Journal of Medicinal Chemistry

VOLUME 16, NUMBER 6 JUNE 1973

Stereochemical Studies on Medicinal Agents. 15.[1] Absolute Configurations and Analgetic Potencies of Enantiomeric Diastereomers of 3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine

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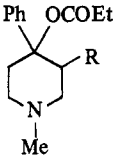
Received November 30, 1972

Enantiomeric diastereomers of the title compound **1a,b** were prepared and their absolute configurations determined by chemically relating them to (3*R*,4*S*)- and (3*S*,4*R*)-1,3-dimethyl-4-phenylpiperidin-4-ol. The analgetic potency of (3*R*,4*S*)-**1a** (**8a**) is 40 times that of morphine and 260 times that of its enantiomer **10a**. Enantiomers of **1b** (**8b** and **10b**) exhibited no stereoselectivity and possessed a relatively low order of potency (~$^1/_{12}$ that of morphine). The fact that this is in marked contrast to the reported high antipodal stereoselectivity for β-prodine suggests that the mode of interaction of **1b** with analgetic receptors differs from that of β-prodine. Possible reasons for the change of stereoselectivity are discussed.

In a recent report[1] we described the stereochemical elucidation of the highly potent analgetic, (±)-**1a**, and its weakly active diastereomer, (±)-**1b**.[2] As their rank order of potencies (**1a** > **1b**) was found to be opposite to that reported[2-5] for racemic prodines (**2b** > **2a**) of the same relative stereochemistry, it was suggested that the mode of interaction of (±)-**1b** with analgetic receptors is different from that of (±)-**2b**.

In order to gain greater insight into this phenomenon, we have investigated **1a,b** further by optical resolution of the racemates and correlation of the chiralities of the optical isomers with analgetic potency. If the inversion of the potency ratios of the racemates is indeed a reflection of different modes of drug-receptor interaction, then widely divergent[6-8] enantiomeric potency ratios should also be observed for **1b** and **2b**. The present report describes such studies and provides additional support for different modes of interaction for these analgetics.

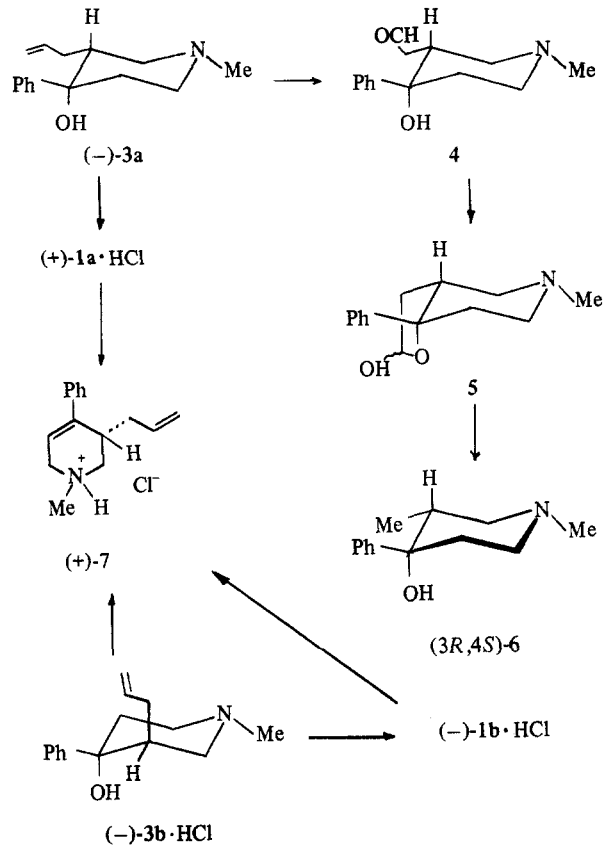


1a, R = $CH_2CH{=}CH_2$ (*trans*-Ph:allyl)
b, R = $CH_2CH{=}CH_2$ (*cis*-Ph:allyl)
2a, R = Me (*trans*-Ph:Me)
b, R = Me (*cis*-Ph:Me)

Absolute Configurational Studies. The optically pure piperidinols **3a,b** used in this study were prepared by fractional crystallization of their dibenzoyltartrate and di-*p*-toluoyltartrate salts, respectively. The propionate esters [(+)- and (−)-**1a**·HCl] were obtained from (−)- and (+)-**3a**, respectively, as described previously[1] for both (±)-**1a**·HCl and (±)-**1b**·HCl. Interestingly, it was found that optically active **1b**·HCl could not be prepared by this procedure because a substantial amount of olefin **7** was formed. Unlike (±)-**1b**·HCl, enantiomeric **1b**·HCl did not precipitate from the reaction mixture and underwent elimination while in solution. When hexane was substituted for toluene as solvent, (+)- and (−)-**3b** afforded the esters [(+)- and (−)-**1b**·HCl, respectively] in good yield because of their insolubility in this medium.

