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 reflects 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

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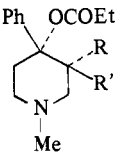
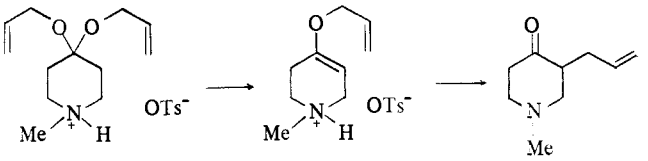
An improved synthesis of diastereomeric (±)-3-allyl-1-methyl-4-propionoxypiperidine (**2a,b**) is described, and the 3-propyl analogs **3a,b** have been prepared. The relative stereochemistries of **2a,b** have been deduced from chemical and nmr studies and are opposite to that proposed originally by 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

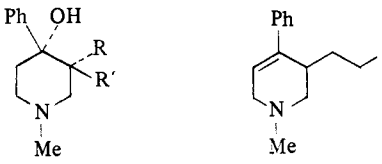
Chemistry. The key intermediate in the synthesis of **2a** and **2b** is piperidone **6** which was obtained previously[4] by the classical route to piperidones. As this procedure is rather lengthy, a more efficient two-step preparation of **6** based on an analogous synthesis of 2-allylcyclohexanone[11] was developed in this study. Thus, ketal exchange between acetone diallyl ketal and 1-methyl-4-piperidone in the presence of *p*-toluenesulfonic acid yielded the diallyloxy tosylate salt **4** which then was subjected to thermal elimination of 1 mol equiv of allyl alcohol to give the allyl vinyl ether **5**. This intermediate was not isolated but allowed to undergo Claisen rearrangement *in situ* to the desired piperidone **6**. The course of the rearrangement was readily followed by the disappearance of the vinyl ether absorption at 1670 cm^{-1}. The overall yield was 55%.



4 5 6

Reaction of **6** with PhLi gave a mixture of diastereomeric alcohols in a ratio of 10:1 (**7a**:**7b**). The racemates were termed α and β by Ziering, *et al.*,[4] who had assigned structures **7b** and **7a**, respectively, to these diastereomers. The fact that the α isomer was produced in greater amount suggests that the original assignment might be incorrect. It is expected that this diastereomer should correspond to structure **7a** due to steric approach control and product development control by analogy with the prodinols **8a,b** where **8a** comprised 60% of the diastereomeric mixture.[12]

The nmr spectra also are consistent with the stereochemical assignment based on the ratio of diastereomers, as the band width at half-weight of the aromatic proton signals is substantially greater for **7a** (14 Hz) than for **7b** (4.5 Hz). This is in accord with similar differences that have been reported[13] for the prodinol diastereomers (14 Hz for **8a**; 5 Hz for **8b**).



7a, R = $CH_2CH{=}CH_2$; R' = H
b, R = H; R' = $CH_2CH{=}CH_2$
8a, R = Me; R' = H
b, R = H; R' = Me
9a, R = Pr; R' = H
b, R = H; R' = Pr

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Additional evidence for the relative stereochemistry was acquired from dehydration studies of the propyl diastereomers **9a,b** obtained from the allyl racemates **7a,b** by catalytic hydrogenation. The propyl derivatives were chosen in order to facilitate spectral identification of any olefinic products without the complication of the allylic double bond. When **9b** was treated with dilute HCl, a single olefin (**10**) was produced, whereas **9a** was unaffected under identical conditions. As this also has been observed with the prodinols,[14] the α diastereomers of both the allyl- and methyl-substituted piperidinol have the same relative stereochemistry. The stereochemistries of the α- and β-racemates **2a,b** therefore are opposite to that originally proposed[4] and actually correspond to structures **2a** and **2b**, respectively.

