Chemistry of Natural Compounds, Vol. 46, No. 6, 2011

LITHIATION OF DEOXYPEGANINE AND CHIRAL SYNTHESIS OF DEOXYPEGANINE DERIVATIVES

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A method was developed for lithiation of deoxypeganine. The reaction of organolithium deoxypeganine derivatives with isobutyraldehyde and benzaldehyde to produce its derivatives was studied. A chiral synthesis of substituted deoxypeganines was performed. The synthesized diastereomers and enantiomers were separated successfully using HPLC and a chiral column.

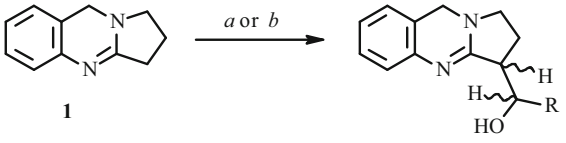
Keywords: deoxypeganine, lithiation, enantiomers, racemates, configuration.

The natural alkaloid deoxypeganine (1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline) (**1**) and its analogs are broadly used in medical practice [1, 2]. Its reactivity and transformations were the subject of comprehensive studies in order to establish the directions of reactions and the biological activity.

Deoxypeganine derivatives containing various substituents in the α-position are difficultly accessible because **1** and its derivatives are produced mainly by reduction of the corresponding deoxyvasicinones [3] formed via condensation of anthranilic acid with lactams [4, 5]. Several lactams with various substituents in the α-position are unavailable. Furthermore, lactams with a functional group (e.g., hydroxyl) can themselves undergo chemical transformations upon condensation with anthranilic acid in the presence of inorganic acid chlorides.

Therefore, we decided to follow one of the possible pathways for preparing derivatives of **1** especially because it was reported that its reaction with ketones [4] results in the formation of a racemic mixture.

Herein we present results from a study of the reaction of **1** with isobutyraldehyde and benzaldehyde at –78°C in the presence of *sec*-BuLi in Et_2O. This produced stereoisomers of 2-methyl-1-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)propan-1-ols and phenyl(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)methanols.



1 **2a,b; 3a,b**

2a, b: R = $CH(CH_3)_2$; E = $(CH_3)_2CH$-CHO
3a, b: R = C_6H_5; E = C_6H_5CHO

a. 1) *sec*-BuLi (2 eq.), Et_2O, 1 h; 2) –78°C, E (3 eq.); 3) –78°C (15 min), 20°C (1 h); 4) MeOH, 10 min.
b. 1) *sec*-BuLi (2 eq.), Et_2O, 1 h; 2) –78°C, chiral catalyst (2 eq.), 1 h; 3) –20°C (1 h); 4) E (3 eq.) at –20°C (1 h); 5) 20°C, 1 h; 6) MeOH, 10 min.

Reaction of **1** with isobutyr- and benzaldehyde in the presence of *sec*-BuLi formed a mixure of diastereomers of **2** and **3**. The pure diastereomers were separated successfully using column chromatography.

We synthesized racemates of **2** and **3** with two asymmetric centers (reaction conditions *a*) in order to check the possibility of creating a chiral center on the α-C atom and the $C^{1'}$ carbonyl C atom. The synthesized diastereomers **2a**,**b** and

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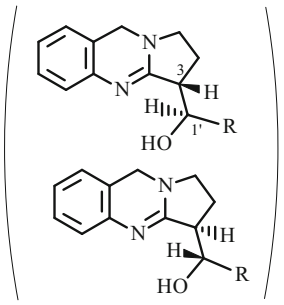
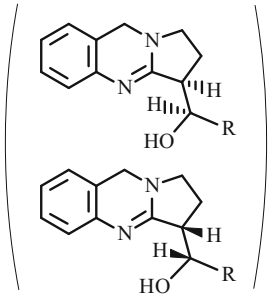
3a,**b** each contained two pairs of enantiomers. The ratio of principal diastereomer **2a** to the minor one **2b** for isobutyraldehyde was 4.6:1 with overall yield 86%. Principal diastereomer **2a** contained two enantiomers (1′*S*,3*R*; 1′*R*,3*S*); minor diastereomer **2b**, (1′*S*,3*S*; 1′*R*,3*R*). The ratio of principal diastereomer **3a** to minor one **3b** was 2.3:1 for the reaction with benzaldehyde with overall yield 76%. Diastereomer **3a** also consisted of two enantiomers (1′*R*,3*S*; 1′*S*,3*R*); diastereomer **3b**, of the two enantiomers (1′*R*,3*R*; 1′*S*,3*S*).



