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DOI
10.1021/jo00103a048

Publication date
1994

Published in
Journal of Organic Chemistry

Stereoselective Synthesis of the Indole Alkaloids Nitrarine, Nitramidine, and Isomers. A Biomimetic Approach

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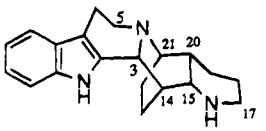
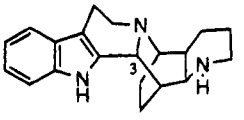
Received June 20, 1994[⊗]

Starting from tryptamine and dimeric piperidine derivative **8**, the synthesis of **4**, an immediate precursor in the biosynthesis of the *Nitraria* alkaloids, was accomplished. Cyclization of this achiral intermediate in aqueous solution produced a mixture of natural nitramidine **17** and one of its stereoisomers. Stereoselective reductions of these iminium salts with several reductors produced nitrarine (**1**), isonitrarine (**2**), and two new isomeric Nitraria indole alkaloids.

The dipiperidine indole alkaloids isolated from *Nitraria Schoberi* and *Nitraria Komarovii*[1] form a relatively unexplored group of alkaloids, possessing pharmacologically interesting properties.[2] Although several publications[3] describing isolation, structure and activity of these alkaloids have appeared, only minimal effort towards the synthesis of these structurally unique alkaloids can be found in the literature. X-ray supported structural proof for the new, azatryptycene ring system of nitrarine and its isomers, has initiated our synthesis based on biosynthetic considerations.



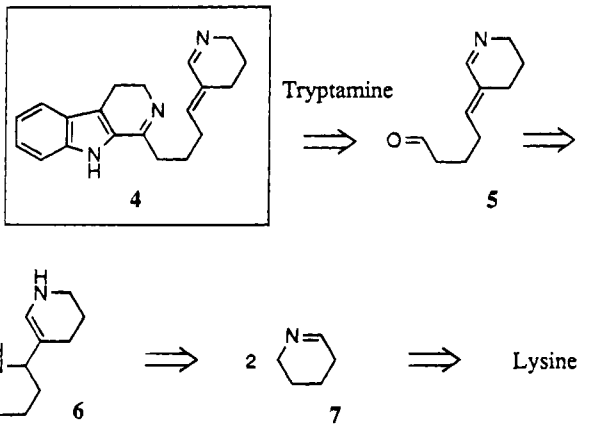


1. H-3β: Nitrarine
2. H-3α: Isonitrarine

3a. H-3α
3b. H-3β

Biosynthesis. Most of the known indole alkaloids are biosynthetically derived from diterpenes, although after several rearrangements, the original secologanine branching is often difficult to recognize. The Nitraria indole alkaloids possess the same number of carbon atoms: tryptamine plus a C10 fragment, and in many instances a yohimbine skeleton was incorrectly assigned to these alkaloids.[1] The carbon skeleton of the nitrarine family is more likely originated from two dehydropiperidine units **7**, leading via a Pictet–Spengler reaction with aldehyde **5** to an achiral intermediate **4**, as is shown in the biosynthetic retroscheme (Scheme 1). Piperidine dimer **6** (tetrahydroanabasine) is a well known bioprecursor for alkaloid synthesis in lupine species[4] and can be transformed into aldehyde **5** in two steps. From this hypothetical intermediate **4** the azabicyclooctane ring system of nitrarine (**1**) can be formed via simple, probably

Scheme 1



non-enzyme catalyzed Michael and imino-aldol reactions. Support for the assumption of uncatalyzed cyclization is found in an interesting property of these *Nitraria* indole alkaloids: they all appear as natural racemates, a phenomenon which is also observed for several of the *Nitraria* spiro alkaloids. Based on biosynthetic considerations, we published a revised structure of racemic nazlinine, confirmed by synthesis via the condensation of tryptamine and dehydropiperidine.[5] The presence of racemic alkaloids in *Nitraria* species has led us to develop a hypothesis on the evolution of these alkaloids in the plants, which will be published elsewhere. The chemical synthesis of these alkaloids via **4** (Scheme 1) offers an attractive route, exploiting the natural reactivity of the imine/enamine functionalities.

Chemistry. Due to stability problems, attempts to synthesize aldehyde **5** were thus far unsuccessful, therefore, glutarimide-aldehyde **8**[6] was used in a Pictet–Spengler reaction as is shown in Scheme 2. Under near neutral conditions with tryptamine hydrochloride in water, a slow reaction with low stereoselectivity took place. A clean and selective cyclization reaction occurred when excess TFA[7] was added to a preformed solution of the imine[8] in dichloromethane, providing a 72:28 mixture

[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1994.

(1) For a review on Nitraria alkaloids see: Wanner, M. J.; Koomen, G. J.: *Stereoselectivity in Synthesis and Biosynthesis of Lupine an Nitraria Alkaloids* in: *Studies in Natural Products Chemistry 14*, 731, Atta-ur-Rahman ed., Elsevier: Amsterdam 1994.

(2) Aminov, S. D.; Vakhabov, A. A. *Khim.-Farm. Zh.* **1991**, *25*, 56; *Chem. Abstr. 114*: 240320.

(3) (a) Nitrarine: Nasirov, S.-M.; Ibragimov, A. A.; Adrianov, V. G.; Maekh, S. Kh.; Struchkov, Yu. T.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1976**, 334; *Chem. Nat. Compounds*, **1976**,*12*, 294. (b) Ibragimov, A. A.; Maekh, S. Kh.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1975**, 273–277; *Chem. Nat. Compounds* **1975**, *12*, 293–298. See also ref. 1.

(4) For a review on the biosynthesis of Lupine alkaloids see: Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, *63*, 2707.

(5) Nazlinine is 1-(4-butylamino)-1,2,3,40-tetrahydro-β-carboline: Wanner, M. J.; Koomen, G. J. *J. Chem. Soc. Chem. Comm.* **1993**, 174.