Table I. Analgetic Potencies of Diastereomers of (±)-3-Propyl- and (±)-3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine

Compd[a]	ED_{50} (mg/kg)[b]	Onset[c]	Peak[d]	Duration[e]
2a	0.08 (0.07–0.10)	3.4	28.4	122.0
2b	9.3 (7.0–12.3)	4.1	22.4	146.8
3a	1.9 (1.5–2.3)	3.8	21.7	135.1
3b	15.0 (11.5–19.5)	4.4	25.8	114.6
Morphine	1.2[f]			

[a] Tested as the HCl salts. [b] Tested sc in mice according to the hot-plate procedure.[15] [c] Onset of analgesia (minutes). [d] Time required (minutes) for peak analgesia. [e] Duration of analgesia (minutes). [f] A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965).

Stereostructure–Activity Relationship. The analgetic ED_{50} values of the α- and β-racemates of **2** and **3** were determined in mice by the hot-plate procedure[15] and are listed in Table I. In agreement with Ziering, *et al.*,[4] we have found the α-allyl diastereomer (whose stereochemistry from this study is known to correspond to **2a**) to be more potent than the β-racemate **2b**. However, where these authors reported an α:β potency ratio of approximately 4:1, we obtain a value of 115:1. It is quite possible that the lower reported potency ratio arose as a consequence of contamination of **2b** with the highly potent **2a**, as evidenced by the lower reported[4] melting point of **2b**·HCl when compared to our value.

Since the onset, peak, and duration of action of all four racemates are very similar (Table I), it appears likely that the large potency differences between all four compounds reflect events at the receptor rather than possible differences in distribution, metabolism, or excretion. It is significant that the rank order of potencies for the prodine diastereomers (**1b** > **1a**) is opposite to that of the allyl (**2a** > **2b**) and propyl (**3a** > **3b**) analogs. This reversal is a consequence of the much lower potencies of the β isomers **2b,3b** when compared to β-prodine (**1b**). These data suggest that the mode of interaction[16] of the β isomers **2b,3b** with the analgetic receptors is different from that of **1b**. This might be due to the presence of a hydrophobic pocket[1,10] on the receptor which is capable of accommodating an axial 3-Me group but not an axial 3-allyl or 3-propyl group. Thus, in the case of β-prodine (**1b**), the presence of the 3-Me group would enhance drug-receptor association. On the other hand, when the axial group is lengthened to three carbons sufficient steric hindrance is encountered to markedly decrease affinity of the drug for the receptor. Interestingly, the α- and β-racemates of the 3-ethyl analog of prodine have nearly identical potencies,[4] and this can be explained by assuming that the affinity gained through hydrophobic bonding is offset by steric hindrance of the 3-Et group.

The fact that the allyl diastereomer **2a** is considerably more potent than the propyl compound **3a** containing the same relative stereochemistry suggests a strong contribution of the allylic double bond to the receptor interaction, particularly since **3a** possesses a potency close to that of (±)-α-prodine (**1a**).[10] The remarkable ability of the equatorial allyl substitutent to substantially enhance analgetic activity may be due to one or a combination of the possibilities listed below. (1) The equatorial allylic group alters some key conformational features in the molecule (*e.g.*, aromatic ring and/or ester group) so that its overall geometry possesses greater complementarity in the receptor interaction. (2) The double bond of the allylic group is interacting with an accessory area on the receptor which usually accepts a second aromatic ring (*e.g.*, the second

aromatic ring of methadone), thereby leading to enhanced affinity.

Whatever the role played by the allyl group, it appears that there are some highly specific steric requirements associated with the double bond in this substituent, as it is known that replacement of the allyl group in **2a** by $CH_2CH{=}CHCH_3$ causes a dramatic decrease ($^1/_{375}$ of **2a**) in activity.[4]

The fact that the α-racemates **2a**,**3a** are more potent than the β-racemates **2b**,**3b** while the prodines exhibit a reverse rank order of activity (**1b** > **1a**) suggests that the potency difference between the prodines diastereomers is not related primarily to the possible presence of a skew-boat conformation[9] of the piperidine ring or to the presence of a greater population of axial-phenyl conformer[5] in the β isomer.

