was obtained (GC 95.6%).

1-(2-Butyl-2,4-dichlorophenylethyl)-1*H*-imidazole (176). To a solution of **130** (18 g, 0.073 mol) in pyridine (50 ml), methanesulfonyl chloride (9.7 g, 0.085 mol) was added dropwise over a period of 10 min, while cooling on ice. The reaction mixture was stirred for 3 h. Then H_2O was added and the mixture extracted with *i*-Pr_2O. The organic layer was washed with diluted HCl solution, dried ($MgSO_4$), and evaporated in vacuo. The oily residue (21.5 g, 0.066 mol) was refluxed overnight with a fivefold excess of imidazole (22 g, 0.33 mol) in DMF (200 ml). After cooling and dilution with H_2O, the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), stirred with SiO_2, filtered, and evaporated in vacuo. The oily residue was dissolved in *i*-Pr_2O, and after addition of a slight excess of HNO_3, 65% solution in water, the nitrate salt crystallized. The solid was filtered and recrystallized from a mixture of *i*-PrOH–*i*-Pr_2O yielding 11.7 g (49%) of **176**: mp 140 °C.

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Stereochemical Studies on Medicinal Agents. 20.[1] Absolute Configuration and Analgetic Potency of α-Promedol[2] Enantiomers. The Role of the C-4 Chiral Center in Conferring Stereoselectivity in Axial- and Equatorial-Phenyl Prodine Congeners

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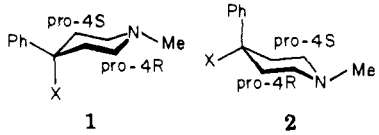
Optical antipodes of the axial phenyl analgetic, α-promedol hydrochloride (**3**), were prepared and the absolute stereochemistry was determined by relating one of the enantiomers to its γ diastereomer having the 2*S*,4*S*,5*R* configuration. The analgetic potency of (+)-(2*R*,4*S*,5*S*)-**3** is 20 times that of morphine, while its enantiomer, (–)-(2*S*,4*R*,5*R*)-**3**, is inactive at 50 mg/kg. These results are in accord with prior reports which indicate that substitution of a 3- or 5-alkyl group on the pro-4*S* enantiotopic edge of the piperidine ring leads to enantiomers which have greater potency than those substituted in an identical position on the pro-4*R* edge. This, coupled with the fact that the torsion angle between the axial phenyl group and piperidine ring in (+)-**3** is of the same sign as its equatorial congeners, suggests that the C(3)–C(4)–C(5) moiety and its substituents at C(4) are located in a similar chiral environment on the receptor. In contrast, the C(2)–N–C(6) portion of the axial and equatorial molecules does not bind in the same receptor environment, and it is suggested that different modes of interaction in the prodine series arise from different orientations of this moiety.

The concept that many enzymes can distinguish between the pro-*R* and pro-*S* enantiotopic edges of substrates containing an sp^3 prochiral center has been recognized for nearly 30 years.[3,4] Although this phenomenon, which is usually referred to as the "Ogston effect" after its original proponent,[5] has considerable precedent in enzymatic reactions, until recently[6] it had not been discussed in connection with nonenzymatic interaction between drugs and receptors.

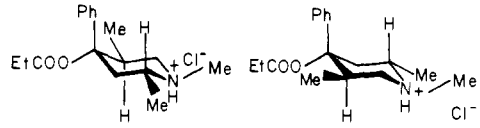
Over the past several years we have investigated[1,6-11] this phenomenon with 4-phenylpiperidine analgetics because meperidine (**1a**) and its reversed esters (**1b**) possess enantiotopic edges (pro-4*R* and pro-4*S*) and are known to interact with receptors that have a high degree of antipodal stereoselectivity.[12] These studies have demonstrated that analgetic receptors are capable of distinguishing between the enantiotopic edges of the piperidine ring, and it has been pointed out that the sign of the torsion angle between the phenyl group and piperidine ring is also correlated with analgetic potency.



