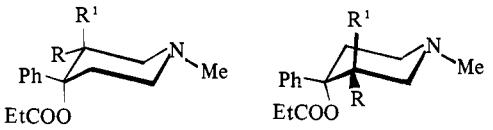
Stereochemical Studies on Medicinal Agents. 13.[1] Correlation of the Solid-State Conformations of 1,3,5-Trimethyl- and 1,3-Dimethyl-4-phenyl-4-propionoxypiperidine Enantiomers with Their Absolute Stereoselectivity at Analgetic Receptors

Philip S. Portoghese,* Zeinab S. D. Gomaa, Dennis L. Larson,
Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

and Eli Shefter
School of Pharmacy, State University of New York, Buffalo, New York 14214. *Received September 7, 1972*

Optical antipodes of γ-1,3,5-trimethyl-4-phenyl-4-propionoxypiperidine (**4**) were prepared and the absolute configuration was determined by degradation to (*R*)-3-dimethylamino-2-methylpropiophenone. Analgetic testing in mice by the sc route indicated that the (+)-3*S*,5*S* isomer is equipotent with morphine and five times more potent than its (−) antipode. X-Ray studies of **4**·HCl indicate that the conformational features of the more active enantiomers of **4**·HCl and α- and β-prodine HCl are very similar. It is suggested that the methyl groups adjacent to the C-4 center in the more active enantiomers of **4** and the prodines induce a preferred, chiral arrangement of the phenyl and OCO groups which allow more facile association with analgetic receptors.

We have reported[1] that the 4*S* isomers of α- and β-prodine (**1a,b**) possess substantially greater analgetic potency than their antipodes **2a,b**. It was found further that the desmethyl analog **3** is much more potent than **2** but less potent than **1**. On this basis it was proposed that antipodal stereoselectivity arises because the analgetic receptor has the ability to distinguish between the enantiotopic edges of the piperidine ring. In this regard two possibilities were suggested, both of which would operate simultaneously. (1) The 3-Me group on the pro-4*R* edge of the piperidine ring sterically interferes with drug-receptor association, whereas identical substitution on the pro-4*S* edge leads to enhance affinity, possibly as a consequence of the 3-Me group fitting into a hydrophobic pocket. (2) The 3-Me group on the pro-4*S* edge induces a preferred, chiral conformation of the aromatic and/or OCO function which allows more facile association of the more active enantiomers **1** with the receptor.



1

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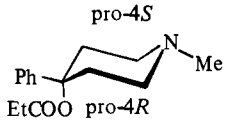
a, R = Me; R¹ = H
b, R = H; R¹ = Me



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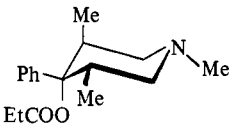
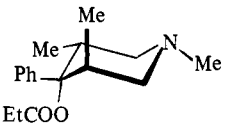
In an attempt to gain greater insight into the role of methyl substitution, we have investigated the 5-methyl derivative of prodine, γ-1,3,5-trimethyl-4-phenyl-4-propionoxypiperidine (**4**), which has been reported by Sorokin[2] to possess analgetic activity greater than that of morphine. This analgetic is of particular interest because each enantiomer possesses a different orientation (axial or equatorial) of the methyl group on the pro-*R* and pro-*S* edges of the piperidine ring and could provide information on the relative abilities of axial and equatorial methyl groups to determine antipodal stereoselectivity.

Chemistry. The synthesis of racemic **4**·HCl was carried out according to the procedure of Sorokin[2] with some modification. The piperidinol diastereomers **5** and **6** that were obtained through this procedure were separated either by column chromatography or preparative gc. The piperidinol **7** reported by Sorokin[2] could not be detected in the reaction mixture.

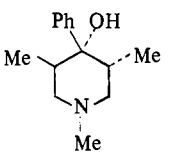


(+)-4 (3*S*,5*S*)



(−)-4 (3*R*,5*R*)

Since the relative stereochemistry of **5** had not been rigorously determined, we wished to prove unequivocally whether the original assignment was correct before we attempted to resolve this compound. Nmr appeared to be a facile method of differentiating between **5** and the other diastereomers since it can be noted that the *C*-methyl groups of **5** could possess different chemical shifts and/or small differences in vicinal coupling[3] because of their axial and equatorial orientations. On the other hand, **6** and **7** should show magnetically equivalent methyl groups because they are meso compounds. The nmr spectrum of **5** proved that the assignment was indeed correct, as the methyl groups were seen as an overlapping pair of doublets having slightly different coupling constants. Isomer **6** showed only a single methyl doublet.



