Synthesis, Antinociceptive Activity, and Opioid Receptor Profiles of 10-Substituted-6-oxamorphinans

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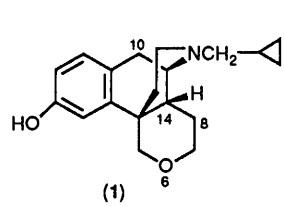
A concise synthesis of the 6-oxamorphinan ring system has been designed which allows introduction of functionality at the 10-position. This has provided a series of 10-methylene-, 10-oxo-, and 10α-methyl-6-oxamorphinans, (**24a–e**), (**25a–d**), and (**26a–c**) respectively. The enamine 8a-(3-methoxyphenyl)-6-methyl-3,4,6,7,8,8a-hexahydro-1*H*-pyrano[4,3-*c*]pyridine (**4a**) is converted in three steps, *via trans*-8a-(3-methoxyphenyl)-6-methyloctahydropyrano[4,3-*c*]pyridine-5α-carbonitrile (**7a**) and the corresponding 5α-acetyl derivative (**9a**), to the tetracyclic 10-methylene-6-oxamorphinan (**11a**). Oxidative cleavage of the 10-exocyclic methylene group of (**11a**) provides entry into the 10-oxo series. The antinociceptive activity and opioid receptor profiles of (**24a–e**), (**25a–d**), and (**26a–c**) have been evaluated and structure–activity relationships are discussed.

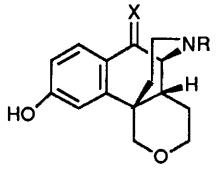
It is now firmly established that exogenous and endogenous opioids may interact with at least three distinct subtypes of opioid receptor, designated as μ-, κ-, and δ-receptors.[1] From the different profiles of μ- and κ-agonists it has been suggested that opioids with a prominent κ-agonist component might provide a safer analgesic than the traditional morphine-like or μ-agonists.[2]

It has recently been disclosed that 6-oxamorphinans [*e.g.* proxorphan (**1**)] display good antinociceptive activity, but with reduced narcotic side-effects when compared with other morphinans.[3] For proxorphan this favourable profile might be ascribed to its partial agonist activity at κ-opioid receptors.[4] We therefore decided to evaluate the effect on biological activity of certain structural modifications to the 6-oxamorphinan system, focusing on 10-oxo substitution by analogy with the prototype κ-agonist ketocyclazocine (**3**).[5] In this paper we describe a concise synthesis of 10-methylene-6-oxamorphinans (**2a**) and their subsequent conversion into 10-oxo- and 10-methyl-derivatives (**2b**) and (**2c**) respectively.

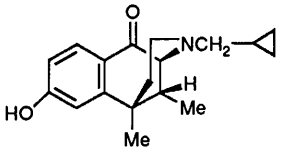
At the outset of our work there had been few reports on the introduction of 10-oxo substitution into morphinan structures and in no case were any biological data presented.[6] Subsequently, Archer *et al.*[7] described the synthesis of 10-keton-altrexone and 10-keto-oxymorphone and reported on their binding to opioid receptor subtypes. In this paper we describe the antinociceptive activity of the title compounds and, where possible, we have assessed their interaction with μ- and κ-opioid receptor subtypes.



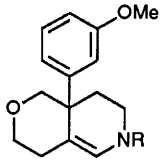
(1)



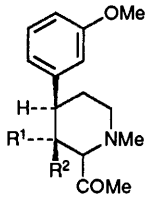
(2) (**a**); X = CH_2
(**b**); X = O
(**c**); X = H, Me



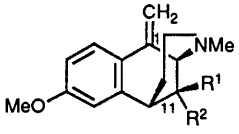
(3)



(4) **a**; R = Me
b; R = Pr



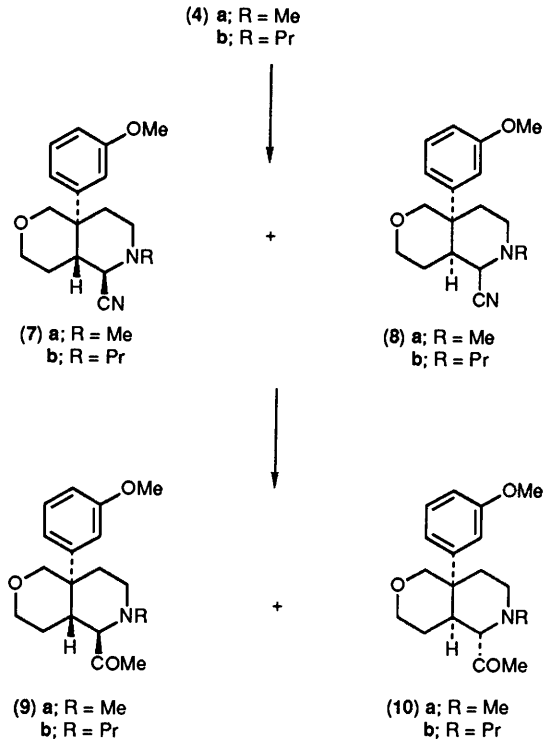
(5) **a**; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H



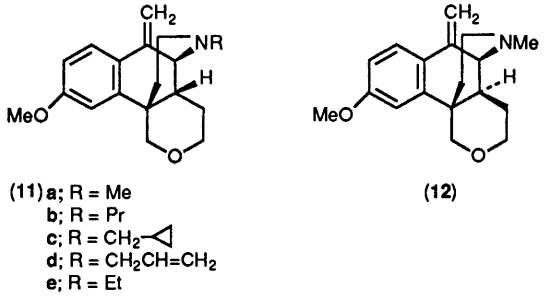
(6) **a**; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H

Chemistry.—The requirement of introducing substitution into the 6-oxamorphinan skeleton required a considerably shorter, more appropriate synthesis than that described in the original work.[3] Accordingly, our strategy for the synthesis of 6-oxamorphinans was based on our recently described preparation of the bicyclic enamine (**4a**).[8] We envisaged that the 6-oxamorphinan system could be constructed from (**4a**) by bridging a one-carbon unit between the aromatic ring and the α-position of the enamine. This approach has been employed previously for the preparation of 14-*epi*-morphinans *via* cyclization of chloromethyl,[9] carbaldehyde,[10] acetyl,[11] or aziridinium[12] intermediates onto the aromatic ring. However, attempts to effect similar cyclizations to give the natural morphine stereochemistry have either been unsuccessful or have involved further elaboration to epimerize C-14.[10,13] This is in contrast with the benzomorphan ring system where both the 11-methyl epimers of the l-methylene derivative (**6a, b**) can be prepared *via* cyclization of the corresponding α-acetylamines (**5a, b**) with boron trifluoride diethyl ether.[14] We now demonstrate that this benzomorphan-related chemistry can be extended to the synthesis of 10-methylene-6-oxamorphinans.

Treatment of the enamine (**4a**) with potassium cyanide in aqueous methanol at pH 7.9 gave a 5:1 mixture of the nitriles (**7a**) and (**8a**) together with *ca.* 15% recovered enamine (Scheme 1). The stereochemistry of the major product (**7a**) was confirmed

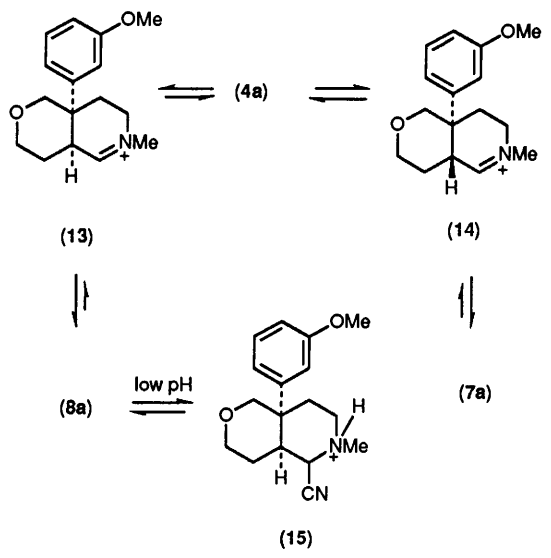


Scheme 1.



by NMR spectroscopy: the 4aα-H signal showed two *trans*-diaxial couplings (*J* 12 and 13 Hz) and a small axial-equatorial coupling of 3 Hz, consistent only with a *trans*-ring fusion and α-stereochemistry of the nitrile substituent. The minor product (**8a**) could not be isolated. However, treatment of the 5:1 mixture of (**7a**) and (**8a**) with methyl-lithium followed by acid hydrolysis gave a quantitative conversion to a 5:1 mixture of α-acetylamines (**9a**) and (**10a**), from which the minor component (**10a**) was readily isolated by chromatography. The *cis*-ring fusion of (**10a**) was unambiguously confirmed by its cyclization to the 14-*epi*-6-oxamorphinan (**12**), in 63% yield, using boron trifluoride–diethylether (*vide infra*). It therefore follows that (**8a**) must also possess a *cis*-ring fusion stereochemistry.

