filtered, yielding 1.12 g (55%) of the free base **15**, mp 190–192 °C. Anal. ($C_9H_{11}N_3O_3S$) C, H, N, S.

6-[(Dimethylamino)methyl]-2-methyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-Dioxide Hydrochloride (16·HCl). A solution of 1.8 g (6.47 mmol) of 14·HCl in 20 mL of formic acid and 18 mL of 37% aqueous formaldehyde was heated to reflux for 2 h. The reaction was then evaporated to dryness, 100 mL of 1 N Na_2CO_3 was added to the residue, and the mixture was extracted with 3 × 100 mL of EtOAc. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to leave 1.42 g of crude solid product. This was dissolved in 50 mL of MeOH, and a slight excess of dry HCl gas was passed into the solution, which was then evaporated to dryness. The solid residue was triturated with 10 mL of MeOH, and the solid was filtered and dried to give 1.32 g (67%) of 16·HCl, mp 256–260 °C dec. Anal. ($C_{11}H_{15}N_3O_3S$·HCl) C, H, Cl, N, S.

Biological Methodology. Preparation of Synaptosomes. A crude synaptosomal preparation (P_2) was prepared at 4 °C by homogenizing whole rat brain minus cerebellum in 10 volumes of 0.32 M sucrose with eight strokes of a motor-driven (500 rpm) Teflon–glass homogenizer (Type B, A.H. Thomas, Philadelphia, PA). The resultant homogenate was centrifuged at 1000*g* for 10 min, and the supernatant was decanted and centrifuged at 27000*g* for 20 min. The final P_2 pellet was then used to study GABA synaptosomal processes.

GABA Uptake and Transaminase. GABA uptake and transaminase in rat synaptosomes were measured simultaneously. Synaptosomes were incubated in the presence of 100 μM test compound and [^{3}H]GABA (25 μM) in Krebs–Ringer phosphate buffer for 10 min at room temperature. The reaction was terminated by the addition of 1 mL of a solution of 1 mM unlabeled GABA and 1 mM succinic acid. The reaction tubes were then centrifuged at 1500*g* for 3 min, and 1 mL of the resultant supernatant was transferred to a Dowex 50 column. The [^{3}H]-succinate was eluted with 3 mL of water, and the combined effluent was mixed with 10 mL of Econofluor scintillation cocktail (New England Nuclear, Boston, MA) and counted by liquid scintillation spectroscopy.

The pellet remaining was washed twice with saline, and 0.5 mL of Protosol (NEN) was added to solubilize the tissue. An aliquot (0.25 mL) of the solubilized tissue was added to a scintillation vial, and 10 mL of Econofluor scintillation cocktail was added to determine residual radioactivity. Activity was expressed as a percent of control where this parameter = (counts per minute of drug/counts per minute of control) × 100. Control tissue contained no drug.

GABA Release. GABA release from rat forebrain synaptosomes was measured by a modification of the method of Cotman et al.,[16] the [^{3}H]GABA released being isolated by centrifugation using the microfuge (Beckman Instruments).

GABA Receptor Binding. Interaction of the test compounds with rat brain synaptosomal GABA receptors was measured using [^{3}H]muscimol exactly as described by Williams and Risley.[17]

Taurine Antagonism. Conventional single unit recording and iontophoretic techniques in the cerebellar cortex of male, Sprague–Dawley rats (Charles River Laboratories, 240–350 g) were employed. Multibarrel micropipettes, fabricated using W-P instruments, Inc., Omega Dot capillary tubing (tip diameter 5–10 μM), were filled with the following solutions: NaCl (2 M, used for recording and automatic current balancing barrels), taurine TAU, 0.2 M, pH 8.0, Sigma Chemical Co.), GABA (0.2 M, pH 3.8, Aldrich Chemical Co.), and compound 7 (TAG, 0.05 or 0.1 M, pH 7.0–7.2). All compounds, including taurine, were ejected with anodal currents through the use of a Dagan 6400 current pump. The animals were anesthetized with 350 mg/kg ip of chloral hydrate with supplemental injections as required. They were placed in a stereotaxic frame, and body temperature was maintained at 37 °C via a rectal probe and a servo device connected to a heating pad under the animal. After exposure of the cerebellar vermin cortex and placement of the micropipette, 4% agar in 0.9% saline was applied to prevent drying. Purkinje neurons, identified by their characteristic irregular, high-frequency firing and the presence of inactivation potentials were studied.