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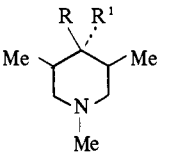
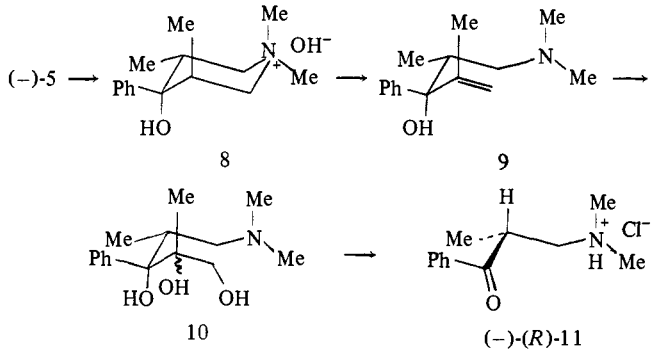


6, R = OH; R¹ = Ph
7, R = Ph; R¹ = OH

Optical resolution of (±)-**5** was achieved through fractional crystallization of the acid dibenzoyltartrate salt. The absolute stereochemistry of optically pure **5** was determined by chemical degradation to amino ketone **11** of known chirality.[4] Heating methohydroxide **8** derived from (−)-**5** afforded the desired olefin **9**. Although it is possible that elimination can occur from either side of the piperidine ring, this presents no problem because the C-3 and C-5 positions must possess the same chirality by virtue of the established relative stereochemistry of **5**.

Conversion of olefin **9** to triol **10** followed by *in situ*



glycol cleavage was carried out using OsO_4-$NaIO_4$ according to the method of Lemieux.[5] The amino ketone obtained from this reaction was converted to the HCl salt which was identical with authentic (−)-(*R*)-**11**. From the established relative stereochemistry of (±)-**5**, the absolute configuration of (−)-**5** therefore is 3*R*,4*R*. Esterification of (−)-**5** and conversion to the HCl salt yielded (−)-(3*R*,5*R*)-**4**·HCl. Its (+) enantiomer was prepared in an identical fashion.

X-Ray Studies. The X-ray analysis of (±)-**4**·HCl was undertaken to determine whether there are any conformational features that the more potent enantiomers [(+)-**1a**, (+)-**1b**, (+)-**4**] might have in common.

The conformational parameters of (±)-**4**·HCl and those reported[6-8] for the salts of (±)-α- and (±)-β-prodine are shown in Table I. For correlation purposes, only the torsion angles of the more active enantiomers are listed. The biggest conformation difference between the three structures is in the O(1)-C(10)-C(11)-C(12) grouping of atoms. However, since the energy of rotation about the C(10)-C(11) bond is no doubt relatively small, crystal-packing forces probably give rise to this difference. That this is indeed the case is suggested from the solid-state conformation of **1b**·HBr[8] which is very close to that of **1b**·HCl except about C(10)-C(11). The computer-drawn projection formulas for the HCl salts of these compounds are illustrated in Figure 1.

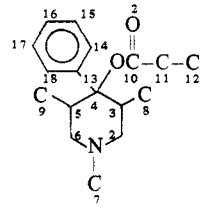
Pharmacology. The analgetic potencies of racemic and optically active **4**·HCl were determined in mice 15 min after sc administration by a modified hot-plate procedure. The ED_{50} values (Table II) indicate that (+)-**4**·HCl is as active as morphine and about five times more potent than the (−) isomer.

Stereostructure-Activity Relationship. The fact that the more potent enantiomer, (+)-**4**, is approximately one-half as active as desmethyl compound **3**[1] suggests that the Me group attached to the pro-*R* edge of the piperidine ring, to some degree, sterically interferes with receptor affinity.

