spectrum, m/e (relative intensity) 257 (9.9), 256 (M^+, 55.4), 255 (100), 227 (4.5), 226 (18.1), 225 (3.4), 224 (4.3), 200 (3.4), 128 (7.6), 127 (7.4), 114 (3.4), 113 (11.4), 112 (2.3), 101 (5.0), 100 (5.3). Anal. Calcd for $C_{19}H_{12}O$: C, 89.04; H, 4.72. Found: C, 89.25; H, 4.80.

(*E*)-8-Styryl-1-naphthoic acid (8). A mixture of **2** (0.8 g, 3 mmol), absolute ethanol (20 mL), and potassium hydroxide (0.2 g, 3.6 mmol) was gradually heated under nitrogen with magnetic stirring to 180 °C. Ethanol evaporated, and the mixture was kept at 180 °C for 2 h. After cooling to room temperature, the mixture was treated with sodium borohydride (0.034 g, 0.9 mmol) and dry THF (6 mL) followed by freshly distilled borontrifluoride etherate (0.17 g) in dry THF (2.5 mL). After 1 h at room temperature, second portions of sodium borohydride (0.034 g, 0.9 mmol) and borontrifluoride etherate (0.17 g) were added. After another hour at room temperature, the reaction mixture was treated with propionic acid (20 mL) and refluxed for 1 h. The solvents were removed under vacuum, and the residue was extracted with dichloromethane. The organic fraction was washed with hydrochloric acid and water and dried ($MgSO_4$), and the solvent was evaporated. Sublimation at 95 °C (0.05 mm) followed by recrystallization from benzene afforded **8** as colorless needles: mp 159-160 °C; 0.084 g (10.5% yield); IR (KBr) 1682 (C=O), 973 ((*E*)-CH=CH); UV λ_{max} (EtOH) 328 nm (ϵ 25 100), 272 (20 000), 231 (60 000); ^{1}H NMR (270 MHz, CD_2Cl_2) δ 6.98 (AB d, J = 16.7 Hz, 1 H, (*E*)-CH=CH), 7.32-7.43 (m, 3 H), 7.54-7.63 (m, 5 H), 7.68 (d, J = 7.5 Hz, 1 H), 7.79 (d, J = 7.5, 1 H), 7.93 (d, J = 8.2, 1 Hz), 8.08 (m, 1 H); mass spectrum, m/e (relative intensity) 275 (22.0), 274 (M^+, 100), 257 (14.0), 255 (19.8), 231 (14.3), 230 (M - CO_2, 48.0) 229 (38.3), 227 (14.4), 226 (22.3), 202 (11.4), 183 (53), 169 (10.8), 168 (57.6), 152(10.9), 128 (14.2), 127 (16.7), 114 (13.1), 113 (20.0), 107 (10.6), 105 (14.9), 77 (12.4). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 82.84; H, 5.16.

Acknowledgment. We thank the Israel Center for Psychobiology—Charles E. Smith Family Foundation for supporting this research.

Registry No. **2**, 73873-14-0; **3**, 73873-15-1; **4**, 73873-16-2; **8**, 73873-17-3; 1,8-naphthoic anhydride, 81-84-5; phenylacetic acid, 103-82-2.

Stereospecific Synthesis of the 6α- and 6β-Amino Derivatives of Naltrexone and Oxymorphone

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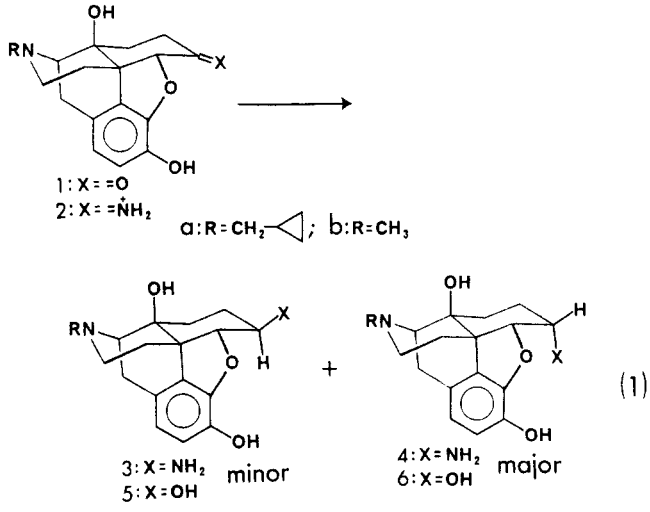
We have recently reported[1-4] on a group of affinity labeling agents as probes for opioid receptors. These ligands are all derivatives of β-naltrexamine **3a** or β-oxymorphamine **3b** in which an alkylating moiety is attached to the 6β-amino group. Because these compounds represent the first reported opioid receptor site-directed alkylating agents that are effective both in vitro and in vivo, we have devoted some effort to improving the synthesis of the amines **3** which are used as their precursors. The previously reported[5] synthesis of β-naltrexamine **3a**, which involved the $NaCNBH_3$ reductive amination of naltrexone **1a**, has the disadvantage of affording a mixture of C-6 epimers (**3a:4a** ~1:2), the separation of which is not very efficiently accomplished, especially on a large scale. This report describes a novel approach to the stereospecific synthesis of the 6β-amines (**3a,b**) and 6α-amines (**4a,b**).

