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Stereochemical Studies on Medicinal Agents. 19. X-Ray Crystal Structures of Two (±)-Allylprodine Diastereomers. The Role of the Allyl Group in Conferring High Stereoselectivity and Potency at Analgetic Receptors[1]

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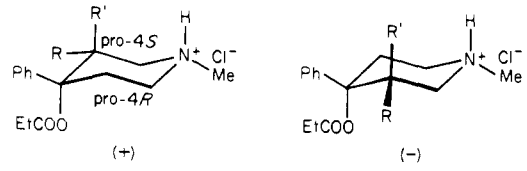
X-Ray crystallographic studies have been performed on the two diasteromeric racemates of 3-allyl-1-methyl-4-propionoxypiperidine hydrochloride (allylprodine hydrochloride) in an effort to determine the role of conformation in their interaction with analgetic receptor sites. The chiral orientation of the phenyl group in the highly potent isomer, (+)-1, is qualitatively in conformity with the stereostructure–activity relationship found among other analgetic 4-phenylpiperidines. The fact that (+)-2, a relatively weak analgetic with no stereoselectivity, also possesses this feature indicates that this conformational arrangement per se does not ensure high potency. The data suggest that the very high potency and stereoselectivity which the allylic double bond confers to (+)-1 are due primarily to the interaction of this bond with an accessory site on the receptor.

Investigations of the stereostructure–activity relationship of enantiomeric 4-phenylpiperidine analgetics containing substitution vicinal to the aromatic group have shown that the more potent isomer possesses the 4*S* configuration.[2-5] Moreover, where the crystal structures of these compounds are known,[5-8] there appears to be a relationship between the handedness of the torsion angle between the phenyl group and the piperidine ring and the more potent enantiomers.[2,3,9] These data have led to the proposal[2,3,9] that antipodal stereoselectivity arising from 4-phenylpiperidine analgetics is a consequence of two inseparable effects: a configurational effect related to the ability of the receptor to distinguish between the pro-4*R* and pro-4*S* enantiotopic edges of the piperidine ring (1) and, secondly, the effect of an alkyl substituent vicinal to C-4 to induce a chiral, preferred conformation of the phenyl group.



1, R = $CH_2CH{=}CH_2$; R' = H
2, R = H, R' = $CH_2CH{=}CH_2$

Among the compounds studied, (+)-allylprodine[4] [(+)-1] distinguished itself by possessing a very high analgetic potency (40 times greater than morphine) with an enantiomeric potency ratio, (+)-1/(−)-1 = 260, one order of magnitude greater than other 4-phenylpiperidine analgetics. It was found[4,5] that the enhanced analgetic properties and stereoselectivity of this drug were due to the allylic double bond. However, it was not known whether the allyl group exerted its effect directly or indirectly in the drug–receptor interaction; its interaction with an accessory site on the receptor would constitute a direct effect, while the ability of the allyl group to alter the torsion angle between the phenyl and piperidine ring would represent an indirect effect.

Another facet of this problem was concerned with the observation that (+)-1 is ~460 times more potent than its β diastereomer [(+)-2] which possesses virtually no stereoselectivity.[4] This was attributed to the receptor possessing a hydrophobic pocket of limited volume which would accept an axial methyl or ethyl, but not an allyl or propyl group.[5]

The purpose of this study was to further delineate the role of the allyl group in the interaction of allylprodine with analgetic receptors. In an effort to accomplish this we have performed single-crystal X-ray analysis of racemic 1 and 2 in order to examine their conformational features.

Experimental Section

Monoclinic prisms of the racemates of the α- and β-allylprodine hydrochlorides [(±)-1 and (±)-2] were obtained from ethyl acetate–benzene. The following crystallographic data were measured for these crystals. For (±)-1: a = 15.319 (3) Å, b = 12.190 (2) Å, c = 11.066 (2) Å, β = 117.47 (2)°, space group $P2_1/c$, A = 4, and density (calcd) = 1.162 g cm^{-3}. For (±)-2: a = 5.928 (1) Å, b = 28.481 (5) Å, c = 11.470 (2) Å, β = 107.33 (2)°, space group $P2_1/c$, A = 4, density (calcd) = 1.155 g cm^{-3}.

