Cinnamoyl Derivatives of 7α-Amino- and 7α-(Aminomethyl)-*N*-(cyclopropylmethyl)-6,14-*endo*-ethanotetrahydronororipavines are High-Potency Opioid Antagonists

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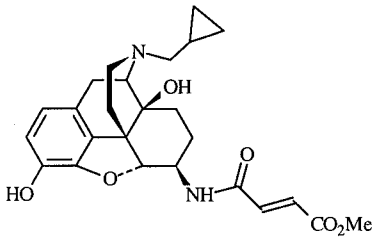
Methods have been developed for the synthesis of 7α-amino- and 7α-(aminomethyl)-*N*-cyclopropylmethyl-6,14-*endo*-ethanotetrahydronororipavines and their cinnamoyl derivatives (*Schemes 1* and *3*). In displacement binding assays, the cinnamoyl derivatives **4c** and **5c** had high affinity for opioid receptors, but no particular selectivity for any receptor type or differences in affinity between **4c** and **5c** (*Table 1*). In tissue assays for opioid receptor function, in which both **4c** and **5c** were potent antagonists, the aminomethyl derivative **5c** was 20- to 70-fold more potent than the amino derivative **4c** (*Table 2*). These data are in keeping with previously reported *in vivo* data and confirm the major effect of the methylene spacer in **5c**.

Introduction. – Understanding of the function of receptor systems is dependent on the availability of selective antagonists and enhanced by the availability of selective irreversible antagonists or affinity ligands. The first selective irreversible μ-opioid antagonist was β-funaltrexamine (β-FNA; **1**) [1–3], which has been widely used but suffers from short-lived κ-agonist activity that must be allowed to wane before it can be effectively used. More recently, a series of cinnamoyl derivatives of 14β-amino-*N*-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxymorphinan-6-one), including clocinnamox (C-CAM; **2a**) and methcinnamox (M-CAM; **2b**), have been reported [2] to have selective irreversible μ-antagonist activity without any agonist activity. The ring-C-bridged series of oripavine derivatives called orvinols, *e.g.* **3**, have a variety of opioid profiles including the antagonist diprenorphine (*Revivon*®; **3a**) and the partial agonist buprenorphine (*Temgesic*®; **3b**), which is used clinically as an analgesic and for the pharmacotherapy of opiate abuse [3]. In the orvinol series, the side chain at C(7) critically determines the opioid profile. In the orvinol series **3**, very few pure opioid antagonists were discovered. Diprenorphine (**3a**) is a μ antagonist but also has partial κ-agonist effects; only the primary and secondary alcohols **3c**–**e** had no agonist effects in rodent antinociceptive tests [4]. It was thus of interest to introduce at the 7α position the cinnamoylamino group present in C-CAM (**2a**) and M-CAM (**2b**). We here report the synthesis of the precursor amines **4a** and **5a**[1]) and two cinnamoylamino derivatives **4c** and **5c** in which this group is attached in α-position at C(7) of the bridged oripavine structure directly or separated by a methylene

[1]) Preliminary accounts of this research were given at the 'International Narcotics Research Conference', St. Andrews, Scotland, 1995, and 'College on Problems of Drug Dependence', San Juan, Puerto Rico, 1996.

spacer, respectively. For these derivatives, we also report *in vitro* pharmacological evaluation.



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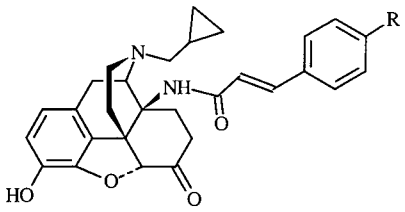
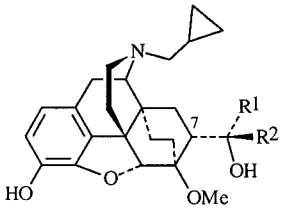
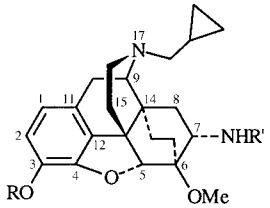


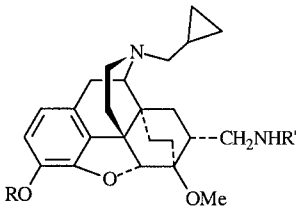
2a R = Cl
b R = Me



3a $R^1 = R^2$ = Me (diprenorphine)
b R^1 = Me, R^2 = ^{t}Bu (buprenorphine)
c $R^1 = R^2$ = H,
d R^1 = Me, R^2 = H
e R^1 = H, R^2 = Me



4a R = R' = H
b R = Me, R' = H
c R = H, R' = (*E*) – PhCH = CHCO
d R = Me, R' = MeCO