Treatment of 6-keto opiates by various hydride reagents[6-12] or methyllithium[12,13] leads to the corresponding 6α-alcohol as the sole or major epimer. This fact, and the observed predominance of the 6α-amine (**4a**) from $NaCNBH_3$ reduction of the iminium species **2a**,[5] is explicable in terms of a chair-like conformation for ring C



(1)

(eq 1),[14] with hydride (or CH_3^-) transfer occurring mainly on the β face. The α face of ring C is sterically hindered due mainly to a 1,3-diaxial interaction with the aromatic ring.

On the other hand, it has been reported[2,3] that $NaCNBH_3$ reduction of the iminium salts **7a,b** stereospecifically affords the corresponding 6β-diethanolamino derivatives (**8a,b**). This was attributed[3] to ring C assuming a boat conformation (**7**) due to steric repulsion between the vicinal ether oxygen and the *syn*-CH_2CH_2OH group. There is ample precedent for similar steric effects (A strain) in cyclohexane systems.[15] With ring C in the boat conformation, hydride transfer from $NaCNBH_3$ occurs exclusively on the more accessible α face, thereby leading to the 6β isomers (**8a,b**).

Using a similar rationale, we have prepared amines **3a** and **3b** in a stereospecific fashion (eq 2). This involved formation of the dibenzyliminium salts (**9**) from the corresponding ketones (**1**) and dibenzylamine by azeotropic removal of water, followed by reduction with $NaCNBH_3$. Strictly anhydrous conditions must be observed or substantial amounts of the corresponding 6-hydroxy compounds **5** and **6** are produced. The intermediates **10a,b** were then debenzylated to the desired products by catalytic hydrogenolysis. None of the 6α epimers (**4a,b**) could be detected, even when the reaction sequence was performed

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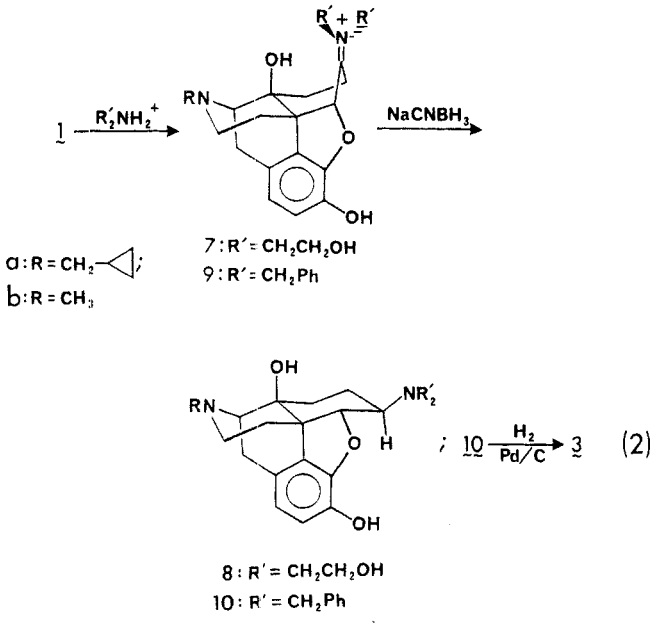
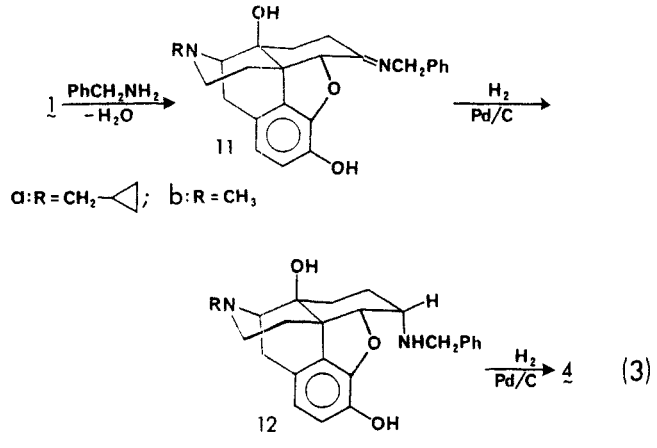


without purification and isolation of the dibenzylamino intermediate **10**.

