will show an additional pressor effect due to action at α-adrenergic receptors. The dopamine dose used in this work was 3 μg/kg; in dopamine responsive dogs, this dose produces a mean blood pressure drop of from 17 to 21%. In every case, 3 μg/kg produced a transient pressor effect before the longer and quantitatively greater depressor action supervened. When **4** was deployed against dopamine given at 3 μg/kg, a dose-related reduction in the depressor response occurred. The threshold dose for this antagonism was from 0.7 to 1.2 μmol/kg. Reduction of the dopamine depressor effect was accompanied by enhancement of the pressor phase of its action. In the presence of this transitory elevation in blood pressure, it was particularly difficult to determine when blockade was complete. As expected, the pressor action was eliminated by predosing with phenoxybenzamine. Dose–response studies of dopamine blockade by **4** were made in the α-adrenergic blocker treated animals. In this population, even though subject to much interanimal variability, complete blockade of the dopamine depressor action occurred at doses of **4** ranging from 12 to 17 μmol/kg. As determined from a linear plot of log dose vs. percent antagonism of dopamine depressor effect, the ED_{50} varied from **4** to 5 μmol/kg. The time course of **4** action was studied in one animal dosed with 6 μ/kg of the compound. The residual blockade was determined at 5-min intervals with 5 μg/kg of dopamine challenge. Using the linear plot of log residual blockade against time, the half-life of drug action was determined to be 18 min.

Apomorphine-induced climbing stereotypy was antagonized by pretreatment with 0.1 mg/kg of haloperidol (Table I). In contrast, compound **4** potentiated climbing behavior, the trend reaching statistical significance at 42.5 and 59.4 μmol/kg. The climbing inhibition obtained with 237 μmol/kg of **4** is evidence of the toxicity seen with this dose rather than a specific antagonism.[8] Chronic administration (7 days) of **4** yielded greater climbing potentiation, the maximal effect following 5.6 μmol/kg dosage.

This measure of stereotypy, as previously employed in this laboratory,[11] is a reliable method of assessing mouse striatal dopaminergic stimulation.[12] The failure of **4** to attenuate the climbing behavior indicates a lack of striatal dopamine blocking activity in contrast to the antidopamine properties of **4** seen peripherally. Thus, **4** is one of a few dopamine antagonists which provides evidence for the existence of multiple dopamine receptors.

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Synthesis and Antinociceptive Activity of 7-Methoxycodeine

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(−)-7-Methoxycodeine was synthesized from (−)-1-bromosinomeninone in three steps with an overall yield of 29%. The introduction of the 7-methoxy group into the C ring of codeine did not decrease its oral activity. 7-Methoxycodeine was unstable in acidic media. Its oral activity was, however, not likely to be due to conversion to the acid-stable (−)-sinomeninone, since the latter was orally inactive.

During model studies pertaining to our syntheses of (+)-morphine, (+)-codeine, (+)-heroin, and (+)-naloxone,[1,2] we prepared (−)-1-bromosinomeninone (**1**) both as a possible precursor of (−)-codeine and as the starting material for (−)-7-methoxycodeine (**6**). Since a vinylic methoxy group in the C ring of the opioids represents an uncommon substitution pattern, and was accessible by these methods, we decided to examine the antinociceptive activity of the compound.

The aromatic methoxy group in codeine reduces overall antinociceptive activity, when compared with the effect of the phenolic hydroxyl of morphine. However, the ratio of parenteral to oral activity is greater in codeine than in morphine (see Table I), possibly because the more hydrophobic molecule can more easily reach the opiate receptors in the brain and because of a decreased rate of metabolic removal due to the blocked phenolic hydroxyl group. It has been noted that the relatively high in vivo potency of codeine, when compared with its remarkably low binding affinity to the opiate receptors in rat-brain homogenate assays,[3] could be caused by a metabolic conversion to morphine in situ.[4-7] We were, then, interested in seeing whether a vinylic methoxy group would further effect the antinociceptive activity of codeine.