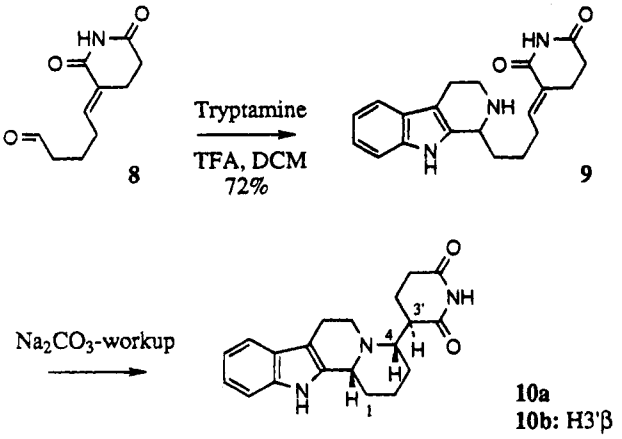
(6) Wanner, M. J.; Koomen, G. J. *Tetrahedron* **1991**, *47*, 8431.

(7) For the use of TFA/DCM for Pictet-Spengler reactions: Plate, R.; van Hout, R. H. M.; Behm, H.; Ottenheym, H. C. J. *J. Org. Chem.* **1987**, *52*, 555.

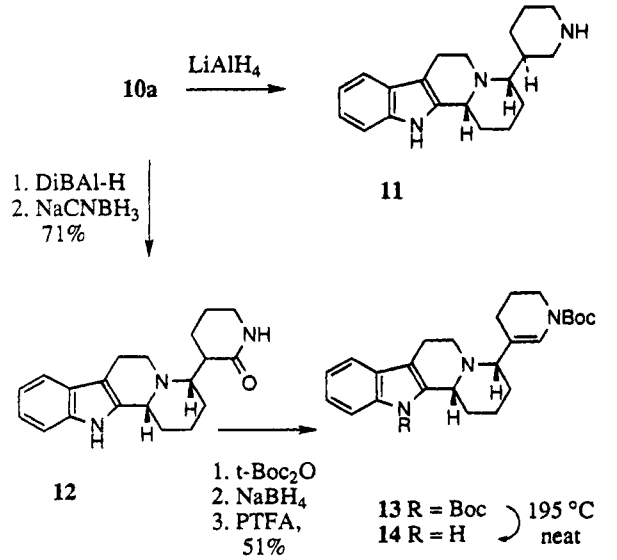
(8) For a so-called kinetically controlled Pictet-Spengler reaction with preformed, waterfree imines see: Bailey, P. D.; McLay, N. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 441.

0022-3263/94/1959-7479$04.50/0

Scheme 2



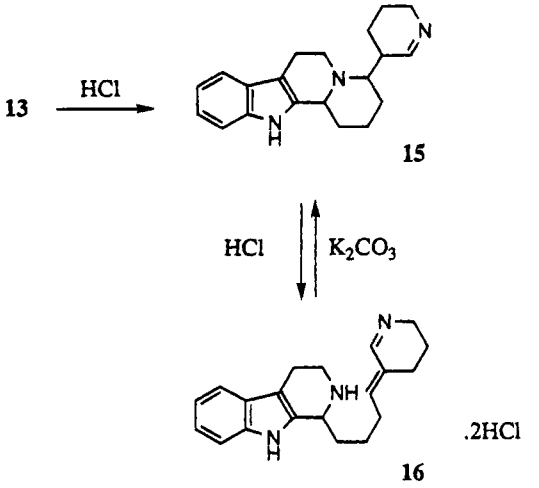
Scheme 3



of two isomeric trans-indoloquinolizines **10** in 72% yield. The initially formed Pictet–Spengler product **9** was not isolated since workup of the reaction mixture with sodium carbonate immediately resulted in a Michael type cyclization. Protonation of the Michael adduct anion probably is not a stereoselective process and a mixture of isomeric glutarimides is formed, as we have observed previously in the lupinine synthesis.[6] Both isomers **10** were isolated separately as their crystalline 1:1 complexes with dichloromethane; without inclusion of dichloromethane or chloroform the glutarimides could not be obtained in a crystalline form. The structure of the main isomer **10a** was confirmed by X-ray analysis.[9] Since the glutarimide stereogenic carbon will be destroyed during the next steps of the synthesis, both isomers are suitable for the subsequent conversions leading to compound **13**. The sequence of reactions described herein will be illustrated by starting with the main isomer **10a**.

As shown in Scheme 3, reduction of **10a** with $LiAlH_4$ gave piperidine **11**, which was subjected to a number of oxidation and halogenation conditions. None of the desired imine could be obtained presumably due to the instability of the products under the reaction conditions. Thus, a stepwise synthesis of **15** via a regioselective reduction of the glutarimide carbonyl group was attempted. Reduction of the least hindered carbonyl in **10a** was accomplished with DiBAl-H; whereas reducing agents such as Selectride or $NaBH_4$ gave lower yields and/or less regioselectivity. The mixture of hydroxylactams was immediately reduced to the corresponding lactam **12** with sodium cyanoborohydride in a mixture of acetic acid and acetonitrile. Reduction of this lactam to imine **15** appeared to be more problematic due to the susceptability of the resulting imine towards the reducing agents. After several unsuccessful attempts, a three-step procedure was developed, making use of the regioselective reduction of *N*-(*tert*-butoxycarbonyl)lactams.[10] Introduction of a t-Boc group on the amide nitrogen of **12** required excess di-*tert*-butyl dicarbonate and DMAP. Thus, under this condition both nitrogens were protected with a t-Boc group. Reduction of the activated lactam with sodium borohydride in methanol followed by elimination of water under weakly acidic conditions gave enamine **13** in 51% from **12** in 3 steps. By treatment of **13** with concentrated HCl, both t-Boc's were removed,[11] leading to the retro-Michael product **16**, a trans ene-imine, based on NMR (Scheme 4). Addition of base generated the Michael adduct **15**, which could be reversed to **16** with acid.

