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Tetrahedron Letters 44 (2003) 6459–6462

TETRAHEDRON LETTERS

Synthesis of aminothiazole derived morphinans

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Received 30 May 2003; revised 19 June 2003; accepted 23 June 2003

Abstract—Two aminothiazole derived morphinans **9** and **11** were prepared for our ongoing opioid ligands study. The synthesis was initiated from levorphanol **1**, which was first triflated, and then subjected to Pd-catalyzed reduction followed by nitration. The resulting two nitrated isomers were characterized by analogy to known compounds. The formation of the aminothiazole ring occurred highly selectively to yield only one product from each of the anilines **6** and **7**.

(−)-*N*-Methyl-3-hydroxymorphinan (**1**, levorphanol), which was first synthesized in optically pure form in 1951,[1] is a potent μ agonist and at least four times more potent than morphine.[2–4] Its greater lipophilicity allows for higher concentrations to reach the brain which may result in excessive sedation.[5] To obtain effective analgesics with improved pharmacological properties, a number of analogues have been synthesized and evaluated, but most of them were derived by substitution at the N–CH_3 with different alkyl groups.[5–7] Substantial studies have been made to elaborate the function of the phenol moiety in the benzomorphan ring system by substitution of the phenol moiety with pyrido,[8] thieno[9,10] or pyrrolo[11] moiety resulting in compounds with antinociceptive activity. Similar modifications in the morphinan series have not been carried out except the masking or substitution of the phenolic hydroxyl group producing less active compounds.[12,13] Recently, the 2-aminothiazole functionality has been successfully applied as a heterocyclic bioisostere of the phenol moiety in dopamine agonists such as B-HT 920,[14] PD 118440[15] and pramipexole[16–18] (Chart 1) resulting in improved pharmacological properties. These findings led us to investigate the effect of replacing the phenol moiety of levorphanol **1** with a 2-aminothiazole moiety (Chart 1). Although, the 2-aminothiazole moiety cannot be considered as a bioisosteric replacement of the phenol group,[19] we envisage that this replacement can be viewed as an extension of the aromatic functionality of the molecule, and that the 2-amino group may effectively replace the phenolic hydroxyl group to form a presumed hydrogen bond with an appropriate opioid receptor binding site which may result in improved opioid pharmacological properties.

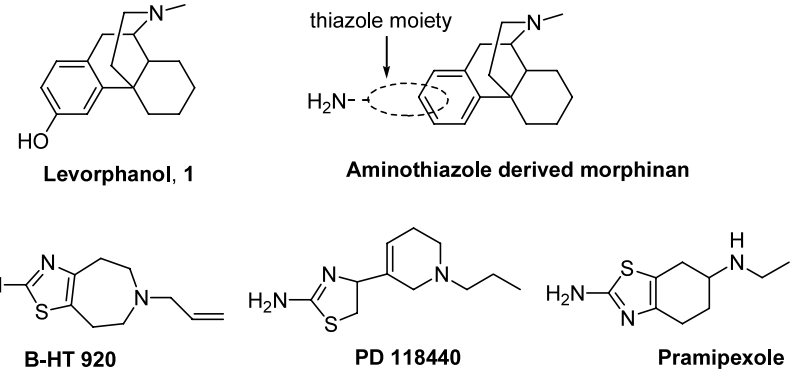

Chart 1.

