Bridged Nicotines. Synthesis of *cis*-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline

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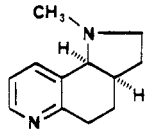
A short synthesis of *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline (**1c**), a bridged nicotine, has been achieved. The key feature of this process is the alkylation of 7,8-dihydro-5(6*H*)-quinolone (**4**) with nitroethylene. The stereochemistry of the ring juncture of **1c** was assigned by analysis of the NOE difference spectrum of the bridged nornicotine *cis*-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*f*]quinoline (**2c**), the precursor to **1c**.

In recent years, a number of studies have been published which attempt to examine the role of particular conformations on the pharmacological properties of important biologically active molecules. One approach to such a study is to alter the parent molecule in such a fashion that its original conformational mobility is severely limited to one particular conformation.[1] We now report the synthesis of the "bridged" nicotine *cis*-2,3,3a,4,5,9b-hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]quinoline (**1c**) and its



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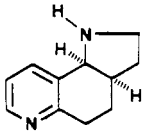

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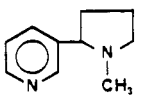

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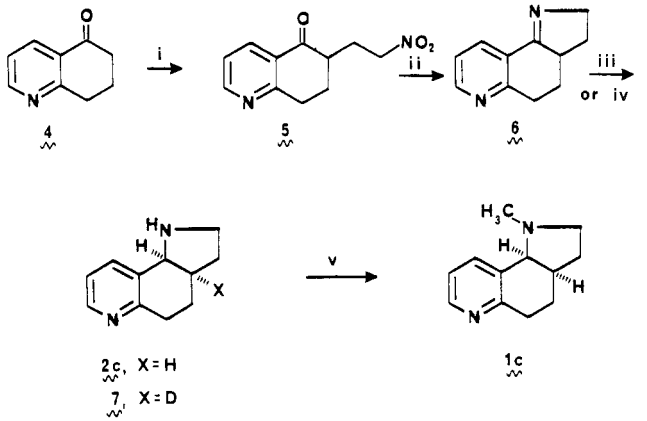
nornicotine analogue **2c**,[2] members of a class of conformationally restricted nicotine (**3**) analogues of which little information exists in the literature.[3-5]

7,8-Dihydro-5(6*H*)-quinolone (**4**) was utilized as the starting point for our synthesis of **1c**. A key feature involves the use of nitroethylene as a synthon for completing the pyrrolidine ring of **1c** and **2c**, as shown in Scheme I.[6] Treatment of **4** with lithium diisopropylamide in THF at −70 °C followed by the addition of nitroethylene[7,8] afforded a 63% yield of nitroketone **5** (Scheme I). No dinitro byproduct was isolated. Reduction of **5** with hydrogen (50 psi) and Raney nickel in ethanol directly provided the desired bridged myosmine **6** in 76% yield, presumably involving an intermediate amino ketone which undergoes an intramolecular Schiff base cyclization.[9] Reduction of **6** with sodium cyanoborohydride in methanol[10] proceeded smoothly to afford the bridged nornicotine **2c** in a yield of 53%. ^{1}H NMR analysis of **2c** (at 80 and 500 MHz) revealed the presence of only one of the two possible ring-juncture epimers. Reductive methylation of **2c** with sodium cyanoborohydride and aqueous formaldehyde in acetonitrile led to the desired bridged nicotine **1c** in 60% yield.

It is interesting to note that the methylation of **2c** proceeded quite slowly to completion. We have previously observed that nornicotine and a number of its conformationally mobile analogues undergo rapid reductive methylation by the above procedure.[10] The slow formation of **1c** indicated that there is substantial steric hindrance toward the pyrrolidine nitrogen in conformationally restricted **2c**, presumably due to the cross-ring peri interactions.

Scheme I



[a] i, LDA followed by nitroethylene; ii, RaNi, H_2; iii, $NaCNBH_3$; iv, CD_3CO_2D/CD_3OD; $NaCNBH_3$; v, HCHO, $NaCNBH_3$.

