The hydrobromide was converted to the free base and the salt was formed with HCl (g) in dry Et_2O. The crude material was recrystallized from *i*-PrOH to give 18.8 g (71%) of the title compound as colorless crystals: mp 240–242 °C; $[\alpha]^{24}_{365}$ −58.0° (*c* 1.0, 95% EtOH). Anal. ($C_{12}H_{18}BrNO_2$·HCl) C, H, N.

(*R*)-2-Amino-1-(2,5-dimethoxy-4-iodophenyl)butane Hydrochloride [(*R*)-18c]. Concentrated HCl (3.52 mL, 42.3 mmol) was added all at once to a hot, stirred solution of 5.0 g (14.1 mmol) of (*R*)-15 in 200 mL of 100% EtOH. The darkened solution was cooled rapidly to 15 °C. Water (120 mL) was added (a gelatinous precipitate dissolved) and the solution was cooled to 2–3 °C and maintained at this temperature while a solution of 1.07 g (15.51 mmol) of $NaNO_2$ in 20 mL of H_2O was added dropwise with stirring. After 40 min, a solution of 2.57 g (15.51 mmol) of KI in 20 mL of H_2O was added dropwise with stirring to the reaction mixture; a dark red-brown semisolid began to separate.

Stirring was continued at 2–3 °C for 3 h. The cooling bath was then removed and stirring continued for an additional 2 h; the temperature of the reaction mixture had risen to 20 °C. The temperature was then held at 40–50 °C for 30 min. The dark reaction mixture was diluted with an equal volume of H_2O and extracted with 3 portions of Et_2O. The combined extracts were washed successively with 2 portions of 10% $NaHSO_3$, 5% HCl, 5% NaOH, and finally H_2O (3 portions). The Et_2O solution was dried ($MgSO_4$) and evaporated to give 2.91 g of dark red oil.

The crude material was chromatographed on 300 g of activity III alumina. Elution was with 25% CH_2Cl_2 in Skellysolve B and progress was followed by TLC (alumina, 1:1 CH_2Cl_2–Skellysolve B, visualization with shortwave UV). The material first eluted was (*R*)-1-(2,5-dimethoxy-4-iodophenyl)-2-(*N*-phthalimido)butane: yield 1.06 g (16%) of clear, yellowish oil 97% pure by GC.

Without further purification, the phthalimido compound was hydrazinolyzed as described for (*R*)-13a. The crude hydrochloride salt of the product was recrystallized from *i*-PrOH to give 0.376 g (44%) of colorless needles: mp 255.5–257 °C dec; $[\alpha]^{24}_{365}$ −56.8° (*c* 1.0, 95% EtOH). Anal. ($C_{12}H_{18}INO_2$·HCl) H, N, I; C: calcd, 38.78; found, 39.27.

Pharmacology. Cat Behavior. This procedure represents a modification of that described by Wallach et al.[19] Adult female cats were placed in separate cages approximately 12–15 sq ft in floor area. The animals could see the experimenter and each other across the room and could have auditory and olfactory contact among themselves in adjacent cages.

After animals had become accustomed to this environment (30 min), test compounds were administered subcutaneously into the back of the neck. Following dosing, animals were observed for 3 h. Scoring was done at the time of peak drug-induced effects, usually about 1 h postdosing. The effects were scored using an observational checklist consisting of 12 categories, each containing 2 items. Each item was worth 1 point, with a maximum total numerical score of 24. A total score of 10 or greater was considered "DOM-like".

The categories were: body posture, arched back/stiff tail; extension of limbs, legs/legs and toes; muscle rigidity, legs/abdomen, abnormal leg/immobility; motor coordination, ataxia/loss of righting reflex, open mouth/protruding tongue, claws out/attempts to bite or claw, teeth baring/hissing or growling; contact with environment, reduced/absent; piloerection, tail/back; pupillary constriction, moderate/extreme; salivation/emesis.

Either two or four animals were used per test. For $N = 2$, an average of the individual scores was taken. For $N = 4$, means plus or minus standard error were reported.

Avoidance-Response Acquisition. Male, retired breeder rats of the Long–Evans strain (Blue Spruce Farms, 600–800 g) were given 120 massed acquisition trials in a shuttle box (BRS/LVE, Model 146-04) as described elsewhere.[18] Briefly, each trial was 30 s in duration and consisted of a 5-s light (conditioned stimulus, CS) presented on the side of the shuttle cage occupied by the subject. If the rat did not cross to the other side of the chamber within the 5-s CS period (avoidance response), the grid floor under the animal was electrified with 0.8 mA of scrambled shock (BRS/LVE, Model 1531 shocker). The animal was permitted 5 s to make an escape response before termination of the light and shock stimuli. Avoidance responses turned the CS off, while an escape response terminated both the CS and the shock. Either response initiated the intertrial interval (ITI), which was 20–30 s, depending on the response of the subject during the CS or shock periods. Responses during the ITI were taken as a measure of nonspecific motor activity and were not punished. Drugs were dissolved in a distilled water vehicle and injected ip 5–10 min or administered by intragastric gavage (po) 30 min prior to the 1-h behavioral test. Differences between the means of control and drug groups were tested for statistical significance by a Student's *t*-test. The accepted level of significance was set at $p < 0.05$. Potency differences between some of the drugs were determined by comparing the minimal effective doses (MED) required to increase avoidance responding significantly (see Table VI). The MED was established by evaluating a set order of doses within the 0.25–20 mg/kg ip range (i.e., 5, 2, or 10, 1 or 20, followed by 0.5, 30, or 40 mg/kg, if necessary).