Scheme 4



Mercuric acetate/EDTA catalyzed oxidation[12] of the C1–N bond in **15/16** to an imine **4** was attempted. However, this led to fragmentation and oxidation. We therefore returned to di-t-Boc protected enamine **13**, and first selectively removed the indole t-Boc-substituent by a carefully controlled thermal deprotection method,[13] giving **14** in 70% yield. Now the mercuric acetate/EDTA catalyzed oxidation of this electron rich β-carboline was extremely facile, yielding an air-sensitive intermediate which was immediately dissolved in 6% HCl and cyclized via **4** at 80 °C in 3 h (Scheme 5). This reaction proceeded cleanly whereas in acetic acid/water both starting material and products appeared to be more sensitive towards traces of oxygen, resulting in a considerably lower yield.

(9) We wish to thank K. Goubitz and H. Schenk of the Department of Crystallography of this University for the X-ray crystal structure determination of compound **10a**. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

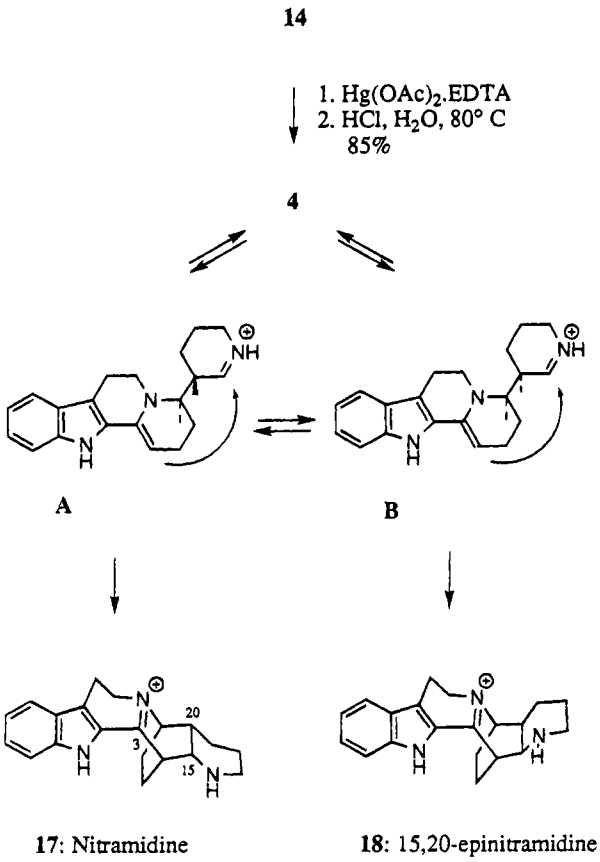
(10) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231.

(11) With dilute aqueous HCl, the amide t-BOC group could be removed selectively.

(12) Fujii, T.; Ohba, M.; Sasaki, N. *Chem. Pharm. Bull.* **1989**, *37*, 2822.

(13) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

Scheme 5



The mixture of natural nitramidine **17**[14] and 15,20-epinitramidine **18** (38:62) could be separated chromatographically in the form of their N_1–N_4 zwitterions after deprotonating the indolic N-H.

An explanation for the observed isomer distribution can be attributed in intermediates A and B, which are formed from **4** via a Michael reaction. Imine/enamine isomerization, as a result of thermodynamic equilibration between A and B, cannot be excluded. Comparison can be made with the stereochemical outcome of the glutarimide ring closure (**9** → **10**, Scheme 2) where the isomer ratio was found to be 72:28. Isomers with a trans configuration around the C15–C20 bond should be highly unfavorable and were indeed not observed.

What remains in the synthesis of nitrarine is the reduction of the C3–N4 iminium bonds in **17** and **18**. All of the 4 possible nitrarine isomers could be obtained, the ratios depending on the reduction method (see Tables 1 and 2). Reduction of nitramidine **17** with sodium borohydride produced nitrarine (**1**) as the main product, while

(14) Ibragimov, A. A.; Maekh, S. Kh.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1975**, 275; *Chem. Nat. Compounds* **1975**, *12*, 295.

Table 1. Reduction of Nitramidine 17

reagent	nitrarine (1)	isonitrarine (2)
sodium borohydride	85	15
zinc in HCl	40	60
L-Selectride	50	50
N-benzyldihydronicotinamide or Hantsch ester	no reaction	no reaction

Table 2. Reduction of 15,20-Epinitramidine 18

reagent	15,20-epinitrarine (3b)	3,15,20-epinitrarine (3a)
sodium borohydride	88	12
Zinc in HCl	>95	<5
L-Selectride	<5	>95
N-benzyldihydronicotinamide or Hantsch ester	no reaction	no reaction

zinc/aqueous HCl showed slight preference for isonitrarine (**2**).[15]

Reduction of the 15,20-isomer **18** is directed by much stronger steric effects. Hydrogen approach from the β-face of the molecule was possible using both zinc/HCl and sodium borohydride, leading to isomer **3b**. Reduction of **18** from the α-side produces the 3,15,20 isomer **3a**[16] of nitrarine, which shows strong hindrance between the β-carboline en piperidine part of the molecule, according to model studies. Release of this steric strain is expressed by its extremely easy autoxidation to form the starting material **18**, when exposed to air. Both the iminium salts **17** and **18** were surprisingly resistant towards reduction with NADH analogs. Stereochemical assignment of all compounds is based on ^1H–^1H-correlation and NOE spectroscopy. Direct comparison of spectra[17] was only possible with nitrarine, which was recently isolated from *Nitraria Billardieri* by Quirion.[18] Except for **3a**, all compounds have a *cis* quinolizidine ring junction[19] between the tetrahydro-β-carboline ring and the rest of the molecule, around the C3–N4 bond. The rigid stereochemistry of the azabicyclooctane ring system also forces the piperidine ring at the other side of the ring system (C15–C20 bond) into a boat conformation.