Configurational data alone, however, cannot explain the fivefold greater potency of (+)-**4** over (−)-**4**, and for this reason the solid-state conformational features of **4** also were analyzed. The data in Table I indicate that the torsion angles [C(14)-C(13)-C(4)-C(5)] for the phenyl group in the more active isomers of prodine (**1a**,**b**) and its 5-Me derivative (+)-**4** range between −152 and −167°. The overall similarities of their conformations are apparent from the projection formulas obtained from the X-ray data (Figure 1). Space-filling molecular models indicate that this arrangement is more favorable in the (+)-prodine isomers **1** because of steric hindrance by the 3-Me group. Moreover, the aromatic ring in (+)-**4** is in a similar conformation in order to maintain the most favorable equilibrium distance between the axial and equatorial methyl groups. It also can be noted that the torsion angles for the C(4)-O(1)-C(10)-O(2) atomic grouping of all three (+) isomers are of similar magnitude.

It appears, therefore, that the C-3 and C-5 chiral centers of 4 induce preferred, chiral conformations of the phenyl

Table I. Conformational Parameters for Methyl-Substituted 4-Phenyl-4-propionoxypiperidines



Atomic grouping	Torsion angles[a] (+)-**4**·HCl[b]	(+)-**1a**·HCl[c]	(+)-**1b**·HCl[d]	(+)-**1b**·HBr[e]
N-C(2)-C(3)-C(4)	−57	−55	−56	−55
C(2)-C(3)-C(4)-C(5)	56	52	54	55
C(3)-C(4)-C(5)-C(6)	−54	−55	−55	−58
C(4)-C(5)-C(6)-N	53	60	58	58
C(5)-C(6)-N-C(2)	−54	−61	−58	−56
C(6)-N-C(2)-C(3)	54	59	58	56
C(8)-C(3)-C(4)-O(1)	174	59	171	172
C(8)-C(3)-C(4)-C(13)	57	−60	55	56
C(8)-C(3)-C(4)-C(5)	−71	175	−73	−71
C(3)-C(4)-O(1)-C(10)	−162	176	179	180
C(4)-O(1)-C(10)-C(11)	173	−178	176	−178
C(4)-O(1)-C(10)-O(2)	−6	1	−4	−5
O(1)-C(10)-C(11)-C(12)	165	171	−80	−175
C(14)-C(13)-C(4)-O(1)	−38	−28	−43	−38
C(14)-C(13)-C(4)-C(5)	−164	−152	−167	−163
C(14)-C(13)-C(4)-C(3)	73	82	68	73
C(9)-C(5)-C(4)-O(1)	−67			
C(9)-C(5)-C(4)-C(13)	59			
C(9)-C(5)-C(4)-C(3)	−177			

[a] Expressed in degrees. [b] Obtained from X-ray data of (±)-**4**·HCl. [c] Data obtained from X-ray data[6] of (±)-**1a**·HCl. [d] Data obtained from X-ray data[7] of (±)-**1b**·HCl. [e] Data obtained from X-ray data[8] of (±)-**1b**·HBr.