Synthesis. Enol methylation of the known (−)-1-bromosinomeninone (**1**)[8] gave a 1:1 mixture of (+)-1-bromosinomenine (**2**) and (−)-1-bromoisosinomenine (**3**) (Scheme I). Compound **2** was essentially identical, except

Table I. Antinociceptive Activity of (−)-7-Methoxycodeine, (−)-Sinomeninone, and Precursors

compd	ED_{50}[a,b]	ED_{50}[b,c]	ratio[d]
6	43.1 (30.1-61.8)	30.4 (22.8-40.5)	1.42
2[e]	inactive[f]		
3[e]	inactive[g]		
4[e]	40.4 (27.8-58.7)		
7	26.7 (18.9-38.0)	inactive[h]	
(−)-codeine[i]	14.6 (11.1-18.9)	34.0 (24.4-47.1)	0.43
(−)-morphine[j]	3.3 (2.5-4.4)	18.8 (14.1-24.8)	0.18

[a] Eddy hot-plate assay, subcutaneous injection in mice in μmol/kg.[13,14] [b] Parenthesized numbers represent 95% SE limits, as obtained by probit analysis, in μmol/kg. [c] Eddy hot-plate assay, oral administration in mice in μmol/kg. [d] Ratio of parenteral (via subcutaneous injection) to oral activity. [e] Hydrochloride salt. [f] Only three out of ten mice were effected at 100 mg/kg. [g] Only four out of ten mice were effected at 100 mg/kg. [h] Only five out of ten mice were effected at 100 mg/kg. [i] Phosphate salt. [j] Sulfate salt.

for the opposite optical rotation, with the (−) enantiomer of **2**, obtained from the natural (−)-sinomenine series.[9] Treatment of **2** with bromine closed the oxide bridge, giving (−)-1-bromosinomeneine (**4**). When **4** was reacted with $LiAlH_4$ for a short time, at low temperature, (−)-1-bromo-7-methoxycodeine (**5**) could be isolated in good yield. The use of a higher temperature and longer reaction time resulted in both the reduction of the 6-keto group and the concomitant removal of bromine to give (−)-7-methoxycodeine (**6**) in 85% yield. The overall yield of **6** from **1** was 29%. Compound **6** was unstable in acidic media. (−)-Sinomeninone (**7**), identical with that obtained from 7-bromodihydrocodeinone dimethyl ketal,[10] was formed almost quantitatively when **6** was allowed to stand in dilute HCl.

