the addition of CH_3CN: mp 240–250 °C dec; ^1H NMR (D_2O) δ 4.11 (s, 2 H, CH_2O), 4.27 (s, 2 H, CH_2O), 4.40 (br m, 2 H, CH_2N), 5.73 (t, 1 H, J = 8 Hz, =C*H*), 7.73 (s, 1 H, H-8); FAB mass spectrum (glycerol), m/z (relative intensity) 252 (MH^+, 79), 152 (b + 2 H, 45). Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

Acknowledgment. We express our gratitude to Dr. James A. Kelley, LMC, NCI for mass spectral determinations, to Robert I. Glazer, Laboratory of Biological Chemistry, NCI for the AdoHcy-ase inhibition studies, and to Wen-Jee Lee for exemplary technical assistance during the summer of 1985. We thank Drs. Gussie Arnett and William M. Shannon of the Southern Research Institute, Birmingham, AL, who performed the viral inhibition studies under contract to the National Cancer Institute. Support for an early sabbatical leave for David R. Haines came through an Intergovernmental Personnel Agreement (IPA) between Wellesley College and the National Cancer Institute. Special thanks are due to Dr. John S. Driscoll for arranging the IPA appointment and for helpful discussions and support.

Registry No. **5**, 99776-28-0; **6**·HCl, 107053-43-0; **10**, 77356-14-0; **11**, 107053-40-7; **12**, 107053-41-8; **13**, 99776-39-3; **14**, 107053-42-9; **15**, 10310-21-1; **16**, 99796-40-4; **17a**, 107053-44-1; **17b**, 107053-45-2; triethyl phosphonoacetate, 867-13-0; adenine, 73-24-5.

Hexahydro-1*H*-1-pyrindines from Acid Rearrangement of 9-Alkylidene-5-(*m*-methoxyphenyl)-2-methylmorphans. A New Structural Type of Narcotic Antagonists

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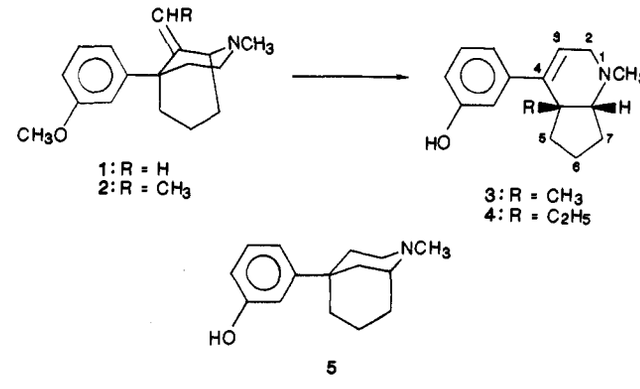
9-Methylene- and 9-ethylidene-5-(*m*-methoxyphenyl)-2-methylmorphans (1, 2) and refluxing 48% HBr have given rearrangement products 3 and 4, respectively. The structure of 4 [4a-ethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-1-pyrindine] was determined by X-ray crystallography and that of 3 [1,4a-dimethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-pyrindine] follows from analogy and NMR data. Compounds 3 and 4 are opioid antagonists of about the potency of nalorphine in the tail-flick vs. morphine assay and precipitate a complete abstinence syndrome in morphine-dependent monkeys. Both are nearly devoid of antinociceptive activity and they have about 0.025 times the affinity of nalorphine for the μ opioid receptor.

5-(*m*-Hydroxyphenyl)-2-methylmorphan[1,2] (5) (a flexible molecule compared with morphine) and its optical isomers[3] have strong antinociceptive properties. The (−)-isomer will not substitute for morphine in dependent monkeys and in fact, like nalorphine and related antagonists, precipitates a strong withdrawal syndrome[3-5] but binds weakly to μ receptors.[4] Addition of a 9-methyl substituent to 5 virtually abolishes antinociceptive activity and induces properties of antagonism to the molecule.[4] It seemed of interest to "freeze" the (equatorial) phenyl substituent of 5 to the cyclohexane ring in order to provide a more rigid structure. Synthesis and biological study of several derivatives of 5, in which the *m*-hydroxyphenyl substituent is conformationally restricted by oxide bridging to the morphan moiety, have been described.[6-10] Attempts to bridge the phenyl and cyclohexane rings of 9-methylene- and 9-ethylidene-5-(*m*-methoxyphenyl)-2-methylmorphans (1, 2) gave rearrangement products 3 and 4. The constitution and some biological properties of 3 and 4 are described herein.