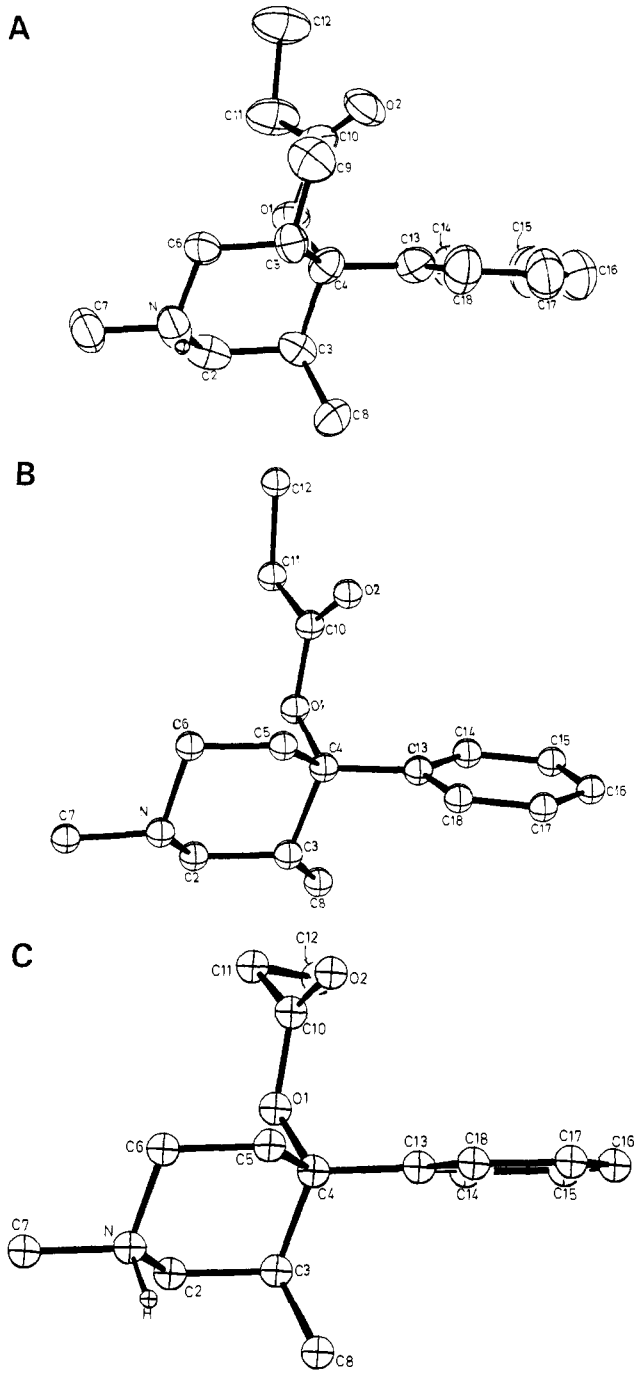


Figure 1. A comparison of the conformational structures of the more potent enantiomers: (A) (3*S*,5*S*)-**4**·HCl, (B) (3*R*,4*S*)-**1a**·HCl, (C) (3*S*,4*S*)-**1b**·HCl.

and OCO groups and that the chirality of this conformational arrangement in (+)-**4** allows for more facile association with the receptor when compared to that of its antipode. This does not necessarily imply that these molecules bind to the analgetic receptor with their aromatic rings and/or OCO function in the most favorable conformation, since it is also conceivable that complex formation might lead to a less energetically favorable torsion angle for these groups. The important feature of this similarity is that the groups surrounding the C-4 center might be in a preferred conformation which is more conducive to drug-receptor association regardless of the final conformational state of the ligand when in the complexed state.

The report[2] that the propionate esters of meso isomers **6** and **7** are inactive as analgetics is consistent with the view

Table II. Analgetic Activities of 1,3,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride Antipodes

Compound	Configuration	ED_{50}, μmol/kg[a] (95% limits)
(±) **-4**·HCl		12.57 (10.42–14.27)
(+) **-4**·HCl	3*S*,5*S*	4.91 (3.37–5.87)
(-) **-4**·HCl	3*R*,5*R*	25.01 (22.54–27.61)
Meperidine HCl		28.79 (16.03–35.91)
Morphine sulfate		5.44 (5.26–15.23)

[a] Administered sc in mice.

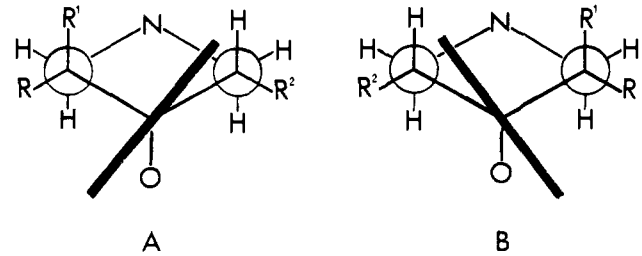


Figure 2. The relationship between the phenyl group and the piperidine ring in the more potent (A) and less potent (B) enantiomers of α-prodine (R = Me; $R^1 = R^2 = H$), β-prodine (R = R^2 = H; R^1 = Me), and **4** (R = H; $R^1 = R^2$ = Me).

that enantiotopically situated diequatorial methyl groups interfere with drug-receptor association by direct steric hindrance with the receptor. In addition to this possibility the diequatorial methyl groups in **6** propionate restrict the conformation of the phenyl group perpendicular to the plane of the ring, thereby preventing it from assuming the necessary orientation when bound to the receptor.