In summary, an efficient imine/enamine based synthesis of the nitrarine alkaloids has been accomplished, using a glutarimide system as a stable piperidine equivalent. The preparation of a common aldehyde precursor **4**, containing the proper oxidation state for the synthesis of all *Nitraria* di- and tripiperidine alkaloids[1] remains a target for synthetic efforts in the future.

Experimental Section

General Information. Infrared spectra were obtained from a Perkin-Elmer 1310 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained from Bruker AMX 300 (300 MHz) and Bruker ARX 400 (400 MHz) spectrophotometers. These machines were also used for ^{13}C NMR (APT) spectra at 75 resp. 100 MHz. Mass spectra were recorded on a VG Micromass ZAB-HFqQ instrument or on a

(15) The Zn/HCl reduction method for nitramidine was briefly reported as additional structural proof for natural isonitrarine: Ibragimov, A. A.; Maekh, S. Kh.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1975**, 276; *Chem. Nat. Compounds* **1975**, *12*, 298.

(16) Since we are dealing with racemic compounds, this 3,15,20 isomer is identical to the nitrarine 14,21 isomer.

(17) The NMR-spectra of the alkaloids obtained from Nitraria Schoberi were incomplete and described without detail. See ref. 3.

(18) We wish to thank dr. J.-C. Quirion for sending us NMR-spectra of nitrarine and several other Nitraria alkaloids.

(19) Rubiralta, M.; Giralt, E.; Diez, A.: *Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its derivatives*, Elsevier: Amsterdam, 1991.

JEOL JMS-SX/SX102A Tandem mass spectrometer. A resolving power of 10,000 (10% valley definition) for high resolution electron impact or FAB mass spectrometry was used. Thin layer chromatography (TLC) was performed on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}). Chromatography refers to flash chromatography, using Janssen Chimica silica gel (0.030–0.075 mm). When ammonia containing eluents were used, the silica gel was pretreated with this solvent.

4-[3-(2,6-Dioxopiperidyl)]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines (10a and 10b). A solution of aldehyde **8** (1.95 g, 10 mmol) in CH_2Cl_2 (120 mL, dest. from CaH_2) was treated with tryptamine (1.68 g, 10.5 mmol). The resulting solution was evaporated to a syrup in vacuo, with a bath temperature not exceeding 25 °C. This evaporation was repeated with addition of CH_2Cl_2 (2 × 50 mL). A vigorously stirred solution of this imine in CH_2Cl_2 (300 mL) at 0 °C was treated with TFA (10 mL), added in one portion. After allowing to stand overnight in the refrigerator the reaction mixture was quenched by pouring it into a stirred mixture of aqueous Na_2CO_3 and ether. The organic layer was washed with aqueous Na_2CO_3 and the aqueous layers were extracted twice with ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Crystallization from CH_2Cl_2 yielded isomer **10a** as an off-white solid (1.66 g). Isomer **10b** and additional **10a** could be isolated from the filtrate by flash chromatography (1% methanol in CH_2Cl_2) followed by crystallization from CH_2Cl_2. Total yield: 3.04 g (72%). Isomer ratio 72:28. **10a**: mp 178–184 °C, CH_2Cl_2-evolution at 138–140 °C; ^1H NMR ($CDCl_3$) δ 8.02 (br, 1H), 7.73 (s, 1H), 7.43 (m, 1H), 7.3–7.0 (m, 3H), 5.29 (s, 2H), 3.59–3.56 (m, J = 9.1 Hz, 1H), 3.47–3.44 (m, J = 11.3 Hz, 1H), 2.89–2.60 (m, 4H), 2.58–2.30 (m, 3H), 2.20–1.90 (m, 4H), 1.8–1.5 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 174.64, 173.14, 135.93, 135.05, 126.92, 121.01, 118.97, 117.79, 110.65, 107.21, 60.17, 58.77, 53.50, 47.11, 31.69, 30.93, 28.97, 24.15, 21.75, 17.72; IR ($CHCl_3$) 3475, 3375, 2740, 1720, 1700 cm^{-1}; HRMS obsd mass 337.1801, calcd for $C_{20}H_{23}N_3O_2$ 337.1790. Additional crystallographic data are available.

10b: mp 150–160 °C (with CH_2Cl_2-evolution); ^1H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.75 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.17–7.07 (m, 2H), 5.30 (s, 2H), 3.53 (bd, J = 8.9 Hz, 1H), 3.33 (m, 1H), 3.22–3.11 (m, 2H), 2.98–2.76 (m, 3H), 2.59–2.37 (m, 2H), 2.21–1.88 (m, 4H), 1.77–156 (m, 2H), 1.51–1.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.33, 172.89, 136.00, 135.10, 126.88, 121.13, 119.09, 117.83, 110.70, 107.37, 61.14, 61.06, 53.25, 46.94, 43.14, 31.69, 29.69, 26.33, 23.62, 22.07, 17.35; IR ($CHCl_3$) 3475, 3363, 2740, 1715, 1702 cm^{-1}; HRMS obsd mass 337.1782, calcd for $C_{20}H_{23}N_3O_2$ 337.1790. Anal. Calcd for $C_{20}H_{23}N_3O_2 \cdot CH_2Cl_2$: C, 59.72; H, 5.97; N, 9.95; Cl, 16.79. Found: C, 59.67; H, 5.90; N, 9.91; Cl, 16.69.

