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An investigation of the N-demethylation of 3-deoxymorphine and the affinity of the alkylation products to μ, δ, and κ receptors

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Abstract—The N-demethylation of 3-deoxymorphine (**1**) was investigated using methyl chloroformate and hydrazine. 3-Deoxynormorphine (**2**) was obtained in 70% yield, and 3-deoxydihydronormorphine (**3**) was also obtained as a side product. The μ, δ, and κ receptor binding affinity of a series of N-substituted 3-deoxynormorphines **6** and **7** and N-substituted 3-deoxydihydronormorphines **8**–**11** was also determined.

1. Introduction

N-Demethylation is an important step in the synthesis of various morphinoids and morphinandienes. N-Demethylation of the naturally occurring opiates can be achieved in numerous ways. One of the oldest methods for N-demethylation of morphine and its congeners is the von Braun reaction.[1] Nowadays the use of this method is limited due to the toxicity of the reagent (BrCN). Alternatively, N-demethylation of opiates can proceed via the formation of N-oxide of the substrate.[2,3] Diethyl azodicarboxylate[4,5] is also a widely used reagent for N-demethylation of morphinandienes.[6,7] However, the most common method for N-demethylation of morphinans is the use of chloroformate esters as the N-demethylation agent. Such esters, include ethyl,[8] phenyl,[9,10] and benzyl[11] chloroformates. Methyl chloroformate was recently used for the N-demethylation of morphinans.[12–14] In this report, we investigated the structural modification and opioid receptor binding affinity of N-substituted-3-deoxymorphine and N-substituted-3-deoxydihydronormorphine derivatives as part of our continuing study on the development of novel chemical entities as potential analgesics and as pharmaceutical agents for cocaine abuse.

Keywords: Morphine; Codeine; N-demethylation; Opioid receptor; Binding affinity.
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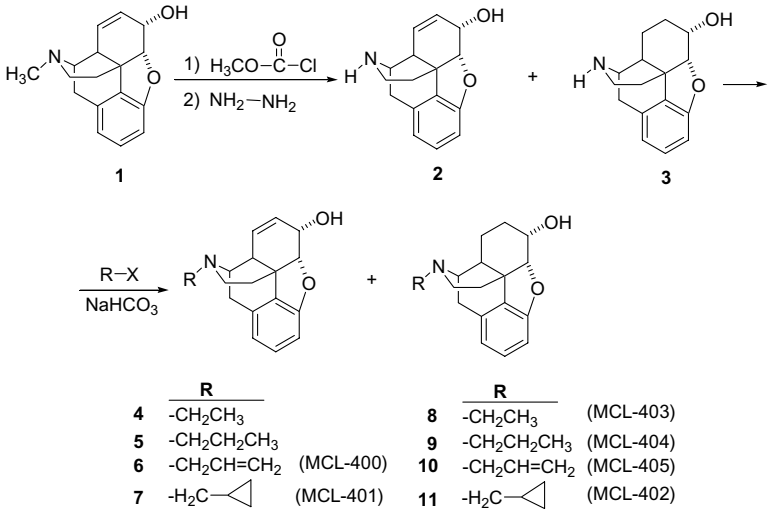
2. Results and discussion

The N-demethylation of 3-deoxymorphine (**1**)[14] with methyl chloroformate to 3-deoxynormorphine (**2**), followed by N-alkylation to the corresponding N-substituted 3-deoxynormorphines **4**–**7** proceeded in moderate yields (Scheme 1). In this reaction, 3-deoxydihydronormorphine (**3**) was also formed in varying ratios, depending on the reflux time used for the decomposition of the carbamate ester intermediate with hydrazine (Table 1). Both compounds **2** and **3** were very polar, and their R_f values on TLC were very close, which made them difficult to be separated by column chromatography. However, the formation of **3** during the N-demethylation of **1** could be detected by GC–MS and was further confirmed by the alkylation products **8**–**11**.

