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Diastereomeric 6-Desoxy-6-spiro-α-methylene-γ-butyrolactone Derivatives of Naltrexone and Oxymorphone. Selective Irreversible Inhibition of Naltrexone Binding in an Opioid Receptor Preparation by a Conformationally Restricted Michael Acceptor Ligand[1]

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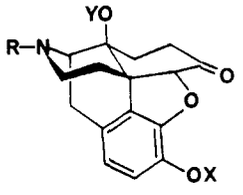
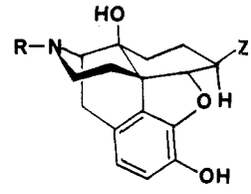
The diastereomeric 6-desoxy-6-spiro-α-methylene-γ-butyrolactone derivatives of naltrexone (**4a** and **5a**) and of oxymorphone (**4b** and **5b**) were prepared from their parent ketones. Diastereomers **4a** and **4b** were obtained from the 3,14-diacetate derivatives of naltrexone (**6a**) and oxymorphone (**6b**) by reaction with the Reformatsky reagent prepared from methyl α-(bromomethyl)acrylate. Deacetylation with methanol completed the synthesis. Diastereomers **5a** and **5b** were obtained from oxiranes **8a** and **8b**, respectively. The oxiranes were allowed to react with the sodium salt of ethyl acetoacetate, followed by methenation and deprotection to complete the synthesis of **5a** and **5b**, respectively. Compound **5a** was the most potent agent tested in competition against [^{3}H]naltrexone in the opioid radioreceptor assay. At a concentration of 5 nM this compound produced a 50% inhibition of binding. The majority of this inhibition (30%) was irreversible, i.e., it remained even after extensive washing of the membrane preparation in the presence and absence of Na^+. Naloxone protected against this irreversible effect. The data suggest a receptor nucleophile, perhaps a sulfhydryl group, is located where it can add to the α,β-unsaturated carbonyl system of **5a**.

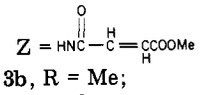
The use of chemoaffinity labels derived from opioid agonist and antagonist molecules is an important approach to aid the characterization of opioid receptors.[2] Compounds related to naltrexone (**1a**) and oxymorphone (**1b**) with alkylating groups at the C-6 position, e.g., chloronaltrexamine and chloroxymorphamine (**2a** and **2b**; nitrogen mustards[3]) and funaltrexamine and fuoxymorphamine (**3a** and **3b**; fumaramide methyl esters[4]) have shown interesting binding characteristics in opioid receptor preparations. These compounds clearly demonstrate that



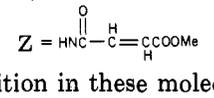


1a, R = CPM; X = Y = H (naltrexone)
1b, R = Me; X = Y = H (oxymorphone)
6a, R = CPM; X = Y = Ac
6b, R = Me; X = Y = Ac
7a, R = CPM; X = 2-THF; Y = H
7b, R = Me; X = 2-THF; Y = H

2a, R = CPM; Z = $N(CH_2CH_2Cl)_2$
2b, R = Me; Z = $N(CH_2CH_2Cl)_2$
3a, R = CPM,

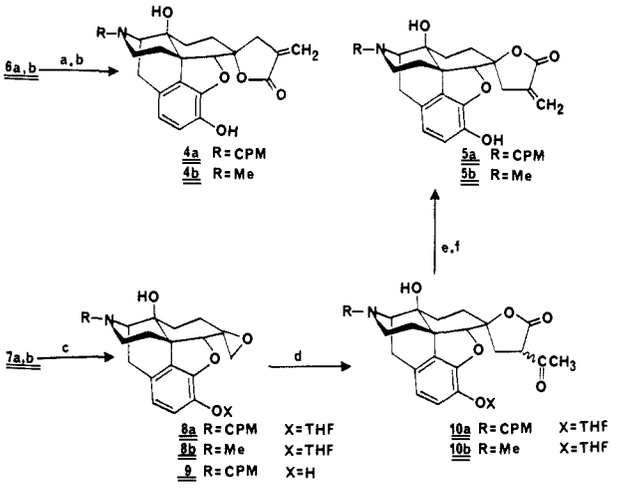


3b, R = Me;



substitution at the C-6 position in these molecules is a suitable way to add additional groups that may act as alkylating functionalities. On the basis of inactivation of opioid receptor binding with sulfhydryl reagents like *N*-ethylmaleimide,[5] it has been suggested that alkylation of sulfhydryl groups occurs at or near the opioid binding site. It has also been suggested recently that morphinone may undergo covalent binding in a similar way.[6] Portoghese et al. have suggested that the opioid receptor may bear a sulfhydryl group as a secondary recognition site and that when binding of the ligand to receptor occurs (primary recognition), if an electrophilic reagent is properly aligned, formation of a covalent bond may result in irreversible inactivation.[7] To gain more information concerning this interesting concept and to develop more insight concerning

Scheme I[a]



[a] Reagents: a, $BrZnCH_2C(CH_2)COOMe$; b, MeOH; C, $CH_2S(O)(CH_3)_2$; d, CH_3COCH_2COOEt, NaH; e, $(CH_2O)_n$, LDA; f, MeOH, HOAc.

the binding of opioid receptor ligands, we prepared compounds in which a conformationally restricted electrophilic

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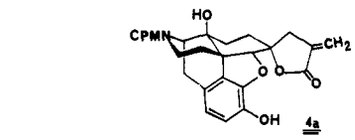
(1) Portions of this work were presented at the 185th National Meeting of the American Chemical Society, Seattle, WA, March, 1983; MEDI 70.
(2) Venn, R. F.; Barnard, C. A. *J. Biol. Chem.* **1981**, *256*, 1529. Hazum, E.; Chang, K. J.; Shecter, Y.; Wilkinson, S.; Cuatrecasas, P. *Biochem. Biophys. Res. Commun.* **1979**, *88*, 841. Castell, J. V.; Eberle, A. N.; Krivacek, V. M.; Tunkyi, A.; Shiller, P. W.; Do, K. Q.; Thanes, P.; Schwyzer, R. *Helv. Chim. Acta* **1979**, *62*, 525. Rice, K. C.; Jacobson, A. E.; Burke, T. R., Jr.; Bajala, B. D.; Streaty, R. A.; Klee, W. A. *Science* **1983**, *220*, 314. Klee, W. A.; Simonds, W. F.; Sweat, F. W.; Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C. *FEBS Lett.* **1982**, *150*, 125. Maryanoff, B. E.; Simon, E. J.; Gioannini, T.; Gorissen, H. *J. Med. Chem.* **1982**, *25*, 913.
(3) Sayre, L. M.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1983**, *26*, 1229. Sayre, L. M.; Takemor, A. E.; Portoghese, P. S. *J. Med. Chem.* **1983**, *26*, 503. Portoghese, P. S.; Larson, D. L.; Jiang, J. B.; Takemori, A. E.; Caruso, J. P. *J. Med. Chem.* **1978**, *21*, 598. Caruso, T. P.; Larson, D. L.; Portoghese, P. S.; Takemori, A. E. *J. Pharmacol. Exp. Ther.* **1980**, *213*, 539. Portoghese, P. S.; Larson, E. L.; Jiang, J. B.; Caruso, T. P.; Takemori, A. E. *J. Med. Chem.* **1979**, *22*, 168. Tantozzi, R. F.; Mullikin-Filpatrick, D.; Blume, A. J. *Mol. Pharmacol.* **1981**, *20*, 8.