Intensity data were collected by the stationary crystal–stationary counter technique using a GE XRD-6 diffractometer with Cu Kα radiation monochromatized by balanced nickel and cobalt filters. A total of 2732 reflections were measured for the α compound (2θ <120°) and 2330 reflections for the β compound (2θ <110°). Corrections were applied to the data for α_1–α_2 splitting, Lorentz–polarization effects, and absorption.

The structures were solved by use of Patterson and electron density Fourier syntheses. The positional and thermal parameters of the atoms were refined by block diagonal least squares. Those hydrogens on atoms showing large thermal motion could not be located with any degree of accuracy and were thus not included in the calculations. The final conventional R indices were 6.2 and 6.9% for the observed reflections ($I < 3\sigma$) of 1, and 2, respectively.

The nonhydrogen atomic parameters (positional and intramolecular bonding) appear in the microfilm edition of the journal (see paragraph at end of paper regarding supplementary material). A tabulation of the structure factors and hydrogen parameters will be supplied on request to E. Shefter.

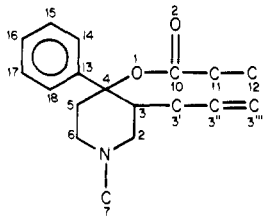
The allyl moiety in both structures has a large thermal motion associated with it (see thermal ellipsoids drawn in Figure 1 of the molecules). These alkyl groups reside in hydrophobic pockets in the two structures that permit a great degree of motion; all intermolecular contacts with C(3'') and C(3''') are greater than normal van der Waals distances.

The chloride ion in both structures is involved in a similar N–H···Cl hydrogen bond. The N to Cl distance is 3.04 Å in both structures. Analogous type interactions were found in other piperidine hydrochloride structures. Aside from this intermolecular bond, no other distances were found which are shorter than normal van der Waals contacts.

Results and Discussion

Racemic 1 and 2 share similar conformational features in that the piperidine ring is in the chair conformation and the phenyl group is oriented equatorially. The

Table I. Conformational Parameters for Allylprodine Diastereomers



Atomic grouping	Torsion angles[a] (+)-1·HCl	(+)-2·HCl
N-C(2)-C(3)-C(4)	-58.4	-55.3
C(2)-C(3)-C(4)-C(5)	55.4	53.4
C(3)-C(4)-C(5)-C(6)	-55.3	-56.5
C(4)-C(5)-C(6)-N	56.7	58.8
C(5)-C(6)-N-(2)	-56.4	-57.3
C(6)-N-C(2)-C(3)	58.8	56.7
C(3')-C(3)-C(4)-O(1)	60.7	166.2
C(3')-C(2)-C(4)-C(13)	-56.2	50.3
C(3')-C(3)-C(4)-C(5)	179.5	-77.6
C(3'')-C(3')-C(3)-C(4)	102.2	-146.1
C(3''')-C(3'')-C(3')-C(3)	-125.4	111.0
C(3)-C(4)-O(1)-C(10)	167.2	180.0
C(4)-O(1)-C(10)-C(11)	178.3	172.4
C(4)-O(1)-C(10)-O(2)	-1.9	-6.6
O(1)-C(10)-C(11)-C(12)	-178.4	-174.6
C(14)-C(13)-C(4)-O(1)	-1.3	-37.5
C(14)-C(13)-C(4)-C(3)	110.8	73.6
C(14)-C(13)-C(4)-C(5)	-127.5	-162.2
C(7)-N-C(2)-C(3)	-174.7	-177.7
C(7)-N-C(6)-C(5)	179.6	177.7

[a] Although X-ray studies were conducted on the racemates, for comparison purposes the torsion angles (degrees) are tabulated for isomers in the 4S series.