The optimum conditions for the decomposition of the carbamate ester intermediate during N-demethylation of **1** were found to be 72 h stirring at 80–90 °C, with hydrazine. In this case the desired product **2**, contaminated with **3** was obtained in 77% yield. N-Alkylation of the mixture of **2** and **3** led to the formation of N-substituted 3-deoxynormorphines **4**–**7** and N-substituted 3-deoxydihydronormorphines **8**–**11**. These *N*-alkyl derivatives can be easily separated by column chromatography. The isolation and characterization of **8**–**11** further confirmed the formation of **3** in the N-demethylation step. The formation of a saturated product was previously reported by Rice and May[9] in the N-demethylation of morphine and codeine with phenyl chloroformate and hydrazine.



Scheme 1.

Table 1. Decomposition of the carbamate ester intermediate with hydrazine at 80–90 °C

Reaction time (h)	Yield for **2** (%)	Ratio* of **2**:**3**
24	35	1:0
48	50	20:1
72	70	10:1
120	55	5:1

* Based on GC–MS analysis.

Brine et al.[12] and Gao et al.[13] have also reported N-demethylation of codeine using methyl chloroformate and hydrazine, but they did not report the formation of the reduced side product in this process. Repeating this procedure, we found that the reduced by-product could be the major product (60% yield) after allowing the reaction mixture to reflux for 5 days with anhydrous hydrazine, while the formation of the reduced product could be suppressed (<30%) under such optimized conditions. Apparently, hydrazine also acted as a hydrogen donor as for example in catalytic hydrogen transfer reactions.[15–17] Prolonged heating of **2** with hydrazine can cause its partial reduction to **3**.

We also investigated the in vitro binding of **6**–**11** at μ, δ, and κ receptors in comparison with morphine and nalorphine (Table 2). Our findings in the in vitro binding affinity are in agreement with the results reported by Reden et al.,[18] who investigated the role of the 3-phenolic hydroxyl group on opioid receptor interactions. The μ, δ, and κ binding affinities of compounds **6**–**11** showed that the lack of the phenolic hydroxyl group at the 3-position decreased the binding affinity when compared to the phenolic compounds such as morphine and nalorphine.

The μ receptor binding affinity of **6**, **7**, and **10**, **11** showed that in accordance with the earlier findings[18] the saturated morphinoids **10** and **11** had greater affinity on this receptor than the unsaturated morphinoids **6** and **7**.

3. Conclusion

We identified a side product **3** in the N-demethylation of **1** using methyl chloroformate. Alkylation of **2** yielded **4**–**7** whereas alkylation of **3** yielded **8**–**11**. As previously reported by Reden et al.,[18] the phenolic hydroxyl group in morphinoids is not essential for effective antinociception or binding to μ, δ, and κ receptors. The in vitro binding affinity of the 3-deoxynormorphine derivatives **6** and **7** were somewhat lower than the 3-deoxydihydronormorphine derivatives **10**, **11**.

Table 2. The μ, δ, and κ opioid receptor binding to CHO membranes by 3-deoxydehydromorphines (K_i values, nM)[a]

Compound	(^{3}H) DAMGO (μ)	(^{3}H) Naltrindole (δ)	(^{3}H) U69,593 (κ)
Morphine	0.88 ± 0.14	140 ± 18	24 ± 2
Nalorphine	0.52 ± 0.03	59 ± 5.1	0.74 ± 0.01
6 (MCL-400)	130 ± 12	>10 μM	50 ± 3.2
7 (MCL-401)	29 ± 3.1	>10 μM	30 ± 0.85
8 (MCL-403)	570 ± 16	6.8 ± 2.6	1100 ± 6.2
9 (MCL-404)	140 ± 6.2	>10 μM	300 ± 2.8
10 (MCL-405)	94 ± 4.5	>10 μM	110 ± 3.1
11 (MCL-402)	13 ± 1.5	3000 ± 398	31 ± 2.5

[a] CHO membranes, 0.5 mg of protein/sample, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C, in a final volume of 1 mL of 50 mM Tris–HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone. Data are the mean values SEM from three experiments, performed in triplicate.

