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Studies into the Direct Conversion of Indolomorphinans to their 4-Phenolic Derivatives

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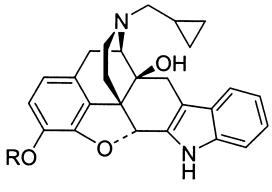
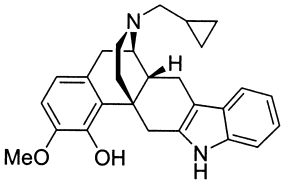
Abstract—A one step method to convert 3-*O*-methyl substituted indolomorphinans into their 4-phenolic derivatives through reductive opening of the 4,5-bridge is described.

The delta opioid receptor system is an attractive target for the development of a range of therapeutic agents,[1,2] such as immunoregulators[3–5] and agents to reverse the respiratory depression caused by mu opioid agonists.[6] Further, the intriguing finding that delta antagonists prevent the development of dependence and tolerance to morphine,[7–10] underscores the necessity for the development of selective non-peptide delta opioid ligands to further investigate this system. One of our approaches has been to modify the structure of the moderately selective indolomorphinans, such as naltrindole **1**,[11] in order to improve their delta opioid selectivity. We have shown that masking of the 3-phenol as a 3-methyl ether (**2**) increases delta selectivity in binding assays,[12] and that the 3-methoxy-4-phenolic indolomorphinan **3** is an extremely selective ligand.[13]



1 R = H Naltrindole
2 R = Me



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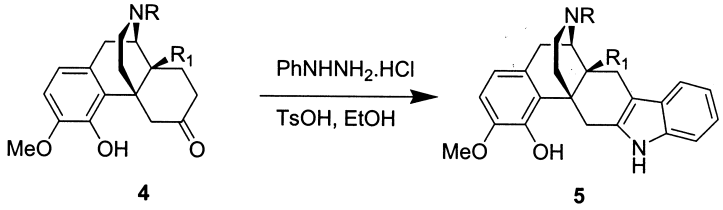
Our initial studies showed that the structure–activity relationships of the 4-phenolic ligands appear very different to the parent indolomorphinans,[13] and further studies are required to fully delineate the differences and similarities. The 3-methoxyl-4-phenolic ligands (**5**) were prepared via our recently developed novel synthesis of *N*-substituted nordihydrothebainone-A derivatives (**4**) from *N*-substituted norcodeine derivatives, or by reductive opening of the 4,5-bridge in the 14-hydroxyl series.[13,14] Fischer indole formation from the 4-phenolic ketones gave the desired products, but in low yield (Scheme 1). This approach proved valuable in the initial preparation of analogs of well known indolomorphinans, but for a definitive study, a range of different *N*-substitutions is required. Such a study requires the synthesis of the *N*-substituted indolomorphinans and their 3-methyl ethers, and the *N*-substituted 3-methoxyl-4-phenolic analogs, and we considered that the development of a method to directly convert the indolomorphinans and their 3-methyl ethers to the 4-phenolic derivatives would offer benefits in terms of less synthetic steps and remove the low yielding indole formation reaction on the 4-phenolic ketones.

Our synthetic design focused on that fact that the chemistry



4 **5**

Scheme 1.

Keywords: indolomorphinans; 4-phenolic derivatives; 4,5-bridge.
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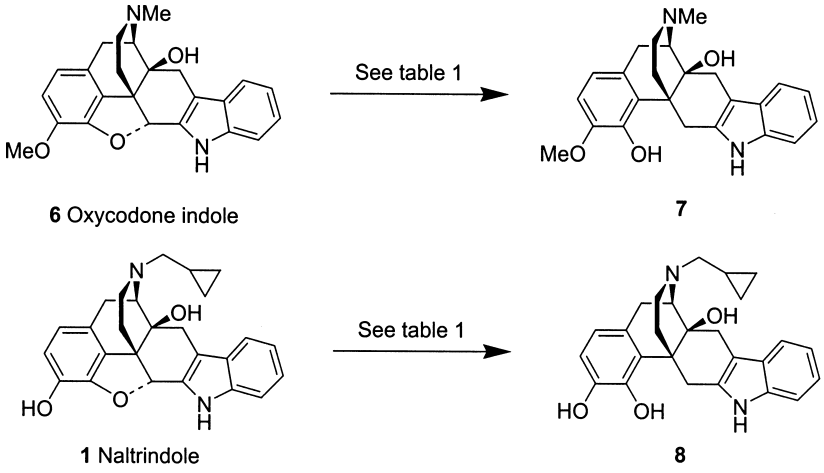