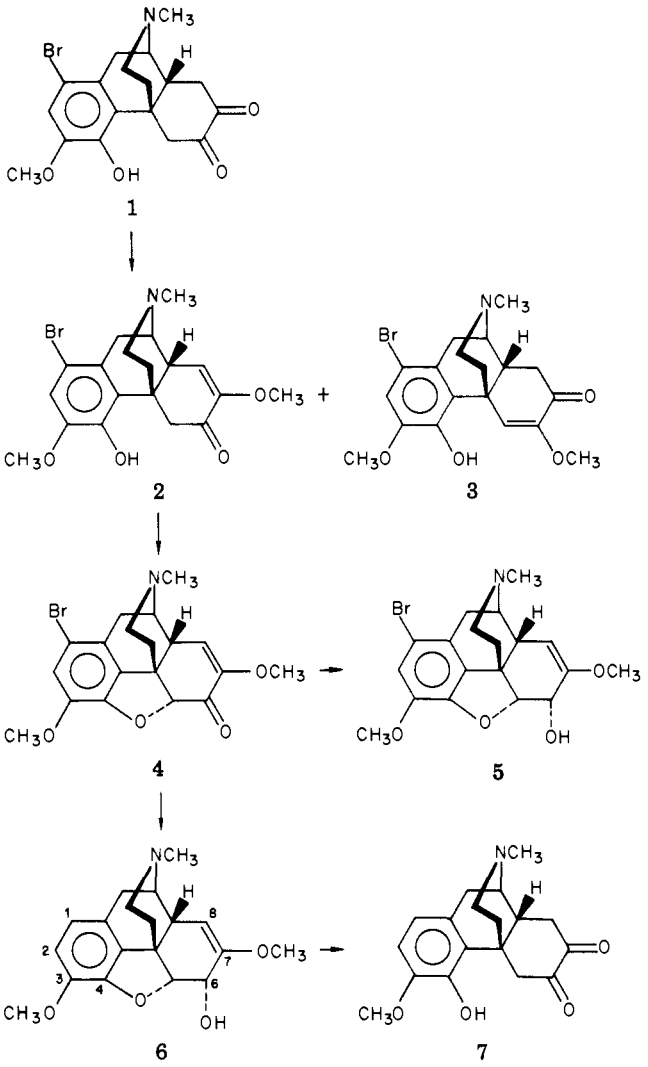
Results and Discussion

The antinociceptive activity of (−)-7-methoxycodeine (**6**) was found to be about one-third that of natural codeine when given subcutaneously (hot-plate assay, mice, μmol/kg) but equivalent to, or perhaps a little more active than, codeine orally (Table I). It had about two-thirds of morphine's potency on oral administration. Since (−)-7-methoxycodeine is unstable under acidic conditions, it might be presumed to undergo conversion to (−)-sinomeninone (**7**) on oral administration. However, although **7** was somewhat more potent than **6** as an antinociceptive on parenteral administration, it was found to be inactive orally. It would appear to be rather doubtful, then, whether the oral activity of 7-methoxycodeine could be due to its in vivo conversion to **7**.

The data indicate that **6** is more potent orally than parenterally, but the standard-error limits (Table I) were overlapping for the two methods of administration. Conceivably, there is little or no real difference between these sets of numbers. However, compounds, which can be metabolized differently on oral and parenteral administration or those which are not absorbed well parenterally, have been noted to have greater oral than parenteral activity (e.g., *levo*-α-acetylmethadol) in the hot-plate and Nilsen assays.

The introduction of the 7-methoxy moiety into the codeine molecule would appear to decrease the activity of the molecule in parenteral administration, leaving its oral activity uneffected. The additional methoxy group altered the ratio of parenteral to oral activity of codeine (from a ratio of 0.43 in codeine to a ratio of 1.42 in **6**). Unfortunately, the altered ratio resulted from the lessened parenteral activity, caused by the C-7 methoxy group.

Scheme I



Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. IR, ^1H NMR (using tetramethylsilane at 0.0 ppm as internal reference), and mass spectra were obtained on a Perkin-Elmer 257, a Varian Model HR-220, and a Hitachi RMU-6E (70 eV), respectively. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Silica gel GF plates for analytical and preparative TLC were purchased from Analtech, Inc., Newark, DE.

(+)-1-Bromosinomenine (2). (−)-1-Bromosinomeninone (**1**)[8] (1.97 g, 5.0 mmol) was dissolved in MeOH saturated with HCl gas (30 mL) and allowed to stand at room temperature for 18 h. The solution was cooled and made alkaline with $NaHCO_3$, and the solvent was removed in vacuo. The residue was treated with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo to give 2.0 g of a mixture of **2** and (−)-1-bromoisosinomenine (**3**). The compounds were separated by TLC (Et_2O–methanol, 9:1). Isolation of the material from the lower R_f layer gave **2** (0.86 g, 42%), which was recrystallized from MeOH–Et_2O to give colorless prisms: mp 188 °C; $[\alpha]^{20}_D$ +12.1° (*c* 1.0, $CHCl_3$) [lit. [for (−) enantiomer of **2**] mp 188–189 °C;[11] $[\alpha]_D$ 8.87° (*c* 3.989, $CHCl_3$)[9]]; IR ($CHCl_3$) 3500 (OH), 1687 (C=O), and 1630 cm^{-1} (C=C); NMR ($CDCl_3$) 2.41 (s, 3, N–CH_3), 3.48 (s, 3, C_7–OCH_3), 3.77 (s, 3, C_3–OCH_3), 4.38 (d, 1, J = 16 Hz, C_5–H), 5.48 (d, 1, J = 2 Hz, C_8–H), and 6.91 ppm (s, 1, C_2–H); mass spectrum *m/e* (rel intensity) 409 (43, M^+), 407 (43, M^+), 394 (96), 392 (100), 381 (44), and 379 (46). Anal. ($C_{19}H_{22}BrNO_4 \cdot 0.5H_2O$) C, H, N.

