Stereochemical Studies on Medicinal Agents. 12.[1] The Distinction of Enantiotopic Groups in the Interaction of 1-Methyl-4-phenyl-4-propionoxypiperidine with Analgetic Receptors

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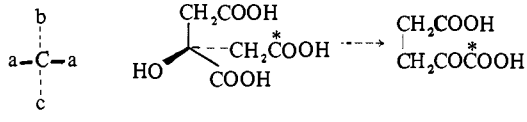
The four optical isomers of α- and β-prodine have been prepared and their absolute stereochemistries determined by chemical correlation with (2*R*)-3-dimethylamino-2-methylpropiophenone. The sc analgetic ED_{50} values of the prodines in mice indicate that the two isomers which possess the 4*S* configurations are considerably more potent than their antipodes. This, coupled with the fact that the potency of 4-phenyl-4-propionoxy-1-methylpiperidine (**5**), a molecule with enantiotopic edges, is greater than that of the prodines having a 4*R* chiral center, suggests that the "Ogston effect" is operative in the interaction of **5** with analgetic receptors. It is proposed that the discrimination of the enantiotopic edges by the receptor is due to a combination of configurational and conformational factors.

It first was recognized by Ogston[2] that chemically like, paired groups in a substrate of the Caabc type **1** can be differentiated by an enzyme. In his now classical paper, Ogston described the concept of three-point attachment in order to illustrate how a nondissymmetric molecule such as citrate **2** could afford α-ketoglutarate (**3**)[3] labeled in only one carboxyl group. It is now recognized that although the model is a useful device for illustrating the nonequivalence of chemically like, enantiotopic paired groups, it should not be taken as a literal description of the forces between enzyme and substrate.[4,5]

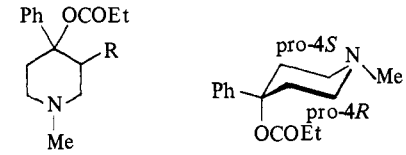


1 **2** **3**

Since the appearance of the Ogston model, there have been a number of compounds in which enantiotopic groups have been differentiated enzymatically,[5] and systematic nomenclature[6] therefore was devised in order to define the steric relationships in such systems. Accordingly, the general term "prochiral" was introduced to cover all cases of the Caabc type.

Although this phenomenon appears well documented in enzymology, there have been no reports which discuss prochirality in explaining certain facets of drug stereoselectivity. In connection with our continued interest in the stereochemical aspects of strong analgetics,[7,8] we thought that likely candidates to investigate this problem (for a preliminary report, see ref 9) would be α- and β-prodine (**4a,b**)[10] and 4-phenyl-4-propionoxy-1-methylpiperidine (3-desmethyl analog **5**).[11]

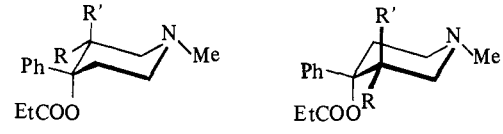
As **5** possesses enantiotopic paired groups, it contains a C-4 prochiral center which, according to recent terminology,[6c] is classified as graphochiral-apherochiral.† We wished to determine whether the analgetic action of **5** involves a receptor site that distinguishes to a significant extent the enantiotopic edges of the molecule. These edges are designated pro-4*R* and pro-4*S* as depicted in projection formula **5a**. However, since **5** apparently does not exert its action through a metabolite,[1] the approaches utilized in enzymology[5] to detect this differentiation are not applicable