Acknowledgment. We thank S. C. Ho of Merck Frosst Laboratories for the pK_a measurements.

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Common Anionic Receptor Site Hypothesis: Its Relevance to the Antagonist Action of Naloxone

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Appropriate modification of 14β-methoxy- and 14β-ethoxycodeinone (prepared by alkylation of 14β-hydroxycodeinone) has generated four alkoxy analogues (**3a–d**) of naloxone and naltrexone. These agents were pure narcotic antagonists in contradiction to the predictions of the common anionic receptor site hypothesis, postulated to be of importance in the enhanced antagonism of naloxone. The molecular change from allyl to cyclopropylmethyl on the N atom increased selectivity of these antagonists for the μ receptor to the same extent as found for naloxone. Increase in the length of the C_{14} O-substituent had no effect on receptor selectivity, and ether formation in most cases did not significantly alter oral/parenteral ratios or durations of action.

A number of different hypotheses have been advanced to explain the antagonism conferred on opiates by a variety of *N*-alkyl substituents. The orientation of the N-substituent was shown to be critical for agonist activity in a rigid morphine analogue.[2] In contrast, however, both axially and equatorially confined substituents have been identified in a number of homobenzomorphan agonists.[3] It was suggested that the essential feature of antagonists was that the antagonist substituent was confined to the axial position.[4] Quantum-mechanical calculations of allyl group conformational minima suggested that N-substituent conformation was a key determinant of antagonist activity,[5a,b] while other calculations support the idea that subtle conformational changes in the piperidine ring cause different interactions with the amine binding site.[6]

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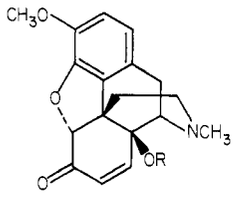
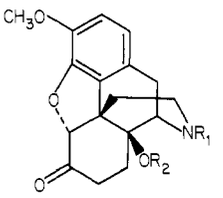
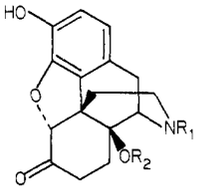
The introduction of a C_{14}-OH substituent in morphine and benzomorphan derivatives enhances antagonist properties.[7,8] There is considerable speculation on the role of this substitution in changing profiles of both agonists and antagonists.[5a,b,9,10] The suggestion of direct steric interference with the equatorial N-substituent was refuted by quantum-mechanical (PCILO) calculation.[10] It has been postulated that a C_{14}-OH group interacts with both the protonated N atom and low-energy conformers of the N-substituent via a common anionic receptor site,[11] thereby causing preferential selection of antagonist conformations of the allyl substituent in the drug–receptor complex. Substitutions affecting the strict geometric requirements apparently necessary for complex formation, such as methylation of the C_{14}-OH group, were hypothesized to enhance the agonist/antagonist potency ratio.[10] However, there is little available information on the effects of modifications to the C_{14}-OH group of antagonists, with the exception of the acetate and sulfate esters of naloxone.[12] We have therefore prepared and evaluated the four alkoxy analogues of naloxone and naltrexone (**3a–d**) to test the common anionic receptor site hypothesis.



1a, R = H
b, R = CH_3
c, R = C_2H_5



2a, R_1 = R_2 = CH_3
b, R_1 = CH_3; R_2 = C_2H_5
c, R_1 = $CO_2CH{=}CH_2$; R_2 = CH_3
d, R_1 = $CO_2CH{=}CH_2$; R_2 = C_2H_5
e, R_1 = $CO_2CHClCH_3$; R_2 = CH_3
f, R_1 = $CO_2CHClCH_3$; R_2 = C_2H_5
g, R_1 = H; R_2 = CH_3
h, R_1 = H; R_2 = C_2H_5
i, R_1 = $CH_2CH{=}CH_2$; R_2 = CH_3
j, R_1 = $CH_2CH{=}CH_2$; R_2 = C_2H_5
k, R_1 = CH_2-c-C_3H_5; R_2 = CH_3
l, R_1 = CH_2-c-C_3H_5; R_2 = C_2H_5



3a, R^1 = $CH_2CH{=}CH_2$; R_2 = CH_3
b, R^1 = $CH_2CH{=}CH_2$; R_2 = C_2H_5
c, R_1 = CH_2-c-C_3H_5; R_2 = CH_3
d, R_1 = CH_2-c-C_3H_5; R_2 = C_2H_5

In addition, since metabolism of phenolic drugs is known to be a function of substrate lipophilicity,[13] these compounds provide the opportunity for investigating the effects of lipophilicity on duration of action.[14–18] The effects of increased lipophilicity have important consequences for the oral/parenteral ratio, and **3a–d** therefore allow further investigation of the influence of increased lipophilicity as revealed by differences between naloxone and naltrexone.

