The two metabolites were isolated and purified as previously reported.[1] Metabolite 4, recrystallized from a methanol and ethyl ether mixture, had mp 211–212° (lit.[1] mp 226–228°).§ *Anal.* ($C_{20}H_{24}N_2O_3$) C, H, N.

Metabolite 4 maleate salt, recrystallized from an methanol and ether mixture, had mp 225–226°. *Anal.* ($C_{24}H_{28}H_2O_7$) C, H, N.

Metabolite 5 had mp 230–232° dec (lit.[1] mp 229–232°).

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§The melting point reported in ref 1 for metabolite 4 may have actually been the melting point of the maleate salt.

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Stereochemistry and Absolute Configuration of the Analgesic Agonist-Antagonist (−)-5-*m*-Hydroxyphenyl-2-methylmorphan

Todd G. Cochran

School of Pharmacy, Duquesne University, Pittsburgh, Pennsylvania 15219, and Department of Crystallography, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received April 19, 1974*

The absolute configuration of the title compound was established to be 1*R*,5*S* by single-crystal X-ray analysis of its hydrobromide salt (−)-1·HBr. Both rings of the 2-azabicyclo[3.3.1]nonane system exist in chair conformations with the phenyl and methyl substituents equatorial. The distance between the cationic nitrogen and the aromatic ring is 5.66 Å, which is 1.0 Å greater than that in morphine and other axially oriented phenylpiperidine analgesics. The analgetically more potent enantiomers of 1 [(+)-1*S*,5*R*] and of the α- and β-prodines have substitution on the same enantiotopic edge of the piperidine ring, suggesting a similar stereochemical preference in the interaction of these molecules with the analgetic receptor.

The series of strong analgesics known as the phenylmorphans possesses significant enantiomeric stereoselectivity in their biological actions. May and coworkers[1] reported that (±)-5-*m*-hydroxyphenyl-2-methylmorphan (1) possesses an analgesic potency nearly equivalent to that of morphine. Its enantiomers, however, have a fourfold difference in analgesic activity, with the (+) isomer being the more active.[2] More importantly, it was found that (−)-1 exhibits a weak narcotic antagonist activity and only a mild physical dependence capacity,†[3] while (+)-1 has no antagonist activity and has a high physical dependence capacity.[4] Recently, the *N*-propyl, allyl, and cyclopropylmethyl derivatives of (+)-1 and its racemate were shown to have about 1/5–1/10 the analgesic activity of the parent *N*-methyl compound and to have only a very weak antagonist activity.[4] Because of this demonstrated antipodal stereoselectivity it became of interest to establish the absolute configuration of 1. This has been accomplished by single-crystal X-ray analysis of (−)-5-*m*-hydroxyphenyl-2-methylmorphan hydrobromide (−)-1·HBr.

Experimental Section

The hydrobromide salt of (−)-1 ($C_{15}H_{22}NOBr$) crystallizes from methanol–acetone as colorless needles: mp 232–233°; $[\alpha]^{20}D$ −4.2° (H_2O). The space group is $P2_12_12_1$ with unit cell parameters a = 10.347, b = 22.215, c = 6.213 Å, z = 4, and d (calcd) = 1.45 g/cm³. Intensity data were collected from a 0.25 × 0.20 × 0.35 mm crystal on a computer controlled Picker FACS 1 diffractometer in a θ–2θ scan mode using graphite monochromated Mo Kα radiation. Two octants of data were collected, hkl to 2θ = 45° and $hk\bar{l}$ to 2θ = 55°, to give 2219 independent observed reflections (intensity > 2σ). The data were corrected for Lorentz and polarization factors but no corrections were made for absorption. The structure was solved by Patterson and Fourier methods using the hkl data set and was refined by full-matrix least-squares procedures. The 22 hydrogen atoms were located in a difference Fourier and the complete structure was refined (nonhydrogen atoms anisotropically) to an agreement residual R of 0.047 for the 1000 observed hkl reflections, using weights based on counting statistics and without correction for anomalous dispersion. The absolute configuration of the molecule was established from the anomalous dispersion of the bromine atom by use of the Hamilton R factor ratio[5] and by comparison of Friedel pairs. The R factor ratio of the enantiomers was 0.041/0.059 for the hkl data set and 0.049/0.063 for the $hk\bar{l}$ data set. The 1*R*,5*S* enantiomer gave the lower R value with both data sets and is thus unequivocally shown to be the correct absolute configuration. Two final cycles of full-matrix least-squares refinement on the combined interscaled data sets using correction for the anomalous dispersion of the bromine atom produced a final R of 0.039 for the 2219 independent observed reflections. (See paragraph at end of paper regarding supplementary material.)