Chemistry. On treatment of 5-(*m*-methoxyphenyl)-9-methylene-2-methylmorphan (1)[4] with boiling 48% HBr, contraction of the cyclohexane ring occurred, giving the hexahydro-1*H*-pyrindine (3) instead of the desired fusion of the 9-methylene carbon to the benzene ring (Scheme I). The same type of rearrangement occurred with the 9-ethylidene homologue (2), giving 4, despite the presumed hyperconjugative–inductive effect of the ethylidene group of 2.[11]

Scheme I



The structure of 4 was determined by X-ray crystallography of the hydrobromide salt. NMR and mass

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Table I. Antinociceptive Agonist and Antagonist Action and Receptor-Binding Affinity of 4a-Methyl- and 4a-Ethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-1-pyrindines (**3** and **4**, Respectively)

compound	antinociceptive act.: ED50, mg/kg sc, or % effect[a]			antagonist act. vs. morphine: AD50, mg/kg sc, TF vs. M	inhibn constant:[b] K_i,[c] nM
	TF	PPQ	hot plate		
3	I	I	40% at 50	1.7 (0.5-6.0)[d]	81
4	I	35.5 (22.5-56.7)[d]	I	2.1 (1.2-3.7)[d]	84
nalorphine hydrochloride	I	0.6 (0.3-1.4)[d]	9.9 (5.7-17.1)[d]	2.6 (0.7-9.8)[d]	2

[a] I means inactive at 1, 10, or 30.0 mg/kg. The antinociceptive and antagonist activity were determined in mice. [b] Displacement of [^{3}H]DAGO from rat brain. The K_i values were calculated from the Cheng and Prussoff equation (see ref 22). [c] Average of three experiments run in duplicate. [d] 95% confidence limits.

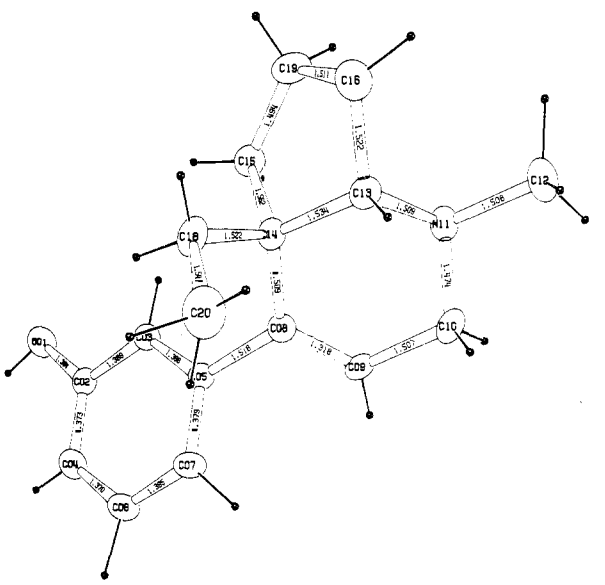

Figure 1. Observed crystal conformation and bond lengths of 4·HBr.

spectral data were accommodative of **4**. By analogy and on the basis of spectral data, the product from **2** was assigned the structure **3**. Both **3** and **4** sluggishly absorbed 1 equiv of platinum-catalyzed hydrogen, characteristic of a styrene-type of double bond.

Results of X-ray Structural Determination. The observed crystal conformation is depicted in Figure 1.[12] The final atomic parameters for the heavier atoms of 4·HBr are given in Table II and the molecular dimensions in Table III.