We had hoped to assign the stereochemistry of the ring juncture of **1c** and **2c** by determination of the proton–proton coupling constant J_{3a-9b} for the ring juncture protons, H_{3a} and H_{9b} (see Figure 1). On the basis of inspection of a Dreiding model of the cis-fused ring system **2c** (and **1c**), enough mobility exists to allow a range of possible conformations in which the H_{3a}–C–C–H_{9b} dihedral angle could be 10°–40°. Depending on the conformation, the coupling constant J_{3a-9b} could range from ca. 4.8 to 8

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(1) See, for example: (a) Woodruff, G. N. *Trends Pharmacol. Sci.* **1982**, *3*, 59–61. (b) Law, S.-J.; Morgan, J. M.; Masten, L. W.; Borne, R. F.; Arana, G. W.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1982**, *25*, 213–216.

(2) All of the chiral compounds prepared herein are racemates, although only one enantiomer is illustrated in Scheme I.

(3) Haglid, F. *Acta Pharm. Suec.* **1967**, *4*, 117–138.

(4) Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125–2127.

(5) Rondahl, L. *Acta Pharm. Suec.* **1980**, *17*, 288–291.

(6) Alternate procedures involving (a) the alkylation of quinoline **4** with ethyl and *tert*-butyl bromoacetate followed by reductive amination and (b) alkylation of the *O*-methyl oxime of **4** with ethyl bromoacetate resulted in low yields of the desired products. These routes were abandoned.

(7) For recent examples of the utility of nitroalkanes, see: (a) Seebach, D.; Lietz, H. F.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924–1945. (b) Yanami, T.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1975**, 726–727. (c) Cory, R. M.; Anderson, P. C.; McLaren, F. R.; Yamamoto, R. R. *Ibid.* **1981**, 73–74.

(8) For the preparation of nitroethylene, see: Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185–1189. We have observed that nitroethylene is stable for several months when stored *neat* in a sealed container in the refrigerator.

(9) Stein, M. L.; Burger, A. *J. Am. Chem. Soc.* **1957**, *79*, 154–156.

(10) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040–3048.

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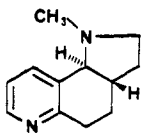
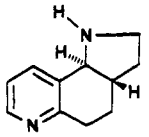
Hz. The trans-fused system **2t** (and **1t**) is fixed in a rather



1t



2t

rigid conformation in whcih the H_{3a}–C–C–H_{9b} dihedral angle is ca. 175°. For this fixed geometry, the predicted coupling would be ca. 8 to 10 Hz. The experimental value determined at 80, 220, and 500 MHz is 6.8 Hz, more consistent with a cis ring fusion but high enough to cast doubt on a firm stereochemical assignment of **2c** and **1c** obtained in our syntheses.

The stereochemistry in **2c** and, as a consequence, in **1c** was established unambiguously by NOE experiments. We reasoned that irradiation at the resonance of the bridgehead proton at the pyridylic position (H_{9b}) would result in an enhancement of the resonance of the other bridgehead proton (H_{3a}) only if the protons are syn to each other. An anti relationship should not afford an NOE. The converse experiment (irradiation at the H_{3a} resonance and observation at the H_{9b} resonance) follows the same stereochemical arguments. The first step in this experimental design is the unambiguous assignment of the resonances of H_{3a} and H_{9b}.

Inspection of the ^1H NMR spectrum of **2c**, part of which is illustrated in Figure 1A, clearly allows a rapid assignment of the resonance for H_{9b} consistent with literature NMR assignments of nicotine and other nicotine analogues.[11,12] Unfortunately, it is not immediately obvious which resonance is due to H_{3a}. This latter resonance was assigned by synthesis and ^1H NMR analysis of the deuterated nornicotinoid **7** which was prepared as shown in Scheme I.

Treatment of **6** with acetic acid-d_4/methanol-d_4 at 50 °C effected exchange[13] of the bridgehead proton for deuterium; the deuterated analogue of **6** was not isolated but was immediately reduced with sodium cyanoborohydride to afford **7** (Scheme I). Mass spectral analyses of **7** confirmed the incorporation of one deuterium atom. The 500-MHz ^1H NMR spectrum of **7** established that the resonance of the proton replaced by the deuterium at the bridgehead is δ 2.36 (Figure 1B).

