tallized from methanol/acetone/ethyl acetate (2:1:2) (723 mg, 83%). This β-lactam was found to be identical with the one described above on the basis of their mp, specific rotation, IR, NMR, and mass spectral analysis.

(3*R*,4*S*)-*cis*-1-(*p*-Anisyl)-3-hydroxy-4-(1,2-dihydroxyethyl)azetidin-2-one (36). To a solution of **22j** (150 mg, 0.045 mmol) in absolute methanol (25 mL) were added *p*-toluenesulfonic acid monohydrate (10 mg, 0.052 mmol) and 10% Pd/C (15 mg). The solution was refluxed overnight under a nitrogen atmosphere and filtered through Celite. Evaporation of the solvent gave **36** (95 mg, 83%) identical with the one described earlier on the basis of their mp, specific rotation, IR, NMR, and mass spectral analysis.

2-Methoxy-3-[(4-methoxyphenyl)amino]-5-hydroxy-γ-valerolactone (38). β-Lactam **22d** (3.0 g, 10 mmol) was refluxed in 90% trifluoroacetic acid (20 mL) for 12 h under a nitrogen atmosphere. The reaction mixture was then cooled and dried in vacuum and the residue chromatographed over a silica gel column (1:1 ethyl acetate/hexane) to afford lactone **38** (1.70 g, 64%) as an oil: $[\alpha]^{26}_D$ +86.9° (*c* 0.5, MeOH); IR ($CDCl_3$) 3380, 1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.9–6.6 (dd, aromatic, 4 H), 4.7 (d, *J* = 7.3 Hz, 1 H), 4.45–4.25 (m, 2 H), 4.0–3.7 (m, 4 H), 3.75 (s, 3 H), 3.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) 174.11, 153.11, 140.29, 115.20, 114.93, 8.20, 78.87, 60.57, 58.98, 58.77, 55.71 ppm; MS (FAB), *m/e* 268 (M + 1)$^+$.

2-Azido-3-[(4-methoxyphenyl)amino]-5-hydroxy-γ-valerolactone (39) was prepared from **22a** in 63% yield as an oil by using the same procedure as above: $[\alpha]^{26}_D$ +74.5° (*c* 0.5, MeOH); IR (neat) 3290, 2100, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85–6.6 (dd, AB pattern, 4 H), 4.75 (d, *J* = 7.6 Hz, 1 H), 4.6 (d, *J* = 9.6 Hz, 1 H), 4.3 (dd, *J* = 7.6 Hz and 9.6 Hz, 1 H), 4.0–3.8 (m, 3 H), 3.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) 172.2, 153.2, 139.8, 115.3, 79.4, 62.8, 60.88, 58.7, 55.8 ppm; MS (FAB), *m/e* 279 (M + 1)$^+$.

Acknowledgment. We are grateful to Stevens Institute of Technology for the research facilities and a grant from Stanley funds. We are also thankful to the New Jersey Commission on Science and Technology for an Innovation Partnership grant in partial support of this research and a Biotechnology Instrumentation grant in partial support of an NMR spectrometer facility. We thank Arvind Mathur and Ashok Krishnaswami for NMR spectra.

Reduction of Lactams and Thiolactams by Sodium Borohydride: Application in the Synthesis of Some Alkaloids

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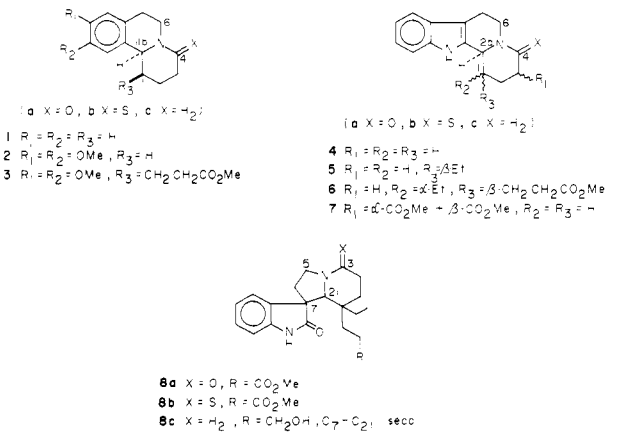
Lactams **1a–8a** and thiolactams **1b–8b**, **9a**, **10b–12b**, and **13** could be reduced to their corresponding amines in 70–98% yield by using sodium borohydride–*tert*-butyl alcohol–methanol mixtures under reflux. Even the vinylogous amide **19** underwent reduction to afford deplancheine (**18**) in 53% yield. The use of this reagent has also been extended to the synthesis of bharatamine (**10d**), aspidospermidine (**12d**), and quebrachamine (**17**).

Introduction

Deoxygenation of lactams to their respective amines is usually brought about by direct reduction with lithium aluminum hydride[1] or diborane[2] or indirectly by desulfurization of the corresponding thiolactams[3] with Raney nickel and in some cases with aluminum amalgam in neutral alcoholic solution. Sodium borohydride itself was not known so far to effect such transformation, though it reduces[4] imino ethers and imino chlorides of the amides and lactams to the corresponding amines, and in combination with anhydrous $AlCl_3$ in diglyme,[5] it reduces many functional groups, including some open-chain amides. We, therefore, tried to use $NaBH_4$-*t*-BuOH–MeOH for the preferential reduction of an ester[6] in the presence of an amide group in compound **7a** in connection with the synthesis of (±)-deplancheine (**18**), an indole alkaloid. To our surprise, the lactam moiety also underwent simultaneous reduction. Subsequently, we extended the use of this reagent to the reduction of a series of lactams (**1a–8a**) and thiolactams (**1b–8b**, **9a**, **10b–12b**, **13**), the preliminary accounts of which have been published.[7,8] (The structures given for **8** and **12** are shown with alternate biosynthetic numbering.)



We now report further application of this reagent in the synthesis of some more alkaloids, including deplancheine

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(1) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941.
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(3) (a) Kuehne, M. E. *J. Am. Chem. Soc.* **1964**, *86*, 2946. (b) Johnson, W. R.; Buchanan, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2103.
(4) (a) Borch, R. F. *Tetrahedron Lett.* **1968**, 61. (b) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1972**, 1081. (c) Rahman, A.; Basha, A.; Waheed, N. *Tetrahedron Lett.* **1976**, 219. (d) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.
(5) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582.
(6) Soai, K.; Oyamada, H.; Ookawa, A. *Synth. Commun.* **1982**, *12*, 463.