Further studies are in progress which, hopefully, will clarify the role of the 3-allyl substituent in contributing to the high analgetic potency of **2a**.

Experimental Section

Elemental analyses were performed by MHW Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of the elements, they are within ±0.4% of the theoretical values. Ir spectra were obtained with Perkin-Elmer 237B and Beckman IR9 instruments on $CHCl_3$ solutions in 0.1-mm cells. Nmr spectra were measured with a Varian A-60D spectromer at ambient temperature on approximately 10% solutions in $CDCl_3$ or CCl_4 (Me_4Si). The ir and nmr data of all the compounds were consistent with the proposed structures. Melting points were determined with a Mel-Temp apparatus and are corrected. Tlc was carried out on Eastman 6060 silica gel sheets.

4,4-Diallyloxy-1-methylpiperidinium *p*-Toluenesulfonate (4). A solution of anhydrous TsOH in PhH was prepared by refluxing a mixture of the monohydrate (101 g of 96%, 0.51 mol) and PhH (500 ml) under a Dean-Stark water separator until 9 ml of H_2O had collected. An additional 100 ml of PhH was distilled off to remove final traces of moisture. To the above cooled solution was added a solution of 1-methyl-4-piperidone (56.5 g, 0.5 mol) and 2,2-diallyloxypropane[17] (86 g, 0.55 mol) in PhH (100 ml). The mixture was refluxed under a 120-cm insulated column packed with 0.25-in. glass rings and fitted with a variable take-off head. The head temperature was maintained at 56–58° until 35 ml of Me_2CO distillate had collected. Another 10 ml of distillate was collected up to 70°. Chilling the residual solution yielded colorless crystals (88.4 g, mp 110–112°). Further crops were obtained by diluting with hexane, combined yield 134.5 g (71%). A second recrystallization (PhH) afforded pure **4**, mp 125.5–126°. *Anal.* ($C_{19}H_{29}NO_5S$) C, H, N.

In an alternate procedure, a mixture of the piperidone (56.5 g, 0.5 mol), 2,2-dimethoxypropane (57.2 g, 0.505 mol), allyl alcohol (69.5 g, 1.2 mol), anhydrous TsOH (from 101 g of 96% monohydrate, 0.51 mol), and PhH (400 ml) was fractionated under conditions identical with those described above. Me_2CO and PhH–MeOH azeotrope were distilled and the product isolated as before, combined yield 96 g (50%).

3-Allyl-1-methyl-4-piperidone (6). A mixture of **4** (113 g), PhMe (400 ml), and TsOH · H_2O (0.2 g) was refluxed under a 75-cm column packed with 0.25-in. glass rings and fitted with a variable take-off head. The head temperature was maintained at 91–92° until 35 ml of the 1:1 PhMe–allyl alcohol azeotrope had collected (4 hr) and then allowed to rise gradually until an additional 20 ml of distillate was collected. Refluxing was continued for 1.5 hr; the lower phase was separated from the residual mixture and run into H_2O (100 ml). The upper PhMe phase was shaken with H_2O (50 ml) and the combined aqueous solutions were basified with 20% aqueous NaOH. Extraction with Et_2O (2 × 100, 4 × 50 ml), drying the combined extracts over K_2CO_3, removal of solvent, and distillation of the residue gave **6** as a colorless oil (34.6 g, 77%), bp 93–94° (10 mm) [lit.[4] bp 117–122° (31 mm)].