4. Experimental

4.1. Chemical syntheses

Melting points were measured with a Thomas Hoover Capillary Melting Point Apparatus, and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on Varian 300 spectrometer, chemical shifts are reported in ppm (δ) from internal TMS and coupling constants (J) are measured in Hz. Thin layer chromatography was performed on precoated Merck 5554 Silica gel 40 F_{254} foils, the spots were visualized with Dragendorff's reagent. GC–MS analyses were performed with a Hewlett-Packard (Wilmington, DE.) 5890 gas chromatograph interfaced with a Hewlett-Packard 5972 mass selective detector. Elemental analyses were measured by the Atlantic Microlab Inc., Georgia.

4.1.1. N-Demethylation of 1. To a stirred mixture of **1**[14] (5.19 g, 19.25 mmol), and $NaHCO_3$ (26 g) in anhydrous chloroform (270 mL) was slowly added methyl chloroformate (28 mL, 362 mmol) under nitrogen, at 40 °C. The temperature was increased to 60 °C, and the reaction mixture was stirred overnight, filtered, washed with chloroform, and evaporated in vacuo. The oily residue (carbamate intermediate) was then dissolved in anhydrous methanol (16 mL), and was added dropwise hydrazine (98%, 31 mL) under nitrogen. After stirring for 3 days at 90–100 °C, the reaction mixture was quenched with water (50 mL) upon cooling, and then was extracted with dichloromethane/methanol = 3:1 (5×25 mL). The organic layer was washed with brine (50 mL), dried with sodium sulfate, filtered, and evaporated in vacuo. The white solid product was crystallized from anhydrous ether. The crystals were filtered and washed with anhydrous ether, affording a 10:1 mixture of **2** and **3** (3.71 g, 77%). The major product **2** was separated by column chromatography (chloform/methanol = 10:1) as a solid: mp 216–220 °C. ^{1}H NMR ($CDCl_3$) δ 1.9 (2H, m, C–H), 2.6 (1H, m, C–H), 2.925 (3H, m, C–H), 2.88 (1H, s, N–H), 3.67 (1H, m, H-9), 4.19 (1H, m, H-6), 4.82 (1H, d, $J_{5,6} = 8.0$ Hz, H-5), 5.28 (1H, m, H-8), 5.71 (1H, m, H-7), 6.59 (1H, d, $J_{2,3} = 10$ Hz, H-3), 6.64 (1H, d, $J_{1,2} = 10$ Hz, H-1), 7.02 (1H, t, H-2). Anal. Calcd ($C_{16}H_{17}NO_2$) C 75.29, H 6.67, N 5.49. Found: C 75.11, H 6.70, N 5.48. The minor product **3** was obtained as a mixture of **2** and **3** (10:1). GC–MS indicated: 3-deoxynormorphine (**2**) with a $t_R = 16.06$ min (91%, $M^+ = 255$) while 3-deoxydehydronormorphine (**3**) with a $t_R = 16.11$ min (9%, $M^+ = 257$).

4.1.2. General procedure for the N-alkylation of 2 and 3. To a stirred mixture of **2** and **3** (0.5 g, 1.96 mmol) and $NaHCO_3$ (0.25 g, 2.98 mmol) in anhydrous EtOH (10 mL), the appropriate alkyl halide (2.5 mmol) was added slowly, under nitrogen. The reaction mixture was allowed to reflux at 80–90 °C for 24 h. The reaction was cooled and diluted with water (40 mL), and nextracted with ethyl acetate (3×20 mL). The organic layers were combined and washed with brine (20 mL), dried with sodium sulfate, filtered, and evaporated in vacuo. The oily crude product was subjected to column chromatography (chloroform/methanol = 9:1) to afford two components as oils.