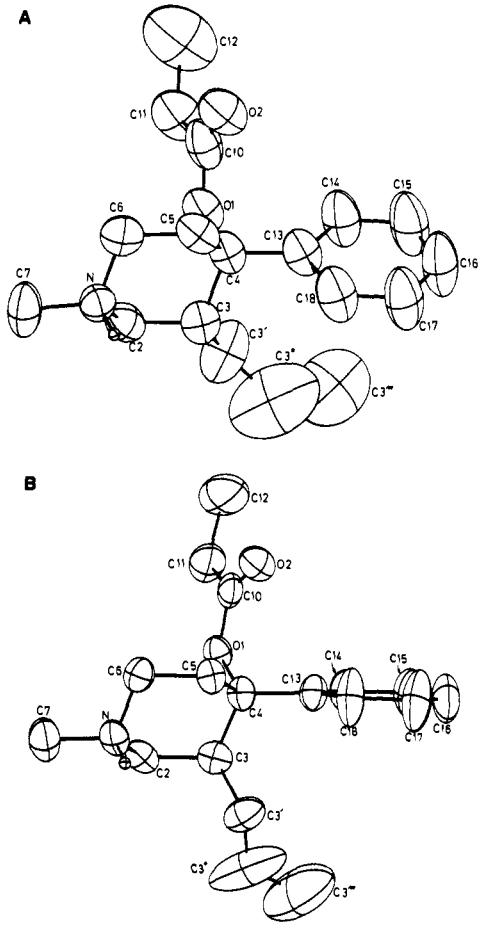


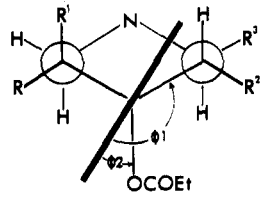
Figure 1. Conformational structures of (A) (+)-1 and (B) (+)-2 as determined from the X-ray crystallographic data.

computer-generated perspective formulas of the two diastereomers possessing the 4S configuration [(+)-1, (+)-2] are shown in Figure 1. To facilitate comparison these are illustrated in a perspective which is identical with other related compounds published previously.[9]

The conformational parameters obtained from the crystallographic data are listed in Table I. For correlation purposes, only the torsion angles of the 4S isomers [(+)-1, (+)-2] are presented. The torsion angles which are of particular interest are C(14)-C(13)-C(4)-C(5) and C(14)-C(13)-C(4)-O(1) (φ_1 and φ_2, respectively), as they define the conformational relationship between the phenyl and piperidine ring. The fact that $\varphi_1 - \varphi_2$ is greater than the idealized angle of 120° for both allylprodine diastereomers (Table I) as well as for other 4-phenylpiperidines (Table II) reflects the presence of nontorsional distortions at C(4) due to nonbonded interactions.

It can be seen (Table II) that the aromatic ring of the more potent enantiomer, (+)-1, is located in the negative quadrants.[10] This relationship is present in all of the more potent enantiomers as well. However, it should be noted that while this correlation defines the conformational arrangement of the phenyl group of the more potent enantiomer in a racemate, it cannot be extended to compounds of low potency. Thus, (+)-2, a relatively weak analgetic with no stereoselectivity, also has its phenyl group

Table II. Torsion Angles ϕ_1 and ϕ_2 in the More Potent Enantiomers of Alkyl-Substituted 4-Phenyl-4-propionoxypiperidines



More potent enantiomer	Config	Alkyl substitution	Torsion angle ϕ_1, C(14)-C(13)-C(4)-C(5)[a]	Torsion angle ϕ_2, C(14)-C(13)-C(4)-O(1)[a]	Enantiomeric potency ratio, more potent/less potent
(+)-α-Prodine	3R,4S[b]	R = Me; R¹ = R² = R³ = H	-152°[c]	-28°	25[b]
(+)-β-Prodine	3S,4S[b]	R¹ = Me; R = R² = R³ = H	-167°[d]	-43°	13[b]
(+)-γ-5-Methylprodine	3S,5S[e]	R¹ = R² = Me; R = R³ = H	-164°[e]	-38°	5[e]
(+)-Trimeperidine	2S,4S,5R[f]	R = R³ = Me; R¹ = R² = H	-139°[g]	-17°	12[f]
(+)-Allylprodine [(+)-1]	3R,4S[h]	R = $CH_2CH{=}CH_2$; R¹ = R² = R³ = H	-128°	-1.3°	260[h]

[a] With the exception of trimeperidine ϕ_1 and ϕ_2 were obtained from X-ray data of the racemate as the HCl salt. [b] Reference 3. [c] Reference 6. [d] Reference 7. [e] Reference 9. [f] Reference 2. [g] Value obtained from free base of (±)-trimeperidine alcohol.[8] [h] Reference 4.