The results of the NOE difference experiments are shown in Table I. Irradiation of the resonance of either bridgehead proton resulted in enhancement of the resonance of the other bridgehead proton. On the basis of these results coupled with the arguments presented above, we assign the cis ring juncture to the bridged nicotinoids formed via Scheme I, namely, **1c** and **2c**. It is interesting to speculate that **1c** and **2c** are likely to be less strained than the corresponding **1t** and **2t**. In addition, we note again that the coupling constant J_{3a-9b} for the ring juncture protons in **2c** is more consistent with a cis fusion than a

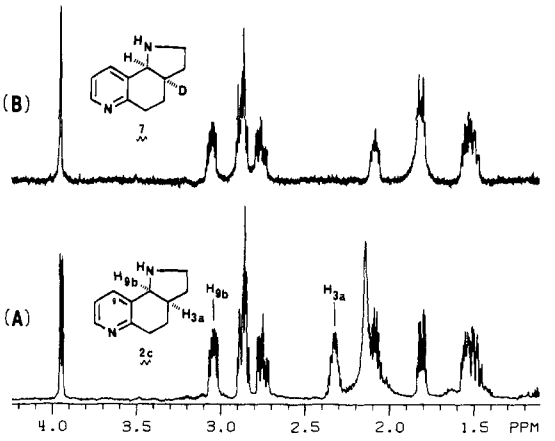


Figure 1. Upfield portion of ^1H spectrum of **2c** (A) and of **7** (B) obtained in $CDCl_3$ at 500 MHz.

Table I. Steady-State NOE Difference Experiments of 2c[a]

expt	proton irradiated	proton obsd	% NOE	proton obsd	% NOE
1	H_{3a} (δ 2.36)	H_{9b}	9		
2	H_{9b} (δ 3.99)	H_{3a}	8	H_9[b]	9

[a] In $CDCl_3$. Performed on a NT-500 spectrometer with a 5-s preirradiation; 768 scans. [b] δ 7.69.

trans fusion. This synthetic approach should also be applicable to the preparation of the isomeric nicotinoid **8** from isoquinolone **9**.

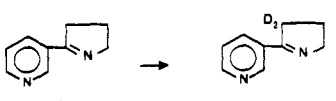
8 **9**

Experimental Section

Melting points and boiling points are uncorrected. The 80-MHz ^1H NMR spectra were determined on a Bruker WP-80 spectrometer. The 500-MHz ^1H NMR spectra were determined on a Nicolet NT-500 spectrometer. IR spectra were determined on a Perkin-Elmer 735B infrared spectrophotometer. Low-resolution mass spectra were obtained on a Finnigan 3300 mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Methoxyamine hydrochloride was obtained from Eastman Organic Chemicals, and 7,8-dihydro-5(6*H*)-quinolone (**4**) was obtained from Aldrich.

6-(2-Nitroethyl)-7,8-dihydro-5(6*H*)-quinolone (5). To a solution of 3.42 mL (24.5 mmol) of diisopropylamine in 60 mL of THF, under nitrogen and below −20 °C, was added 9.0 mL (22.4 mmol) of 2.5 M *n*-butyllithium in hexane such that the temperature did not rise above −20 °C. The solution was stirred below −20 °C for 15 min and then cooled to −70 °C. To the solution of lithium diisopropylamide was added 3.0 g (20.4 mmol) of 7,8-dihydro-5(6*H*)quinolone[14] (**4**) in 15 mL of THF over 5 min. The rate of addition was adjusted such that the temperature remained below −60 °C. The dark solution was stirred at −70 °C for 20 min followed by the addition of 1.56 g (21.4 mmol) of nitroethylene[8] in 15 mL of THF over 5 min. On completion of the addition, a yellowish precipitate resulted. The mixture was stirred at −70 °C for 30 min, at 0 °C for 1 h, and at room temperature for 16 h. The mixture was quenched with 35 mL of 10% aqueous acetic acid and extracted with ether (50 mL) followed by methylene chloride (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to a yellow, viscous oil. Two bulb-to-bulb distillations [oven temperature 145–155 °C (0.25 torr)] afforded 2.835 g (63%) of **5** as a viscous oil; picrate, mp

(11) Whidby, J. F.; Seeman, J. I. *J. Org. Chem.* **1976**, *41*, 1585–1590.
(12) Pitner, T. P.; Edwards, W. B., III; Bassfield, R. L.; Whidby, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 246–251.
(13) Treatment of myosmine (i) under identical conditions affords 3',3'-dideuteriomyosmine (ii), as previously found by J.I.S. and subsequently published (Glenn, D. F.; Edwards, W. B., III *J. Org. Chem.* **1978**, *43*, 2860–2870).



