**Studies in the (+)-Morphinan Series. 5.** Synthesis and Biological Properties of (+)-Naloxone

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(+)-Naloxone was prepared in 26% overall yield in eight steps from (+)-7-bromodihydrocodeinone dimethyl ketal by a synthesis which excluded enantiomeric contamination. (+)-Naloxone was examined in three assay systems and found to have no more than 1/90th of the activity of (-)-naloxone; it can, thus, serve to test the stereospecificity of the biochemical and pharmacological actions of (-)-naloxone.

(-)-Naloxone (the enantiomer of 9), prepared from natural thebaine (enantiomer of 2), is in many assay systems a pure narcotic antagonist with no agonist activity. It is, therefore, widely used clinically to reverse opiate overdose symptoms and biochemically as a test for opiate receptor mediated phenomena. Since (-)-naloxone may exhibit pharmacological actions of its own, reversal of a particular biological response by (-)-naloxone is not necessarily evidence that this activity is mediated by opiate receptors. Such ambiguities could be resolved by parallel experiments with the enantiomer, (+)-naloxone (9). This enantiomer would presumably not interact with the opiate receptor and would not share the specific actions of (+)-naloxone (enantiomer of 9). Accordingly, we have prepared (+)-naloxone by a stereoechemically controlled synthesis from (-)-sinomenine and have compared its activity to that of (-)-naloxone in several in vitro systems.

**Chemistry.** Our goal could be achieved only after marked improvements had been made in the synthesis of (+)-dihydrocodeinone from natural (-)-sinomenine and in the conversion of (+)-dihydrocodeinone into natural (-)-thebaine. Bromo ketal 1, prepared in five steps from sinomenine, was the intermediate of choice since its (-) enantiomer had successfully been converted into (-)-thebaine, starting material for the commercial synthesis of (-)-naloxone. Starting with bromo ketal 1, reactions carried out in the (+) series were as follows. Treatment of 1 with t-BuOK in Me3SO at 80-90 °C afforded (+)-thebaine (2), identical with the natural alkaloid except for its opposite optical rotation. Model experiments carried out in the (-) series suggested that oxidation of 2 with peroxide could be performed with performic acid prepared in situ, affording the desired 14-hydroxy ketone 3 in excellent yield. Catalytic hydrogenation of unsaturated ketone 4 gave saturated ketone 4 which, upon O-demethylation with BBr3, gave phenolic hydroxy ketone 5. Protection of the hydroxy groups by acetylation, followed by N-demethylation with cyanogen bromide in chloroform, yielded the N-cyano derivative 7, via diacetoxy compound 6. Refluxing the N-cyano compound 7 in 25% sulfuric acid effected deacetylation, hydrolysis, and decarboxylation and led to the desired secondary amine 8 in high yield. Since amine 8 is difficult to purify, it is a prerequisite in this synthesis that its precursors are chemically and optically pure. Synthesis of (+)-naloxone (9) was completed by routine N-allylation which gave the final product 9 as colorless prisms. This material was identical in every respect with a commercial sample of (-)-naloxone, except for its opposite optical rotation.

**Biological Results.** (+)-Naloxone, prepared by a synthesis which excludes enantiomeric contamination, was examined in a brain receptor binding assay, in the guinea pig ileum assay, and in the neuroblastoma X glioma hybrid cell adenylate cyclase assay.

**Rat Brain Receptor Binding Assay.** Comparison of displacement of [3H](-)-naloxone from opiate receptors...
in rat brain membranes by (-)-naloxone and (+)-naloxone

Figure 1. Displacement of [3H]-(-)-naloxone from opiate receptors in rat brain membranes by (-)-naloxone (O-O) and (+)-naloxone (●-●).

Figure 2. Reversal by (-)-naloxone (O-O) and (+)-naloxone (●-●) of the inhibition of electrically stimulated contractions of the guinea pig ileum due to (-)-normorphine (3 × 10^{-5} M).

Effectively, at concentrations of 5 × 10^{-7} M and above, in reversing inhibition of enzyme activity due to morphine. The data (Figure 3) show that potency of (+)-naloxone as an antagonist of morphine in this assay is less than 1/1000th that of (-)-naloxone.

Discussion

(+)-Naloxone appears to meet the necessary criteria for it to be used in parallel experiments with its enantiomer. Any pharmacological actions displayed by (-)-naloxone can now be tested for enantiomeric specificity (e.g., action at a receptor level) because of our findings that (+)-naloxone has no more than 1/1000th the activity of (-)-naloxone in these three assays.

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 and mass spectra were obtained on a Perkin-Elmer 257 and Hitachi Perkin-Elmer RMU-6E, respectively. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Thin-layer chromatography (silica gel GF, Analtech, Newark, Del.) was used to compare enantiomeric compounds throughout the synthesis. All synthesized products had Rf values identical with those of their (-) enantiomers.