1 **2**

X = OCOEt or COOEt

All of these investigations[6-11] have dealt with 4-phenylpiperidines in which the phenyl group is situated in an equatorial preferred conformation. However, there is no report pertaining to the role of the Ogston effect among members of this series containing an axially oriented aromatic group (**2**). Such studies not only should provide information on the stereostructure–activity relationship between equatorial and axial 4-phenylpiperidines but, in addition, might establish whether or not there is a correlation between members of the above series and structures related to morphine. In this report we describe the preparation, absolute configuration, and biological evaluation of enantiomers of α-promedol (**3**),[2,13-15] a highly potent analgetic whose phenyl group resides preferentially in the axial conformation.[12,16-18]



2*R*,4*S*,5*S* (+)-**3** 2*S*,4*R*,5*R* (–)-**3**

Chemistry. Synthesis of a diastereomeric mixture of promedol alcohols was accomplished by the method described previously.[10] The α isomer, (±)-**4**, constitutes ~5% of the mixture and was isolated by preparative GLC

Table I. Analgetic Potencies of α-Promedol and Its Enantiomers

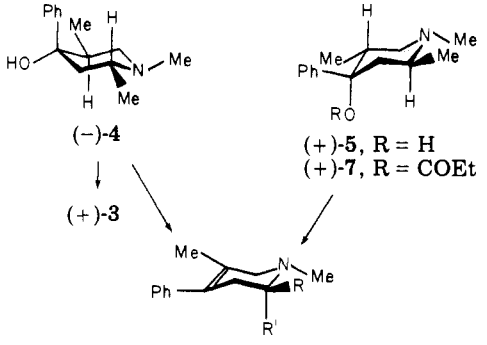
Compd[a]	Confign	ED_{50}, mg/kg[b]	Onset[c]	Peak[d]	Duration[e]
(+)-3	2R,4S,5S	0.06 (0.04-0.08)[f]	2.7	14.0	91.5
(−)-3	2S,4R,5R	Inactive to 50			
(±)-3		0.10 (0.07-0.13)	2.5	20.7	103
Morphine		1.2[g]			

[a] Tested as HCl salts. [b] Tested sc in mice by the hot-plate procedure.[19] [c] Onset of analgesia (minutes). [d] Time required (minutes) for peak analgesia. [e] Duration of analgesia (minutes). [f] Confidence interval (95%). [g] A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

or by fractional crystallization of its HCl salt. Compared to the other diastereomers (±)-4 has a longer retention time on chromatographic columns than the β- or γ-racemate due to the more accessible equatorial orientation of the hydroxy group.[19]

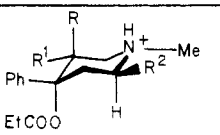
Optical resolution of (±)-4 was accomplished by fractional crystallization of the salts formed with optically pure di-*p*-toluoyltartaric acid. The enantiomeric bases obtained from the salts then were esterified with propionyl chloride using $KHCO_3$ as a proton scavanger. It was noted that some olefin formation took place during the esterification if no precaution was taken to eliminate all proton sources.

The approach employed for determining the absolute configuration of optically active α-promedol [(+)-3, (−)-3] involved relating one of the precursors [(−)-4] to its γ diastereomer [(+)-5] having the 2S,4S,5R configuration.[10] Thus, destruction of the C-4 and C-5 chiral centers in (−)-4 and (+)-5 by acid-catalyzed dehydration afforded olefins [(−)-6 and (+)-6, respectively] which were enantiomeric at C-2. Since the absolute stereochemistry of (−)-4 and (+)-5 are opposite at C-2, it follows from the known[13-18] relative stereochemistry of (±)-4 that the absolute configuration of (−)-4 is 2R,4S,5S. Its ester, (+)-3, possesses the same configuration since none of the chiral centers are disturbed by this conversion.