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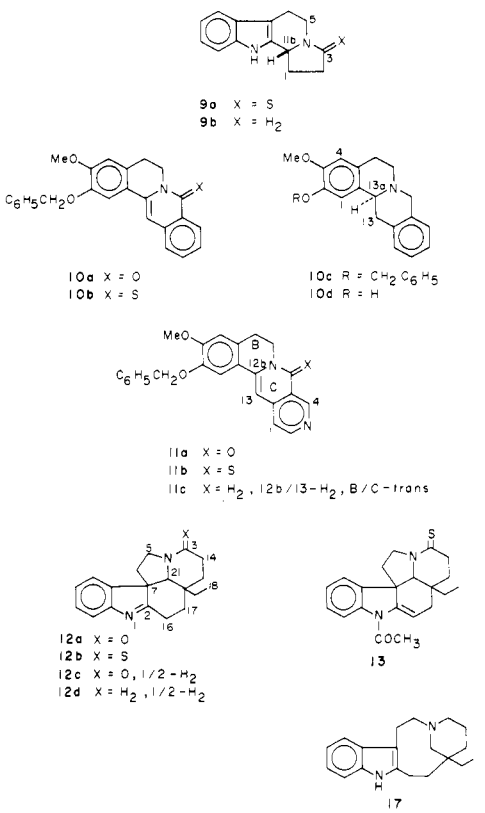
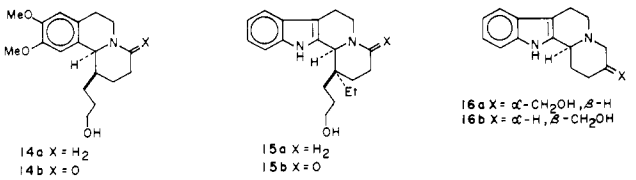


(18), quebrachamine (17), aspidospermidine (**12d**), and the unique protoberberine alkaloid, bharatamine (**10d**).

Results and Discussion

Most of the lactams and thiolactams used in our study were prepared by known procedures except for **4a**,**4b** and **7a**,**b**, which were synthesized according to Schemes I and II.

While conventional procedures for $NaBH_4$ reduction, i.e., in MeOH, EtOH, or *t*-BuOH at room temperature or under reflux, failed, the use of *t*-BuOH as solvent and dropwise addition of MeOH to the refluxing solution effectively reduced the lactams **1a**–**8a** and desulfurized thiolactams **1b**–**8b**, **9a**, **10b**–**12b**, and **13** to their respective amines in very good yields (Table I). In the case of lactams **3a** and **6a**, the partially reduced products **14b** (8%) and **15b** (10%) respectively were also obtained as minor components.



The IR spectra of the products showed complete disappearance of the characteristic bands for lactam/thiolactam. Besides, the Bohlmann bands[9] between 2740 and 2810 cm^{-1} clearly indicated the trans geometry of their quinolizidine ring system. The NMR signals at δ 4.8–5.2 in the lactams ascribed to H_e-6 and to H-12b (for the indole derivatives) or H-11b (for the isoquinolines) exhibited the expected upfield shift ($<\delta$ 4.0) in the products. A similar shift was also observed in the thiolactam series with the signals for H-11b or H-12b ($\sim\delta$ 5.0) and for H_e-5 or H_e-6 (δ 5.5–6.2) as the case may be.

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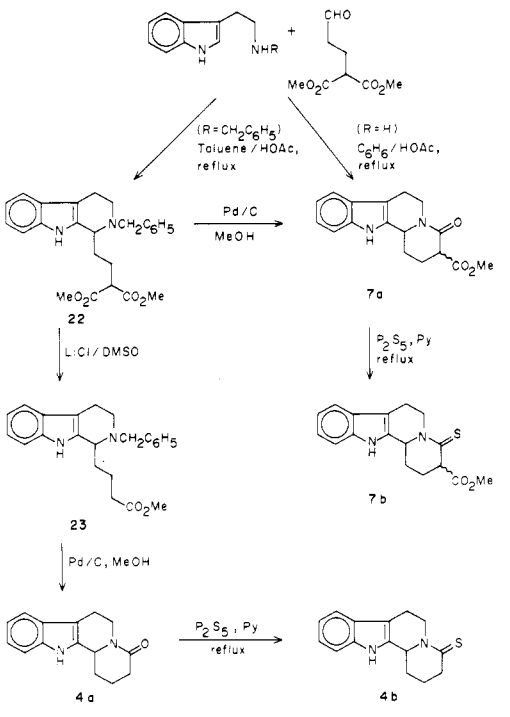
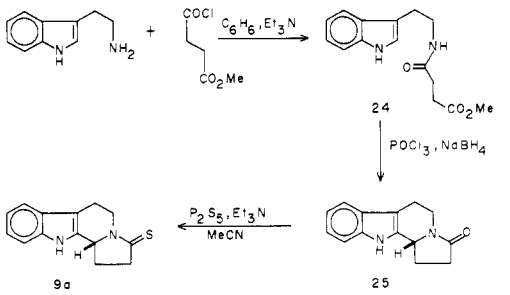
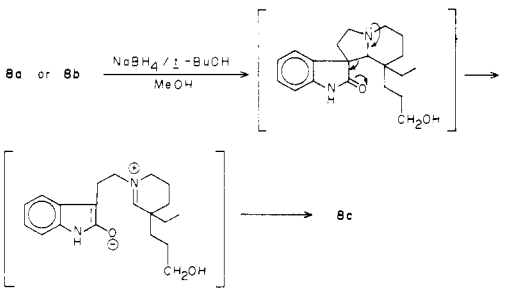
Scheme I



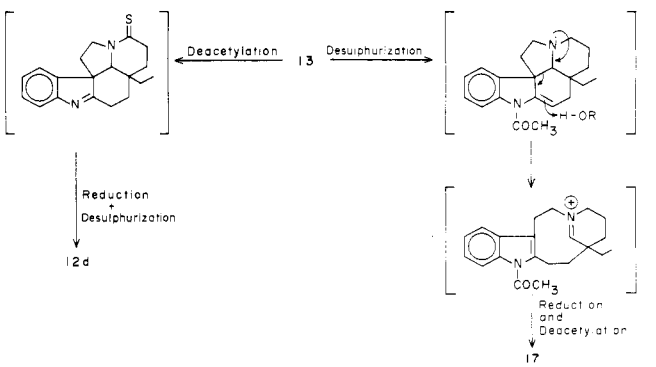
Scheme II



Scheme III



Scheme IV



Incidentally, the lactams **10a** and **11a** were not amenable to such reduction. On the other hand, the corresponding