In summary, the available evidence suggests that a chiral center will determine the preferred conformation of a vicinal phenyl and/or OCO group and that this in part is responsible for the different analgetic activities between enantiomers. The relationships of aromatic group to the piperidine ring in the more active and less active enantiomers are illustrated in Figure 2. Although this relationship pertains only to analgetics with equatorial phenyl groups, it might be expected that there would be a different but internally consistent correlation among analgetics with an axially oriented aromatic group. The different conformational correlation could arise as a consequence of the different modes of interaction[9-11] of equatorial- and axial-phenyl analgetics with receptors.

This study indicates that configuration and conformation are inseparable features which must be dealt with together in analyzing stereostructure-activity relationships of analgetics. We are currently conducting studies on other analgetics in an effort to study this in greater depth.

Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are not corrected. Ir spectra were recorded on a Perkin-Elmer 237 B spectrophotometer as liquid film or KBr disks. Nmr data (τ) were determined in $CDCl_3$ (Me_4Si) or D_2O (DSS) with a Varian A-60D spectrometer; all spectra were consistent with the proposed structures. Optical rotations were determined in a 1-dm cell using a Perkin-Elmer Model 114 polarimeter. Gc analyses were determined on a Perkin-Elmer Model 900 or a Varian Aerograph Model 700 gas chromatograph. Elemental analyses were performed by M. H. W. Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theoretical values.

1,3,5-Trimethyl-4-phenyl-4-piperidinol (5, 6). The synthetic procedure was essentially the same as that employed by Sorokin.[2]

The only modification involved dehydrobromination of 2,4-dibromo-2,4-dimethyl-3-pentanone (271.9 g, 1 mol) at 110° using $LiCO_3$ (200 g) and LiBr (33 g) in DMF (500 ml). The product, 2,4-dimethyl-1,4-pentadien-3-one (yield, 71%), then was transformed to 1,3,5-trimethyl-4-piperidone followed by conversion to a mixture of 5 and 6 employing the reported[2] procedure.

Separation of α- and γ-1,3,5-Trimethyl-4-phenyl-4-piperidinol (6, 5). The mixture of isomers was chromatographed on basic alumina (AG 10, 100–200 mesh) using C_6H_6 containing increasing amounts of EtOAc (1–10%). Crystallization (C_6H_{12}) of the first fraction afforded (±)-5: mp 128–130° (lit.[2] mp 134°); nmr ($CDCl_3$) 9.22 (overlapping d, J = 5.5 and 7.5 Hz, 6 H, CCH_3). The second compound to be eluted was the α isomer 6: mp 127–130° (lit.[2] mp 131.5°); nmr ($CDCl_3$) 9.40 (d, J = 6 Hz, 6 H, CCH_3).

Preparative gc (30% SE-30, 20 ft × 3/8 in., 170°) also was employed to separate 5 and 6 (retention times 80 and 72 min, respectively).

(−)-(3*R*,5*R*)-1,3,5-Trimethyl-4-phenyl-4-piperidinol (+)-Dibenzoyl Acid Tartrate. A solution (Me_2CO) of 5 (0.430 g, 0.002 mol) was mixed with (+)-dibenzoyltartaric acid (0.752 g, 0.002 mol) dissolved in the same solvent and the solvent removed. Crystallization (MeOH) afforded 0.320 g of crude salt: mp 173–175°; $[\alpha]^{25}D$ +51° (*c* 0.5, MeOH). Recrystallization (MeOH) gave 0.185 g of the pure salt: mp 187–189°; $[\alpha]^{25}D$ +40.5° (*c* 0.5, MeOH). *Anal.* ($C_{32}H_{35}O_9N$) C, H, N.

(+)-(3*S*,5*S*)-1,3,5-Trimethyl-4-phenyl-4-piperidinol (−)-Dibenzoyl Acid Tartrate. The solvent was removed from the above mother liquors and the residue was suspended in H_2O, rendered alkaline with NH_3, and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and the solvent was removed. The residue was dissolved in MeOH and treated with 1 equiv of (−)-dibenzoyltartaric acid in a minimum volume of MeOH. After allowing the solution to stand 10 hr at 25°, the salt was collected and recrystallized (MeOH) to afford 0.170 g of the salt: mp 188–190°; $[\alpha]^{25}D$ −39° (*c* 0.5, MeOH). *Anal.* ($C_{32}H_{35}O_9N$) C, H, N.