Hydrogen bonding between the proton on the piperidine nitrogen and the bromide ion and between the phenolic hydroxyl proton and the bromide ion is indicated by the following parameters: N···Br, 3.22 Å; N–H, 0.91 Å; H···Br, 2.36 Å; <N–H···Br, 160°; O···Br, 3.38 Å; O–H, 0.71 Å; H···Br, 2.67 Å; <O–H···Br, 176°.

Results and Discussion

The absolute configuration of (−)-1·HBr, as determined from the anomalous dispersion of the bromine atom, is 1*R*,5*S* and is shown correctly in Figures 1 and 2.‡ From these drawings it is apparent that both rings of the 2-azabicyclo[3.3.1]nonane system are in chair conformations with the phenyl and methyl substituents equatorial. However, these chairs have become somewhat distorted in order to relieve the steric interaction between carbon atoms 3 and 7. If both rings were in true chair conformations these two atoms would be separated by a distance of approximately 2.5 Å, which is the same as the sterically unfavorable 1–4 distance in the boat conformation of cyclohexane. The steric interaction is relieved in this molecule by bending the ends of the chairs outward so that the actual C(3)–C(7) distance is 3.08 Å. This deformation causes the interplanar angles of the chairs to be in-

†E. L. May, personal communication.

‡Computer controlled perspective drawing using the three-dimensional atomic coordinates from the X-ray data: C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report ORNL-3794, 1965.

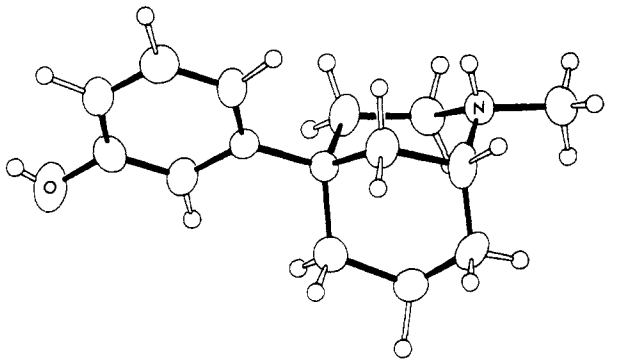


Figure 1. Perspective drawing of (−)-1·HBr from the X-ray data. The thermal vibrational ellipsoids of the nonhydrogen atoms are scaled to 50% probability. The hydrogen atoms are shown as spheres of an arbitrary size.

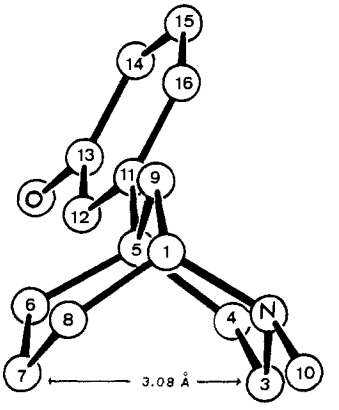


Figure 2. Perspective drawing of (−)-1 showing the C(3)-C(7) bond distance.

creased from an undistorted value of 120° to approximately 136° in the piperidine ring and 146° in the cyclohexane ring, as shown in Figure 3. In addition, the endocyclic angles around carbon atoms 4, 6, and 8 are strained to 116–117° from the normal tetrahedral value of 109°. A more complete description of the distortion in the bicyclononane ring system of 1 is given by the torsion angles shown in Table I.

Chair-chair conformations similar to that found in 1 have been observed in other crystallographic studies[6] of derivatives of the bicyclo[3.3.1]nonane system. In one of these studies[6a] a small contribution from a chair-boat conformation was observed. However, this molecule differs from 1 by having an additional fused ring and an unsaturated carbon atom in the single atom bridge, adding further strain to the molecule. Only the chair-chair conformation was observed in the crystal structure of (−)-1·HBr. Since little or no relief of steric interaction would appear to be gained by 1 adopting a chair-boat conformation, it is reasonable to assume that the azabicyclo[3.3.1]nonane system of 1 would have essentially the same conformation in solution as in the crystalline state.

