Some 14β-Substituted Analogues of N-(Cyclopropylmethyl)normorphine

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A series of N-(cyclopropylmethyl)-14β-substituted-normorphine analogues was synthesized and tested for opioid agonist and antagonist activity in the guinea pig ileum and mouse vas deferens preparations. The 14β-bromo compound proved to be a pure antagonist equal in potency to naloxone in the guniea pig ileum assay. In contrast to N-(cyclopropylmethyl)-14β-hydroxynormorphine which was a pure antagonist, the corresponding sulfur analogue was about equal to nalorphine in agonist and antagonist potency.

Recently we reported the synthesis and narcotic agonist activity of a series of 14β-substituted analogues of morphine.[1] In order to study the effect of these 14β-substituents on narcotic antagonist activity, we prepared a series of 14β-substituted analogues of N-(cyclopropylmethyl)normorphine and evaluated their agonist and antagonist activity in the guinea pig ileum and mouse vas deferens preparations. The 14β-substituents were hydroxyl, nitro, mercapto, bromo, and chloro groups.

Chemistry. N-(Cyclopropylmethyl)-14β-hydroxymorphine was prepared as shown in Scheme I. (CPM = cyclopropylmethyl). N-(Cyclopropylmethyl)northebaine (1), prepared as previously described,[2,3] was treated with performic acid[4] to give **2**. This low-melting compound was reduced with sodium borohydride to furnish the oily diol **3**, characterized as the diacetate **4**. O-Demethylation with boron tribromide gave the desired compound **5**, which was isolated as the crystalline hydrochloride.

Treatment of 1 with N_2O_4, followed by hydrolysis, gave a mixture of the desired 14β-nitro analogue **6** and N-(cyclopropylmethyl)-14β-nitronorthebaine (**7**) in low yields (Scheme II). The NMR of **7** was compatible with the assigned structure. A similar mixture was encountered when thebaine was treated with N_2O_4.[1] Demethylation of **6** afforded N-(cyclopropylmethyl)-14β-nitronormorphinone (**8**).

N-(Cyclopropylmethyl)-14β-mercaptonormorphine (**11**) was prepared by treating **1** with thiocyanogen, followed by $LiAlH_4$ reduction of the 14β-(thiocyanato) derivative, **9**, to N-(cyclopropylmethyl)-14β-mercaptonorcodeine (**10**). O-Demethylation with boron tribromide gave **11**.

Treatment of **1** with N-bromosuccinimide, followed by hydrolysis, gave N-(cyclopropylmethyl)-14β-bromonorcodeinone (**12**), which on demethylation with BBr_3 gave the required 14β-bromo-N-(cyclopropylmethyl)normorphinone (**13**). The analogous 14β-chloro derivative **15**, was obtained by substituting N-chlorosuccinimide for NBS in the above sequence.

Pharmacology. The agonist and antagonist activities of these compounds were determined in the guinea pig ileum and mouse vas deferens preparations using the procedures developed by Kosterlitz and his colleagues.[5] The results are summarized in Table I. For comparative purposes we have included the values determined previously for morphine (**16**), naloxone (**17**), naltrexone (**18**), nalorphine (**19**), and N-(cyclopropylmethyl)normorphine (**20**). The IC_{50} (nM) and the K_e (nM) values are a measure of agonist and antagonist potencies, respectively.[6]

All of the cyclopropylmethyl derivatives proved to have moderate to excellent opioid antagonist action in the guinea pig ileum preparation. Each was less potent in the mouse vas deferens, which is in accord with previous observations.

We had reported earlier[1] that 14β-nitromorphinone was an extremely weak agonist in the guinea pig ileum. In contrast, the corresponding cyclopropylmethyl analogue is more potent than morphine as an agonist and about equal to nalorphine as an antagonist and slightly less potent as an agonist.

N-(Cyclopropylmethyl)-14β-hydroxynormorphine (**5**) is an antagonist without agonist activity in both preparations. The corresponding sulfur analogue is a mixed agonist–antagonist. Both 14β-halogen derivatives are antagonists devoid of agonist effects. The bromo compound **13** is equal to naloxone in potency in the guinea pig ileum preparation and in the mouse vas deferens.

It is clear from these results that functional groups other than hydroxyl at the 14β position can furnish mixed agonist–antagonist activity, as well as pure antagonists comparable to naloxone in potency.