The ratio of (**7a**) to (**8a**) was found to depend critically on the pH of the reaction medium. Changing the pH to 6.5 gave a 3:2 mixture of (**7a**) and (**8a**), whereas at pH 10 (**7a**) was obtained with >8:1 selectivity. Reaction pathways consistent with the observations are outlined in Scheme 2. The *cis*-ring-fused iminium salt (**13**) is known to be more thermodynamically stable in solution than the *trans*-ring-fused iminium salt (**14**) and under the equilibrating conditions this isomer will predominate.[15] Upon addition of potassium cyanide, rapid attack of cyanide on the iminium salt (**13**) would give the *cis*-ring-fused nitrile (**8a**) as the kinetic product. At low pH (**8a**) will exist mainly in the protonated form (**15**) and the reverse reaction [of (**8a**)] to the enamine (**4a**) will be inhibited, thereby leading to a

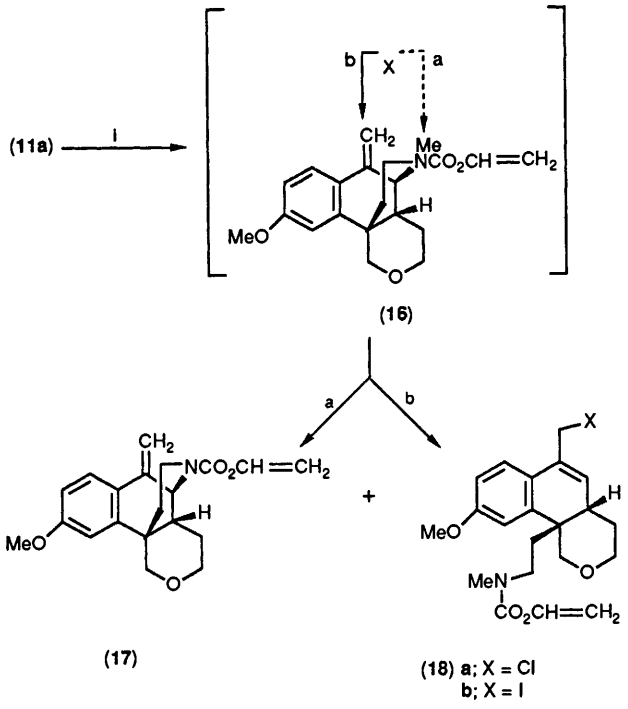


Scheme 2.

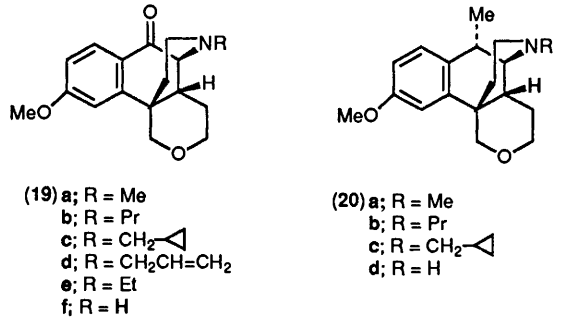
greater preponderance of the *cis*-ring-fused product. With high pH, equilibration can occur *via* (**4a**) and (**14**) to give the thermodynamically more stable *trans*-ring-fused nitrile (**7a**).

Treatment of the *trans*-ring-fused α-acetylamine (**9a**) with two equivalents of boron trifluoride–diethyl ether in 1,2-dichlorobenzene (120 °C; 24 h) gave only partial cyclization (*ca.* 40%) to the 10-methylene-6-oxamorphinan (**11a**). This contrasts with the *cis*-ring-fused isomer (**10a**) which cyclized completely under the same conditions. However, as found by Rapoport *et al.* for the analogous benzomorphan cyclization,[14] resubmission of the initial product mixture (*trans*-fused case) to the same reaction conditions caused complete conversion of (**9a**) to (**11a**) in 75% overall yield. Increasing the proportion of boron trifluoride–diethyl ether in this reaction resulted in lower yields and no cyclization was observed when the solvent was changed to 1,4-dioxane or acetic acid at reflux. The structural assignment of (**11a**) and (**12**) was made on the basis of NMR spectral data in comparison with that for proxorphan (**1**). An analogous sequence of reactions, commencing with the *N*-propyl-enamine (**4b**), provided the corresponding 10-methylene-6-oxamorphinan (**11b**).

Since the nature of the *N*-substituent significantly influences the biological profile of morphinans,[16] including agonist *vs.* antagonist properties, we investigated replacement of the *N*-methyl group by alternative substitutions. In this respect, it was of interest to introduce the *N*-cyclopropylmethyl substitution characteristic of the partial κ-agonist proxorphan. Attempts to *N*-demethylate (**11a**) with vinyl chloroformate[17] were frustrated by formation of substantial amounts (*ca.* 60%) of the allylic chloride (**18a**) along with a *ca.* 30% yield of the required carbamate (**17**). This is presumably due to competing S_N2' attack of chloride ion on the intermediate acylammonium species (**16**) (Scheme 3). Addition of sodium iodide to the reaction mixture gave exclusive conversion to the allylic iodide (**18b**). To circumvent this problem, 10-methylene-6-oxamorphinans (**11c–e**) were prepared *via* the corresponding 10-oxo-derivatives (**19c–e**). Oxidative cleavage of (**11a,b**) with Jones reagent[18] gave (**19a,b**) in good yield. Efficient *N*-demethylation of (**19a**) could now be achieved *via* vinyl chloroformate methodology and the resultant secondary amine (**19f**) was alkylated to afford the *N*-substituted analogues (**19c–e**). Reintroduction of the 10-methylene functionality was conveniently achieved in a two-step procedure involving addition of methyl-lithium to the ketones (**19c–e**) followed by dehydration of the intermediate tertiary alcohol with boron trifluoride–diethyl ether.

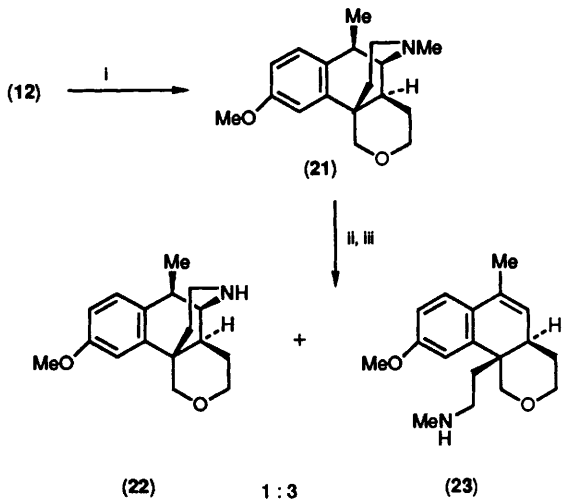


Scheme 3. *Reagents:* i, $ClCO_2CH{=}CH_2$, $ClCH_2CH_2Cl$, heat.



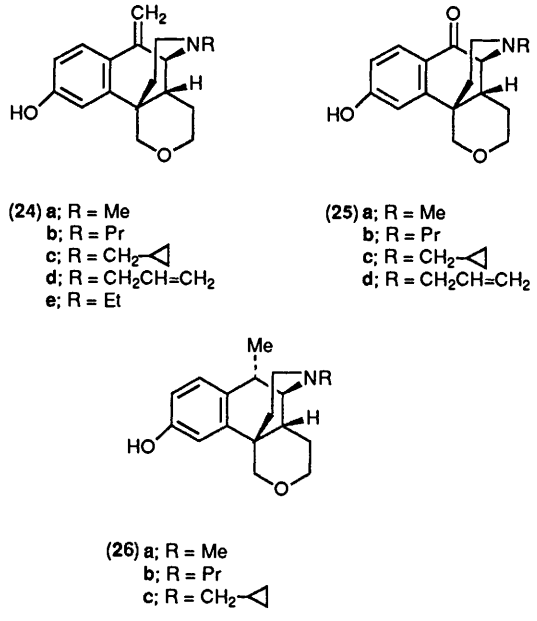
Catalytic hydrogenation of (**11a,b**) gave the 10α-methyl derivatives (**20a,b**) with >90% stereoselectivity, presumably because the α-face of the 10-methylene group in (**11a,b**) is sterically hindered by C-8 of the pyran ring. In contrast, hydrogenation of the C-14 epimer (**12**) gave the 10β-methyl compound (**21**) with >90% stereoselectivity (Scheme 4). The assignment of the 10-methyl stereochemistry in (**20a**) and (**21**) was made on the basis of a 1 Hz coupling between the 9-H and 10-H protons in the 10α-methyl isomer (**20a**) and a corresponding coupling of 7 Hz in the 10β-methyl analogue (**21**). Compound (**20a**) was cleanly *N*-demethylated using vinyl chloroformate methodology and the resultant secondary amine (**20d**) was converted into the *N*-cyclopropylmethyl analogue (**20c**) in good yield. However, *N*-demethylation of the 14-*epi*-10β-methyl isomer (**21**), under the same conditions, caused extensive elimination leading to a 1:3 mixture of (**22**) and (**23**) (Scheme 4). This difference in reactivity between (**20a**) and (**21**) is ascribed to the *trans*-disposition of the 10α-hydrogen and the amine functionality in the latter compound, thereby accelerating the elimination reaction.

The methoxy derivatives (**11a–e**), (**19a–d**), and (**20a–c**) were *O*-demethylated to the corresponding phenols (**24a–e, 25a–d, 26a–c**) using standard procedures (Table 1). The hydrochloride salts of the 10-methylene analogues (**24a–e**) were found to be unstable and these compounds were isolated and purified as their free bases.



Scheme 4. *Reagents:* i, H_2, Pd–C, EtOH; ii, $ClCO_2CH{=}CH_2$, $ClCH_2CH_2Cl$, heat; iii, HCl, MeOH.