The 6α-amines were prepared (eq 3) via the stereospe-



cific catalytic reduction of the imines **11a** and **11b**, which are derived from the ketones **1a,b** and benzylamine by azeotropic removal of water. Continued hydrogenation results in debenzylation of the intermediates **12a** and **12b** to the desired products. The stereochemistry of the reduction is consistent with the known catalytic hydrogenation of dihydrocodeinone, which yields exclusively the 6α-alcohol, dihydrocodeine.[16] As with the 6-ketones, it is reasonable to assume a chair-like conformation for ring C in the imine **11** as well, since the *N*-benzyl group would be expected to be in the less hindered anti orientation relative to the vicinal ether oxygen.[15] In this case, the stereochemical outcome of the catalytic hydrogenations is explicable in the same manner as is the hydride reduction of the C-6 ketones[12] and the iminium compound **2a**,[5] in as much as the α side at C-6 is sterically less accessible. However, it is noteworthy that the catalytic hydrogenations are stereospecific, whereas the hydride reductions produce at least some of the β isomers, even when the bulky reagent lithium tri-*sec*-butylborohydride is employed.[17]

The stereochemical assignment of the epimeric naltrexamines (**3a**, **4a**) has been previously deduced on the basis of NMR evidence.[5] The assignment of the oxymorphamines (**3b**, **4b**) follows by analogy with the naltrexamines and closely related congeners. As shown in Table I, the 5β-hydrogen of the 6α series absorbs downfield from that of the 6β series. Also, $J_{5\beta-6\beta}$ for the 6α series is always smaller than $J_{5\beta-6\alpha}$ in the 6β series. For the 6β series, the J values of 6 to 7.4 Hz are consistent with the expected thermodynamically more stable distorted chair conformation for ring C with the 6β substituent being equatorial.[14] For the 6α series the conformation of ring C cannot be unambiguously interpreted from the measured $J_{5\beta-6\beta}$ values, as they are consistent with both twist-boat and chair conformations. These conformers may be thermodynamically competitive, since the C-6 substituent could occupy a pseudoequatorial position in the former case.

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were taken at ambient temperature with tetramethylsilane as internal standard on either a Varian T-60 or A-60D instrument. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. The TLC R_f values reported pertain to EtOAc–MeOH–NH_4OH (80:20:2) as eluant.

6β-Amino-14-hydroxy-17-(cyclopropylmethyl)nordesomorphine (β-Naltrexamine, 3a). A mixture of **1a**·HCl (2.0 g, 5.3 mmol) and silver benzoate (1.27 g, 5.56 mmol) were stirred in MeOH–H_2O (9:1, 80 mL) at 40 °C for 90 min. The resulting suspension was filtered to remove the AgCl. The filtrate was taken to dryness at reduced pressure, and azeotropic removal of water from the residue was accomplished with ethanol–toluene. A mixture of the resulting naltrexone·PhCOOH, dibenzylamine (1.31 g, 6.62 mmol), benzoic acid (0.808 g, 6.62 mmol), and a trace of *p*-toluenesulfonic acid in toluene (200 mL) was refluxed for 20 h, using a Dean–Stark trap for azeotropic removal of water. The solution was then concentrated to 50 mL by slow distillation at 1 atm. Anhydrous EtOH (220 mL), $NaCNBH_3$ (0.264 g, 4.2 mmol), and 3-Å molecular sieves were added, and the resulting solution was stirred under dry N_2 for 8 h. The mixture was diluted with MeOH (100 mL) and filtered, and the residue obtained after removal of solvent was partitioned between $CHCl_3$ and 3% aqueous NH_4OH. The combined $CHCl_3$ extracts were taken to dryness and the residue was crystallized from MeOH–H_2O (9:1) to afford 2.07 g (75%) of **10a**: mp 234–237 °C; $[\alpha]^{25}_D$ −208° (*c* 1.3, $CHCl_3$); R_f 0.78; mass spectrum (20 eV), *m/e* 522 (M^+, 26%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.35 and 6.23 (2 d, 1 H each, J = 7.5 Hz, Ar H), 4.56 (d, 1 H, J = 6.5 Hz, C_5-H).