Synthesis and Analgesic Activity of Some 14β-Substituted Analogues of Morphine

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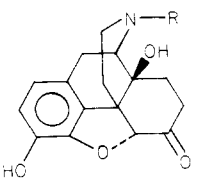
Treatment of 14β-nitrocodeinone with sodium borohydride gave the codeine derivative which was reduced with zinc dust in acetic anhydride–acetic acid solution to give 14β-acetamidocodeine 6-acetate. 14β-Thiocyanatocodeinone was obtained from the reaction of thebaine with thiocyanogen and was reduced to 14β-mercaptocodeine with lithium aluminum hydride. 14β-Bromo- and 14β-chlorocodeinone were prepared by the reaction of thebaine with *N*-bromosuccinimide and *N*-chlorosuccinimide, respectively. These 14β-substituted codeine and codeinones were O-demethylated to the corresponding morphine analogues with boron tribromide. With the exception of 14β-nitromorphinone, which was weak in activity, all the other 14β-substituted morphine derivatives were approximately equal in potency to normorphine in the guinea pig ileum preparation.

The substitution of hydroxyl groups at the 14β position of the morphine skeleton has produced compounds possessing significant pharmacological activities. Oxymorphinone (1, R = CH_3) is approximately ten times as potent as morphine sulfate as a narcotic analgesic[1] and naloxone (1, R = $CH_2CH{=}CH_2$) is a useful narcotic antagonist which possesses no agonist properties in humans.[2]



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Other than such compounds having oxygen functionalities at the 14β position, there is a paucity of analogues of morphine bearing other functional groups at this position.[3]

(1) N. B. Eddy, *J. Chronic Dis.*, 4, 59 (1956).
(2) D. R. Jasinski, W. R. Martin, and C. A. Haertzen, *J. Pharmacol. Exp. Ther.*, 157, 420 (1967).

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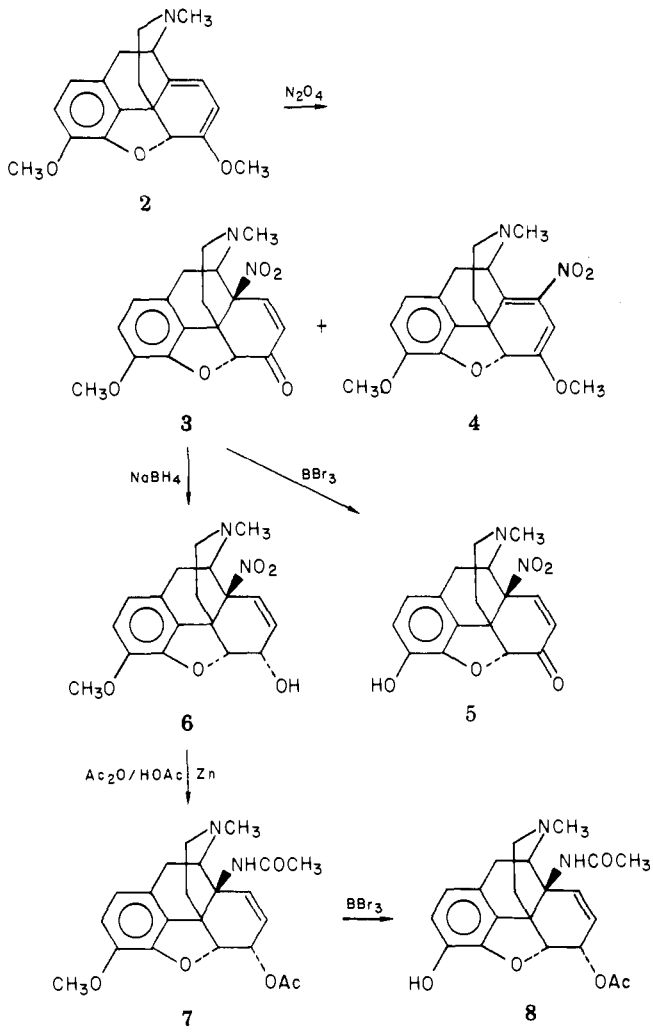
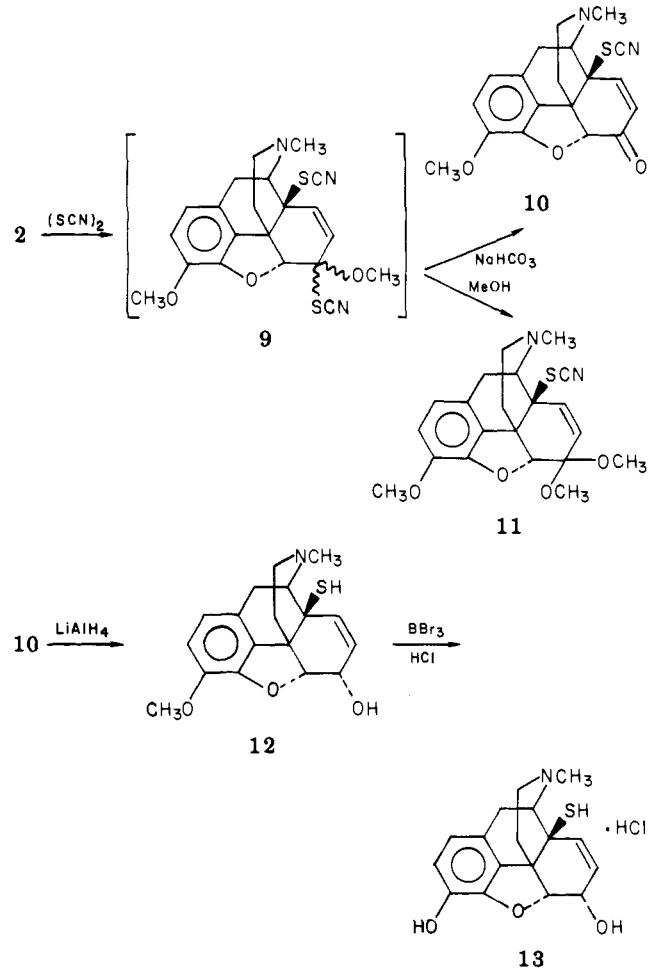
Scheme I