Isolation of the material from the higher R_f layer gave **3** (0.89 g, 44%), which was recrystallized from methanol to give colorless

prisms: mp 212–213 °C; $[\alpha]^{20}_D$ −149.6° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3500 (OH), 1685 (C=O), and 1620 cm^{-1} (C=C); NMR ($CDCl_3$) 2.40 (s, 3, N–CH_3), 3.68 (s, 3, C_6–OCH_3), 3.86 (s, 3, C_3–OCH_3), 6.73 (s, 1, C_5–H), and 7.03 ppm (s, 1, C_2–H); mass spectrum *m/e* (rel intensity) 409 (90, M^+), 407 (91, M^+), 394 (100), 392 (100), 323 (34), and 321 (33). Anal. ($C_{19}H_{22}BrNO_4$·0.5MeOH) C, H, N, Br.

(−)-**1-Bromosinomeneine (4).** Bromine (99%, 4.01 g, 25.0 mmol) in HOAc (50 mL) was added, dropwise, over 15 min at 20 °C to a stirred solution of **2** (10.2 g, 25.0 mmol) in HOAc (150 mL) containing HBr–HOAc (30%, 7.0 mL). After 1.5 h, the solution was evaporated in vacuo, and the residue was treated with MeOH (50 mL), made alkaline with 33% NaOH, diluted with H_2O, and extracted with CH_2Cl_2. The extracts were washed with H_2O and dried ($MgSO_4$) to give, after removal of the solvent in vacuo, **4**. Recrystallization from EtOH gave **4** as colorless needles: mp 217 °C; $[\alpha]^{23}_D$ − 85.6° (c 1.0, $CHCl_3$) [lit.[9] [for (+) enantiomer of **4**] mp 217 °C; $[\alpha]_D$ +83.08° (c 3.89, $CHCl_3$)]; IR ($CHCl_3$) 1690 (C=O) and 1622 cm^{-1} (C=C); NMR ($CDCl_3$) 2.46 (s, 3, N–CH_3), 3.50 (s, 3, C_7–OCH_3), 3.85 (s, 3, C_3–OCH_3), 4.80 (s, 1, C_5–H), 5.55 (d, 1, J = 2 Hz, C_8–H), and 6.90 ppm (s, 1, C_2–H); mass spectrum *m/e* (rel intensity) 407 (98, M^+), 405 (100, M^+), 392 (31), 390 (36), 364 (24), and 362 (24). Anal. ($C_{19}H_{20}BrNO_4$) C, H, N.

(−)-**1-Bromo-7-methoxycodeine (5).** A THF (50 mL) solution of **4** (1.02 g, 2.5 mmol) was added, over 10 min, to a stirred suspension of $LiAlH_4$ (0.3 g, 7.9 mmol) in THF (20 mL) at 0 °C. After stirring for 30 min at 0 °C, the excess $LiAlH_4$ was decomposed with aqueous THF. The resultant mixture was filtered and the precipitate washed with THF. The filtrate was dried ($MgSO_4$) and the solvent removed in vacuo to give **5** (1.0 g), which was recrystallized from EtOH to give colorless needles (0.84 g, 82%): mp 170–171 °C; $[\alpha]^{23}_D$ −56.1° (c 1.0, MeOH) [lit.[12] (for (+) enantiomer of **7**) mp 171 °C, $[\alpha]_D$ +53.5 (c 2.055, MeOH)]; IR ($CHCl_3$) 3550 (OH) and 1640 cm^{-1} (C=C); NMR ($CDCl_3$) 2.43 (s, 3, N–CH_3), 3.32 (s, 3, C_7–OCH_3), 3.80 (s, 3, C_3–OCH_3), 4.90 (d, 1, J = 6.2 Hz, C_5–H), and 6.83 ppm (s, 1, C_2–H); mass spectrum *m/e* (rel intensity) 409 (100, M^+), 407 (100, M^+), 393 (35), 391 (43), 365 (24), and 363 (24). Anal. ($C_{19}H_{22}BrNO_4$) C, H, N.

