Journal of Medicinal Chemistry

Volume 22, Number 6 June 1979

Articles

Intramolecular Hydrogen Bonding and Conformational Studies of Bridged Thebaine and Oripavine Opiate Narcotic Agonists and Antagonists

Gilda H. Loew* and Donald S. Berkowitz

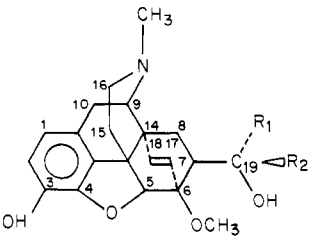
Molecular Theory Laboratory, Genetics Department, Stanford University, Stanford, California 94305.
Received August 18, 1978

A conformational study of a series of oripavine derivatives is reported using the PCILO semiempirical quantum mechanical method. Low-energy conformers of carbinol substituents on C_7–C_{19}-R_1R_2OH are found with and without intramolecular hydrogen bonding to the C_6-OCH_3 group. The relative energies of these conformers depend on the R_1 and R_2 groups and the diastereoisomerism of the alcohol. The results are consistent with available NMR and IR studies of intramolecular hydrogen bonding and with crystallographic data. The importance of interaction between specific conformations of C_{19} carbinols and a lipophilic receptor site is suggested. A hypothesis is formulated to explain observed differences in pharmacological activity between diastereoisomers at C_{19} in the oripavine series and also to explain how these diastereoisomers alter the established pattern of N-substituent effects on relative agonist/antagonist potency found in other rigid opiates. By contrast, conformational studies of the C_{19} optical isomers of the C_7–C_8 etheno form of buprenorphine lead to the prediction of greatly reduced intrinsic potency differences between C_{19} diastereoisomers for this compound and for buprenorphine itself.

In the search for clinically useful narcotic agonists and antagonists, Lewis and co-workers[1] synthesized a large number of compounds in both the oripavine (1) and thebaine (C_3-OCH_3) series. The compounds are structurally similar to morphine and dihydromorphine but contain a C_6–C_{14} etheno bridge and C_7 substituents. Among other reasons, the series became a focus of attention because some of the compounds had unexpectedly high agonist [>1000 × morphine (M)] and antagonist [>100 × nalorphine (N)] potencies and these potencies differ between diastereoisomers at C_{19}. Also, some of the relative agonist/antagonist potencies of N-substituted compounds were dramatically sensitive to substitution at C_7 and some of the compounds showed unique pharmacological profiles.

In this study we have addressed two of these structure–activity characteristics: differences in agonist potency between diastereoisomers of carbinol substituents at C_7 and dependence of agonist/antagonist potency ratios on chain lengthening of carbinol substituents on C_7. To this end we have made a conformational study of a series of oripavine derivatives using quantum chemical methods. Specifically, calculations were performed on compounds **1a**–**1k** to determine the most energetically feasible conformations of the C_7 substituents.

The pharmacology of this series has been reviewed,[1,2] and only aspects relevant to this study will be mentioned here. The oripavine analogue without a substituent on C_7, i.e., structure 1 with C_7-H, is only six times as potent as morphine methylated at C_6.[3] Thus, the greatly enhanced agonist activity of compounds such as etorphine (**1i**) [(1100 × M, rat tail pressure (RTP)] must be strongly linked to the substituents on the C_7 position.



	R_1	R_2
1a	H	H
b (*S*)	CH_3	H
c (*R*)	H	CH_3
d	CH_3	CH_3
e	CH_2CH_3	CH_3
f (*R*)	CH_3	CH_2CH_3
g	CH_2CH_3	CH_2CH_3
h (*S*)	$(CH_2)_2CH_3$	CH_3
i (*R*)	CH_3	$(CH_2)_2CH_3$
j (*S*)	$C(CH_3)_3$	CH_3
k (*R*)	CH_3	$C(CH_3)_3$

Table I summarizes the in vivo analgesic potency data for compounds **1a**–**k**, demonstrating the dependence of agonist activity on the nature and stereospecificity of substituents on C_{19}. Table II illustrates how lengthening one C_{19} substituent from CH_3 (**1d**) to *n*-propyl (**1i**) changes the activity of the *N*-allyl- and *N*-methylcyclopropyloripavine analogues from potent antagonists to potent agonists.