Synthetic procedures for preparing these compounds have been unavailable. In this report, we describe short schemes to convert thebaine (**2**) to morphine derivatives bearing nitro, acetamido, thiocyanato, mercapto, bromo and chloro groups at the 14β position. The narcotic analgesic properties of these compounds were studied in the guinea pig ileum.[12,13]

Chemistry. Advantage has been taken of the reactivity of the ring C diene system to chemical reagents to convert thebaine to codeine and morphine.[4] The diene system also represents a means of entry to 14-hydroxymorphine derivatives.[5] Recently,[6] we reported that dinitrogen tetroxide added 1,4 and 1,2 to thebaine to give 14β-nitrocodeinone (**3**) and 8-nitrothebaine (**4**), respectively (Scheme I). The former compound was O-demethylated with boron tribromide[7] to give the corresponding morphinone **5**. Treatment of **3** with sodium borohydride to give **6**,[16] followed by reduction of the nitro group with zinc dust in acetic anhydride–acetic acid solution, proceeded with concomitant acetylation of the amino and hydroxyl groups to give 14β-acetamidocodeine 6-acetate (**7**). O-Demethylation of **7** with boron tribromide yielded **8**.

Scheme II

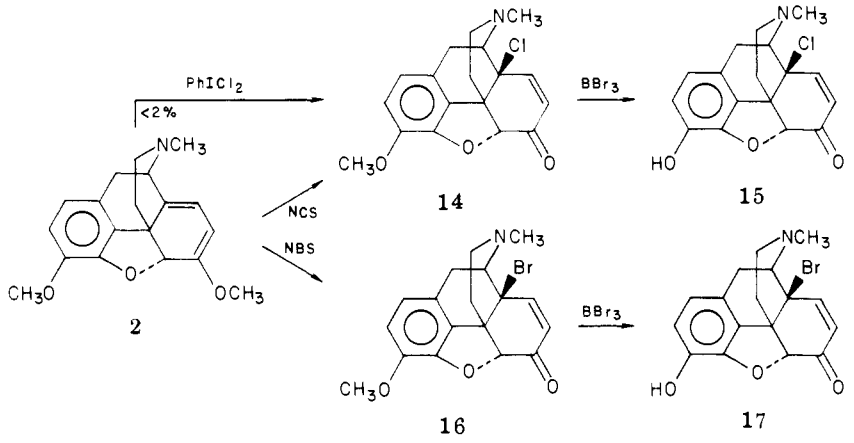


It seemed likely that thiocyanogen, $(SCN)_2$, like dinitrogen tetroxide would add across the diene of thebaine. Thus, the reaction of thebaine with free thiocyanogen in acetic acid proceeded to give, after hydrolysis, 14β-(thiocyanato)codeinone (**10**; Scheme II). The latter compound was probably formed through the intermediate compound **9** which would arise from the initial homolytic fission of thiocyanogen and subsequent 1,4 addition of the radicals to the diene system of thebaine. Evidence which tends to support this hypothesis was obtained from the treatment of the crude reaction product with methanol to produce 14β-(thiocyanato)codeinone dimethyl ketal (**11**). This compound was apparently derived from the unhydrolyzed intermediate **9**. Treatment of **10** with lithium aluminum hydride yielded 14β-mercaptocodeine (**12**). The 100-MHz proton NMR of **12** revealed complex but well-resolved splitting patterns for the ring C protons and were similar to those observed for codeine isomers by other investigators.[8,9] O-Demethylation of **12** with boron tribromide afforded **13**, which was converted to the hydrochloride salt.