Pharmacology. The analgetic potencies of (±)-α-promedol and its enantiomers were determined by the hot-plate procedure[20] after subcutaneous administration in mice (Table I). The (+) isomer is approximately twice as potent as the racemic compound and 20 times more potent than morphine. The (−) isomer was inactive to a dose of 50 mg/kg indicating that resolution was essentially complete. The fact that the racemate is approximately one-half as potent as (+)-3 suggests that the inactive enantiomer possesses little or no affinity for the receptors and is functioning as a diluent rather than as an antagonist. The observed enantiomeric potency ratio of greater than 800 is unprecedented in any of the previously investigated nonrigid analgetics. Such a large difference in activity of enantiomers cannot be explained by metabolism or distribution phenomenon but, rather, must be directly related to selectivity in receptor binding.

Table II. More Potent Enantiomers of Equatorial-Preferred 4-Phenylpiperidine Analgetics



Compd	R	R¹	R²	Confign of more potent enantiomer
(+)-γ-Promedol [(+)-7]	H	Me	Me	2S,4S,5R[a]
(+)-α-Allylprodine	H	Allyl	H	3R,4S[b]
(−)-α-Propylprodine	H	Pr	H	3R,4S[c]
(+)-α-Ethylprodine	H	Et	H	3R,4S[c]
(+)-α-Prodine	H	Me	H	3R,4S[d]
(+)-β-Prodine	Me	H	H	3S,4S[d]

[a] Reference 10. [b] Reference 8. [c] Reference 9. [d] Reference 6.

Stereostructure–Activity Relationship. The stereochemical feature common to the more potent enantiomers of α-promedol [(+)-3 (Table I)] and γ-promedol [(+)-7[10]] is the 4S configuration. As can be seen in Table II, this relationship is found among all the 4-phenylpiperidines having alkyl groups either at C(5) or at C(3). Further, it appears that methyl substitution at C(2) does not profoundly affect 4S stereoselectivity, although it can exert a modifying influence.[10]

Results of the present study are in accord with prior reports[1,6-11] which indicate that substitution of a 3- or 5-alkyl group on the pro-4S edge of the piperidine ring leads to enantiomers that have greater analgetic potency than those substituted in an identical position on the pro-4R enantiotopic edge. Moreover, the fact that the axial phenyl compound, (+)-3, also conforms to the stereostructure–activity relationships of the equatorial phenyl ligands (Table II) suggests that all are interacting with a common topographical component of the receptor. Thus, it appears that the receptor distinguishes between the C(3) and C(5) positions on the enantiotopic edges of both conformers in a similar fashion.

That the Ogston effect[3-5] operates in a consistently stereoselective fashion despite differences in the overall conformation cannot be explained on the basis of a receptor-induced conformational change of the ligand because of the large energy barrier[12] for transforming the all-equatorial form of (+)-7 to its flip-axial conformation. A conformational inversion of (+)-3 to the less energetically stable equatorial phenyl form also seems unlikely in view of the high (+)-3/(−)-3 potency ratio (>800). Thus, if a significant fraction of 3 were in the equatorial phenyl conformation, its enantiomeric potency ratio would be expected to be considerably lower by analogy with β-prodine (Table II) [(+)/(−) ratio = 12][6] whose stereochemistry is identical with 3 at the common chiral centers. Furthermore, congeners whose aromatic groups are fixed in either conformation have been reported to display comparable potency.[12]

Another piece of evidence which is consistent with the idea of a common topographical receptor component which binds axial and equatorial phenyl conformers is obtained from x-ray crystallographic studies.[16,17] The x-ray data for (±)-4 together with our absolute configurational assignment reveal that the axial phenyl group in the more potent enantiomer, (+)-3, assumes a torsion angle whose

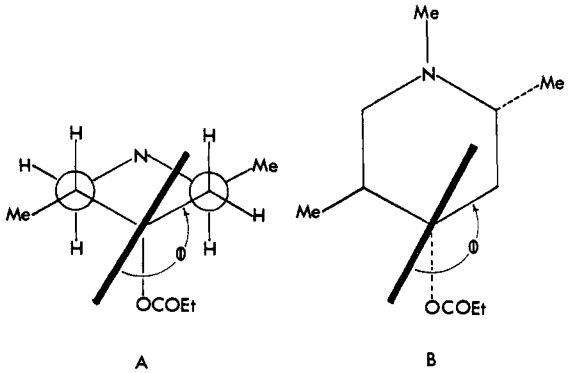


Figure 1. Projection formulas of the more potent enantiomers of γ-promedol [(+)-7 (A)] and α-promedol [(+)-3 (B)]. Note that the phenyl groups in both show torsion angles, ϕ, of identical sign.