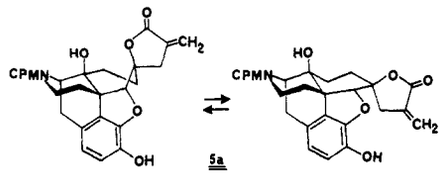
0022-2623/84/1827-1718$01.50/0

group at the C-6 position is incorporated. These compounds are the diastereomeric 6-desoxy-6-spiro-α-methylene-γ-butyrolactone derivatives of naltrexone (**4a** and **5a**) and of oxymorphone (**4b** and **5b**), in which a conformationally restricted α,β-unsaturated carbonyl system, an α-methylene-γ-butyrolactone, is incorporated into each structure as a potential Michael acceptor.

Chemistry. The conversion of **1a** and **1b** to the diastereomeric α-methylene-γ-butyrolactones is outlined in Scheme I. Direct alkylation of the 3,14-diacetate esters of naltrexone and oxymorphone (**6a** and **6b**) with the Reformatsky reagent prepared from methyl α-(bromomethyl)acrylate[8] afforded a single lactone from each ketone. Deacetylation in the presence of methanol afforded the desired 6-spiro-α-methylene-γ-butyrolactone derivatives **4a** and **4b** in approximately 60% yield.



4a



5a

The diastereomeric lactones **5a** and **5b** were prepared from 6-desoxy-6-methylene 6β-epoxide derivatives **8a** and **8b**, obtained from **1a** and **1b** respectively. Suitable protection of phenolic groups was necessary throught the synthetic sequence. The 2-tetrahydrofuranyl group[9] provided adequate protection and facile deprotection. Compound **7a**, the O^3-(2-tetrahydrofuranyl) ether of **1a**, was converted to oxirane **8a** in 95% yield, by reaction with trimethylsulfoxonium ylide. The stereochemistry of oxirane **8a** was consistent with observations in related systems where formation of the β-oxirane was noted.[10] Lithium aluminum hydride reduction of oxirane **9** (deprotected **8a**) afforded methylcarbinol **11**, which was diastereomeric with methylcarbinol **12**, formed by methyllithium addition to **1a**. Methyllithium has been previously shown to occur predominantly from the β-face in very closely related molecules.[11,12] Treatment of oxirane **8a** with the sodium salt of ethyl acetoacetate according to the method of Bensel et al.[13] gave a mixture of keto lactones **10a** in 80% yield. Subsequent methenation and deacetylation was accomplished by the method of Uneno[14] in 90% yield. Deprotection (MeOH, HOAc) afforded the desired lactone **5a** in 60% yield. Conversion of oxymorphone (**1b**) to **5b** followed a similar series of steps.

Table I. In Vitro Opioid Receptor Binding Competition against 1 nM [^{3}H]Naltrexone

compd	IC_{50}, nM		Na ratio
	no NaCl	100 mM NaCl	
4a, N = CPM	15	12.5	0.8
5a	5	2.0	0.4
4b, N = Me	115	880	7.6
5b	35	250	7.1

Opioid Receptor Binding. Affinity of the 6-desoxy-spiro-α-methylene-γ-butyrolactone derivatives **4a**, **4b**, **5a**, and **5b** for opioid binding sites was determined in the crude rat brain membrane preparation[15] by competition against [^{3}H]naltrexone in the presence and absence of Na^+. Results are described in Table I. Antagonist analogues **4a** and **5a** (R = CPM) are more potent in displacing [^{3}H]-naltrexone than the corresponding agonist analogues **4b** and **5b** (R = Me). The Na^+ ratios are similar to those observed for closely related compounds. *N*-Methyl analogues **4b** and **5b** behave as relatively pure agonists showing Na^+ ratios of 7–8, and *N*-CPM analogues **4a** and **5a** behave as "pure" antagonists showing Na^+ ratios less than one. The 6-desoxy-spiro-α-methylene-γ-butyrolactone derivatives **5a** and **5b** were more potent than their diastereomeric analogues **4a** and **4b** by 3–7-fold, suggesting a small but significant difference in steric and/or electronic effects in the binding between the diastereomeric α-methylene-γ-lactones.

In competition with a selective μ receptor ligand, [^{3}H]oxymorphone, 15 nM **5a** inhibited binding of [^{3}H]-oxymorphone by about 50%. A higher concentration, 30 nM, was required to inhibit the binding of the δ ligand, [D-Ala-^{2}-D-Leu^5]enkephalin (DADLE), in the presence of 100 nM [D-Ala^2-N-Me-Phe^4-Gly-ol^5]enkephalin (DAGO), a saturating concentration of a highly selective μ receptor ligand. Compound **5a** had even weaker affinity at the κ site. The IC_{50} vs. bremazocine in the presence of 100 μM DADLE and 100 μM DAGO (to block δ and μ sites) was ca. 100 nM. Compound **5a** threfore, as expected, has a somewhat higher affinity for μ- than for δ- or κ-type opioid binding sites.