Treatment of thebaine with phenyliodo dichloride[10] provided an unsatisfactory yield of 14β-chlorocodeinone (**14**). An improvement in the yield of **14** was achieved by the reaction of thebaine with *N*-chlorosuccinimide in

(3) R. J. Kobylecki, I. G. Guest, J. W. Lewis, and G. W. Kirby, German Offen. 2812581; *Chem. Abstr.*, **90**, 39100r.
(4) W. G. Dauben, C. P. Baskin, and H. C. H. A. van Riel, *J. Org. Chem.*, **44**, 1567 (1979), and references cited therein.
(5) F. M. Hauser, T.-K. Chen, and F. I. Carroll, *J. Med. Chem.*, **17**, 1117 (1974).
(6) S. Archer and P. Osei-Gyimah, *J. Heterocycl. Chem.*, **16**, 389 (1979).
(7) K. C. Rice, *J. Med. Chem.*, **20**, 164 (1977).
(8) T. J. Batterham, K. H. Bell, and U. Weiss, *Aust. J. Chem.*, 18, 1799 (1965).
(9) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.*, **12**, 104 (1964).
(10) H. W. Bradley and R. E. Lutz, *Proc. Va. Acad. Sci.*, **2**, 189 (1941).

Scheme III



aqueous acetone (Scheme III). Similarly, by the method of Conroy,[11] thebaine was treated with *N*-bromosuccinimide to give 14β-bromocodeinone (**16**). These 14β-halocodeinones were O-demethylated with boron tribromide to give the corresponding morphinones, **15** and **17**, which have not been previously reported.

Pharmacology. The analgesic activities of the 14β-substituted codeine and morphine derivatives were determined in the guinea pig ileum by the method of Gyang and Kosterlitz.[12] Normorphine was used as the standard compound. All the codeine derivatives (**3**, **7**, **9**, **11**, **13**, and **15**) were extremely weak. However, in this preparation codeine itself shows very low activity.[13] The analgesic activity of the 14β-substituted morphine series is summarized in Table I.

Experimental Section

Melting points were determined using a Laboratory Devices Melt-Temp apparatus and were corrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. The NMR spectra were recorded using Varian T60-A and Varian HA-100 spectrometers with Me_4Si as internal standard. Chemical analyses were determined by Instranal Laboratory, Rensselaer, N.Y. Analytical results for the elements indicated were within ±0.4% of the theoretical values.

14β-Nitromorphinone (5). A solution of **3**[6] (0.3 g, 0.88 mmol) in 6 mL of $CHCl_3$ was added over a 3-min period to a stirred solution of BBr_3 (2.19 g, 8.8 mmol) in 25 mL of $CHCl_3$ at room temperature. After 0.5 h, the mixture was poured into a mixture of ice and 10 mL of concentrated NH_4OH solution. After the mixture was stirred for 0.5 h at 0 °C, the organic phase was removed. The aqueous portion was saturated with salt and extracted with $CHCl_3$–EtOH solution (2:1, 2 × 60 mL). The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo. The oil was purified by column chromatography on silica gel ($CHCl_3$–Et_2O, 1:1). The resulting oil crystallized from EtOH to give **5** as yellow microcrystals: yield 0.144 g (50%); mp 142–145 °C; IR (KBr) 1695 cm^{-1} (C=O), 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.8 (d, 1 H, J = 10 Hz, 7-H), 6.7 (2 H, aromatic), 6.3 (d, 1 H, J = 10 Hz, 8-H), 5.2 (s, 1 H, 5-H), 4.15 (d, 1 H, J = 6 Hz, 9-H), 2.5 (s, NCH_3). Anal. ($C_{17}H_{16}N_2O_5 \cdot 0.5H_2O$) C, H, N.

14β-Nitrocodeine (6). Sodium borohydride (0.39 g, 0.011 mol) was added in portions to a stirred suspension of **3** (1.2 g, 0.0035 mol) in 100 mL of MeOH while maintaining the system at room temperature. After 2 h, 50 mL of H_2O was added to the reaction mixture and extracted with $CHCl_3$ (3 × 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil solidified on trituration in EtOH to afford **6**, 0.87 g (72%), which was recrystallized from EtOH. The mother liquor was concentrated and column chromatographed on silica gel ($CHCl_3$–MeOH, 49:1) to provide an additional 0.08 g of **6**: total yield 0.95 g (78.5%); mp 156–158 °C; IR (KBr) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.6 (2 H, aromatic), 6.0 (br d, 1 H, J = 10 Hz, 7-H), 5.45 (dd, 1 H, $J_{7,8}$ = 10 Hz, $J_{6,8}$ = 3 Hz, 8-H), 5.25 (d, J = 6.3 Hz, 5-H), 4.55 (br, 1 H, 6-H), 4.05 (d, 1 H, J = 6 Hz, 9-H), 3.85 (s, OCH_3), 3.25 (d, 1 H, J = 18 Hz, 10β-H), 2.4 (s, NCH_3). Anal. ($C_{18}H_{20}N_2O_5$) C, H, N.