The aromatic ring is not coplanar with the C(08)–C(09) double bond but is skewed with a C(07)–C(06)–C(08)–C(09) torsion angle of 46.3 (7)°. The five- and six-membered rings are cis-fused, and the six-membered ring has the usual monoplanar conformation, long recognized as the most stable in the cyclohexene molecule.

Pharmacology and Receptor-Binding Studies. Antinociceptive activity was determined by the tail-flick (TF),[13] *p*-phenylquinone-writhing (PPQ),[13] and hot-plate (HP)[14] tests in mice. Opioid antagonist activity vs. morphine was determined in the TF antagonism (TF vs. M)[13] test (mice) and in morphine-dependent rhesus monkeys.[5] Antinociceptive and narcotic antagonist results for rearrangement products **3** and **4** and a standard (nalorphine hydrochloride) are given in Table I. Both **3** and **4** were devoid of, or showed very weak, antinociceptive activity; the ethyl compound (**4**) was slightly more potent than the

Table II. Final Atomic Parameters for the Heavier Atoms[a]

atom	x	y	z	U_{eq}
Br	12210 (4)	-18830 (8)	-7599 (4)	537 (2)
O(1)	146 (3)	2169 (6)	2459 (3)	602 (15)
C(2)	716 (3)	725 (7)	2507 (4)	424 (18)
C(3)	1171 (4)	452 (7)	3302 (4)	404 (17)
C(4)	874 (4)	-375 (8)	1793 (4)	512 (21)
C(5)	1777 (3)	-964 (7)	3393 (3)	387 (16)
C(6)	1479 (4)	-1760 (9)	1884 (4)	581 (21)
C(7)	1936 (4)	-2078 (8)	2678 (4)	554 (21)
C(8)	2325 (3)	-1252 (6)	4233 (3)	360 (17)
C(9)	3196 (4)	-1454 (7)	4170 (4)	395 (18)
C(10)	3807 (4)	-1811 (9)	4950 (4)	491 (20)
N(11)	3393 (3)	-1190 (6)	5777 (3)	423 (15)
C(12)	4013 (5)	-1609 (9)	6543 (5)	625 (24)
C(13)	2473 (4)	-1996 (8)	5874 (4)	466 (18)
C(14)	1859 (3)	-1390 (6)	5110 (3)	378 (18)
C(15)	1503 (4)	473 (8)	5452 (4)	494 (21)
C(16)	2010 (5)	-1334 (12)	6705 (5)	759 (30)
C(18)	1087 (4)	-2726 (7)	5025 (4)	457 (21)
C(19)	1539 (5)	411 (11)	6439 (5)	672 (28)
C(20)	1325 (6)	-4690 (9)	4749 (7)	705 (35)

[a] Positional parameters are multiplied by 10 000 and an additional factor of 10 has been applied to the Br positional parameters. The equivalent U values are the harmonic means of diagonal terms of the vibration tensors.

Table III. Bond Distances (Å) and Angles (deg)

Bond Distances			
O(1)-C(2)	1.364 (6)	C(2)-C(3)	1.389 (7)
C(2)-C(4)	1.373 (8)	C(3)-C(5)	1.388 (7)
C(4)-C(6)	1.370 (9)	C(5)-C(7)	1.379 (7)
C(5)-C(8)	1.518 (6)	C(6)-C(7)	1.395 (8)
C(8)-C(9)	1.318 (7)	C(8)-C(14)	1.509 (7)
C(9)-C(10)	1.507 (8)	C(10)-N(11)	1.474 (7)
N(11)-C(12)	1.507 (8)	N(11)-C(13)	1.509 (7)
C(13)-C(14)	1.534 (7)	C(13)-C(16)	1.521 (9)
C(14)-C(15)	1.562 (7)	C(14)-C(18)	1.522 (7)
C(15)-C(19)	1.494 (9)	C(16)-C(19)	1.517 (11)
C(18)-C(20)	1.547 (9)		