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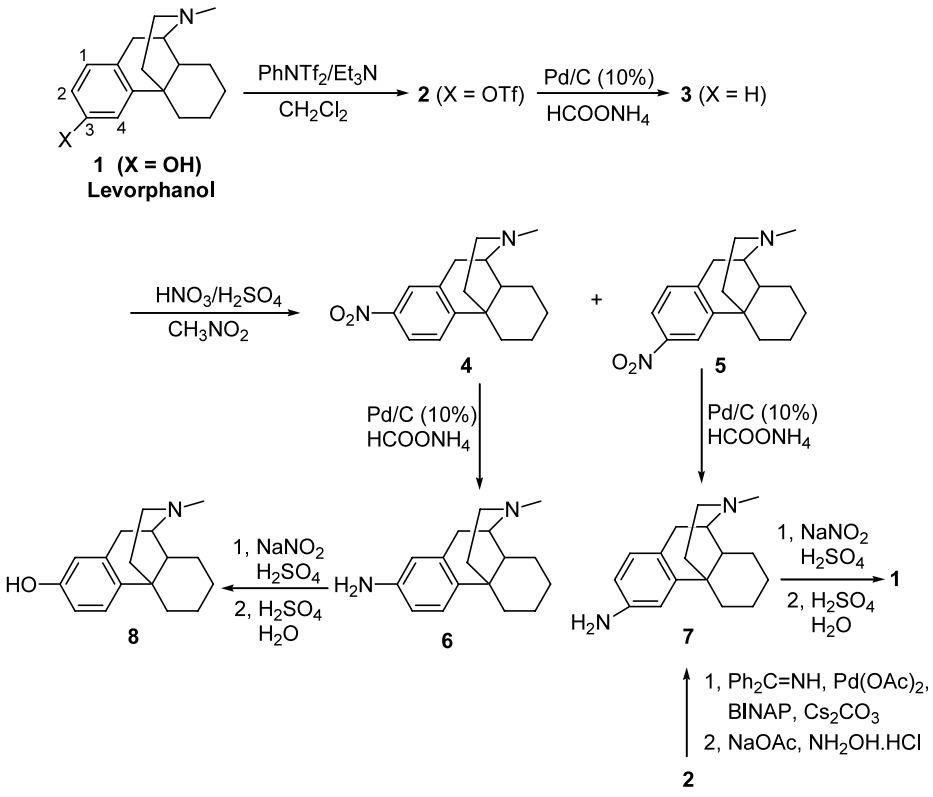
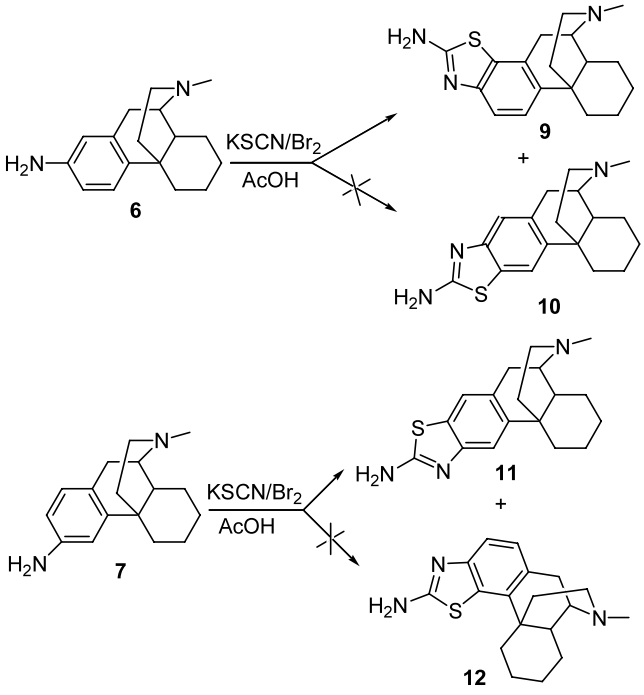
doi:10.1016/S0040-4039(03)01560-0



Scheme 1.

Although there are several methods to prepare the aminothiazole analogues,[9e,14–18] the most facile access is from the corresponding anilines. To find the optimal choice of attachment of the aminothiazole moiety to the aromatic ring, we decide to prepare such derivatives from different aniline precursors (1-, 2-, 3- or 4-substitution pattern) and evaluate their pharmacological properties. The synthesis was initiated from levorphanol **1**, which is commercially available.[20] Thus **1** was treated with *N*-phenyl bis(trifluoromethanesulfonimide) and triethylamine to yield **2** in 85% yield (Scheme 1).[21] Reduction of triflate **2** using Pd/C (10%) as the catalyst and ammonium formate as the H-source gave *N*-methylmorphinan **3** in almost quantitative yield.[22] Nitration of **3** was performed with mild nitration mixture[23] (nitric acid and conc. sulfuric acid in nitromethane) to afford a mixture of two isomers as an oil (1:1 from GC–MS analysis) which could not be separated by chromatography. After conversion of the oil to the corresponding dibenzyl-D-tatrate salt, repeated recrystallization of the salt from $EtOH/H_2O$ (100/40) gave one pure isomer in 22% yield. The mother liquid was evaporated, and the residue was repeatedly recrystallized from $^{i}PrOH/H_2O$ (2/1) until GC analysis indicated it was pure (10% yield) to afford the other isomer (Scheme 1).

Although the two isomers were successfully separated, the similar NMR data could not allow us to identify their absolute chemical structures. The single peaks (8.12 and 8.25 ppm, respectively) in their $^{1}HNMR$ suggested that they were 2- and 3-nitro morphinans (**4** and **5**), and not 1- or 4-substituted isomers.[24] The same process has been carried out earlier by Schnider and Grąssner,[25] who identified the 3-nitro isomer by reducing the nitro compound to the corresponding amine followed by conversion to the phenol, a known com-



Scheme 2.

pound. These investigators did not determine the other nitrated product (2- or 4-substitued).[13,25,26] Using the same strategy, we reduced both of the nitro compounds (**4** and **5**) to their corresponding amines (**6** and **7**) using Pd/C (10%) and ammonium formate in methanol in 80 and 85% yields, respectively. The resulting amines **6** and **7** were diazotizated and then hydrolyzed to the corresponding phenols **8** and **1** in 68 and 73% yields, respectively. Comparison of the ^{1}H NMR data and melting points of the resulting phenols with levorphanol **1** allowed us easily identify the 3-substituted morphinans, and the remaining isomer was deduced to be the 2-substituted phenol **8**. The 3-amino morphinan **7** can be alternatively prepared from triflate **2** by the recently developed Pd-catalyzed amination strategy that gave **7** as the only product in 54% yield.[27]