Pharmacology.—The 6-oxamorphinans (**24a–e**), (**25a–d**), and (**26a–c**) were assayed *in vivo* for antinociceptive activity using either the mouse abdominal constriction test[19] or the rat-paw pressure test[20] and for their effect on urine output in the water-loaded rat (Table 2). The latter test is a useful model for *in vivo* characterization of different types of opioid receptor agonists: μ-agonists induce antidiuresis whereas κ-agonists cause diuresis.[21]



Compounds having activity at both μ- and κ-opioid receptors produce a biphasic effect: an initial antidiuretic effect followed by a more sustained diuresis.[22]

In vitro assessment of the μ/κ selectivity of the title compounds was made using the guinea-pig ileum (GPI) preparation. Blockade at μ-receptors was produced by the irreversible opioid antagonist β-funaltrexamine (β-FNA). An effective κ-receptor blockade was produced using the non-selective irreversible antagonist β-chlornaltrexamine (β-CNA), with concomitant μ-receptor protection using the selective μ-agonist [D-Ala^2, MePhe^4, Gly(ol)^5] enkephalin (DAGO). Agonists which are μ-selective show large β-FNA dose ratios and small β-CNA dose ratios; those which are κ-selective display the opposite profile.[23] The κ-agonist (or antagonist) activity of

Table 1. *O*-Demethylation of 3-methoxy-10-substituted-6-oxamorphinans.

Compound	N-Substituent, R	Method[a]	Product	% Yield	Formula	M.p. t/°C	Found (Required) %C	%H	%N
(11a)	Me	A	**(24a)**	64	$C_{17}H_{21}NO_2$	257–259[b]		M^+ 271.1569 (271.1573)	
(11b)	Pr	A	**(24b)**	43	$C_{19}H_{25}NO_2$	210–215		M^+ 299.1881 (299.1885)	
(11c)	$CH_2\overline{CHCH_2CH_2}$	C	**(24c)**	36	$C_{20}H_{25}NO_2$	223–225	76.8 (77.1)	8.05 (8.1)	4.4 (4.5)
(11d)	$CH_2CH{=}CH_2$	A	**(24d)**	42	$C_{19}H_{23}NO_2$	185–190[b]		M^+ 297.1724 (297.1729)	
(11e)	Et	B	**(24e)**	38	$C_{18}H_{23}NO_2$	234–236[b]		M^+ 285.1730 (285.1729)	
(19a)	Me	C	**(25a)**	45	$C_{16}H_{19}NO_3$	250–251	70.1 (70.3)	7.1 (7.0)	5.0 (5.1)
(19b)	Pr	C	**(25b)**	55	$C_{18}H_{23}NO_3$	210–212	71.3 (71.7)	7.7 (7.8)	4.5 4.6)
(19c)	$CH_2\overline{CHCH_2CH_2}$	C	**(25c)**	38	$C_{19}H_{23}NO_3$	220–221	72.9 (72.8)	7.4 (7.4)	4.6 (4.5)
(19d)	$CH_2CH{=}CH_2$	C	**(25d)**	50	$C_{18}H_{21}NO_3$	220–223[b]		M^+ 299.1520 (299.1521)	
(20a)	Me	A	**(26a)**	45	$C_{17}H_{23}NO_2$	213–215		M^+ 273.1726 (273.1730)	
(20b)	Pr	C	**(26b)**	66	$C_{19}H_{27}NO_2{\cdot}HCl$	162–164	65.4 (65.8)	8.6 (8.4)	3.8 (4.0)
(20c)	$CH_2\overline{CHCH_2CH_2}$	C	**(26c)**	26	$C_{20}H_{27}NO_2$	199–200		M^+ 313.2035 (313.2042)	

[a] A: BBr_3, CH_2Cl_2, room temp.; B: MeSLi, dimethylformamide, 130 °C; C: EtSNa, dimethylformamide, 150 °C; [b] Decomp.

Table 2. *In vivo* activities of 10-substituted-6-oxamorphinans.

Compound[a]	N-Substituent, R	Antinociceptive[b] ED_{50}	Urine output[d]
(24a)	Me	0.13 (0.08–0.19)[c]	Antidiuretic
(24b)	Pr	0.05 (0.03–0.1)	NT
(24c)	$CH_2\overline{CHCH_2CH_2}$	0.25 (0.13–0.43)	NT
(24d)	$CH_2CH{=}CH_2$	0.06 (0.04–0.11)	NT
(24e)	Et	0.65 (0.29–1.59)	Mixed activity
(25a)	Me	>20[c]	NT
(25b)	Pr	>10	NT
(25c)	$CH_2\overline{CHCH_2CH_2}$	0.63 (0.33–1.1)[c]	NT
(25d)	$CH_2CH{=}CH_2$	10	NT
(26a)	Me	0.9 (0.5–1.8)[c]	NT
(26b)	Pr	0.9 (0.5–1.7)	NT
(26c)	$CH_2\overline{CHCH_2CH_2}$	0.03 (0.02–0.05)	Diuretic
Proxorphan		0.02 (0.013–0.029)	Diuretic
Ethylketocyclazocine		0.12 (0.04–0.3)	Mixed activity

[a] Compounds are racemic. [b] Mouse acetylcholine-induced abdominal constriction test, mg/kg, s.c. [c] Rat-paw pressure test. [d] Water-loaded rat.

compounds was also determined using the rabbit vas deferens (LVD) preparation, which contains only κ-opioid receptors.[24] However, this tissue only detects compounds with high efficacy and partial κ-agonists, which have insufficient efficacy to produce agonist effects, behave as antagonists.[25]

Introduction of the 10-oxo (**25c**) and 10-methylene (**24c**) functionality into the proxorphan structure (**1**) resulted in a *ca.* 30 and 10 fold falls in antinociceptive activity, respectively. In contrast, the 10α-methyl derivative (**26c**) displayed similar potency to proxorphan (Table 2). All three compounds (**24c**), (**25c**), and (**26c**), like proxorphan, possessed a predominantly κ-agonist profile: (**24c**) exhibited a high β-CNA dose ratio, (**25c**) a low β-FNA dose ratio, and the selective κ-agonist profile of (**26c**) was established *in vivo* by its diuretic effect in water-loaded rats. However, in contrast to proxorphan, (**24c**), (**25c**), and (**26c**) were all full agonists in the rabbit vas deferens indicating their higher efficacy at the κ-receptor (Table 3).

Within the 10-oxo-6-oxamorphinan series, changing the nitrogen substituent from cyclopropylmethyl (**25c**) to allyl (**25d**) resulted in a large fall in antinociceptive activity and, more dramatically, activity was abolished in the case of the *N*-methyl and *N*-propyl analogues (**25a**) and (**25b**), respectively (Table 2). A different trend was observed in the 10-methylene series: the *N*-propyl and *N*-allyl analogues (**24b**) and (**24d**) possessed greater antinociceptive activity than the *N*-cyclopropylmethyl derivative (**24c**), all three compounds displaying comparable κ-receptor selectivity (β-CNA shift in GPI, Table 3). However, whereas the *N*-cyclopropylmethyl and *N*-allyl analogues (**24c**) and (**24d**) were full agonists in the LVD preparation (Table 3), the *N*-propyl analogue (**24b**) showed a markedly reduced maximum response in this tissue indicating lower efficacy at the κ-receptor. Reducing the size of the nitrogen substituent to *N*-ethyl (**24e**) or *N*-methyl (**24a**) results in compounds which display a prominent μ-agonist component to their profile. Thus, the *N*-methyl analogue (**24a**) is a selective μ-agonist with a β-FNA dose ratio larger than that for normorphine whereas the *N*-ethyl analogue (**24e**), although showing some κ-agonist selectivity *in vitro* (GPI, Table 3), has mixed antidiuretic/diuretic activity in the water-loaded rat, indicative of a substantial μ-agonist component to its *in vivo* activity.

In summary, we have developed a short, efficient synthesis of 6-oxamorphinans bearing functionality at the 10-position which provides a useful handle for structural modification. Our approach could potentially be extended to the synthesis of other C-ring hetero-substituted morphinan structures. Several of the compounds described in this work, notably (**24b**), (**24d**), and (**26c**), possessed similar antinociceptive activity to that of proxorphan (**1**). However, the 10-oxo and 10-methylene analogues of proxorphan were markedly less active than proxorphan itself. In several instances the selective κ-agonist profile of proxorphan was retained.

Table 3. *In vitro* activities of 10-substituted-6-oxamorphinans.

Compound[a]	N-Substituent, R	IC_{50} (μM) in Rabbit vas deferens	IC_{50} (μM) in Guinea-pig ileum	β-FNA Dose ratio	β-CNA Dose ratio
(24a)	Me	Antagonist, pA_2 6.8	0.11	60 (61[b])	NT
(24b)	Pr	Antagonist, pA_2 6.3	0.017	1.8 (15[c])	77 (6.5[b])
(24c)	$CH_2\overline{CHCH_2}CH_2$	0.02	0.02	NT	96 (7.1[b])
(24d)	$CH_2CH{=}CH_2$	0.2	0.005	NT	66 (4.1[b])
(24e)	Et	Antagonist, pA_2 5.9	0.15	2.3 (36[c])	16.4 (4.1[c])
(25c)	$CH_2\overline{CHCH_2}CH_2$	0.17	0.015	0.72 (11[b])	NT
(26a)	Me	*d*	2.3	3.4 (22[b])	NT
(26b)	Pr	*e*	0.13	NT	4.2 (1.4[b])
(26c)	$CH_2\overline{CHCH_2}CH_2$	0.023	NT	NT	NT
Proxorphan		*f*	0.02	1.2 (20[b])	105 (2.3[c])

[a] Compounds are racemic. [b] Data for the μ-agonist normorphine. [c] Data for the μ-agonist DAGO. [d] Low maximum (23%) effect at 10^{-5} M. [e] Low maximum (34%) effect at 10^{-5} M. [f] E_{max} 28% at 0.1 μM.