Bond Angles			
O(1)-C(2)-C(3)	117.4 (4)	O(1)-C(2)-C(4)	122.1 (4)
C(3)-C(2)-C(4)	120.5 (5)	C(2)-C(3)-C(5)	120.6 (4)
C(2)-C(4)-C(6)	118.7 (5)	C(3)-C(5)-C(7)	119.1 (4)
C(3)-C(5)-C(8)	122.3 (4)	C(7)-C(5)-C(8)	118.4 (4)
C(4)-C(6)-C(7)	121.9 (5)	C(5)-C(7)-C(6)	119.2 (5)
C(5)-C(8)-C(9)	118.7 (4)	C(5)-C(8)-C(14)	119.6 (4)
C(9)-C(8)-C(14)	121.6 (4)	C(8)-C(9)-C(10)	123.7 (4)
C(9)-C(10)-N(11)	110.6 (4)	C(10)-N(11)-C(12)	109.1 (4)
C(10)-N(11)-C(13)	110.8 (4)	C(12)-N(11)-C(13)	113.6 (4)
N(11)-C(13)-C(14)	110.6 (4)	N(11)-C(13)-C(16)	112.4 (4)
C(14)-C(13)-C(16)	104.7 (4)	C(8)-C(14)-C(13)	113.8 (4)
C(8)-C(14)-C(15)	113.3 (4)	C(8)-C(14)-C(18)	109.2 (4)
C(13)-C(14)-C(15)	102.1 (4)	C(13)-C(14)-C(18)	108.8 (4)
C(15)-C(14)-C(18)	109.4 (4)	C(14)-C(15)-C(19)	107.2 (5)
C(13)-C(16)-C(19)	105.5 (5)	C(14)-C(18)-C(20)	116.7 (5)
C(15)-C(19)-C(16)	107.6 (5)		

(11) It was hoped that in **2** this effect would be sufficient to give a carbonium ion favorable for cyclization.

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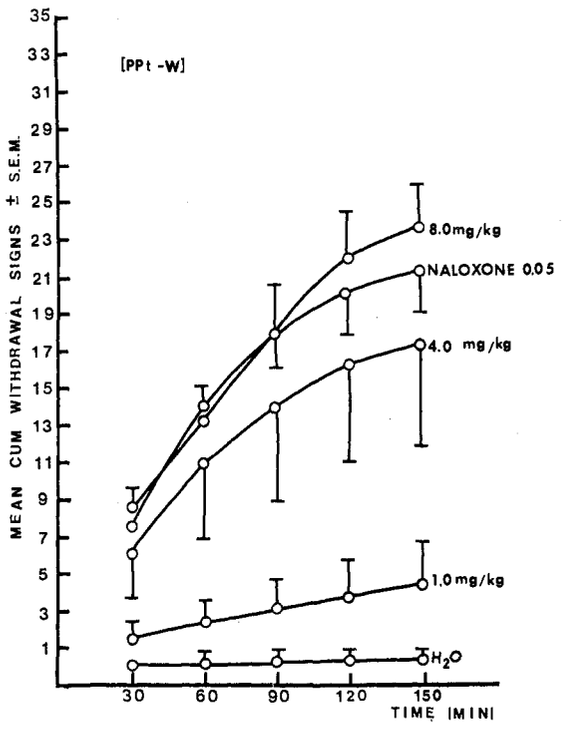

Figure 2. Antagonist action of **3** in morphine-dependent rhesus monkeys. Data for positive control (naloxone) and vehicle control (H_2O) are also included.