To determine whether any of the compounds had irreversible effects on ligand binding in the opioid receptor preparation, concentrations of **4a**, **4b**, **5a**, annd **5b** that were approximately 50% inhibitory in the absence of Na^+ were incubated for 15 min with rat brain membranes. The membranes were then washed thoroughly as described in the Experimental Section and bound with [^{3}H]naltrexone to determine the amount of binding capacity restored by the washing procedure. Only antagonist analogue **5a** produced irreversible effects, described in Table II. By preincubation with a concentration of **5a** that produces 50% inhibition of opioid binding, a significant amount of the binding capacity (30%) was lost. In the presence of

(4) Portoghese, P. S.; Larson, D. L.; Sayre, L. M.; Fries, D. S.; Takemori, A. E. *J. Med. Chem.* **1981**, *23*, 233. Takemori, A. E.; Larson, D. L.; Portoghese, P. S. *Eur. J. Pharmacol.* **1981**, *70*, 455.
(5) Smith, J. R.; Simon, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 281. Simon, E. J.; Groth, J. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2404. Pasternak, G. W.; Wilson, H. A.; Snyder, S. H. *Mol. Pharmacol.* **1975**, *11*, 340.
(6) Nagamatsu, K.; Kido, Y.; Terao, T.; Ishida, T.; Toki, S. *Drug Metab. Dispos.* **1983**, *11*, 190. Nagamatus, K.; Kido, Y.; Terao, T.; Ishida, T.; Toki, S. *Life Sci.* **1982**, *31*, 1421.
(7) Portoghese, P. S.; Takemori, A. E. "The Chemical Recognition of Biological Mechanisms"; Creighton, A. M., Turner, S., Eds.; Whitstable Litho, Ltd.: Whitstable, England, 1982; p 181.
(8) Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457. Lee, K. H.; Ibuka, J.; Kim, S. H.; Vestal, B. R.; Hall, I. H. *J. Med. Chem.* **1975**, *18*, 812.
(9) Kruse, C. G.; Jonkers, F. L.; Dert, V.; van der Gem, A., *Recl. Trav. Chim. Pays-Bas* **1975**, *98*, 371.
(10) Hahn, E. F.; Fishman, J.; Heilman, R. D. *J. Med. Chem.* **1975**, *18*, 259. Sargent, L. J.; Jacobson, A. E. *J. Med. Chem.* **1972**, *15*, 843.
(11) Hahn, E. F.; Fishman, J.; Heilman, R. D. *J. Med. Chem.* **1975**, *18*, 259.
(12) Hahn, E. F.; Fishman, J. *J. Org. Chem.* **1975**, *40*, 31.
(13) Bensel, N.; Klinkmuller, K. D.; Marshall, H.; Weyerstahl, P. *Liebigs. Ann. Chem.* **1977**, 1572.
(14) Uneno, Y.; Setoi, H.; Okawara, M. *Tetrahedron Lett.* **1978**, 3753.
(15) Simon, E. J.; Hiller, J. M.; Groth, J.; Edelman, I. *J. Pharmacol. Exp. Ther.* **1975**, *192*, 531.

Table II. Irreversible Inhibition of [^{3}H]Naltrexone Binding by **5a** and Protection by Naloxone

preincubation condtn	% control[a]			
	−NaCl		+NaCl	
	unwashed	washed	unwashed	washed
control (no ligand)	100	100	100	100
10 nM naloxone	25 ± 2 (n = 5)	105 ± 7 (n = 5)	15 ± 3 (n = 3)	108 ± 4 (n = 3)
5 nM **5a**	52 ± 4 (n = 4)	68 ± 5 (n = 4)	20 ± 2 (n = 4)	39 ± 4 (n = 4)
10 nM naloxone + 5nM **5a**	28 (n = 2)	93 (n = 2)	13 (n = 2)	80 (n = 2)

[a] Specific binding of [^{3}H]naltrexone is expressed as percent of control ± SEM.

Na^+, where 5 nM **5a** produced 80% inhibition of binding, a 60% loss in binding activity was observed. In the presence of 10 nM naloxone, the binding was almost completely protected against inactivation by 5 nM **5a**, both in the presence and absence of NaCl. These preliminary studies indicate that irreversible binding occurs at the opioid binding sites. The fact that considerable irreversible binding is observed at 5 nM **5a**, a concentration that barely inhibits DADLE binding, suggests that it occurs primarily at μ-type sites.

The ^{1}H NMR spectrum of **5a** was examined to obtain information about the conformation of the C ring in solution. Previous ^{1}H NMR work suggested that the C ring existed in the flattened chair conformation in 6α- and 6β-naltrexol,[16] naltrexone,[16,17] and 6β-naltrexamine hydrochloride salt.[18] On the other hand, the ^{1}H NMR spectrum of 6α-naltrexamine hydrochloride salt suggested a twist-boat conformation for the C ring. In the 500-MHz ^{1}H NMR spectrum of **5a**, the protons at C-7 and C-8 were separated from each other. Expected large $J_{a,a}$ coupling ($J_{7a,8a}$ = 13.5 Hz) and smaller $J_{a,e}$ and $J_{e,e}$ coupling constants ($J_{7a,8e}$ = 2.5 Hz, $J_{7e,8a}$ = 2.5 Hz, $J_{7e,8e}$ = 4.0 Hz) were observed, consistent with the flattened chair being the predominant conformation of the C ring in solution. In Dreiding models $\theta_{ee} \sim 50°$ and $\theta_{ae} \sim 70°$. These coupling constants are also similar to those observed for protons in the C ring of naltrexone. Assignments of protons and coupling constants were confirmed by decoupling experiments and by examining the ^{1}H NMR spectrum of [5,7,7-$^2H_3$]naltrexone.

The C ring of spiro-α-methylene-γ-lactones **4a** and **5a** has the potential of undergoing chair to boat interconversion in solution and at the receptor sites. In the chair to boat conformational change, the terminal carbon of the α-methylene-γ-lactone ring is rotated through an arc of about 45° as measured from C-14 in Dreiding models. In the flattened chair conformation of **4a**, the terminal end of the exocyclic methylene group is located at a position relative to the aromatic ring, basic nitrogen atom, and C-14, that is not far from its location in the twist-boat conformation of **5a**. Since in the flattened chair conformation the terminal end of the electrophilic olefin **5a** is located at a position relative to the aromatic ring, basic nitrogen atom, and C-14 that cannot be accommodated by any C-ring conformation possible for **4a** and since only **5a** showed irreversible activity, it is suggested that the C ring of **5a** probably adopts a conformation at the receptor that is closely related to its conformation in solution. More information concerning structural requirements for interaction of electrophilic opioid ligands in opioid receptor preparations should be available with the design, synthesis, and testing of other conformationally defined systems.