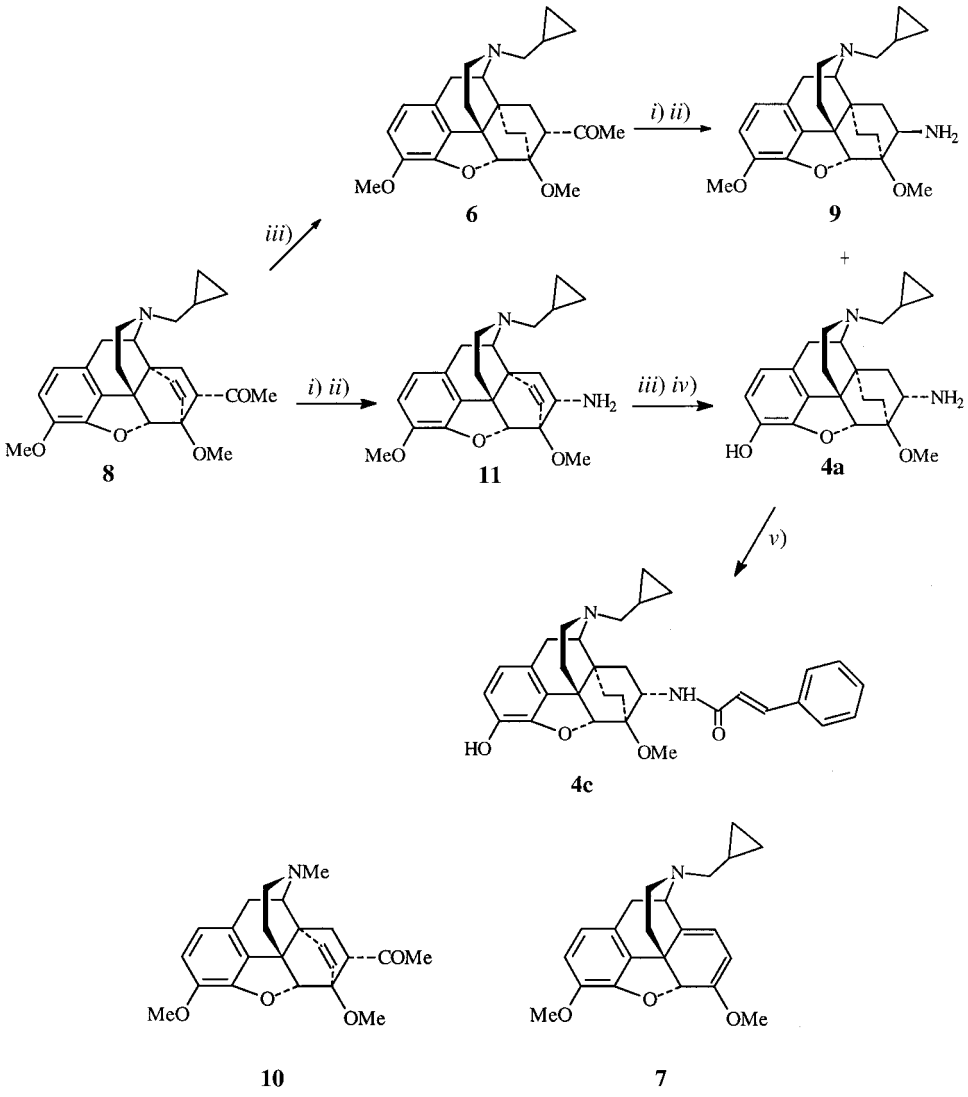


5a R = R' = H
b R = Me, R' = H
c R = H, R' = (*E*) – PhCH = CHCO
d R = Me, R' = MeCO

Synthesis. – The planned route to the 7α-amino precursor **4a** involved initial *Schmidt* reaction with *N*-(cyclopropylmethyl)nordihydrothevinone **6** to give the 7α-(acetylamino) derivative **4d**. The thevinone derivative **6** was prepared by *Diels-Alder* reaction of *N*-(cyclopropylmethyl)northebaine **7** with methyl vinyl ketone and hydrogenation of the adduct **8** (*Scheme 1*). However, the *Schmidt* reaction conditions promoted epimerization of the ketone **6** and resulted in formation of a substantial amount of the epimeric 7β-amino derivative **9** [5]. Since the *Schmidt* reaction with thevinone (**10**) had not been reported to give any epimerization [6], the route to the

amino-ethano derivative **4a** was modified to delay hydrogenation of the etheno bridge until after the *Schmidt* reaction and hydrolysis of the acetylamino group (*Scheme 1*). The 7α-amino-etheno intermediate **11** had been previously reported [7] but was prepared by a different route from thevinone (**10**) *via* the *Schmidt* reaction followed by conversion of the *N*-methyl to the *N*-(cyclopropylmethyl) group. In our synthesis, **11** was obtained in 42% overall yield from **7**. Hydrogenation and 3-*O*-demethylation with KOH in digol (=diethylene glycol) at 210° afforded the oripavine derivative **4a**, which