4.1.3. *N*-Ethyl-3-deoxynormorphine (4) and *N*-ethyl-3-deoxydihydronormorphine (8). In this case iodoethane was added in higher molar ratio (3 mL, 37.5 mmol). The first eluted compound was the *N*-ethyl-3-deoxynormorphine (**4**): 0.4 g (72%), mp (HCl-salt): 241–244 °C. ^{1}H NMR (from salt, CD_3OD) δ 1.40 (3H, t, CH_3), 2.20 (2H, m, C–H), 3.2 (7H, m, C–H), 4.26 (2H, m, H-6, H-9), 4.90 (1H, m, H-5), 5.36 (1H, m, H-8), 5.77 (1H, m, H-7), 6.61 (1H, d, $J_{2,3} = 8$ Hz, H-3), 6.69 (1H, m, H-1), 7.07 (1H, t, H-2); MS m/z (relative intensity) 283 (M^+, 50%), 268 (M^+-15, 30%). Anal. Calcd ($C_{18}H_{21}NO_2HCl$): C 67.60, H 6.88, N 4.38. Found: C 67.48, H 6.91, N 4.36. The second eluted compound was identified as *N*-ethyl-3-deoxydehydronormorphine (**8**): 50 mg (8.9%), mp (HCl-salt): 150–154 °C. ^{1}H NMR (base, $CDCl_3$) δ 1.18 (3H, t, CH_3), 1.48 (3H, m, C–H), 1.70 (1H, m, C–H), 2.00 (1H, m, C–H) 2.30 (2H, m, C–H), 2.62 (5H, m, C–H), 2.97 (1H, d, $J = 19.6$ Hz, H-10β), 3.34 (1H, m, C–H), 4.02 (1H, dd, H-6), 4.57 (1H, d, $J = 5.7$ Hz, H-5), 6.64 (1H, d, $J = 8.2$ Hz, H-3), 6.68 (1H, d, $J = 8$ Hz, H-1), 7.07 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 12.2, 19.0, 20.9, 26.7, 36.6, 39.3, 41.7, 45.0, 48.6, 56.7, 67.2, 89.5, 105.9, 118.4, 128.5, 128.9, 134.2, 158.8; GC–MS m/z (relative intensity) 285 (M^+, 100%), 270 (M^+-15, 85%). Anal. Calcd (C_{18} H_{23} NO_2·HCl): C 67.17, H 7.52, N 4.35. Found: C 66.98, H 7.59, N 4.33.

4.1.4. *N*-Propyl-3-deoxynormorphine (5) and *N*-propyl-3-deoxydihydronormorphine (9). The reaction was carried out with iodopropane. The first eluted compound was the *N*-propyl-3-deoxynormorphine **(5)**: 0.33 g (57%), mp (HCl-salt): 244–246 °C. ^{1}H NMR (from the salt, CD_3OD) δ 1.07 (3H, t, CH_3), 1.86 (2H, m, C–H), 2.05 (1H, m, C–H), 2.37 (1H, m, C–H), 3.20 (7H, m, C–H), 3.00 (1H, s, OH), 4.27 (2H, m, H-6, H-9), 4.90 (1H, m, H-5), 5.35 (1H, m, H-8), 5.75 (1H, m, H-7), 6.61 (1H, d, $J_{2,3} = 7$ Hz, H-3), 6.69 (1H, d, $J_{1,2} = 7$ Hz, H-1), 7.07 (1H, t, H-2); MS m/z (relative intensity) 297 (M^+, 20%), 268 ($M-29$, 95%). Anal. Calcd ($C_{19}H_{23}NO_2$·HCl): C 68.36, H 7.19, N 4.20. Found: C 68.18, H 7.21, N 4.19. The second eluted compound was identified as *N*-propyl-3-deoxydihydronormorphine (**9**): 55 mg (9.4%), mp (HCl-salt): 164–167 °C; ^{1}H NMR (base, $CDCl_3$) δ 0.93 (3H, t, CH_3), 1.50 (5H, m, C–H), 1.66 (1H, m, C–H), 1.90 (1H, m, C–H) 2.32 (6H, m, C–H), 2.62 (1H, m, C–H), 2.97 (1H, d, $J = 19.5$ Hz, H-10β), 3.19 (1H, m, C–H), 4.00 (1H, m, H-6), 4.56 (1H, d, $J = 5.7$ Hz, H-5), 6.62 (1H, d, $J = 8.0$ Hz, H-3), 6.66 (1H, d, $J = 8.0$ Hz, H-1), 7.05 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 11.9, 19.3, 20.7, 21.2, 26.6, 37.2, 39.6, 42.0, 45.0, 56.9, 57.4, 67.5, 89.7, 105.7, 118.4, 128.3, 128.9, 135.0, 158.8; GC–MS m/z (relative intensity) 299 (M^+, 15%), 270 (M^+-29, 100%). Anal. Calcd ($C_{19}H_{25}NO_2$·HCl): C 67.94, H 7.80, N 4.17. Found: C 67.81, H 7.85, N 4.15.