4a, R = Me (*trans*-Ph:Me)
4b, R = Me (*cis*-Ph:Me)
5, R = H

5a

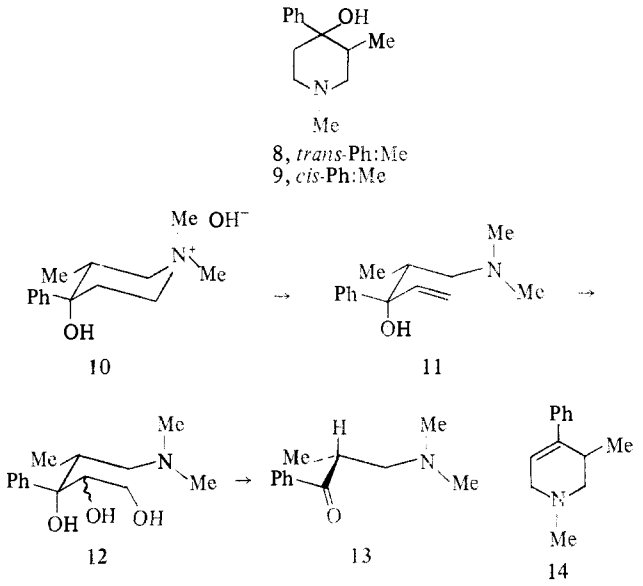
to this study. Therefore, we decided to label the piperidine ring with a 3-Me group in an attempt to determine whether or not the analgetic receptor is capable of such differentiation. Thus, one set of prodine isomers **6a,b** possesses an unsubstituted pro-*R* edge while the other set **7a,b** has a free pro-*S* edge. If the chiral environment of the receptor can distinguish the two halves of **5** which are separated by a plane of symmetry, then introduction of a 3-Me group on either the pro-*R* or pro-*S* edge might be expected to give rise to substantial potency differences between enantiomers.



6 (3*R*,4*S*) (3*S*,4*S*) a, R = Me; R′ = H b, R = H; R′ = Me **7** (3*S*,4*R*) (3*R*,4*R*)

Configurational Studies. The preparation of optically pure antipodes for our sterochemical studies was accomplished through resolution of the tartrate and dibenzoyltartrate salts of α- and β-prodinol (**8, 9**). Determination of the chirality of (+)-**8** at C-3 was carried out by a stepwise degradation of the unsubstituted ethylene moiety of the piperidine ring in order to transform the molecule into the configurationally known amino ketone **13**.[12] Heating methohydroxide **10** derived from (+)-**8** afforded olefin **11** as the sole product. The structure of **11** was confirmed by the nmr spectrum which showed a doublet methyl resonance, thus indicating that elimination occurred from the unsubstituted side of the piperidine ring. The selectivity of the olefin formation can be explained on the basis that the Hofmann elimination requires a coplanar orientation between a β hydrogen and the quaternary ammonium group on the α carbon.[13] This arrangement is fulfilled by the methohydroxide compound assuming the energetically favorable chair conformation as depicted in **10**. Accordingly, only C-5 possesses the requisite hydrogen for olefin

†In order to simplify the stereochemical designation, the nitrogen is regarded as being without configuration.



product and this results in exclusive formation of olefin **11**.

Hydroxylation of **11** with OsO_4 followed by *in situ* cleavage of triol **12** with sodium metaperiodate produced (−)-**13** which was isolated as the maleate salt. This salt was identical in all respects with the maleate salt derived from authentic (−)-**13**·HCl.[12] As (−)-**13** is known to possess the *R* configuration, the chemical sequence establishes the chirality of (+)-**8** as 3*R*,4*S* by virtue of the known *trans*-Ph:Me relationship in the α diastereomer.[14-17]

Esterification of (+)- and (−)-8 with propionyl chloride gave (+)- and (−)-α-prodine (**4a**). Since esterification does not affect the stereochemical integrity of C-4, the chiralities of (+)- and (−)-α-prodine are as depicted in perspective formulas **6a** and **7a**, respectively.

The chirality of optically active **4b** was determined by converting both **4a** and **9** to tetrahydropyridine **14**. Ester pyrolysis of (+)-**4a** according to the procedure of Diamond[18] gave (−)-**14**; no formation of the tetrasubstituted olefin was detected. This was not unexpected, as only the C-5 proton is in a cis relationship to the ester group as required in the ester pyrolysis mechanism.[19] The olefin (−)-**14** is assigned the *S* configuration† since its chiral center remains intact. Acid-catalyzed dehydration of (+)-**9** by the method of Casy, *et al.*,[20] afforded (+)-**14**. As (+)-**14** is in the *R* series, the C-3 chiral center of (+)-**9** therefore is *S*.‡ From the known *cis*-Ph:Me relationship,[15,16,21] it follows that the complete stereochemical designation for (+)-**9** is 3*S*,4*S*. Propionylation of the antipodal alcohols gave (+)- and (−)-**4b** whose chiralities are illustrated in perspective formulas **6b** and **7b**, respectively.