(16) Brine, G. A.; Prakash, D.; Hart, C. K.; Kotchmar, D. J.; Moreland, C. G.; Carroll, F. I. *J. Org. Chem.* **1976**, *41*, 3445.
(17) Okuda, S.; Yamaguchi, S.; Kawazol, Y.; Tsuda, K. *Chem. Pharm. Bull.* **1964**, *12*, 104.
(18) Crouch, R. C.; Bhatia, A. V.; Lever, O. W., Jr. *Tetrahedron Lett.* **1983**, *24*, 4801.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 283 spectrometer. Absorptions are expressed in units of frequency (cm^{-1}). NMR spectra were routinely recorded on a Varian EM-360 spectrometer. Chemical shifts are expressed in parts per million (δ) relative to Me_4Si used as the internal standard and deuteriochloroform as solvent. High-resolution NMR spectra were recorded on a Bruker WM 500-MHz spectrometer. CI mass spectra were obtained on a VG-7070 mass spectrometer by direct insertion probe and using methane as the reagent gas. Optical rotations were measured on a JASCO-DIP-4 digital polarimeter. Analytical thin-layer chromatography (TLC) was performed on precoated plates (either Merck EM silica gel 60F-254 or Analtech silica gel HLF, 20 × 20 × 0.25 cm, glass support). Merck silica gel 60 (230–400 mesh) was used for preparative flash column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

4,5α-Epoxy-3,14-diacetoxy-6-oxo-17-(cyclopropylmethyl)-morphinan (6a). A solution of 1.54 g (4.50 mmol) of naltrexone (**1a**) in 20 mL of acetic anhydride was heated with stirring to 105 °C for 30 min under argon. The solvent was evaporated to give 1.92 g of a solid, which was recrystallized from dichloromethane/petroleum ether to afford 1.79 g (93%) of **6a**: mp 146–147 °C; ^{1}H NMR δ 6.60–7.00 (AB system, J = 8 Hz, 2 H, aromatic), 4.71 (s, 1 H, C5-H), 4.50 (d, J = 5 Hz, 1 H, C9-H), 2.33 (s, 3 H, C3-acetyl CH_3), 2.21 (s, 3 H, C14-acetyl CH_3); IR (KBr) 1765 (s, C3-acetyl C=O), 1725 cm^{-1} (s, C14-acetyl C=O).

4,5α-Epoxy-3,6α,14-trihydroxy-6β-(2-carboxyallyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (4a). A solution of 773 mg (4.32 mmol) of methyl α-(bromomethyl)acrylate in 8 mL of dry tetrahydruran was added over 20 min to a mixture of 1.53 g (3.60 mmol) of **6a** and 355 mg (5.40 mol, 20 mesh) of activated zinc in 9 mL of THF stirring at 40 °C uncer argon. Stirring was continued at 40–45 °C for 2.5 h. The solvent was evaporated, the residue was dissolved in dichloromethane and pH 7.5 phosphate buffer, and the pH was adjusted to 8.5. The mixture was extracted with of dichloromethane, and the combined extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to give 1.91 g of the crude 14-acetate ester of **4a** as a white solid. Purification by flash column chromatography on 80 g of silica gel (1:1 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 1.24 g of the 14-acetate ester of **4a**, which was shown to contain ca. 5% of starting material. Continued elution with ethyl acetate + 1% triethylamine afforded 91 mg (6%) of **4a**. The 14-acetate ester of **4a** was recrystallized from dichloromethane/petroleum ether to afford 1.04 g (64%) of 14-acetate ester of **4a**: mp 235–235.5 °C; $[\alpha]^{23}_D$ −152.0° ($CHCl_3$, c 1.0); CI mass spectrum, m/e (relative intensity) 452 (QM, 69), 392 (QM − HOAc, 16), 61 (100); IR (KBr) 1755 (s, lactone C=O), 1725 (s, C14-ester C=O); R_f value of 0.30 in this solvent system.

A solution of 1.10 g (2.44 mmol) of the 14-acetate ester of **4a** in 100 mL of methanol was heated with stirring to 45 °C for 20 h under argon. The solvent was evaporated, the residue was dissolved in dichloromethane and pH 9.0 phosphate buffer, and the pH was adjusted to 8.5. The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to give 1.00 g of the crude product. Purification by flash column chromatography (1:1 ethyl acetate/dichloromethane + 1% tirethylamine elutne) afforded 0.92 g (92%) of **4a**. Recrystallization from dichloromethane/diethyl ether/petroleum ether afforded 0.83 g

(83%) of **4a**: mp 209.5–210.5 °C; $[\alpha]^{23}_D$ −154.6° ($CHCl_3$, *c* 1.0); CI mass spectrum, *m/e* 410 (QM); 500-MHz ^1H NMR δ 6.207 (t, *J* = 2.9 Hz, 1 H, vinyl *E* proton), 5.617 (t, *J* = 2.5 Hz, 1 H, vinyl *Z* proton), 4.464 (s, 1 H, C5-H), 3.061 (dt, *J* = 2.5, 2.5, 17.5 Hz, 1 H, lactone C4 proton), 2.789 (dt, *J* = 3.0, 3.0, 17.0 Hz, 1 H, lactone C4 proton); IR (KBr) 1760 (s, lactone C=O); R_f 0.37 (98:2 ethyl acetate/triethylamine), naltrexone has an R_f value 0.38 in this solvent system; R_f 0.14 (9:1 ethyl acetate/methanol), naltrexone has an R_f value of 0.30 in this solvent. Anal. ($C_{24}H_{27}NO_5$) C, H, N.

4,5α-Epoxy-3,14-diacetoxy-6-oxo-17-(cyclopropylmethyl)morphinan (6b). A solution of 3.98 g (13.2 mmol) of oxymorphone (**1b**) in 80 mL of acetic anhydride was heated with stirring to 100 °C for 30 min under argon. The solvent was evaporated to give 5.10 g of a solid, which was recrystallized from dichloromethane/petroleum ether to afford 4.84 g (95%) of **6b**: mp 217.5–218.5 °C; ^1H NMR δ 6.60–7.00 (AM system, *J* = 8 Hz, 2 H, aromatic), 4.71 (s, 1 H, C5-H), 4.25 (d, *J* = 5 Hz, 1 H, C9-H), 2.33 (s, 6 H, C3-acetyl CH_3 and NCH_3), 2.20 (s, 3 H, C14-acetyl CH_3); IR (KBr) 1765 (s, C3-acetyl C=O), 1725 cm^{-1} (s, C14-acetyl C=O).