4.1.5. *N*-Allyl-3-deoxynormorphine (6) and *N*-allyl-3-deoxydihydronormorphine (10). The reaction was carried out with allyl bromide, and purified via column chromatography (chloroform/methanol = 19:1). The first eluted compound was the *N*-allyl-3-deoxynormorphine (**6**): 0.32 g (56%), mp (HCl-salt): 166–168 °C. ^{1}H NMR (base, $CDCl_3$) δ 1.66 (1H, s, OH), 1.85 (1H, m, C–H), 2.06 (1H, m, C–H), 2.35 (2H, m, C–H), 2.70 (2H, m, C–H), 3.03 (1H, d, $J = 20$ Hz, H-10β), 3.20 (2H, m, C–H), 3.48 (1H, m, C–H), 4.19 (1H, m, H-6), 4.84 (1H, m, H-5), 5.20 (3H, m, =C–H), 5.68 (1H, m, H-7), 5.86 (2H, m, =C–H), 6.58 (1H, d, $J = 8.5$ Hz, H-3), 6.62 (1H, d, $J = 8.5$ Hz, H-1), 7.00 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 21.7, 35.7, 40.8, 42.7, 44.5, 56.2, 58.2, 66.6, 90.6, 106.1, 117.6, 119.0, 128.1, 128.6, 129.7 135.4, 135.7, 158.8; MS *m*/*z* (relative intensity) 295 (M^+, 100%). Anal. Calcd ($C_{19}H_{21}NO_2 \cdot HCl \cdot H_2O$): C 65.23, H 6.91, N 4.00. Found: C 65.33, H 6.89, N 3.99. The second eluted compound was identified as *N*-allyl-3-deoxydihydronormorphine (**10**): 52 mg (8.9%), mp (HCl-salt): 145–149 °C (lit[18]: 217–218 °C); ^{1}H NMR (base, $CDCl_3$) δ 1.46 (2H, m, C–H), 1.65 (1H, m, C–H), 1.85 (3H, m, C–H), 2.20 (2H, m, C–H), 2.21 (1H, m, C–H), 2.62 (1H, m, C–H), 2.97 (1H, d, $J = 20$ Hz, H-10β), 3.16 (3H, m, C–H), 4.01 (1H, dd, H-6), 4.57 (1H, d, $J = 5.4$ Hz, H-5), 5.20 (2H, m, =C–H), 5.87 (1H, m, =C–H), 6.63 (1H, d, $J = 8.5$ Hz, H-3), 6.68 (1H, d, $J = 8.5$ Hz, H-1), 7.07 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 19.3, 21.2, 26.7, 37.2, 39.9, 42.0, 44.7, 57.2, 58.3, 67.5, 89.7, 105.7, 117.6, 118.5, 128.4, 128.9, 135.0, 135.6, 158.8; GC–MS *m*/*z* (relative intensity) 297 (M^+, 100%). Anal. Calcd ($C_{19}H_{23}NO_2HCl$): C 68.35, H 7.25, N 4.20. Found: C 68.45, H 7.21, N 4.22.