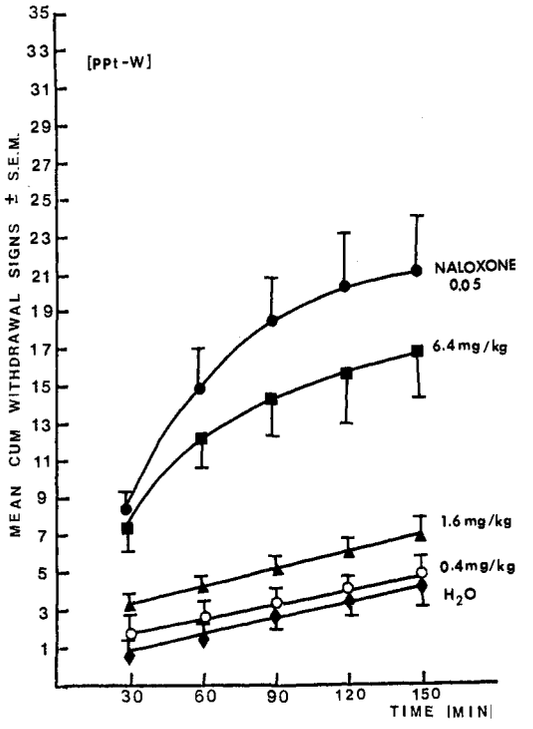

Figure 3. Antagonist action of **4** in morphine-dependent rhesus monkeys. Data for positive control (naloxone) and vehicle control (H_2O) are also included.

lower homologue (**3**) in the PPQ test. Both were as potent as nalorphine as narcotic antagonists in the TF vs. M assay.

As shown in Figures 2 and 3, both **3** and **4** precipitated withdrawal with onset and duration of actions similar to those of the reference compound, naloxone. They were estimated to be less than $^1/_{100}$ as potent as naloxone.

The profile of activity of **3** and **4** closely resembles that of the racemic and (−)-2,9-dimethyl-5-(*m*-hydroxyphenyl)morphans.[4] To our knowledge, such activity (nearly pure opioid antagonism) has not been observed before for the hexahydro-1*H*-1-pyrindine ring system. Zimmerman and colleagues[15] did, however, report pure (fairly strong) antagonism for certain 3-methyl-substituted *N*-methyl-4-(*m*-hydroxylphenyl)piperidines. Compounds **3** and **4** can be viewed as unsaturated 3-alkyl-substituted 4-(*m*-hydroxyphenyl)piperidines. From that viewpoint, the Zimmerman et al. piperidines and the pyrindines **3** and **4** may be bioisosteric in their narcotic antagonist properties.

As noted in Table I, compounds **3** and **4** were both found to have about 0.025 times the affinity of nalorphine for the μ opioid receptor, as defined by their displacement of [^{3}H]DAGO ([D-Ala^2-MePhe^4-Gly-ol]enkephalin) from homogenized rat brain minus cerebellum. Their affinity for the μ opioid receptor is clearly significantly less than would be predicted from the in vivo data in Table I (tail-flick vs. morphine assay). Either these compounds manifest their narcotic antagonist activity through other opioid receptors or their metabolism and/or transport to the central nervous system is considerably different from that of the 4,5-epoxymorphinans exemplified by nalorphine.

While Pert and Snyder[16] have noted that narcotic agonists display lower affinities for opioid receptors in the presence of Na^+, more recent work[17] has shown that the affinity of opioid ligands in the presence of Na^+ may not be predictive of their agonist or antagonist actions in vivo. However, in agreement with the in vivo data, the affinities of **3** and **4** were not significantly effected by Na^+, while a standard narcotic agonist, codeine, had a 1.8-fold reduction in affinity in the presence of Na^+. These binding studies were run in 5 mM Tris buffer with and without 50 mM NaCl. Naloxone, a pure narcotic antagonist, showed marginally greater affinity for the opioid receptors in the presence of Na^+ (the experiments with and without Na^+ in Tris buffer are not shown in Table I).

Experimental Section

Melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. IR spectra (Beckman Acculab 8 instrument) are consistent with the structures shown. NMR data were obtained with a 60-MHz Hitachi Perkin-Elmer Model R-24 and a Varian HR-220 MHz spectrometer. Electron-ionization (EIMS) mass spectra and analytical data are from the Laboratory of Analytical Chemistry, (Dr. David Johnson, Chief), National Institutes of Health. C, H, N values are within 0.4% of theory.