Pharmacology. The analgetic potencies of the prodines were evaluated by a modified hot-plate procedure[22] employing meperidine as the reference standard. The ED_{50} values 15 min after sc administration are given in Table I. The relative potencies of the two racemates were found to be in agreement with literature values.[23,24] Of significance is the substantial difference in potency between the enantiomorphs. Thus, α-prodine (**4a**) enantiomers differ by a factor of 25, and those of β-prodine (**4b**) show a 13-fold difference. Moreover, all of the prodine isomers and 3-desmethylprodine (**5**) show significant differences in potencies between one another.

‡Because of the reversed order of priority of the group about the C-3 chiral center, the stereochemical designation differs from that in 4a and 4b.

Table I. Analgetic Activity of Prodine Stereoisomers

Compd	Configuration	ED_{50},[a] mg/kg (95% limits)
(±)-4a·HCl		1.7 (1.5–2.6)
(+)-4a·HCl (6a·HCl)	3*R*,4*S*	0.91 (0.72–1.04)
(−)-4a·HCl (7a·HCl)	3*S*,4*R*	22.4 (18.3–28.3)
(±)-4b·HCl		0.32 (0.33–0.88)
(+)-4b·HCl (6b·HCl)	3*S*,4*S*	0.25 (0.20–0.32)
(−)-4b·HCl (7b·HCl)	3*R*,4*R*	3.3 (2.0–5.5)
5·HCl		1.3 (1.1–1.5)
Meperidine HCl		13.1 (7.6–15.1)

[a]Administered subcutaneously in mice.

Table II. Potency Ratios and Brain Level Ratios of Prodine Isomers

Comparison	ED_{50} ratio[a] (95% limits)	Brain level ratio[b] (95%)
(+)-4a/(+)-4b	3.60 (2.67–4.74)	2.52 (1.87–3.32)
(−)-4a/(+)-4a	24.6 (19.3–33.3)	29.9 (29.0–30.9)
(−)-4a/(+)-4b	88.5 (63.4–125)	78.5 (72.1–78.6)
(−)-4a/(−)-4b	6.79 (3.72–12.3)	7.16 (7.09–7.24)
(−)-4a/5	16.98 (13.7–21.4)	25.5 (24.6–26.4)
(−)-4b/(+)-4a	3.62 (2.31–6.08)	4.17 (4.05–4.31)
(−)-4b/(+)-4b	13.1 (8.36–20.8)	10.5 (10.1–11.0)
(−)-4b/5	2.50 (1.48–4.35)	3.56 (3.44–3.68)
5/(+)-4a	1.45 (1.17–1.86)	1.17 (1.12–1.23)
5/(+)-4b	5.21 (3.86–7.08)	2.95 (2.79–3.12)

[a]Ratio of higher to lower ED_{50} value (Table I, μmol/kg). [b]Ratio of higher to lower brain level (μmol/g) obtained using ED_{50} dose and same time interval.[1]

It was reported earlier[1] that in no case was the potency difference between any two prodine isomers accounted for by metabolism or distribution, although in some instances small but significant differences in brain levels were observed. Since direct correlation between the degree of analgesia and brain levels has been demonstrated for a number of analgetics,[1,25,26] it is reasonable as a first approximation that the relative brain levels of the prodines at their ED_{50} dose should more accurately reflect their receptor activities, since this should eliminate the problem of differential distribution and metabolism among these compounds. Comparisons of the sc ED_{50} ratios and brain level ED_{50} ratios[1] (Table II) indicate that this adjustment of the relative potencies is in most cases not significant; nonetheless, these "brain level potency ratios" are employed as the basis for subsequent discussion.

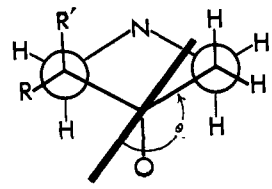
Stereostructure-Activity Relationship. It can be noted that the more potent enantiomers of α- and β-prodine [(+)-**4a**, (+)-**4b**] possess a 4*S* chiral center but opposite chiralities at C-3.

The fact that the more active antipodes have different C-3 chiralities and are both substituted on the pro-*S* edge of the piperidine ring reflects the critical nature of the phenyl and propionoxy group to the interaction of **5** with analgetic receptors. The biological data suggest there are two factors which contribute to the antipodal stereoselectivity of the prodines.

(1) *Direct discrimination of the enantiotopic edges of the molecules by the receptor.* Thus, the fact that **5** possesses a potency which is much greater than the (−) isomers (**7**) and less than that of the (+) isomers (**6**) is consistent with the idea that the 3-Me group on the pro-*R* edge sterically interferes with drug-receptor association, whereas identical substitution on the pro-*S* edge leads to enhanced affinity due to the 3-Me group fitting into a hydrophobic pocket.