Table I. Physical and Analytical Data for Naloxone, Naltrexone, and Analogues

compd	mp, °C	formula[a]	log *P* calcd[b,c]
3a	197-199	$C_{20}H_{23}NO_4$	2.522
3b	146-147	$C_{21}H_{25}NO_4$	3.047
3c	187-188	$C_{21}H_{25}NO_4$	3.052
3d	165-166	$C_{22}H_{27}NO_4 \cdot 0.5H_2O$	3.577
naloxone			1.91
naltrexone			3.047

[a] Elemental analyses for C, H, and N were within ±0.4% of theoretical values. [b] See A. E. Jacobson, *NIDA Res. Monogr.*, no. 22, 129 (1978). [c] See also R. F. Rekker and H. M. de Kort, *Eur. J. Med. Chem.*, 14, 479 (1979).

Chemistry. The key step in the synthetic sequence was the preparation of 14β-alkoxycodeinones[19,20] by alkylation of 14β-hydroxycodeinone. Attempted alkylation of the sodium, lithium, and potassium salts of 14β-hydroxycodeinone was largely unsuccessful with a number of alkyl halides and *p*-toluenesulfonate esters under a variety of conditions. Dimethyl and diethyl sulfates, however, cleanly alkylated the sodium salt of 14β-hydroxycodeinone in dry dimethylformamide solution, and codeinones **1b,c** were isolated in moderate yield.

Catalytic hydrogenation of **1b,c** gave the dihydrocodeinones **2a,b** in good yield. The conversion of **2a,b** to the corresponding nor compounds was performed by a minor modification of the procedure of Olofson,[21] by reaction of the *N*-methyl substrates with vinyl chloroformate. The intermediate vinyl carbamates **2c,d** gave the nor compounds **2g,h** in high yield by reaction with anhydrous hydrogen chloride and base cleavage of the hydrogen chloride adduct **2e,f** in the manner described by Olofson. The products **2g,h** were each contaminated with a small proportion of an unknown impurity which proved difficult to remove and were therefore each divided into two portions, which were alkylated with allyl bromide and cyclopropylmethyl bromide; this procedure provided in moderate yield the four desired alkoxycodeinone analogues of naloxone and naltrexone **2i–l** as easily purified crystalline solids.

A number of reactions using 14β-methoxycodeinone and 14β-ethoxycodeinone as model substrates were carried out in order to examine various 3-O-dealkylation procedures. In our hands, treatment of codeinone derivatives (as opposed to codeine derivatives) with strongly basic reagents, such as sodium alkylmercaptides[22,23] or lithium di-

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phenylphosphide,[24] caused base-catalyzed ring opening of the 4,5-oxygen bridge. Reaction with boron tribromide, however, under conditions slightly modified from those outlined in the literature[25] gave 14β-methoxymorphinone, albeit in moderate yield (not surprisingly the other product was 14β-hydroxymorphinone). Dealkylation of **2i–l** was similarly achieved, and the desired materials **3a–d** were isolated in moderate yield after chromatographic separation.

Biological Evaluation. (1) In vitro narcotic agonist activity was assessed in mouse isolated vas deferens (mvd) by a modification[26a] of the procedure of Henderson, Hughes, and Kosterlitz[26b] and in the guinea pig isolated ileum (gpi) by a modification[26a] of the method of Kosterlitz and Watt.[27]

All four compounds were tested as antagonists of normorphine (a prototype μ agonist[28]) and Met⁵-enkephalin (a prototype δ agonist[28]) in the mouse vas deferens. The results are shown in Table II with naloxone and naltrexone as reference. It can be seen that **3a–d** were all potent antagonists at both μ and δ receptors. Like naloxone, **3a** and **3b** have an affinity at the μ receptor which is approximately 20 times greater than that at the δ receptor.