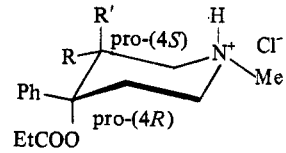
Determination of the chirality of optically active **3a** was achieved by degradation of each antipode to the corresponding enantiomeric α-prodinol (**6**) of known absolute stereochemistry.[3] Accordingly, oxidation of (+)- and (−)-**3a** with OsO_4-$NaIO_4$ yielded the desired aldehyde **4** in the form of hemiacetal **5**. Its ir spectrum showed no carbonyl band and the nmr spectrum exhibited absorptions (triplet at δ 5.88; doublet of doublets at δ 5.70) of approximately equal integrals attributable to the anomeric proton of each epimer of **5**. The facility with which cyclization occurs is likely a consequence of the cis relationship between the OH and CH_2CHO groups, since it would be expected that the trans diastereomer could undergo a similar cyclization only in the highly unfavorable flip conformation. Decarbonylation of **5** (**4**) with tris(triphenylphosphine)rhodium(I) chloride[9] yielded optically active α-prodinol (**6**). Since (+)- and (−)-**3a** afforded (3*S*,4*R*)- and (3*R*,4*S*)-**6**, respectively, by a route which did not affect the integrity of the chiral centers, this establishes their structures as (+)-(3*S*,4*R*)-**3a** and (−)-(3*R*,4*S*)-**3a**, respectively.

The chirality of the optically active **3b** was determined by converting (−)-**3b** and (+)-**1a**·HCl [derived from (−)-(3*R*,4*S*)-**3a**] to a common intermediate [(+)-**7**] by destroying the C-4 chiral center. This was accomplished by mild acid-catalyzed dehydration[1,10] of (−)-**3b** and facile elimination of propionic acid from (+)-**1a**·HCl by reaction with BF_3 etherate. This, together with the known relative stereochemistry of **3b**,[1] establishes the absolute stereochemistry of (−)-

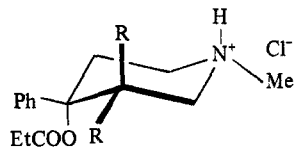


3b as (3*R*,4*R*) and (+)-**3b** as (3*S*,4*S*).

The absolute stereochemistries of the propionate ester hydrochlorides **1a,b** follow from that of the alcohol precursors **3a,b** as the chiral centers are unaffected in the transformation and are depicted in perspective formulas **8a,b** and **10a,b**.



8a [(+)-**1a**·HCl], R = $CH_2CH{=}CH_2$; R′ = H
b [(+)-**1b**·HCl], R = H; R′ = $CH_2CH{=}CH_2$
9a, R = Me; R′ = H
b, R = H; R′ = Me
c, R = H; R′ = H



10a [(−)-**1a**·HCl], R = $CH_2CH{=}CH_2$; R′ = H
b [(−)-**1b**·HCl], R = H; R′ = $CH_2CH{=}CH_2$
11a, R = Me; R′ = H
b, R = H; R′ = Me

Pharmacology. The analgetic potencies of the optical isomers were determined by the hot-plate procedure[11] after sc administration in mice (Table I). The (+)-α-isomer **8a** was found to be highly active (40 times more potent than morphine) and possessed a 260-fold greater potency than its enantiomer **10a**. In contrast, the β enantiomers **8b** and **10b** showed no stereoselectivity and a relatively low order of potency ($\sim^1/_{12}$ that of morphine). As the onset, peak, and duration of action of the potent isomer **8a** do not differ substantially from those of the three other isomers, it seems likely that the large potency difference seen between **8a** and the latter isomers is related to events at the receptor level rather than to differential access into the CNS.

