extracts were evaporated to dryness, and the residue was recrystallized from hexane to yield 4.1 g of **5**.

(+)-2α-Tropanyl (±)-Tropate (6). A mixture of 5.3 g (0.03 mol) of 2α-tropanol hydrochloride and 12.2 g (0.054 mol) of freshly prepared *O*-acetyltropoyl chloride[17] was stirred at 90–95 °C for 2.5 h and became homogeneous. The mixture was heated on a steam bath for 30 min with 60 mL of H_2O to remove the acetyl group. A small amount of unreacted oil was removed by extraction into ether. The aqueous phase was made basic and extracted with CH_2Cl_2. The extract was evaporated to give 4.5 g of an oil whose NMR spectrum indicated the presence of both tropate and atropate (sharp doublets at 5.88 and 6.34 ppm) esters.

The desired tropate was recovered by repeated leaching of the oil with hexane at room temperature until just 0.5 g remained undissolved. The combined leachings were stored for 5 days at 0 °C, during which 1.2 g of a solid, mp 74–100 °C, separated. NMR showed the absence of atropate. The N-CH_3 absorption showed sharp singlets at 2.24 and 2.29 ppm, indicating the presence of approximately equal amounts of the two expected diastereoisomers.

(+)-2α-Tropanyl Chlorodiphenylacetate Hydrochloride (8). A mixture of 5.6 g (0.04 mol) of 2α-tropanol, 13.8 g (0.05 mol) of chlorodiphenylacetyl chloride, 4.1 g (0.05 mol) of pyridine, and 50 mL of $CHCl_3$ was stirred at room temperature for 3 days, during which it became homogeneous. It was worked up in the usual way to yield 12 g of a hexane-soluble oil that could not be crystallized. The hydrochloride was prepared in ether and then leached with 500 mL of boiling EtOAc: yield 7 g. When a solution of the salt in water was warmed on a steam bath for just 10 min, the compound was hydrolyzed to (±)-2α-tropanyl benzilate.

(±)-3-Quinuclidinyl (±)-Tropate (17). A mixture of 6.5 g (0.04 mol) of 3-quinuclidinol hydrochloride and 15.8 g (0.07 mol) of freshly prepared *O*-acetyltropoyl chloride was treated exactly as described above for the preparation of compound **6**. In the present case, the 8.5 g of crude oily product contained no atropate ester. The oil was leached with several portions of boiling hexane, from which pure material crystallized on partial evaporation and cooling. The product was optically inactive, and the tropic acid obtained on hydrolysis was racemic.

Registry No. **1**, 87395-51-5; **2**, 87395-52-6; **3**, 87395-53-7; **4**, 87395-54-8; **5**, 87395-55-9; **6** (isomer 1), 87421-55-4; **6** (isomer 2), 87479-98-9; **7**, 87395-56-0; **8**, 87395-57-1; **8**·HCl, 87421-56-5; **9**, 87421-57-6; **10**, 87395-58-2; **10**·HCl, 87421-58-7; **11**, 87395-59-3; **12**, 87395-60-6; **13**, 87421-59-8; **14**, 87421-60-1; **15**, 87395-61-7; **16**, 87395-62-8; **16**·HCl, 87395-63-9; **17**, 87395-64-0; **18**, 87395-65-1; **19**, 87395-66-2; benzophenone, 119-61-9; (+)-2α-tropanyl acetate, 64530-37-6; (+)-2α-tropanol, 36127-54-5; (+)-2α-tropanol hydrochloride, 87421-61-2; (+)-3-quinuclidinol hydrochloride, 25333-43-1.

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14β-(2-Bromoacetamido)morphine and 14β-(2-Bromoacetamido)morphinone

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14β-(2-Bromoacetamido)morphine (**6**) and 14β-(2-bromoacetamido)morphinone (**9**) were prepared preferably from the adduct of thebaine and 1-chloro-1-nitrosocyclohexane, which on reduction in methanol solution gave 14-aminocodeinone (**2**) and the corresponding ketal (**3**). When tested in a receptor-binding assay, the IC50 values of **6** and **9** were 15 and 10 nM, respectively. If the incubation time during the assay was increased from 15 to 30 min, irreversible binding of both ligands was observed.