The majority of published work in the series was performed on whole animals by administrative routes that do not allow easy distinction between intrinsic and apparent potencies. There are also some gaps in activity data in the series chosen. Rat brain receptor-binding studies are even

0022-2623/79/1822-0603$01.00/0

Table I. Analgesic Potencies[a] of Oripavine and Thebaine Analogues

compd	ED_{50}, mg/kg oripavine (C_3-OH)	ED_{50}, mg/kg thebaine (C_3-OCH_3)
1a	17[b]	
1b	15[b]	
1c	37[b]	
1d	63[b]	
1e		0.4[c]
1f	330[b]	13.3
1g	55[b]	
1h	24[c]	0.7[c]
1i	1200[c]	67[c]
1j[d]	20[d]	
1k[d]		

[a] Potency as ED_{50} (mg/kg) in rat tail pressure relative to morphine. [b] Reference 11. [c] Reference 1. [d] Reference 26.

Table II. Effect of the C_7 Substituent on the Agonist/Antagonist Potencies of N-Substituted Oripavines 1d and 1i

N-R	compd	potency: agonism[a]	potency: antagonism[a]
$-CH_2$-c-C_3H_5	1d		50
$-CH_2$-c-C_3H_5	1i	1000	0.3
$-CH_2CH{=}CH_2$	1d		2
$-CH_2CH_2{=}CH_2$	1i	60	

[a] Reference 1. Agonism relative to morphine = 1; antagonism relative to nalorphine = 1.

more scarce. They have been performed only on a few of the most potent agonist and antagonists such as diprenorphine and etorphine.[5] In these binding studies, diprenorphine [the C_{17}–C_{18} saturated, *N*-methylcyclopropyl derivative of **1d**] was equipotent with naltrexone in stereospecifically displacing [^{3}H]naloxone from receptor fractions, and etorphine (1i) was the strongest binding agonist studied. Without more extensive structure-binding strength studies, however, it is difficult to assign the cause of the strong binding to any specific structural feature.

In spite of these limitations, certain trends are obvious: (1) C_7 substituents are important in determining relative agonist potencies, (2) differences in agonist potency among diastereoisomers increases with chain lengthening of R_1 or R_2 substituents on C_{19}, and (3) the longer chain substituents on C_{19} impart greatly diminished antagonist potency and enhanced agonist activity to *N*-allyl and *N*-methylcyclopropyl analogues.

It is, in general, possible that differences in transport and metabolism in a series of compounds may contribute to apparent potency differences such as the well known N-demethylation of morphine[6] or N-deallylation of nalorphine.[7] However, it is not likely that differences in transport, unless they are related to specific internal conformation differences at C_7, contribute to apparent agonist potency differences in diastereoisomers or that N-dealkylation, which occurs by hydroxylation of the ethyl carbon bound to the nitrogen, would be highly sensitive to substitution at the distant C_7 position.

Thus, the stereospecificity of agonist potencies and the sensitivity of agonist/antagonist potency ratios to C_7 substituents is more likely related to binding and interaction of the C_7 substituent at the receptor site.

To explain the effect of C_7 substituents on the observed activity of oripavines, several hypotheses have been presented. Based on the Becket and Casy[8] receptor model, it has been proposed that the C_7 substituents interact with a lipophilic receptor site, since polar C_7 substituents reduce agonist activity[9] while large lipophilic substituents substantially enhance it.[1] This idea has been extended to suggest that in phenethyletorphine (R_1 = CH_3, R_2 = CH_2CH_2Ph) the aromatic ring of the phenethyl moiety, by complementarity, reaches a similar receptor site which stabilizes a conformation of the receptor associated with agonism.[10] Without the results of extensive binding studies, however, the importance of aromaticity is unclear, since at least five other compounds with saturated R_2 have been synthesized[11] with higher in vivo potencies than the phenethyl derivatives. It has also been suggested, from an analysis of X-ray crystallographic data, that there may be some sensitivity of agonist/antagonist activity to the relative positions of the phenyl A ring and the region near the C_7 position in different rigid opiates.[12] Such a relationship could help explain the effect on activity of substituents at the C_7 position in the oripavines and thebaines, although the position of C_7 is displaced a few angstroms from that in morphine.

It is hoped that conformational studies of the C_7 substituents will provide some insight into the observed effect of different diastereoisomers on agonist potency and also how they modulated agonist/antagonist activity.