Table I. Reduction of Lactams and Thiolactams to Amines

compd no.	$NaBH_4$: mol ratio	period of reflux, h	product (yield, %)	mp, °C obsd	mp, °C lit.
1a	8	4	**1c** (96)	gum	–
1b	6	2	**1c** (88)		
2a	6	3	**2c** (98)	220–222[a]	220–225[16]
2b	6	2	**2c** (95)		
3a	12	2	**14a** (87)	109–110[b]	–
			14b (8)	198–199[b]	–
3b	10	2	**14a** (90)		
4a	8	4	**4c** (90)	151–152[b]	153–155[17]
4b	8	2	**4c** (96)		
5a	8	6	**5c** (70)	118–119[b]	116–119[18]
5b	8	3	**5c** (85)		
6a	12	2	**15a** (85)	128–129[b]	–
			15b (10)	170–172[b]	–
6b	10	2	**15a** (92)		
7a	16	3	**16a** (63)	220[c]	ref 19
			16b (19)	180–184[c]	ref 19
7b	12	2	**16a** (65)		
			16b (21)		
9a	12	5	**9b** (83)	168–169[b]	172.5–173.5[20]
10b	12	3	**10c** (70)	98–101[d]	100–102[21]
11b	12	4	**11c** (78)	foam	–
8a	10	3	**8c** (83)	wax	–
8b	10	3	**8c** (86)		
12b	10	2	**12d** (79)	104–107[e]	108–110[12]
13	10	3	**12d** (38)		
			17 (32)	113–114[f]	113–114[11]

Crystallizing solvents: [a] 2-Propanol–ether. [b] CH_2Cl_2–PE. [c] $CHCl_3$–MeOH–PE. [d] $CHCl_3$–MeOH. [e] PE. [f] MeOH.

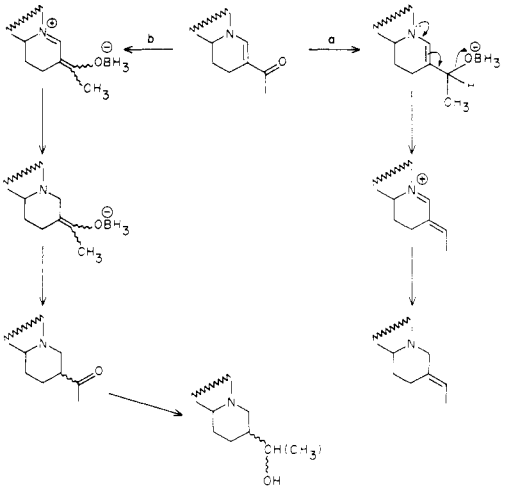
thiolactams **10b** and **11b** did react (TLC). However, the unstable enamines apparently formed underwent spontaneous aerooxidation to the lactams during the isolation procedure. Nevertheless, their formation could be realized by in situ reduction of the double bond with $NaBH_4$–HOAc to the amines **10c** and **11c**.

Again, both the compounds **8a** and **8b** suffered facile reduction to the amine **8c** with concomitant cleavage of the C_7–C_{21} bond. As envisaged in Scheme III, the amine initially formed by the preferential reduction of the tertiary lactam would be in equilibrium with the seco immonium intermediate[10] which could furnish **8c**. It therefore appeared that under identical conditions **12a** or **12b** would lead to quebrachamine **17** in fewer steps.[11] Unfortunately, reduction of C=N preceded that of the lactam/thiolactam function, precluding any such ring opening. Thus, **12a** yielded **12c** as the major product while thiolactam **12b** solely furnished **12d**,[12] a compound also obtained in minor yield from **12c** when refluxed for a longer period.

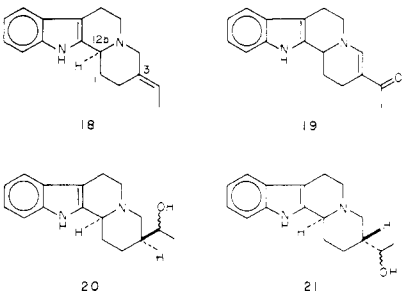
Now, for our intended use of the reagent for the synthesis of (±)-quebrachamine (**17**)[11] involving cleavage of the C_7–C_{21} bond of an aspidosperma skeleton, it was necessary to protect the imine double bond of **12b** prior to reduction of the thiolactam function. For this, the N-acetylated compound **13** was envisaged as the ideal precursor. Reduction of **13** indeed afforded quebrachamine (**17**) in 32% yield, though compound **12d** was also formed to the extent of 38%, indicating that both desulfurization and deacetylation compete with each other (Scheme IV).

It was also of interest to ascertain whether the reagent could be used to reduce vinylogous amides which are usually not affected by $NaBH_4$ in alcohol. For this, we

Scheme V



utilized the readily available 3-acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (**19**)[13] employed in our recent synthesis of the indole alkaloid (±)-deplancheine (**18**).[14] Indeed, compound **19** underwent smooth reduction to the desired product **18** with much-improved yield (53% against 23%, the maximum yield obtained so far) along with a mixture of isomeric 1,2,3,4,6,7,12,12b-octahydro-3-(1-hydroxyethyl)indolo[2,3-*a*]quinolizines, with an axial hydroxyethyl group in **20** and an equatorial one in **21**.[15]



The formation of the above products could be rationalized by assuming two routes a and b for the reduction as depicted in Scheme V. Stereospecific reduction to the *E* isomer in such a system has already been reported.[14b]

It was further observed that while dioxane, an aprotic solvent, could replace *t*-BuOH, the reduction of neither the lactam nor thiolactam could be brought about in any of the solvents used individually. Thus, addition of MeOH

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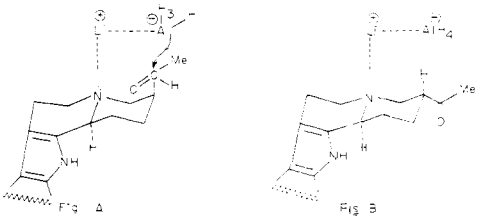
(15) Compound **20** was obtained as a pair of diastereoisomers, as evident from the pair of doublets at δ 1.02 and 1.07 in the ^1H NMR spectrum, against a pure diastereoisomer[13] obtained with $LiAlH_4$. The equatorial isomer gave, however, a similar mixture (**21**) with both the reagents. The difference is due plausibly to a complex formation between the lone pair of nitrogen and $LiAlH_4$ that facilitated exclusive attack from one side (figure A) in the case of axial but not in the equatorial form (figure B). On the other hand, $NaBH_4$ apparently could not form such a complex, allowing the hydride attack from either side of the carbonyl group in both axial and equatorial isomers.



in either of the other two refluxing solvents appeared to be a necessary condition for the reduction. Therefore, methoxy borohydride was presumed to be the reactive species requiring at least the temperature of refluxing *t*-BuOH to effect the desired reduction.