A direct comparison of the absolute configuration of (−)-1 to that of morphine and its congeners is not possible because of the difference in the orientation of the aromatic substituent in these molecules. The aromatic group in 1 is rigidly held in an equatorial orientation while in morphine the aromatic ring is axial to the piperidine ring. It is of interest, however, to compare the absolute configuration of (−)-1 to that found in the conformationally mobile phenylpiperidine analgesics, since these molecules can adopt conformations in which the phenyl group is equatorially oriented. Portoghese and Larson[7] have established

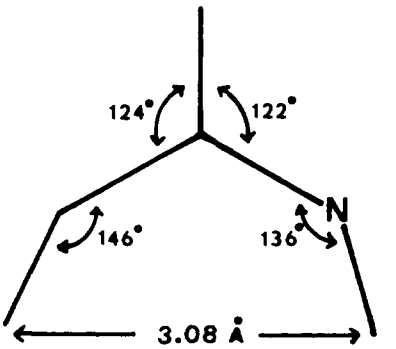
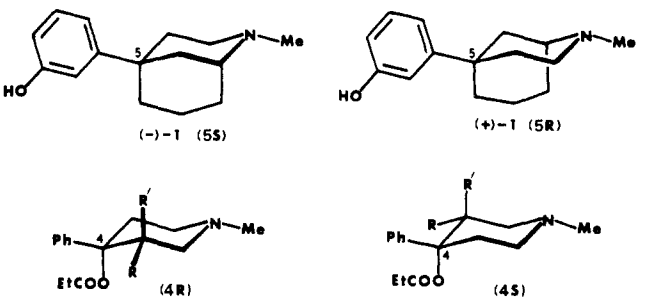


Figure 3. Interplanar angles for the 2-azabicyclo[3.3.1]nonane system of (−)-1.

that the α- and β-prodines **2a,b** with a 4*S* configuration have significantly more analgetic activity than their corresponding 4*R* enantiomers. They attribute this stereoselectivity in part to the ability of the analgetic receptor to discriminate between the pro-4*R* and pro-4*S* enantiotopic edges of the phenylpiperidine structure. Since atom 5 of 1 corresponds to atom 4 of **2**, it is apparent that the more potent enantiomers of both 1 [(+)-5*R*] and of **2** [(+)-4*S*]



2a, R = Me; R′ = H
b, R = H; R′ = Me

have substitution on the same enantiotopic edge of the piperidine ring. This would suggest that a similar discrimination of enantiotopic edges exists in the binding of these molecules by the analgetic receptor. However, it should be noted that the enantiomeric potency ratio for 1 is considerably less than that observed for the prodines, suggesting that the interaction of 1 and **2** with the analgetic receptor is not identical. The enantiomeric stereoselectivity demonstrated by 1 cannot be attributed simply to a difference in biodistribution since (+)-1 is a potent agonist while (−)-1 has both agonist and antagonist activity.

The conformation adopted by the phenyl ring of (−)-1 in the crystalline state is shown in Figure 4. This conformation is nearly identical with the solid-state conformation of the phenyl ring in the more potent prodine enantiomers.[7,8] Portoghese and coworkers[7,8] suggested that in the prodines this phenyl ring conformation is induced by the presence of the methyl substituent on C(3) of the piperidine ring and that this conformational preference contributes to the enantiomeric stereoselectivity of the prodines. However, in the phenylmorphans there is no substituent on the piperidine ring to induce this conformational preference, and a number of sterically equivalent conformations are possible. It is highly probable that the phenyl ring conformation observed in the crystal structure of (−)-1·HBr results, at least in part, from the hydrogen bond that exists between the phenolic hydroxyl proton and the bromide ion, and thus no pharmacological significance should be attributed to this conformation.

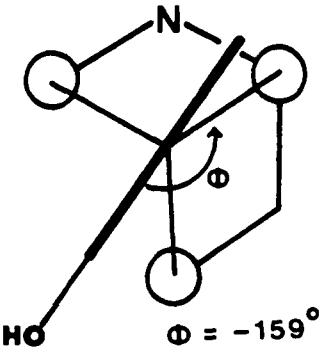


Figure 4. Torsion angle between the phenyl and piperidine rings of (−)-1.