Scheme 1

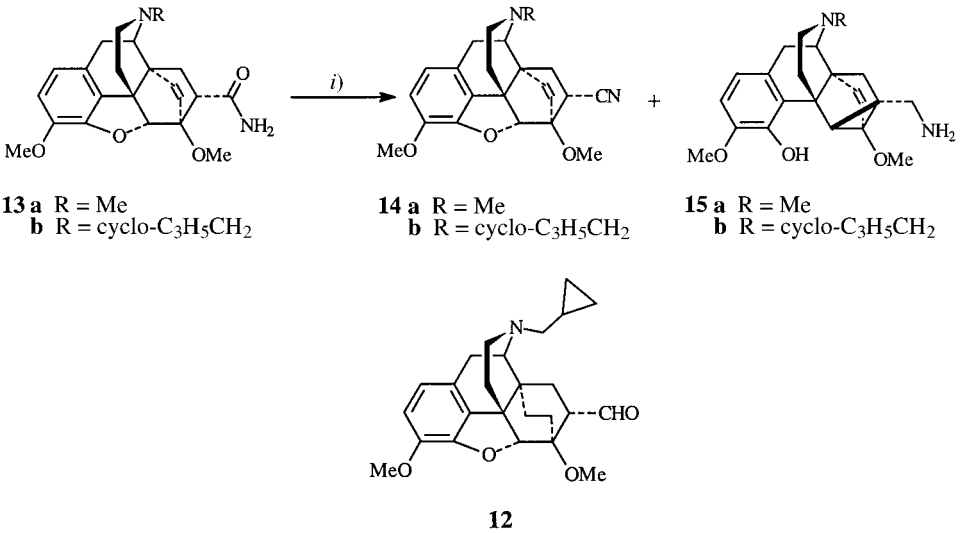


i) $HClO_4$, NaN_3. *ii*) 5N HCl, 10°. *iii*) H_2, Pd/C, 30 psi. *iv*) KOH, digol, reflux. *v*) $NaHCO_3$, cinnamoyl chloride, DCM then MeOH/H_2O 9:1, K_2CO_3.

was converted to the cinnamamide **4c** *via* the 3-(cinnamoyloxy)-7α-(cinnamoylamino) derivative followed by mild base hydrolysis in 57% overall yield from **11**.

For the synthesis of the required 7α-(aminomethyl) precursor **5a**, the direct route from *N*-(cyclopropylmethyl)dihydronorthevinal (**12**), involving reductive amination or reduction of the oxime, gave, in our hands, very poor yields of the 7α-(aminomethyl) intermediate **5a**. Furthermore, reduction of a primary amide, *e.g.* of **13b**, could be ruled out since, on treatment with $LiAlH_4$, the *N*-methyl analogue **13a** was shown to undergo dehydration ($\rightarrow$**14a**) and rearrangement before reduction ($\rightarrow$**15a**; *Scheme 2*) [8]. Thus, an indirect route was chosen, taking advantage of the finding that secondary and tertiary amides equivalent to **13** were reduced smoothly with $LiAlH_4$ to the corresponding amines [8]. This route is shown in *Scheme 3*.

Scheme 2



13 a R = Me
b R = cyclo-$C_3H_5CH_2$

14 a R = Me
b R = cyclo-$C_3H_5CH_2$

15 a R = Me
b R = cyclo-$C_3H_5CH_2$

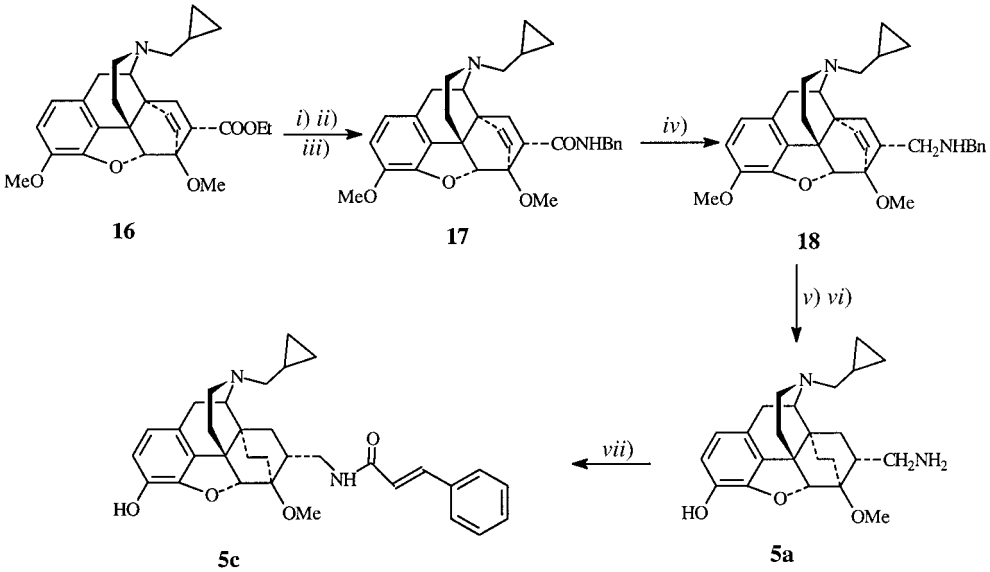
12

i) $LiAlH_4$.

The ethyl 7α-carboxylate derivative **16** [9] was hydrolysed, and the acid converted *via* its chloride to the benzylamide **17**. The latter was reduced by $LiAlH_4$ to the corresponding 7α-[(benzylamino)methyl]-etheno derivative **18**, which was hydrogenated to reduce the etheno bridge and hydrogenolyse the benzylamino group. 3-*O*-Demethylation gave the (aminomethyl)oripavine derivative **5a**, which was acylated with excess of the cinnamoyl chloride to give the 3-*O*, 7-*N*-biscinnamoyl derivative from which the free phenol derivative **5c** was generated under mildly basic conditions.