The derivatives of naltrexone (**3c** and **3d**) maintain similar selectivity to naltrexone itself, namely, a 60 times higher affinity for the μ receptor. This increase in μ selectivity in the naltrexone analogues could arise from increased μ-receptor affinity without significant change in δ-receptor affinity. Alternatively, if the increased lipophilicity of *N*-cyclopropylmethyl analogues has produced an increased concentration of antagonists at the receptor site, it may be that the increased μ selectivity is due to decreased affinity at the δ receptors with unchanged affinity at the μ receptor.[29a] Substituting cyclopropylmethyl for allyl would appear to favor μ- rather than δ-receptor interactions, whereas increasing the 14-*O*-alkyl chain has not affected receptor selectivity.

Even at concentrations of 200 ng/mL (i.e., 20–40 times the concentration necessary to occupy half of the δ receptors and 400–2800 times the concentration necessary to occupy half of the μ receptors) none of the compounds showed any agonist activity in the MVD. It can be concluded that these compounds possess neither μ nor δ agonist activity in this preparation.

In the gpi concentrations, up to 0.6 μg/mL (i.e., 1000-fold that concentration occupying half of the μ receptors in the mvd) were tested. IC_{50} values to normophine in these preparations were approximately 20 ng/mL. No agonism was seen with **3a** and **3c**. A small partial agonist effect was seen with **3b** and **3d**. The maximum depression of twitch height was 20%. Since the gpi is believed to contain a mixture of μ and K receptors,[29b] it was concluded that the

Table II. Results of Biological and Pharmacological Comparison of Naloxone, Naltrexone and their Analogues

compd	IC_{50},[a,b] nmol		mvd agonist potency ratio (Nm = 1)[c]	concn required to give a dose ratio of 2		RTF AD_{50}, mg/kg sc	RTF AD_{99},[h] mg/kg sc	duration action of AD_{99} dose, h	RTF AD_{50}, mg/kg po	oral/ parenteral ratio
	−Na^+	+Na^+		vs. Met⁵-E, ng/mL	vs. normorphine, ng/mL					
3a	90	55	<0.025 (3)	7.3 ± 2.8 (3)	0.46 ± 0.11 (3)	0.041[d]	0.15	4	>30	>700
3b	26	22	<0.12 (3)	7.9 ± 3.5 (3)	0.33 ± 0.06 (3)	0.034[e]	0.14	6	3.8[i]	112
3c	18	16	<0.063 (3)	11.5 ± 3.5 (2)	0.26 ± 0.03 (3)	0.019[f]	0.25	8	4.4[j]	232
3d	8.0	3.8	<0.12 (5)	4.1 ± 0.59 (5)	0.07 ± 0.017 (5)	0.005[g]	0.14	4	1.5[k]	300
naloxone	150	44	0 (6)	10.05 ± 2.3 (6)	0.51 ± 0.031 (8)	0.023	0.10	3	13	565
naltrexone	22	14	0 (4)	9.00 ± 2.9 (3)	0.165 ± 0.0012 (4)	0.009	0.05	5	1.35	150

[a] IC_{50} value is that concentration required to inhibit the stereospecific [³H]diprenorphine binding by 50%. [b] The sodium index, IC_{50} +Na^+/IC_{50} −Na^+, was for each example less than unity. [c] Nm = normorphine. [d] (0.032–0.053). [e] (0.010–0.036). [f] (0.020–0.053). [g] (0.002–0.012). [h] AD_{99} dose levels were obtained by extrapolation from AD_{50} values. [i] (2.45–5.89). [j] (2.5–7.7). [k] No limits available.

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former two compounds, **3a** and **3c**, were devoid of μ or K agonist activity, whereas **3b** and **3d** possess a very low level of either μ (too low to be detected in the mvd) or K agonist activity.

(2) Inhibition of the binding of [^{3}H]diprenorphine to rat brain homogenates was determined by a method modified[30] from that of Pert et al.[31] Stereospecificity of binding was determined by incubation with and without either levorphanol or dextrorphan (final concentrations 1 μmol). The concentration of [^{3}H]diprenorphine used was 2.0 nmol. Binding assays were performed in the absence and presence of 100 mmol of NaCl in an attempt to discriminate the inherent degree of agonist and antagonist characteristics.[32]

In the absence of Na^+ there appeared to be an increase in opiate receptor binding affinity with lipophilicity (Table II). Like naloxone and naltrexone, **3a** and **3d** showed increased binding affinity in the presence of Na^+, whereas **3b** and **3c** showed no increase.