4,5α-Epoxy-3,6α,14-trihydroxy-6β-(2-carboxyallyl)-17-methylmorphinan γ-Lactone (4b). A solution of 2.57 g (14.3 mmol) of methyl α-(bromomethyl)acrylate in 20 mL of dry tetrahydrofuran was added over 25 min to a mixture of 4.60 g (11.9) mmol) of **6b** and 1.18 g (17.9 mol) of activated zinc in 35 mL of THF stirring at 43 °C under argon. Stirring was continued at 43 °C for 2.5 h. The solvent was evaporated, the residue was taken up in dichloromethane and pH 7.5 phosphate buffer, and the pH was adjusted to 8.5. The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, amd evaporated to give 5.97 go of the crude product. Purification by flash column chromatography twice on 100 g of silica gel (ethyl acetate + 1% triethylamine eluent) afforded 0.85 g (16%) of starting material **6b**, 2.88 g (58%) of the 14-acetyl ester of **4b**, and 0.50 g (11%) of **4b**. The crude 14-acetyl ester of **4b** was recrystallized from dichloromethane/petroleum ether to afford 2.15 g (49%) of the pure product: mp 228.5–230 °C; $[\alpha]_D^{23}$ −133.2° (CH_3OH, *c* 1.0); CI mass spectrum, *m/e* (relative intensity) 412 (QM, 100), 352 (67); ^1H NMR δ 6.50–6.90 (AB system, *J* = 8 Hz, 2 H, aromatic), 6.25 (t, *J* = 3 Hz, 1 H, vinyl *E* proton), 5.66 (t, *J* = 3 Hz, 1 H, vinyl *Z* proton), 5.30 (br s, 1 H, OH), 4.47 (s, 1 H, C5-H), 4.15 (d, *J* = 5 Hz, 1 H, C9-H), 2.32 (s, 3 H, NCH_3), (s, 3 H, C14-acetyl CH_3), 1.20–3.20 (m, 18 H); IR (KBr) 1760 (s, lactone C=O), 1730 (s, C14-acetyl C=O); R_f 0.52 (1:1 ethyl acetate/methanol). Oxymorphone has an R_f value of 0.30 in this solvent system.

A solution of 450 mg (1.09 mmol) of the 14-acetyl ester of **4b** in 25 mL of methanol was heated with stirring to 45 °C for 14 h under argon. The acetate salt of **4b** began to crystallize out of solution under these conditions. The solvent was evaporated, the residue was dissolved in dichloromethane and pH 7.5 phosphate buffer, and the pH was adjusted to 8.5. The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give 400 mg of the nearly pure α-methylene-γ-lactone **4b**: ^1H NMR δ 6.45–6.87 (AB system, *J* = 8 Hz, 2 H, aromatic), 6.19 (t, *J* = 3 Hz, 1 H, vinyl *E* proton), 5.60 (t, *J* = 3 Hz, 1 H, vinyl *Z* proton), 5.20 (br s, H, OH), 4.44 (s, 1 H, C5-H), 3.35 (s, 3 H, NCH_3). Compound **4b** (400 mg, 1.08 mmol) was dissolved in dichloromethane, heated to 40 °C with stirring, and crystallized by the addition of 90 mg (1.50 mmol) of acetic acid to afford 388 mg (83%) of the actate salt of **4b**; mp 233–234 °C; $[\alpha]^{23}_D$ −131.1° (CH_3OH, *c* 1.0); CI mass spectrum, *m/e* (relative intensity) 370 (QM); IR (KBr) 1760 (s), lactone C=O). Anal. ($C_{23}H_{27}NO_7$) C, H, N.

***O*^{3}-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,14-dihydroxy-6-oxo-17-(cyclopropylmethyl)morphinan (7a).** Sulfuryl chloride (1.29 mL, 16.0 mmol) was added rapidly to 40 mL of dry THF stirring at room temperature under argon, the temperature rising to 40–50 °C during the chlorination. After 15 min this reaction mixture was added simultaneously with a solution of 5.02 mL (36.0 mmol) of dry triethylamine in 5 mL of THF to a stirred solution of 3.42 g (10.0 mmol) of naltrexone (**1a**) in 20 mL of THF over 30 min at room temperature. The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue parrtitioned between dichloromethane and aqueous sodium carbonate. The organic layer was washed with brine, dried over potassium carbonate, and evaporated, affording 4.08 g (99%) of the diastereomeric mixture of 3-O-protected naltrexone **7a** as a white foam: ^1H NMR δ 5.80–6.07 (m, 1 H, THF methine proton).

***O*^{3}-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,14-dihydroxy-6-methylene-17-(cyclopropylmethyl)morphinan 6β-Oxide (8a).** Sodium hydride (1.15 g, 24.0 mmol, 50% mineral oil dispersion) was washed three times with 5-mL portions of dry hexanes under a positive pressure of argon. Trimethyloxosulfonium chloride (3.09 g, 24.0 mmol) and 35 mL of dry dimethyl sulfoxide were introduced, and the reaction mixture was stirred at room temperature for 30 min (until hydrogen evolution ceased). Compound **7a** (4.08 g, 9.91 mmol) in 20 mL of dry THF was added via a cannula with stirring over 10 min. Stirring was continued at room temperature for 1.5 h and then at 50 °C for 1 h. After cooling, 150 mL of water was added, and the mixture was extracted with dichloromethane. The organic extracts were washed with water and brine, dried over potassium carbonate, and evaporated, affording 4.11 g of the oxirane **8a** as a foam. Purification by flash column chromatography on 80 g of silica gel (1:2 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 4.03 g (95%) of **8a**: ^1H NMR δ 6.45–7.00 (AB system, *J* = 8 Hz, 2 H, aromatic), 5.73–6.00 (m, 1 H, THF methine proton), 4.90 (br s, 1 H, OH), 4.60 (s, 1 H, C5-H), 3.7–4.3 (m, 2 H, THF methylene proton).

4,5α-Epoxy-3,6β,14-trihydroxy-6α-methyl-17-(cyclopropylmethyl)morphinan (11). A solution of 851 mg (2.00 mmol) of **8a** in 60 mL of 1:1 acetic acid/methanol was heated with stirring to 55 °C for 20 h under argon. The solvent was evaporated, and the residue was taken up in aqueous disodium hydrogen phosphate and dichloromethane, and the pH was adjusted to 8.5. The reaction mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to give 701 mg of a solid, which was purified by flash column chromatography on 30 g of silica gel (1:1 ethyl acetate/dichloromethane + 1% triethylamine eluent) to afford 608 mg (85%) of **9**. Recrystallization from dichloromethane/petroleum ether afforded 562 mg (79%) of **9**, mp 184.5–185 °C.

A mixture of 130 mg (0.37 mmol) of 6-methylenenaltrexone 6β-oxide (**9**) and 30 mg (0.79 mmol) of lithium aluminum hydride in 7 mL of dry THF was heated with stirring to 50 °C for 2 h under argon. The solvent was evaporated and the residue was dissolved in dichloromethane and water, and the pH was adjusted to 8.5 with pH 7.5 aqueous phosphate buffer. The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to yield 127 mg of a solid. Recrystallization from dichloromethane/petroleum ether afforded 111 mg (84%) of 11: mp 207–209 °C; $[\alpha]^{23}_D$ −158.5° (CH_3OH, *c* 1.0); CI mass spectrum, *m/e* (relative intensity) 358 (QM, 100), 340 (19); ^1H NMR δ 4.34 (s, 1 H, C5-H), 1.27 (s, 3 H, $C6_{eq}$-CH_3); R_f 0.16 (98:2 ethyl acetate/triethylamine), naltrexone has an R_f value of 0.38 in this solvent system; R_f 0.16 (2:1 ethyl acetate/methanol), naltrexone has an R_f value of 0.31 in this solvent system. Anal. ($C_{21}H_{27}NO_4$) C, H, N.