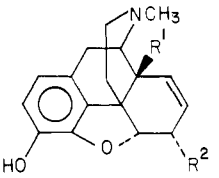
14β-Acetamidocodeine 6-Acetate (7). Zinc dust (1.23 g, 0.0188 mol) was added in portions to a stirred solution of **6** (1.3 g, 0.0038 mol) in 20 mL of Ac_2O–HOAc solution (1:1). The mixture was heated to 90 °C (oil bath) for 1.5 h under N_2. The color of the reaction mixture changed from clear to pinkish and then to brown during this period. After the mixture was cooled to room temperature, the solid suspension was removed by filtration and washed with HOAc. The filtrates were diluted with H_2O, then cautiously neutralized with $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic extract was washed with $NaHCO_3$ solution and brine and dried ($MgSO_4$). After the solvent was removed, the residue was suspended in EtOH and stored at 0 °C overnight. The solid was removed by filtration and recrystallized from EtOH to give **7** as white crystals: yield 0.35 g (22%); mp 265–267 °C; IR (KBr) 3400 (NH), 1750 (ester), 1680 cm^{-1} (amide); NMR ($CDCl_3$) δ 6.85 (1 H, NH), 6.55 (AB system, 2 H, aromatic), 5.2–5.9 (m, 3 H, 6-H, 7-H, 8-H), 5.0 (d, 1 H, J = 7 Hz, 5-H), 3.8 (s, OCH_3), 2.35 (s, NCH_3), 2.05, 2.0 (2 s, 2 × $COCH_3$). Anal. ($C_{22}H_{26}N_2O_5$) C, H, N.

14β-Acetamidomorphine 6-Acetate (8). A solution of **7** (0.22 g, 0.544 mmol) in dry $CHCl_3$ (10 mL) was added over a 3-min period to a stirred solution of BBr_3 (1.1 g, 4.35 mmol) in 25 mL of dry $CHCl_3$ at room temperature. After 0.5 h, the mixture was poured into a stirred mixture of ice and concentrated NH_4OH solution. After the mixture was stirred for 0.5 h at 0 °C, the $CHCl_3$ portion was removed. The aqueous portion was saturated with salt and extracted with $CHCl_3$–EtOH (2:1, 3 × 50 mL). The combined organic portions were dried ($MgSO_4$) and concentrated in vacuo to afford an oil which crystallized under MeOH to give **8**, yield 66 mg (31.6%). The compound was recrystallized from MeOH and dried over refluxing EtOH: mp 258–260 °C; IR (KBr) 3400 (br, NH, OH), 1750 (ester), 1670 cm^{-1} (shoulder, amide). Anal. ($C_{21}H_{24}N_2O_5 \cdot 0.5H_2O$) C, H, N.

14β-(Thiocyanato)codeinone (10). Free thiocyanogen was generated by the addition of Br_2 (4.8 g, 0.03 mol) in 10 mL of glacial HOAc to a stirred suspension of 12.0 g (0.037 mol) of $Pb(SCN)_2$ in 100 mL of glacial HOAc maintained at 18 °C. After complete decolorization of Br_2 had occurred, the suspension of

(11) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5968 (1955).
(12) E. A. Gyang and H. W. Kosterlitz, *Br. J. Pharmacol. Chemother.*, **27**, 514 (1966).
(13) H. W. Kosterlitz and A. A. Waterfield, *Annu. Rev. Pharmacol.*, **15**, 32 (1975).
(14) I. Iijima, I.-I. Minamikawa, A. E. Jacobson, A. Brossi, and K. C. Rice, *J. Med. Chem.*, **21**, 398 (1978).
(15) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958); 14β-hydroxymorphine was prepared in our laboratory by O-demethylation of 14β-hydroxycodeine with boron tribromide, mp 248–250 °C (lit.[16] mp 250 °C).
(16) U. Weiss and S. J. Daum, *J. Med. Chem.*, **8**, 123 (1965).

Table I. Analgesic Activity of Some 14β-Substituted Morphine Analogues in the Guinea Pig Ileum Preparation



no.	R^1	R^2	act. rel to normorphine = 1[a]
5	NO_2	=O	0.006
8	$NHCOCH_3$	$OCOCH_3$	0.6
13	SH	OH	0.4
15	Cl	=O	0.5
17	Br	=O	0.4
	OH	OH	0.8[b]

[a] The opiate action of these compounds was reversed by naloxone. The values reported in the table are the results of single determinations using the free bases of all compounds except **13**, which was tested as the HCl salt. [b] Prepared according to procedures described in ref 14 and 15.