(+)-(3*S*,5*S*)-1,3,5-Trimethyl-4-phenyl-4-piperidinol [(+)-5]. A solution (MeOH) of (+)-5-(−)-dibenzoyl acid tartarate (0.893 g, 0.0015 mol) was mixed with H_2O (40 ml), rendered alkaline (10% NaOH), and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O (15 ml) and dried ($MgSO_4$). Removal of solvent gave (+)-5 which was converted to the HCl salt (ethereal HCl). Crystallization (EtOH) afforded 0.284 g (74%) of (+)-5·HCl: mp 279–281°; $[\alpha]^{29}D$ +76.2° (*c* 1, EtOH). *Anal.* ($C_{14}H_{22}ONCl$) C, H, N.

(−)-(3*R*,5*R*)-1,3,5-Trimethyl-4-phenyl-4-piperidinol [(−)-5]. A solution (MeOH) of (−)-5-(+)-dibenzoyl acid tartarate (1.133 g, 0.002 mol) was rendered alkaline (10% NaOH) and extracted using a procedure identical with that employed for the (+) antipode. Conversion to the HCl salt and crystallization (EtOH) afforded 0.332 g (yield 70%) of (−)-5·HCl: mp 279–281°; $[\alpha]^{28}D$ −75.8° (*c* 1, EtOH). *Anal.* ($C_{14}H_{22}ONCl$) C, H, N.

(−)-(3*R*,5*R*)-1,3,5-Trimethyl-4-phenyl-4-piperidinol Methiodide [(−)-8]. A solution of (−)-(5) (0.241 g, 0.0011 mol) in 25 ml of Et_2O was mixed with MeI (2 g) and allowed to stand at 25° for 7 days. The crude product was crystallized (Me_2CO–EtOAc) to afford 0.307 g (84% yield) of (−)-8, mp 211–213°. Recrystallization gave mp 212–214°, $[\alpha]^{23}D$ −51.2° (*c* 1, EtOH). *Anal.* ($C_{15}H_{24}NOI$) C, H, N.

(+)-5-Dimethylamino-2,4-dimethyl-3-phenyl-3-hydroxy-1-pentene [(+)-9]. An aqueous solution (10 ml) of (−)-8 (0.289 g, 0.0008 mol) was shaken for 1 hr with an equivalent amount of Ag_2O. The aqueous suspension was filtered and the solvent removed *in vacuo*. The residue was heated for 1 hr at 170–175° under N_2. The reaction mixture was cooled and extracted with Et_2O, and the Et_2O extracts were dried ($MgSO_4$). The solvent was removed leaving an oil which was chromatographed on basic alumina (C_6H_6–EtOAc) and then converted to the HCl salt (0.0978 g, yield 45%), mp 222–224°. Recrystallization (EtOH–EtOAc) gave mp 226–227°, $[\alpha]^{27}D$ +37.2° (*c* 1, EtOH). *Anal.* ($C_{15}H_{24}NOCl$) C, H, N.

(−)-(*R*)-3-Dimethylamino-2-methylpropiophenone Hydrochloride [(−)-11]. To a stirred mixture of 12 ml each of H_2O and Et_2O was added one crystal of OsO_4 followed by (+)-9 (0.089 g, 0.00033 mol). Two drops of pyridine and 0.290 g (0.0014 mol) of $NaIO_4$ were added to the reaction mixture and stirring was continued at 25° for 24 hr. The aqueous layer was separated and rendered alkaline with NH_3. It then was extracted with Et_2O and dried ($MgSO_4$), and the Et_2O was removed. The oily residue was converted to the HCl salt and crystallized from EtOH–EtOAc: mp 177–179°, $[\alpha]^{27}D$ −66.5° (*c* 1, EtOH); authentic sample,[4] mp 179–181°, $[\alpha]^{32}D$ −67.8° (*c* 1, EtOH), mmp 178–180°. *Anal.* ($C_{12}H_{18}NOCl$) C, H, N.