Experimental

^{1}H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM250 (250 MHz) spectrometer using 16 K data points and a spectral width of 4.5 kHz. IR spectra were recorded on Perkin-Elmer 357 or 377 spectrometers. Mass spectral data were obtained using a VG 7070E instrument interfaced to an 11-250 data system. Spectroscopic and microanalytical data were obtained by Glaxo Chemical Analysis Department. All m.p.s are uncorrected. Column chromatography was performed using either Merck Kieselgel 60 (Art 9385, flash chromatography) or alumina UGI (Phase Separations Ltd.). Solvents were dried according to standard procedures.[26]

trans-8a-(3-*Methoxyphenyl*)-6-*methyloctahydropyrano*[4,3-c]*pyridine*-5α-*carbonitrile* (**7a**).—Glacial acetic acid (*ca.* 1 ml) was added dropwise over 10 min to a stirred solution of potassium cyanide (0.65 g, 10 mmol) in a mixture of methanol (10 ml) and water (6 ml) at 0 °C until the pH was 7.6. A solution of (**4a**) (1.3 g, 5 mmol) in methanol (15 ml) was added over 2 min and the reaction mixture was allowed to warm to room temperature. The resultant solution was poured into aqueous sodium hydroxide (0.35 M; 200 ml) and the mixture extracted with dichloromethane (3 × 150 ml). The combined extracts were dried and concentrated to give an oil. This was purified by flash column chromatography on triethylamine-treated silica gel (120 g; 10 ml of triethylamine), with dichloromethane–hexane (1:1) followed by dichloromethane as eluant, to give the title compound (**7a**) (1.25 g, 87%) as a pale brown viscous oil, containing (NMR) 15% of the *cis*-fused isomer (**8a**); ν_{max}(film) 2 240 cm^{-1}; major isomer; δ($CDCl_3$) 1.68 (1 H, dt, *J* 3, and 13 Hz, 8α-H), 1.86–2.0 (2 H, m, 4α-H and 8β-H), 2.02 (1 H, ddd, *J* 3, 11.5, and 13 Hz, 7β-H), 2.28 (1 H, ddd, *J* 3, 12, and 13 Hz, 4aα-H), 2.48 (1 H, dq, *J* 5 and 12.5 Hz, 4β-H), 2.48 (3 H, s, NMe), 2.71 (1 H, dt, *J* 12, and 3 Hz, 7α-H), 3.29 (1 H, d, *J* 11 Hz, 1α-H), 3.60 (1 H, dt, *J* 3 and 11.5 Hz, 3α-H), 3.73 (1 H, d, *J* 12 Hz, 5β-H), 3.82 (3 H, s, OMe), 4.16 (1 H, dd, *J* 5 and 11.5 Hz, 3β-H), 4.21 (1 H, d, *J* 11 Hz, 1β-H), 6.78 (1 H, dd, *J* 2. and 7.5 Hz, ArH), 6.9–7.05 (2 H, m, 2 × ArH), and 7.3 (1 H, t, *J* 7.5 Hz, ArH).

trans-5α-*Acetyl*-8a-(3-*methoxyphenyl*)-6-*methyloctahydropyrano*[4,3-c]*pyridine* (**9a**) and cis-5α-*Acetyl*-8a-(3-*methoxyphenyl*)-6-*methyloctahydro*[4,3-c]*pyridine* (**10a**).—A solution of (**7a**) (1.25 g, containing *ca.* 15% of the *cis*-fused isomer (**8a**) (4.4 mmol) in dry THF (10 ml) was added dropwise over 10 min to a stirred solution of methyl-lithium (6.5 ml; 1.35 M in diethyl ether; 8.8 mmol) in dry THF (30 ml) at 0 °C under nitrogen. Stirring was continued for a further 10 min at 0 °C. Aqueous sulphuric acid (40 ml; 0.5 M) was added carefully and the reaction mixture was warmed to room temperature and stirred vigorously. It was then poured into saturated aqueous sodium hydrogen carbonate (150 ml) and extracted with dichloromethane (3 × 100 ml). The combined extracts were dried and concentrated to give a dark brown oil. This oil was purified by flash column chromatography on triethylamine-treated silica gel (200 g; 10 ml of triethylamine), with chloroform as eluant, to give initially (**10a**) as a pale brown oil, ν_{max}(film) 1 705 cm^{-1}; δ($CDCl_3$) 1.0–1.15 (1 H, m), 1.46–1.70 (2 H, m), 2.04–2.44 (2 H, m), 2.24 (6 H, s, COMe and NMe), 2.44–2.57 (1 H, m), 2.7–2.87 (1 H, m), 3.22 (1 H, d, *J* 10 Hz, 5-H), 3.66 (1 H, ddd, *J* 3, 4, and 12 Hz, $CH_2CH_AH_BO$), 3.79 (1 H, dt, *J* 3 and 12 Hz, $CH_2CH_AH_BO$), 3.81 (3 H, s, OMe), 4.04 (2 H, br s, CH_2O), 6.80 (1 H, ddd, *J* 1, 2, and 7.5 Hz, ArH), 7.13–7.21 (2 H, m, 2 × ArH), and 7.30 (1 H, t, *J* 7.5 Hz, ArH), followed by (**9a**) (0.98 g, 74%) as a pale brown oil. This compound was characterised as its *maleate salt*, m.p. 163–165 °C (Found: C, 63.0; H, 7.0; N, 3.3. $C_{22}H_{29}NO_7$ requires C, 63.0; H, 7.0; N, 3.3%); ν_{max}(film) 1 710 cm^{-1}; δ($CDCl_3$) (free base) 1.12 (1 H, dt, *J* 13 and 3 Hz, 4α-H), 1.74 (1 H, dt, *J* 3 and 13 Hz, 8α-H), 1.91 (1 H, dt, *J* 13 and 3 Hz, 8β-H), 1.98–2.5 (2 H, m, 4aα-H and 7β-H), 2.10 (3 H, s, COMe), 2.22 (3 H, s, NMe), 2.36 (1 H, dq, *J* 5 and 13 Hz, 4β-H), 2.66 (1 H, dt, *J* 12 and 3 Hz, 7α-H), 3.34 (1 H, d, *J* 12 Hz, 1-H), 3.36 (1 H, d, *J* 12 Hz, 5β-H), 3.49 (1 H, dt, *J* 3 and 11 Hz, 3α-H), 3.82 (3 H, s, OMe), 4.05 (1 H, dd, *J* 11 and 5 Hz, 3β-H), 4.25 (1 H, d, *J* 12 Hz, 1-H), 6.76 (1 H, dd, *J* 8 and 2 Hz, ArH), 7.04 (1 H, t, *J* 2 Hz, ArH), 7.12 (1 H, br d, *J* 8 Hz, ArH), and 7.26 (1 H, t, *J* 8 Hz, ArH). Irradiation at δ 2.66 gave δ 1.74 (1 H, t, *J* 13 Hz) and 1.91 (1 H, dd, *J* 13 and 3 Hz). Irradiation at δ 1.12 gave δ 3.49 (1 H, t, *J* 11 Hz). Irradiation at δ 4.05 gave δ 3.49 (1 H, dd, *J* 3 and 11 Hz).

trans-5α-*Acetyl*-8a-(3-*methoxyphenyl*)-6-*propyloctahydropyrano*[4,3-c]*pyridine* (**9b**).—Glacial acetic acid (*ca.* 1 ml) was added dropwise to a stirred solution of potassium cyanide (3.88 g, 59.7 mmol) in a mixture of water (25 ml) and methanol (120 ml) at room temperature until the pH was 10.0. The resulting solution was cooled to 0 °C and a solution of (**4b**) (6.98 g, 24.3 mmol) in methanol (25 ml) was added. The reaction mixture was stirred at room temperature for 5 h, poured into aqueous sodium hydroxide (0.35 M; 600 ml), and extracted with dichloromethane (3 × 250 ml). The combined extracts were dried and evaporated to give crude (**7b**) as an oil. This material was dissolved in dry tetrahydrofuran (50 ml) and the resulting solution was added dropwise to a stirred solution of methyl-lithium (48.5 ml; 1.5 M in diethyl ether; 72.9 mmol) in dry tetrahydrofuran (130 ml), at 0 °C under nitrogen, during 15 min. The reaction mixture was stirred for 15 min at 0 °C and then quenched by the addition of aqueous sulphuric acid (200 ml;

0.5M). The resulting mixture was stirred vigorously, basified by the portionwise addition of solid sodium carbonate, and extracted with dichloromethane (3 × 250 ml). The combined extracts were dried and concentrated to give a pale yellow oil. This material was purified by column chromatography on triethylamine-deactivated silica, with dichloromethane–hexane (1:1) followed by dichloromethane as eluant, to give the title compound (**9b**) (6.1 g, 76%) as an oil which was used directly in the next stage.