The sodium index for **3a–d** was less than unity, suggesting antagonist character.[32]

(3) In vivo activity was determined in rats, and a group of 10 animals was used at each dose level. Drugs were administered as bases in a saline vehicle. None of the compounds exhibited any agonist activity in the tail-pressure test at doses up to 10 mg/kg sc.[33] The hot-water tail-flick test[34] was used to determine antagonist activity, and the results are presented in Table II. Antagonist potencies after subcutaneous administration for **3a–c** were not significantly different from those of naloxone, whereas compound **3d** displayed antagonist potency approximately twice that of naltrexone.

Durations of action of **3a–d** were determined at the AD_{99} dose level. Naloxone analogues **3a** and **3d** had durations of 4 and 6 h, respectively, marginally longer than that of naloxone. While the duration of action of the naltrexone analogue **3c** was significantly longer than that of naltrexone (8 h), that of **3d**, which had greater opiate receptor binding affinity, had greater potency in the mvd antagonist assay, and was approximately twice as potent in vivo as naltrexone, was slightly shorter (4 h).

Oral activities of derivatives **3b–d** were greater than that of naloxone, and that of **3d** was approximately equivalent to that of naltrexone. Compound **3a**, surprisingly, lacked oral activity up to the highest dose studied (30 mg/kg).

Discussion and Conclusion

The four analogues of naloxone and naltrexone appear essentially devoid of any opiate agonist activity in the mvd agonist assay, and this was confirmed by their in vitro binding characteristics. In vivo, after subcutaneous administration they were potent, pure narcotic antagonists (no agonism was detected at 30 mg/kg sc) with potencies equivalent to that of naloxone and in one case surpassing that of naltrexone.

There was no evidence for the predicted increase in narcotic agonist activity upon alkylation of the C_{14}-OH.[10] Furthermore, the increase in receptor affinity (Table II) for these compounds compared with naloxone or naltrexone suggested that, if anything, the effect of removal of a potential hydrogen-bonding interaction was to stabilize rather than to destabilize the drug–receptor complex.

It must therefore be concluded that, since the C_{14} ether oxygen atom is extremely unlikely to be protonated at physiological pH[35] (which might have enabled an interaction similar to that envisaged), there is no evidence to support the postulate that the C_{14}-OH is involved in a common anionic receptor site interaction responsible for the increased antagonist effect of either naloxone or naltrexone.

The N-methylated quaternary derivative of naloxone[36] still antagonizes the affect of both Met^5-E and normorphine in the mvd (albeit with some 20 times lower affinity[37]). Since the quaternized N atom is unable to contribute to a potential drug–receptor stabilization of the type envisaged, this observation also appears to support the above conclusion.

Results obtained from the comparison of **3a–d**, naloxone, and naltrexone n the mvd indicate that greater μ selectivity was obtained with the cyclopropylmethyl analogues, whereas alteration of C_{14}-*O*-alkyl chain length had no significant effect on receptor selectivity. Comparisons of the antagonist effects of naloxone and naltrexone have apparently failed to pinpoint this small differentiation of receptor selectivity, and this novel observation could have implications in the rational design of more receptor-selective antagonists.

There appeared to be no significant correlation of lipophilicity (Table I) with either duration of action or oral/parenteral ratio within this limited series. However, **3b**, which has an identical estimated lipophilicity with naltrexone, possessed a very similar oral/parenteral ratio.

Experimental Section

Melting points were obtained using a Kofler hot-stage apparatus and are uncorrected. The structures of all compounds were confirmed by their elemental analyses and IR and NMR spectra, the latter being determined in $CDCl_3$ solution. The IR spectra were determined as KBr pellets with a Perkin-Elmer 237 spectrophotometer, and the ^{1}H NMR spectra were obtained with a Varian Associates T60 spectrometer. Thebaine was purchased from McFarlan-Smith and was converted to 14β-hydroxycodeinone by the procedure of Iijima et al.[38] Vinyl chloroformate was a generous gift from Societé National des Poudres et Explosifs, Paris.