Table I. Analgetic Potencies of Enantiomeric Diastereomers of 3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine

Compd[a]	ED_{50}, mg/kg[b]	Onset[c]	Peak[d]	Duration[e]
8a [(+)-**1a**]	0.03 (0.02–0.04)[f]	3.7	22.5	122.4
10a [(−)-**1a**]	7.8 (6.1–10.0)	3.7	22.3	122.5
8b [(+)-**1b**]	13.7 (10.6–17.6)	3.5	20.5	128.4
10b [(−)-**1b**]	15.5 (12.2–19.5)	4.8	27.6	141.1
Morphine	1.2[g]			

[a]Tested as the HCl salts. [b]Tested sc in mice according to the hot-plate procedure.[11] [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).

Stereostructure-Activity Relationship. The stereoselectivity of the α-allyl enantiomers **8a** and **10a** is qualitatively the same as that reported[3] for the prodines **9a** and **11a** in that the more potent antipodes **8a** and **9a** have identical chiralities (3*R*,4*S*). The fact that the desmethyl compound **9c** possesses a potency[3] which is less than that of **8a** but greater than that of **10a** is in harmony with the idea that a 3-alkyl group on the pro-(4*R*) edge of the piperidine ring interferes with drug-receptor association, while identical substitution on the pro-(4*S*) edge leads to enhanced affinity.[3]

It is particularly noteworthy that in the case of the α-allyl enantiomers the stereoselectivity is extremely high (enantiomeric potency ratio, **8a**:**10a** = 260:1). This is in contrast to the α-prodine enantiomers where the potency ratio (**9a**:**11a**) has been found[3] to be 25:1. The tenfold greater stereoselectivity of **8a** is very likely associated with its high potency and suggests that the allylic double bond is playing an important role in the drug-receptor interaction. The involvement of the allylic double bond is also suggested from our study of the corresponding α-propyl racemate,[1] as it was found to be much less potent than **8a**.

It is not known whether the allyl group in **8a** exerts its effect directly or indirectly in the drug-receptor interaction. In this regard, its interaction with an accessory site on the receptor would constitute a direct effect, while a difference in the conformational preference of key groups in **8a** (relative to that of **9a**) due to the presence of the allyl substituent would represent an indirect effect.[1,3,12] Since a correlation has been shown[3,12] between the sign of the torsion angles (for the phenyl and OCO groups) and analgetic potency in closely related compounds, it would not be surprising if the indirect effect were chiefly responsible for the enhanced potency of **8a**. Further studies are in progress to investigate this possibility.

The striking differences between the enantiomeric potency ratio of the β-allyl diastereomer (**8b**:**10b** ~ 1) and that of β-prodine (**9b**:**11b** = 13) support our earlier proposal (based on the reversed rank order of the potencies of the racemates: **1a** > **1b**; **2b** > **2a**)[1] that their modes of interaction with receptors are dissimilar. This difference could be attributed to the analgetic receptor possessing a hydrophobic pocket of limited volume. The pocket would be capable of accommodating an axial 3-Me substituent attached to the pro-(4*S*) edge of the piperidine ring (**9b**), but not an allyl group (**8b**). When the allyl group is situated on the pro-(4*R*) edge, this also would sterically hinder drug-receptor association in very much the same way as described previously[3] for **11b**. Thus, the low potency and absence of

stereoselectivity in the β diastereomer **(9b, 11b)** are a consequence of the axial allyl group attached to the pro-(4*R*) or pro-(4*S*) edges of the piperidine ring presenting steric hindrances of comparable magnitude in the receptor interaction.

Experimental Section

Elemental analyses were performed by M-H-W 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 Beckmann IR9 instruments on $CHCl_3$ solutions in 0.1-mm cells. Nmr spectra were measured with a Varian A-60D spectrometer at ambient temperature on approximately 10% solutions in $CDCl_3$ (Me_4Si). All spectra were consistent with the proposed structures. Melting points were determined with a Mel-Temp apparatus and are corrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter on 1% solutions in MeOH at 22°.

Resolution of (±)-*r*-3-Allyl-1-methyl-4-phenyl-*c*-4-piperidinol [(±)-3a]. A solution of (±)-**3a** (3 g, 0.013 mol) in warm EtOH (3 ml) was added to a hot solution of (−)-dibenzoyl-*d*-tartaric acid (4.89 g, 0.013 mol) in EtOH (20 ml). Hot H_2O (20 ml) was added and the solution was allowed to cool slowly. After 3 days, the acid dibenzoyltartrate salt was collected (3.12 g, 80%): mp 130–131°; [α]D −71.2°. Further recrystallization from aqueous EtOH gave a constant [α]D −71.6°, mp 130–131°. *Anal.* ($C_{33}H_{35}NO_9 \cdot H_2O$) C, H, N. Treatment of an ethanolic solution of the salt with NH_4OH gave (+)-3a which was recrystallized from hexane: overall yield 68%; mp 148–148.5°; [α]D +4.4°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