***O*^{3}-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,14-dihydroxy-6-oxo-17-methylmorphinan (7b).** Sulfuryl chloride (1.31 mL, 16.4 mmo6) was added rapidly to 70 mL of dry THF stirring at room temperature under argon, the temperature rising to 40–50 °C during the chlorination. After 15 min this reaction mixture was added over 45 min to a mixture of 3.08 g (10.2 mmol) of oxymorphone and 7.07 mL (40.9 mmol) of *N,N*-diisopropylethylamine in 60 mL of THF stirring at −30 °C under argon. Hydrogen chloride gas was blown off with argon, and the temperature of the reaction mixture was allowed to rise to −15 °C. After 15 min the reaction was shown to be complete by thin-layer chromatography, and the solvent was evaporated. The reaction mixture was diluted with dichloromethane and pured into aqueous sodium carbonate. The mixture was extracted three times with 60 mL of dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, and evaporated, affording 3.69 g (97%) of the diastereomeric mixture of protected oxymorphones **7b** as a white foam; ^1H NMR δ 5.85–6.10 (m, 1 H, THF methine proton).

***O*^{3}-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,14-dihydroxy-6-methylene-17-methylmorphinan 6β-Oxide (8b).** Sodium hy-

dride (1.15 g, 24.0 mmol, 50% mineral oil dispersion) was washed three times with 5-mL portions of dry hexanes under a positive pressure of argon. Trimethyloxosulfonium chloride (3.09 g, 24.0 mmol) and 3.0 mL of dry dimethyl sulfoxide were introduced, and the reaction mixture was stirred under argon at room temperature for 30 min (until hydrogen evolution ceased). O^3-(2-Tetrahydrofuranyl)oxymorphone (**7b**; 3.69 g, 9.9 mmol) in 35 mL of dimethyl sulfoxide was added via cannula over 30 min. Stirring was continued at room temperature for 1.5 h and then at 50 °C for 1 h. After cooling, 150 mL of brine was added, and the mixture was extracted four times with 75 mL of dichloromethane. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to afford 3.74 g (97%) of the protected oxirane **8b** as a foam: ^{1}H NMR δ 5.76–6.03 (m, 1 H, THF methine proton).

4,5α-Epoxy-3,6α,14-trihydroxy-6β-methyl-17-(cyclopropylmethyl)morphinan (12). A solution of 472 mg (1.00 mmol) of O^3-[[β-(trimethylsilyl)ethoxy]methyl]naltrexone, prepared from naltrexone and [β-(trimethylsilyl)ethoxy]methyl chloride, in 3 mL of dry THF was added over 5 min via cannula to a solution of 1.58 mL (1.39 M in diethyl ether, 2.20 mmol) of methyllithium in 4 mL of tetrahydrofuran stirring at −78 °C under argon. The reaction mixture was stirred at −78 °C for 1.5 h, warmed to −10 °C over 30 min, and poured into pH 7.5 aqueous phosphate buffer. The mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, and evaporated to 495 mg of a colorless solid, which appeared homogeneous by thin-layer chromatography and was deprotected: ^{1}H NMR δ 4.35 (s, 1 H, C5-H), 1.35 (s, 3 H, C_{6ax}-CH_3).

A mixture of 495 mg of the crude product and 2.00 mL (1 M in THF, 2.00 mmol) of tetra-*n*-butylammonium fluoride was stirred at 35 °C for 3 days under argon. The reaction mixture was diluted with dichloromethane and water, the pH was adjusted to 8.5, and the mixture was extracted with dichloromethane. The combine extracts were washed with brine, dried over magnesium sulfate, and evaporated to give 393 mg of the crude product. Purification by flash column chromatography on 25 g of silica gel (ethyl acetate + 1% triethylamine eluent) afforded 291 mg of a solid, which was recrystallized from dichloromethane/petroleum ether to afford 233 mg (65%) of **12**: mp 178–179 °C; $[\alpha]^{23}_D$ −178.5° (CH_3OH, *c* 1.0); CI mass spectrum, *m/e* (relative intensity) 358 (QM, 64) 340 (QM − H_2O, 100); ^{1}H NMR δ 4.34 (s, 1 H, C5-H), 1.34 (s, 3 H, C_{6ax}-CH_3); R_f 0.18 (98:2 ethyl acetate/triethylamine), naltrexone as an R_f value of 0.38 in this solvent system; R_f 0.19 (2:1 ethyl/methanol), naltrexone has an R_f value of 0.31 in the solvent system. Anal. ($C_{21}H_{27}NO_4$) C, H, N.

O^3-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,6β,14-trihydroxy-6α-(2-carboxy-3-oxobutyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (10a). Sodium hydride (0.96 g, 20.0 mmol, 50% mineral oil dispersion) was washed three times with 5-mL portions of dry hexanes under a positive pressure of argon. Dry dioxane (15 mL) was added followed by 2.68 mL (21.0 mmol) of ethyl acetoacetate. After the mixture was stirred at room temperature for 5 min (hydrogen evolution ceased), 4.03 g (9.47 mmol) of **8a** in 25 mL of dioxane was added, and the reaction mixture was heated to reflux with stirring for 20 h under argon. The reaction mixture was cooled, the solvent was evaporated, and the mixture was dissolved in dichloromethane, washed with aqueous sodium carbonate and brine, dried over magnesium sulfate, and evaporated, affording 5.79 g of the crude product. Purification by flash column chromatography on 80 g of silica gel (1:2 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 3.14 g (65%) of **10a** as a foam, preceded by a small amount of the unreacted oxirane **8a**: ^{1}H NMR δ 6.55–7.10 (AB system, 2 H, aromatic), 5.75–6.10 (m, 1 H, THF methine proton), 4.72 and 4.74 (2 s, 1 H, C5-H), 3.6–4.3 (m, 3 H, THF methylene protons and lactone C2 proton), 2.40 (s, 3 H, CH_3CO); IR (film) 1765 (s) 1720 (s) cm^{-1}.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxyallyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (5a). To 1.29 mL (9.18 mmol) of diisopropylamine in 10 mL of dry THF was added 4.45 mL (7.34 mmol) of a 1.65 M solution of *n*-butyllithium over 10 min while stirring at −20 °C under argon. The solution of lithium diisopropylamide was stirred at 0 °C for 15 min and cooled to −78 °C, and 3.12 g (6.12 mmol) of **10a** in 30 mL of THF was added over 20 min. Stirring was continued at −78 °C for 10 min, the cooling bath was removed, and 1.05 g (35.0 mmo6) of paraformaldehyde was added. The reaction mixture was stirred at room temperature for 1 h and heated to reflux for 4 h. After cooling, the solvent was evaporated and the residue was taken up in dichloromethane. The extract was wahsed with water and brine, dried over magnesium sulfate, and evaporated to give 3.07 g of the crude THF-protected lactone. Purification by flash column chromatography on 80 g of silica gel (1:2 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 2.19 g (75%) of the THF-protected derivative of **5a**.