4.1.6. *N*-Cyclopropylmethyl-3-deoxynormorphine and (7) *N*-cyclopropylmethyl-3-deoxydihydronor-morphine (11). The reaction was carried out with bromomethylcyclopropane. The first eluted compound was the *N*-cyclopropylmethyl-3-deoxynormorphine (**7**): 0.34 g (57%), mp (HCl-salt): 194–197 °C. ^{1}H NMR (base, $CDCl_3$) δ 0.16 (2H, m, cyclopropyl C–H), 0.55 (2H, m, cyclopropyl C–H), 0.88 (1H, m, cyclopropyl C–H), 1.64 (1H, s, OH), 1.86 (1H, m, C–H), 2.10 (1H, m, C–H), 2.38 (4H, m, C–H), 2.70 (1H, m, C–H), 2.83 (1H, m, C–H), 2.98 (1H, d, $J = 20$ Hz, H-10β), 3.70 (1H, m, C–H), 4.19 (1H, m, H-6), 4.84 (1H, d, H-5), 5.32 (1H, m, H-8), 5.69 (1H, m, H-7), 6.59 (2H, t, H-3, H-1), 7.00 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 3.7, 3.9, 9.3, 21.6, 35.7, 40.8, 42.8, 44.8, 56.2, 59.8, 66.6, 90.7, 106.0, 118.9, 128.1, 128.7, 133.1 135.5, 141.6, 158.8; MS *m*/*z* (relative intensity) 309 (M^+, 100%). Anal. Calcd (C_{20} H_{23} $NO_2 \cdot HCl$): C 69.46, H 6.66, N 4.05. Found: C 69.08, H 6.71, N 4.02. The second eluted compound was identified as *N*-cyclopropylmethyl-3-deoxydihydronormorphine (**11**): 58 mg (9.5%), mp (HCl-salt): 165–170 °C; ^{1}H NMR (base, $CDCl_3$) δ 0.16 (2H, m, cyclopropyl C–H), 0.56 (2H, m, cyclopropyl C–H), 0.90 (1H, m, cyclopropyl C–H), 1.10 (1H, m, C–H), 1.49 (3H, m, C–H), 1.70 (1H, m, C–H), 1.97 (1H, m, C–H), 2.30 (5H, m, C–H), 2.81 (1H, m, C–H), 2.94 (1H, d, $J = 20$ Hz, H-10β), 3.44 (1H, m, C–H), 4.01 (1H, m, H-6), 4.58 (1H, d, H-5), 6.63 (1H, d, $J = 8.5$ Hz, H-3), 6.66 (1H, d, $J = 8.5$ Hz, H-1), 7.06 (1H, t, H-2); ^{13}C NMR (base, $CDCl_3$) δ 3.8, 3.9, 9.1, 19.3, 21.2, 26.7, 37.1, 39.6, 42.0, 45.1, 57.2, 59.8, 67.5, 89.7, 105.8, 118.5, 128.4, 128.9, 136.1, 158.8; GC–MS *m*/*z* (relative intensity) 311 (M^+, 100%). Anal. Calcd ($C_{20}H_{25}NO_2HCl$): C 69.05, H 7.53, N 4.03. Found: C 68.95, H 7.56, N 4.02.

4.2. Receptor binding assays

The μ, δ, and κ receptor binding affinities of the synthesized compounds were evaluated using a previously reported procedure.[19,20] Nalorphine was purchased from Sigma/RBI.

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