Experimental Section

Melting points taken in open capillaries are uncorrected. IR spectra were recorded on a Perkin-Elmer 177 infrared spectrophotometer using KBr pellets, ^{1}H NMR spectra were measured on a JEOL FX-100 FT NMR spectrometer using TMS as internal standard and $CDCl_3$ as the solvent unless otherwise stated, and the mass spectra (EI) were taken on a Hitachi RMU-6L instrument. The lactams **1a–3a**,[16] **5a**,[22] **6a**,[3] **8a**,[24] and **12a**[25] were prepared according to the literature procedures.

Thiolactams 1b, 2b, 3b, and 6b. General Procedure. Phosphorus pentasulfide (200 mg, 0.9 mmol) and then triethylamine (1 mL) were added to the lactam **1a** (150 mg, 0.75 mmol) in acetonitrile (15 mL) with stirring. After 12 h at room temperature, the solvent was evaporated and the residue basified with ammonia solution and extracted with CH_2Cl_2 (3 × 15 mL). The organic solution was washed with water, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography over neutral alumina. Elution with (1:1) CH_2Cl_2–petroleum ether (PE) afforded the thiolactam **1b** (101 mg, 62%): mp 78–79 °C; IR 1605 and 1585 (Ar), 1540 (NCS) cm^{-1}; ^{1}H NMR δ 1.68–2.20 (m, 3 H), 2.40–3.68 (m, 6 H), 4.76 (dd, 1 H, J = 10, 6 Hz, H-11b), 5.42 (td, 1 H, J = 12, 6 Hz, H_e-5), 7.20 (s, 4 H, Ar); MS, m/z (relative intensity) M$^+$, 217 (100), 184 (44).

Compound **2b**: yield, 85%; mp 158–160 °C ($CHCl_3$–PE) [lit.[16] mp 164 °C ($CHCl_3$–PE)].

Compound **3b**: yield, 80%; mp 148–150 °C; IR 1720 (CO_2Me), 1490 (>NCS) cm^{-1}; ^{1}H NMR δ 1.20–3.40 (m, 12 H), 3.58 (s, 3 H, CO_2Me), 3.86 (s, 6 H, OMe), 4.84 (d, 1 H, J = 4 Hz, H-12b), 5.70 (td, 1 H, J = 12, 4 Hz, H_e-6), 6.62 (s, 1 H, Ar H) 6.66 (s, 1 H, Ar H); MS, m/z (relative intensity) M$^+$, 363 (100), 348 (27), 277 (31). Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.86; H, 6.94; N, 3.86. Found: C, 62.90; H, 6.89; N, 3.91.

Compound **6b**: yield, 80%; mp 164–165 °C ($CHCl_3$–PE) [lit.[3] mp 163–165 °C]; IR 3480–3100 (NH), 1725 (CO_2Me), 1430 (>NCS) cm^{-1}; ^{1}H NMR δ 1.16 (t, 3 H, J = 6.5 Hz, CH_3), 1.40–2.28 (m, 8 H), 2.88–3.48 (m, 5 H), 3.56 (s, 3 H, CO_2Me), 4.88 (s, H-12b), 5.84 (ddd, 1 H, J = 12, 4, 1 Hz, H_e-6), 7.12–7.68 (m, 4 H, Ar H), 7.92 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 370 (100), 228 (48), 227 (70).

Compound 22. γ,γ-Dicarbomethoxybutyraldehyde (940 mg, 5 mmol) in toluene (5 mL) was added to *N*-benzyltryptamine (1 g, 4 mmol) in boiling toluene (45 mL). After 30 min, glacial HOAc (2 mL) was added and the mixture was refluxed for 2 h. The solvent was evaporated, $NaHCO_3$ solution (2%) was added, and the mixture was extracted with $CHCl_3$ (3 × 35 mL). The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography using neutral alumina. Elution with $CHCl_3$–PE (1:1) afforded the compound (1.34 g, 80%) as a thick liquid: IR (neat) 3400 (NH), 1730 (CO_2Me) cm^{-1}; ^{1}H NMR 1.64–3.32 (m, 10 H), 3.60 (s, 3 H), 3.62 (s, 3 H), 3.64 (s, 2 H), 7.00–7.48 (m, 9 H), 7.84 (br s, 1 H); MS, m/z (relative intensity) M$^+$, 420 (2), 261 (100), 91 (96). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.49; H, 6.72; N, 6.67. Found: C, 71.40; H, 6.76; N, 6.61.

Compound 23. The thick liquid **22** (2.4 g, 5.8 mmol) in DMSO (10 mL) containing lithium chloride (272 mg, 6.4 mmol) and water (1 mL) was refluxed for 2 h under nitrogen atmosphere. The reaction mixture was poured into ice–water and extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo. The product on column chromatography over neutral alumina furnished compound **23** (1.52 g, 73%): IR (neat) 3400 (NH), 1720 (CO_2Me) cm^{-1}; ^{1}H NMR δ 1.72–2.32 (m), 3.64 (s, 3 H), 7.00–7.60 (m, 4 H), 7.92 (br s, 1 H); MS, m/z (relative intensity) M$^+$, 362 (5), 203 (100). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.31; H, 7.24; N, 7.74. Found: C, 76.28; H, 7.21; N, 7.68.

Lactam 4a. The compound **23** (1.5 g, 4.2 mmol) in methanol (20 mL) was subjected to hydrogenation over 10% Pd/C (200 mg). The reaction mixture was filtered, the solvent was evaporated, and the residue was chromatographed by using CH_2Cl_2–MeOH (49:1) to afford the lactam **4a** (795 mg, 80%): mp 226–230 °C (CH_2Cl_2–MeOH–PE); IR 3225 (NH), 1600 (>NCO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.48–3.00 (m, 6 H), 3.60 (br t, 1 H), 4.84 (m, 2 H, H_e-6, H-12b), 6.80–7.48 (m, 4 H), 10.88 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 240 (100), 169 (85).