4-[3-Piperidinyl]-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizine (11). Glutarimide **10a** (CH_2Cl_2-complex, 0.211 g, 0.5 mmol) was evaporated twice with THF, dissolved in THF (3 mL) and refluxed with $LiAlH_4$ (0.076 g, 2 mmol) during 3 h. Excess reagent was destroyed with ethyl acetate and the reaction mixture was quenched with 1M NaOH. Extraction with ether, drying (Na_2SO_4) and evaporation of the solvents gave a syrup which crystallized during sonication in the presence of some ether. Filtration produced **11** (92 mg, 59%): mp 186–192 °C; ^1H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.46 (d, J = 6.7 Hz, 1H), 7.29–7.04 (m, 3H), 3.53–3.45 (m, 2H), 3.18 (m, J = 11.6 Hz, 1H), 3.05 (m, J = 11.8 Hz, 1H), 2.85–2.68 (m, 2H), 2.54 (ddd, J = 2.5, 12.0, 12.0 Hz, 1H), 2.5–2.3 (m, 3H), 2.05 (m, 1H), 1.94 (m, 1H), 1.8–1.3 (m, 9H); IR ($CDCl_3$) 3475, 1450 cm^{-1}; HRMS obsd mass 309.2221, calcd for $C_{20}H_{27}N_3$ 309.2205; fragment obsd mass 225.1387, calcd for $C_{15}H_{17}N_2$ 225.1392.

4-[3-(2-Oxopiperidinyl)]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (12). To a solution of glutarimide **10a** (0.84 g, 2 mmol) in a 1:1 mixture of CH_2Cl_2 and THF (40 mL) at −18 °C was added DiBAL-H (1 M in toluene, 6.2 mL) over a period of 1 h. The reaction was carefully quenched with MeOH, diluted with ether (50 mL), and stirred with semi-saturated aqueous potassium sodium tartrate during 2 h. The aqueous layer was made alkaline with K_2CO_3 and the organic layer was separated. After two extractions with ethyl acetate the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in a mixture of acetonitrile (10 mL) and acetic acid (3 mL), and stirred overnight with sodium cyanoborohydride (0.252 g, 4 mmol) at 50–55 °C. The solvents were evaporated in vacuo, the residue was treated with M NaOH and extracted with four portions ethyl acetate. Drying (Na_2SO_4), evaporation of solvents and crystallization from ethyl acetate (4 mL) yielded **12** as a white solid (0.37 g). Chromatography (MeOH/CH_2Cl_2) and crystallization of the filtrate gave a combined yield of **12** (0.46 g, 71%): mp 228–230.5 °C; ^1H NMR ($CDCl_3$) δ 7.80 (bs, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.30 (dd, J = 7.0, 1.0 Hz, 1H), 7.14–7.04 (m, 2H), 5.94 (bs, 1H), 3.47 (m, 2H), 3.37 (m, 2H), 2.9 (m, 2H), 2.6 (m, 1H), 2.43 (m, 1H), 2.2–1.5 (m, 11H); ^{13}C NMR ($CDCl_3$ + 2 drops of CD_3OD) δ 174.74, 136.07, 135.31, 127.02, 120.93, 118.91, 117.77, 110.76, 107.28, 60.66, 60.38, 47.27, 42.43, 42.19, 31.70, 29.40, 24.33, 22.50, 21.80, 20.44; IR (KBr) 3400, 3290, 3190, 2720, 1645 cm^{-1}; HRMS obsd mass 323.1994, calcd for $C_{20}H_{25}N_3O$ 323.1998; fragment obsd mass 225.1380, calcd for $C_{15}H_{17}N_2$ 225.1392. Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.35; H, 7.88; N, 12.94.

N-(*tert*-Butyloxycarbonyl)-4-[3-(*N*-(*tert*-butyloxycarbonyl)-1,4,5,6-tetrahydropyridyl)]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (13). Di-*tert*-butyl dicarbonate (0.69 mL, 3 mmol) was added dropwise to a stirred suspension of piperidone **12** (0.705 g, 2.18 mmol) and DMAP (0.244 g, 2 mmol) in dry CH_2Cl_2 (10 mL). After stirring overnight at room temperature, additional di-*tert*-butyl dicarbonate (1.38 mL, 6 mmol) and DMAP (0.122 g, 1 mmol) was added and the reaction mixture was refluxed during 48 h. The solution was diluted with PE 60/80 and directly purified by flash chromatgraphy using PE/EtOAc/triethyl amine 90/10/2 as eluent, yielding di-*tert*-butyloxycarbonyl protected **12** as a white foam (0.96 g, 84%). This product was not further analyzed, but directly reduced with $NaBH_4$ (0.38 g, 10 mmol) in dry MeOH at 0 °C during 2 h. The solution was concentrated in vacuo and the residue treated with dilute aqueous K_2CO_3 and extracted three times with diethyl ether. The organic layer was washed with aqueous K_2CO_3, dried over Na_2SO_4, concentrated in vacuo and the resulting syrup was coevaporated with toluene (10 mL). A solution of this mixture of isomeric alcohols in toluene (20 mL) containing pyridinium trifluoroacetate (0.1 g) was refluxed during 5 min. Evaporation and crystallization from EtOH gave **13** as white crystals (0.45 g). Chromatography of the filtrate gave a combined yield of **13** (0.55g, 50%): mp 194–195.5 °C; ^1H NMR at 55 °C ($CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 1H), 7.37 (dd, J = 1.3, 7.8 Hz, 1H), 7.25–7.17 (m, 2H), 6.8 (broad, 1H), 4.2 (bd, J = 9.9 Hz, 1H), 3.66 (bm, 1H), 3.44 (m, 1H), 3.21 (bd, J = 8.7 Hz, 1H), 3.01 (m, 1H), 2.70 (m, 1H), 2.65–2.53 (m, 2H), 2.20 (m, 1H), 2.06 (m, 2H), 1.93–1.40 (m, 8H), 1.67 (s, 9H), 1.52 (s, 1H); ^{13}C NMR at 55 °C ($CDCl_3$) δ 150.34, 138.04, 136.97, 129.40, 123.62, 122.44, 117.70, 116.58, 115.42, 83.34, 80.36, 66.84, 60.27, 28.36, 28.23, 24.94, 22.70, 22.51, 21.81; IR ($CHCl_3$) 1715, 1680, 1660 cm^{-1}; HRMS obsd mass 507.3114, calcd for $C_{30}H_{41}N_3O_4$ 507.3097.