The method of Pert et al. to determine binding to rat brain homogenates was modified by omission of cooling of tissues to 0–4 °C after equilibration, which has been shown to have a differential effect on the binding of agonists and antagonists.[30]

14β-Methoxycodeinone (1b). A suspension of 14β-hydroxycodeinone (60 g, 0.192 mol) and ether-washed sodium hydride (15 g, 0.624 mol) in dry dimethylformamide (170 mL) was vigorously stirred at room temperature until solution was complete (ca. 10 min), dimethyl sulfate (29.04 g, 0.23 mol) was added in one portion with external cooling, and the mixture was stirred at room temperature for 4 h. The reaction mixture was poured into water, the aqueous solution was extracted with diethyl ether (6 × 50 mL), and the combined extracts were washed with water (50 mL), dried (Na_2SO_4), and evaporated to dryness to give a yellow solid. Further extraction of the aqueous solution with dichloromethane (3 × 50 mL) gave a brown oil, which was purified by chromatography (silica gel, dichloromethane/2% methanol) to give a further sample of the same faintly yellow solid. The combined solids were recrystallized from petroleum ether (bp 60–80 °C):

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yield 34.8 g (55%); mp 158.5–160.5 °C; IR (KBr disk) 1680 (α,β-unsaturated ketone), absence of H-bonded OH and free OH at approximately 3370–3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (N-CH_3), 3.26 (s, 14-OCH_3), 3.82 (s, 3-OCH_3), 4.88 (s, H_5), 6.10–6.78 (AB q, H_7 and H_8), 6.63 (s, H_1 and H_2). Anal. ($C_{19}H_{21}NO_4$) C, H, N. Subsequent to the completion of this work, a broadly similar procedure was described,[39] giving a product of different melting point but essentially identical spectral characteristics.

IR and NMR spectra for other dihydrocodeinones and -morphinones were fully in accord with those expected from their molecular structures.

14β-Ethoxycodeinone (1c) was prepared by the same procedure using diethyl sulfate and was recrystallized from petroleum ether (bp 60–80 °C): yield 41%; mp 163–164 °C. Anal. ($C_{20}H_{23}NO_4$) C, H, N.

14β-Methoxy-7,8-dihydrocodeinone (2a). A suspension of 14β-methoxycodeinone (1b; 33 g, 0.11 mol) and 10% Pd/C (2.0 g) in ethanol (120 mL) was hydrogenated under a starting pressure of 3 atm. After 24 h the catalyst was removed by filtration through Celite, the solvent was removed to give a colorless solid, which was purified by column chromatography (silica gel, dichloromethane/3% methanol), and the pure material recrystallized from diethyl ether: yield 22 g (66%); mp 146–147 °C. Anal. ($C_{19}H_{23}NO_4$) C, H, N.

14β-Ethoxy-7,8-dihydrocodeinone (2b) was prepared similarly and recrystallized from ethyl acetate/petroleum ether (bp 60–80 °C): yield 69%; mp 192–193 °C. Anal. ($C_{20}H_{25}NO_5$) C, H, N.

14β-Methoxy-7,8-dihydronorcodeinone (2g). A solution of 14β-methoxy-7,8-dihydrocodeinone (**2a**; 20 g, 0.07 mol) in redistilled 1,2-dichloroethane (70 mL) was treated with vinyl chloroformate (13.52 g, 0.14 mol) and heated to 50 °C.[22] The reaction was very slow: at 72 h and at 96 h, further portions of vinyl chloroformate (13.52 g, 0.14 mol) were added and heating was continued; the reaction appeared complete at 120 h. The mixture was poured into a saturated $NaHCO_3$ solution, extracted with dichloromethane (3 × 50 mL), dried (Na_2SO_4), and evaporated to dryness to give a colorless foam; this foam was purified by column chromatography (silica gel, dichloromethane/2% methanol) to give the pure material as a colorless foam (23 g, 97%), which was used without crystallization.

Anhydrous hydrogen chloride was bubbled through a solution of 14β-methoxy-7,8-dihydro-*N*-[(vinyloxy)carbonyl]norcodeinone (**2c**; 22.7 g, 0.06 mol) in dry dichloromethane (100 mL) for 1 h. The solvents were removed in vacuo to leave a colorless foam, **2e**, which was redissolved in methanol (50 mL) and heated under reflux for 1 h. The reaction mixture was diluted with water, neutralized with a saturated $NaHCO_3$ solution, and extracted with dichloromethane (3 × 50 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo to leave 14β-methoxy-7,8-dihydronorcodeinone, **2g** (18.9 g, 96%), as a viscous glassy solid.