Lactam 7a. γ,γ-Dicarbomethoxybutyraldehyde (2.1 g, 11 mmol) was added to tryptamine (1.6 g, 10 mmol) in boiling benzene (40 mL). After a 30-min reflux, glacial HOAc (4 mL) was added and the mixture further refluxed for 6 h. The solvent was evaporated and the residue crystallized from $CHCl_3$ to give 2.2 g (74%) of **7a**: mp 254–256 °C; IR 3220 (NH), 1725 (CO_2Me), 1615 (>NCO) cm^{-1}; ^{1}H NMR ($CDCl_3$ + TFA) δ 3.72 and 3.82 (2 s, 3 H, each, 2 × CO_2Me), 5.00 (m, 2 H, H_e-6, H-12b), 7.04–7.72 (m, 4 H), 10.00 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 298 (100), 239 (48), 184 (50), 169 (66).

Thiolactams 4b, 5b, and 7b. General Procedure. Phosphorus pentasulfide (200 mg, 0.9 mmol) was added to the lactam **4a** (60 mg, 0.25 mmol) in dry pyridine (3 mL) and the mixture refluxed for 3 h. The solvent was evaporated under vacuum and the residue basified with ammonia solution and extracted with $CHCl_3$ (3 × 20 mL). The organic solution was washed with water, dried (Na_2SO_4), and concentrated in vacuo. The product was purified by column chromatography over neutral alumina. Elution with CH_2Cl_2–MeOH (49:1) afforded thiolactam **4b** (41 mg, 62%): mp 202–203 °C (CH_2Cl_2–PE); IR 3250 (NH), 1495 (>NCS) cm^{-1}; ^{1}H NMR δ 1.68–2.20 (m, 3 H), 2.40–3.56 (m, 6 H), 4.88 (dd, 1 H, J = 10, 6 Hz, H-12b), 6.20 (m, 1 H, H_e-6), 7.08–7.60 (m, 4 H), 7.84 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 256 (100), 223 (22). Anal. Calcd for $C_{15}H_{16}N_2S$: C, 70.37; H, 6.30; N, 10.94. Found: C, 70.28; H, 6.32; N, 10.82.

Compound **5b**: yield, 65%; mp 192–193 °C ($CHCl_3$–PE); IR (Nujol) 3340 (NH), 1610 (Ar), 1500 (>NCS) cm^{-1}; ^{1}H NMR δ 0.68–1.44 (m, 5 H), 1.92 (m, 2 H), 2.28 (m, 1 H), 2.88 (m, 2 H), 3.00–3.48 (m, 3 H), 4.98 (br s, 1 H, H-12b), 6.06 (td, 1 H, J = 12, 4 Hz, H_e-6), 7.12–7.64 (m, 4 H, Ar H), 8.00 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 284 (98), 251 (80), 170 (78), 169 (78), 168 (100). Anal. Calcd for $C_{17}H_{20}N_2S$: C, 71.89; H, 7.10; N, 9.86. Found: C, 71.95; H, 7.14; N, 9.88.

Compound **7b**: yield, 43%; mp 136 °C ($CHCl_3$–PE); IR 3400–3150 (NH), 1735 and 1725 (CO_2Me), 1490 (>NCS) cm^{-1}; NMR δ 1.76–3.48 (m, 9 H), 3.68 and 3.80 (2 s, 3 H each, 2 × CO_2Me), 4.90 (m, H-12b), 6.18 (m, H_e-6), 7.08–7.68 (m, 4 H), 7.88 (br s, 1 H, NH); MS, m/z M$^+$, 314. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 65.02; H, 5.78; N, 8.92. Found: C, 65.11; H, 5.72; N, 8.99.

***N'*-[3-(Methoxycarbonyl)propanoyl]tryptamine (24).** Tryptamine (1.1 g, 6 mmol) and triethylamine (1 mL, 7 mmol) were added to dry benzene (80 mL). While the mixture was stirred at 0 °C, 3-(methoxycarbonyl)propanoyl chloride (1.1 g, 7.3 mmol) was added dropwise, and the stirrring continued for 24 h. Water (20 mL) was added to the reaction mixture, and the mixture was basified with ammonia solution, extracted with benzene, dried (Na_2SO_4), and concentrated in vacuo to yield **24** (1.7 g, 94%). The residue was recrystallized from $CHCl_3$–PE: mp 115–116 °C; IR 3340–3280 (NH), 1730 (CO_2Me), 1650 (NHCO) cm^{-1}; ^{1}H NMR δ 2.30–2.75 (m, 4 H), 2.96 (t, 2 H, J = 6 Hz, Ar CH_2), 3.56 (t, 2 H, J = 6 Hz, NCH_2), 3.60 (s, 3 H, CO_2Me), 5.68 (br s, 1 H, $NHCH_2$), 7.00–7.72 (m, 4 H, Ar H), 8.16 (br s, 1 H, NH); MS, m/z (relative intensity) M$^+$, 274 (100), 243 (45), 242 (44), 223 (22), 205 (19). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.75; H, 6.62; N, 10.22. Found: C, 65.69; H, 6.59; N, 10.18.

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1,2,5,6,11,11b-Hexahydro-3*H*-indolo[2,3-*a*]indolizin-3-one (25). Phosphorus oxychloride (5 mL) was added dropwise to a solution of the amide **24** (54 mg, 2 mmol) in toluene (60 mL) with stirring and the mixture refluxed for 4 h. Excess $POCl_3$ and toluene were removed under reduced pressure. The residue was dissolved in dry EtOH (10 mL), the reaction mixture was cooled, and $NaBH_4$ (190 mg, 5 mmol) was added in portions. Addition of water (5 mL) to the cooled mixture was followed by extraction with CH_2Cl_2 (3 × 18 mL), drying (Na_2SO_4), and evaporation in vacuo. Chromatography of the residue over basic alumina yielded the lactam **25** (225 mg, 50%) as the major product. It was recrystallized from $CHCl_3$–PE, mp 251–252 °C: IR 3260 (NH), 1660 (>NCO), 1620 (Ar) cm^{-1}; ^1H NMR δ 1.80–3.20 (m, 7 H), 4.50 (m, 1 H, H-5), 4.94 (t, 1 H, H-11b), 7.10–7.60 (m, 4 H), 7.96 (br s, 1 H, NH); MS, *m/z* (relative intensity) M^+, 226 (100), 225 (76), 169 (24).