(-)-7-Bromodihydrocodeinone Dimethyl Ketal (1). (+)-7-Bromodihydrocodeinone dimethyl ketal (1) was prepared from sinomenine as described.

(+)-Thebaine (2), A mixture of 1 (1.00 g, 2.36 mmol) and potassium tert-butoxide (656 mg, 5.85 mmol) in MeSO (25 mL) was heated at 80–90 °C for 1.5 h, diluted with saturated NaCl solution (25 mL), and extracted with benzene, and the extracts were dried (MgSO4). Removal of solvent gave crude 2, which was recrystallized from MeOH–H2O: 529 mg (72%); mp 193–194 °C; [a]_D^20 +218.6° (c 0.9, EtOH) [lit.10 (for enantiomer of (+)-thebaine) mp 193.5 °C; [a]_D^20 +19° (c 0.2, EtOH)]. Anal. (C_{10}H_{19}NO_3) C, H, N.

(-)-14-Hydroxycodeinone (3). Hydrogen peroxide (30%, 1.3 mL, 13 mmol) was added to a solution of 2 (3.11 g, 10 mmol) in a mixture of formic acid (88%, 1.3 mL) and H_2SO_4 (0.7%, 4.1 mL). The mixture was heated at 40 °C (bath temperature) for 6.5 h, cooled, diluted with water (10 mL), and made basic with concentrated NH_4OH. The precipitate was filtered, washed with H_2O, and dried (MgSO_4). Recrystallization from EtOH–CHCl_3 gave 3: 2.70 g (86%); mp 275–276 °C; [a]_D^20 +108.7° (c 1.06, 10% HOAc) [lit.11 (for enantiomer of 3) mp 275–276 °C; [a]_D^20 +111° (c 0.9, 10% HOAc)]. Anal. (C_{12}H_{19}NO_3) C, H, N.

(+)-14-Hydroxydihydrocodeinone (4). A solution of 2 (2.00 g, 6.38 mmol) in acetic acid (10%, 40 mL) was hydrogenated [Pd–BaSO_4 (5%, 1.00 g)]. The catalyst was filtered and washed with H_2O, and the filtrate was made basic with concentrated NH_4OH. The solution was saturated with NaCl and extracted with CHCl_3. The extracts were washed with saturated NaCl...
solution and dried (MgSO₄), and the solvent was removed. The crystalline solid 4 which was obtained was washed with Et₂O and dried: 1.91 g (95%); mp 218 °C; [α]₂⁰D +166.9° (c 1.03, 10% HOAc) [authentic sample of enantiomer of 4, mp 218 °C; [α]₂⁰D -160.9° (c 1.09, 10% HOAc)]. Anal. (C₁₈H₂₀NO₄·0.5H₂O) C, H, N.

(+)-14-Hydroxydihydromorphinone (5). A solution of 4 (1.70 g, 5.4 mmol) in CHCl₃ (15 mL) was added, dropwise, to a stirred solution of BB₃ (8.0 g, 32 mmol) in CH₂Cl₂ (15 mL) at 10 °C over 10 min. The mixture was stirred for 50 min at 10–20 °C and poured into ice-H₂O (40 mL). The solution was made basic with NH₄OH, saturated with NaCl, extracted with CH₂Cl₂ (8 × 50 mL), washed with saturated NaCl solution, and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄). Removal of solvent gave solid 5, which was recrystallized from EtOH and H₂O and dried (MgSO₄).

We recently reported the synthesis and antitetrabenazine activity of a series of 3-phenylspiro[isobenzofuran-1(3H),4'-piperidines] 11 and their corresponding derivatives 2 with an additional heteroatom attached directly to the piperidine nitrogen. 2 In both series potent antitetrabenazine activity was shown to be associated with

References and Notes

(7) K. Arima, Sankyo Co., Ltd., Japan, personal communication.
(13) See ref 10, (+)-naloxone, no. 6182.

Spiro[isobenzofuran-1(3H),4'-piperidines]. 3. Diuretic and Antihypertensive Properties of Compounds Containing a Sulfur Attached to Nitrogen

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The synthesis and antihypertensive and diuretic activity of several N-sulfur derivatives of 3-phenylspiro[isobenzofuran-1(3H),4'-piperidines] are reported. Benzenesulfonamide 3 possessed marked, species-specific diuretic and antihypertensive activity in rats.

We recently reported the synthesis and antitetrabenazine activity of a series of 3-phenylspiro[isobenzofuran-1(3H),4'-piperidines] 11 and their corresponding derivatives 2 with an additional heteroatom attached directly to the piperidine nitrogen. 2 In both series potent antitetrabenazine activity was shown to be associated with