Anal. Calcd for $C_{34}H_{38}N_2O_3 \cdot 0.5H_2O$: C, 76.81; H, 7.39; N, 5.27. Found: C, 77.00; H, 7.29; N, 5.13.

Hydrogenolysis of **10a** (6.2 g, 11.9 mmol) with 1.0 g of 10% Pd/C was conducted at 40 psi in MeOH containing 2.5 mL of concentrated HCl (30 mmol) for 3 days. The catalyst was filtered, the filtrate was taken to dryness, and the residue was recrystallized from methanol–2-propanol (1:9). The yield of two crops of **3a**·2HCl,[5] mp >260 °C, R_f 0.29, was 4.7 g (95%).

6β-Amino-14-hydroxydesomorphine (β-Oxymorphamine, 3b). In the same manner as discussed above, **1b** (2.0 g, 5.92 mmol) and silver benzoate (1.424 g, 6.22 mmol) were used to prepare anhydrous oxymorphone·PhCOOH. To this salt were added dibenzylamine (1.46 g, 7.4 mmol), benzoic acid (0.18 g, 1.5 mmol), a trace of *p*-toluenesulfonic acid, and 250 mL of toluene–ethanol (4:1). Azeotropic removal of water[18] was accomplished by slow distillation of the resulting solution until the head temperature exceeded 95 °C. Ethanol (50 mL) was re-added, and the slow distillation was resumed until 100 mL of solution remained. To this was added 3-Å molecular sieves and another solution of $NaCNBH_3$ (0.44 g, 7 mmol) and benzoic acid (0.723 g, 5.9 mmol)

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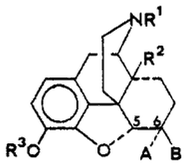
(18) In contrast to the *N*-cyclopropylmethyl case, for the *N*-methyl case, refluxing toluene does not permit efficient formation of the intermediate **9b** due to the lower solubility of the pertinent benzoate salts.

Table I. NMR Spectral Data of 6-Substituted Desomorphines



				A = R⁴; B = H		A = H; B = R⁴	
R¹	R²	R³	R⁴	5β-H, δ	$J_{5\beta-6\beta}$, Hz	5β-H, δ	$J_{5\beta-6\alpha}$, Hz
CH_3	H	CH_3	OH[d]	4.58	5.1	4.34	6.0
CH_3	H	CH_3	OAc[d]	4.59	5.7	4.43	6.5
CH_2-c-C_3H_5	OH	H	OH[e]	4.64	4.0	4.53	6.0
$CH_2CH{=}CH_2$	OH	H	OH[c]	4.62	4.0	4.52	6.0
CH_2-c-C_3H_5	OH	H	NH_2[b]	4.68	4.0	4.28	7.4
$CH_2CH{=}CH_2$	OH	H	NH_2[b]	4.55	4.0	4.28	7.4
CH_3	OH	H	NH_2[a]	4.64	3.2	4.28	6.8

[a] This work. [b] Reference 5. [c] Reference 12. [d] Reference 14. [e] Reference 17.

in anhydrous EtOH (150 mL). The mixture was stirred 8 h under dry N_2, diluted with MeOH (100 mL), and filtered. The residue obtained after removal of solvent was partitioned between $CHCl_3$ and 3% aqueous NH_4OH. The combined $CHCl_3$ extracts were taken to dryness and the residue was crystallized from 75% aqueous EtOH, affording two crops of slightly impure **10b**. This material was purified by conversion to the dihydrochloride, which was crystallized from ethanol–acetone (9:1), and then reconverted to the free base. Recrystallization from 75% aqueous EtOH yielded 1.71 g (60%) of pure **10b**: mp 238–240 °C; $[\alpha]^{25}_D$ −211° (*c* 1.2, $CHCl_3$); R_f 0.69; mass spectrum (70 eV), *m/e* 482 (M^+, 8.5%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.54 and 6.36 (2 d, 1 H each, *J* = 8.1 Hz, Ar H), 4.66 (d, 1 H, *J* = 7.4 Hz, C_5-H).