The latter property is of practical importance, since it is now generally thought that compounds possessing potent analgesic activity yet having some degree of antagonist properties are good candidates for clinically useful analgesics with low addiction potential. Thus, a more satisfactory understanding of the structural correlates to opiate agonism and antagonism in this series of opiates could be of benefit in the search for a dependent free analgesic with reduced side effects, although the idea that there is a direct relationship between dependence and receptor-related events[13] has recently been both confirmed[14] and disputed.[15]

The calculations reported here were done on unsolvated, isolated molecules which are most relevant to receptor-related behavior if, as believed,[8] the receptor is in a lipophilic environment.

Experimental Section

Calculations were performed using the PCILO method which has been thoroughly documented in the literature.[16] The geometry of the basic six fused-ring structure was taken from a recent crystal structure of 3-methoxyetorphine.[17] C_7 substituents were assumed to be tetrahedral, and standard bond lengths were used.[18] Each rotatable single-bond axis was labeled with a number, as shown for etorphine (Figure 1). Torsion angles were defined with the convention that τ_i (ABCD) equals the clockwise rotation of atom A into atom D while looking along the B–C axis from atom B to C. All calculations were done on the protonated molecule thought to be the active form.[19,20]

Calculations were performed to determine the low-energy conformational forms (local minima) and their relative energies for the C_7 substituents of structures **1a–k** which would be present at the receptor site. Torsion angles for substituents at other positions which would not interact with the C_7 substituent or with each other were determined by independent variation. In this way, τ_8 was fixed at 0°, τ_9 at 60°, and τ_2 at 60°. For the C_6-OCH_3 group (τ_1), the only group whose conformation could be coupled to the C_7 substituent conformation, rotations of τ_1 were performed in etorphine with the C_7 substituent in hydrogen bonding and nonbonding conformations. In all cases, the τ_1 = 60° conformer was the only local minima and was held fixed in all subsequent calculations. The remaining torsion angle variations were determined from consideration of molecular models to eliminate high-energy conformers and to decide the most important rotations for each compound. These rotations were made in 30° steps. The most extensive calculations were performed for the lowest energy intramolecularly hydrogen-bonded structures (τ_3 = 300°, τ_1 = 60°, τ_{10} = 60°) where energies were determined for

Table III. Local Minima Energies and Geometries for C_7 Substituents[a-c]

A. structures 1a-d

C_{19} primary alcohol (1a)			C_{19} sec. alcohol (1c, *R*)			C_{19} sec. alcohol (1b, *S*)			C_{19} dimethylcarbinol (1d)		
τ_3	τ_{10}	ΔE, kcal/mol	τ_3	τ_{10}	ΔE, kcal/mol	τ_3	τ_{10}	ΔE, kcal/mol	τ_3	τ_{10}	ΔE, kcal/mol
67	184	0.0	301	52	0.0*	298	50	0.0*	301	50	0.0*
299	51	0.4*	163	169	0.3	72	169	0.3	164	172	0.1
174	175	0.7	56	178	1.0	163	177	0.5	56	184	2.4

B. structures 1e,f,g

$R_1 = CH_3$, $R_2 = C_2H_5$ (1f, *R*)				$R_1 = C_2H_5$, $R_2 = CH_3$ (1e, *S*)				$R_1 = R_2 = C_2H_5$ (1g)				
τ_3	τ_4	τ_{10}	ΔE, kcal/mol	τ_3	τ_4	τ_{10}	ΔE, kcal/mol	τ_3	τ_4	τ_6	τ_{10}	ΔE, kcal/mol
299	157	49	0.0*	301	198	49	0.0*	301	200	82	49	0.0*
161	159	171	1.9	164	186	177	0.9	299	217	149	47	0.3*
166	163	73	2.4	167	187	79	2.0	165	285	163	265	3.4

C. structures 1h,i

R isomer (1i)					*S* isomer (1h)				
τ_3	τ_4	τ_5	τ_{10}	ΔE, kcal/mol	τ_3	τ_4	τ_5	τ_{10}	ΔE, kcal/mol
299	156	182	49	0.0*	301	199	181	47	0.0*
298	156	278	50	0.3*	164	186	185	176	1.4
300	150	82	49	1.5*	166	189	176	80	2.2

[a] Additional higher energy conformers for all structures available on request. [b] Hydrogen-bonded structures are indicated by an asterisk. [c] All τ values are in degrees.