(+)- and (−)-γ-1,3,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(+)- and (−)-4·HCl]. A mixture of (+)-5 (0.75 g, 0.008 mol), propionic anhydride (1 ml), and pyridine (1 ml) was heated (100°) under N_2 for 24 hr. The reaction mixture was cooled, and the volatile components were removed *in vacuo*. The residue was dissolved in water, rendered alkaline with NH_3, and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$), the solvent removed, and the ester converted to the HCl salt. Two crystallizations (Me_2CO–Et_2O) and drying *in vacuo* gave (+)-4·HCl: mp 142–146°; $[\alpha]^{27}D$ +119.6° (*c* 0.5, EtOH). *Anal.* ($C_{17}H_{26}O_2NCl \cdot H_2O$) C, H, N.

The (−) isomer was prepared from (−)-5 using a procedure identical with that described above: mp 147–150°; $[\alpha]^{24}D$ −112.8° (*c* 0.5, EtOH). *Anal.* ($C_{17}H_{26}O_2NCl \cdot H_2O$) C, H, N. The racemate [(±)-4·HCl] was crystallized from EtOH–Et_2O; mp 198–200° (lit.[2] 183–184°).

Analgetic Testing. Analgetic potencies for the compounds given in Table I were determined in mice using a modification of the hot-plate procedure of Eddy.[12] The hot plate was the top enclosing surface of a glass bath through which thermostatically controlled hot water was circulated. The bath was 12.5 cm in diameter and 10.5 cm high. Under the conditions used, the temperature on the surface of the cylinder was maintained at 65°. The compounds were administered to the mice sc in physiological saline solution. For each dose level, the solutions were prepared so that each mouse received 0.01 ml/g of body weight. A group of 20, 25–35-g male white Swiss-Webster mice was used for each dose level examined. The mice were placed, one at a time, on the hot surface and the time recorded until the animal jumped off. The sum of the contact times for three consecutive exposures was recorded as the reaction time. Reaction times were determined three times for every mouse at 15-min intervals before injecting the drug to establish a reaction time control value. The mean value for the second and third preinjection reaction times for each mouse was taken as the control value, each mouse being used as its own control. The average of the mean reaction times for the second and third preinjection intervals for 374 mice was 9.15 sec, SD = 4.54. Mice having a mean reaction time greater than 21.6 sec were excluded as nonresponders. The pooled mean reaction time for the second and third preinjection intervals was 8.99, SD = 6.6, excluding the nonresponders. Reaction times were recorded 15, 30, and 45 min after sc administration of the drug, the 15-min interval being taken as the response metameter. A mouse was judged to exhibit analgesia when its 15-min postinjection reaction time was greater than double its second and third preinjection intervals mean value and greater than the pooled mean value. A cut-off time of 45 sec was used for animals which did not leave the hot surface. The average of the means for the second and third preinjection intervals for saline control (30 mice) was 8.89, SD = 5.38, and the average for the post 15-min interval was 8.2, SD = 3.12. The ED_{50} values (Table I) were determined by probit analysis according to the methods of Stanley[13] and with the aid of a Hewlett-Packard Calculator, Model 9100A.

X-Ray Studies. Lath shaped orthorhombic crystals were obtained from alcoholic ether. The following crystallographic data were measured for these crystals: a = 13.592 (2), b = 29.026 (3), c = 9.430 (1) Å; space group *Pccn*; density (measured by flotation) 1.24 g/cm³; density (calculated) 1.210 g/cm³ (based on 12 water molecules in unit cell); Z = 8.

The stationary crystal–stationary counter technique was employed for measuring the intensity data. A total of 1430 reflections out of the 1920 measured (range between 0 and 100° in 2θ) had intensities which were significantly greater than their respective backgrounds. Aside from corrections for $\alpha_1 - \alpha_2$ splitting and Lorentz–polarization effects, an approximate correction for absorption was applied (based on anisotropy of transmission of X-rays as a function of the diffractometer angle ϕ). All X-ray data were collected on a General Electric XRD-6 diffractometer equipped with single-crystal orientor.

Application of the Sayre relationships[14] to 241 reflections having normalized structure factors greater than 1.5 enabled a trial structure to be obtained. A program written by Long[15] was utilized for this purpose. Refinement using difference electron density maps and least squares (block diagonal approximation to normal equations) enabled the positions and thermal parameters of all the nonhydrogen atoms to be established.