Pharmacology. – The cinnamoyl derivatives **4c** and **5c** were evaluated in opioid receptor displacement binding assays in guinea pig brain membranes in which the displaced radioligands were [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ), and [^{3}H]U69593 (κ) (*Table 1*) [10]. The new ligands displayed high affinity for all the opioid receptor types with no selectivity. The order of affinity was $\mu = \delta \geq \kappa$, whereas for the standard μ-affinity ligand β-FNA (**1**), there was significant selectivity for μ over δ but not over κ.

Scheme 3



i) 12N HCl, steam bath. *ii*) oxalyl chloride, DCM, DMF. *iii*) $PhCH_2NH_2$, DCM, NEt_3. *iv*) $LiAlH_4$, THF, reflux. *v*) H_2, 30 psi, 45°, EtOH. *vi*) cinnamoyl chloride, DCM, $NaHCO_3$ then MeOH/H_2O 9 : 1, K_2CO_3.

Table 1. *Affinities of Ligands* **4c**, **5c**, *and* **1** *in Opioid Receptor Binding Assays in Guinea Pig Brain Membranes*

	K_i/nM		
	μ: [^{3}H]DAMGO	δ: [^{3}H]Cl-DPDPE	κ: [^{3}H]U69593
4c	0.9 ± 0.35	1.1 ± 0.35	1.3 ± 0.45
5c	0.7 ± 0.25	0.7 ± 0.05	2.6 ± 0.00
β-FNA (**1**)	0.4 ± 0.05	7.7 ± 2.4	0.9 ± 0.05

The cinnamoylamino derivative **4c** had no agonist activity in the mouse *vas deferens* opioid functional assay [10] but was a potent antagonist, again without selectivity (*Table 2*). Of particular interest was the extreme potency of the (cinnamoylamino)-methyl analog **5c**; as a μ antagonist, it was 70-times more potent than the equivalent cinnamoylamino derivative **4c**. The potency of **5c** as a δ and a κ antagonist was also 20-fold greater than that of **4c**. The (cinnamoylamino)methyl derivative **5c** had no agonist activity in the guinea pig *ileum* functional assay [10], but the cinnamoylamino derivative **4c** displayed partial agonist activity with 37% maximum inhibition at

Table 2. *Opioid Antagonist Activity of* **4c** *and* **5c** *in Mouse* Vas Deferens *Preparation*

	K_e/nM		
	μ: *vs.* DAMGO	δ: *vs.* Cl-DPDPE	κ: *vs.* U69593
4c	0.56 ± 0.15	0.94 ± 0.14	1.24 ± 0.12
5c	0.008 ± 0.0006	0.044 ± 0.005	0.052 ± 0.003

12.5 nM. This activity could not be removed by repeated washing of the tissue nor reversed by the selective opioid antagonists CTAP (μ) and norBNI (κ). This indicates that opioid receptor binding in this tissue is noncompetitive.

These data are complementary to those from mouse antinociceptive tests reported earlier [11]. In these *in vivo* assays, the (cinnamoylamino)methyl derivative **5c** had very little opioid agonist activity and was a powerful irreversible μ-selective antagonist. In contrast, the cinnamoylamino derivative **4c** was a full agonist in the AcOH-induced writhing assay and had very modest μ-antagonist activity.

It can be concluded that irreversible binding and potent μ-antagonist activity is sensitive to the position of the cinnamoylamino group and requires a methylene spacer to link it to C(7) in the α-position.

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Experimental Part

General. All reagents were used as supplied by *Aldrich*. Flash column chromatography (FC): silica gel *60* (*Fluka*). TLC: Al-sheets coated with silica gel F_{254}. M.p.: *Reicher* hot-stage microscope; uncorrected. IR Spectra: *Perkin-Elmer 881* spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: at 300 and 75 MHz, resp.; *Jeol-JNM-GX-FT-300* spectrometer, at 20° in $CDCl_3$ unless otherwise stated, with $SiMe_4$ as internal standard; δ in ppm, J in Hz. Mass spectra: *Fisons Autosampler* instrument; electron-impact ionisation (70 eV). Elemental analyses were obtained by means of a *Perkin-Elmer-240C* analyser.

1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,6-dimethoxy-6,14-ethenomorphinan-7-yl]ethenone (**8**). Methyl vinyl ketone (18.6 ml, 229 mmol) containing *N*-(cyclopropylmethyl)northebaine =17-cyclopropylmethyl)-6,7,8,14-tetradehydro-4,5α-epoxy-3,6-diepoxymorphinane, **7**; 7.0 g, 19.9 mmol) and two crystals of quinol were refluxed for 2 h. After cooling to r.t., the soln. was diluted with AcOEt (50 ml) and extracted with 1N HCl (2 × 75 ml). The combined aq. phases were alkalinised to pH 10 with NH_4OH, and the product was extracted with AcOEt (3 × 150 ml). The combined org. phase was dried (Na_2SO_4) and evaporated. FC (SiO_2 (45 ml), Et_2O yielded 8.4 g (100%) of **8**. Off-white foam. IR: 1700 (CO). ^{1}H-NMR: 6.62 (*d*, *J* = 8, H–C(2)); 6.51 (*d*, *J* = 8, H–C(1)); 5.89 (*d*, *J* = 9, H–C(18)); 5.59 (*d*, *J* = 9, H–C(19)); 4.59 (*d*, *J* = 1.4, H–C(5)); 3.81 (*s*, MeO–C(3)); 3.60 (*s*, MeO–C(6)); 2.14 (*s*, MeCO). ^{13}C-NMR: 208.99, 147.97, 141.75, 136.10, 134.03, 128.05, 125.63, 119.15, 113.34, 95.21, 81.40, 59.82, 57.15, 56.73, 53.54, 50.64, 48.27, 43.99, 43.26, 33.67, 30.45, 29.91, 23.16, 9.45, 4.12, 3.39. EI-MS: 421 (100, M^+).