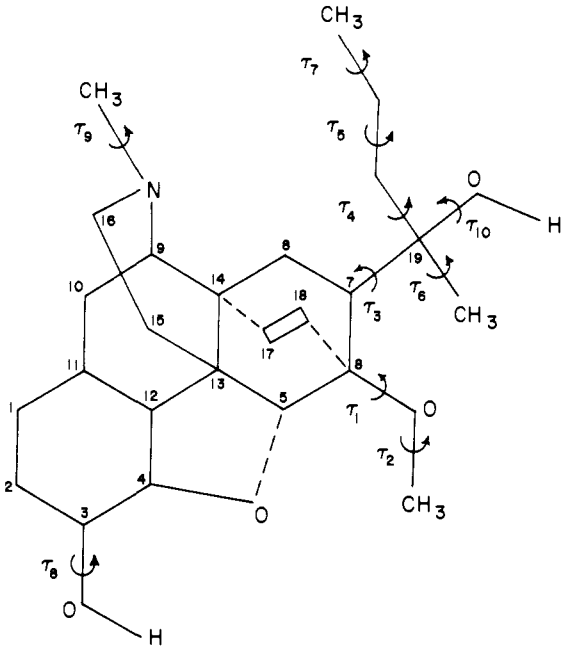


Figure 1. Rotation axis numbering used in all calculations. Twist angle convention is described under the Experimental Section.

C_{19} alkyl groups(s) using all combinations of rotation angles for each optical isomer. For example, for etorphine in its hydrogen-bonded conformation, τ_4 and τ_5 were each varied in 30° increments, with τ_6 and τ_7 assumed staggered, for a total of 144 points. Then, R_1 and R_2 were switched to the less active diastereoisomer and the process was repeated. Minima located in this way for hydrogen-bonded forms, as well as those determined for non-hydrogen-bonded forms using models and less complete rotational variations, were then optimized to determine local minima accurate to a few degrees and energies accurate (within the computational method) to a tenth of a kcal/mol.

Results

Table III, section A, shows the conformational results for compounds **1a–d** with R_1 and/or R_2 = H, Me. Since these are relatively small groups, the most interesting aspect of their structures is the possibility of C_6-O--H-O-C_{19} intramolecular hydrogen bonding. Such hydrogen bonding has been explored extensively by NMR and IR spectroscopy in the bridged-thebaine series.[21] From proton chemical shifts observed,[21] the primary alcohol **1a** and dimethylcarbinol **1d** did not appear to be hydrogen bonded ($\tau_3 \simeq 300°$, $\tau_{10} \simeq 50°$), the *S* diasteriomer of the secondary alcohol **1b** did appear to be hydrogen bonded, and the *R* form **1c** was believed to exist in two conformations, one of which was a hydrogen-bonded structure. From temperature-dependence studies, however, evidence for more than one conformation was found for all of these compounds. The conformational results obtained here are consistent with the above experimental results. Low-energy mixtures of H bonded and nonbonded conformations differing only a few tenths of a kcal/mol were obtained whose relative energy would be sensitive to small solvent effects. They also show qualitative agreement in that the difference in energy, between H-bonded and non-H-bonded structures (E = H bond − no H bond), is in the order: primary alcohol (0.4 kcal/mol) > dimethylcarbinol (−0.1 kcal/mol) > *R* secondary alcohol (−0.3 kcal/mol) ≈ *S* secondary alcohol (−0.4 kcal/mol).

Table III, section B, shows the results for compounds **1e–g**. Hydrogen bonding is a dominant conformational feature in these compounds, consistently being the minimum energy conformer (MEC). Nonbonded conformers are 1–4 kcal/mol higher in energy.

Table III, section C, shows the calculated local minima for the two etorphine diastereoisomers, the potent *R* diastereoisomer **1i** and the less potent *S* diastereoisomer **1h**. As with the compounds with ethyl substituents (**1e,f**), H-bonded structures are lowest in energy, consistent with the NMR[21] and crystallographic[17] results.