2a,b



3a,b

The next step of our study was to carry out a chiral synthesis of **2** and **3** in the presence of chiral catalyst *L*,*L*-prolineprolinol (reaction conditions *b*). This produced **2** and **3**, as was noted above, with two asymetric centers. The synthesized diastereomers each contained two pairs of enantiomers in different ratios. For isobutyraldehyde, the ratio of principal diastereomer **2a** to the minor one **2b** was 2.9:1 in overall yield 41%. Principal diastereomer **2a** consisted of two enantiomers (1′*S*,3*R*; 1′*R*,3*S*) in a 16:84 ratio. Minor diastereomer **2b** contained two enantiomers (1′*S*,3*S*; 1′*R*,3*R*) in a 50:50 ratio. For benzaldehyde, an equal mixture of diastereomers **3a** and **3b** formed in overall yield 85%. Diastereomer **3a** contained two enantiomers (1′*R*,3*S*; 1′*S*,3*R*) in a 26:74 ratio; **3b**, (1′*R*,3*R*; 1′*S*,3*S*) in a 55:45 ratio.

EXPERIMENTAL

The structures of the synthesized compounds were elucidated using IR, PMR, and mass spectra. Melting points were determined on a Mel-Temp instrument (USA). The course of reactions was monitored using Silufol UV-254 plates and EtOAc:MeOH:petroleum ether (PE) (7:2:1) with detection by $KMnO_4$ (4%) in dilute H_2SO_4. The prepared diastereomers were separated by column chromatography over silica gel (Davisil, 40–63 μm) with the ratio determined by the yield.

IR spectra were taken on a Perkin–Elmer model 2000 Fourier IR spectrometer in pressed KBr disks. PMR spectra were recorded in $CDCl_3$ with HMDSO internal standard on a Bruker instrument at operating frequency 400 MHz. Mass spectra were obtained in a Kratos MS-30 spectrometer (England) at ionizing potential 70 eV and source temperature 220°C. Enantiomers were analyzed by HPLC (Agilent-1100) at wavelength 254 nm using Kromacell 3-Cellucoat and AS chiral columns.

Synthesis of (±)-2-Methyl-1-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)propan-1-ol (2a,b). A solution of deoxypeganine (**1**, 50 mg, 0.29 mmol) in anhydrous Et_2O (10 mL) was stirred in a flask, treated dropwise with *sec*-BuLi in hexane (0.45 mL, 1.3M, 0.58 mmol) at –78°C under a stream of N_2, stirred for 1 h at –78°C, treated dropwise over 5–10 min with isobutyraldehyde (0.08 mL, 0.87 mmol), stirred for another 15 min, held at –78°C, heated to room temperature (20°C), stirred another 1 h, and treated with MeOH (2.5 mL). The resulting product was purified by column chromatography.

(1′*R*,3*S*;1′*S*,3*R*)-(±)-2-Methyl-1-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)propan-1-ol (2a). Eluent EtOAc:PE (3:7), yield 70.6%, R_f 0.27, mp 81–82°C. IR spectrum (KBr, ν, cm^{-1}): 3070, 2955, 1620, 1590, 1570, 1485.

PMR spectrum (δ, ppm, J/Hz): 0.96 (3H, d, J = 7.0, Me), 1.13 (3H, d, J = 7.0, Me), 1.68–1.77 (1H, m, H-2′), 1.94–2.02 (1H, m, H-2), 2.20–2.30 (1H, m, H-2), 3.03 (1H, td, ^2J = 9.5, ^3J = 2.0, H-1a), 3.19 (2H, dd, ^2J = 9.0, ^3J = 5.5, H-1b,3), 4.01 (1H, dd, J = 9.0, 2.0, H-1′), 4.08 (1H, d, ^2J = 13.5, H-9), 4.34 (1H, d, ^2J = 13.5, H-9), 6.75 (1H, d, J = 7.5, H-8), 6.93 (1H, td, J = 7.0, 2.0, H-5), 7.09–7.14 (2H, m, H-6,7).

HR-MS-ES: found: $[MH]^+$ 245.1660. $C_{15}H_{21}N_2O$. calcd: $[MH]^+$ 245.1654.

(1′*S*,3*S*;1′*R*,3*R*)-(±)-2-Methyl-1-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)propan-1-ol (2b). Eluent EtOAc:MeOH (23:2), yield 15.4%, R_f 0.24, mp 96–97°C.