Deprotection of 13. Acid/Base Equilibrium between 15 and 16. A suspension of **13** (25 mg, 0.05 mmol) in concentrated HCl (0.5 mL) was sonicated during 3 h, diluted with ethanol and evaporated to dryness. The residue was coevaporated three times with ethanol, leaving **16** as a glass (one isomer according to NMR, 100%). Ring closure of **16** was performed in aqueous K_2CO_3 followed by CH_2Cl_2 extraction, leaving **15** as a glass (80%). This compound could not be crystallized and was only moderately stable when exposed to air. Addition of aqueous HCl again produced **16** (NMR). **15**: ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.12–7.04 (m, 2H), 6.13 (s, 1H), 3.46–3.42 (m, 1H), 3.31 (m, J = 8.6 Hz, 1H), 3.1–3.05 (m, 2H), 2.9–2.82 (m, 1H), 2.71–2.66 (m, 1H), 2.57 (dd, J = 11.1 Hz, J = 2.5 Hz, 1H), 2.15–1.15 (m, 11H); **16**: ^1H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.32–7.28 (m, 1H), 7.23–7.19 (m, 1H), 6.95–6.91 (m, J = 7.3 Hz, 1H), 4.76–4.73 (m, 1H), 3.78–3.73 (m, 1H), 3.66–3.63 (m,

2H), 3.49–3.42 (m, 1H), 3.14–3.05 (m, 2H), 2.57–2.51 (m, 4H), 2.29 (ddd, J = 14.5, 10.8, 6.9 Hz, 1H), 2.15–1.70 (m, 5H).

4-[3-(*N*-(*tert*-Butyloxycarbonyl)-1,4,5,6-tetrahydropyridyl)]-1,2,3,4,6,7,12,12b-octahydroindolo[2, 3-*a*]quinolizine (14). A solution of **13** (0.1 g, 0.20 mmol) in CH_2Cl_2 (5 mL) was evaporated to a glass in vacuo, and immersed in a preheated oil bath of 195 °C. The reaction mixture was kept at this temperature for 10 min, during which time gas evolution occurred. Too long reaction times and temperatures of 200 °C and higher results in fragmentation of the product. Chromatographic separation of starting material (12 mg, 12%) and crystallization from MeOH yielded **14** as a white solid (47 mg, 70% based on recovered starting material): mp 214.5–216.5 °C; ^{1}H NMR at 55 °C($CDCl_3$) δ 7.67 (bs, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 7.13–7.05 (m, 2H), 7.0–6.65 (b, 1H), 3.69 (bm, 1H), 3.44–3.36 (m, 2H), 3.27 (dd, J = 11.6, 5.1 Hz, 1H), 3.9–3.75 (m, 1H), 2.67 (m, J_{AB} = 15.3 Hz, 1H), 2.3–1.5 (m, 11H), 1.52 (s, 9H); ^{13}C NMR at 55 °C ($CDCl_3$) δ 136.17, 135.79, 127.59, 122.55, 121.13, 119.29, 117.99, 110.60, 108.86, 80.42, 68.38, 60.47, 49.35, 31.88 (br), 29.99, 28.37, 24.10, 22.21, 21.81; IR ($CHCl_3$) 3470, 1680, 1660 cm^{-1}; HRMS obsd mass 407.2542, calcd for $C_{25}H_{33}N_3O_2$ 407.2573. Anal. Calcd for $C_{25}H_{33}N_3O_2$: C, 73.68; H, 8.16; N, 10.32. Found: C, 73.72; H, 7.84; N, 10.35.

Nitramidine (17) and 15,20-Epinitramidine (18). A suspension of **14** (24 mg, 0.059 mmol) in ethanol (1.2 mL) was treated with 0.1 M aqueous $Hg(OAc)_2$·EDTA[12] (1.8 mL, 0.18 mmol). Nitrogen gas was bubbled into the solution during 10 min and the reaction mixture was heated at 70 °C (bath temperature) during 30 min. After cooling to room temperature aqueous K_2CO_3 (1 mL) and ethyl acetate (3 mL) were added under a N_2 atmosphere, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were filtrated over anhydrous K_2CO_3, diluted with an equal volume of hexane and extracted with 6% HCl (4 × 1 mL). The combined aqueous HCl layers were heated at 80–85 °C (bath temperature) under N_2 during 3 h. Evaporation of the solvent, addition of aqueous K_2CO_3 and CH_2Cl_2 extraction yielded a 38:62 mixture of the yellow, zwitterionic **17** and **18**. This mixture was separated by chromatography using as eluent a mixture of CH_2Cl_2/MeOH/concd NH_4OH 75/25/2.5 and as stationary phase silica gel, pretreated with eluent. After evaporation of the solvents, the zwitterionic compounds were dissolved in ethanol and converted to their di-HCl salts by acidification with conc. HCl. Coevaporation with ethanol (three times) yielded pure products. NMR-samples in D_2O were coevaporated with D_2O (0.5 mL) before recording.