$PbBr_2$ was removed by gravity filtration. The clear, colorless solution of $(SCN)_2$ in HOAc was added dropwise over 10 min to a stirred solution of thebaine (**2**; 3.4 g, 0.011 mol) in 100 mL of HOAc. After 2 h at 18 °C, the polymerized (SCN) was removed by filtration. The filtrate was cautiously neutralized with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$. The organic extract was washed with $NaHCO_3$ solution and brine and concentrated in vacuo. The oily residue was chromatographed on preparative TLC plates (silica gel), using Et_2O as eluant, to give **10** (R_f 0.8) as an oil, which crystallized on trituration in EtOH, yield 0.81 g (22%). The compound, which recrystallized from EtOH, gradually darkened above 200 °C but did not melt even at 300 °C: IR (KBr) 2190 (C≡N), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.68 (2 H, aromatic), 6.6 (d, 1 H, J = 10 Hz, 7-H), 6.35 (d, 1 H, J = 10 Hz, 8-H), 4.8 (s, 1 H, 5-H), 3.82 (s, OCH_3), 2.42 (s, NCH_3). Anal. ($C_{19}H_{18}N_2O_3S·0.5H_2O$) C, H, N.

14β-(Thiocyanato)codeinone Dimethyl Ketal (11). This compound was prepared using a procedure similar to the preparation of **10**. After removal of the $CHCl_3$ extract by evaporation, the oily residue was dissolved in MeOH and allowed to stand at room temperature for 48 h. The crystals were removed by filtration and purified by preparative TLC on silica gel ($CHCl_3$) to give **11** (R_f 0.7): mp 141–142.5 °C; NMR ($CDCl_3$) δ 6.55 (AB system, 2 H, aromatic), 5.83 (AB system, 2 H, J = 10 Hz, 7-H and 8-H), 4.65 (s, 1 H, 5-H), 3.8, 3.42, 3.22 (3 s, 3 × OCH_3), 2.4 (s, N-CH_3). Anal. ($C_{21}H_{24}N_2O_4S$) C, H, N.

14β-Mercaptocodeine (12). To a stirred suspension of $LiAlH_4$ (0.25 g, 6.7 mmol) in 20 mL of dry THF kept at 0 °C and under N_2 was added, in portions, a suspension of **10** (0.8 g, 2.2 mmol) in 8 mL of dry THF. The mixture was allowed to warm to room temperature and heated to reflux for 1 h. After the mixture was cooled to 0 °C and following deactivation of the excess $LiAlH_4$ with aqueous THF, the inorganic salts were removed by filtration. The filtrate was poured into H_2O, extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residual oil solidified on trituration in EtOH to give **12**, 0.35 g (45%), which was recrystallized from EtOH: mp 153–156 °C; IR (KBr) 3600 (OH), 2550 cm^{-1} (SH); NMR ($CDCl_3$, 100 MHz) δ 6.6 (AB system, 2 H, J = 7 Hz, aromatic), 5.75 (td, 1 H, $J_{7,8}$ = 10 Hz, 7-H), 5.5 (dd, 1 H, $J_{7,8}$ = 10 Hz; $J_{6,8} \simeq$ 2.8 Hz, 8-H), 4.92 (dd, 1 H, $J_{5,6}$ = 6 Hz, 5-H), 4.62 (br, 1 H, 6-H), 3.8 (s, OCH_3), 3.1 (d, J = 19 Hz, 10β-H), 3.05 (d, J = 6 Hz, 9-H), 2.4 (s, NCH_3). Anal. ($C_{18}H_{21}NO_3S$) C, H, N.

14β-Mercaptomorphine (13) Hydrochloride. A solution of **12** (0.3 g, 0.9 mmol) in 10 mL of dry $CHCl_3$ was added over a 3-min period at room temperature to a stirred solution of BBr_3 (2.26 g, 9.0 mmol) in 20 mL of dry $CHCl_3$. After it was stirred for 0.5 h, the reaction mixture was poured into a mixture of ice and 10 mL of concentrated NH_4OH solution. The two-phase system was stirred at 0 °C for 0.5 h and separated. The aqueous layer was saturated with salt and extracted with 250 mL of a $CHCl_3$–EtOH solution (2:1) in 50-mL portions. The total organic portions were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (MeOH) and converted to the HCl salt in the following manner: A 0.5-mL solution of the oil in MeOH was added dropwise into Et_2O saturated with dry HCl gas and then stored at 0 °C overnight. After decanting the Et_2O and drying thoroughly, a 2-mL solution of the residue in MeOH was filtered through Celite to remove insoluble materials. The volume of the filtrate was reduced by half, and crystallization was induced by scratching and slight warming to give 70 mg (21%) of the HCl salt of **13**: mp 253–254 °C; IR (KBr) 3400 cm^{-1} (OH). Anal. ($C_{17}H_{19}NO_3S·HCl·H_2O$) C, H, N.