Table IV. Local Minima Energies and Geometries for C_7 Substituent of the C_7-C_8 Unsaturated Analogue of Buprenorphine[c]

τ_3	τ_4	τ_5[b]	τ_6	τ_7[b]	τ_{10}	τ_{12}[b]	ΔE[c]
A. *S* diastereoisomer 1j							
314	160	173	38	47	180	84	2.3
313	158	178	35	48	−58	86	3.4
309	159	182	39	48	56	91	0.0*
B. *R* diastereoisomer 1k							
73	157	168	72	49	312	93	0.0

[a] Hydrogen-bonded structure is indicated by an asterisk. [b] $\tau_{5,7,12}$ correspond to methyl hydrogen conformations of the *t*-Bu group. [c] ΔE in kcal/mol. [c] τ values in degrees.

Rotations of the *n*-propyl chain (τ_4,τ_5) in the hydrogen-bonded structure ($\tau_3 \simeq 300°$, $\tau_{10} \simeq 50°$) were obtained for both diastereoisomers. Low-energy minima are found for only one value of τ_4 in each diastereoisomer (150° in *R* and 210° in *S* diastereoisomer), indicating that the isopropyl chain is relatively inflexible in the hydrogen-bonded structures. For the *R* diastereoisomer, the MEC is the crystal conformation of 3-methoxyetorphine (τ_4 = 150°, τ_5 = 180°).

Table IV, sections A and B, show the local minima calculated for diastereoisomers **1j** (*S*) and **1k** (*R*), the C_{17}–C_{18} unsaturated analogue of buprenophine. Only in the *S* diastereoisomer is hydrogen bonding to the C_6-OCH_3 group possible. However, in both isomers, the tertiary butyl substituent is accommodated in the same position in the lowest energy conformers, one with and one without the intramolecular H bonding (*S* and *R* diastereoisomers, respectively).

Discussion

Intramolecular hydrogen bonding to the C_6-OCH_3 in oripavines does not appear to play a dominant role in determining the conformation of C_{19} carbinol substituents on C_7 if R_1 and R_2 are hydrogen or methyl groups (**1a–d**). With these small groups the C_7 substituents have substantial conformational freedom in binding to the receptor. Thus, it is not surprising that their apparent potencies are similar, increasing somewhat with lipophilicity of the alcohol group (17, 15, 37, and 63 × M RTP for **1a–d**, respectively) and that the relative agonist–antagonist activities conferred by different N substituents are consistent with structure–activity relationships found in other fused-ring opiates. Specifically, these carbinols seem to follow the idea of Archer and Harris[22] that in morphine-like fused-ring structures, antagonist potency of an N-substituted compound varies as the agonist potency of its *N*-methyl counterpart. The nonspecific nature of the binding of these small groups is emphasized by the fact that the C_7,C_8-dimethyloripavine produces a more potent agonist (200 × M RTP)[23] than any of the four C_7 carbinols (**1a–d**). It might be postulated from the combination of pharmacological and conformational results that these small C_7 substituents interact only slightly with the hypothesized "lipophylic site" at the receptor and result in a "morphine-like" overall contact.

In compounds with tertiary carbinol substituents of the type C_{19}-$CH_3(CH_2)_nCH_3OH$ with $n \geq 1$ (Table III, sections B and C), hydrogen bonding is favored in both diastereoisomers. This constraint fixes the C_7 substituent in one of two distinct spatial regions which are different for the *R* and *S* diastereoisomers (Figure 2). It is suggested that this difference in orientation determines the extent to which the long alkyl group of the C_{19} carbinol can be accommodated at the postulated lipophilic receptor and could account for the difference in observed agonist potencies in the *R* and *S* diastereoisomers of N-CH_3 compounds. For example, in compounds **1e,f** and **1h,i** the *R* diastereoisomers are much more potent than either the *S* diastereoisomers or compounds **1a–d** with smaller alkyl groups. The calculated low-energy conformers of the more potent *R* diastereoisomers place the longer alkyl chain in a different spatial region which should, by complementarity, define optimum binding to a lipophilic receptor site.