Recently, we reported the partial purification of an opiate receptor from rat brain using an affinity column prepared from Aminohexylsepharose and 14β-(2-bromoacetamido)morphine (**6**).[1] The latter was prepared from 14β-nitrocodeinone,[2] but the yields were unsatisfactory. Because of the interest in the ligand, **6**, alternate synthetic approaches were investigated. In the course of this work, 14β-(2-bromoacetamido)morphinone (**9**) was prepared and tested in the receptor-binding assay for opiates[3] along with **6**. Both ligands were active, a prerequisite for use in affinity chromatography.

Chemistry. An improved procedure for the preparation of **6** and also for **9** is shown in Scheme I.

Thebaine (**1**) was treated with 1-chloro-1-nitrosocyclohexane and dry HCl to give an adduct, which was reduced with Zn and then partially hydrolyzed to a mixture of the ketone **2** and the ketal **3**.[4] Reduction of **2** with $NaBH_4$ gave **4**, which on demethylation gave **5**. Bromoacetylation, followed by treatment with 1 N HCl gave **6** in 30% overall yield from **2**.

The codeinone **2** was hydrogenated smoothly to **7**, but bromoacetylation gave a thermally unstable amide, which precluded further investigation in the dihydro series. On the other hand, bromoacetylation of either **2** or **3** proceeded uneventfully to afford **10** and **8**, respectively, both of which gave the morphinone **9** on treatment with BBr_3.

Biological Results

Rat neural membranes were prepared according to the method of Bidlack and Abood,[5] and the receptor binding assay was carried out according to Pert and Snyder.[3] [^{3}H]Dihydromorphine (80 Ci/mmol) at a concentration of 4 nM was used as the competing ligand. Under these conditions, the IC_{50} value of morphine was 4 nM. The ability of **6** and **9** to inhibit the binding of 4 nM [^{3}H]dihydromorphine to rat neural membranes was determined using seven different concentrations of each ligand in three different experiments. The IC_{50} value for each compound was determined from log-probit plots of the data. IC_{50} values of 15 and 10 nM were obtained for **6** and **9**, respectively.