Experimental Section

Melting points were determined using Laboratory Devices Melt-Temp apparatus and were corrected. Chemical analyses were determined by Instranal Laboratory, Rensselaer, N.Y. Analytical results for the elements indicated were within ±0.4% of the theoretical values.

N-(Cyclopropylmethyl)-14β-hydroxynorcodeinone (2). Hydrogen peroxide (30%, 1.3 mL, 13 mmol) was added in one portion to a stirred solution of 1 (3.51 g, 10 mmol), in a mixture of formic acid (92%, 1.3 mL) and H_2SO_4 (0.7%, 4.1 mL). The mixture was heated at 40 °C (bath temperature) for 6 h. After cooling to room temperature, the mixture was diluted with ice-cold water and then made basic with concentrated NH_4OH while stirring and cooling the mixture in an ice bath. The precipitate was filtered out and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), and concentrated. The residual oil crystallized from EtOH at 0 °C to give 1.42 g (41%) of **2**. The compound was recrystallized from EtOH: mp 51–52 °C. Anal. ($C_{21}H_{13}NO_4$) C, H, N.

N-(Cyclopropylmethyl)-14β-hydroxynorcodeine (3). To a stirred solution of **2** (1.43 g, 0.004 mol) in 25 mL of MeOH was added in portions $NaBH_4$ (0.5 g, 0.012 mol) while keeping the temperature of the system at 25 °C. After 1 h, the mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution

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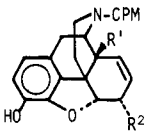
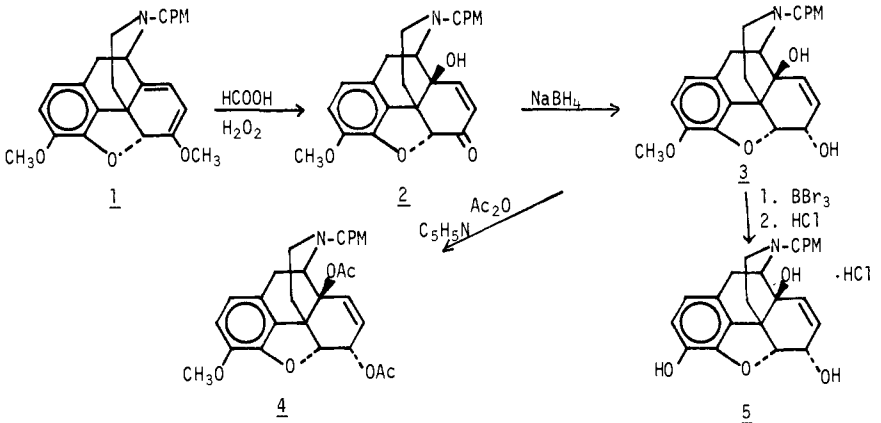
Table I. Opioid Agonist and Antagonist Activity of Some 14β-Substituted Analogues of *N*-(Cyclopropylmethyl)normorphine in the Guinea Pig Ileum and Mouse Vas Deferens Preparations



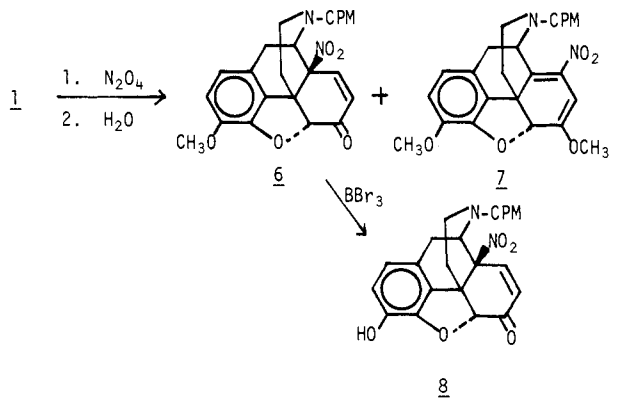
			guinea pig ileum[a]		mouse vas deferens[a]	
no.	R^1	R^2	agonist act.: IC_{50}, nM	antagonist act. against normorphine: K_e, nM	agonist act.: IC_{50}, nM	antagonist act. against normorphine: K_e, nM
5	OH	H, OH	∞	2.35 ± 0.60 (3)	∞	10.5, 9.0
8	NO_2	=O	41.2 ± 19.1 (3)	4.44 ± 0.97 (3)	580, 330	14.9 ± 1.6 (3)
11	SH	H, OH	39.1 ± 6.9 (5)	1.69, 1.26	218 ± 29 (3)	22.9, 20.0
13	Br	=O	∞	1.36 ± 0.06 (3)	∞	2.35, 2.83
15	Cl	=O	∞	3.92 ± 0.57 (3)	∞	16.6 ± 2.1 (3)
16	morphine[b]		68.2 ± 15.0 (6)	none	492 ± 53 (7)	none
17	naloxone[b]		∞	1.22 ± 0.03 (6)	∞	3.66 ± 0.29 (4)
18	naltrexone[b]		max inhibn 25%	0.38 ± 0.07 (6)		
19	nalorphine[b]		24.3 ± 1.3 (6)	4.47 ± 0.59 (6)	535 ± 23 (3)	28.7 ± 3.2 (8)
20	H	H, OH	2.16 ± 0.14 (4)	0.80 ± 0.11 (4)		