1,4a-Dimethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-1-pyrindine (3). Compound 1[4] (0.6 g, 2.3 mmol) and 10 mL of 48% HBr were refluxed for 12 h, cooled, poured into ice–H_2O (50 mL), made alkaline with NH_4OH, and extracted with three 60-mL portions of CH_2Cl_2–EtOH (10:1). The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated, giving 0.56 g (99%) of **3**, which was recrystallized from Me_2CO: mp 153.5–154.5 °C; IR (KBr) 1100, 1075, 990 cm^{-1}, ($CHCl_3$) 1089, 1008 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3 H, s, CCH_3), 1.30–1.98 (6 H, m), 2.30 Hz (3 H, s, NCH_3), 2.66 (1 H, dd, J = 7, 7 Hz, C-7a H), 2.91–3.14 (2 H, sym m, C-2 H), 5.36 (1 H, dd, J = 3, 3 Hz, C-3 H), 6.45–6.61 (3 H, m, Ar H), 6.93 (1 H, dd, J = 7, 7 Hz, Ar H); EIMS, m/e 243 (M^+). Anal. ($C_{16}H_{21}NO$) C, H, N.

4a-Ethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-1-pyrindine (4). To a stirred mixture of 99% NaH

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(0.35 g, 14.5 mmol) and 10 mL of dry Me_2SO was added dropwise 5.0 g (13.5 mmol) of ethyltriphenylphosphonium bromide in 20 mL of Me_2SO during 20 min (at room temperature, N_2 atmosphere). After 20 min (stirring), 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan[1,2] (1.75 g, 6.7 mmol) in 10 mL of dry Me_2SO was added dropwise during 10 min. The mixture was stirred for 6 h at 40–50 °C, poured into 50 mL of saturated brine, and extracted four times with a total of 75 mL of Et_2O. The extracts were washed with brine and then shaken with 30 mL of 1 N HCl in four portions. The HCl extracts were washed with Et_2O, made alkaline with dilute NH_4OH, treated with 0.1 g of NH_4Cl, and extracted with Et_2O (50 mL in four portions). The extracts were washed with brine, dried (Na_2SO_4), and evaporated, giving 1.8 g of an oil: NMR ($CDCl_3$) δ 0.76 (3 H, d, J = 8 Hz, CCH_3), 2.45 (3 H, s, OMe), 5.30 (1 H, q, J = 8 Hz, C=CH).

This oil (**2**, 1.44 g) and 10 mL of 48% HBr were refluxed for 13 h, cooled, made alkaline with NH_4OH, and extracted with 75 mL of Et_2O in four portions. The Et_2O extracts were washed with H_2O, dried, and evaporated, giving 1.2 g of oil, which was distilled in vacuo (160 °C (0.5 mm)) to yield **4** as a viscous distillate: 0.66 g (38%); IR (Nujol) 3215 cm^{-1} (*m*-OH).

The HBr salt (HBr gas, EtOH) was recrystallized from MeOH–Me_2CO to give pure **4**·HBr as prisms: mp 208–209 °C; NMR (base, $CDCl_3$) δ 0.82 (3 H, t, J = 7.5 Hz, CCH_3), 1.36–2.07 (8 H, m), 2.34 (3 H, s, NCH_3), 2.82 (1 H, dd, J = 6, 6 Hz, C-7a H), 2.95 (1 H, dd, J = 3, 16.5 Hz, C-2 H), 3.18 (1 H, dd, J = 4, 16.5 Hz, C-2 H), 5.66 (1 H, dd, J = 3, 4 Hz, C-3 H), 6.65–6.84 (3 H, m, Ar H), 7.11 (1 H, dd, J = 8, 8 Hz, Ar H); EIMS (**4**·HBr), m/e 257 (M^+ - HBr). Anal. ($C_{17}H_{24}BrNO$) C, H, N.