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Scheme I

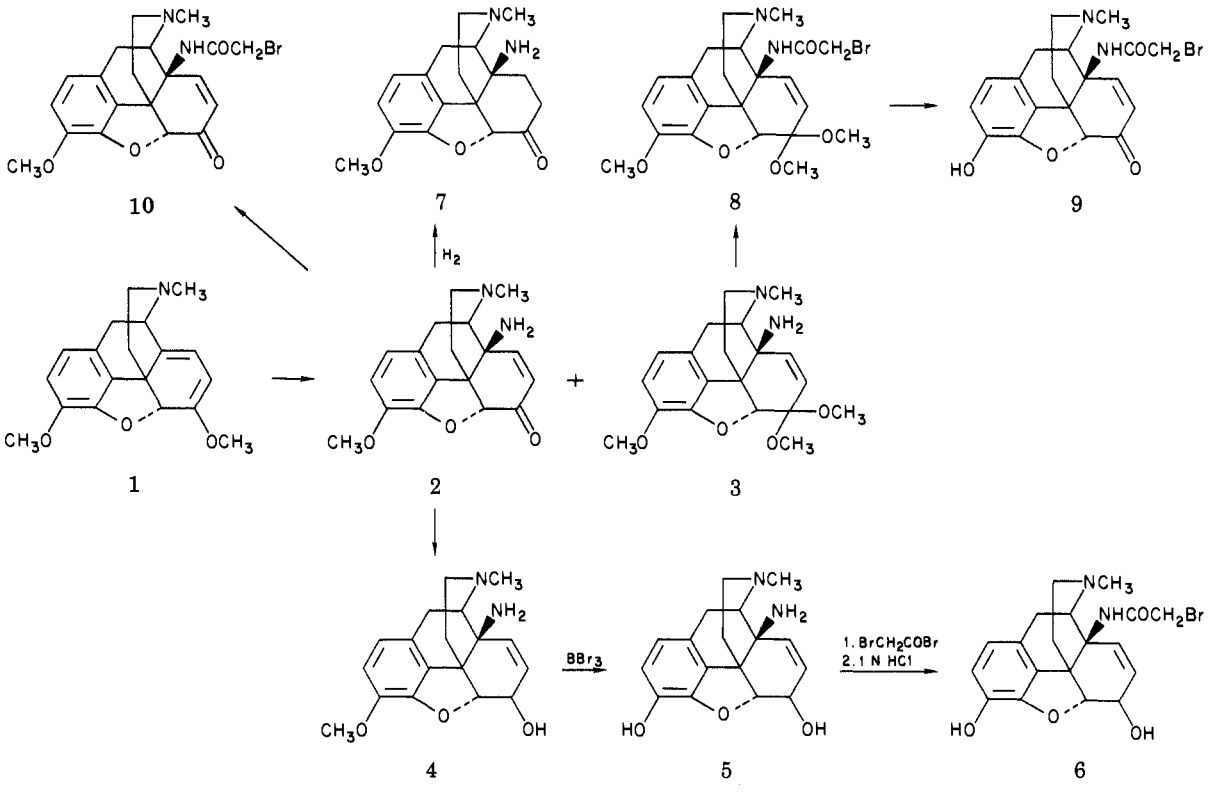

Table I

compd	% inhibition[a] [^{3}H]dihydromorphine	[^{3}H]naloxone
6	19 ± 4	37 ± 3
9	35 ± 3	36 ± 2
morphine	1 ± 3	2 ± 2

[a] Neural membranes were incubated with 20 nM concentrations of the compounds for 30 min at 37 °C. After the membranes were washed 4 times, the ability of neural membranes to stereospecifically bind 4 nM [^{3}H]dihydromorphine or 4 nM [^{3}H]naloxone was measured by the glass-fiber filter technique in the presence of either 10^{-6} M dextrorphan or 10^{-6} M levorphanol. The data are reported as the mean percent inhibition plus or minus standard error for five experiments.

The ability of these two ligands to covalently bind to the opioid receptor was determined in the following manner. Neural membranes were incubated with 20 nM concentrations of **6** or **9** at 37 °C for 30 min. An equal concentration of morphine served as a control. The membranes were then centrifuged at 100000*g* for 15 min. The pellet was resuspended in 50 mM Tris buffer, pH 7.5, and the washing procedure was repeated 4 times. The membranes were then resuspended in 50 mM Tris buffer, pH 7.5, and opiate binding was measured. [^{3}H]Dihydromorphine and [^{3}H]naloxone (37.7 Ci/mmol) were used at a final concentration of 4 nM. The results are shown in Table I. The morphine control was indistinguishable from membranes that had not been incubated with any drug. Both ligands were equipotent in inhibiting [^{3}H]naloxone binding, but **9** appeared to be more potent in inhibiting the agonist, [^{3}H]dihydromorphine. By using the ligands at a concentration of 20 nM and an incubation time of 30 min at 37 °C, it was possible to selectively inactivate the opioid receptor.

The binding of [^{3}H]quinuclidinyl benzilate and [^{3}H]-nicotine to neural membranes was not affected by this treatment. A greater inhibition of opiate binding could be obtained by using increasing concentrations of the ligands and longer incubation times. However, larger concentrations of ligands resulted in increased nonspecific labeling. When the phenolic ring of **9** was iodinated with ^{125}I and membranes were incubated with a 20 nM concentration of this iodinated ligand at 37 °C for 30 min, essentially only three major proteins were labeled.[6] Longer incubation times and increasing ligand concentrations resulted in an increase in nonspecific labeling. When used at 20 nM concentrations for limited periods of time, these two ligands appear to covalently bind specifically to the opioid receptor.

Experimental Section

Melting points were taken on a laboratory device Mel-Temp apparatus and are corrected. The ^{1}H NMR spectra were run on a 100-MHz Varian HA-100 with $CDCl_3$ or $(CD_3)_2SO$ as solvents and with $(CH_3)_4Si$ as the internal standard. The mass spectra were run on a JEOL 0156 mass spectrometer at the Sterling-Winthrop Research Institute. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. All analytical results were within ±0.4% of the theoretical values.

14β-Aminocodeinone (2). The procedure of Horsewood and Kirby[4] was used, except that the reaction time at 0 °C was extended to 68 h. After recrystallization from MeOH, there was obtained 12.7 g (37.3%) of the desired product, mp 188–191 °C (Horsewood and Kirby reported 35% yield and mp 194–195 °C).