(2) *Indirect discrimination of the enantiotopic edges of the molecules by the receptors.* When X-ray data[17,18,21]

for racemic **4a** and **4b** are analyzed in light of the configurational assignments, it is apparent that the torsion angles of groups attached to the C-4 chiral center are of the same sign in the more potent enantiomers. This suggests that the 3-Me group also gives rise to antipodal stereoselectivity by a second mechanism, namely, by its ability to determine the sign of the torsion angle of the phenyl and/or OCO function. Projection formula **15** illustrates the similarity of the torsion angles between the aromatic and piperidine rings in the more active enantiomers of **4a** and **4b**. The fact that the more potent enantiomer of γ-5-methylprodine[27] also exhibits a similar torsion angle supports this idea.



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4a·HCl, R = Me; R' = H; $\theta = -152°$
4b·HCl, R = H; R' = Me; $\theta = -167°$

Studies on this aspect of the stereostructure-activity relationship are in progress in order to determine whether a similar conformational arrangement of phenyl and ester functions is found in the more potent enantiomers of other structurally related analgetics which possess equatorially oriented phenyl groups.

In summary, the conversion of the C-4 prochiral center of **5** into a chiral center by substitution of a Me group in the 3 position affords enantiomers which exhibit large potency differences. The results of this study, when analyzed together with the reported[16,17,21] solid-state conformations of racemic **4a** and **4b**, raise the possibility that the stereoselectivity associated with the C-4 chiral center may be a consequence of both direct and indirect discrimination of the enantiotopic edges of these molecules by the analgetic receptor. Thus, the data suggest the "Ogston effect" to be operative in nondissymmetric, analgetic ligands such as **5**.

Experimental Section

All melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. Optical rotations were obtained using a Perkin-Elmer 114 polarimeter and a 1-dm cell. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Microanalytical Laboratory, University of Minnesota. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theoretical values. The ir spectra were obtained with a Perkin-Elmer 237B spectrophotometer, liquid film or KBr disk. The nmr data (ppm, δ) were obtained with a Varian A-60D spectrometer using Me_4Si as the internal reference with $CDCl_3$ as the solvent and DSS as the internal standard with D_2O as the solvent. The nmr spectra were recorded at the ambient temperature of the magnet and the concentrations employed were approximately 10%. The ir and nmr data of all of the compounds were consistent with the proposed structures.

Resolution of (±)-1,*r*-3-Dimethyl-*t*-4-phenyl-4-piperidinol (8). Racemic α-prodinol (5.0 g, 24.4 mmol) was dissolved in 60 ml of acetone and mixed with 3.68 g (1 equiv) of (+)-tartaric acid in 57 ml of MeOH. Sufficient Me_2CO was added to make a total volume of 800 ml. After 3 days at room temperature, the (+)-base·(+)-acid tartrate salt (4.0 g, 93% of theory) was isolated and recrystallized to optical purity from EtOH or MeOH-Me_2CO (1:10): mp 162–163°; $[\alpha]^{25}D$ +13.5° (*c* 1, H_2O). *Anal.* ($C_{17}H_{25}NO_7$) C, H, N. The (+)-base was regenerated from an aqueous solution of the salt with excess NH_3, partitioned into Et_2O, and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Recrystallization from petroleum ether (bp 60–70°) gave 1.40 g: mp 90–91°; $[\alpha]^{27}D$ +11.8° (*c* 1, Me_2CO).

The resolution liquor was concentrated *in vacuo* and treated with excess NH_3 to liberate the crude (−)-base. This was isolated as a solid (2.88 g) and purified through the enantiomeric salt by mixing with 2.12 g of (−)-tartaric acid in 430 ml of Me_2CO and 32 ml of MeOH. After standing 1 day at 25°, the (−)-base·(−)-acid tartrate (3.92 g, 80% of theory) was isolated and recrystallized from MeOH-Me_2CO (1:10): mp 163–164°; $[\alpha]^{25}D$ −12.9° (*c* 1, H_2O). *Anal.* ($C_{17}H_{25}NO_7$) C, H, N. Reconversion to the base in the usual way gave pure (−)-**8**: mp 89–90°; $[\alpha]^{20}D$ -12.0° (*c* 1, Me_2CO).

