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

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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 Komarovi form a relatively unexplored group of alkaloids, possessing pharmacologically interesting properties. Although several publications 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 structural proof available for the new, azatryptcene ring system of nitrarine and its isomers, has initiated our synthesis based on biosynthetic considerations.

Scheme 1

Bio-synthesis. Most of the known indole alkaloids are biosynthetically derived from diterpenes, although after several rearrangements, the original secolignan branching is often difficult to recognize. The Nitraria indole alkaloids possess the same number of carbon atoms: tryptamine plus a C10 fragment, in many instances a yohimbine skeleton was incorrectly assigned to these alkaloids. The carbon skeleton of the nitrarine family is more likely originated from two dehydr~piperidine units, 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 biopre-cursor for alkaloid synthesis in lupine species and can be transformed into aldehyde 5 in two steps. From this hypothetical intermediate 4 the azacyclooctane ring system of nitrarine (1) can be formed via simple, probably 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. 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 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 was added to a preformed solution of the imine in dichloromethane, providing a 72:28 mixture of 5 and 8.


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The initially formed Pictet–Spengler product isomer probably is not a stereoselective process and a mixture cyclization. Protonation of the Michael adduct anion were isolated separately as their crystalline 1:1 complexes with dichloromethane or chloroform the glutarimides could not be isolated since workup of the reaction mixture with Na₂CO₃-workup the next steps of the synthesis, both isomers are suitable for the subsequent conversions leading to compound 10a. However, this led to fragmentation and oxidation. We therefore returned to di-t-Boc protected enamine 10a, and first selectively removed the indole t-Boc-substituent by a carefully controlled thermal deprotection method, 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.

As shown in Scheme 3, reduction of 10a with LiAlH₄ 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 DiBAI-H; whereas reducing agents such as Selectride or NaBH₄ 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 susceptibility 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-butylocarbonyl)lactams. 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, 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.

Mercuric acetate/EDTA catalyzed oxidation of the C1–N bond in 15/16 to an imine 4 was attempted. With dilute aqueous HCl, the amide t-BOC group could be removed selectively.

![Scheme 2](image1)

![Scheme 3](image2)

![Scheme 4](image3)

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(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.


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


Synthesis of Nitrarine, Nitramidine, and Isomers

Scheme 5

14

1. Hg(OAc)_2·EDTA
2. HCl, H_2O, 80°C

85%

4

B

17: Nitramidine

18: 15,20-epinitramidine

Isomer ratio: 17:18 = 38:62

[H]

see Table 1

<table>
<thead>
<tr>
<th>reagent</th>
<th>nitrarine (1)</th>
<th>isonitrarine (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium borohydride</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>zinc in HCl</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>N-benzylhydronicotiamide</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
<tr>
<td>or Hantsch ester</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Reduction of 15,20-epinitramidine 18

<table>
<thead>
<tr>
<th>reagent</th>
<th>15,20-epinitrarine (3b)</th>
<th>3,15,20-epinitrarine (3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium borohydride</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>Zinc in HCl</td>
<td>&gt;95</td>
<td>&lt;5</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>&lt;5</td>
<td>&gt;95</td>
</tr>
<tr>
<td>N-benzylhydronicotiamide</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
<tr>
<td>or Hantsch ester</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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. Stereoc hemical 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 stereoch emistry 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 nitranine 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 13C NMR (APT) spectra at 75 resp. 100 MHz. Mass spectra were recorded on a VG Micromass ZAB-HPqQ instrument or on a

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^{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. 9.

^{18} We wish to thank dr. J.-C. Quirion for sending us NMR-spectra of nitrarine and several other *Nitraria* alkaloids.

JEOL JMS-SX5102A 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 F254). Chromatography refers to flash chromatography, using Jansen Chimica silica gel (0.030–0.075 mm). When ammonia containing eluents were used, the silica gel was pretreated with this solvent.

4-[2,6-Dioxopiperidyl]-1,2,3,4,6,7,12-diboc-tahydrindolo[2,3-a]quinolizine (10a and 10b). A solution of aldehyde 8 (1.95 g, 10 mmol) in CH2Cl2 (120 mL, dest. from CaH2) was treated with triptamine (1.68 g, 10.5 mmol). The reaction mixture was warmed up to 50 °C, poured to a second mixture of bath temperature not exceeding 25 °C. This evaporation was repeated with addition of CH2Cl2 (2 × 50 mL). This vigorously stirred solution of this imine in CH2Cl2 (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 Na2CO3 and the aqueous layers were extracted three times with addition of CH2Cl2 (2 × 10 mL), filtered and concentrated. Crystallization from CH2Cl2 (CDCl3) δ 174.64, 173.14, 135.93, 135.05, 126.92, 121.01, 118.97, 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, calculated for C30H41N30: 323.1995. Crystallized and was only moderately stable when exposed to air. Addition of aqueous HCl again produced 12 as a white solid (0.55 g, 50%). Found: C, 74.35; H, 7.88; N, 12.94.

N-(tert-Butylxycarbonyl)-4-[3-(tert-butylxocarbonyl)-1,2,3,4,6,7,12-diboc-tahydrindolo[2,3-a]quinolizine (13). Di-tert-butyl carbonate (0.69 mL, 3 mmol) was added dropwise to a stirred suspension of piperidine 12 (0.705 g, 2.18 mmol) and DMAP (0.055 g, 0.50 mmol) in CH2Cl2 (10 mL). After stirring overnight at room temperature, addition of di-tert-butyl carbonate (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 chromatography using PE/EtOAc/triethylamine 90/10/2 as eluent, yielding di-tert-butylxocarbonyl protected 12 as a white foam (0.96 g, 84%). This product was not further analyzed, but directly used with NMR data for 12, found: C, 71.80; H, 7.79; N, 12.99.

Synthesis of Nitrarine, Nitramidine, and Isomers

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), 1.30–1.27 (m, 1H).

4-(N-(Tert-Butylxycarbonyl)-1,4,5,6-tetrahydro-pyridyl)-1,2,3,4,6,7,12b-octahydropyridolo[2,3-a]quinolizine (14). A solution of 13 (0.1 g, 0.20 mmol) in CHCl₃ (5 mL) was evaporated to a glass in vacuo, and immersed in a pre-heated oil bath at 195 °C. The reaction mixture was stirred 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 214.5–215.5 °C; H NMR at 55 °C (CDCl₃) δ 7.67 (bs, 1H), 7.44 (d, J = 7.2, 1H), 7.33 (d, J = 8 Hz, 1H), 4.55–4.29 (m, 3H), 3.81–3.65 (m, 2H), 3.52–3.45 (m, 1H), 2.84–2.66 (m, 2H), 2.67 (bs, J = 15.3 Hz, 1H), 2.13–1.6 (m, 11H), 0.96–0.88 (m, 2H); IR (KBr) 3470, 1680, 1660 cm⁻¹; HRMS obsd mass 387.2048, calcd for C₂₁H₂₁N₃O₂ 387.2044.

(20) Nitrarine is insoluble in CDCl₃. Since protic solvents cause shifting of several important protons. H NMR spectra are preferably taken from the di-HCl salts in D₂O.
3,15,20-Epinitrarine$\text{HCl}$ is slowly oxidized to 18 during spectroscopy, even though an argon atmosphere was present: $^1$H NMR (D$_2$O) $\delta$ 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$_2$O) $\delta$ 139.80, 127.36, 126.13, 64.30, 59.75, 52.44, 46.00, 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$_2$CO$_3$/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 iminium salt 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.