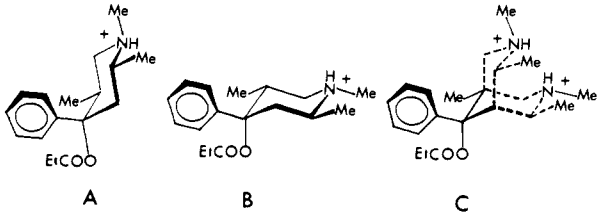


Figure 2. The more potent axial phenyl (A) and equatorial phenyl (B) diastereomers superimposed (C) upon one another. Portions which are not superimposed are designated by dashed lines in C.

sign is identical with that of the more potent enantiomers in the equatorial series.[1,6-11] This relationship is illustrated in Figure 1.

Superimposition of the more potent axial phenyl and equatorial phenyl diastereomers [(+)-3 and (+)-7, respectively] reveals an intriguing relationship between these compounds. As can be seen in Figure 2, the C(3)–C(4)–C(5) moiety containing the aromatic group and ester function in the axial phenyl (A) and equatorial phenyl (B) conformers can be superimposed (C). The portions of A and B which are not superimposed (C) are designated by the dashed lines, and it can be noted that the nitrogen in each conformer is located in a different position. If the superimposed moieties represent portions of the molecule which are located in the same chiral receptor environment, this would explain the fact that both conformers possess 4S stereoselectivity. On the other hand, the C(2)–N–C(6) portion of the molecules, being in different locations, do not bind in the same receptor environment.

This model therefore suggests that the binding of axial and equatorial 4-phenylpiperidines to analgetic receptor sites involves different modes of interaction. Although the idea of the multiple modality concept[21] of binding to analgetic receptors was developed over 10 years ago, the detailed aspects of this phenomenon were not well understood, and, hence, the concept was described only in general terms. The present study now has clarified an important aspect of this concept relative to the 4-phenylpiperidines. Since the receptor recognition locus for the C(3)–C(4)–C(5) moiety and its C-4 substituents appears to be invariant in its absolute stereoselectivity toward axial and equatorial 4-phenylpiperidines, it is conceivable that the different modes of interaction between the two conformers arise from the different orientations of the C(2)–N–C(6) groups. This also is consistent with the absence of a linear-free-energy relationship[21] between series of axial and equatorial phenyl analgetics containing identical changes in the N-substituent. The mechanism

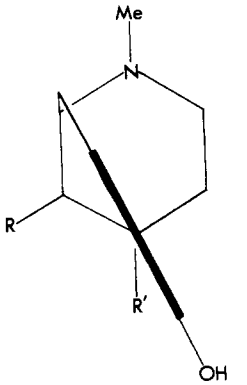
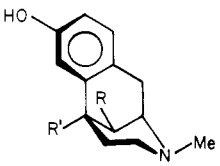


Figure 3. A projection formula of the partial structure of morphine-related structures (8) illustrating the torsion angle of the aromatic moiety with respect to the piperidine ring.

by which the C(2)–N–C(6) moiety is accommodated in both the axial and equatorial 4-phenylpiperidines remains to be clarified. One possibility is a conformational change of the anionic site. Ion-pair formation of either conformer with the receptor also could occur if the anionic site were juxtaposed between the two receptor loci occupied by the protonated nitrogen of each conformer (Figure 1, C). A combination of these mechanisms also is plausible.

