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A SYNTHESIS OF (±)-DIHYDRONITRARAINE

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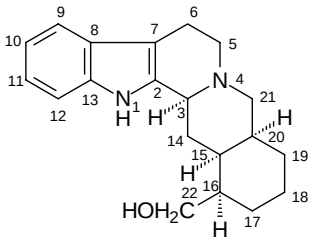
Abstract - A short synthesis of (±)-dihydronitraraine (**1**) from an unknown 5,6,7,8-tetrahydroisoquinoline ester (**3**) is presented. The Fry reaction of tetrahydroisoquinolinium salt (**4**), followed by cyclization and hydrogenation, gave an alloyohimbane derivative (**6**), which was reduced to yield dihydronitraraine (**1**). Complete ^{1}H NMR and ^{13}C NMR data of dihydronitraraine (**1**) and intermediate (**6**) are reported.

INTRODUCTION

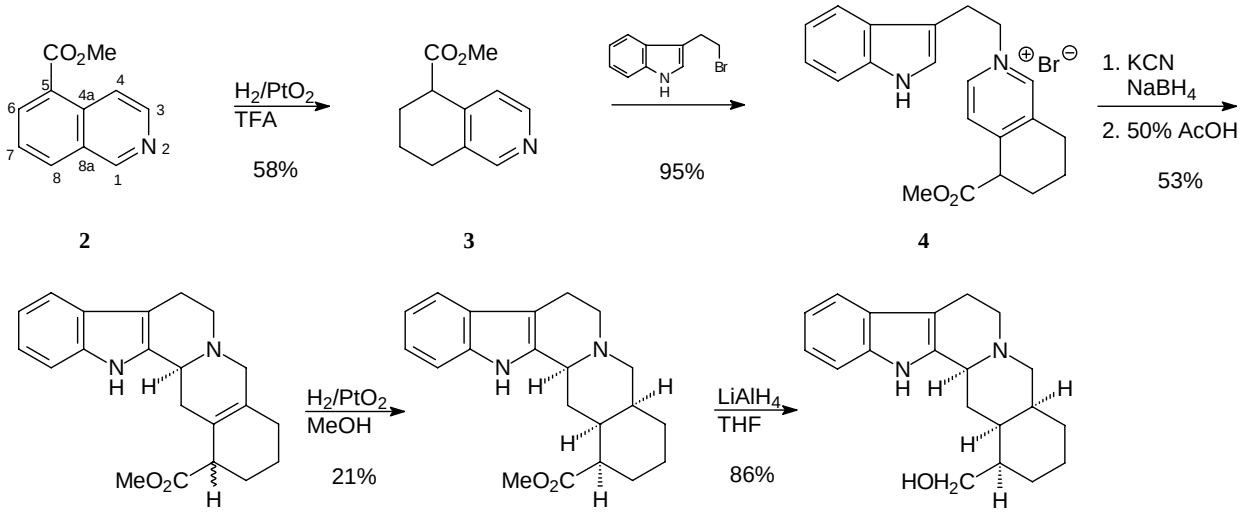
Due to their wide range of pharmacological properties, the development of syntheses of yohimbane alkaloids has gained considerable attention during the last few decades.[1] A racemic α-yohimbane alkaloid dihydronitraraine (**1**) with a hydroxymethyl group at C-16[2] and lacking the hydroxyl at C-17 was isolated from the epigeal part of *Nitraria schoberi* in 1985.[3] Direct spectroscopic evidence for the unusual yohimbane structure (**1**) was not, however, given. To our knowledge, only one synthesis of dihydronitraraine has been published so far.[4] Here we present a new synthesis of dihydronitraraine from the isoquinoline derivative (**2**) (Scheme 1). Selective hydrogenation of the benzene ring of compound (**2**) was a prerequisite for our synthetic plan.



RESULTS AND DISCUSSION

Isoquinoline derivative (**2**), prepared from 5-cyanoisoquinoline[5] in two steps, was chosen as the starting compound for the synthesis of dihydronitraraine. As far as we know, hydrogenation of the benzene moiety of isoquinolines containing electron-withdrawing substituents on the benzene ring has not been previously reported. No problems were encountered, however, as compound (**2**) was hydrogenated catalytically under strongly acidic conditions[6] to yield the unknown 5,6,7,8-tetrahydroisoquinoline ester (**3**) (Scheme 1).

The short synthetic method used for the yohimbane skeleton in our laboratory[7] was then applied in the synthesis of dihydronitraraine. Alkylation of tetrahydroisoquinoline derivative (**3**) with tryptophyl bromide yielded tetrahydroisoquinolinium salt (**4**). The Fry[8] reaction of salt **(4**) followed by immediate acid-induced cyclization led to an inseparable mixture (**5a**) and (**5b**) (1:1) of epimers.