3-*Methoxy*-17-*methyl*-10-*methylene*-6-*oxamorphinan* (**11a**).—Freshly distilled boron trifluoride–diethyl ether (3.0 ml, 24 mmol) was added in one portion to a stirred solution of (**9a**) (3.0 g, 10 mmol) in dry 1,2-dichlorobenzene (50 ml) at room temperature under nitrogen. The reaction mixture was heated at 120 °C under nitrogen for 22 h and then allowed to cool to room temperature. Aqueous sodium hydroxide (150 ml; 2 M) was added and the resulting mixture was stirred vigorously until all the precipitate had dissolved. Water (150 ml) was added and the mixture was extracted with dichloromethane (3 × 100 ml). The combined extracts were dried and concentrated to give an oil. The NMR spectrum of this crude material showed that only 35% conversion to product had occurred so it was resubmitted to the above reaction conditions to yield an oil which contained no starting material (by NMR and TLC). This crude product was purified by flash column chromatography on triethylamine-deactivated silica gel (150 g; 15 ml of triethylamine), with chloroform followed by chloroform–methanol (50:1) as eluant, to give the title compound (**11a**) (1.85 g, 65%) as an oil (Found: C, 75.8; H, 8.2, N, 4.9. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%); δ($CDCl_3$) 1.24 (1 H, ddd, *J* 2, 3.5, and 12.5 Hz, 15β-H), 1.31 (1 H, br d, *J* 13 Hz, 8β-H), 1.50 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.69 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.95 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.11 (1 H, ddd, *J* 3, 4, and 13 Hz, 14β-H), 2.28 (3 H, s, NMe), 2.51 (1 H, ddd, *J* 2, 5, and 12.5 Hz, 16α-H), 3.14 (1 H, d, *J* 3 Hz, 9α-H), 3.30 (1 H, d, *J* 12 Hz, 5β-H), 3.58 (1 H, ddd, *J* 3, 11, and 12.5 Hz, 7β-H), 3.82 (3 H, s, OMe), 3.94 (1 H, dd, *J* 5 and 11 Hz, 7α-H), 4.51 (1 H, d, *J* 12 Hz, 5α-H), 4.80 (1 H, s, =CH_AH_B), 5.76 (1 H, s, =CH_AH_B), 6.80 (1 H, dd, *J* 3 and 8 Hz, 2-H), and 6.87 (1 H, d, *J* 3 Hz, 4-H), 7.70 (1 H, d, *J* 8 Hz, 1-H). Irradiation at δ 2.51 gave δ 1.24 (1 H, dd, *J* 3.5 and 12.5 Hz), 1.69 (1 H, t, *J* 12.5 Hz), and 1.95 (1 H, dd, *J* 3.5 and 12.5 Hz). Irradiation at δ 3.14 gave δ 2.11 (1 H, dd, *J* 4 and 12 Hz).

3-*Methoxy*-10-*methylene*-17-*propyl*-6-*oxamorphinan* (**11b**).—This compound was prepared from (**9b**) using the method described for the preparation of (**11a**). Compound (**11b**) (46%) was purified by flash column chromatography on silica, with dichloromethane–methanol–aqueous ammonia (*d* 0.880) (93:6:1) as eluant, and was obtained as an oil.

N-*Demethylation of* (**11a**).—Vinyl chloroformate (0.045 ml, 0.53 mmol) was added in one portion to a stirred solution of the oxamorphinan (**11a**) (100 mg, 0.35 mmol) in dry 1,2-dichloroethane (2 ml) at −30 °C under nitrogen. The resulting solution was heated at reflux for 1 h, cooled, and evaporated to dryness. The residue was purified by preparative TLC on alumina, with dichloromethane–hexane (3 : 1) as eluant, to give 3-methoxy-10-methylene-17-(vinyloxycarbonyl)-6-oxamorphinan (**17**) (40 mg, 33%) as an oil; ν_{max}($CHBr_3$) 1 700 cm^{-1}; δ($CDCl_3$) (mixture of rotamers) 1.25–1.70 (4 H, m), 2.02 (1 H, br m, 14β-H), 2.6–2.83 (1 H, m, 16β-H), 3.30 (1 H, d, *J* 12 Hz, 5β-H), 3.58 (1 H, dt, *J* 3.5, and 11 Hz, 7β-H), 3.85 (3 H, s, OMe), 3.85–4.0 (2H, m), 4.4–4.6 (2 H, m), 4.7–4.95 (2 H, m), 5.18 and 5.30 (1 H, 2 × s, =CH_AH_B), 5.67 and 5.69 (1 H, 2 × s, =CH_AH_B), 6.84 (1 H, dd, *J* 3, and 8 Hz, 2-H), 6.92 (1 H, d, *J* 3 Hz, 4-H), 7.2–7.35 (1 H, m, C*H*=CH_2), 7.69 and 7.71 (1 H, 2 × d, *J* 8 Hz, 1-H) and a lower running component *cis*-vinyl 2-{6-(chloromethyl)-9-methoxy-3,4,4a,-10b-tetrahydro-1*H*-naphtho[1,2-*c*]pyran-10b-yl}ethyl(methyl) carbamate (**18a**) (80 mg, 58%) as a pale brown oil; ν_{max}($CHBr_3$) 1 700 cm^{-1}; δ($CDCl_3$) (mixture of rotamers) 1.25–1.8 (3 H, m), 2.16 (1 H, br m), 2.43 (1 H, m, *J* 5 Hz, 4a-H), 2.73 and 2.78 (3 H, 2 × s, NMe), 2.88 (1 H, br m), 3.2–3.6 (3 H, m), 3.86 (3 H, s, OMe), 3.8–3.95 (1 H, m), 4.37 (1 H, d, *J* 12 Hz, ClCH_AH_B), 4.44 (2 H, m), 4.57 and 4.59 (1 H, 2 × d, *J* 12 Hz, ClCH_AH_B), 4.72 and 4.77 (1 H, 2 × d, CH=CH_AH_B), 5.97 (1 H, d, *J* 5 Hz, 5-H), 6.84 (1 H, br d, *J* 8 Hz, ArH), 7.0 and 7.01 (1 H, 2 × d, *J* 2 Hz, ArH), 7.2 and 7.21 (1 H, dd, *J* 7 and 13 Hz, C*H*=CH_2), 7.38 and 7.39 (1 H, 2 × d, *J* 8 Hz, ArH). Irradiation at δ 4.58 gave δ 4.37 (1 H, s). Irradiation at δ 2.43 gave δ 5.97 (1 H, s).

cis-*Vinyl*-2-{(6-*Iodomethyl*)-9-*methoxy*-3,4,4a,10b-*tetrahydro*-1H-*naphtho*[1,2-c]*pyran*-10b-*yl*}*ethyl*(*methyl*) *carbamate* (**18b**).—Vinyl chloroformate (0.035 ml, 1.1 equiv.) was added in one portion to a stirred suspension of 3-methoxy-17-methyl-10-methylene-6-oxamorphinan (**11a**) (100 mg, 0.35 mmol) in dry acetonitrile (1 ml) at −30 °C under nitrogen. Sodium iodide (100 mg) in acetonitrile (1 ml) was added and the mixture was stirred at room temperature for 1 h. Water (10 ml) was added and the mixture extracted with dichloromethane (3 × 15 ml). The combined extracts were dried and concentrated and the residue purified by preparative TLC on alumina, with dichloromethane–hexane (3:1) as eluant, to give the title compound (**18b**) as a pale yellow oil; ν_{max}($CHBr_3$) 1 700 cm^{-1}; δ(C_6D_6; 348 K) 1.0–1.5 (3 H, m), 1.82 (1 H, br m, 4a-H), 1.95 (1 H, br m), 2.42 (3 H, br s, NMe), 2.60 (1 H, br m), 2.9–3.4 (3 H, m), 3.40 (3 H, s, OMe), 3.60 (1 H, dt, *J* 10 and 4 Hz, 3β-H), 3.84 and 4.02 (2 H, ABq, *J* 10 Hz, CH_2I), 4.27 (1 H, d, *J* 6 Hz, CH=CH_AH_B), 4.2–4.4 (1 H, br m, 1β-H), 4.70 (1 H, d, *J* 14 Hz, CH=CH_AH_B), 5.60 (1 H, d, *J* 6 Hz, 5-H), 6.64 (1 H, br m, ArH), 7.16 (2 H, br s, 2 × ArH), and 7.46 (1 H, dd, *J* 6 and 14 Hz, C*H*=CH_2). Irradiation at δ 7.46 gave δ 4.70 (1 H, s) and 4.27 (1 H, s). Irradiation at δ 1.20 gave δ 3.60 (1 H, d, *J* 10 Hz).

17-(*Cyclopropylmethyl*)-3-*methoxy*-10-*methylene*-6-*oxamorphinan* (**11c**).—Methyl-lithium (2.0 ml of a 1.5 M solution in diethyl ether; 3 mmol) was added over 1 min to a stirred solution of 17-(cyclopropylmethyl)-3-methoxy-6-oxamorphinan-10-one (**19c**) (280 mg, 0.86 mmol) in dry tetrahydrofuran (15 ml) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 16 h before being quenched with water (50 ml) and extraction with dichloromethane (3 × 30 ml). The combined extracts were dried and concentrated to give an oil which was dissolved in 1,2-dichlorobenzene (4 ml) and treated with freshly distilled boron trifluoride–diethyl ether (0.2 ml, 1.5 mmol). The reaction mixture was heated at 120 °C under nitrogen for 16 h before cooling and addition of aqueous sodium hydroxide (20 ml; 5 M). Stirring was continued until the precipitate had dissolved. Water (30 ml) was added and the resulting solution was extracted with dichloromethane (3 × 30 ml). The combined extracts were dried and concentrated to give an oil. This crude product was purified by column chromatography on alumina, with ethyl acetate–hexane (1 : 1) as eluant, to give the title compound (**11c**) (240 mg, 85%) as an oil; δ($CDCl_3$) 0.0–0.14 and 0.36–0.60 (4 H, m, 2 × cyclopropyl CH_2), 0.76–0.96 (1 H, m, NCH_2CH), 1.2–1.4 (2 H, m, 8β-H and 15β-H), 1.50 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.71 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.78–1.93 (2 H, m, 16β-H and NCH_AH_B), 2.18 (1 H, dt, *J* 13 and 3.5 Hz, 14β-H), 2.75 (1 H, dd, *J* 5 and 13 Hz, NCH_AH_B), 2.92 (1 H, ddd, *J* 2,5, and 12 Hz, 16α-H), 3.27 (1 H, d, *J* 3 Hz, 9α-H), 3.32 (1 H, d, *J* 12 Hz, 5β-H), 3.58 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.81 (3 H, s, OMe), 3.94 (1 H, dd, *J* 5 and 11 Hz, 7α-H), 4.51 (1 H, d, *J* 12 Hz, 5α-H), 4.80 (1 H, s, =CH_AH_B), 5.66 (1 H, s, =CH_AH_B), 6.77 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.86 (1 H, d, *J* 3 Hz, 4-H), and 7.65 (1 H, d, *J* 8 Hz, 1-H).