Biochemical Assay. The procedure used was a modified version of that of Zajac and Rocques.[18] Binding experiments were conducted with adult male Sprague–Dawley rats (Taconic Farms, Germantown, NY), which were decapitated, and the brains were quickly placed in ice-cold potassium phosphate buffer (20 mM, pH 7.4). The whole brain minus the cerebellum was homogenized (Brinkmann Polytron, setting 6, 30 s) with 25 vol of potassium phosphate buffer. The membrane suspension was centrifuged 27000*g* for 15 min at 5 °C, and the pellet was resuspended with fresh buffer. This washing step was repeated three times. The final resuspension was in 25 vol of buffer and kept on ice prior to use. The total incubation volume for the binding assay was 1 mL, consisting of 500 μL of tissue homogenate (ca. 1 mg of protein), 300 μL of buffer, 100 μL of 2 nM [^{3}H]DAGO (60 Ci/mmol, Amersham), and 100 μL of buffer or naloxone (final concentration 10 μM for nonspecific binding). The assay tubes were incubated at 25 °C for 45 min and filtered through Schleicher and Schuel No. 32 glass fiber filters using a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed with two 5-mL aliquots of ice-cold buffer and transformed to vials containing 4 mL of Hydrofluor scintillation cocktail (National Diagnostics). The samples were allowed to stand overnight prior to counting in a Packard 4000 Series liquid scintillation counter.

X-ray Structural Determination. Crystals of **4**·HBr appeared to be monoclinic prismatic, and preliminary X-ray investigation confirmed the monoclinic symmetry. The crystal used for data collection had dimensions 0.20 × 0.20 × 0.10 mm. With 23 reflections, measured at $\pm\theta$ angles between 15 and 30°, least-squares refinement produced a cell with dimensions a = 14.974 (2) Å, b = 7.539 (1) Å, c = 15.122 (2) Å, β = 90.69 (1)°, V = 1666.23 Å^3 (assumed wavelength for Cu Kα, 1.5418 Å). The space group was initially assumed to be $P2_1$. With the final formula, $C_{17}H_{24}NOBr$, the asymmetric unit weight is 338.29 and the calculated density is 1.348 g cm^{-3} (Z = 4).

The intensity data were measured with Cu Kα X-radiation, and the intensity pattern suggested that the true space group was $P2_1/n$ and that the compound was racemic. The application of MULTAN[19] in $P2_1$ did not show much in the way of reasonable light atom peaks, but there were two large peaks in the asymmetric unit that appeared consistent with $P2_1/n$. A Patterson map agreed with the peak positions, and it was decided to proceed with this space group. A weighted Fourier map using the MULTAN[19] programs gave 17 reasonable peaks, one more than had been expected. The structure was refined by using the programs of XRAY72[20] (isotropic followed by anisotropic refinement of heavy atoms). It was possible to assign atomic labels on the bases of temperature factors and bond lengths.

At this point the XTAL[21] system became available and all further refinement used that system. After anisotropic refinement of the heavier atoms, a difference map gave plausible H-atom positions, and these were included in the calculation with isotropic thermal parameters. It became apparent that the X-ray data did not justify refinement of H-atom thermal parameters, and these were fixed at values suggested by those of the attached heavy atoms. The hydroxyl H atom was placed near a peak on the line O(1)···Br and it refined to a distance of 2.49 Å from the Br atom. The distance is consistent with the presence of a hydrogen bond. The O···Br distance is 3.271 Å. Consistent with the compound being a salt, a hydrogen atom was found attached to the N atom. This H atom is 2.34 Å from the Br atom, and thus there is another hydrogen bond (the N···Br distance is 3.222 (4) Å) and the two hydrogen bonds together with electrostatic attraction between N and Br seem to be the strongest influences in the crystal packing. Other short contacts correspond to van der Waals[22] interactions. Again consistent with ionized nitrogen, the C–N bonds at the N atom are 1.47 Å or greater (Table III).

The final R factor was 0.077, R_W was 0.062, and the goodness-of-fit parameter was 1.371. There were 3365 measured reflections with 2533 having $I > \sigma(I)$ and the maximum $\sin\theta/\lambda$ was 0.6322 Å^{-1}. The anisotropic temperature factor used had the form: $\exp(2\pi^2(\sum_i\sum_j(U_{ij}h_ih_ja^*_ia^*_j)))$.

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Supplementary Material Available: Table V listing final atomic parameters (2 pages); Table IV listing refinement parameters and observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.

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