14β-Aminocodeinone Dimethyl Ketal (3). A solution of dry HCl was prepared by adding 7.85 g (0.1 mol) of acetyl chloride to 400 mL of absolute MeOH. Then, 31.1 g of thebaine was dissolved with stirring, and the resulting solution was treated with 20 g (0.130 mol) of 1-chloro-1-nitrosocyclohexane. After 48 h at 0 °C, the mixture was carefully added to 2500 mL of saturated $NaHCO_3$ with stirring. The suspension was extracted with 2 × 500 mL portions of $CHCl_3$, and the combined extracts were dried

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and evaporated to leave an oily residue, which was stirred and refluxed for 1 h in 2 L of MeOH to which 50 g of zinc dust and 50 g of NH_4Cl had been added. The mixture was filtered hot, and the collected solid was washed with MeOH. The combined filtrates were taken to dryness, and the residue was dissolved in 500 mL of $CHCl_3$. The solution was washed with 1.5 L of H_2O, and the organic layer was evaporated to leave a brown gum, which, upon chromatography on basic alumina with $CHCl_3$ as the eluant, gave a fraction that, after crystallization from MeOH, melted at 130–132 °C (yield 6 g, 16.7%). The mother liquor was evaporated to dryness, the residue was dissolved in 0.5 N HCl, and the solution was left at room temperature for 2 h. The solution was neutralized with saturated $NaHCO_3$ and then extracted with $CHCl_3$. Evaporation of the solvent left a gum, which on chromatography on neutral alumina, gave a fraction that, after crystallization from MeOH, melted at 192–193 °C: yield 2.46 g (8%) of the 14β-aminocodeinone.

14β-Aminomorphine (5). Five grams (16 mmol) of 14β-aminocodeinone (**2**) in 3 L of CH_3OH was stirred at room temperature while 8.4 g (0.22 mol) of $NaBH_4$ was added portionwise. After 4.5 h, the mixture was concentrated under reduced pressure to 250 mL, and an equal volume of H_2O was added. The mixture was extracted with 3 × 600 mL portions of $CHCl_3$, and after washing with H_2O, the organic extracts were evaporated to leave a tan crystalline solid suitable for use in the next step: yield 4.8 g (95.4%); mp 182–185 °C. After crystallization from MeOH, the melting point rose to 186–187 °C (Allen et al.[7] reported mp 185–186 °C). The NMR spectrum of the sample was identical with that reported.[7]

A quantity of 4.95 g of the above 14β-aminocodeine (**4**) was dissolved in 1 L of dry CH_2Cl_2 and cooled to −80 °C with stirring in a flask protected from moisture. A solution of 20 mL of BBr_3 in 100 mL of CH_2Cl_2 was added dropwise over a period of 1.5 h, and the mixture was allowed to warm slowly to 0 °C during the next 4.5 h. Then, 200 mL of cold CH_3OH was added, followed by 240 mL of cold 4 N NaOH. The organic phase was separated and shaken with 60 mL of 2 N NaOH, washed with H_2O, dried, and concentrated to dryness, leaving 1.02 g (20.6%) of recovered 14β-aminocodeine. The cold alkaline extracts were neutralized with HCl, and the pH was adjusted to 7 with aqueous $NaHCO_3$. The solution was thoroughly extracted with $CHCl_3$–MeOH (9:1). Evaporation of the combined organic extracts left 3.71 g of a tan crystalline solid which after recrystallization from MeOH melted at 230–235 °C dec: yield 3.15 g (67%); IR (KBr) 3100–3600 cm^{-1} (NH_2 and OH); NMR (Me_2SO-d_6) δ 1.40–2.00 (m, 2 H, H-15), 2.00–2.45 (m, 2 H, H-16), 2.35 (s, 3 H, NCH_3), 2.50 (br d, 1 H, H-10α), 2.80 (d, 1 H, H-9α, s, in Me_2SO–D_2O at δ 2.85), 3.12 (d, 1 H, H-10β), 3.35–4.30 (m, 4 H, NH_2, C-3 OH, C-6 OH, disappear in Me_2SO–D_2O), 4.65 (br m, 2 H, H-5β, H-6β), 5.52 (br m, 2 H, H-7, H-8), 6.42 (s, 2 H aromatic H); MS, *m/e* 300 (M^+), 283 (M^+ − OH), 250 (M^+ − 2 OH − NH_2). Anal. ($C_{17}H_{20}N_2O_3$) C, H, N.