1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,6-dimethoxy-6,14-ethanomorphinan-7-yl]ethenone (**6**). A mixture of **8** (22.8 g, 54.2 mmol) and 10% Pd/C (1.05 g) in EtOH was hydrogenated at 60°/50 psi for 122 h. The catalyst was then removed by filtration through *Celite* and the filtrate evaporated to leave a foam. Recrystallization from EtOH yielded 14.9 g (65%) of **6**. White prisms. M.p. 111–112°. IR: 1705 (CO). ^{1}H-NMR: 6.71 (*d*, *J* = 8, H–C(2)); 6.56 (*d*, *J* = 8, H–C(1)); 4.51 (*s*, H–C(5)); 3.87 (*s*, MeO–C(3)); 3.44 (*s*, MeO–C(6)); 2.27 (*s*, MeCO). ^{13}C-NMR: 211.1, 146.8, 141.7, 132.7, 128.8, 119.2, 113.9, 94.7, 76.6, 59.8, 58.4, 56.7, 52.2, 49.7, 46.5, 43.8, 35.3, 33.8, 30.4, 28.7, 22.8, 17.5, 9.4, 4.1, 3.3. EI-MS: 423 (100, M^+).

(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,6-dimethoxy-6,14-ethenomorphinan-7-amine (**11**). To a vigorously stirred soln. of **8** (8.4 g, 20.0 mmol) in 35% aq. perchloric acid soln., NaN_3 (0.35 g, 53.9 mmol) was added. The mixture was then heated to 70° for 5 h. After cooling to r.t., conc. NH_4OH soln. was added (→ pH 10), the mixture extracted with AcOEt (3 × 100 ml), the combined extract dried (Na_2SO_4) and evaporated and the residue submitted to FC (2.5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 7.66 g (88.0%) of acetamide. IR: 1662. ^{1}H-NMR: 6.62 (*d*, *J* = 8, H–C(2)); 6.52 (*d*, *J* = 8, H–C(1)); 5.65 (*d*, *J* = 9, H–C(18)); 5.58 (*d*, *J* = 9, H–C(19)); 4.55 (*d*, *J* = 6, NHCO); 4.72 (*s*, H–C(5)); 3.82 (*s*, MeO–C(3)); 3.48 (*s*, MeO–C(6)); 1.96 (*s*, MeCO). ^{13}C-NMR: 169.8, 147.9, 141.9, 138.2, 134.2, 127.9, 126.7, 119.3, 113.0, 90.5, 80.1, 59.8, 57.1, 56.3, 51.1, 47.8, 45.4, 43.8, 42.3, 36.0, 33.1, 23.3, 23.0, 9.4, 3.9, 3.5. EI-MS: 436 (89, M^+).

A soln. of the acetamide (7.64 g, 17.5 mmol) in 5N HCl (25 ml) was stirred at 10° for 22 h. The mixture was cooled to r.t. and then alkalinised with conc. NH_4OH soln. (→ pH 10). After extraction with AcOEt (3 × 50 ml), the combined org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to FC (5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.). 4.12 g (60%) of **11**. R_f (5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH

soln.) 0.40. IR: 3369 (NH_2). ^{1}H-NMR: 6.62 (d, $J=8$, H–C(2)); 6.52 (d, $J=8$, H–C(1)); 5.73 (d, $J=10$, H–C(18)); 5.58 (d, $J=10$, H–C(19)); 4.52 (s, H–C(5)); 3.82 (s, MeO–C(3)); 3.62 (s, MeO–C(6)). ^{13}C-NMR: 147.9, 141.9, 136.9, 134.6, 128.1, 119.2, 113.3, 94.4, 82.5, 59.7, 57.1, 49.1, 47.9, 44.0, 42.4, 35.3, 33.1, 23.0, 9.4, 4.1, 3.4. EI-MS: 394 (82, M^+). HR-MS: 394.225685 ($C_{24}H_{30}N_2O_3^+$; calc. 394.225643).