Resolution of (±)-1,*r*-3-Dimethyl-*c*-4-phenyl-4-piperidinol (9). A solution containing 5.0 g (24.4 mmol) of (±)-**9** in 96 ml of hot MeOH was treated with 1 equiv (9.16 g) of (−)-dibenzoyltartaric acid. Water (26 ml) was added and the solution set aside at room temperature. After 3 days 4.02 g (58.5% of theory) of the (+)-base·(−)-acid dibenzoyltartrate salt was isolated. One recrystallization from MeOH afforded optically pure material: mp 164–165°; $[\alpha]^{25}D$ -43.0° (*c* 1, MeOH). *Anal.* ($C_{13}H_{33}NO_9$) C, H, N. A solution of the salt (3.25 g) in 40 ml of MeOH was made basic with 10% NaOH and diluted with 20 ml of H_2O. After removing the MeOH *in vacuo*, the suspended base was partitioned into Et_2O and dried ($MgSO_4$), and the solvent removed under reduced pressure. Crystallization from petroleum ether (bp 60–70°) afforded 1.04 g (86%) of (+)-**9**: mp 137–138°; $[\alpha]^{20}D$ +74.5° (*c* 1, Me_2CO).

Crude (−)-**9** (2.5 g), recovered from the above resolution liquor after basification, was dissolved in 48 ml of hot MeOH and treated with 4.59 g of (+)-dibenzoyltartaric acid and 13 ml of H_2O. The (−)-base·(+)-acid dibenzoyltartrate salt was isolated (3.19 g, 93%) after 24 hr at room temperature and recrystallized from MeOH: mp 165–166°; $[\alpha]^{22}D$ +42.9° (*c* 1, MeOH). *Anal.* ($C_{31}H_{33}NO_9$) C, H, N. Reconversion to the base in the manner described above, followed by crystallization from petroleum ether (bp 60–70°), yielded 1.01 g (93%) of optically pure (−)-**9** [mp 137–138°; $[\alpha]^{21}D$ −75.0° (*c* 1, Me_2CO)] from 3.0 g of the (+)-salt.

(+)-α-Prodinol Methiodide (10). Methyl iodide (2.0 ml) was added to a solution of (+)-**8** (0.52 g, 2.5 mmol) in 30 ml of Et_2O and the mixture allowed to stand at 10° for 24 hr. The product (0.87 g, 98%) was collected and recrystallized once from EtAc–Me_2CO to give prisms: mp 185–187°; $[\alpha]^{27}D$ +0.5° (*c* 1, EtOH). *Anal.* ($C_{14}H_{22}INO$) C, H, N.

(+)-(3*S*,4*R*)-5-Dimethylamino-4-methyl-3-phenyl-3-hydroxypentene-1 (11). A solution of (+)-**10** (0.60 g, 1.74 mmol) in 20 ml of H_2O was shaken in the dark with Ag_2O (freshly prepared from 2.4 g of $AgNO_3$ and 0.54 g of NaOH) until a filtered aliquot gave a negative iodide test. The mixture was filtered and the filtrate concentrated *in vacuo* to a thick syrup. The syrup was heated under nitrogen at 170–180° for 45 min, and the oil that formed was taken up in Et_2O, washed with water, and dried over $MgSO_4$. After removal of solvent there was obtained 0.32 g (85%) of **11** as an oil, $[\alpha]^{26}D$ +85.6° (*c* 1.3, Et_2O). Tlc showed a single component present; ir (neat) 3400–3100 (OH), 1645 (C=C), 1600 (phenyl), 920 cm^{-1} (C=CH_2); nmr ($CDCl_3$) 0.82 (d, 3, CH_3CH), 5.13 (q, 1, HCH=CH), 5.44 (q, 1, HCH=CH), 6.40 ppm (q, 1, CH_2=CH). Vinyl protons exhibited correct 2:1 integral ratio of terminal methylene to methine. A portion of the base was treated with ethereal maleic acid. Two recrystallizations from EtOAc gave crystals of the acid maleate salt: mp 107–108°; $[\alpha]^{27}D$ +48.3° (*c* 1, EtOH). *Anal.* ($C_{18}H_{25}NO_5$) C, H, N.