Thiolactam 9a. The lactam **25** was converted to thiolactam **9a** by following the procedure described for **1b**: yield, 85%; mp 206–208 °C dec ($CHCl_3$–PE); IR 3350 (NH), 1500 (>NCS) cm^{-1}; ^1H NMR δ 2.02 (dq, 1 H, *J* = 12, 10 Hz), 2.40–2.78 (m, 1 H), 2.84–3.44 (m, 5 H), 5.04–5.44 (m, 2 H, H-11b, H-5), 7.08–7.60 (m, 4 H), 7.84 (br s, 1 H, NH); MS, *m/z* (relative intensity) M^+, 242 (100), 209 (49), 182 (51). Anal. Calcd for $C_{14}H_{14}N_2S$: C, 69.48; H, 5.83; N, 11.58. Found: C, 69.51; H, 5.80; N, 11.60.

Thiolactams 10b and 11b. The compounds **10b** and **11b** were prepared from the corresponding lactams[23] in 60 and 65% yields respectively according to the procedure described for compound **4b**.

Compound **10b**: mp 168–171 °C ($CHCl_3$–PE); IR 1605 (Ar), 1500 (>NCS) cm^{-1}; ^1H NMR δ 2.80–3.12 (m, 3 H), 3.88 (s, 3 H, OMe), 5.20 (s, 2 H, OCH_2 Ar), 5.98 (td, 1 H, *J* = 12, 4 Hz, H_e-6), 6.72 and 6.80 (2 s, 2 H, Ar H), 7.12–7.80 (m, 10 H, Ar H); MS, *m/z* (relative intensity) M^+, 399 (15), 384 (31), 91 (100). Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.25; H, 5.31; N, 3.51. Found: C, 75.21; H, 5.28; N, 3.46.

Compound **11b**: mp 188–189 °C ($CHCl_3$–PE) (lit.[23] mp 186–189 °C).

1-Desmethyl-3-thioxovincatine (8b). The thiolactam **8b** was prepared from lactam **8a** by following the procedure as described for **4b**: yield, 70%; mp 228–230 °C ($CHCl_3$–PE); IR 3240 (NH), 1710 (CO_2Me), 1680 (NHCO), 1495 (>NCS) cm^{-1}; ^1H NMR δ 0.60 (t, 3 H, *J* = 6 Hz, CH_2CH_3), 1.08–3.28 (m, 12 H), 3.60 (s, 3 H, CO_2Me), 4.16 (s, 1 H, H-21), 4.34 (m, 2 H), 6.88–7.60 (m, 4 H, Ar H), 8.68 (br s, 1 H, NH).

1,2-Dehydro-3-thioxoaspidospermidine (12b). The thiolactam **12b** was prepared, by following the method used for the preparation of **1b**, in 86% yield; ^1H NMR δ 0.68–1.44 (m, 7 H), 1.64–2.20 (m, 5 H), 2.28–2.72 (m, 2 H), 2.92 (m, 3 H), 3.44 (s, 1 H, H-21), 3.96 (dt, 1 H, *J* = 12, 6 Hz, H-5), 4.86 (dd, 1 H, *J* = 12, 8 Hz, H-5), 7.12–7.80 (m, 4 H, Ar H).

3-Oxoaspidospermidine (12c). A mixture of 1,2-dehydro-3-oxoaspidospermidine (**12a**) (294 mg, 1 mmol) and $NaBH_4$ (380 mg, 10 mmol) in *tert*-butyl alcohol (10 mL) was refluxed with occasional addition of MeOH (3 mL) in portions for 2 h. Water (5 mL) was added to the cooled mixture, and it was extracted with CH_2Cl_2 (90 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo to yield a solid, which on recrystallization from $CHCl_3$–PE furnished product **12c** (290 mg, 98%): mp 210–211 °C; IR 3220 (NH), 1620 (>NCO), 1605 (Ar) cm^{-1}; ^1H NMR δ 0.76 (m, 3 H, CH_2CH_3), 1.04–2.00 (m, 10 H), 2.12–2.64 (m, 3 H), 3.28 (dd, 1 H, *J* = 10, 6 Hz), 3.60 (dd, 2 H, *J* = 10, 6 Hz), 3.80 (s, 1 H, H-21), 6.60–7.20 (m, 4 H, Ar H).

(±)-Quebrachamine (17) and (±)-Aspidospermidine (12d). A mixture of 1-acetyl-2,3-dehydro-3-thioxoaspidospermidine[11] (**13**) (352 mg, 1 mmol) and $NaBH_4$ (380 mg, 10 mmol) in *tert*-butyl alcohol (10 mL) was refluxed for 3 h with addition of MeOH (3 mL) in portions. The mixture was cooled, water added, and the mixtures extracted with CH_2Cl_2 (80 mL). The CH_2Cl_2 solution after drying (Na_2SO_4) was concentrated to give a residue, which was chromatographed over silica gel to furnish (±)-quebrachamine (**17**) (87 mg, 32%) and (±)-aspidospermidine (**12d**) (108 mg, 38%) in the ratio of 9:11. The IR spectra of the synthetic products were superimposable with authentic samples available in the laboratory.

(±)-Deplancheine (18). Sodium borohydride (200 mg, 5.3 mmol) was added in portions to the amide **19** (200 mg, 0.75 mmol) in 1,4-dioxane (6 mL). The mixture was refluxed for 2 h, during which methanol (4 mL) was added dropwise. The reaction mixture after workup with CH_2Cl_2 was purified by column chromatography over neutral alumina. Elution with CH_2Cl_2–PE (4:1) afforded (±)-deplancheine (**18**) [100 mg, 53%; mp 158 °C (Et_2O) [lit.[14] mp 139–141 °C (Et_2O)]], and elution with CH_2Cl_2–MeOH (49:1) gave a mixture of **20** and **21**, which were separated by preparative TLC using ethyl acetate as the developing solvent, to obtain 22 mg (11%) of **20**, mp 164 °C, and 20 mg (10%) of **21**, mp 192–194 °C.