(5α,7α)-7-Amino-17-(cyclopropylmethyl)-4,5-epoxy-6-methoxy-6,14-ethanomorphinan-3-ol (**4a**). A soln. of **11** (4.12 g, 10.4 mmol) in EtOH (100 ml) was hydrogenated over 10% Pd/C (0.5 g) for 13 h at 30 psi. The catalyst was filtered off and the filtrate evaporated: 3.92 g (95%) of pure ethano-amine. R_f (5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH) 0.46. IR: 3409 (NH_2). ^{1}H-NMR: 6.70 (d, $J=9$, H–C(2)); 6.53 (d, $J=9$, H–C(1)); 4.41 (s, H–C(5)); 3.89 (s, MeO–C(3)); 3.50 (s, NH_2–C(7)); 3.43 (s, MeO–C(3)). ^{13}C-NMR: 146.9, 141.8, 132.7, 128.5, 119.0, 113.6, 92.4, 77.4, 59.8, 58.4, 56.6, 51.1, 48.1, 46.0, 43.7, 37.4, 35.5, 35.1, 28.8, 22.6, 16.5, 9.4, 3.9, 3.4. EI-MS: 396 (100, M^+). HR-MS: 396.241249 ($C_{24}H_{32}N_2O_3^+$; calc. 396.241293).

KOH (23.7 g, 422 mmol) was added to the ethano-amine (3.32 g, 8.4 mmol) in digol (=diethylene glycol; 50 ml), and the mixture was refluxed for 11 h before cooling to r.t. Orthophosphoric acid (1M, 534 ml) was added and the soln. washed with Et_2O (540 ml) before alkalinising the aq. layer with conc. NH_4OH soln. and extracting with CH_2Cl_2 (4 × 350 ml). The combined extract was dried (Na_2SO_4) and evaporated and the crude product purified by FC (5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 2.21 g (69%) of **4a**. R_f (10% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) 0.41. ^{1}H-NMR: 6.68 (d, $J=8$, H–C(2)); 6.52 (d, $J=8$, H–C(1)); 4.42 (s, H–C(5)); 3.40 (s, MeO–C(6)). EI-MS: 382 (100, M^+). HR-MS: 382.224571 ($C_{23}H_{32}NO_6^+$; calc. 382.225643).

N-*[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3-phenylprop-2-enamide* (**4c**). To a soln. of **4a** (0.44 g, 1.15 mmol) in CH_2Cl_2 (15 ml), $NaHCO_3$, (0.68 g, 8.05 mmol) was added. To this suspension, a soln. of freshly prepared cinnamoyl chloride (0.42 g, 2.53 mmol) in CH_2Cl_2 (15 ml) was added, and then, 5 min later, H_2O (3 ml) was added. The mixture was agitated vigorously for 15 min. Then the aq. layer was neutralized with 2N HCl and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. phase was dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH/H_2O 9:1, K_2CO_3 (0.80 g, 5.75 mmol) added, and this suspension stirred for 12 h. The MeOH was removed *in vacuo*, the crude product extracted with CH_2Cl_2 (3 × 20 ml), the combined extract dried (Na_2SO_4) and evaporated, and the residue purified by FC (5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 0.51 g (87%) of **4c**. M.p. 162–164°. R_f (AcOEt + 1% conc. NH_4OH soln.) 0.45. IR: 1666 (NHCO). ^{1}H-NMR: 7.65 (d, $J=16$, C=CH); 7.51 (m, 2 H of Ph); 7.36 (m, 3 H of Ph); 6.72 (d, $J=8$, H–C(2)); 6.53 (d, $J=8$, H–C(1)); 6.47 (d, $J=16$, C=CH); 4.64 (s, H–C(5)); 3.38 (s, MeO–C(6)). ^{13}C-NMR: 166.2, 145.5, 141.0, 137.8, 134.6, 132.1, 129.4, 128.7, 128.5, 127.9, 127.6, 127.3, 120.5, 119.5, 116.9, 88.3, 76.0, 59.7, 58.2, 50.0, 45.7, 45.0, 43.4, 35.3, 34.9, 28.6, 22.5, 19.5, 9.2, 3.7, 3.5. EI-MS: 512 (97, M^+). HR-MS: 512.269058 ($C_{32}H_{36}N_2O_4^+$; calc. 512.267508). Anal. calc. for $C_{32}H_{36}N_2O_4 \cdot (CO_2H)_2 \cdot 2.5\ H_2O$: C 63.1, H 6.4, N 4.3; found: C 63.1, H 6.1, N 4.0.

(5α,7α)-N-*Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-3,6-dimethoxy-6,14-ethenomorphinan-7-carboxamide* (**17**). A soln. of **16** (13.5 g, 29.9 mmol) in 2M HCl (65 ml) was heated on a steam bath for 3 h. The resulting soln. was diluted with ice-water and the resulting precipitate filtered off and recrystallized (2×) from EtOH. To this solid (8.13 g, 17.7 mmol) in CH_2Cl_2 (120 ml), oxalyl chloride (3.08 ml, 35.4 mmol) was added under N_2. DMF (0.1 ml) was added and the resulting soln. stirred at r.t. for 1.5 h before evaporating the solvents to leave the crude acid chloride as an off-white solid. This was dissolved, without purification, in CH_2Cl_2 (100 ml) under N_2 at 0° before adding Et_3N (5.4 ml, 38.9 mmol), followed by benzylamine (2.12 ml, 19.4 mmol). The temp. was allowed to rise to r.t. within 1.5 h before filtration. The filtrate was evaporated and the crude product purified by FC (1% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 5.72 g (63%) of **17**. M.p. 94–95°. R_f (2.5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) 0.54. IR: 1663 (CONH). ^{1}H-NMR: 7.4–7.1 (m, *Ph*CH_2); 6.58 (d, $J=8$, H–C(2)); 6.50 (m, CON*H*); 6.45 (d, $J=8$, H–C(1)); 5.90 (d, $J=9$, H–C(18)); 5.55 (d, $J=9$, H–C(19)); 4.51 (s, H_β–C(5)); 4.41 (m, PhC*H*$_2$); 3.79 (s, MeO–C(3)); 3.60 (s, MeO–C(6)). ^{13}C-NMR: 172.37, 147.77, 141.66, 138.45, 136.88, 134.23, 128.34, 128.11, 127.27, 127.00, 125.51, 119.30, 113.31, 94.76, 80.53, 59.61, 56.86, 56.42, 52.94, 47.72, 44.65, 43.80, 43.33, 42.79, 33.30, 30.64, 23.02, 9.30, 3.99, 3.26. EI-MS: 512 (94.5, M^+). HR-MS: 512.268539 ($C_{32}H_{36}N_2O_4^+$; calc. 512.267508).