It is noteworthy that the piperidine ring of morphine and active enantiomers of structurally related ligands (8)[22] also possess an unsubstituted enantiotopic edge which is identical with that of (+)-3 and its equatorial counterparts (Table II). This could be interpreted to mean that the mode of interaction of 8



8

is identical with that of (+)-3. However, it is not certain whether this conclusion is warranted for two reasons. Firstly, there are a sufficient number of differences in functionality between 3 and 8 which might contribute to different modes of interaction of these ligands with analgetic receptors. In this regard the critical C(4) chiral center in 3 and the equivalent position in 8 contain different substituents (ester vs. alkyl; phenyl vs. phenolic) which might contribute differently to binding in the drug–receptor interaction. The second reason is concerned with the opposite torsion angles of the aromatic rings in (+)-3 and 8 (compare Figure 3 with Figure 1, B). In this connection it is of course possible that the barrier to rotation is not large and the aromatic group of (+)-3 can be transformed to a conformation similar to that found in 8 or, alternately, that the torsion angle of the aromatic ring in 8 is not optimal. Studies are currently underway to investigate these aspects of the stereostructure–activity relationship.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by NHW Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theoretical values. Ir spectra were obtained with Perkin-Elmer Models 237B or 457 spectrophotometers as liquid films or KBr disks, unless otherwise stated. NMR data (δ) were recorded with a Jeol MH100 spectrometer in $CDCl_3$ (Me_4Si). All ir and NMR spectra were consistent with assigned structures. GC

separations were performed with a Varian Aerograph Model 700 or Perkin-Elmer Model 900 chromatograph. Optical rotations were taken in a 1-dm cell utilizing a Perkin-Elmer Model 241 polarimeter.

(±)-α-1,2,5-Trimethyl-4-phenyl-4-piperidinol [(±)-4]. The diastereomeric promedol alcohol mixture obtained from reacting 1,2,5-trimethyl-4-piperidinone with phenyllithium (8.2 g) was crystallized several times to remove excess (±)-5. GC analysis of the oil showed it to consist predominately of the γ isomer with two other major fractions which were attributed to the α and β isomers. The α-alcohol has the longest retention time due to the stronger interaction of its equatorial hydroxy group with the stationary phase of the column. Complete separation of (±)-4 could be accomplished by injection of 200 μl of the diastereomeric alcohol mixture onto a preparative GC column (20 ft, 0.25 in.) packed with 3% OV-17 (150 °C). Crystals obtained by this procedure were identical with those obtained by the simpler process of precipitating (±)-4 by bubbling HCl gas into an Me_2CO solution of the diastereomeric mixture. After converting (±)-4·HCl to the base, it was partitioned into Et_2O (3 × 20 ml) and evaporated, and the residue was crystallized from petroleum ether. The total yield of (±)-4 was 0.50 g (about 5% of isomeric mixture), mp 106–107° (lit. 106–107,[23] 102–103°[13]).

Resolution of (±)-α-1,2,5-Trimethyl-4-phenyl-4-piperidinol [(±)-4]. Solutions of 0.4 g (0.0018 mol) of (±)-4 in MeOH (5 ml) and 0.72 g (0.0018 mol) of (+)-di-*p*-toluoyltartaric acid in MeOH (5 ml) were combined and filtered, and the solvent was removed to afford an oil which then was dissolved in hot MeOH (5 ml) and cooled to −10° for 12 h. The salt which crystallized was collected and dried in vacuo to give 0.52 g of partially resolved material: $[\alpha]^{21}D$ +81.7° (*c* 1, MeOH). Two additional recrystallizations of the salt from MeOH gave a constant rotating solid with $[\alpha]^{23}D$ +80.2° (*c* 1, MeOH), mp 159–160°. Anal. ($C_{34}H_{39}NO_9$) C, H, N. The free base was generated by adding aqueous, 5% NaOH (2 ml) to the salt and extraction with Et_2O (3 × 3 ml). The Et_2O extracts were dried (Na_2SO_4) and the solvent was removed to leave an oil which was crystallized from petroleum ether (bp 30–60°) to give (+)-4: mp 106–107°; $[\alpha]^{23}D$ +20.3° (*c* 1, MeOH).