(−)-**7-Methoxycodeine (6).** A THF (10 mL) solution of **4** (0.3 g, 0.73 mmol) was added, over 5 min, to a stirred suspension of $LiAlH_4$ (0.05 g, 1.3 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 18 h at 20 °C. An additional amount of $LiAlH_4$ (0.05 g, 1.3 mmol) in THF (5 mL) was then added to the reaction mixture, and stirring was continued for 2 h at 20 °C. The workup procedure was identical with that in **5** and gave a colorless oil. Purification by TLC ($CHCl_3$–MeOH, 9:1) gave **6** as a solid (0.2 g, 85%). Recrystallization from Et_2O gave colorless needles: mp 138–140 °C; $[\alpha]^{23}_D$ −18.9° (c 0.8, MeOH); IR ($CHCl_3$) 3540 (OH) and 1640 cm^{-1} (C=C); NMR ($CDCl_3$) 2.45 (s, 3, N–CH_3), 3.32 (s, 3, C_7–OCH_3), 3.83 (s, 3, C_3–OCH_3), and 4.91 ppm (d, 1, J = 6.2 Hz, C_5–H); mass spectrum *m/e* (rel intensity) 329 (43, M^+), 314 (17), 286 (11), 83 (100). Anal. ($C_{19}H_{23}NO_4$) C, H, N.

(−)-**Sinomenine (7).** A solution of **6** (0.04 g, 0.12 mmol) in 5.0 M HCl (2 mL) was allowed to stand at room temperature for 24 h. It was made alkaline with 0.5 M Na_2CO_3 and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give **7** (0.043 g). Purification by preparative TLC ($CHCl_3$–MeOH, 9:1) gave pure **7** (0.036 g, 90%), mp 139–140.5 °C. The IR was identical with that of an authentic sample prepared from 7-bromodihydrocodeinone dimethyl ketal.[10]

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2,6-Methano-3-benzazocine-11-propanols. Lack of Antagonism between Optical Antipodes and Observation of Potent Narcotic Antagonism by Two *N*-Methyl Derivatives

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Resolution of a 2,6-methano-3-benzazocine-11-propanol analogue of buprenorphine showed that the biological activity resides in the levo antipode. An attempt to enhance agonist activity by preparation of *N*-methyl derivatives resulted in two compounds three and five times as potent as nalorphine as antagonists of phenazocine. These compounds are the most potent *N*-methyl narcotic antagonists reported to date.

We recently reported the synthesis and narcotic agonist–antagonist evaluation of some 2,6-methano-3-benzazocine-11-propanols analogous to the ring C bridged oripavine-7-methanols.[1] Because the effects on biological activity of identical changes in peripheral substituents on the 2,6-methano-3-benzazocine and 4,5-epoxymorphinan ring systems in general are of similar magnitude and direction,[2-4] we were surprised to find major differences in the structure–activity profiles of ours and the parent series. In particular, when compared with buprenorphine (**2**), neither **1a** nor **1b** showed very much agonist activity (Table I), while **1a** showed considerably more antagonist activity than either **1b** or **2**. Our NMR data suggested that the relative configurations of the alcohol-bearing carbons of **1b** and **2** were the same. If one assumes that the antagonist activity of **1a** is largely or totally confined to the (−) antipode,[2] one might expect **1c**, the (+) antipode of isomer II, to show some antagonist activity since the absolute

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