Supplementary Material (ESI) for Green Chemistry

Supplementary Information

Fischer Indole Synthesis in Water: Simple, Efficient Preparation of Naltrindole, Naltriben and Analogs

Romain A. Duval and John R. Lever*

Departments of Radiology and the Radiopharmaceutical Sciences Institute, and Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri 65212, and Research Service, Harry S. Truman Veterans Administration Medical Center, Columbia, Missouri 65201

* leverj@health.missouri.edu

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1. Experimental Procedures

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-5′-methoxy-indolo [6,7:2′,3′] morphinan Hydrochloride (5′-Methoxynaltrindole•HCl, 4). A mixture of NTX•HCl (0.15 g, 0.40 mmol) and *p*-methoxyphenylhydrazine•HCl (0.072 g, 0.40 mmol) was dissolved in water (3 mL) using a 15 mL plastic centrifuge tube as the reaction vessel. After heating in a boiling water bath for 1.5 h, the mixture was cooled to ambient temperature and then chilled at 4 °C for 30 min. After centrifugation (10,000 rpm, 4 °C; 5 min), the supernatant was discarded and the precipitate dried in vacuo at 45 °C to furnish 5′-OMe-NTI•HCl (0.12 g, 61%) as a beige powder of 95% purity by reversed-phase HPLC. Characteristic ^{1}H NMR signals[1] for the free base ($CDCl_3$, 300 MHz): δ 8.12 (s, 1H), 7.11 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H), 6.77 (dd, J = 2.2 Hz, J = 8.7 Hz, 1H), 3.76 (s, 3H). HRMS (ESI) calcd for $C_{27}H_{29}N_2O_4$ $[M+H]^+$ 445.2122; found: 445.2138.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-7′-fluoro-indolo[6,7:2′,3′] morphinan Hydrochloride (7′-Fluoronaltrindole•HCl, 6). A solution of NTX•HCl (0.092 g, 0.24 mmol) and *o*-fluorophenylhydrazine•HCl (0.042 g, 0.25 mmol) in water (1.85 mL) was heated in a boiling water bath for 1.5 h using a 15 mL plastic centrifuge tube as the reaction vessel. The mixture was cooled to ambient temperature, and then chilled at 4 °C overnight. After centrifugation (10,000 rpm, 4 °C; 5 min), the supernatant was discarded and the precipitate suspended in ice-cold 0.1 N HCl (1.5 mL), vortexed thoroughly, and then centrifuged again. The supernatant was discarded, and the resulting solid was dried in vacuo at 45 °C to furnish 7′-F-NTI•HCl (0.061 g) as a beige powder of 71% purity by reversed-phase HPLC,

giving an effective 53% molar yield when adjusted for purity. Characteristic ^{1}H NMR signals[1] for the free base ($CDCl_3$, 300 MHz): δ 8.42 (s, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.80-6.96 (m, 2H). HRMS (ESI) calcd for $C_{26}H_{26}FN_2O_3$ $[M+H]^+$ 433.1922; found: 433.1922.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-1′-ethyl–5′,7′-dibromo-indolo[6,7:2′,3′] morphinan Hydrochloride (*N*1′-Ethyl-5′,7′-dibromo-NTI•HCl, 7). A mixture of NTX•HCl (0.092 g, 0.24 mmol) and *N*-ethyl-2,4-dibromophenylhydrazine•HCl[4a] (0.16 g, 0.50 mmol) in water (13 mL) was refluxed 24 h, cooled to ambient temperature, treated with solid $NaHCO_3$, and then extracted with CH_2Cl_2 (5 x 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was passed through a short silica gel column (EtOAc : cyclohexane; 2:3 v/v containing 1% NEt_3) and concentrated. This mixture of title compound and residual phenylhydrazine was suspended in MeOH (6 mL), acidified with HCl (1.0 N, 3 mL), brought to homogeneity by gentle heating and concentrated under reduced pressure. Reversed-phase C18 column chromatography (CH_3CN : H_2O; 50 : 50 v/v containing 1 % 3.0 N HCl) furnished *N*1′-ethyl-5′,7′-dibromo-NTI•HCl (0.042 g, 27%) as an off-white powder of 98% purity by reversed-phase HPLC. Characteristic ^{1}H NMR signals[4a] for the free base ($CDCl_3$, 300 MHz): δ 7.44 (d, *J* = 1.8 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 4.71 (m, 1H), 4.55 (m, 1H), 1.44 (dd, *J* = 6.9 Hz, *J* = 7.2 Hz, 3H). HRMS (ESI) calcd for $C_{28}H_{29}Br_2N_2O_3$ $[M+H]^+$ 599.0539; found: 599.0556.

2. Analytical HPLC Conditions and Data

Reversed-phase, ion-pair HPLC separations were run using a stainless steel column (Nova-Pak® C18, 4 μm, 3.9 x 150 mm, Waters) on a Waters HPLC system with UV (254 nm) detection. A ternary mobile phase was used at a flow rate of 1.5 mL / min that consisted of a mixture of organic (MeOH : CH_3CN; 50 : 50, v/v), and aqueous (H_2O : HOAc : Et_3N; 95.1 : 2.8 : 2.1, v/v/v) phases. Samples were dissolved in the mobile phase (1.0 mg / mL) for analysis under isocratic conditions using runs of 40 min duration. The composition of the mobile phase, retention times (t_R) and capacity factors (k') for each compound are given in the Table below.

TABLE. HPLC Conditions and Parameters for Analysis of NTI, NTI Congeners and NTB

Compound	% Aqueous	% Organic	t_R	k'
NTI (**1**)	75	25	12.2 min	14.2
NTB (**2**)	75	25	11.2 min	13.0
*N*1′-Methyl-NTI (**3**)	70	30	8.5 min	9.6
5′-OMe-NTI (**4**)	75	25	8.2 min	9.2
7′-Cl-NTI (**5**)	70	30	12.6 min	14.7
7′-F-NTI (**6**)	70	30	7.8 min	8.7
*N*1′-Ethyl-5′,7′-dibromo-NTI (**7**)	53	47	13.8 min	15.4
naltrexone *o*-nitrophenylhydrazone (**9**)	70	30	19.0 min	22.7