(*R*)-3-Dimethylamino-2-methylpropiophenone (13). A solution of the (+)-**11** (0.27 g, 1.24 mmol) in 5 ml of Et_2O was added to a mixture of 25 ml of Et_2O, 25 ml of water, 0.05 g of OsO_4, and 2 drops of pyridine. The reaction mixture was rapidly stirred for 1 hr at room temperature and then 1.5 g (7.05 mmol) of powdered sodium metaperiodate was added over a 35-min period. After continued stirring for 24 hr, the phases were separated, and the water phase was made basic with NH_3 and quickly extracted with Et_2O. The combined Et_2O extracts were washed once with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure leaving (−)-**13** which was immediately converted to the maleate salt by treatment with excess ethereal maleic acid. The salt was crystallized (EtOAc) affording 0.114 g of (−)-**13** maleate: mp 122–123°; $[\alpha]^{20}D$ −52.6° (*c* 1, EtOH). The maleate salt prepared in the same way from a sample of authentic (−)-amino ketone[12] base had mp 123–124°, $[\alpha]^{20}D$ −53.2° (*c* 1, EtOH). A mixture of the two (−)-maleates showed no melting point depression. The ir spectra of both salts were identical. *Anal.* ($C_{16}H_{21}NO_5$) C, H, N.

(3*R*,4*S*)-α-Prodine Hydrochloride [(+)-4a·HCl]. A 2.5-fold molar excess of propionyl chloride was added to 1.0 g (4.0 mmol) of (+)-α-prodinol [(+)-**8**] in 15 ml of dry toluene and the mixture stirred and refluxed for 6 hr in a moisture-free atmosphere. The material that separated from the reaction mixture after 10 hr at room temperature was collected by filtration and washed with cold toluene and then Et_2O to yield 1.26 g (87%) of 4a·HCl.

Three recrystallizations from Me_2CO–Et_2O afforded 0.62 g of hydroscopic crystals [mp 194–196°; $[\alpha]^{21}D$ +26.5° (*c* 1, EtOH)] after drying *in vacuo* (100°, 12 hr). *Anal.* ($C_{16}H_{24}ClNO_2$) C, H, N.

(3*S*,4*R*)-α-Prodine Hydrochloride [(−)-4a·HCl]. (−)-α-Prodinol [(−)-8] (1.40 g, 6.84 mmol) was converted to (−)-**4a**·HCl in the same manner as its antipode. The crude HCl salt (1.34 g, 67%) was recrystallized three times from Me_2CO–Et_2O to give hydroscopic needles [mp 196–197°; $[\alpha]^{21}D$ −27.9° (*c* 1, EtOH)] after drying under vacuum at 100° for 12 hr. *Anal.* ($C_{16}H_{24}ClNO_2$) C, H, N.

(*R*)-1,5-Dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine [(−)-14]. (+)-β-Prodinol [(+)-9] was dehydrated according to a procedure of Casy, *et al.*[20] This was accomplished by heating (+)-9 (0.207 g, 1.01 mmol) in 14 ml of 17% HCl at 52° for 24 hr. Excess NH_3 was added to the cooled reaction mixture and the liberated base was extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give the (−)-**14** as an oil: yield 0.162 g (87%); $[\alpha]^{27}D$ −130° (*c* 1.4, Et_2O); ir (neat) 1650 (C=C), 1600 (phenyl), 860 cm^{-1} (trisubstituted C=C, CH bending); nmr ($CDCl_3$) 1.00 (d, 3, CH_3CH), 5.79 (t, 1, CH=C), 7.22 ppm (s, 5, Ph). Treatment of the base with ethereal HCl yielded the salt which was recrystallized from Me_2CO–Et_2O: mp 205–206°; $[\alpha]^{27}D$ −57.2° (*c* 0.5, EtOH); ir (KBr) 2500 (N^+H), 1652 (C=C), 1600 (phenyl), 860 cm^{-1} (CH=C, bending). *Anal.* ($C_{13}H_{18}ClN$) C, H, N.

(*S*)-1,5-Dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine [(+)-14]. Using the procedure of Diamond,[18] (+)-**4a** (0.365 g, 1.40 mmol) was dissolved in 25 ml of mineral oil and then was kept under N_2 at 300° for 1 hr. Et_2O (25 ml) was added to the cooled reaction mixture and the organic layer was extracted with 10% HCl. The aqueous extract was made basic with 20% NaOH and extracted with Et_2O. The Et_2O extracts were washed with H_2O and dried ($MgSO_4$), and the Et_2O was removed (vacuum) leaving (+)-14: yield 0.162 g (62%); $[\alpha]^{27}D$ +106° (*c* 1.2, Et_2O). Tlc showed the product to be homogeneous; the ir and nmr spectra were identical with those of (−)-**14**. The amine base was converted to the HCl salt in the usual manner and then was recrystallized twice from Me_2CO–Et_2O to give (+)-14·HCl: mp 204–205°; $[\alpha]^{27}D$ +64.5° (*c* 0.5, EtOH); ir (KBr) spectrum was identical with that of (−)-14·HCl. *Anal.* ($C_{13}H_{18}ClN$) C, H, N.