Molecules containing either an axially or equatorially oriented phenylpiperidine moiety can have substantial analgetic activity even though the distance between the nitrogen atom and the aromatic ring is significantly different in these two conformational isomers.[9-11] An accurate value of this structural difference can be obtained by comparison of the results of the X-ray study of (−)-1·HBr with those from crystal structure determinations of other narcotic analgesics. From Table II it is apparent that the distance between the cationic nitrogen and the center of the phenyl ring is at least 1.0 Å greater in the equatorially oriented phenylpiperidine analgesics [(−)-1·HBr and the prodines] than in morphine and its congeners. This difference would appear to make unlikely, if not impossible, an identical binding of axial and equatorial phenylpiperidines to the anionic and "phenyl" sites of the analgetic receptor, as previously discussed by Portoghese.[9] However, since these molecules would be at least 90% protonated at a physiologic pH of 7.4, the potential for hydrogen bonding by the proton on the cationic nitrogen should be considered. Table II shows the results of interatomic distance calculations using the observed position of this hydrogen atom in (−)-1·HBr and the estimated or calculated position of this hydrogen atom in cyclazocine hydrobromide, β-prodine hydrochloride, and morphine hydroiodide. Even though these values must be assumed to be approximations because of the uncertainty of the exact hydrogen atom positions, it can be seen that the hydrogen to phenyl distances are more nearly the same in the axial and equatorial phenylpiperidines than the corresponding nitrogen to phenyl distances. This may suggest that a similar interaction of axial and equatorial phenylpiperidines with the analgetic receptor is possible *via* hydrogen bonding. However, the importance of hydrogen bonding is unknown, since the exact nature of the binding forces that occur between analgetics and their receptors has not been elucidated.

Thus, the information obtained from the crystal structure determination of (−)-1·HBr allows certain stereochemical and configurational correlations to be made between the phenylmorphans and other narcotic analgetics. However, definitive conclusions regarding differences or similarities in receptor binding of these agents must await further experimental results.

Acknowledgment. I wish to thank Dr. E. L. May for providing crystals of (−)-1·HBr and for his interest and encouragement in this project.

Supplementary Material Available. Tables of the atomic parameters, interatomic bond distances and angles, and structure factor amplitudes of 80 Friedel pairs showing the effects of anomalous dispersion will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-987.

Table I. Torsion Angles (degrees) in the Bicyclononane Ring System of (−)-1·HBr

Atom grouping	Angle	Atom grouping	Angle
C(1)-N-C(3)-C(4)	52	C(3)-C(4)-C(5)-C(11)	169
C(1)-C(8)-C(7)-C(6)	−36	C(4)-C(3)-N-C(10)	−178
C(1)-C(9)-C(5)-C(4)	−59	C(4)-C(5)-C(6)-C(7)	63
C(1)-C(9)-C(5)-C(6)	63	C(5)-C(6)-C(7)-C(8)	43
C(1)-C(9)-C(5)-C(11)	−176	C(5)-C(9)-C(1)-C(8)	−59
N-C(1)-C(8)-C(7)	−75	C(7)-C(6)-C(5)-C(9)	−56
N-C(1)-C(9)-C(5)	65	C(7)-C(6)-C(5)-C(11)	−176
N-C(3)-C(4)-C(5)	−46	C(7)-C(8)-C(1)-C(9)	45
C(3)-N-C(1)-C(8)	61	C(8)-C(1)-N-C(10)	−67
C(3)-N-C(1)-C(9)	−62	C(9)-C(1)-N-C(10)	169
C(3)-C(4)-C(5)-C(6)	−68	C(9)-C(5)-C(11)-C(12)	−159
C(3)-C(4)-C(5)-C(9)	50		

Table II. Nitrogen to Phenyl[a] (N-Ph) and Amino Hydrogen[b] to Phenyl (H-Ph) Distances (Å) Calculated from Atomic Coordinates from Crystal Structure Data

Compd	N-Ph	H-Ph
Morphine hydroiodide[f]	4.67	5.33[c,d]
Codeine hydrobromide[g]	4.66	*c*
Cyclazocine hydrobromide[h]	4.67	5.66[e]
(−)-1 hydrobromide	5.66	5.48
α-Prodine hydrochloride[i]	5.76	*c*
β-Prodine hydrochloride[j]	5.83	5.94[e]
β-Prodine hydrobromide[k]	5.82	*c*

[a] Average N-C or H-C distance to the six atoms of the aromatic ring. [b] Hydrogen atom on the cationic nitrogen. [c] The positions of the hydrogen atoms were not determined. [d] Calculated value, assuming tetrahedral geometry for the nitrogen atom and an N-H distance of 1.0 Å. [e] Approximate value; the positions of the hydrogen atoms were not refined. [f] M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955). [g] G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **15**, 326 (1962). [h] I. L. Karle, R. D. Gilardi, A. V. Fratini, and J. Karle, *Acta Crystallogr., Sect. B*, **25**, 1469 (1969). [i] G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **13**, 525 (1960). [j] F. R. Ahmed and W. H. Barnes, *ibid.*, **16**, 1249 (1963). [k] F. R. Ahmed, W. H. Barnes, and L. D. M. Masironi, *ibid.*, **16**, 237 (1963).

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