14β-Chlorocodeinone (14). Thebaine (3.0 g, 9.6 mmol) was suspended in 30 mL of Me_2CO–H_2O (2:1). A solution of 1.33 g (10.0 mmol) of NCS in 60 mL of Me_2CO–H_2O (2:1) was added with stirring under N_2 over a 15-min period, keeping the temperature of the system between 15 and 18 °C. Ten minutes after the addition, 120 mL of H_2O was added dropwise, and the mixture was cooled to 0 °C and stirred for 1 h. The solid suspension was removed by filtration, washed with H_2O, and air-dried. The crude solid crystallized from EtOH after treatment with charcoal to give **14**, 1.3 g (41%), as needles: mp 176–178 °C; IR (KBr) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.8 (d, 1 H, J = 10 Hz, 7-H), 6.65 (2 H, aromatic), 6.05 (d, 1 H, J = 10 Hz, 8-H), 4.66 (s, 1 H, 5-H), 3.8 (s, OCH_3), 3.23 (d, 1 H, J = 6 Hz, 9-H), 2.5 (s, NCH_3). Anal. ($C_{18}H_{18}NO_3Cl$) C, H, N.

14β-Chloromorphinone (15). To a stirred solution of BBr_3 (4.86 g, 19.4 mmol) in 25 mL of $CHCl_3$ was added dropwise a solution of 0.644 g (1.94 mmol) of **14** in 10 mL of $CHCl_3$ at room temperature. After 0.5 h, the mixture was poured into a mixture of ice and 10 mL of concentrated NH_4OH solution, and the two-phase system was stirred for 0.5 h at 0 °C. The $CHCl_3$ layer was separated, and the aqueous portion was saturated with salt and extracted with 2 × 60 mL portions of $CHCl_3$–EtOH (2:1). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 2:1) to give an oil which crystallized from MeOH as a pale-yellow compound, 0.14 g (21%). The compound gradually darkened above 200 °C and did not melt even at 300 °C: IR (KBr) 3400 (OH), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.9 (d, 1 H, J = 10 Hz, 7-H), 6.7 (2 H, aromatic), 6.1 (d, 1 H, J = 10 Hz, 8-H), 4.7 (s, 1 H, 5-H), 3.4 (d, 1 H, J = 6 Hz, 9-H), 3.35 (d, 1 H, J = 18 Hz, 10β-H), 2.5 (s, 3 H, NCH_3). Anal. ($C_{17}H_{16}NO_3Cl$) C, H, N.

14β-Bromocodeinone (16). To a stirred suspension of 3.0 g (9.6 mmol) of thebaine in 30 mL of Me_2CO–H_2O (2:1) under N_2, a solution of NBS (1.78 g, 10.0 mmol) in 65 mL of Me_2CO–H_2O (2:1) was added over a 15-min period. The temperature of the mixture was maintained at 15–18 °C during the addition and thereafter for 10 min. After adding 140 mL of H_2O over a 15-min period at 18 °C, 14-bromocodeinone started to crystallize. The mixture was cooled to 0 °C and stirred for 1 h. The suspended solid was removed by filtration, washed with H_2O (20 mL), and air-dried to afford 3.14 g (87%) of **16**. The compound was recrystallized from EtOH to give pale yellow needles. The compound melted immediately when a sample of it was inserted in the melting point apparatus heated to 157 °C. When inserted before heating started, the compound did not melt even above 300 °C.

14β-Bromomorphinone (17). A solution of 0.31 g (0.82 mmol) of **16** in 10 mL of dry $CHCl_3$ was added dropwise over a 3-min period to a stirred solution of BBr_3 (1.23 g, 4.9 mmol) in 20 mL of $CHCl_3$ at 25 °C. A 2-mL portion of $CHCl_3$ was used to rinse the addition funnel. After it was stirred for 0.5 h, the mixture, consisting of a yellow suspension, was poured into a mixture of ice and 10 mL of concentrated NH_4OH solution. The two-phase system was stirred for 0.5 h at 0 °C and the organic phase was separated. The aqueous portion was saturated with salt and extracted with 120 mL of a $CHCl_3$–EtOH solution (2:1) in 60-mL portions. The total organic portions were dried ($MgSO_4$) and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 49:1). The resulting oil crystallized under EtOH to give **17** as yellow crystals, 0.68 g (22%). The compound gradually charred above 200 °C and did not melt at 300 °C: IR (KBr) 3400 (OH), 1675 cm^{-1} (C=O); NMR

($CDCl_3$) δ 6.98 (d, 1 H, J = 10.5 Hz, 7-H), 6.65 (2 H, aromatic), 5.95 (d, 1 H, J = 10.5 Hz, 8-H), 4.62 (s, 1 H, 5-H), 3.3 (d, J = 6.0 Hz, 9-H), 2.45 (s, 3 H, NCH_3). Anal. ($C_{17}H_{16}NO_3Br$) C, H, N.