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(14) Zylmalkowski, F.; Rimek, H. *Arch. Pharm.* **1961**, *294*, 759–765.

153.5–155.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.81 (dd, J = 5, 2 Hz, 1) 8.33 (dd, J = 8, 2 Hz, 1), 7.35 (dd, J = 8, 5 Hz, 1), 4.73 (t, J = 6.5 Hz, 2), 3.13–3.43 (m, 2), 1.55–3.0 (m, 5); IR (film) 1690, 1550, 1385 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_5O_{10}$ (picrate): C, 45.44; H, 3.37; N, 15.59. Found: C, 45.60; H, 3.52; N, 15.53.

2,3,4,5-Tetrahydro-3a*H*-pyrrolo[2,3-*f*]quinoline (6). A mixture of 2.5 g (11.36 mmol) of **5**, Raney nickel (2.5 g of wet catalyst washed with ethanol prior to use), and 75 mL of ethanol was hydrogenated at 50 psi of H_2 in a Parr apparatus for 10 h. The mixture was filtered through Celite, and the solution was evaporated to a yellow oil. Bulb-to-bulb distillation [oven temperature 85–100 °C (0.2 torr)] provided 1.475 g (76%) of **6** as a straw-colored oil: dipicrate, mp 186–189 °C; ^{1}H NMR ($CDCl_3$) δ 8.63 (dd, J = 5, 2 Hz, 1), 8.38 (dd, J = 8, 2 Hz, 1), 7.25 (dd, J = 8.5, 5 Hz, 1), 4.03–4.45 (m, 1), 3.5–4.03 (m, 1), 2.63–3.35 (m, 3), 2.1–2.58 (m, 2), 1.13–1.98 (m, 2); IR (film) 1625, 1590, 1420 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_8O_{14}$ (dipicrate): C, 43.81; H, 2.86; N, 17.78. Found: C, 43.61; H, 2.91; N, 17.65.

***cis*-2,3,3a,4,5,9b-Hexahydro-1*H*-pyrrolo[2,3-*f*]quinoline (2c).** To a solution of 1.30 g (7.56 mmol) of **6**, 0.665 g (10.58 mmol) of sodium cyanoborohydride, and a trace of bromcresol green indicator was added, in portions, 6 mL of 2 N HCl/methanol such that the yellow end point was barely maintained. The resultant yellow solution was stirred at room temperature for 20 min, followed by the addition of 3 mL of 2 N HCl/methanol. The solution was then stirred for 1 h and concentrated. To the mixture was added 10 mL of water, and the solution was basified with aqueous sodium hydroxide and extracted with methylene chloride (3 × 15 mL). The methylene chloride solution was dried ($MgSO_4$) and evaporated to an oil. Bulb-to-bulb distillation [oven temperature 90–100 °C (0.2 torr)] afforded 0.694 g (53%) of **2c**, a viscous oil which solidified on cold storage: dipicrate, mp 220–223 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (dd, J = 5, 2 Hz, 1), 7.69 (dd, J = 8, 2 Hz, 1), 7.06 (dd, J = 8, 5 Hz, 1), 3.99 (d, J = 6.6 Hz, 1), 2.66–3.4 (m, 4), 1.13–2.63 (m, 4), 2.19 (s, NH, 1); IR (CCl_4) 3350, 1575, 1450 cm^{-1}. Anal. Calcd for $C_{23}H_{20}N_8O_{14}$ (dipicrate): C, 43.67; H, 3.16; N, 17.72. Found: C, 43.66; H, 3.23; N, 17.59.