(5α,7α)-N-*Benzyl-17-(cyclopropylmethyl)-4,5-epoxy-3,6-dimethoxy-6,14-ethenomorphinan-7-methanamine* (**18**). A soln. of **17** (5.72 g, 11.2 mmol) in THF (20 ml) was added dropwise to a refluxing soln. of $LiAlH_4$ (0.95 g, 24.5 mmol) in THF (10 ml). The mixture was cooled to r.t. after 20 h, $Na_2SO_4 \cdot 10H_2O$ (2 g) added, and the mixture stirred for a further 1 h. The mixture was filtered through *Celite*; the filtrate evaporated, and the residue submitted to FC (2.5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 3.94 g of **18** (71%). Colorless foam. R_f (10% MeOH/CH_2Cl_2 + 1% *conc.* NH_4OH soln.) 0.59. IR: 3350 (NH_2). NMR: complex due to rotamers. EI-MS: 498 (84.7, M^+). HR-MS: 498.286774 ($C_{32}H_{38}N_2O_3^+$; calc. 498.288243).

(5α,7α)-7-(Aminomethyl)-17-(cyclopropylmethyl)-4,5-epoxy-6-methoxy-6,14-ethanomorphinan-3-ol (**5a**). A soln. of **18** (2.25 g, 1.26 mmol) in EtOH was hydrogenated at 45°/30 psi over 10% Pd/C (445 mg) for 2.5 h. The mixture was then filtered through *Celite*, the filtrate evaporated, and the crude product purified by FC (7.5% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.): 1.41 g of ethano-amine (76%). R_f (10% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) 0.47. IR: 3383 (NH_2). ^{1}H-NMR: 6.65 (*d*, *J* = 8, H−C(2)); 6.58 (*d*, *J* = 8, H−C(1)); 4.53 (*s*, H−C(5)); 3.88 (*s*, MeO−C(3)); 3.41 (*s*, MeO−C(3)). ^{13}C-NMR: 146.90, 141.70, 132.74, 128.61, 118.94, 113.37, 92.27, 76.90, 59.93, 58.53, 56.53, 50.73, 45.60, 43.93, 43.78, 38.42, 35.52, 35.40, 33.44, 29.30, 22.59, 19.25, 9.44, 4.07, 3.45. EI-MS: 410 (100, M^+). HR-MS: 410.256607 ($C_{25}H_{34}N_2O_3^+$; calc. 410.256943).

To the ethano-amine (1.41 g, 3.43 mmol), digol (25 ml) was added, followed by freshly ground KOH (10 g, 178.2 mmol). The mixture was stirred under reflux for 8 h before cooling to r.t. and adding 1M orthophosphoric acid (222 ml). The resulting soln. was washed with Et_2O (250 ml) and then the aq. layer basified with conc. NH_4OH soln. and extracted with CH_2Cl_2 (4 × 220 ml). The combined extract was washed with H_2O (2 × 100 ml), dried (Na_2SO_4), and evaporated. FC (10% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) gave 0.96 g (71%) of **5a**. M.p. 116–119°. R_f (10% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) 0.24. IR: 3576 (NH_2). ^{1}H-NMR: 6.68 (*d*, *J* = 8, H−C(2)); 6.48 (*d*, *J* = 8, H−C(1)); 4.49 (*s*, H−C(5)); 3.38 (*s*, MeO−C(6)). ^{13}C-NMR: 145.65, 137.90, 132.42, 127.58, 119.50, 116.85, 92.07, 77.14, 59.97, 58.68, 50.55, 45.87, 43.77, 43.68, 38.02, 35.70, 35.38, 33.50, 29.22, 22.75, 15.40, 9.45, 4.02, 3.47. EI-MS: 396 (100, M^+). HR-MS: 396.240959 ($C_{24}H_{32}N_2O_3^+$; calc. 396.241293).