2 **3** **4**

5a: H-16 α
5b: H-16 β

6 **1**

Scheme 1.

Catalytic hydrogenation of the pair (**5a**) and (**5b**) of epimers gave ester (**6**), which was isolated in 21% yield in addition to unreacted starting material. Comparing the ^{1}H NMR spectra of unreacted **5a** and **5b** and the starting **5a** and **5b**, we concluded that only the less hindered epimer (**5a**) was reduced. Finally, reducing compound (**6**), the yield of which can be improved by recycling and epimerization, gave dihydronitraraine (**1**) in 86% yield.

The complete spectral data of dihydronitraraine (**1**) have not been published, although some signals of the ^{1}H NMR spectrum measured in TFA-*d* are given in the original paper of Ibragimov and Yunusov.[2] ^{1}H NMR data of compounds (**1**) and (**6**) in $CDCl_3$, confirmed by 2D NMR and in full agreement with the presented structures, are given in Table 1. The ^{13}C NMR data of compounds (**1**) and (**6**) are presented in Chart 1.

Table 1. ^{1}H NMR data of compounds (**1**) and (**6**).

Proton	**1**	**6**
H-3	3.13 br d	3.19 dd
H-5α	2.5 def	2.5 def
H-5β	2.95 ddd	2.96 ddd
H-6α	2.67 ddd	2.68 ddd
H-6β	2.93 dddd	2.95 dddd
H-9	7.45 d	7.45 d
H-10	7.06 dd	7.07 dd
H-11	7.11 dd	7.12 dd
H-12	7.29 d	7.28 d
H-14α	1.78 ddd	1.62 ddd
H-14β	1.66 ddd	1.81 ddd
H-15	2.14 dddd	2.38 dddd
H-16	1.8 m	2.58 ddd
H-17α	1.41 br d	1.7 br d
H-17β	1.06 dddd	1.53 dddd
H-18α	1.31 ddddd	1.29 ddddd
H-18β	1.8 m	1.8 m
H-19α	1.44 br dd	1.43 br dd
H-19β	1.95 dddd	1.96 dddd
H-20	1.68 br d	1.72 br dd
H-21α	2.55 dd	2.58 dd
H-21β	2.80 dd	2.82 dd
H-22	3.60 d	-
-NH	7.97 br s	7.82 br s
-CO_2Me	-	3.76 s

Coupling constants:

Compound (**1**): $J_{3,6\beta}$ = 2.5; $J_{3,14\alpha}$ = 3; $J_{3,14\beta}$ = 11; $J_{5\alpha,5\beta}$ ≈12; $J_{5\alpha,6\alpha}$ = 4; $J_{5\alpha,6\beta}$ = 11; $J_{5\beta,6\alpha}$ = 1.5; $J_{5\beta,6\beta}$ = 6; $J_{6\alpha,6\beta}$ = 16; $J_{9,10}$ = 8; $J_{10,11}$ = 8; $J_{11,12}$ = 8; $J_{14\alpha,14\beta}$ = 12; $J_{14\alpha,15}$ = 4; $J_{14\beta,15}$ = 12; $J_{15,16}$ = 4; $J_{15,20}$ = 3, $J_{16,17\beta}$ = 13; $J_{16,22}$ = 7; $J_{17\alpha,17\beta}$= 13; $J_{17\alpha,18\alpha}$= 4; $J_{17\beta,18\alpha}$= 12; $J_{17\beta,18\beta}$= 2; $J_{18\alpha,18\beta}$= 13; $J_{18\alpha,19\alpha}$ = 4; $J_{18\alpha,19\beta}$ = 13; $J_{19\alpha,19\beta}$ = 13; $J_{19\beta,20}$ = 13; $J_{20,21\alpha}$= 3; $J_{20,21\beta}$ = 2; $J_{21\alpha,21\beta}$ = 11.5.

Compound (**6**): $J_{3,6\beta}$ = 2.5; $J_{3,14\alpha}$ = 3; $J_{3,14\beta}$ = 11; $J_{5\alpha,5\beta}$ ≈12; $J_{5\alpha,6\alpha}$ = 4; $J_{5\alpha,6\beta}$ = 11; $J_{5\beta,6\alpha}$ = 1.5; $J_{5\beta,6\beta}$ = 6; $J_{6\alpha,6\beta}$ = 16; $J_{9,10}$ = 8; $J_{10,11}$ = 8; $J_{11,12}$ = 8; $J_{14\alpha,14\beta}$ = 12; $J_{14\alpha,15}$ = 4; $J_{14\beta,15}$ = 12; $J_{15,16}$ = 4; $J_{15,20}$ = 3, $J_{16,17\alpha}$ = 4; $J_{16,17\beta}$ = 13; $J_{17\alpha,17\beta}$= 13; $J_{17\alpha,18\alpha}$= 4; $J_{17\beta,18\alpha}$= 12; $J_{17\beta,18\beta}$= 2; $J_{18\alpha,18\beta}$= 13; $J_{18\alpha,19\alpha}$ = 4; $J_{18\alpha,19\beta}$ = 13; $J_{19\alpha,19\beta}$ = 13; $J_{19\beta,20}$ = 13; $J_{20,21\alpha}$= 3; $J_{20,21\beta}$ = 2; $J_{21\alpha,21\beta}$ = 11.5.