14β-(2-Bromoacetamido)morphine Hydrochloride (6). One gram (3.3 mmol) of 14β-aminomorphine (**15**) was dissolved in 160 mL of dry CH_2Cl_2 containing 3 mL of triethylamine, and the solution was cooled to −80 °C and stirred while protected from moisture. A solution of 2.2 g (0.01 mol) of bromoacetyl bromide in 40 mL of dry CH_2Cl_2 was added over the course of 1.5 h. The mixture was allowed to warm to 0 °C, and stirring was continued for another 1.5 h. The reaction mixture was washed with H_2O (2 × 10 mL), and the CH_2Cl_2 was evaporated to dryness. The residue was dissolved in a solution of 100 mL of MeOH and 20 mL of 0.5 N HCl, refluxed for 3.5 h, and evaporated to dryness.

The residue from two such runs were combined and crystallized from MeOH–CH_2Cl_2 to give three crops of the desired product: yield 1.12 g. An additional 400 mg was obtained by chromatography of the residue from the mother liquors using silica gel as the absorbant and CH_3OH–$CHCl_3$ as the eluant: total yield 1.52 g (50%) of the desired product; mp >310 °C dec; IR (KBr) 3140–3500 (NH and OH), 1675 (amide C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 1.60–2.15 (m, 2 H, H-15), 2.60–3.00 (m, 2 H, H-16), 2.90 (s, 3 H, NCH_3), 3.25–3.75 (m, 2 H, H-10α, H-10β), 4.10 (d, 1 H, H-9), 4.25 (s, 2 H, $COCH_2Br$), 4.30–4.80 (m, 2 H, H-6, OH), 4.98 (d, 1 H, H-5), 5.76 (q, 2 H, H-7, H-8), 6.55 (q, 2 H, aromatic H), 8.83 and 9.30 (2 s, 2 H, NH, OH); MS, *m/e* 421, 423, (M^+ ^{79}Br and ^{81}Br peaks); M_r of free base 421.3. Anal. ($C_{19}H_{21}BrN_2O_4$·HCl) C, H, N.

14β-Amino-7,8-dihydrocodeinone (7). A solution of 1.0 g (3.2 mmol) of 14β-aminocodeinone in 150 mL of CH_3OH was hydrogenated at 15 psi with 250 mg of 10% Pd/C as the catalyst. After 2.5 h, the mixture was filtered. The filtrate was concentrated to dryness to leave a residue, which was taken up in $CHCl_3$. The solution was passed over a short column of neutral alumina before being concentrated to leave a crystalline yellow solid, which, after crystallization from MeOH, melted at 147–149 °C: yield 0.84 g (84%); IR (KBr) 3347 (NH_2), 1717 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.30–2.50 (m, 6 H, H-8, H-15, H-16), 2.08 (br s, 2 H, NH_2, disappears on addition of D_2O), 2.40 (s, 3 H, NCH_3), 2.50–2.85 (m, 3 H, H-7, H-10α), 3.05 (d, 1 H, H-9), 3.23 (d, 1 H, H-10β), 3.90 (s, 3 H, OCH_3), 4.65 (s, 1 H, H-5), 6.88 (s, 2 H aromatic H); MS, *m/e* 314 (M^+). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