N-*{[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]methyl}-3-phenylprop-2-enamide* (**5c**). As described for **4c**, with **5a** (0.22 g, 0.55 mmol), CH_2Cl_2 (10 ml), $NaHCO_3$ (0.32 g, 3.85 mmol), cinnamoyl chloride (0.20 g, 1.2 mmol), CH_2Cl_2 (10 ml) and H_2O (2 ml). Hydrolysis with MeOH/H_2O 9 :1 and K_2CO_3 (0.39 g, 2.8 mmol). FC (10% MeOH/CH_2Cl_2 + 1% conc. NH_4OH soln.) gave 0.21 g (71%) of **5c**. M.p. 178°. R_f (AcOEt + 1% conc. NH_4OH soln.) 0.34. IR: 1662 (CONH). ^{1}H-NMR: 7.62 (*d*, *J* = 15, C=CH); 7.49 (*d*, *J* = 9, 2 H of Ph); 7.25 (*m*, 3 H of Ph); 6.73 (*d*, *J* = 8, H−C(1)); 6.52 (*d*, *J* = 8, H−C(2)); 6.48 (*m*, CONH); 6.38 (*d*, *J* = 15, C=CH); 4.47 (*s*, H−C(5)); 3.49 (*s*, MeO−C(6)). ^{13}C-NMR: 166.07, 145.6, 140.9, 137.8, 134.9, 132.4, 129.6, 128.8, 127.8, 127.6, 121.0, 119.5, 116.9, 93.0, 77.7, 59.9, 58.5, 51.2, 46.0, 43.7, 41.8, 35.5, 35.1, 33.2, 29.0, 22.7, 18.4, 9.4, 3.5. EI-MS: 526 (85, M^+). HR-MS: 526.282455 ($C_{33}H_{38}N_2O_4^+$; calc. 526.283158). Anal. calc. for $C_{33}H_{38}N_2O_4 \cdot 2\,H_2O$: C 64.4, H 6.8, N 4.3; found: C 64.9, H 6.4, N 4.0.

REFERENCES

[1] P. S. Portoghese, D. L. Larson, L. M. Sayre, D. S. Fries, A. E. Takemori, *J. Med. Chem*. **1980**, *23*, 233; A. E. Takemori, D. L. Larson, P. S. Portoghese, *Eur. J. Pharmacol*. **1981**, *70*, 445; S. J. Ward, P. S. Portoghese, A. E. Takemori, *J. Pharmacol. Exp. Ther*. **1982**, *220*, 494.

[2] J. W. Lewis, C. F. C. Smith, P. S. McCarthy, D. S. Walter, R. Kobylecki, M. Myers, A. S. Haynes, C. J. Lewis, K. Waltham, *NIDA Research Monograph* **1988**, *90*, 136; S. D. Comer, T. F. Burke, J. W. Lewis, J. H. Woods, *J. Pharmacol. Exp. Ther*. **1992**, *262*, 1051; M. D. Aceto, E. R. Bowman, E. L. May, L. S. Harris, J. H. Woods, C. B. Smith, F. Medizhradsky, A. E. Jacobson, *Arzneim.-Forsch. Drug Res.* **1989**, *39*, 570; J. H. Broadbear, T. L. Sumpter, T. F. Burke, S. H. Husbands, J. W. Lewis, J. H. Woods, J. R. Traynor, *J. Pharmacol. Exp. Ther*. **2000**, *294*, 933.

[3] 'Buprenorphine, Combatting Drug Abuse with a Unique Opioid', Eds. A. Cowman and J. W. Lewis, Wiley-Liss, New York, 1995, p. 326.

[4] J. W. Lewis, 'Ring-C-Bridged Derivatives of Thebaine and Oripavine', in 'Narcotic Antagonists', Eds. M. C. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villarreal, 'Advances in Biochemical Psychopharmacology', Raven Press, New York, 1974, Vol. 8, p. 123.

[5] I. Derrick, A. Coop, S. M. Al-Mousawi, S. M. Husbands, J. W. Lewis, *Tetrahedron Lett.*, submitted.

[6] K. W. Bentley, D. G. Hardy, A. C. B. Smith, *J. Chem. Soc*. **1969**, 2235; T. R. Burke Jr., B. S. Bajwa, A. E. Jacobson, K. C. Rice, R. A. Streaty, W. A. Klee, *J. Med. Chem*. **1984**, *27*, 1570.

[7] R. A. Lessor, B. S. Bajwa, K. C. Rice, A. E. Jacobson, R. A. Streaty, W. A. Klee, C. B. Smith, M. D. Aceto, E. L. May, L. S. Harris, *J. Med. Chem*. **1986**, *29*, 2136.

[8] K. W. Bentley, J. D. Bower, J. W. Lewis, M. J. Readhead, A. C. B. Smith, G. R. Young, *J. Chem. Soc. C* **1969**, 2237.

[9] K. W. Bentley, J. D. Bower, J. W. Lewis, *J. Chem. Soc. C* **1969**, 2569.

[10] L. Toll, I. P. Berzetei-Gurske, W. E. Polgar, S. R. Brandt, I. D. Adapa, L. Rodriguez, R. W. Schwartz, D. Haggart, A. O'Brian, A. White, *NIDA Research Monograph* **1997**, *178*, 440.
[11] I. Derrick, J. W. Lewis, J. H. Woods, J. Broadbear, H. Plumer, *Analgesia* **1995**, *1*, 386.
[12] I. Derrick, J. W. Lewis, J. H. Broadbear, H. Plumer, J. H. Woods, *NIDA Res. Monogr.* **1997**, *174*, 102.

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