3-Allyl-1-methyl-4-phenyl-4-piperidinol (7a,b). A solution of **6** (15.3 g, 0.1 mol) in dry Et_2O (100 ml) was added dropwise with stirring to ethereal PhLi (131 ml of 1.14 *M*, 0.15 mol, prepared and standardized according to Jones and Gilman[18]) at 0°. The temperature was maintained at 5–7° during the addition which was conducted under dry N_2. After complete addition, the reaction mixture was stirred at room temperature for 2 hr and then decomposed with H_2O (75 ml). The aqueous phase was separated and washed with Et_2O. The combined Et_2O extracts were washed with H_2O and saturated NaCl and dried (K_2CO_3), and the solvent was removed leaving a pale yellow oil which rapidly solidified. Recrystallization (hexane) gave colorless needles of **7a** (15.4 g), mp 110–111° (lit.[2] 110–111°). The filtrate was reduced to 20 ml and seeded with pure **7b** yielding 1.26 g of **7b**, mp 86–87° (lit.[2] mp 85–86°). The filtrate was evaporated and the residue chromatographed (silica gel, 350 g, Baker 60-200 mesh) in EtOAc to give an additional quantity of pure **7a** (0.37 g) and **7b** (0.62 g). The total yields of product were 16.02 g (70%) for **7a** and 1.63 g (7%) for **7b**. *Anal.* ($C_{15}H_{21}NO$, **7a** and **7b**) C, H, N.

1-Methyl-4-phenyl-3-*n*-propyl-4-piperidinols (9a,b). Olefin **7a** (1 g) was hydrogenated in EtOH (50 ml) at room temperature and pressure in the presence of PtO_2 (0.05 g). After the theoretical uptake of H_2 (10 min), the mixture was filtered, and the filtrate was evaporated to dryness. Recrystallization (hexane) afforded **9a** (0.88 g, 88%), mp 106–106.5° (lit.[19] 105–106°). *Anal.* ($C_{15}H_{23}NO$) C, H, N. Similar hydrogenation of **7b** yielded **9b** as a colorless oil. *Anal.* ($C_{15}H_{23}NO$) C, H, N.

1,2,5,6-Tetrahydro-1-methyl-4-phenyl-3-*n*-propylpyridine Hydrochloride (10 · HCl). A solution of **9b** (0.482 g) in concentrated HCl (10 ml) and H_2O (10 ml) was stirred and heated at 50–55° under N_2 for 24 hr. The cooled solution was made alkaline with 20% aqueous NaOH. The liberated oil was taken into Et_2O, the extract washed with H_2O and saturated NaCl and dried ($MgSO_4$), and the solvent removed leaving 0.354 g (80%) of **10**: nmr δ 7.26 (partially resolved s, 5, Ar *H*), 5.78 (t, 1, C=CH–, *J* = 3.5 Hz), 2.32 (s, 3, NCH_3). The alkene was dissolved in dry Et_2O and treated with ethereal HCl to yield the hygroscopic HCl salt, mp 169–170° (EtOAc–Me_2CO). *Anal.* ($C_{15}H_{22}NCl$) C, H, N.

Preparation of Propionate Ester Hydrochlorides (2a,b; 3a,b HCl). A mixture of the alcohol (0.002 mol), freshly distilled propionyl chloride (0.35 ml, 0.004 mol), and dry PhMe (4 ml) was stirred at 100–110° under dry N_2 for 5 hr. The reaction mixture was then chilled; the crystals were collected, washed (PhMe, Et_2O), dried, and recrystallized (acetone). The following compounds were obtained in the yields indicated: **2a** · HCl (95%), mp 185.5° (lit.[2] 185–186°) [*Anal.* ($C_{18}H_{26}NClO_2$) C, H, N]; **2b** · HCl (93%), mp 210–211° (lit.[2] 205–206°) [*Anal.* ($C_{18}H_{26}NClO_2$) C, H, N]; **3a** · HCl (95%), mp 201–202° (lit.[19] 202–204°) [*Anal.* ($C_{18}H_{28}NClO_2$) C, H, N]; **3b** · HCl (92%), mp 194–195° [*Anal.* ($C_{18}H_{28}NClO_2$) C, H, N].

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