Compound **18**: IR 3420–3100 (NH), 2810 and 2760 (Bohlmann band) cm^{-1}; ^1H NMR δ 1.62 (d, 3 H, *J* = 6 Hz), 1.80–3.52 (m), 5.44 (q, 1 H, *J* = 6 Hz), 7.04–7.60 (m, 4 H), 7.72 (br s, 1 H); MS, *m/z* (relative intensity) M^+, 252 (100), 251 (66).

Compound **20**: IR 3340–3100 (NH, OH), 2810 and 2760 (Bohlmann band) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.05 and 1.07 (2 d, 3 H, *J* = 6 Hz), 1.28–2.20 (m), 2.36–3.12 (m), 3.80 (m, 1 H), 4.48 (br s, 1 H), 6.80–7.48 (m, 4 H), 10.64 (s, 1 H); MS, *m/z* M^+, 270.

Compound **21**: IR 3500–3100 (NH, OH), 2810 and 2750 (Bohlmann band) cm^{-1}; ^1H NMR δ 1.22 (d, 3 H, *J* = 6 Hz), 1.40–3.40 (m, 13 H), 3.66 (q, 1 H), 7.00–7.60 (m, 4 H), 7.80 (br s, 1 H); MS, *m/z* M^+, 270.

General Procedure for the Conversion of Lactams/Thiolactams to the Amines. Methanol (2–4 mL) was added dropwise over a period of 2–6 h to a refluxing solution of a lactam/thiolactam (0.5 mmol) and $NaBH_4$ (6–8 mmol) in *tert*-butyl alcohol (4 mL). After complete disappearance of the starting material, water (5 mL) was added to the cooled mixture and extracted with CH_2Cl_2 (3 × 15 mL). The organic solution was dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by column chromatography over neutral alumina. Elution was made successively with PE, CH_2Cl_2–PE (1:1), CH_2Cl_2, and CH_2Cl_2–MeOH (49:1) to afford the desired amine.

In the case of compounds **10b** and **11b**, since during purification the products were getting easily transformed to the lactams, further reduction of the enamine double band was ensured to characterize the products. The reaction mixture was cooled to 0 °C on completion of reflux, followed by successive addition of HOAc (5 mL) and $NaBH_4$ (~2 mmol) and stirring for 20 min at room temperature. It was then basified, worked up with CH_2Cl_2, and purified by chromatography over neutral alumina with CH_2Cl_2–MeOH (49:1) as the eluting solvent.

1c: IR (neat) 3220 (NH), 2800 and 2750 (Bohlmann band) cm^{-1}; MS, *m/z* (relative intensity) M^+, 187 (72), 186 (100), 158 (55), 131 (40).

2c: IR (neat) 2780 and 2740 (Bohlmann band) cm^{-1}; MS, *m/z* (relative intensity) M^+, 247 (56), 246 (100), 218 (34), 205 (25), 191 (28).

14a: IR 3600–3150 (OH), 2790 and 2750 (Bohlmann band) cm^{-1}; ^1H NMR δ 3.24 (br d, 1 H, H-11b), 3.52 (t, 2 H, *J* = 6 Hz, CH_2OH), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 6.56 and 6.64 (2 s, 2 H, Ar H); MS, *m/z* (relative intensity) M^+, 305 (10), 304 (16), 278 (19), 260 (12), 223 (100), 205 (90). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.88; H, 8.92; N, 4.59. Found: C, 70.81; H, 8.94; N, 4.62.

14b: IR 3560–3150 (OH), 1630 and 1620 (>NCO) cm^{-1}; ^1H NMR δ 0.92–2.88 (m, 13 H), 3.48 (t, 2 H, *J* = 6 Hz, CH_2OH), 3.86 and 3.84 (2 s, 6 H, 2 × OCH_3), 4.82 (d, 1 H, *J* = 4 Hz, H-11b), 4.88–5.12 (m, 1 H, H_e-6), 6.60 (s, 2 H, Ar H); MS, *m/z* (relative intensity) M^+, 319 (53), 233 (79), 232 (44), 192 (98), 191 (100), 190 (95). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.77; H, 7.90; N, 4.39. Found: C, 67.75; H, 7.94; N, 4.31.

4c: IR 3220 (NH), 2800 and 2750 (Bohlmann band) cm^{-1}; MS, *m/z* (relative intensity) M^+, 226 (98), 225 (100), 197 (35), 170 (28), 169 (33).

5c: IR 3380 (NH), 2810, 2750 and 2740 (Bohlmann band) cm^{-1}; ^1H NMR δ 0.80 (t, 3 H, *J* = 6 Hz, CH_2CH_3), 1.00–2.12 (m, 7 H), 2.20–3.20 (m, 6 H), 3.40 (d, 1 H, *J* = 2 Hz, H-12b), 7.04–7.56 (m, 4 H, Ar H), 7.64 (br s, 1 H, NH); MS, *m/z* (relative intensity) M^+, 254 (68), 253 (100), 197 (32), 170 (36), 169 (30).

15a: IR 3460 (OH), 3360 (NH), 2800 and 2750 (Bohlmann band) cm^{-1}; ^1H NMR δ 1.12 (t, 3 H, *J* = 6.5 Hz, CH_2CH_3), 1.32–2.08 (m, 1 H), 2.20–3.16 (m, 6 H), 3.34 (s, 1 H, H-12b), 3.48 (t, 2 H, *J* = 6 Hz, CH_2OH), 7.08–7.60 (m, 4 H, Ar H), 7.90 (br s, 1 H, NH); MS, *m/z* (relative intensity) M^+, 312 (100), 311 (70), 268 (30), 197 (36), 185 (23), 170 (46), 169 (25). Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.99; H, 9.05; N, 8.98. Found: C, 77.02; H, 9.11; N, 9.01.

15b: IR 3500–3150 (NH, OH), 1955 (>NCO) cm^{-1}; ^1H NMR δ 1.12 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.32–2.00 (m, 10 H), 2.46 (t, 2 H, J = 6 Hz, H-3), 2.78 (m, 3 H), 3.54 (m, 2 H, CH_2OH), 4.80 (s, 1 H, H-12b), 5.14 (m, 1 H, H_e-6), 7.04–7.60 (m, 4 H, Ar H), 8.30 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 326 (27), 223 (50), 205 (47), 195 (60), 170 (100). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.68; H, 8.04; N, 8.59. Found: C, 73.71; H, 8.01; N, 8.66.