14β-Ethoxy-7,8-dihydronorcodeinone (2h) was prepared using the same procedure outlined above and was also obtained as a viscous glassy solid (11.9 g, 98%).

These two materials proved difficult to separate from a minor impurity present in each and so were used without further purification in the preparation of the alkylated analogues.

14β-Methoxy-7,8-dihydro-*N*-allylnorcodeinone (2i). A suspension of 14β-methoxy-7,8-dihydronorcodeinone (**2g**; 9.5 g, 0.03 mol), sodium iodide (22.5 g, 0.15 mol), sodium carbonate (15.9 g, 0.15 mol), and allyl bromide (5.5 g, 0.045 mol) in 10% aqueous acetone (300 mL) was heated to reflux with stirring for 1 h. The mixture was poured into water and extracted with dichloromethane (3 × 80 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to dryness to give a brown oil; this oil was purified by column chromatography (silica gel, dichloromethane/1% methanol) to give a pure material, which was recrystallized from a diethyl ether/hexane mixture: yield 3.27 g (30%); mp 167–168 °C. Anal. ($C_{21}H_{25}NO_4$) C, H, N.

14β-Ethoxy-7,8-dihydro-*N*-allylnorcodeinone (2j) was prepared by an analogous procedure and was recrystallized from a diethyl ether/hexane mixture: yield 57%; mp 178–179 °C. Anal. ($C_{22}H_{27}NO_4$) C, H, N.

14β-Methoxy-7,8-dihydro-*N*-(cyclopropylmethyl)norcodeinone (2k) was prepared by an analogous procedure and was recrystallized from a diethyl ether/hexane mixture: yield: 35%; mp 131–132 °C. Anal. ($C_{22}H_{27}NO_4$) C, H, N.

14β-Ethoxy-7,8-dihydro-*N*-(cyclopropylmethyl)norcodeinone (2l) was prepared by an analogous procedure and was recrystallized from a diethyl ether/hexane mixture: yield 53%; mp 182–183 °C. Anal. ($C_{23}H_{29}NO_4$) C, H, N.

14β-Methoxy-7,8-dihydro-*N*-allylnormorphinone (3a). A solution of 14β-methoxy-7,8-dihydro-*N*-allylnorcodeinone (**2i**; 1.0 g, 0.0028 mol) in dichloromethane (100 mL) was cooled to −70 °C, treated with boron tribromide (2.68 mL, 0.028 mol), warmed to −30 to −20 °C, and stirred at this temperature for 50 min, at which time TLC showed no remaining starting material. The mixture was cooled to −70 °C; the remaining boron tribromide was destroyed by the addition of methanol (5 mL), basified with 2 N sodium hydroxide, left to stand 5 min, and back-neutralized with 2 N hydrochloric acid; the solution was extracted with dichloromethane/20% methanol; and the combined extracts were dried (Na_2SO_4) and evaporated to give a red solid. This was purified by column chromatography (silica gel, dichloromethane/1% methanol) to give the pure material, which was recrystallized from petroleum ether (bp 60–80 °C): yield 0.445 g (47%); mp 197–199 °C. Anal. ($C_{20}H_{23}NO_4$) C, H, N.

14β-Methoxy-7,8-dihydro-*N*-(cyclopropylmethyl)normorphinone (3c) was prepared similarly and was recrystallized from petroleum ether (bp 60–80 °C): yield 32%; mp 187–188 °C. Anal. ($C_{21}H_{25}NO_4$) C, H, N.

14β-Ethoxy-7,8-dihydro-*N*-allylnormorphinone (3b) was prepared similarly and was recrystallized from a diethyl ether/petroleum ether (bp 60–80 °C) mixture: yield 35%; mp 146–147 °C. Anal. ($C_{21}H_{25}NO_4$), C, H, N.

14β-Ethoxy-7,8-dihydro-*N*-(cyclopropylmethyl)normorphinone (3d) was prepared similarly and was recrystallized from a diethyl ether/petroleum ether (bp 60–80 °C) mixture: yield 52%; mp 165–66 °C. Anal. ($C_{22}H_{27}NO_4 \cdot 0.5H_2O$) C, H, N.

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(39) Sisa, Inc. U.S. Patent 4 232 028 (Nov 4, 1980).