With the structures established, amines **6** and **7** were treated with potassium thiocyanate and bromine in acetic acid.[28] Surprisingly, the aminothiazoles **9** and **11** were formed in 60 and 68% yields, respectively, and no aminothiazoles **10** and **12** were observed[29] (Scheme 2). The structure of **9** produced from amine **6** was confirmed by its ^{1}H NMR spectra where the two aromatic protons gave ABq complex at 7.25 and 7.18 ppm ($J=19.5$ Hz, both d with 8.1 and 8.7 Hz). As to the product formed from amine **7**, its ^{1}HNMR gave two single peaks at 7.31 and 7.36 ppm for the two aromatic protons confirmed the structure of **11**. It is noteworthy that the thiazole ring closure always occurred in one direction. The reasons for this cyclization pattern are not clear although the steric and/or electrostatic factors may be responsible. Further preparation of other aminothiazole derived opiates and their biological assays are in progress.

In conclusion, two aminothiazole derived morphinans **9** and **11** were prepared for our continuing opioid ligands study. The synthesis was initiated from levorphanol **1**, which was first triflated, and then subjected to reduction followed by nitration. The resulting two nitrated isomers were characterized by analogy. The formation of aminothiazole ring occurred highly selectively and only one product was observed from each of the anilines **6** and **7**.

Acknowledgements

This work was supported, in part, by NIDA Grant R01-DA14251.

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24. For 2-nitro-*N*-methylmorphinan **4** (hydrochloride): MS *m*/*z* (%) 287 (M^+–Cl); ^{1}H NMR (CD_3OD, 300 MHz) δ: 8.14 (d, J=9.1 Hz, 1H), 8.12 (s, 1H), 7.66 (d, J=8.5 Hz, 1H), 3.31 (m, 4H), 2.96 (s, 3H), 2.62 (d, J=13.8 Hz, 2H), 2.18 (m, 1H), 2.08 (m, 1H), 1.60 (m, 6H), 1.10 (m, 2H). Anal. calcd for $C_{17}H_{23}N_2O_2Cl$: C, 63.25; H, 7.18; N, 8.68. Found: C, 63.12; H, 7.21; N, 8.68. For 3-nitro-*N*-methylmorphinan **5** (hydrochloride): MS *m*/*z* (%) 287 (M^+–Cl); ^{1}H NMR (CD_3OD, 300 MHz) δ: 8.25 (s, 1H), 8.11 (d, J=8.4 Hz, 1H), 7.52 (d, J=8.4 Hz, 1H), 3.30 (m, 4H), 2.94 (s, 3H), 2.61 (d, J=13.4 Hz, 2H), 2.17 (d, J=12.5 Hz, 1H), 2.02 (m, 1H), 1.63 (m, 6H), 1.23 (m, 1H), 1.07 (m, 1H). Anal. calcd for $C_{17}H_{23}N_2O_2Cl$: C, 63.25; H, 7.18; N, 8.68. Found: C, 63.24; H, 7.35; N, 8.60.
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29. For aminothiazole **9**: pale yellow foam. MS *m*/*z* (%) 314 (M^++1); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.25 and 7.18 (ABq, J=19.5 Hz, both d with 8.7 and 8.1 Hz, respectively, 2H), 4.87 (brs, 2H), 3.30 (m, 1H), 2.87 (m, 2H), 2.62 (m, 1H), 2.41 (m, 1H), 2.36 (s, 3H), 2.01 (m, 1H), 1.73 (m, 3H), 1.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.2, 150.6, 134.2, 131.1, 130.2, 124.3, 117.3, 59.1, 48.0, 46.3, 42.8, 42.7, 37.7, 27.7, 27.6, 25.2, 23.2. Anal. calcd for $C_{18}H_{23}N_3S{\cdot}0.5H_2O$: C, 67.04; H, 7.50; N, 13.03. Found: C, 66.99; H, 7.33; N, 12.70. For aminothiazole **12**: pale yellow foam. MS *m*/*z* (%) 314 (M^++1); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.36 (s, 1H), 7.31 (s, 1H), 4.20 (brs, 2H), 3.09 (d, J=18.0 Hz, 1H), 2.81 (m, 2H), 2.44 (m, 1H), 2.39 (m, 3H), 2.12 (m, 1H), 1.75 (m, 3H), 1.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.2, 150.6, 134.2, 131.1, 130.0, 124.3, 117.3, 59.1, 48.1, 46.3, 42.8, 42.7, 37.7, 27.7, 27.6, 25.2, 23.2. Anal. calcd for $C_{18}H_{23}N_3S.0{\cdot}5H_2O$: C, 67.04; H, 7.50; N, 13.03. Found: C, 67.43; H, 7.30; N, 12.79.