A peak of significant electron density was found along the twofold axis (x = 0.25, y = 0.25). It was treated as a water molecule (O(4)-H_2O) in the refinement process, as it could be

weakly hydrogen bonded to the carbonyl oxygen of an adjacent ester group. The refined O···O distance is 2.96 (0.12) Å. The large thermal parameter obtained for this oxygen probably relects the partial occupancy for this water.

The final R value (usual reliability index) for the observed data was 0.082. The final positional and thermal parameters for the nonhydrogen atoms are given in Table III.† Those for the hydrogens will be supplied on request.

There is another water molecule (O(3)-H_2O) in the crystal which appears to be participating in hydrogen bonds with the chlorine atom. There are two chlorines about this water at distances of 3.19 (1) and 3.18 (1) Å and with an angle between them of 103.8 (2)°.

The only other intermolecular contact which appears to be of significance is between the nitrogen and the chlorine [3.09 (1) Å]. A proton located on the piperidine nitrogen (N-H distance 0.6 Å) was 2.51 Å away from the chlorine. The N-H···Cl angle of 170° is also indicative of a hydrogen bond.

The intramolecular bond distances and angles derived for this molecule are similar within experimental error to those obtained for α- and β-prodine. Since the conformational parameters are the principal reason for this study, a discussion of the intramolecular bond lengths and angles is not felt to be warranted. A tabulation of the same will be supplied on request, or they can be easily calculated from the least-squares thermal parameters in Table III of the microfilm edition.†

†This material will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, 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-73-199.

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Stereochemical Studies on Medicinal Agents. 14.[1] Relative Stereochemistries and Analgetic Potencies of Diastereomeric 3-Allyl and 3-Propyl Derivatives of 1-Methyl-4-phenyl-4-propionoxypiperidine

Kevin H. Bell and Philip S. Portoghese*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.
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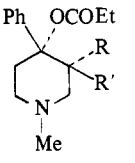
An improved synthesis of diastereomeric (±)-3-allyl-1-methyl-4-propionoxypiperidine (**2a,b**) is described, and the 3-propyl analogs **3a,b** have been prepared. The relative stereochemistries of **2a,b** have been deduced from chemical and nmr studies and are opposite to that proposed originally by others. The analgetic potency of **2a** is 15 times greater than that of morphine and 116 times greater than **2b**. The propyl analog **3a** is much less potent ($^1/_{24}$) than **2a**, indicating that the double bond of the 3-allyl group is responsible for the increased activity. The fact that the rank orders of potencies for the allyl (**2a** > **2b**) and propyl (**3a** > **3b**) diasteromers are opposite to that found in the prodines (**1b** > **1a**) suggests that the mode of interaction of **2b** and **3b** with analgetic receptors is different from that of β-prodine (**1b**). A stereochemically positioned hydrophobic pocket of limited size on the receptor has been proposed to rationalize this reversal of stereoselectivity. Certain aspects of the role of conformational isomerism in the action of these analgetics are discussed.

The prodine isomers **1a,b**[2] have been the subject of extensive stereochemical investigations for a number of years in attempts to explain the difference in analgetic potency between these diastereomers.[3-10] In an early paper describing some of these stereochemical studies, Ziering, *et al.*, also reported[4] the preparation, relative stereochemical assignment, and analgetic activities of several related compounds. One of these, the allyl analog of prodine (**2a,b**), stimulated our interest because the order of activity of the racemates is opposite to that of the prodines (**1a,b**) of the same stereochemistry. However, the tentative stereochemical assignments of **2a,b** were in doubt because their stereochemistries were based on spectral studies which led to an erroneous assignment of **1a,b**.[5-8] We therefore undertook an investigation of the allyl diastereomers **2a,b** to establish with certainty their relative stereochemistries and to reexamine their analgetic activities. In addition, the anticipated ready conversion of the allyl compounds into their propyl counterparts **3a,b** offered an opportunity to investigate the affect of electronic factors in the stereoselectivity of the 3 substituent in the analgetic receptor interaction.



1a, R = Me; R' = H
b, R = H; R' = Me
2a, R = $CH_2CH{=}CH_2$; R' = H
b, R = H; R' = $CH_2CH{=}CH_2$
3a, R = Pr; R' = H
b, R = H; R' = Pr