The resolution liquor was treated with an excess of NH_4OH and the crude (−)-base was converted to (−)-**3a**-(+)-acid dibenzoyltartrate: [α]D +72.1°; mp 130–131° after recrystallization (aqueous EtOH). *Anal.* ($C_{33}H_{35}NO_9 \cdot H_2O$) C, H, N. The liberated base [(−)-**3a**], mp 148–148.5°, [α]D −4.4°, after recrystallization (hexane), was obtained in an overall yield of 62%. The ir spectrum of each enantiomer was identical with that of the racemate. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

Resolution of (±)-*r*-3-Allyl-1-methyl-4-phenyl-*t*-4-piperidinol [(±)-3b]. A mixture of (±)-**3b** (1.55 g, 0.005 mol) and (−)-di-*p*-toluoyl-*d*-tartaric acid (1.9315 g, 0.005 mol) was dissolved in MeOH (10 ml) by warming. Hot H_2O (1 ml) was added and the solution was was allowed to cool slowly to room temperature. After 24 hr the (−)-amine-(−)-acid salt, [α]D −106.9°, was collected. Two recrystallizations (10% aqueous MeOH) raised the rotation to a constant [α]D −111.1°, mp 168–169° dec. *Anal.* ($C_{35}H_{39}NO_9$) C, H, N. The base was generated in the usual way and recovered by Et_2O extraction. Recrystallization (hexane) gave pure (−)-**3b**: mp 113–114°; [α]D −60.1°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

The crude (+)-amine, recovered from the resolution liquor, was similarly allowed to react with (+)-di-*p*-toluoyl-*l*-tartaric acid and the (+)-amine-(+)-acid salt obtained from 10% aqueous MeOH. One recrystallization gave material of [α]D +111.8°, mp 168–169° dec. *Anal.* ($C_{35}H_{39}NO_9$) C, H, N. Recrystallized (hexane) (+)-**3b** obtained from the above salt had mp 112–113°, [α]D +59.9°. *Anal.* ($C_{15}H_{21}NO$) C, H, N. The ir spectrum of each enantiomer was identical with that of the racemate.

(−)-(3*S*,4*R*)-4-Hydroxy-1-methyl-4-phenyl-3-piperidinylacetaldehyde Hemiacetal [(−)-5]. A stirred solution of (+)-(3*S*,4*R*)-**3a** (0.462 g, 2 mmol) in dioxane (9 ml) and H_2O (3 ml) maintained under N_2 was treated with OsO_4 (5.1 mg, 0.02 mmol). After 10 min, $NaIO_4$ (0.900 g, 4.2 mmol) was added in small portions over a period of 20 min. After complete addition the mixture was stirred for 1 hr and then filtered. The iodate precipitate was washed with dioxane and the filtrate was evaporated to near dryness. The residue was treated with H_2O (10 ml) and extracted with Et_2O. The combined ethereal extracts were washed (H_2O, saturated NaCl) and dried ($MgSO_4$), and the solvent was removed leaving a solid. Recrystallization (benzene–hexane) gave (−)-**5** (289 mg, 62%): mp 127–128°; [α]D −59.5°. *Anal.* ($C_{14}H_{19}NO_2$) C, H, N. Similarly, (−)-**3a** yielded (+)-**5**: mp 127–128°; [α]D +58.9°. *Anal.* ($C_{14}H_{19}NO_2$) C, H, N. Racemic **3a** yielded (±)-**5**: mp 148–149°; nmr δ 7.5 (m, 5, Ar H), 5.88, 5.70 (t, J = 6 Hz, doublet of doublets, J_{ac} = 7 Hz, J_{bc} = 1.2 Hz, OC*H*(OH)CH_2, total 1), 2.43 (s, NCH_3); ir 3580 (sharp, free OH), 3380 (broad, bonded OH), 1600 cm^{-1} (aromatic C=C). *Anal.* ($C_{14}H_{19}NO_2$) C, H, N.