17-*Allyl*-3-*methoxy*-10-*methylene*-6-*oxamorphinan* (**11d**).—

This compound was prepared from (**19d**) using the method described for (**11c**). Compound (**11d**) (84%) was isolated as an oil (Found: C, 75.3; H, 7.8; N, 4.4. $C_{20}H_{25}NO_2 \cdot 0.15C_6H_4Cl_2$ requires C, 75.3; H, 7.7; N, 4.2%).

17-*Ethyl*-3-*methoxy*-10-*methylene*-6-*oxamorphinan* (**11e**).—This compound was prepared from (**19e**) using the method described for (**11c**). Compound (**11e**) (86%) was isolated as an oil and used directly in the next stage.

14-epi-3-*Methoxy*-17-*methyl*-10-*methylene*-6-*oxamorphinan* (**12**).—Freshly distilled boron trifluoride–diethyl ether (3.0 ml, 24 mmol) was added in one portion to a stirred solution of (**10a**) (3.5 g, 11.5 mmol) in distilled 1,2-dichlorobenzene (50 ml) at room temperature under nitrogen. The reaction mixture was heated at 120 °C for 16 h. The cooled mixture was treated with methanol (20 ml) followed by aqueous sodium hydroxide (30 ml; 5 M) and then stirred vigorously until the precipitate had dissolved. Water (100 ml) was added and the resulting mixture was extracted with dichloromethane (3 × 50 ml). The combined extracts were dried and concentrated to give an oil. This material was purified by column chromatography on alumina with graded elution from diethyl ether–hexane (1:1) to diethyl ether to give the title compound (**12**) (2.05 g, 63%) as an oil; δ($CDCl_3$) 1.15 (1 H, ddt, *J* 13.5, 4, and 1.5 Hz, 15β-H), 1.42 (1 H, br d, *J* 12 Hz, 8α-H), 2.00 (1 H, dt, *J* 4 and 12 Hz, 16 β-H), 2.02 (1 H, br d, *J* 11 Hz, 14α-H), 2.31 (3 H, s, NMe), 2.59 (1 H, dd, *J* 12 and 5 Hz, 16α-H), 2.64 (1 H, dq, *J* 5 and 12 Hz, 8β-H), 2.78 (1 H, dt, *J* 5 and 13 Hz, 15α-H), 3.22 (1 H, d, *J* 2 Hz, 9α-H), 3.44 (1 H, ddd, *J* 2.5, 11.5, and 12 Hz, 7α-H), 3.51 (1 H, d, *J* 11 Hz, 5α-H), 3.83 (3 H, s, OMe), 4.16 (1 H, dd, *J* 5 and 11.5 Hz, 7β-H), 4.24 (1 H, d, *J* 11 Hz, 5β-H), 4.80 (1 H, s, $=CH_AH_B$), 5.76 (1 H, s, $=CH_AH_B$), 6.51 (1 H, d, *J* 3 Hz, ArH), 6.79 (1 H, dd, *J* 3 and 8 Hz, ArH), and 7.72 (1 H, d, *J* 8 Hz, ArH). Irradiation at δ 1.42 gave δ 3.44 (1 H, t, *J* 12 Hz) and simplified the signal at δ 2.64. Irradiation at δ 3.22 simplified the signal at δ 2.02. Irradiation at δ 4.16 simplified the signals at δ 3.44, 2.64, and 1.42.

3-*Methoxy*-17-*methyl*-6-*oxamorphinan*-10-*one* (**19a**).—Sulphuric acid (2 M; 1.0 ml, 2.0 mmol) was added in one portion to a stirred solution of 3-methoxy-17-methyl-10-methylene-6-oxamorphinan (**11a**) (0.5 g, 1.75 mmol) in acetone (5 ml) at room temperature. Jones reagent (10 ml of a 2 M solution with respect to chromium trioxide in aqueous sulphuric acid; 20 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous sodium hydrogen carbonate (50 ml) was added and stirring was continued for 15 min before addition of further sodium hydrogen carbonate solution (100 ml) and extraction with dichloromethane (3 × 80 ml). The combined extracts were dried and concentrated to give a pale yellow solid. Purification by short path column chromatography on alumina, with ethyl acetate as eluant, gave the title compound (**19a**) (403 mg, 80%) as a crystalline solid, m.p. 144–145 °C (from ethyl acetate) (Found: C, 71.0; H, 7.6; N, 4.8. $C_{17}H_{21}NO_3$ requires C, 71.0; H, 7.4; N, 4.9%); ν_{max}($CHBr_3$) 1 660 cm^{-1}; δ($CDCl_3$) 1.3–1.5 (2 H, m, 8β-H and 15β-H), 1.56 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.80 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 2.12 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.31 (1 H, ddd, *J* 3, 4, and 12.5 Hz, 14β-H), 2.37 (3 H, s, NMe), 2.66 (1 H, ddd, *J* 2, 5, and 12.5 Hz, 16α-H), 3.06 (1 H, d, *J* 3 Hz, 9α-H), 3.33 (1 H, d, *J* 12 Hz, 5β-H), 3.56 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.88 (3 H, s, OMe), 3.93 (1 H, m, 7α-H), 4.52 (1 H, d, *J* 12 Hz, 5α-H), 6.8–7.0 (2 H, m, 2-H and 4-H), and 8.08 (1 H, d, *J* 8 Hz, 1-H).

3-*Methoxy*-17-*propyl*-6-*oxamorphinan*-10-*one* (**19b**).—This compound was prepared from (**11b**) using the method described for (**19a**). The title compound (**19b**) (48%) was purified by column chromatography on alumina, with ethyl acetate as eluant, and characterised as its *hydrochloride salt*, m.p. 211–212 °C (from ethyl acetate–hexane) (Found: C, 61.7; H, 7.6; N, 3.7. $C_{19}H_{25}NO_3 \cdot HCl \cdot H_2O$ requires C, 61.7; H, 7.6; N, 3.8%).

17-*Cyclopropylmethyl*-3-*methoxy*-6-*oxamorphinan*-10-*one* (**19c**).—A mixture of 3-methoxy-6-oxamorphinan-10-one (**19f**) (410 mg, 1.5 mmol), bromomethylcyclopropane (265 mg, 1.96 mmol), and anhydrous sodium hydrogen carbonate (168 mg, 2 mmol) in dry dimethylformamide (5 ml) was heated at reflux for 3 h. The cooled reaction mixture was evaporated and the oily residue was partitioned between water (50 ml) and dichloromethane (40 ml). The aqueous layer was extracted with dichloromethane (2 × 50 ml) and the combined organic extracts were dried and concentrated to give an oil. This material was purified by column chromatography on alumina, with dichloromethane as eluant to give the title compound (**19c**) as an oil (470 mg, 88%) (Found: M^+, 327.1837. $C_{20}H_{25}NO_3$ requires *M*, 327.1836); ν_{max}($CHBr_3$) 1 665 cm^{-1}; δ($CDCl_3$) 0.00–0.15, 0.25–0.40, 0.45–0.60 (4 H, m, 2 × cyclopropyl CH_2), 0.8–1.0 (1 H, m, NCH_2CH), 1.34–1.5 (2 H, m, 8β-H and 15β-H), 1.56 (1 H, dq, *J* 5, 12.5 Hz, 8α-H), 1.84 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 2.0 (1 H, dd, *J* 8 and 13 Hz, NCH_AH_B), 2.05 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.36 (1 H, ddd, *J* 3, 4, and 12.5 Hz, 14β-H), 2.70 (1 H, dd, *J* 6 and 13 Hz, NCH_AH_B), 2.99 (1 H, ddd, *J* 2, 5, and 12.5 Hz, 16α-H), 3.29 (1 H, d, *J* 3 Hz, 9α-H), 3.35 (1 H, d, *J* 12 Hz, 5β-H), 3.58 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.88 (3 H, s, OMe), 3.96 (1 H, dd, *J* 5 and 12 Hz, 7α-H), 4.53 (1 H, d, *J* 12 Hz, 5α-H), 6.84–6.96 (2 H, m, 2-H and 4-H), and 8.04 (1 H, d, *J* 8 Hz, 1-H).

17-*Allyl*-3-*methoxy*-6-*oxamorphinan*-10-*one* (**19d**).—This compound was prepared from (**19f**) using the method described for the preparation of (**19c**). The title compound (**19d**) (95%) was purified by column chromatography on alumina, with ethyl acetate as eluant, and was isolated as an oil (Found: C, 71.2; H, 7.5; N, 4.1. $C_{19}H_{23}NO_2 \cdot 0.25CH_3CO_2CH_2CH_3$ requires C, 71.6; H, 7.5; N, 4.2%).

17-*Ethyl*-3-*methoxy*-6-*oxamorphinan*-10-*one* (**19e**).—This compound was prepared from (**19f**) using the method described for the preparation of (**19c**). Compound (**19e**) was isolated as an oil and used directly in the next stage [conversion to (**11e**)].