CONCLUSIONS

The key step in our synthesis of dihydronitraraine (**1**) was selective hydrogenation of the benzene moiety of compound (**2**) to afford the novel 5,6,7,8-tetrahydroisoquinoline (**3**). Compound (**3**) was transformed to the mixture (**5a**) and (**5b**) of epimers (50% yield for three steps). Ester (**6**), the direct precursor for **1**, was then obtained stereoselectively by hydrogenation of this epimeric mixture. The efficiency of this process can be further improved by recycling. Application of 2D NMR techniques permitted all the ^{1}H and ^{13}C NMR chemical shifts of compounds (**1**) and (**6**) to be determined reliably.

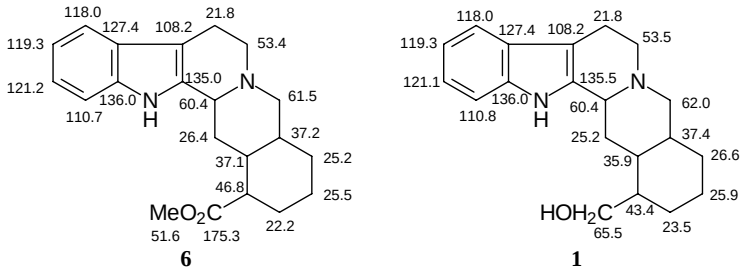


Chart 1. ^{13}C NMR data of compounds (**1**) and (**6**) measured in $CDCl_3$.

EXPERIMENTAL

All reactions were carried out under argon. THF was distilled over sodium and benzophenone. Melting points were determined with Fisher Johns melting point apparatus and are uncorrected. IR spectra (cm^{-1}, KBr) were recorded with Nicolet Magna-IR 750 and Perkin-Elmer 700 IR spectrophotometers. ^{1}H NMR (399.990 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100.587 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded with a Varian Unity 400 spectrometer with $CDCl_3$ as a solvent, unless otherwise noted. Coupling constants (J) are given in Hz. Signal assignments were confirmed by APT, DEPT, DQF-COSY, NOESY and HETCOR experiments. The abbreviations s, d, t, q, m, def and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed and broad, respectively. MS spectrometric determinations (EIMS and HRMS) were made with a Jeol DX 303/DA 5000 mass spectrometer. Elementary analyses were performed with a Perkin Elmer 2400 CHN Elemental Analyzer. Merck Kieselgel 60 (234-400 mesh) was used in column chromatography.

Preparation of 5,6,7,8-tetrahydroisoquinoline-5-carboxylic acid methyl ester (3)

5-Isoquinoline ester (**2**) (0.708 g, 3.785 mmol) (prepared from 5-cyanoisoquinoline) in TFA (13.2 mL) was hydrogenated over PtO_2 (102 mg) overnight at rt. TFA was evaporated and the residue was made

alkaline with saturated aq $NaHCO_3$. CH_2Cl_2 was added and the solution was filtered through Celite. The organic layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and evaporated. The product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH 99:1) to yield 0.421 g (58%) of oily **3**. IR: 1710 (C=O). ^{1}H NMR: 8.36 (1H, s, H-1), 8.32 (1H, d, J=5.5 Hz, H-3), 7.10 (1H, d, J=5.5 Hz, H-4), 3.79 (1H, t, J=7 Hz,H-5), 3.73 (3H, s, -CO_2Me), 2.86-2.71 (2H, m, H-8), 2.16 (1H, m, H-6), 2.05-1.94 (2H, m, H-6, H-7), 1.83 (1H, m, H-7). ^{13}C NMR: 150.8 (C-1), 146.7 (C-3), 141.9 (C-4a), 132.8 (C-8a), 123.8 (C-4), 44.0 (C-5), 25.9 (C-6), 25.9 (C-8), 20.1 (C-7). MS: 191 (M^+, 50), 132 (90), 131 (100), 130 (50), 117 (70). HR-MS: calcd for $C_{11}H_{13}NO_2$: 191.0946, found: 191.0924.