Anal. Calcd for $C_{31}H_{34}N_2O_3$: C, 77.15; H, 7.10; N, 5.80. Found: C, 76.82; H, 7.24; N, 5.83.

Hydrogenolysis of **10b**·2HCl (2.17 g, 3.9 mmol) was conducted at 40 psi in MeOH with 0.25 g of 5% Pd/C for 3 days and then with an additional 0.25 g of catalyst for 2 more days. The catalyst was filtered, the filtrate was taken to dryness, and the residue was recrystallized from methanol–2-propanol–toluene (1:8:1). The yield of two crops of **3b**·2HCl was 1.4 g (95%): mp >260 °C; $[\alpha]^{25}_D$ −91.1° (*c* 1.3, H_2O); R_f 0.24; mass spectrum (70 eV), *m/e* 302 (M^+, 59%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.64 and 6.53 (2 d, 1 H each, *J* = 8.0 Hz, Ar H), 4.28 (d, 1 H, *J* = 6.8 Hz, C_5-H).

Anal. Calcd for $C_{17}H_{24}N_2O_3Cl_2{\cdot}CH_3OH$: C, 53.08; H, 6.93; N, 6.88. Found: C, 52.84; H, 7.18; N, 6.94.

6α-Amino-14-hydroxydesomorphine (α-Oxymorphamine, 4b). A benzene solution (150 mL) containing oxymorphone base (2.5 g, 8.3 mmol), benzylamine (1.0 g, 9.3 mmol), and a trace of *p*-toluenesulfonic acid was refluxed for 10 h, using a Dean–Stark trap for azeotropic removal of water. The mixture was then concentrated (30 mL) at 1 atm, and a solution of $NaBH_4$ (0.12 g, 3 mmol) in absolute EtOH (80 mL) was added.[19] After being stirred under N_2 for 3 h, the resulting solution was diluted with H_2O and concentrated to remove most of the EtOH. Further dilution with H_2O, basification (NH_4OH), extraction ($CHCl_3$), and concentration of the organic phase afforded crude **11b** (R_f 0.58). This was dissolved in MeOH (150 mL) and concentrated HCl was added to pH 2. Hydrogenation was conducted at 40 psi with 0.8 g of 5% Pd/C for 3 days and then with an additional 0.5 g of 5% Pd/C for 3 more days. The catalyst was filtered, the filtrate was taken to dryness, and the residue was recrystallized from methanol–2-propanol–toluene (1:8:1), yielding 1.8 g of **4b**·2HCl (57%): mp >260 °C; $[\alpha]^{25}_D$ −144° (*c* 1.4, H_2O); R_f 0.15; mass spectrum (70 eV), *m/e* 302 (M^+, 87%); NMR (deuterium-exchanged free base in $CDCl_3$) δ 6.71 and 6.48 (2 d, 1 H each, *J* = 8.0 Hz, Ar H), 4.64 (d, 1 H, *J* = 3.2 Hz, C_5-H).

Anal. Calcd for $C_{17}H_{24}N_2O_3Cl_2{\cdot}0.5CH_3OH$: C, 53.71; H, 6.70; N, 7.16. Found: C, 53.25; H, 7.06; N, 7.49.

(19) Treatment with $NaBH_4$ does not reduce the imine **11** but does prevent the accumulation of an unknown byproduct, during the subsequent hydrogenation, which causes poisoning of the catalyst.

6α-Amino-14-hydroxy-17-(cyclopropylmethyl)nordesomorphine (α-Naltrexamine, 4a). By use of the same procedure as described for **4b** above, **4a**·2HCl,[5] mp >260 °C, R_f 0.19, was prepared in 76% yield (first crop).

Acknowledgment. This work was supported by NIDA research grant DA01533. We thank Dr. R. Willette (NIDA) for the generous supply of naltrexone and Dr. D. F. Loncrini (Mallinckrodt, Inc.) for the oxymorphone.

Registry No. **1a**·HCl, 16676-29-2; **1b**, 76-41-5; **3a**·2HCl, 63463-07-0; **3b**·2HCl, 73986-22-8; **4a**·2HCl, 63463-06-9; **4b**·2HCl, 73986-23-9; **10a**, 73986-24-0; **10b**, 73986-25-1; **10b**·2HCl, 73986-26-2; **11b**, 73986-27-3; dibenzylamine, 103-49-1.

O-Alkylation of 2-(Carbomethoxy)cyclopentanone

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The alkylation of ambident anions generated from β-keto esters has been extensively studied,[1-14] especially in

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