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Analgesic Narcotic Antagonists. 1. 8β-Alkyl-, 8β-Acyl-, and 8β-(Tertiary alcohol)dihydrocodeinones and -dihydromorphinones

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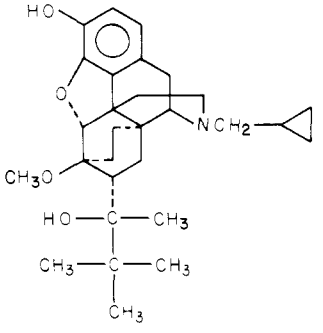
Conjugate addition of lithium dialkyl cuprates to codeinone (**3**) gave as the major product a series of 8β-alkyldihydrocodeinones **4a**–m. A low yield of the 8α-isomer **6** was isolated in several cases. 8β-Acyldihydrocodeinones **10** were prepared by the addition of acyl carbanion equivalents (protected cyanohydrin method or lithium bis(α-ethoxyvinyl)cuprate) to **3** followed by hydrolysis. 8β-Acetyldihydrocodeine (**12**) was reacted with MeLi or *n*-BuLi to give tertiary alcohols **13**, which were oxidized to target dihydrocodeinones **14**. The 8β-substituted compounds with unsaturated (**4c,f,m**), branched (**4d,g,i–k**), or large straight-chain (**4h,l**) alkyl groups, as well as the acyl (**10a–d**) and tertiary alcohol (**14a,b**) derivatives, were less active than dihydrocodeinone (**4n**) in the mouse writhing and rat tail-flick analgesic assays. The analgesically active 8β-methyl (**4a**) and 8β-ethyl (**4b**) compounds were converted to *N*-(cyclopropylmethyl)- and *N*-(cyclobutylmethyl)dihydronorcodeinones (**17** and **18**) and -dihydronormorphinones (**19** and **20**). Some of these compounds had mixed agonist–antagonist profiles of action. One of these compounds, *N*-(cyclopropylmethyl)-8β-ethyldihydronorcodeinone (**17b**), has been selected for further study in man.

The high analgesic potencies of tertiary alcohols derived from Diels–Alder adducts of thebaine[1] have created a target which workers in the strong analgesic area are attempting to emulate. Attempts are being made to dissect out from these analgesics the structural features[2] responsible for their potency and affinity for the opiate receptor.[3] This work is further stimulated by the unique and favorable pharmacological properties of Buprenorphine (**1**), a mixed narcotic agonist–antagonist derived from this series which has been developed as a clinically useful analgesic agent.[4]



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In an attempt to explain the potent analgesic activity of this series of compounds, Lewis, Bentley, and Cowan[5] hypothesized that a lipophilic site exists on the opiate receptor surface. This proposed site was postulated to interact with the alkyl portion of the tertiary alcohol appendage in the C ring. Examination of this receptor site indicates that the lipophilic area is in the proximity of C7 and C8 of the morphine nucleus. It has more recently been suggested,[6] based on the solid-state conformation of [Leu^5]enkephalin, that a complementary hydrophobic region exists on the C7–C8 face in the C ring of morphine.

To investigate these theories further, we initiated a study to determine the effect of hydrophobic alkyl substitution in this region of the morphine nucleus. We also desired to incorporate a major structural feature of **1**, namely, the tertiary alcohol moiety, into the 8 position of the morphine nucleus. The practical objective of this research was to prepare sufficiently potent compounds with a mixture of analgesic and narcotic antagonist properties. A compound with such a mixed profile of activity has potential for use as a nonaddicting analgesic agent in the treatment of severe pain.

This paper presents the results of our studies on the synthesis of 8-alkyl, 8-acyl and 8-(tertiary alcohol) derivatives of dihydrocodeinone and their preliminary pharmacological profiling. The analgesically active members of this series were converted to potential mixed agonists–antagonists. It is well known that a narcotic antagonist component of action may be incorporated into a morphine-derived narcotic agonist by replacement of the *N*-methyl group with moieties such as allyl, cycloalkylmethyl,[7] or tetrahydrofurfuryl.[8]

Chemistry. It appeared at the onset of our work that carbon–carbon bond formation at C8 could be accomplished by a 1,4 addition to codeinone (**3**). In particular,

(1) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (1967); K. W. Bentley and D. G. Hardy, *ibid.*, **89**, 3281 (1967). This work has been extensively reviewed. See K. W. Bentley, *Alkaloids (N.Y.)*, **13**, 1 (1971).
(2) For an excellent example and review of some of the work in this area, see: W. F. Michne, R. L. Salsbury, and S. J. Michalec, *J. Med. Chem.*, **20**, 682 (1977); W. F. Michne, *ibid.*, **21**, 1322 (1978).
(3) E. J. Simon and R. J. Hiller, *Annu. Rev. Pharmacol. Toxicol.*, **18**, 371 (1978).
(4) A. Cowan, J. W. Lewis, and I. R. Macfarlane, *Br. J. Pharmacol.*, **60**, 537 (1977); A. Cowan, J. C. Doxey, and E. J. R. Harry, *ibid.*, 547 (1977); B. C. Hovell and A. F. Ward, *J. Int. Med. Res.*, **5**, 417 (1977).
(5) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, 11, 241 (1971).
(6) G. D. Smith and J. F. Griffin, *Science*, **199**, 1214 (1978).
(7) E. L. May in "Agonist and Antagonist Actions of Narcotic Analgesic Drugs", H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, Eds., University Park Press, Baltimore, MD, 1973, p 17.
(8) H. Merz, A. Langbein, K. Stockhaus, G. Walther, and H. Wick *Adv. Biochem. Psychopharmacol.*, **8**, 91 (1973).

0022-2623/80/1823-0166$01.00/0