyl group of the *Z* isomer and a second methyl group.

We had previously encountered the furanone 8 as a minor metabolite of *S. diemenensis*.⁸

Experimental Section⁹

Chromatography. The acetone extract (500 mg) of *Siphonaria lessona* collected in Chile was fractionated by elution with CH_2Cl_2 :EtOAc (4:1 to 3:1 to 2:1) through silica at medium pressure (3.5 atm). The "polypropionate" fraction (260 mg) was further purified by precipitation of sterols (84 mg, 17%) with acetonitrile followed by LC on silica using ether as eluant to yield a mixture of the furanones 5 and 6 (39 mg, 8% of extract) and norpsectinatone 4 (35 mg, 7% of extract).

Mixtures of furanones 5 and 6: oil; $[\alpha]^{20}_{\text{D}} +90.5^\circ$ (c 2.2, CHCl_3); IR (CHCl_3) 1680 cm^{-1} ; UV (EtOH) 243 nm (ϵ 4900), 308 (ϵ 8300); ^1H NMR (CDCl_3) δ 0.82 (t, 3 H, $J = 6.5$ Hz), 0.86 (d, 6 H, $J = 7$ Hz), 1.02 (d, 3 H, $J = 6.5$ Hz), 1.54 (2 s, 3 H), 1.82 (2 s, 3 H), 1.97 (2 s, 3 H), 2.73 (br m, 1 H), 6.09 (d, 0.5 H, $J = 10$ Hz), 6.13 (d, 0.5 H, $J = 10$ Hz); ^{13}C NMR (CDCl_3) δ 7.7 (q), 11.2 (q), 13.4 (1/2 q, *E* isomer), 19.6 (q), 20.4 (1/2 q), 20.9 (q), 22.3 (q), 28.3 (d), 29.3 (t), 30.9 (d), 31.5 (d), 44.6 (t), 45.1 (t), 101.3 (s), 106.2 (s), 125.8 (s), 147.7 (d), 181.8/182.0 (1/2 s, 1/2 s), 203.6 (s); mass spectrum, m/z 308 (M^+), 265, 209, 195; high-resolution mass spectrum, obsd m/z 308.2355 ($\text{C}_{19}\text{H}_{32}\text{O}_3$ (M^+) requires 308.2351).

Norpsectinatone (4): oil; $[\alpha]^{20}_{\text{D}} +49.2^\circ$ (c 2.5, CHCl_3); IR (CHCl_3) 1680 cm^{-1} ; UV (EtOH) 232 nm (ϵ 13100), 300 (ϵ 7600); ^1H NMR (CDCl_3) δ 0.81 (t, 3 H, $J = 7$ Hz), 0.86 (d, 6 H, $J = 6$ Hz), 0.99 (d, 3 H, $J = 6.5$ Hz), 1.91 (s, 3 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.65 (m, 1 H), 5.36 (d, 1 H, $J = 10$ Hz); ^{13}C NMR (CDCl_3) δ 8.7 (q), 11.2 (q), 11.6 (q), 14.8 (q), 19.6 (q), 20.2 (q), 21.2 (q), 28.2 (d), 29.3 (t), 30.5 (d), 31.5 (d), 44.7 (t), 45.3 (t), 98.7 (s), 106.5 (s), 126.1 (s), 142.8 (d), 159.2 (s), 165.5 (s), 165.9 (s); mass spectrum, m/z 320 (M^+), 221, 207, 181, 168, 82; high-resolution mass spectrum, obsd m/z 320.2367 ($\text{C}_{20}\text{H}_{32}\text{O}_3$ (M^+) requires 320.2351).

Ozonolysis of 4. A solution of norpsectinatone (4, 11 mg) in dichloromethane at -78°C was treated with a stream of ozone in oxygen for 2 min. The reaction mixture was stirred at -78°C for a further 5 min after which Jones reagent (2 drops) was added and the solution allowed to warm to room temperature. The residue after evaporation of the solvent was washed with ether and the ether extract partitioned with 10% NaOH. Acidification of the aqueous phase followed by reextraction with ether yielded (2*S*,4*R*,6*S*)-trimethyloctanoic acid (0.5 mg, 9%): $[\alpha]^{20}_{\text{D}} +40^\circ$ (c 0.04, Et_2O); methylated with ethereal diazomethane to methyl (2*S*,4*R*,6*S*)-trimethyloctanoate: $[\alpha]^{20}_{\text{D}} 46^\circ$ (c 0.4, Et_2O).

Ozonolysis of a Mixture of 5 and 6. Treatment of a solution of 5 and 6 (10 mg) as described above yielded (2*S*,4*R*,6*S*)-trimethyloctanoic acid (1.8 mg, 36%): $[\alpha]^{20}_{\text{D}} +39^\circ$ (c 0.18, Et_2O); methylated with ethereal diazomethane to methyl (2*S*,4*R*,6*S*)-trimethyloctanoate, $[\alpha]^{20}_{\text{D}} +46^\circ$ (c 0.18, Et_2O).

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(2*S*,4*R*,6*R*)-Trimethyloctanoic acid: $^1\text{H NMR}$ (CDCl_3) δ 0.84 (d, 3 H, $J = 7$ Hz), 0.88 (t, 3 H, $J = 7$ Hz), 1.19 (d, 3 H, $J = 7$ Hz), 2.60 (m, 1 H).