14β-(2-Bromoacetamido)codeinone Dimethyl Ketal (8). By the method described above, 1 g of 14β-aminocodeine dimethyl ketal and 0.4 mL of bromoacetyl bromide furnished 950 mg (71%) of the desired ketal after chromatography on silica gel. Recrystallization from C_2H_5OH gave the pure material, which melted at 205–223 °C dec: IR (KBr): 3360 (NH), 1660 (amide C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.20–2.00 (m, 2 H, H-15), 2.00–2.45 (m, 2 H, H-16), 2.33 (s, 3 H, NCH_3), 2.53 (d, 1 H, H-10α), 3.13 (d, 1 H, H-10β), 3.10, 3.43 (s, 6 H, 2 OCH_3 at C-6), 3.87 (s, 5 H, OCH_3 at C-3 and $COCH_2Br$), 4.07 (d, 1 H, H-9), 4.70 (s, 1 H, H-5), 5.57 and 6.20 (dd, 2 H, H-7 and H-8), 6.57 (q, 2 H, aromatic H), 7.20 (br, s, 1 H, amide NH); MS, *m/e* 478, 480 (M^+ ^{79}Br and ^{81}Br), M_r of free base 479.4. Anal. ($C_{22}H_{27}BrN_2O_5$·0.5H_2O) C, H, N.

14β-(2-Bromoacetamido)morphinone (9). To a solution of 3.90 g (7.9 mmol) of 14β-(2-bromoacetamido)codeinone dimethyl ketal in 350 mL of CH_2Cl_2 kept at −80 °C there was added dropwise, with stirring, a solution of 9 mL of BBr_3 in 50 mL of CH_2Cl_2. The reaction mixture was allowed to warm to −30 °C during the course of 1 h and kept between −20 and −30 °C for an additional 2 h. The mixture was then diluted with 40 mL of MeOH and made alkaline with 2 N NaOH. The mixture was neutralized with 6 N HCl. The CH_2Cl_2 phase was separated, and the aqueous layer was extracted with 3 × 150 mL portions of $CHCl_3$–MeOH (3:1). The combined organic layers were concentrated to dryness to leave a brown solid, which, after chromatography on silica gel with $CHCl_3$–CH_3OH (9:1) as the eluant, gave 2.0 g of the crude 14β-(2-bromoacetamido)morphinone, which after crystallization from $CHCl_3$, weighed 1.55 g (45.4%): mp decomposition starts at 240 °C and is complete at 350 °C; IR (KBr) 3510 (OH), 3470–3100 (br NH amide and OH), 1678 (br, C-6 C=O and amide C=O) cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.50–2.50 (m, 4 H, H-15, H-16), 2.47 (s, 3 H, NCH_3), 2.53–2.60 (m, 1 H, H-10α), 3.06–3.36 (d, 2 H, 9-H, 10-β), 3.86 (q, 2 H, $COCH_2Br$), 4.86 (s, 1 H, H-5), 6.18 (s, 2 H, H-7, H-8), 6.63 (q, 2 H, aromatic H), 7.90 and 7.98 (br d, s, 2 H, 3-OH, NH); MS, *m/e* 418 and 420 (M^+ ^{79}Br and ^{81}Br); M_r of the free base 419.3. Anal. ($C_{19}H_{19}BrN_2O_4$) C, H, N.

14β-(2-Bromoacetamido)codeinone (10). By the usual procedure, 2.23 g of 14β-aminocodeinone and 0.8 mL of bromoacetyl bromide furnished a brown solid, which gave 1.44 g of the desired amide after trituration under MeOH–hexane. The solvent was evaporated, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (19:1) to furnish an additional 680 mg of product: total yield 2.12 g (65.4%). After recrystallization from EtOH, the amide melted at 262–265 °C dec; IR (KBr) 3342 (NH amide), 1682 ketone C=O), 1658 (amide C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.50 (m, 4 H, H-15, H-16), 2.47 (s, 3 H, NCH_3), 2.60 (d, 1 H, H-10α), 3.10 (d, 1 H, H-5), 6.17 (s, 2 H, H-7, H-8), 6.63 (m, 2 H aromatic H), 7.80 (br s, 1 H, amide NH); MS, *m/e* 432 and 434 (M^+ ^{79}Br and ^{81}Br); M_r of free base 433.3. Anal. ($C_{20}H_{21}BrN_2O_4$) C, H, N.

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Registry No. **1**, 115-37-7; **2**, 68615-94-1; **3**, 68617-37-8; **4**, 68616-04-6; **5**, 87307-34-4; **6**, 77109-28-5; **6** (free base), 82975-77-7; **7**, 87307-35-5; **8**, 87307-36-6; **9**, 87307-37-7; **10**, 87307-38-8; bromoacetyl bromide, 598-21-0; 1-chloro-1-nitrosocyclohexane, 695-64-7.

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