16a: IR 3500–3185 (NH, OH), 2800 and 2755 (Bohlmann band) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40–3.56 (m, 14 H), 4.40 (br s, 1 H, CH_2OH), 6.80–7.48 (m, 4 H, Ar H), 10.72 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 256 (75), 255 (100), 225 (23), 170 (72), 169 (71). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.06; H, 7.88; N, 10.94. Found: C, 75.14; H, 7.91; N, 10.88.

16b: IR 3500–3300 (NH, OH), 2800 and 2750 (Bohlmann band) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.00–3.36 (m, 14 H), 4.48 (br s, 1 H, CH_2OH), 6.68–7.48 (m, 4 H, Ar H), 10.72 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 256 (67), 255 (100), 225 (26), 170 (61), 169 (58). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.06; H, 7.88; N, 10.94. Found: C, 74.98; H. 7.84; N, 10.98.

9b: IR 3320 (NH) cm^{-1}; ^1H NMR δ 1.68–3.52 (m, 10 H), 4.24 (m, 1 H, H-11b), 7.04–7.60 (m, 4 H, Ar H), 7.80 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 212 (71), 211 (100), 184 (33), 156 (22).

11c: IR 2800 and 2760 (Bohlmann band), 1600 (Ar) cm^{-1}; ^1H NMR δ 2.52–3.40 (m, 6 H), 3.60 (dd, 1 H, J = 4 Hz, H-12b), 3.92 (AB q, 2 H, J = 16 Hz, H-5), 3.86 (s, 3 H, OMe), 5.14 (s, 2 H, OCH_2 Ar), 6.64 and 6.72 (2 s, H-9, H-12), 7.03 (d, 1 H, J = 6 Hz, H-1), 7.20–7.60 (m, 5 H), 8.32 (m, 2 H, H-2, H-4); MS, m/z (relative intensity) M^+, 372 (63), 371 (64), 281 (33), 91 (100). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.48; H, 6.50; N, 7.53. Found: C, 77.39; H, 6.48; N, 7.48.

8c: IR 3500–3100 (NH, OH) and 1650 (>NCO) cm^{-1}; ^1H NMR δ 0.80 (m, 3 H, CH_2CH_3), 1.02–2.60 (m, 19 H), 3.44–3.88 (m, 2 H, CH_2OH), 6.80–7.44 (m, 4 H, Ar H), 8.20 and 8.60 (NH); MS, m/z (relative intensity) M^+, 330 (25), 184 (100). Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.79; H, 9.16; N, 8.49. Found: C, 72.83; H, 9.20; N, 8.41.

12d: IR 3380 (NH), 2780 and 2730 (Bohlmann band) cm^{-1}; ^1H NMR δ 0.62 (t, 3 H, CH_2CH_3), 0.80–2.40 (m, 16 H), 3.10 (br t, 2 H), 3.50 (dd, 1 H, J = 10, 6.5 Hz), 6.62 (d, 1 H, J = 8 Hz), 6.74 (d, 1 H, J = 8 Hz), 7.02 (dt, 2 H, J = 8, 2 Hz); MS, m/z (relative intensity) M^+, 282 (28), 254 (23), 124 (100).

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Regioselective Hydrogenation and Hydrodechlorination of a Pentachloro-2-azanorbornene[1]

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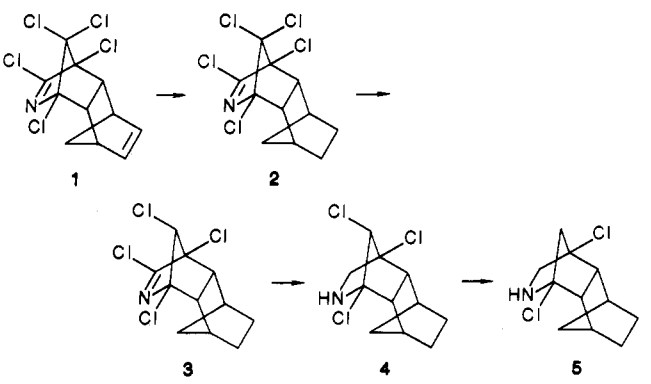
Regioselective reduction of azaaldrin (**1**), a pentachloro-2-azanorbornenyl derivative, was achieved with sodium hydride complex reducing agents or hydrogen over a rhodium or palladium catalyst. Sodium hydride itself did not react with **1**, but the complex with *t*-AmONa led to saturation of the carbon–carbon double bond in **1** to form only dihydroazaaldrin (**2**). Dechlorination occurred in the presence of the NaH–*t*-AmONa–$Ni(OAc)_2$ complex reducing agent (NiCRA), first reducing the 11-anti chlorine at the methano bridge to yield the tetrachloro derivative **3**. With a larger excess of NiCRA, **3** was reduced further to the trichloro compound **4**, in which the imidoyl chloride was saturated and dechlorinated but the 11-syn chlorine remained. X-ray analysis established the structure of **3**, and **4** was determined accordingly based on IR and NMR spectral comparisons. Treatment of **1** with hydrogen over Rh/C initially produced a mixture of **2**, **3**, and **4**. In no cases were the 11-syn chloro group in **4** reduced to form **5**, except when Pd/C was used as the catalyst. The dichloro derivative **5** was stable to further catalytic reduction.

We have reported[2] that 2-azanorbornenes, particularly azaaldrin (**1**), undergo selective substitutions of the imidoyl halide group by hard and basic nucleophiles. Hydride reagents which are soft bases, e.g., NaH in THF, $LiAlH_4$, or $NaBH_4$ in diethyl ether, do not react with **1** at all. As part of our continuing interest in polycyclic amines,[1] various hydrogenation and hydrodechlorination reactions of **1** have been carried out. Sodium hydride complex reducing agents (CRA) and catalytic hydrogenation conditions using rhodium or palladium as catalyst have been found to reduce **1** in a stepwise, regioselective manner. The sequence of relative reactivity of the chlorines and unsaturations in the 2-azanorbornenyl system is shown in Scheme I.

Scheme I



Results

Sodium Hydride Complex Reducing Agents. When azaaldrin (**1**) was refluxed with NaH in dry THF for 3 days, there was no reaction as evidenced by gas chromatography. Upon refluxing **1** with NaH–*t*-$C_5H_{11}ONa$ (2:1) in THF for 8 h, only the C=C bond was reduced, leading to **2** as a single product. When a 1:1 mixture of **1** and NiCRA (NaH–*t*-AmONa–$Ni(OAc)_2$ 4:2:1) was refluxed in THF for 3 h following Caubere's procedure,[3] two products,

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