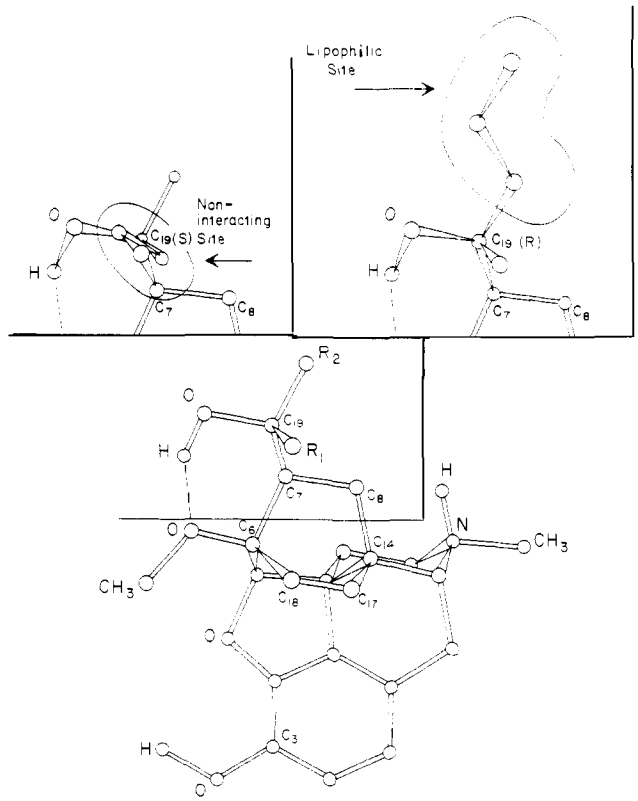


Figure 2. Oripavine fused-ring structure showing by complementarity the hypothesized receptor site for C_{19} carbinol substituents as it would interact with etorphine C_{19} diastereomers.

We further suggest that it is optimum interaction of the conformationally restricted groups on C_7 with this lipophilic site that directs the overall orientation of these compounds at the receptor. Figure 3 demonstrates how optimum fit of the *n*-propyl group of etorphine at the receptor site could displace the contact that the N-R group makes with the receptor relative to that in morphine. The anomalous structure–activity profiles of *N*-allyl and *N*-methylcyclopropyl derivatives of etorphine (**1i**) could then be due to an altered overall drug–receptor interaction relative to morphine-like compounds.

In previous calculations,[24,25] we showed that *N*-allyl and *N*-methylcyclopropyl substituents of morphine exist in two "types" of low-energy conformations and suggested this behavior could in part be responsible for the dual agonist–antagonist activities they confer on many fused-ring, N-substituted compounds. Based on this hypothesis, we predicted that diastereoisomers of α-methyl derivatives of *N*-*n*-propyl-, *N*-allyl-, and *N*-methylcyclopropylnormorphine should have different ratios of agonist/antagonist potencies from each other and from the parent compounds. Subsequent syntheses and tests of these analogues[28] appear to confirm these predictions. In a similar spirit, we suggest that the change in orientation imposed on the N-substituent binding at the receptor by the rather rigid C_{19}-*n*-$CH_2CH_2CH_3$ group could interfere with the antagonist "type" of N-substituent binding mode while enhancing the agonist "type". If this hypothesis is

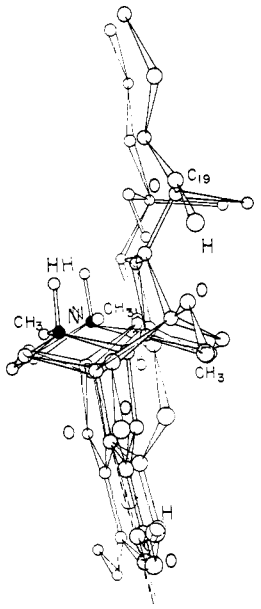


Figure 3. Perspective drawing of etorphine shown perpendicular to the phenyl ring plane with superimposed line drawing of etorphine rotated about the dashed line slightly to show a possible effect of the C_{19} substituent interaction on the overall molecular orientation in the receptor. Note particularly the altered *N*-methyl orientation.

correct, replacement of the C_6-OCH_3 or the C_{19}-OH group by a H or CH_3 substituent should enhance or restore antagonist potency to *N*-allyl and *N*-cyclopropylmethyl derivatives of oripavines and thebaines with long-chain, C_7 carbinol substituents. Colleagues at the University of California, Berkeley,[29] are attempting to synthesize oripavine or thebaine analogues with no possibility of H bonding between C_6 and C_7 substituents. Before long, then, it might be possible to test this hypothesis as well.