***cis*-2,3,3a,4,5,9b-Hexahydro-1-methyl-1*H*-pyrrolo[2,3-*f*]-quinoline (1c).** To a solution of 0.60 g (3.45 mmol) of **6c**, 1.31 mL (16.22) of 37% aqueous formaldehyde, and 10 mL of acetonitrile at 0 °C was added 0.326 g (5.18 mmol) of sodium cyanoborohydride in portions over 1 min. The mixture was stirred at 0 °C for 15 min, followed by the addition of 160 μL of acetic acid and further stirring for 15 min at 0 °C. The mixture was then stirred at room temperature for 16 h. To the mixture was added 5 mL of 10% aqueous HCl, followed by concentration to a small volume. After the addition of a small volume of water, the mixture was washed with ether (10 mL), basified with aqueous sodium hydroxide, and extracted with methylene chloride (3 × 10 mL). The methylene chloride solution was dried ($MgSO_4$) and evaporated to a light-yellow oil. Bulb-to-bulb distillation [oven temperature 85–90 °C (0.2 torr)] afforded 0.392 g (60%) of **1c** as a clear, colorless oil: dipicrate, mp 235–238 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (dd, J = 5, 2 Hz, 1), 7.46 (dd, J = 8, 2 Hz, 1), 7.13 (dd, J = 8, 5 Hz, 1), 1.50–3.25 (m, 10), 2.30 (s, 3); IR (film) 1575, 1440 cm^{-1}; mass spectrum, m/z (relative intensity) 188 (16), 187 (27), 159 (9), 156 (13), 149 (11), 145 (26), 144 (38), 143 (12), 131 (26), 130 (100), 117 (19), 96 (59), 77 (24), 59 (31). Anal. Calcd for $C_{24}H_{22}N_8O_{14}$ (dipicrate): C, 44.58; H, 3.41; N, 17.34. Found: C, 44.33; H, 3.55; N, 17.10.

Procedure for NOE Difference Spectra. The ^{1}H NMR spectra were obtained either on a Bruker WP-80 or a Nicolet NT-500 spectrometer. The steady-state NOE measurements were made at 500 MHz on a vacuum-degassed sample (six freeze–thaw cycles) of **2c** in $CDCl_3$ at room temperature. For each resonance examined, a preirradiation of 5 s was applied at a selected frequency followed by acquisition over 4218 Hz in 16K of computer memory, resulting in an overall repetition rate of 7 s. A control was obtained in a similar fashion but with the irradiation frequency set off resonance. A total of 768 scans were obtained in each case. NOE difference spectra were obtained from the saved free induction decays (FID) by applying a 2-Hz line broadening to each FID followed by Fourier transformation and phase correction. The control spectrum was digitally subtracted from each spectrum corresponding to a different irradiation frequency. NOE enhancements observed in this way are accurate to 0.5%.[15]

Acknowledgment. We thank Dr. Jack S. Cohen for use of the Nicolet NT-500 spectrometer, Dr. E. B. Sanders for helpful discussions, Mr. John Naworal for obtaining the mass spectra, and Mrs. Anne Donathan for secretarial assistance.

Registry No. (±)-**1c**, 84133-33-5; (±)-**1c** 2-picrate, 84133-34-6; (±)-**2c**, 84133-35-7; (±)-**2c** 2-picrate, 84133-36-8; **4**, 53400-41-2; (±)-**5**, 84133-37-9; (±)-**5** picrate, 84133-38-0; (±)-**6**, 84133-39-1; (±)-**6** 2-picrate, 84133-40-4; nitroethylene, 3638-64-0.

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Synthesis of β-Lactams by the Photochemical Extrusion of Sulfur Dioxide from 1,1-Dioxo-4-thiazolidinones[1]

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Photolysis of *cis*-3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (through a Vycor filter, in *t*-BuOH/CH_3CN) gives *cis*-1,3-dimethyl-4-phenyl-2-azetidinone in 43% yield and the corresponding trans β-lactam in 11% yield. Photolysis of *trans*-3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone gives lower yields of β-lactam, with the trans stereoisomer predominating. Thermal reaction of the 1,1-dioxo-2-phenyl-4-thiazolidinones gives only the trans β-lactam. The synthesis and reactivity of several other 1,1-dioxo-2-phenyl-4-thiazolidinones are described. X-ray crystal structures of *cis*-3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone and of (1β,2α,5α)-3,5-dimethyl-1-oxo-2-phenyl-4-thiazolidinone are also reported.

The synthesis of β-lactam compounds has been of continuing interest[3] over the last 40 years because of the medical importance of penicillin and cephalosporin antibiotics. The recent isolation of the antibiotics nocardicin

(1) Presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, CA, March 15, 1978. Based in part on the Ph.D. thesis of M.R.J., Michigan State University, 1978, and on the M.S. thesis of M. J. F., Michigan State University, 1979.

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