located in negative quadrants.[10] In this particular case, steric interference to drug–receptor association afforded by the axial allyl substituent overrides any facilitation of receptor binding due to the advantageous orientation of the phenyl group.[4,5]

Although the stereostructure–activity relationship of the highly potent (+)-1 is in conformity with the correlation found among the other more potent enantiomers (Table II), the magnitude of φ_1 and φ_2 are smaller. It seems unlikely that this difference alone can contribute to the greatly enhanced potency of (+)-1, particularly if the barrier for rotation of the phenyl group is not great. The possibility that the allylic double bond causes stabilization of the phenyl group through π-electron overlap is discounted because none of the distances between the allyl group and the aromatic system are shorter than normal van der Waal contacts.

The most plausible explanation for the high potency of (+)-1 is that the allylic double bond interacts with an accessory site adjacent to the receptor which confers enhanced affinity and stereoselectivity to the molecule. As the corresponding propyl analog[5] exhibits activity in the range of the other enantiomers, it appears that this is a highly specific interaction.

This study suggests the possibility of attaching the allyl group to a comparable position in other analgetic molecules as a probe to determine whether or not their mode of interaction[11,12] with receptors is similar. If, for example, a great enhancement of potency is observed this would suggest that the analgetics are complexing in a similar fashion.

Finally, it is important to point out that although all of the more potent antipodes possess similar conformations (Table II), this does not necessarily mean that drug–receptor association occurs in this conformational state. This study also underscores the fact that absolute configuration and conformation must be dealt with together in the analysis of stereostructure–activity relationships.

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Supplementary Material Available. A listing of the intramolecular bonding parameters (Table III) and of atomic coordinates (Table IV) (2 pp). Ordering information is given on any current masthead page.

References and Notes

(1) This paper is dedicated to our teacher and colleague, Edward E. Smissman.
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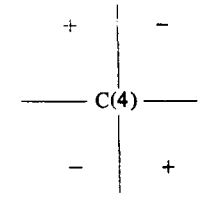
(10) The quadrant system is defined by considering C(4) as the intersection point when the compound is viewed as a Newman projection formula (Table II).



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Chemistry and Antibacterial Activity of Nitrobenzofurans†

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Thirteen 2-methylbenzofurans were synthesized and their antibacterial activity was investigated. 2-Methyl-3-nitrobenzofuran and analogs containing 7-NO_2, 5-NO_2, 7-Br, 7-$CONH_2$, and 7-CF_3 substituents are bacteriostatic. The spectrum of activity of these compounds is similar to nitrofurazone; however, a strain of *E. coli* Br which has increased resistance to nitrofurazone did not show increased resistance to 3,7-dinitro-2-methylbenzofuran (1). The 3-nitro-2-methylbenzofurans are labile in solution ($T_{1/2}$ 0.8–3.5 hr at 37°, pH 7.0). The solvolysis product of 1 was identified as α,6-dinitro-*o*-cresol (15). The 3-nitrobenzofurans are more potent in minimal media than in Penassay broth. This greater potency can be abolished by addition of casamino acids and tryptophan to the minimal media.

Many examples have appeared in the literature of antimicrobial activity of nitro heterocyclic compounds.[1] One of the initial reports of activity by this type of compound was Dodd and Stillman's report of the remarkable increase in antibacterial activity that results from a 5-nitro substituent in a series of 2-substituted furans.[2] Since this report several thousand 5-nitrofurans have been synthesized and evaluated as antibacterial and antiprotozoal agents. In the furan series it has been established that an α-nitro substituent is necessary for antibacterial activity. β-Nitrofurans[3] as well as furans substituted with other electron-withdrawing substituents at the 5 position lack antibacterial activity.[3,4] In contrast to the thorough investigation of the antibacterial activity of substituted furans, the benzofuran ring system has received very little attention. We have reported the antibacterial activity of 3,7-dinitro-2-methylbenzofuran (1) and 3,5-dinitro-2-methylbenzofuran (2).[5] More recently, Royer and co-

† This manuscript is dedicated to Dr. Edward Smissman. While Ed is gone the mark which he leaves on Medicinal Chemistry is indelible.

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