Partially resolved (−)-4 was recovered from the resolution mother liquor by addition of base (5% NaOH) and extraction with Et_2O (3 × 5 ml). Solvent was removed in vacuo to give 0.21 g (0.00096 mol) of crude (−)-4, $[\alpha]^{23}D$ −4.2°. The free base was combined with (−)-di-*p*-toluoyltartaric acid (0.370 g, 0.00096 mol) and treated as described above to afford (−)-4 (−)-di-*p*-toluoyltartrate (0.35 g): mp 159–160°; $[\alpha]^{23}D$ −79.8° (*c* 1, MeOH). Anal. ($C_{34}H_{39}NO_9$) C, H, N. Isolation of the free base as described for the enantiomer gave 0.12 g of (−)-4: mp 106–107°; $[\alpha]^{23}D$ −20.2° (*c* 1, MeOH).

(±)-1,2,5-Trimethyl-4-phenyl-1,2,3,6-tetrahydropyridine [(±)-6]. Racemic 5 (0.00092 mol) was refluxed in concentrated HCl (5 ml) for 15 h, cooled, made basic (Na_2CO_3), and extracted with Et_2O. The residual oil from evaporation of the dried extract (Na_2SO_4) was found to be (±)-6 (0.15 g) by GLC and NMR analysis. The fumarate salt of (±)-6 was obtained as a white solid, mp 144–145°. Anal. ($C_{18}H_{23}NO_4$) C, H, N. Analysis (NMR and GLC) of the dehydration reaction mixture at 3 and 6 h showed considerable amounts of the 3,4-elimination product which isomerized to the more stable olefin on subsequent acid treatment.

Dehydration of (+)-γ-Promedol Alcohol [(+)-5]. A 0.05-g (0.00023 mol) sample of (+)-5 was refluxed 15 h in concentrated HCl (3 ml). The ir spectrum and GC properties of the oil [(+)-6 (45 mg), $[\alpha]^{23}D$ +102° (*c* 4.5, $CHCl_3$)] were identical with that of (±)-6 obtained by the preceding procedure.

Dehydration of (−)-α-Promedol Alcohol [(−)-4]. Treatment of 0.01 g of (−)-4 with concentrated HCl (1 ml) and workup as described above yielded 0.0036 g of an oil, $[\alpha]^{23}D$ −97° (*c* 0.36, $CHCl_3$), with identical ir and GLC characteristics as (±)-6.

(±)-α-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [α-Promedol Hydrochloride, (±)-3·HCl]. A mixture of 0.20 g (0.00092 mol) of (±)-4 and 1 ml of propionyl chloride was allowed to stand at 25° for 4 days under N_2. Ether (5 ml) was added, the mixture filtered, and the solid washed with petroleum ether (2 × 5 ml) and crystallized (Me_2CO) twice to yield 0.1 g of (±)-3·HCl, mp 110–111° (lit.[13] 101–108°). Anal. ($C_{17}H_{26}NO_2Cl$) C, H, N.

(+)-(2*R*,4*S*,5*S*)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(+)-3·HCl]. A threefold molar excess of propionyl chloride was added to 0.10 g (0.00041 mol) of (−)-4 and 0.2 g of $KHCO_3$ in 5 ml of dry toluene and the mixture was stirred and refluxed 12 h in a moisture-free atmosphere. The cooled reaction mixture was filtered, extracted twice with $KHCO_3$ (5%) solution, and evaporated to give an oil whose NMR and ir spectra were consistent with the assigned structure and identical with those of (±)-3. The oil was dissolved in anhydous Et_2O, ethereal HCl added, and the HCl salt washed with Et_2O (2 × 3 ml). Recrystallization from dry methyl ethyl ketone gave pure (+)-3·HCl (70 mg): mp 109–111°; $[\alpha]^{23}D$ +48.2° (*c* 0.5, MeOH).

(−)-(2*S*,4*R*,5*R*)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(−)-3]. This was prepared from (+)-4 using a procedure identical with that described above: mp 108–110°; $[\alpha]^{23}D$ −48.6° (*c* 0.5, MeOH).

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