3-*Methoxy*-6-*oxamorphinan*-10-*one* (**19f**).—Vinyl chloroformate (0.28 ml, 1.42 equiv.) was added in one portion to a stirred solution of 3-methoxy-17-methyl-6-oxamorphinan-10-one (**19a**) (0.58 g, 2.1 mmol) in 1,2-dichloroethane (12 ml) at −30 °C under nitrogen. The resulting solution was brought to reflux over 30 min and then heated at reflux for 2 h. Further vinyl chloroformate (0.35 ml, 1.80 equiv.) was added and the reaction mixture was heated at reflux for 16 h before cooling and concentration to give a brown oil. This crude product was purified by column chromatography on alumina, with ethyl acetate–hexane (3:1) followed by ethyl acetate as eluant to give 3-methoxy-17-(vinyloxycarbonyl)-6-oxamorphinan-10-one (570 mg, 82%). Ethereal hydrogen chloride (10 ml of a 1.33 M solution; 13.3 mmol) was added in one portion to a stirred solution of the above carbamate (570 mg, 1.66 mmol) in methanol (20 ml) at room temperature under nitrogen. The ether was removed by distillation and the residual methanolic solution was heated at reflux for 4 h. The cooled reaction mixture was concentrated and the residue dissolved in water (50 ml). The resultant solution was treated with aqueous hydrochloric acid (10 ml; 2 M) and washed with dichloromethane (2 × 50 ml). The aqueous phase was basified with aqueous sodium hydroxide and extracted with dichloromethane (3 × 80 ml). The organic extracts were combined, dried, and evaporated to give the title compound (**19f**) (425 mg, 90%) as an oil (Found: C, 70.3; H, 6.8; N, 5.1 $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N,

5.1%); $\nu_{max}(CHBr_3)$ 1 660 cm^{-1}; $\delta(CDCl_3)$ 1.25–1.48 (2 H, m, 8β-H and 15β-H), 1.54 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.75 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 2.05 (1 H, br s, NH), 2.31 (1 H, ddd, *J* 3, 4, and 12 Hz, 14β-H), 2.66 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.83 (1 H, ddd, *J* 2, 5, and 12.5 Hz, 16α-H), 3.31 (1 H, d, *J* 3 Hz, 9α-H), 3.36 (1 H, d, *J* 12 Hz, 5β-H), 3.60 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.90 (3 H, s, OMe), 3.94 (1 H, dd, *J* 5 and 12 Hz, 7α-H), 4.49 (1 H, d, *J* 12 Hz, 5α-H), 6.87–7.0 (2 H, m, 2-H and 4-H), and 8.12 (1 H, d, *J* 8 Hz, 1-H).

3-*Methoxy*-10α,17-*dimethyl*-6-*oxamorphinan* (**20a**).—3-Methoxy-17-methyl-10-methylene-6-oxamorphinan (**11a**) (250 mg, 0.87 mmol) in absolute ethanol (5 ml) was hydrogenated over 10% palladium on carbon (50 mg) at room temperature and pressure for 16 h. The reaction mixture was filtered through Celite and the solids were washed with absolute ethanol (30 ml). The combined filtrates were concentrated and evaporated to dryness to give the title compound (**20a**), (250 mg, 99%) as an oil which was used directly in the next stage without purification; $\delta(CDCl_3)$ 1.18–1.5 (2 H, m, 8β-H and 15β-H), 1.35 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.64 (1 H, dt, *J* 5 and 12 Hz, 15α-H), 1.73 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 2.0–2.2 (2 H, m, 14β-H and 16β-H), 2.40 (3 H, s, NMe), 2.35–2.5 (1 H, m, 16α-H), 2.69 (1 H, d, *J* 3 Hz, 9α-H), 3.06 (1 H, q, *J* 7 Hz, 10β-H), 3.30 (1 H, d, *J* 12 Hz, 5β-H), 3.49 (1 H, ddd, *J* 2, 11, and 12.5 Hz, 7β-H), 3.80 (3 H, s, OMe), 3.94 (1 H, br dd, *J* 5 and 11 Hz, 7α-H), 4.50 (1 H, d, *J* 12 Hz, 5α-H), 6.80 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.90 (1 H, d, *J* 3 Hz, 4-H), and 7.24 (1 H, d, *J* 8 Hz, 1-H).

3-*Methoxy*-10α-*methyl*-17-*propyl*-6-*oxamorphinan* (**20b**).—This compound was prepared from (**11b**) using the method described for (**20a**). The title compound (**20b**) (40%) was purified by column chromatography on alumina, with ethyl acetate–hexane as eluant, and was isolated as a colourless oil (Found: C, 75.8; H, 9.5; N, 4.6. $C_{20}H_{29}NO_2$ requires C, 76.1; H, 9.3; N, 4.4%).

17-(*Cyclopropylmethyl*)-3-*methoxy*-10α-*methyl*-6-*oxamorphinan* (**20c**).—A mixture of 3-methoxy-10α-methyl-6-oxamorphinan (**20d**) (143 mg, 0.52 mmol), cyclopropylmethyl bromide (92 mg, 0.68 mmol) and anhydrous sodium hydrogen carbonate (200 mg) in dry dimethylformamide (3 ml) was heated at 125 °C for 3 h. The cooled reaction mixture was evaporated to dryness and the residue purified by column chromatography on alumina with ethyl acetate as eluant, to give the title compound (**20c**) (130 mg, 76%) as an oil (Found: M^+, 327.2196. $C_{21}H_{29}NO_2$ requires *M*, 327.2198); $\delta(CDCl_3)$ 0.0–0.2 (2 H, m), 0.4–0.6 (2 H, m), 0.77–0.95 (1 H, m, NCH_2CH), 1.16–1.4 (2 H, m, 8β-H and 15β-H), 1.34 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.65 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.73 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 2.02 (1 H, dt, *J* 4 and 12 Hz, 16β-H), 2.14 (1 H, dt, *J* 13 and 3 Hz, 14β-H), 2.30 (1 H, dd, *J* 6 and 12 Hz, NCH_AH_B), 2.45 (1 H, dd, *J* 6 and 12 Hz, NCH_AH_B), 2.66 (1 H, br dd, *J* 4 and 12 Hz, 16α-H), 2.93 (1 H, q, *J* 7 Hz, 10β-H), 2.95 (1 H, d, *J* 3 Hz, 9α-H), 3.31 (1 H, d, *J* 12 Hz, 5β-H), 3.48 (1 H, ddd, *J* 2, 11, and 12 Hz, 7β-H), 3.80 (3 H, s, OMe), 3.94 (1 H, br dd, *J* 5 and 11 Hz, 7α-H), 4.50 (1 H, d, *J* 12 Hz, 5α-H), 6.78 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.88 (1 H, d, *J* 3 Hz, 4-H), and 7.20 (1 H, d, *J* 8 Hz, 1-H).

3-*Methoxy*-10α-*methyl*-6-*oxamorphinan* (**20d**).—Vinyl chloroformate (0.25 ml, 2.93 mmol) was added in one portion to a stirred mixture of (**20a**) (250 mg, 0.87 mmol) and anhydrous potassium carbonate (0.25 g) in dry 1,2-dichloroethane (4 ml) at room temperature under nitrogen. The resulting mixture was heated at reflux for 3 h and then cooled and concentrated. The residue was applied directly to an alumina column which was eluted with ethyl acetate–hexane (3:1) to give the intermediate carbamate (200 mg, 67%) as a colourless oil. This compound was dissolved in methanol (2 ml), the solution treated with ethereal hydrogen chloride (1.5 ml of a 1.33 M solution), and the resulting mixture heated at reflux under nitrogen for 4 h. The cooled reaction mixture was evaporated to dryness and the residue dissolved in hydrochloric acid (20 ml; 0.5 M). The resulting solution was washed with dichloromethane (2 × 40 ml), basified by the addition of sodium hydroxide, and then extracted with dichloromethane (3 × 30 ml). The latter extracts were combined, dried, and evaporated to give the title compound (**20d**) (140 mg, 58%) as an oil. This material was used directly in *N*-alkylation reactions without further purification; $\delta(CDCl_3)$ 1.2–1.4 (2 H, m, 8β-H and 15β-H), 1.42 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.55 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.72 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 2.14 (1 H, br d, *J* 12.5 Hz, 14β-H), 2.6–2.9 (3 H, m, 16α-H, 16β-H, and NH), 3.0 (1 H, q, *J* 7 Hz, 10β-H), 3.05 (1 H, br s, 9α-H), 3.32 (1 H, d, *J* 12 Hz, 5β-H), 3.52 (1 H, ddd, *J* 2, 11, and 12 Hz, 7β-H), 3.82 (3 H, s, OMe), 3.94 (1 H, dd, *J* 5, and 11 Hz, 7α-H), 4.46 (1 H, d, *J* 12 Hz, 5α-H), 6.80 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.90 (1 H, d, *J* 3 Hz, 4-H), and 7.24 (1 H, d, *J* 8 Hz, 1-H).