[a] The values are the means ± SEM; the number of observations is given in parentheses. All compounds were tested using their free bases, except 5, which was tested as the HCl salt. [b] The values reported here were taken from ref 5-7.

Scheme I



Scheme II



was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo to give **3** as an oil: yield 1.4 g (98%). The compound was characterized as the diacetate.

***N*-(Cyclopropylmethyl)-14β-hydroxynorcodeine 6,14-Diacetate (4).** Pyridine (0.4 mL, 4.7 mmol) was added in one portion to a stirred solution of **3** (0.42 g, 1.2 mmol) in Ac_2O (0.45 mL, 4.7 mmol), and the mixture was allowed to stir at room temperature for 24 h. The excess reagents were removed in vacuo to leave a residue which was suspended in Et_2O and stored in the refrigerator for 4 h. The solid was removed by filtration to give **4** as white crystals: yield 0.42 g (81%). The compound recrystallized from EtOH, mp 164–165.5 °C. Anal. ($C_{25}H_{29}NO_6$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-hydroxynormorphine Hydrochloride (5).** A solution of **3** (0.253 g, 0.71 mmol) in 10 mL of $CHCl_3$ was added dropwise at room temperature to a stirred solution of BBr_3 (0.67 mL, 7.0 mmol) in 20 mL of $CHCl_3$. After 0.5 h, the reaction mixture was poured into a mixture of ice and 10 mL of a concentrated solution of NH_4OH and stirred at 0 °C for 0.5 h. The organic layer was removed and saved. The aqueous portion was saturated with salt and extracted with $CHCl_3$/EtOH solution (2:1, 3 × 50 mL). The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo to give **5** as an oil: yield 0.45 g (19%). The HCl salt of **5** was prepared in the following manner: A 0.3-mL solution of the oil in $CHCl_3$ was added dropwise into Et_2O saturated with HCl gas and stored at 0 °C overnight. After decanting the Et_2O and drying thoroughly, a 1-mL solution of the residue in EtOH was warmed gently with shaking to induce crystallization and then allowed to stand at 0 °C for 5 h. The solid was removed by filtration to give 35 mg of the HCl salt, which was recrystallized from MeOH. The transparent crystals turned opaque about 120 °C and then melted at 283–285 °C. Anal. ($C_{20}H_{23}NO_4$·HCl·MeOH) C, H, N.

***N*-(Cyclopropylmethyl)-14β-nitronorcodeinone (6) and *N*-(Cyclopropylmethyl)-8-nitronorthebaine (7).** Dinitrogen tetroxide (3.68 g, 0.04 mol) in dry ethyl acetate (15 mL, flushed with N_2) was added dropwise within 1.5 h, from an addition funnel jacketed with a dry ice–acetone bath, to a stirred solution of **1** (13 g, 0.037 mol) in 500 mL of dry THF (flushed with N_2) cooled to −60 °C. After the addition, the mixture was allowed to warm-up to room temperature within 1 h and then a saturated solution of $NaHCO_3$ was added to adjust the pH of the mixture to about 9. After stirring for 1 h, the mixture was diluted with H_2O and