Scheme 2.

in the 4,5-epoxymorphinan series is often troublesome due to reductive opening of the 4,5-bridge.[15] The indolomorphinans possess a 4,5-bridge which is effectively an allylic ether, and such systems are known to open under reductive conditions;[16] such an opening of the bridge in the indolomorphinans would yield the desired 4-phenolic analogs. We thus treated the oxycodone indole (**6**)[17] and naltrindole (**1**)[11] with a range of reducing conditions and the results are summarized in Scheme 2 and Table 1.

Oxycodone indole (**6**) was initially investigated, as an authentic sample of the corresponding ring opened **7** was available from our previous studies,[13] thus allowing a facile determination of the success of the ring opening procedure. **6**·HCl was prepared by the method of Loew,[17] and subjected to all four different conditions described in Table 1. Zn/HCl, conditions known to open the bridge in 6-keto opioids,[13] was found to give rise to a very slow reaction with the desired product **7** only being detected by TLC and MS.

Et_3SiH in the presence of CF_3COOH is a well known procedure for reducing under acidic conditions,[18] and it was hoped that protonation of the epoxy bridge would aid in its opening. When one equivalent of Et_3SiH was employed an encouraging 41% of the desired product was isolated by column chromatography. Although the majority of the material balance was unreacted starting material **6**, all attempts to increase the equivalents of Et_3SiH led only to decreased quantities of **7** and increased quantities of side products which proved difficult to isolate and identify.

$NaBH_4$ in the presence of CF_3COOH was employed for similar reasons as Et_3SiH above. As with the Et_3SiH, best yield of opened product was obtained by the use of one molar equivalent of $NaBH_4$, when a 33% yield was isolated following chromatography. Increased equivalents of $NaBH_4$ gave rise to increased quantities of side products.

Although the above studies indicated that the desired transformation was possible, the overall yields would be little better than the original method of preparing the 4-phenolic analogs of the indolomorphinans. This prompted us to turn our attention to the possibility of hydrogenolysis of the bridge. It was found that the use of transfer hydrogenation with using 10% Pd/C with NH_4HCO_2 as the hydrogen source in EtOH[19] gave rise to an excellent 72% yield of the desired product **7** after 4 h at RT. No starting material remained and any side products were lost during work-up, resulting in a reaction where column chromatography was not necessary.

The success of the ring opening reactions with **6**, led use to consider the possible ring opening reaction of naltrindole (**1**) itself. The product from this reaction would be novel catechol **8**, a potentially interesting compound to investigate pharmacologically, as opioids containing such catechol systems have received little interest due to their potential for oxidation. We found that treatment with both $NaBH_4$/CF_3COOH and NH_4HCO_2/Pd/C gave rise to reactions, but isolation of the product was difficult; a salt could not be precipitated directly from the reaction mixture, and on basification the mixture rapidly colored to give a tar-like material. The rapid decomposition under basic conditions (presumably by oxidation) suggests that the catechol had indeed formed, but was unstable under non-acidic conditions. Catechol analogs of the indolomorphinans would, therefore, not appear to be useful targets for delta opioid drug development.

In summary, we have shown that the 4,5-bridge of the

Table 1. Yields of **7** and **8** from the ring opening of **6** and **1** under different conditions

Substrate	Zn/HCl	Et_3SiH/CF_3COOH	$NaBH_4/CF_3COOH$	NH_4HCO_2/Pd/C
Oxycodone indole (**6**)	<5%	41%	33%[a]	72%[a]
Naltrindole (**1**)	–	–		

[a] An unstable product resulted which spontaneously decomposed on aqueous work-up.

3-*O*-methyl indolomorphinans can be reductively opened to give 4-phenolic analogs directly in high yield by transfer hydrogenation, thus allowing the preparation of both the indolomorphinans (by 3-*O*-demethylation[20]) and the 4-phenolic analogs (by the present procedure) from the same intermediate, while avoiding the low yielding Fischer indole reaction on the 4-phenolic ketones.