PMR spectrum (δ, ppm, J/Hz): 0.97 (3H, d, J = 7.0, Me), 1.10 (3H, d, J = 7.0, Me), 1.59–1.78 (2H, m, H-2′, H-2), 2.05–2.16 (1H, m, H-2), 2.80 (1H, q, J = 9.5, H-1a), 3.30 (2H, dt, J = 9.5, 3.0, H-1b,3), 3.62 (1H, dd, J = 10.0, 2.0, H-1′), 4.60 (2H, s, H-9), 6.89 (1H, dd, J = 7.5, 1.0, H-8), 6.99 (2H, t, J = 9.0, H-6,7), 7.16 (1H, td, J = 8.0, 1.0, H-5).

Synthesis of (±)-Phenyl-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)methanol (3a,b). The reaction was carried out by the above method using deoxypeganine (0.05 g, 0.29 mmol), *sec*-BuLi in hexane (0.45 mL, 1.3M, 0.58 mmol), and benzaldehyde (0.09 mL, 0.87 mmol).

(1′*R*,3*S*;1′*S*,3*R*)-(±)-Phenyl-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)methanol (3a). Eluent EtOAc:PE (1:1), yield 53%, R_f 0.18, mp 103–104°C. IR spectrum (KBr, ν, cm^{-1}): 3235, 2870, 1665, 1620, 1570, 1497.

PMR spectrum (δ, ppm, J/Hz): 1.66–1.78 (2H, m, H-2a,b), 3.02 (1H, q, J = 9.0, H-1a), 3.23 (2H, dd, J = 9.0, 5.0, H-1b,3), 4.62 (2H, s, H-9), 4.71 (1H, d, J = 10.0, H-1′), 6.93 (1H, dd, J = 7.0, 0.5, Ph), 7.03 (1H, td, J = 7.5, 1.5, Ph), 7.11 (1H, dd, J = 8.0, 1.0, Ph), 7.21 (1H, td, J = 7.5, 1.5, Ph), 7.32–7.35 (1H, m, Ph), 7.37–7.40 (2H, m, Ph), 7.44–7.47 (2H, m, Ph).

HR-MS-ES: found: $[MH]^+$ 279.1494. $C_{18}H_{19}N_2O$. calcd: $[MH]^+$ 279.1497.

(1′*S*,3*S*;1′*R*,3*R*)-(±)-Phenyl-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)methanol (3b). Eluent EtOAc:PE (1:0.75), yield 23%, R_f 0.14, mp 118–120°C.

PMR spectrum (δ, ppm, J/Hz): 1.89–1.98 (1H, m, H-2a), 2.22–2.30 (1H, m, H-2b), 3.31–3.43 (2H, m, H-1a), 3.88–3.92 (1H, m, H-1b,3), 4.60 (2H, s, H-9), 5.93 (1H, d, J = 3.0, H-1′), 6.90 (1H, d, J = 7.5, Ph), 7.10 (1H, t, J = 8.0, Ph), 7.18 (1H, t, J = 7.5, Ph), 7.22–7.30 (2H, m, Ph), 7.42–7.46 (2H, m, Ph), 7.53–7.57 (2H, m, Ph).

Chiral Synthesis Method. A solution of deoxypeganine (50 mg, 0.29 mmol) in anhydrous Et_2O (10 mL) was stirred in a flask under a stream of N_2, treated dropwise with a solution of *sec*-BuLi in hexane (0.45 mL, 1.3M, 0.58 mmol) at –78°C, stirred for 1 h at –78°C, treated dropwise with chiral ligand *L*,*L*-prolineprolinol (115 mg, 0.58 mmol), stirred another 1 h at –78°C, heated to –20°C, stirred at that temperature for 1 h, treated dropwise over 1 h at –20°C with the electrophile (0.87 mmol), heated to room temperature (+20°C), stirred for another 1 h, and treated with MeOH (2.5 mL). The resulting product was purified by column chromatography and analyzed by an HPLC equipped with a chiral column.

(–)-2-Methyl-1-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)propan-1-ol (2a). HPLC system (Kromacell 3-Cellucoat column), 2.5% isopropanol in hexane (with added Et_2NH, 0.1%), flow rate 1 mL/min; $[\alpha]_D^{22.5}$ –5° (*c* 1.0, CH_2Cl_2).

(–)-Phenyl-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)methanol (3a). HPLC system (AS chiral column), 2.5% isopropanol in hexane, flow rate 1 mL/min; $[\alpha]_D^{21}$ –17° (*c* 1.12, CH_2Cl_2).

ACKNOWLEDGMENT

The work was supported by the INTAS Foundation (YSF Collaborative Call with Uzbekistan 2006, for a Ph.D. Fellowship INTAS Ref. No. 06-1000023-6035).

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