extracted with $CHCl_3$ (2 × 500 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a dark oil, which was column chromatographed on silica gel (Et_2O). The resulting oil which consisted of compounds **6** and **7** was chromatographed on preparative TLC plates (silica gel, $CHCl_3$). Compound **6** (R_f 0.6) was obtained as an oil, which crystallized on trituration in EtOH to give pale yellow crystals: yield 1.8 g (12%); mp 115–117 °C after crystallization from EtOH; NMR ($CDCl_3$) δ 6.70 (2 H, aromatic), 6.60 (d, 1 H, J = 10.0 Hz, 7-H), 6.21 (d, 1 H, J = 10.0 Hz, 8-H), 5.20 (s, 1 H, 5-H), 4.50 (d, 1 H, J = 6 Hz, 9-H), 3.85 (s, 3 H, OCH_3), 3.30 (d, 1 H, J = 17 Hz, 10β-H). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N. *N*-(Cyclopropylmethyl)-8-nitronorthebaine (**7**; R_f 0.3) was removed by extraction to give an oil, which also crystallized from EtOH: yield, 750 mg (5%); mp 99–102 °C; NMR ($CDCl_3$) δ 6.65 (2 H, aromatic), 5.80 (s, 1 H, 7-H), 5.31 (s, 1 H, 5-H), 4.70 (br d, 1 H, 9-H), 3.82, 3.65 (2 s, S, 6 H, $2OCH_3$). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-nitronormorphinone (8).** A solution of **6** (0.25 g, 0.66 mmol) in 10 mL of dry $CHCl_3$ was added dropwise to a stirred solution of BBr_3 (0.38 mL, 3.9 mmol) in 20 mL of dry $CHCl_3$ at room temperature and stirred for 0.5 h. The mixture, which consisted of a yellow suspension in $CHCl_3$, was poured into a mixture of ice and 10 mL of concentrated NH_4OH and stirred at 0 °C for 0.5 h. The organic phase was separated. The aqueous portion was saturated with salt and extracted with $CHCl_3$/EtOH solution (2:1, 2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was purified by column chromatography on silica gel ($CHCl_3$). After the solvent was removed, the residual oil crystallized in EtOH at 0 °C to give **8**: yield 65 mg (27%); mp 219 °C dec. Anal. ($C_{20}H_{20}N_2O_5$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-(thiocyanato)norcodeinone (9).** Thiocyanogen [$(SCN)_2$] was prepared by the dropwise addition of Br_2 (4.8 g, 0.03 mol) in 8 mL of glacial HOAc to a stirred suspension of $Pb(SCN)_2$ (11.0 g, 0.037 mol in 100 mL of HOAc maintained at 18 °C. After complete decolorization of Br_2 had occurred, the suspension of $PbBr_2$ was removed by gravity filtration. The colorless solution of $(SCN)_2$ was added dropwise within 10 min to a stirred solution of **1** (3.5 g, 0.01 mol) in 80 mL of HOAc. After 2 h at 18 °C, the polymerized $(SCN)_n$ was removed by filtration. The filtrate was cautiously neutralized with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on a preparative TLC plate (silica gel), using Et_2O as eluant, to give **9** (R_f 0.75) as an oil, which crystallized on trituration in EtOH: yield 0.35 g (9%). The compound, which recrystallized from EtOH, turned red around 120 °C and then charred but did not melt even at 300 °C. Anal. ($C_{22}H_{22}N_2O_3S$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-mercaptonorcodeine (10).** To a stirred suspension of $LiAlH_4$ (0.32 g, 010084 mol) in dry THF (20 mL) at 0 °C and under N_2 was added, in portions, a suspension of **9** (1.1 g, 0.0028 mol) in dry THF (10 mL). The mixture was allowed to warm to room temperature and then refluxed for 1 h. After the mixture was cooled to 0 °C and following deactivation of the excess $LiAlH_4$ with aqueous THF, the inorganic salts were removed by filtration. The filtrate was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residual oil crystallized on trituration in EtOH at 0 °C to give **10**: yield 0.36 g (35%). The compound recrystallized from EtOH: mp 118–120 °C. Anal. ($C_{21}H_{25}N_2O_5S$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-mercaptonormorphine (11).