(−)-(3*S*,4*R*)-1,3-Dimethyl-4-phenylpiperidin-4-ol [(+)-6] from Decarbonylation of (−)-(3*S*,4*R*)-5. A mixture of (−)-**5** (0.233 g, 1 mmol), tris(triphenylphosphine)rhodium(I) chloride[9] (1.1178 g, 1.1 mmol), and dry MeCN (60 ml) was stirred and refluxed under dry N_2. As reaction proceeded the red complex gradually went into solution and a yellow precipitate began to appear. After 24 hr the solution was cooled and filtered, and the filtrate was evaporated to dryness. The resulting solid was extracted with Et_2O; the combined extracts were filtered and extracted with 10% aqueous HCl. Basification of the aqueous extracts with 10% NaOH gave an oil (0.106 g, 52%) consisting mainly of (−)-**6** (tlc, ir, nmr). Purification by chromatography over basic alumina (10 g) and elution with PhH–Et_2O gave (−)-**6**, [α]D −5.8°; authentic sample, [α]D −6.0°. From (+)-**5** was obtained (+)-**6**, [α]D +5.6°. The ir spectrum of each enantiomer was identical with that of an authentic sample of optically active **6**.

(+)-5-Allyl-1-methyl-1,2,5,6-tetrahydro-4-phenylpyridine Hydrochloride [(+)-7]. (a) From (−)-3b. Dehydration of (−)-**3b** was carried out as described previously for related compounds.[1,10] The crude product was converted to its HCl salt [(+)-7]: mp 158–159° (Me_2CO–EtOAc); [α]D +58.0°; nmr δ 7.3 (s, 5, Ar H), 4.9–5.8 (m, 4, olefinic H), 2.93 (broad s, 3, NCH_3); ir 2300 (broad, N^+H), 1630 cm^{-1} (C=C). *Anal.* ($C_{15}H_{20}NCl$) C, H, N.

(b) From 8a [(+)-1a·HCl]. A solution of **8a** (0.1 g) in $CHCl_3$ (10 ml) containing $BF_3 \cdot Et_2O$ (0.2 ml) was refluxed under dry N_2. After 24 hr, the solvent was removed *in vacuo* and the residue recrystallized (Me_2CO–EtOAc) giving (+)-7: mp 157–158°; [α]D +56.4°.

(c) From 10b [(−)-1b·HCl]. Refluxing (−)-**3b** with propionyl chloride in toluene as described[1] for the racemate gave (+)-**7** after recrystallization (Me_2CO–EtOAc): mp 158–159°; [α]D +57.8°.

(+)-(3*R*,4*S*)-3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine Hydrochloride (8a). Conversion of (−)-(3*R*,4*S*)-**3a** to **8a** was carried out as described[1] for the racemate, but unlike the latter, no crystals separated from the reaction. The reaction mixture was evaporated *in vacuo* and the residual solid foam washed by decantation with dry Et_2O. The solid was extremely hygroscopic and all transfers were done under dry N_2. Purification was effected by sublimation at 160° (0.1 mm) yielding **8a**: [α]D +0.5°; $[\alpha]_{365}$ −26.0°; mp 70–75° (softens 50°). *Anal.* ($C_{18}H_{26}NClO_2$) C, H, N.

(−)-(3*S*,4*R*)-3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine Hydrochloride (10a). Using an identical procedure, (+)-(3*S*,4*R*)-**3a** yielded **10a**: [α]D −0.6°; $[\alpha]_{365}$ + 26.2°; mp 70–76° (softens 50°). *Anal.* ($C_{18}H_{26}NClO$) C, H, N.

(−)-(3*R*,4*R*)-3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine Hydrochloride (10b). A solution of propionyl chloride (0.5 ml) in hexane (4.5 ml) was added to (−)-(3*R*,4*R*)-**3b** (0.15 g) in PhMe (0.5 ml). The mixture was refluxed under dry N_2 for 3 hr and the crystals were collected and recrystallized (Me_2CO–Et_2O) giving **10b**: [α]D −70.0°; mp 170–171°. *Anal.* ($C_{18}H_{26}NClO$) C, H, N.

(+)-(3*S*,4*S*)-3-Allyl-1-methyl-4-phenyl-4-propionoxypiperidine Hydrochloride (8b). Similarly, from (+)-(3*S*,4*S*)-**3b** was obtained **8b**: [α]D +69.4°; mp 170–171°. *Anal.* ($C_{18}H_{26}NClO_2$) C, H, N.

Acknowledgment. This investigation was supported by NIH Grant NS 05192. The authors wish to thank Dr. Everette L. May of the NIAMD for analgetic testing.

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