Nitramidine·2HCl (17): mp 244–248 °C (EtOH/diethyl ether); ^{1}H NMR (D_2O) δ 7.76 (d, J = 8.2, 1H), 7.58–7.52 (m, 2 H), 7.27 (ddd, J = 1.3, 6.5, 8.2 Hz, 1H), 4.42–4.40 (m, 1H), 4.29 (t, 1H, J = 9.2 Hz, 2H), 4.10–4.09 (m, 1H), 3.74 (ddd, J = 10.7, 3.3, 1.3 Hz, 1H), 3.58–3.50 (m, 1H), 3.43 (t, J = 9.3 Hz, 2H), 3.29–3.22 (m, 1H), 2.65–2.57 (m, 1H), 2.38–2.27 (m, 2H), 2.21–2.12 (m, 1H), 2.06–1.79 (m, 4 H), 1.60 (dq, J = 4.9, 13.7 Hz, 1H); ^{13}C NMR (D_2O) δ 144.52, 132.43, 128.28, 127.28, 126.40, 124.88, 124.64, 116.18, 63.86, 53.86, 52.26, 43.27, 37.60, 37.58, 22.45, 22.17, 20.02, 19.41.

15,20-Epinitramidine·2HCl (18): glass; ^{1}H NMR (D_2O) δ 7.78 (d, J = 8.3 Hz, 1H), 7.77–7.52 (m, 2H), 7.30–7.26 (m, 1H), 4.40–4.39 (m, 1H), 4.38–4.2 (m, 2H), 4.09 (dd, J = 10.1, 2.4 Hz, 1H), 4.07–4.05 (m, 1H), 3.50–3.43 (m, 2H), 3.29 (ddd, J = 13.2, 10.7, 4.7 Hz, 1H), 3.12 (ddd, J = 13.2, 10.1, 6.4 Hz, 1H), 2.81–2.72 (m, 1H), 2.34–2.26 (m, 1H), 2.16–1.80 (m, 6H), 1.39–1.27 (dq, J = 6.1, 13.7 Hz, 1H); ^{13}C NMR (D_2O) δ 168.42, 144.83, 132.72, 128.70, 127.51, 127.33, 125.04, 124.75, 116.25, 65.44, 56.75, 53.70, 42.73, 39.77, 38.73, 27.52, 25.23, 21.95, 20.94, 18.81; HRMS (FAB) obsd mass 306.1838, calcd for $C_{20}H_{24}N_3$ 306.1970.

Reduction of Nitramidine with $NaBH_4$: Nitrarine (1) and Isonitrarine (2). A solution of nitramidine·2HCl (**17**, 19 mg, 0.05 mmol) in ethanol at 0 °C was treated with $NaBH_4$ (8 mg, 0.2 mmol). The rapidly decolorizing solution was stirred at room temperature during 1 h, concentrated in vacuo, and stirred with 1M NaOH. The mixture was extracted with CH_2Cl_2 and dried (1:1 mixture of K_2CO_3 and Na_2SO_4), and the solvents were evaporated, yielding a solid mixture of **1** and **2**. Separation was performed by chromatography using CH_2Cl_2/MeOH/concd NH_4OH 90/10/1 as eluent and silica gel, pretreated with eluent as stationary phase.

Nitrarine (1) ([4α*R*-(4aα,5β,13bα,14β,14aα)]-1,2,3,4,4a,-5,7,8,13,13b,14,14a-dodecahydro-5,14-ethanoindolo[2′,3′:3,4]pyrido[1,2-*g*]-1,6-naphthyridine): solid, mp 210–214 and 228–232 °C dec; ^{1}H NMR ($CDCl_3$ + 1 dr. CD_3OD)[20] δ 7.47 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.13–7.03 (m, 2H), 4.47 (bs, 1H), 3.23–3.11 (m, 3 H), 3.09–3.02 (m, J = 13.4, 10.1 Hz, 1H), 2.91–2.80 (m, 2H), 2.72–2.68 (m, J = 15 Hz, 1H), 2.25–2.1 (m, 1H), 2.06 (bs, 1H), 1.82–1.72 (m, 2H), 1.65–1.3 (m, 5H), 1.26–1.17 (m, 1H); EI-MS 307 (100), 224 (M - piperideine, 48), 223 (53), 169 (52), 144 (58), 83 (59); HRMS (EI) obsd mass 307.2088, calcd for $C_{20}H_{25}N_3$ 307.2048; fragment obsd mass 223.1220, calcd for $C_{15}H_{15}N_2$ 223.1235.

Nitrarine·2HCl: NMR-samples in D_2O were coevaporated with D_2O (0.5 mL) before recording; ^{1}H NMR (D_2O) δ 7.69 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.33–7.31 (m, 1H), 7.26–7.24 (m, 1H), 5.06 (bs, 1H), 4.00–3.97 (m, 1H), 3.81–3.80 (bs, 1H), 3.72–3.65 (m, 2H), 3.53–3.27 (m, 3H), 3.07–3.00 (m, 1H), 2.96 (bs, 1H), 2.86–2.79 (m, 1H), 2.26–1.79 (m, 6H), 1.71–1.57 (m, 2H); ^{13}C NMR (D_2O) δ 139.31, 129.01, 128.04, 125.78, 122.79, 121.15, 114.52, 112.33, 59.79, 58.00, 54.82, 51.13, 43.27, 36.33, 33.90, 20.65, 19.96, 19.41, 16.82, 14.19.

Isonitrarine (2): ^{1}H NMR ($CDCl_3$) δ 8.24 (bs, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.18–7.09 (m, 2H), 4.61 (bs, 1H), 3.29–3.25 (m, 2H), 2.99–2.85 (m, 1H), 2.83–2.78 (m, 1H), 2.70–2.54 (m, 4 H), 2.26 (bs, 1H), 2.1–1.81 (m, 5 H), 1.66–1.60 (m, 1H), 1.43–1.21 (m, 3H); HRMS (EI) obsd mass 307.2032, calcd for $C_{20}H_{25}N_3$ 307.2048; fragments obsd mass 223.1246 (31), calcd for $C_{15}H_{15}N_2$ 223.1235.