** A solution of **10** (0.19 g, 0.51 mmol) in 5 mL of dry $CHCl_3$ was added dropwise to a stirred solution of BBr_3 (0.3 mL, 3.0 mmol) in 25 mL of dry $CHCl_3$. After it was stirred for 0.5 h, the reaction mixture was poured into a mixture of ice and 10 mL of concentrated NH_4OH solution. The two-phase system was stirred at 0 °C for 0.5 h and separated. The aqueous layer was saturated with salt and extracted with $CHCl_3$/EtOH solution (2:1, 2 × 60 mL). The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo. The solid residue, suspended in MeOH and kept in the refrigerator overnight, was removed to give **11**, 90 mg (49%), which recrystallized from MeOH, mp 196–198 °C. Anal. ($C_{20}H_{23}N_2O_3S$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-bromonorcodeinone (12).** To a stirred solution of **1** (3.3 g, 0.0094 mol) in 50 mL of acetone/water solution (2:1, individual solvents degassed before mixing) under N_2 was added, within a 10-min period, a solution of NBS (2.0 g, 0.011 mol) in an acetone/water solution (2:1, 40 mL) while the temperature of the system was maintained between 10 and 15 °C. The stirring was continued for 10 min and then the system was cooled to 0 °C. Fifty milliliters of H_2O was added dropwise to the solution and stirred for 15 min. The solution was extracted with $CHCl_3$ (2 × 60 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel ($CHCl_3/Et_2O$, 1:1) to give an oil, which crystallized under EtOH as yellow plates: yield 0.95 g (21%). The compound gave a broad melting point, 148–152 °C. Anal. ($C_{21}H_{22}NO_3Br$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-bromonormorphinone (13).** A solution of **12** (0.23 g, 0.55 mmol) in 5 mL of dry $CHCl_3$ was added dropwise at room temperature to a stirred solution of BBr_3 (0.32 mL, 3.3 mmol) in 25 mL of $CHCl_3$. After 0.5 h, the mixture was poured into a mixture of ice and 12 mL of concentrated NH_4OH and stirred at 0 °C for 0.5 h. The $CHCl_3$ portion was separated. The aqueous portion was saturated with salt and extracted with a $CHCl_3$/EtOH solution (2:1, 2 × 60 mL). The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 49:1). The resulting oil crystallized from EtOH to give **13** as yellow needles: yield 100 mg (38%). The compound gradually charred above 140 °C and did not melt even at 300 °C. Anal. ($C_{20}H_{20}NO_3Br$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-chloronorcodeinone (14).** To a stirred solution of **1** (1.0 g, 2.8 mmol) in 20 mL of acetone/water (2:1) cooled to 10 °C and under N_2 was added dropwise, over a 10-min period, a solution of NCS (0.4 g, 3.0 mmol) in 20 mL of acetone/water (2:1). The temperature of the solution was maintained between 10 and 15 °C during the addition, and the solution was stirred for 10 min thereafter. Forty milliliters of H_2O was added to the solution dropwise with stirring and then cooled to 0 °C. After 0.5 h at this temperature, the solution was extracted with $CHCl_3$. The organic portion was washed with H_2O, dried, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, $CHCl_3$) to give an oil, 0.29 g (27%). The oil crystallized on trituration in EtOH at 0 °C to give pale, yellow crystals. Analytical sample was recrystallized from EtOH: mp 133–135 °C. Anal. ($C_{21}H_{22}NO_3Cl$) C, H, N.

***N*-(Cyclopropylmethyl)-14β-chloronormorphinone (15).** A solution of **14** (0.7 g, 0.002 mol) in 10 mL of dry $CHCl_3$ was added dropwise to a stirred solution of BBr_3 (1.9 mL, 0.021 mol) in 30 mL of $CHCl_3$ at room temperature. After 0.5 h, the reaction mixture was poured into a mixture of ice and 12 mL of concentrated NH_4OH solution. The two-phase system was stirred at 0 °C for 0.5 h. The $CHCl_3$ portion was removed and the aqueous portion was saturated with salt and extracted with a $CHCl_3$/EtOH solution (2:1, 2 × 100 mL). The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo to give an oil, which was chromatographed on a column of silica gel ($CHCl_3$/MeOH, 49:1). The resulting oil crystallized under EtOH to give **15**: yield 0.31 g (40%); mp 185 °C dec. Anal. ($C_{20}H_{20}NO_3Cl$) C, H, N.

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