A solution of 2.18 g (4.55 mmol) of **5a** in 150 mL of 1:1 acetic acid/methanol was heated with stirring to 55 °C for 20 h under argon. The solvent was evaporated and the residue was taken up in aqueous disodium hydrogen phosphate and dichloromethane, and the pH was adjusted to 8.5. The reaction mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over magnesium sulfate, and evaporated to give 1.87 g of a solid, which was purified by flash column chromatography on 80 g of silica gel (1:1 ethyl acetate/dichloromethane + 1% triethylamine eluent) to yield 1.69 g of **5a**. Recrystallization from dichloromethane/hexanes afforded 1.61 g (86%) of **5a**: mp 200–201.5 °C; $[\alpha]^{23}_D$ −146.2° (CH_3OH, *c* 1.0); CI spectrum, *m/e* (relative intensity) 410 (QM); 500-MHz ^{1}H NMR δ 6.123 (t, *J* = 2.6 Hz, 1 H, vinyl *E* proton), 5.477 (t, *J* = 2.2 H, 1 H, vinyl *Z* proton), 4.832 (s, 1 H, C5-H), 2.459 (dt, *J* = 13.5, 13.5, 2.5 Hz, 1 H, C7-βH), 2.641 [dt, *J* = 2.5, 2.5, 17.0 Hz, 1 H, lactone C4 syn (Ar ring) proton], 2.172 [dt, *J* = 2.3, 2.3, 16.9 Hz, 1 H, lactone C4 anti (Ar ring) proton], 1.662 [dt, *J* = 13.5, 4.0, 2.5, 1 H, C8-βH], 1.560 [dt, *J* = 13.5, 4.0, 2.5 Hz, 1 H, C8-αH], 1.334 [dt, *J* = 13.5, 13.5, 2.5 Hz, 1 H, C8-αH]; IR (KBr) 1760 (s, lactone C=O); R_f 0.42 (98:2 ethyl acetate/triethylamine), naltrexone has an R_f value of 0.38 in this solvent system; R_f 0.32 (2:1 ethyl acetate/methanol), naltrexone has an R_f value of 0.31 in this solvent system. Anal. ($C_{24}H_{27}NO_5$) C, H, N.

O^3-(2-Tetrahydrofuranyl)-4,5α-epoxy-3,6β,14-trihydroxy-6α-(2-carboxy-3-oxobutyl)-17-(cyclopropylmethyl)morphinan γ-Lactone (10b). Sodium hydride n(0.82 g, 17.1 mmol, 50% mineral oil dispersion) was washed four times with 5-mL portions of dry hexanes under an atmosphere of argon. Dry dioxane (30 mL) was added followed by 2.40 mL (18.8 mmol) of ethyl acetoacetate. After the mixture was stirred at room temperature for 5 min (hydrogen evolution ceased), 3.30 g (8.56 mmol) of oxide **8b** in 30 mL of dioxane was added, and the reaction mixture was heated to reflux with stirring for 30 h. The reaction mixture was cooled, the solvent was evaporated, and the mixture was dissolved in dichloromethane, washed with aqueous sodium carbonate and brine, dried over magnesium sulfate, and evaporated, affording 5.17 g of the crude product. Purification by flash column chromatography on 80 g of silica gel (1:1 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 2.55 g (63%) of **10** as a foam: ^{1}H NMR δ 6.55–7.10 (AB system, *J* = 8 Hz, 2 H, aromatic), 5.75–6.10 (m, 1 H, THF methine proton), 4.73 and 4.75 (2 s, 1 H, C5-H), 3.6–4.3 (m, 3 H, THF methylene proton and lactone C-3 proton), 2.42 (s, 6 H, CH_3C and NCH_3); IR (film) 1765 (s), 1715 (s) cm^{-1}.

4,5α-Epoxy-3,6β,14-trihydroxy-6α-(2-carboxyallyl)-17-methylmorphinan γ-Lactone (5b). To 11.2 mL (7.98 mmol) of diisopropylamine in 10 mL of dry THF was added 3.87 mL (6.38 mmol) of a 1.65 M solution of *n*-butyllithium over 10 min while stirring at −20 °C under argon. The solution of lithium diisopropylamide was stirred at 0 °C for 15 min and cooled to −78 °C, and 2.50 g (5.32 mmol) of **10** in 20 mL of THF was added over 15 min. Stirring was continued at −78 °C for 10 min, the cooling bath was removed, and 0.75 g (25.0 mmol) of paraformaldehyde was added. The reaction mixture was stirred at room temperature for 1 h and heated to reflux for 4 h. After cooling, the solvent was evaporated and the residue was taken up in dichloromethane. The organic solution was washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to give 2.41 g of the crude THF-protected lactone. Purification by flash column chromatography on 80 g of silica gel (1:1 ethyl acetate/dichloromethane + 1% triethylamine eluent) afforded 1.77 g (76%) of the THF-protected derivative of **5b**.

A solution of 1.76 g (4.00 mmol) of the THF-protected derivative of **5b** in 100 mL of 1:1 acetic acid/methanol was heated with stirring to 55 °C for 24 h under argon. The solvent was evaporated

and the residue was taken up in 120 mL of water. The aqueous solution was washed three times with 40 mL of dichloromethane. The aqueous phase was stirred over 120 mL of dichloromethane, and the pH was adjusted to 8.5 with aqueous disodium hydrogen phosphate and sodium carbonate at 0 °C. The mixture was extracted four times with 120 mL of dichloromethane and washed with brine, and the combined extracts were dried over magnesium sulfate and evaporated to give 1.50 g of product. Purification by flash column chromatography on 80 g of silica gel (ethyl acetate + 1% triethylamine eluent) afforded 1.35 g of **5b**. Recrystallization from dichloromethane/hexanes afforded 1.26 g (85%) of **5b**: mp 221.5–222 °C; $[\alpha]^{23}_D$ −128.5° (CH_3OH, *c* 1.0); EI mass spectrum, *m/e* (relative intensity) 369.1572 (calcd 369.1568); ^1H NMR δ 6.50–6.90 (AB system, J = 8 Hz, 2 H, aromatic), 6.30 (br s, 2 H, OH), 6.12 (t, J = 3 Hz, 1 H, vinyl *E* proton), 6.50 (t, J = 2 Hz, 1 H, vinyl *Z* proton), 4.80 (s, 1 H, C5-H), 1.00–3.35 (m, 16 H), 2.38 (s, 3 H, NCH_3); IR (KBr) 1760 (s, lactone C=O); R_f 0.35 (98% ethyl acetate + 2% triethylamine, two elutions), oxymorphone has an R_f value of 0.26 in this solvent system. Anal. ($C_{21}H_{23}NO_5$) C, H, N.