14-epi-3-*Methoxy*-10β,17-*dimethyl*-6-*oxamorphinan* (**21**).—This compound was prepared from (**12**) using the method described for (**20a**). The title compound (**21**) (77%) was purified by column chromatography on alumina, with ethyl acetate as eluant, and was isolated as an oil (Found: C, 74.9; H, 8.4; N, 4.6. $C_{18}H_{25}NO_2$ requires C, 75.2; H, 8.8; N, 4.9%); $\delta(CDCl_3)$ 0.98–1.06 (1 H, m, 15β-H), 1.36 (1 H, br d, *J* 13 Hz, 8α-H), 1.50 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.86 (1 H, br d, *J* 11 Hz, 16β-H), 2.4–2.7 (4 H, m), 2.74 (4 H, s, and m, NMe and 9α-H), 3.14 (1 H, m, 10α-H), 3.42 (1 H, ddd, *J* 2.5, 11.5, and 13 Hz, 7α-H), 3.48 (1 H, d, *J* 11 Hz, 5α-H), 3.80 (3 H, s, OMe), 4.08 (1 H, dd, *J* 5 and 11.5 Hz, 7β-H), 4.22 (1 H, d, *J* 11 Hz, 5β-H), 6.50 (1 H, d, *J* 3 Hz, 4-H), 6.76 (1 H, dd, *J* 3 and 8 Hz, 2-H), and 7.26 (1 H, d, *J* 8 Hz, 1-H).

N-*Demethylation of* (**21**).—Vinyl chloroformate (0.5 ml, 5.87 mmol) was added during 1 min to a stirred mixture of (**21**) (0.68 g, 2.4 mmol) and potassium carbonate (0.5 g) in 1,2-dichloroethane (15 ml) at −30 °C under nitrogen. The reaction mixture was heated at reflux for 3 h, cooled, and evaporated to dryness. The residue was purified by column chromatography on alumina, with ethyl acetate–hexane (3:1) as eluant, to give the intermediate carbamate as an oil. This oil was dissolved in methanol (8 ml), the solution treated with saturated ethereal hydrogen chloride (6 ml), and the resulting mixture heated at reflux for 6 h. The cooled mixture was evaporated to dryness and the residue dissolved in hydrochloric acid (40 ml; 1 M). This solution was washed with dichloromethane (2 × 40 ml), basified by addition of aqueous sodium hydroxide, and extracted with dichloromethane (3 × 50 ml). The latter extracts were combined, dried, and concentrated to give an oil (310 mg). The ^1H NMR spectrum of this oil was consistent with a 3:1 mixture of *trans*-9-methoxy-6-methyl-10b-[2-*N*-methylamino)ethyl]-3,4,4a,10b-tetrahydro-1*H*-naphtho[1,2-*c*]pyran (**23**) and 14-*epi*-3-methoxy-10β-methyl-6-oxamorphinan (**22**). Major component (**23**): $\delta(CDCl_3)$ 1.49 (1 H, br dt, *J* 13 and 3 Hz), 1.6–2.13 (8 H, m), 2.27 (3 H, s, NMe), 2.4–2.55 (2 H, m), 3.4–3.55 (2 H, m, 1α-H and 3α-H), 3.81 (3 H, s, OMe), 4.18 (1 H, br dd, *J* 4.5 and 11 Hz, 3β-H), 4.35 (1 H, d, *J* 12 Hz, 1β-H), 5.35 (1 H, br s, 5-H), 6.45 (1 H, d, *J* 3 Hz, 10-H), 6.47 (1 H, dd, *J* 3 and 8 Hz, 8-H), and 7.22 (1 H, d, *J* 8 Hz, 7-H).

O-*Demethylation Reactions*.—The following are typical examples. 17-*Methyl*-10-*methylene*-6-*oxamorphinan*-3-*ol* (**24a**) (*method A*). Boron tribromide (2.1 ml of a 1 M solution in dichloromethane, 2.1 mmol) was added dropwise over 2 min to a stirred solution of 3-methoxy-17-methyl-10-methylene-6-oxamorphinan (**11a**) (200 mg, 0.70 mmol) in 1,2-dichloromethane (6 ml) at −60 °C under nitrogen. The reaction mixture was

warmed to room temperature and stirred for 4 h before addition of aqueous sodium hydroxide (25 ml; 0.35 M). The resulting mixture was stirred vigorously to dissolve all the precipitate. The layers were separated and the aqueous layer was extracted with dichloromethane (25 ml). The aqueous layer was adjusted to pH 7 with 1 M hydrochloric acid and then extracted with dichloromethane (3 × 25 ml). The combined organic extracts were dried and evaporated to give a pale brown solid which was purified by column chromatography on alumina, with chloroform–methanol (20:1) as eluant, to give the title compound (**24a**) (180 mg, 64%) as a colourless solid (see Table 1); δ[$(CD_3)_2SO$] 1.13–1.36 (3 H, m), 1.57 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.79 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.01 (1 H, br m, 14β-H), 2.15 (3 H, s, NMe), 2.41 (1 H, br dd, *J* 4 and 12 Hz, 16α-H), 3.05 (1 H, d, *J* 3 Hz, 9α-H), 3.19 (1 H, d, *J* 12 Hz, 5β-H), 3.4–3.53 (1 H, m, 7β-H), 3.78 (1 H, br d, *J* 11 Hz, 7α-H), 4.37 (1 H, d, *J* 12 Hz, 5α-H), 4.72 (1 H, s, $=CH_AH_B$), 5.74 (1 H, s, $=CH_AH_B$), 6.65 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.76 (1 H, d, *J* 3 Hz, 4-H), 7.64 (1 H, d, *J* 8 Hz, 1-H), and 9.2–9.8 (1 H, br, OH).

17-*Ethyl*-10-*methylene*-6-*oxamorphinan*-3-*ol* (**24e**) (*method B*). A solution of lithium methanethiolate (1.44 g, 6 equiv.) and 17-ethyl-3-methoxy-10-methylene-6-oxamorphinan (**11e**) (1.34 g, 4.45 mmol) in dry dimethylformamide (15 ml) was heated at 130 °C for 4 h under nitrogen. The reaction mixture was cooled, ammonium chloride (1.4 g) was added, and the mixture was evaporated to dryness. The residue was purified by column chromatography on alumina, with dichloromethane–methanol (15:1) as eluant, to give the title compound (**24e**) (486 mg, 38%) as a colourless crystalline solid (see Table 1); δ{$CDCl_3$[$(CD_3)_2SO$]} 1.1 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.18–1.36 (2 H, m, 8β-H and 15β-H), 1.49 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.66 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 1.93 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.27–2.7 (4 H, m), 3.25 (1 H, d, *J* 12 Hz, 5β-H), 3.29 (1 H, br s, 9α-H), 3.54 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.91 (1 H, br dd, *J* 4.5 and 11 Hz, 7α-H), 4.46 (1 H, d, *J* 12 Hz, 5α-H), 4.77 (1 H, s, $=CH_AH_B$), 5.65 (1 H, s, $=CH_AH_B$), 6.72 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.83 (1 H, d, *J* 3 Hz, 4-H), 7.58 (1 H, d, *J* 8 Hz, 1-H), and 8.75 (1 H, br s, OH).

3-*Hydroxy*-17-*methyl*-6-*oxamorphinan*-10-*one* (**25a**) (*method C*). Ethanethiol (0.375 ml, 5 mmol) was added dropwise over 2 min to a stirred suspension of sodium hydride (240 mg of a 50% dispersion in mineral oil, 5 mmol) in dimethylformamide (20 ml) at room temperature under nitrogen. After 15 min a solution of 3-methoxy-17-methyl-6-oxamorphinan-10-one (**19a**) (300 mg, 1.05 mmol) in dimethylformamide (10 ml) was added and the resulting mixture was heated at reflux for 4 h. The reaction mixture was evaporated to dryness and the residue dissolved in methanol (30 ml). Dowex 50W-X8 ion-exchange resin (2 g; methanol-washed) was added and the mixture was stirred for 30 min before the Dowex resin was filtered off and washed with methanol (100 ml). The combined filtrate and washings were concentrated to give an oil which was purified by column chromatography on alumina with dichloromethane followed by dichloromethane–methanol (9:1) as eluants, to give the title compound (**25a**) (130 mg, 45%) as a colourless crystalline solid (see Table 1); ν_{max}(Nujol) 3 110–2 200 (OH) and 1 675 (C=O) cm^{-1}; δ($CDCl_3$) 1.3–1.5 (2 H, m, 8β-H and 15β-H), 1.59 (1 H, dq, *J* 5 and 12.5 Hz, 8α-H), 1.80 (1 H, dt, *J* 5 and 12.5 Hz, 15α-H), 2.13 (1 H, dt, *J* 3.5 and 12.5 Hz, 16β-H), 2.31 (1 H, ddd, *J* 3, 4, and 12.5 Hz, 14β-H), 2.38 (3 H, s, NMe), 2.68 (1 H, ddd, *J* 2, 5, and 12.5 Hz, 16α-H), 3.07 (1 H, d, *J* 3 Hz, 9α-H), 3.36 (1 H, d, *J* 12 Hz, 5β-H), 3.60 (1 H, dt, *J* 3 and 12 Hz, 7β-H), 3.98 (1 H, br dd, *J* 5 and 11 Hz, 7α-H), 4.49 (1 H, d, *J* 12 Hz, 5α-H), 6.75 (1 H, dd, *J* 3 and 8 Hz, 2-H), 6.81 (1 H, d, *J* 3 Hz, 4-H), and 8.02 (1 H, d, *J* 8 Hz, 1-H).

Pharmacological Methods.—In vivo. The mouse acetylcholine-induced abdominal constriction test,[4] the rat-paw pressure test[20] and the rat urine-output experiments[22] were performed as previously described.

In vitro. Activity in the rabbit vas deferens preparation was determined as previously described[25] and pA_2 values were calculated using a single antagonist concentration. Determination of the receptor selectivity of opioid agonists in the guinea-pig ileum using β-FNA[23a] and β-CNA[23b] utilized previously described methodology.

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