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Registry No. 4, 90220-12-5; 5, 90220-13-6.

Probes for Narcotic Receptor Mediated Phenomena. 6.¹ Synthesis of

(\pm)-(1 α ,4 $\alpha\alpha$,9 $\alpha\beta$)-1,3,4,9a-Tetrahydro-2-methyl-2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridin-8-ol, an Oxide-Bridged 5-(3-Hydroxyphenyl)morphan

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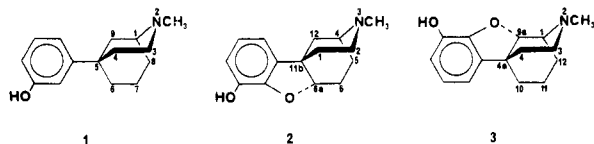
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In our continuing study of the opioid receptor system,¹ we have examined conformationally fixed derivatives of the potent class of narcotic agonists, the 5-(3-hydroxyphenyl)morphans 1.² The parent compounds have a rigid 2-azabicyclo[3.3.1]nonane ring system with a freely rotating phenyl group attached at the 5-position. An unusual feature of this system is that the phenyl ring is held in an equatorial conformation relative to the fixed piperidine portion of the molecule, which consists of atoms 1-5 and 9 of structure 1. This is in contrast to the axial phenyl-piperidine orientation found in the opiates and a number of rigid opioids.



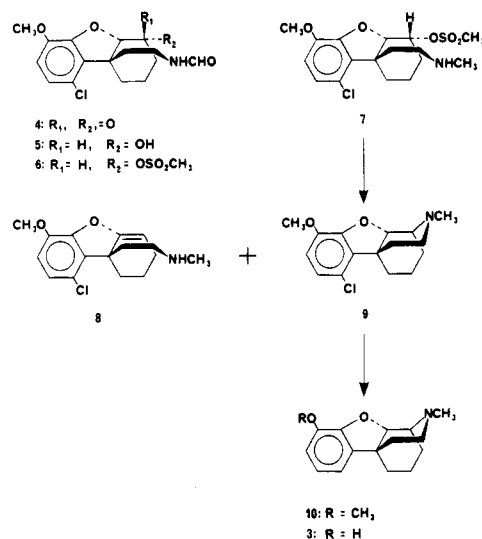
In order to gain additional insight into the topological features of opioid receptor binding sites, we have undertaken a study aimed at determining the optimum torsion angle between the phenyl ring and piperidine ring for binding of the 5-(3-hydroxyphenyl)morphans to an opioid receptor. The approach that we have taken is to conformationally restrict rotation of the phenyl ring by means of an oxide bridge to one of three carbons, 4, 6, or 9 of 1. Since each carbon offers two epimeric sites of attachment, a total of six oxide bridge isomers are possible, each having the phenyl ring rotated at an angle of approximately 60° relative to the previous isomer in the series. The six isomers together sequentially rotate the phenyl ring through a complete 360° revolution. Should

any of these isomers bind well to an opioid receptor, valuable information about the optimum phenyl-piperidine torsion angle would be obtained.

The first isomer in this series, 2, has been synthesized and the torsion angle between the phenyl ring and the piperidine ring (the plane of the piperidine ring was calculated as a least-squares plane through atoms 1, 2, 4, and 12 of 2) was calculated as 86° on the basis of X-ray analysis of 2·HCl.³ The inability of 2 to bind to opioid receptor preparations⁴ might be related to the unsuitable phenyl torsion angle. This paper presents the synthesis of the second isomer in the series, racemic 3, and the determination of its phenyl torsion angle by X-ray analysis. This synthesis of 3 represents the first entry into the 2*H*-1,4a-propanobenzofuro[2,3-*c*]pyridine series.

Synthesis

The synthesis of 3 started with hexahydrodibenzofuran 4,³ which was obtained by using the heteroatom-directed photoarylation developed by Schultz⁵ and previously employed by us as an intermediate in the synthesis of 2. To form the tetrahydropropanobenzofuro[2,3-*c*]pyridine ring system of 3 it was necessary to effect ring closure of the nitrogen onto the carbonyl carbon atom of 4. Attempts



at closure by nucleophilic attack of nitrogen at the carbonyl carbon proved unsuccessful. A less direct route involved reduction of the carbonyl function with NaBH₄ to yield predominately one alcohol 5 which was assigned the α -configuration on the basis of the 3-Hz coupling constant for the 4 $\alpha\beta$ proton of 5. As in the case of the 6 $\alpha\beta$ proton of 2, the low-field absorption of the 4 $\alpha\beta$ proton of 5 is attributed to the deshielding effect of the aromatic ring.³ Crystallization of the crude mixture gave pure 5 in 69% yield. Conversion of 5 to the corresponding methanesulfonate ester 6 was achieved in 90% yield by reaction of 5 with methanesulfonyl chloride in the presence of triethylamine. The *N*-formyl group was reduced with diborane to yield the secondary amine 7. It was anticipated that intramolecular displacement of the methanesulfonate group by nitrogen would occur cleanly to give the desired ring-closed product 9.

However, in addition to 9 obtained in 18% yield from 7, a byproduct was also obtained in 9% yield which pro-

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