Opioid Receptor Binding. [^{3}H]Naltrexone (9.8 Ci/mmol) and unlabeled naltrexone were generously supplied by Dr. Richard Hawks of the National Institute of Drug Abuse. [^{3}H-D-Ala-D-Leu]enkephalin (^{3}H-DADLE) (41 Ci/mmol) and [^{3}H]bremazocine (25 Ci/mmol) were purchased from New England Nuclear and [^{3}H-D-Ala^2-MePhe^4-Gly-ol^5]enkephalin (^{3}H-DAGO) (34 Ci/mmol) from Amersham.

Male Sprague–Dawley rats were decapitated, and a crude membrane fraction was prepared from the brains (minus the cerebellum) by a method previously described.[19] The membrane preparation (1:6 w/v) was stored in 0.32 M sucrose at −70 °C until needed. For binding assays the thawed membrane preparations were diluted with 9 volumes of 50 mM Tris buffer, pH 7.4, 1 mM potassium EDTA ± 100 mM NaCl.

Specific binding on control and treated samples was assayed on duplicate 2-mL samples as previously described.[20] Samples were incubated with ^{3}H opioid ± 1 μM unlabeled drug for 45 min at 25 °C and then filtered through GF/B filters. Filters were rinsed twice with 4 mL of buffer, dried, and counted in a toluene-based scintillation cocktail.

Irreversibility of Opioid Receptor Binding. Membrane preparations were incubated with the drug to be tested for 45 min at 25 °C. After incubation, treated membranes were diluted sixfold with 50 mM Tris buffer, pH 7.4, 1 mM potassium EDTA ± 100 mM NaCl and centrifuged for 15 min at 20000*g*. After the supernatant was removed, the pellet was resuspended in 3 times the original volume and incubated at 37 °C for 15 min. Samples were then spum again as above and finally resuspended in the original volume. In a few experiments, additional washes were done to show that the recovery of binding capacity reached a plateau. When a compound showed some degree of irreversibility, the ability of naltrexone to protect against inactivation was also examined. Fractions were preincubated 10–15 min at 25 °C with naltrexone before addition of the potential label.

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Registry No. **1a**, 16590-41-3; **1b**, 76-41-5; **4a**, 92398-20-4; 14-Ac-**4a**, 92398-21-5; **4b**, 92398-22-6; 14-Ac-**4b**, 92398-23-7; **4b**·AcOH, 92398-24-8; **5a**, 92398-30-6; THF-**5a**, 92398-34-0; **5b**, 92398-32-8; THF-**5b**, 92398-35-1; **6a**, 92398-19-1; **6b**, 64643-76-1; **7a**, 92398-25-9; **7b**, 92398-27-1; **8a**, 92398-26-0; **8b**, 92398-28-2; **9**, 92398-17-9; **10a**, 92398-29-3; **10b**, 92398-31-7; **11**, 92398-18-0; **12**, 55096-33-8; methyl α-(bromomethyl)acrylate, 4224-69-5; trimethyloxosulfonium chloride, 5034-06-0; O^3-[[β-(trimethylsilyl)ethoxy]methyl]naltrexone, 92398-33-9; O^3-[[β-(trimethylsilyl)ethoxy]methyl]-4,5α-epoxy-3,6α,14-trihydroxy-6β-methyl-17-(cyclopropylmethyl)morphinan, 92398-36-2.

(19) Lin, H. K.; Simon, E. J. *Nature (London)* **1978**, 383.

(20) Simon, E. J.; Hiller, J. M.; Edelman, I. Proc. *Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1947.

1-Aryl-3,3-dimethyltriazenes: Potential Central Nervous System Active Analogues of 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC)

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A series of 19 aryldimethyltriazenes were synthesized as potential central nervous system (CNS) active analogues of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC). The compounds were screened in mice against both intraperitoneally (ip) and intracerebrally (ic) implanted L1210 leukemia. Select compounds were further screened against ic implanted ependymoblastoma, and one compound was additionally screened against ic implanted B16 melanoma. Although several compounds were as effective as DTIC at prolonging the life span of mice bearing ip implanted L1210 leukemia, only 4-(3,3-dimethyl-1-triazeno)benzamide (DTB) and 4-(3,3-dimethyl-1-triazeno)benzoic acid (DTBA) were significantly active against the ic implanted tumor. DTB, unlike DTIC, was equally effective against both the ip and the ic implanted tumor, clearly indicating that it penetrated into the CNS in therapeutic concentration. DTB was also active against ic implanted ependymoblastoma and ic implanted B16 melanoma. Aryldimethyltriazenes, particularly DTB, may have a role in the treatment of tumors metastatic to the CNS. They may also be effective against primary brain tumors.

DTIC [5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, imidazole carboxamide, Dacarbazine, DIC, NSC 45388] is the most active single agent in the palliative management of human disseminated malignant melanoma.[1-3] However, it is usually not effective either in the therapy or the prophylaxis of cerebral metastases of this tumor.[2,3] In fact, patients with melanoma undergoing chemotherapy with DTIC, or a DTIC-containing regimen, frequently relapse in the CNS while their peripheral tumor is under good control.[2] Paradoxically, the patients at greatest risk from CNS relapse are those who respond best to chemotherapy. Although comprehensive tissue distribution studies of DTIC have not been reported in man, it seems likely that the poor responsiveness of cerebral tumors to the drug is due to its limited ability to penetrate into the CNS after parenteral administration. Low CNS

(1) Carter, S. K.; Freidman, M. A. *Eur. J. Cancer* **1972**, *8*, 85.
(2) Einhorn, L. H.; Burgess, M. A.; Vallejos, C.; Bodey, G. P.; Gutterman, J.; Mavligit, G.; Hersch, E. M.; Luce, J. K.; Frei, E.; Freireich, E. J.; Gottlieb, J. A. *Cancer Res.* **1974**, *34*, 1995.
(3) Comis, R. L. *Cancer Treat. Rep.* **1976**, *60*, 165.

0022-2623/84/1827-1723$01.50/0