Isonitrarine·2HCl: ^{1}H NMR (D_2O) δ 7.68 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.34 (m, 1H), 7.25 (m, 1H), 5.24 (bs, 1H), 3.82 (bs, 1H), 3.82–3.75 (m, 1H), 3.70–3.64 (m, 1H), 3.37–3.25 (m, 2H), 3.23–3.20 (m, J = 10.9, 3.4 Hz, 1H), 3.16–3.09 (m, 1H), 3.03–2.95 (m, 1H), 2.95 (bs, 1H), 2.71–2.64 (m, 1H), 2.27–2.06 (m, 4H), 2.02–1.95 (m, 1H), 1.85–1.79 (m, 1H), 1.68–1.47 (m, 2H); ^{13}C NMR (D_2O) δ 139.48, 128.80, 128.00, 126.07, 122.98, 121.34, 114.59, 111.07, 60.90, 59.47, 52.05, 51.80, 42.81, 34.11, 32.18, 21.49, 20.06, 19.78, 19.23, 18.98.

Reduction of Isonitramidine (18) with $NaBH_4$. The procedure described for the reduction of nitramidine (**17**) was used. Total yield: 95% (see Table 2).

15,20-Epinitrarine (3b): solid; mp 210–214 °C and >220 °C dec; 1H NMR ($CDCl_3$) δ 8.07 (bs, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.15–6.99 (m, 2H), 4.62 (bs, 1H), 3.25–3.05 (m, 3H), 2.97–2.88 (m, 2H), 2.84–2.77 (m, 1H), 2.63–2.58 (m, J = 13.8 Hz, 1H), 2.41 (bs, 1H), 2.30–2.25 (m, 1H), 1.9–1.32 (m, 8H), 1.28–1.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.93, 135.68, 127.65, 121.19, 119.07, 117.67, 110.75, 110.14, 57.33, 54.77, 50.18, 50.16, 42.00, 39.92, 34.74, 27.25, 20.80, 20.39, 19.88, 19.76; HRMS (EI) obsd mass 307.2055, calcd for $C_{20}H_{25}N_3$ 307.2048; fragments obsd mass 223.1221 (53), calcd for $C_{15}H_{15}N_2$ 223.1235.

15,20-Epinitrarine·2HCl: ^{1}H NMR (D_2O) δ 7.68 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 5.30 (bs, 1H), 4.00–3.97 (m, J = 10.8 Hz, 1H), 3.88 (bs, 1H), 3.73–3.6 (m, 2H), 3.54 (ddd, J = 13.3, 10.1, 3.0 Hz, 1H), 3.27–3.21 (m, 2H), 3.1–2.98 M, 1H), 2.85 (bs, 1H), 2.78–2.68 (m, 1H), 2.43–2.33 (m 1H), 2.26–2.15 (m, 1H), 2.10–1.70 (m, 6H); 13C NMR (D_2O) d 139.35, 128.43, 128.04, 125.79, 122.81, 121.09, 114.55, 112.60, 59.41, 55.48, 53.67, 51.42, 42.50, 37.36, 34.67, 21.85, 20.83, 20.39, 19.52, 19.05.

3,15,20-Epinitrarine (3a): glass; ^{1}H NMR ($CDCl_3$) δ 8.58 (bs, 1H), 7.44 (d, J = 7.0, Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.13–7.06 (m, 2H), 3.87 (bs, 1H), 3.07–3.00 (m, 2H), 2.95–2.92 (m, 1H), 2.76–2.68 (m, 2H), 2.65 (bs, 1H), 2.53 (bs, 1H), 2.0–1.2 (m, 12 H); HRMS obsd 307.2037, calcd for $C_{20}H_{25}N_3$ 307.2048.

(20) Nitrarine is insoluble in $CDCl_3$. Since protic solvents cause shifting of several important protons, ^{1}H NMR spectra are preferably taken from the di-HCl salts in D_2O.

3,15,20-Epinitrarine·2HCl is slowly oxidized to **18** during spectroscopy, even though an argon atmosphere was present: ^{1}H NMR (D_2O) δ 7.68 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.35 (m, 1H), 7.25 (m, 1H), 5.01 (bs, 1H), 3.93–3.89 (m, J = 3.2,11.5 Hz, 1H), 3.80–3.90 (m, 2H), 3.73–3.60 (m, 1H), 3.28–3.25 (m, J = 11.5 Hz, 1H), 3.17–3.08 (m, 2H), 3.09 (bs, 1H), 2.69–2.62 (m, 1H), 2.3–1.8 (m, 6 H), 1.75–1.70 (m, 2H); ^{13}C NMR (D_2O) d 139.80, 127.36, 126.13, 64.30, 59.75, 52.44, 45.00, 36.80, 32.90, 30.60, 26.45, 25.76, 22.68, 21.54, 20.27.

Zinc/HCl Reductions with 17 and 18. Zinc powder (excess) was added in portions to a stirred solution of **17** or **18** in 6% aqueous HCl. After disappearance of the yellow colour, stirring was continued during half an hour, and the reaction mixture was worked up with K_2CO_3/DCM and purified by chromatography as described before. The yields were ca 90% for both isomers (see Tables 1 and 2).

L-Selectride Reduction of Iminium Salt 17. L-Selectride (1 M in THF, 2 equiv) was added to a vigorous stirred suspension of iminium salt **17** in THF at 0 °C. After 30 min at this temperature the reaction was quenched with water. Workup and chromatography yielded a 1:1 mixture of isomers in 90% yield (see Table 1).

L-Selectride Reduction of Iminium Salt 18. L-Selectride (1 M in THF, 5 equiv) was added to a vigorous stirred suspension of iminium salt **17** in THF at 0 °C. After stirring at room temperature during 3 h about 50% of starting material remained unchanged and was recovered by chromatography. Partially deprotonation of the indolic N-H deactivates the iminiumsalt towards reduction. After workup as described before, isomer **3a** was obtained in 90% yield, based on recovered **18**.

Supplementary Material Available: Copies of the ^{1}H NMR spectra of compounds **1**, **2**, **3a**, **3b**, **17**, and **18** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.