Preparation of tetrahydroisoquinolinium salt (4)

Tryptophyl bromide (0.492 g, 2.206 mmol) was dissolved in Et_2O (5 mL) and tetrahydroisoquinoline ester (**3**) (0.421 g, 2.204 mmol) was added. Et_2O was evaporated in N_2 flow and the mixture was stirred at 100°C for 1 h. After cooling, the product was ground finely and washed with ether to give 0.867 g (95%) of pure **4**; mp: 195-197°C (MeOH). IR: 3130 (NH), 1730 (C=O). ^{1}H NMR (DMSO-d_6): 10.97 (1H, br s, NH), 8.77 (1H, s, H-1), 8.67 (1H, d, J=6.5 Hz, H-3), 7.88 (1H, d, J=6.5 Hz, H-4), 7.45-6.92 (5H, m, indole protons), 3.67 (3H, s, -CO_2Me).

Preparation of compounds (5a) and (5b)

KCN (0.184 g, 2.826 mmol) was dissolved in H_2O (0.20 mL) and cooled to 0°C. Hydrochloric acid (6N, 0.20 mL) was added dropwise and the mixture was layered with Et_2O (1.2 mL). MeOH (0.4 mL) and tetrahydroisoquinolinium salt (**4**) (0.200 g, 0.483 mmol) were added. After 15 min stirring, $NaBH_4$ (0.020 g, 0.528 mmol) was added during 30 min, keeping the solution at 0°C. The mixture was stirred for 4 h at rt. The Et_2O layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and evaporated. The crude product was stirred in 50% AcOH (10 mL) at rt for 65 h. AcOH was evaporated and the residue was neutralized with $NaHCO_3$. The solution was extracted several times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and evaporated. The product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH 99.5:0.5) to yield 0.086 g (53%) of a mixture (**5a**) and (**5b**) (1:1) of epimers. IR: 3370 (NH), 2830-2750 (Bohlmann bands), 1710 (C=O). ^{1}H NMR (mixture of **5a** and **5b**): 7.77 (2×1H, br s, NH), 7.49 (2×1H, d, J = 8, H-9), 7.32 and 7.31 (1H, d, J=8, H-12), 7.15 (2×1H, dd, J = 8 and 8, H-11), 7.10 (2×1H, dd, J = 8 and 8, H-10), 3.76 and 3.62 (3H, s, -CO_2Me), 3.64 and 3.57 (1H, br d, J=11, H-3), 3.31 and 3.27 (1H, d, J=16, H-21β). ^{13}C NMR: 175.4 and 174.7 (C=O), 136.2 (2×C-13), 134.6 (2×C-2), 131.4 and 130.9 (C-15), 127.1 (2×C-8), 123.0 and 122.5 (C-20), 121.3 (2×C-11), 119.3 (2×C-10), 118.1 (2×C-9), 110.7 (2×C-12), 108.3 (2×C-

7), 58.6 and 58.5 (C-21), 55.9 and 55.8 (C-3), 51.8 (2×C-5), 51.8 (2×-CH_3), 46.5 and 43.9 (C-16), 34.8 and 34.2 (C-14), 27.4 and 27.1 (C-19), 26.5 and 26.3 (C-17), 21.5 and 21.3 (C-6), 20.5 and 19.2 (C-18). MS: 336 (M^+, 70), 335 (50), 277 (20), 170 (100), 169 (85). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C 74.97, H 7.19, N 8.33, found: C 75.17, H 7.47, N 8.41.

Preparation of compound (6)

The mixture (**5a**) and (**5b**) of epimers (0.052 g, 0.155 mmol) in MeOH (2.5 mL) was hydrogenated over PtO_2 (20 mg) for 60 h at rt. The crude product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH 99.5:0.5) to afford 0.011 g (21%) of **6**; mp: 206-207°C (MeOH) (lit.,[9] mp: 205-206°C). IR: 3410 (NH), 2830-2750 (Bohlmann bands), 1710 (C=O). ^{1}H NMR: See Table 1. ^{13}C NMR: See Chart 1. MS: 338 (M^+, 90), 337 (100), 184 (20), 169 (35), 156 (20). HR-MS: calcd for $C_{21}H_{26}N_2O_2$: 338.1994, found: 338.1992.

Preparation of dihydronitraraine (1)

Compound (**6**) (18 mg, 0.0581 mmol) in THF (5 mL) was reduced with $LiAlH_4$ (23 mg, 0.669 mmol) for 2 h at rt. The crude product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH 98:2) to yield 14.2 mg (86%) of amorphous **1**. IR: 3390 (NH), 3260 (OH), 2830-2750 (Bohlmann bands). ^{1}H NMR: See Table 1. ^{13}C NMR: See Chart 1. MS: 310 (M^+, 85), 309 (100), 279 (10), 169 (20). HR-MS: calcd for $C_{20}H_{26}N_2O$: 310.2045, found: 310.2021.

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