Compounds **1j** and **1k**, related to C_{19} *S* and *R* diastereoisomers of buprenorphine are particularly interesting from a conformational standpoint. The bulky *t*-Bu substituents must be accommodated at nearly identical positions in the two diastereoisomers, allowing an intramolecular C_6-O--H-O-C_{19} hydrogen bond in the *S* diastereoisomer **1j** and not in the other. The pharmacology of the *S* diastereoisomer of buprenorphine has been extensively studied,[26,27] but there appears to be no published data on the *R* diastereoisomer or on any pair of C_{19} *t*-Bu isomers. In contrast to the C_{19} straight-chain derivated compounds (such as **1h** and **1i**), we predict that intrinsic activity in the *t*-Bu compounds **1j** and **1k** should have a rather low sensitivity to C_{19} optical isomerism as the *t*-Bu group occupies similar positions in both isomers. There may still be interesting differences in their pharmacological profiles, however, since the overall lipophilicity of the two diastereoisomers (a factor cited as a possible cause of the unusual pharmacology of buprenorphine[26]) may be rather different due to the lack of intramolecular hydrogen bonding in one and not the other.

Acknowledgment. The support of the National Institute of Drug Abuse (Grant DA 00770-03) is gratefully acknowledged.

References and Notes

(1) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, **11**, 241 (1971), and references cited therein.
(2) J. W. Lewis, M. J. Redhead, and A. C. B. Smith, *J. Med. Chem.*, **16**, 9 (1973).
(3) T. O. Soine and R. E. Willette in "Textbook of Organic Medicinal and Pharmaceutical Chemistry", C. O. Wilson, O. Gisvold, and R. F. Doerge, Eds., Pitman Medical Publishing Co., London, 1966, p 643.
(4) J. W. Lewis and M. J. Redhead, *J. Med. Chem.*, **13**, 525 (1970).
(5) C. P. Pert and S. H. Synder, *Mol. Pharmacol.*, **10**, 868 (1974).
(6) J. Fishman, E. Hahn, and B. I. Norton, *Nature (London)*, **261**, 64 (1976), and references cited therein.
(7) K. Iwamoto and C. D. Klaasen, *J. Pharm. Exp. Ther.*, **203**, 365 (1977).
(8) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).
(9) K. W. Bentley, J. W. Lewis, and A. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 870 (1972).
(10) A. P. Feinberg, I. Creese, and S. H. Synder, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 4215 (1976).
(11) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3281 (1967).
(12) F. A. Gorin and G. R. Marshall, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 5179 (1967).
(13) H. O. J. Collier, *Adv. Drug Res.*, **3**, 171 (1966).
(14) T. Kitano and A. E. Takemori, *Res. Commun. Pathol. Chem. Pharmacol.*, **18**, 341 (1977), and references cited therein.
(15) J. Dum, G. Meyer, V. Hollt, A. Herz, and D. Catlin, *Eur. J. Pharmacol.*, **46**, 165 (1977), and references cited therein.
(16) S. Diner, J. P. Malrieu, F. Jordan, and M. Gilliert, *Theor. Chim. Acta*, **15**, 100 (1969).
(17) J. H. Van den Hende and N. R. Nelson, *J. Am. Chem. Soc.*, **89**, 2901 (1967).
(18) J. Pople and D. Beveridge in "Approximate Molecular Orbital Theory, McGraw-Hill, New York, 1970, p 111.
(19) A. F. Casy, *Mod. Pharmacol.*, **1**, 217 (1973).
(20) K. E. Opheim and B. M. Cox, *J. Med. Chem.*, **19**, 857 (1976).
(21) W. Fulmor, J. E. Lancaster, G. D. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3322 (1967).
(22) S. Archer and L. S. Harris, *Prog. Drug. Res.*, **8**, 261 (1965).
(23) J. W. Lewis and W. I. Rushworth, *J. Chem. Soc. C*, 560 (1970).
(24) G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, **18**, 656 (1975).
(25) G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, **21**, 101 (1978).
(26) A. Cowan, J. W. Lewis, and I. R. MacFarlane, *Br. J. Pharmacol.*, **60**, 537 (1977).
(27) A. Cowan, J. C. Doxey, and E. J. R. Harry, *Br. J. Pharmacol.*, **60**, 547 (1977).
(28) J. I. Degraw, J. A. Lawson, J. Crase, H. Johnson, M. Ellis, E. T. Uyeno, G. H. Loew, and D. S. Berkowitz, *J. Med. Chem.*, **21**, 415 (1978).
(29) H. Rapaport, private communication.