Experimental

All reactions were preformed under an atmosphere of nitrogen, and all solutions were evaporated to dryness on a rotary evaporator. All reagents were used as obtained from Sigma–Aldrich, and solvents were used without purification from VWR. Flash column chromatography was performed on silica gel (230–400 mesh).

6,7-Didehydro-14-hydroxy-3-methoxy-17-methyl-6,7:2′,3′-indolomorphinan (oxycodone indole) (6). **6**·HCl (mp 245–250°C (Dec)) was prepared by the method of Loew, and the compound thus obtained exhibited spectral properties identical with those reported.[17]

6,7-Didehydro-4,14-dihydroxy-3-methoxy-17-methyl-6,7:2′,3′-indolomorphinan (7). *Method A: Zn/HCl:* A solution of **6**·HCl (200 mg, 0.45 mmol) in HCl (6 M, 5 mL) was heated to reflux. Zn (150 mg, 2.25 mmol) was added in small portions over 1 h, and a precipitate was observed. After 4 h, the reaction mixture was cooled, diluted with H_2O (10 mL), basified with NH_4OH, and extracted into $CHCl_3$ (3×15 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), and dried (K_2CO_3). Removal of the solvent gave the crude material as a glass (187 mg) which was shown to be predominantly starting material **6** (TLC, silica $CHCl_3$/MeOH/NH_3 95:5:0.5).

Method B: Et_3SiH/CF_3COOH: **6**·HCl (200 mg, 0.45 mmol) was dissolved in CF_3COOH (5 mL) and cooled in an ice bath. Et_3SiH (52 mg, 0.45 mmol) was added, and the resulting solution was stirred in the ice bath for 3 h. The reaction mixture was then diluted with H_2O (10 mL), basified with NH_4OH, and extracted into $CHCl_3$ (3×15 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), and dried (K_2CO_3). Removal of the solvent resulted in a yellow oil which solidified upon standing (210 mg). The product was purified using flash chromatography using EtOAc/MeOH/NEt_3 (10:1:0.1) as an eluent, to yield desired product **7** (75 mg, 41%). A significant quantity of starting material **6** (103 mg, 56%) was also recovered.

Method C: $NaBH_4/CF_3COOH$: $NaBH_4$ (17 mg, 0.45 mmol) was added to CF_3COOH (5 mL), followed by the addition of **6**·HCl (200 mg, 0.45 mmol) in small portions. After 1 h, the reaction mixture was diluted with H_2O (10 mL), basified with NH_4OH and extracted into $CHCl_3$ (3×15 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), and dried (K_2CO_3). Removal of the solvent resulted in a yellow oil (230 mg). The product was purified using flash chromatography with EtOAc/MeOH/NEt_3 (10:1:0.1) as an eluent, to yield desired product **7** (61 mg, 33%). A significant quantity of starting material **6** (115 mg, 63%) was also recovered.

Method D: NH_4HCO_2/Pd/C: A suspension of 10% Pd/C (50 mg) in EtOH/$H_2$0 (1:1, 1 mL) was added to a solution of **6**·HCl (200 mg, 0.45 mmol) and NH_4HCO_2 (290 mg, 4.5 mmol) in EtOH (10 mL) at room temperature. After 4 h, the reaction was complete by TLC. The solution was filtered through Celite®, and the EtOH was removed under reduced pressure. The residue was redissolved in EtOAc (20 mL), washed with brine (3×15 mL), and dried (Na_2SO_4). Removal of the solvent gave **7** (132 mg, 72%) as an off-white solid. The compound thus obtained exhibited identical spectral properties with those reported,[13] and it was shown to be identical to an authentic sample prepared as in Ref. 13. A sample was converted to the fumaric acid salt from ^{i}PrOH/MeOH mp>270°C (Dec) (lit[13] mp>270°C (Dec)).

6,7-Didehydro-4,14-dihydroxy-17-methyl-6,7:2′,3′-indolomorphinan (8). *$NaBH_4/CF_3COOH$:* **1** was treated as in Method C above. On basification with NH_4OH, the solution rapidly became dark and, after extraction and removal of the solvent, a dark tar-like material resulted.

NH_4HCO_2/Pd/C: **1** was treated as in Method D above. After filtration through Celite®, the solution rapidly became dark and, after removal of the solvent, a dark tar-like material resulted.

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