(3*S*,4*S*)-β-Prodine Hydrochloride [(+)-4b·HCl]. (+)-β-Prodinol [(+)-9] (0.5 g, 24.4 mmol) was esterified with propionyl chloride under the same conditions previously described in the preparation of **4a**·HCl antipodes. The reaction mixture afforded 0.69 g (92%) of crude HCl salt which was recrystallized three times from Me_2CO–Et_2O to give 0.31 g of hygroscopic (+)-4b: mp 188–190°; $[\alpha]^{20}D$ +74.5° (*c* 1, EtOH); ir (KBr) 3400 and 1645 (H_2O hydration), 2250–2450 (N^+H), 1600 and 1580 (phenyl), 1735 (ester C=O), 1175 cm^{-1} (CO-O). *Anal.* ($C_{16}H_{24}ClNO \cdot 0.75\ H_2O$) C, H, N.

(3*R*,4*R*)-β-Prodine Hydrochloride [(−)-4b·HCl]. Employing the usual propionylation procedure, (−)-β-prodinol [(−)-9] (1.0 g, 4.88 mmol) afforded 1.33 g (92%) of crude HCl salt. Repeated crystallization of the salt from Me_2CO–Et_2O gave 0.731 g of pure (−)-4b: mp 188–190°; $[\alpha]^{20}D$ −73.7° (*c* 1, EtOH). The ir spectrum was identical with that of the antipodal salt. *Anal.* ($C_{16}H_{24}ClNO \cdot 0.75\text{-}H_2O$) C, H, N.

Evaluation of Analgesic Activities. Analgetic potencies for the compounds given in Table I were determined in mice using the procedure of Marshall, *et al.*[22] The heat source was a 250-W infrared bulb that was adjusted to a surface temperature of 62° by means of a rheostat. The compounds were administered as a solution of the HCl salt in physiological saline. The solutions for each dose level were prepared so that each mouse received 0.01 ml/g of body weight.

A group of ten to twenty 25–30-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 recorded at three 15-min intervals prior to administering the compound to establish a reaction time control value. The mean value of the second and third interval reaction times was taken as the control value. The mean control reaction time for 450 animals was 5.2 sec.

Reaction times were again recorded 15 and 30 min after sc administration of the compound. The reaction time at the 15-min interval was consistently greater and this interval was used as the response metameter. A mouse was judged to exhibit analgesia when its metameter reaction time was at least twice the preadministration control value. A cut-off time of 45 sec was used for animals which did not leave the bulb. The post 15-min mean reaction time for saline controls (10 animals) was 4.0 sec. The ED_{50} values were determined by probit analysis according to Goldstein[28] with the aid of a Hewlett-Packard calculator, Model 9100A.

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References

(1) M. M. Abdel-Monem, D. L. Larson, H. J. Kupferberg, and P. S. Portoghese, *J. Med. Chem.*, **15**, 494 (1972) (paper 11).
(2) A. G. Ogston, *Nature (London)*, **162**, 963 (1948).
(3) H. G. Wood, G. H. Werkman, A. Hemingway, and O. Nier, *J. Biol. Chem.*, **139**, 483 (1941); E. A. Evans, Jr., and L. Slotin, *ibid.*, **141**, 439 (1941).
(4) A. G. Ogston, *Nature (London)*, **181**, 1462 (1958).
(5) R. Bentley, "Molecular Asymmetry in Biology," Vol. I, Academic Press, New York, N. Y., 1969, Chapter 4; W. L. Alworth, "Stereochemistry and Its Application in Biochemistry," Wiley-Interscience, New York, N. Y., 1972, Chapters 5 and 6.
(6) (a) K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966); (b) H. Hirchmann and K. R. Hanson, *J. Org. Chem.*, **36**, 3293 (1971); (c) H. Hirschmann and K. R. Hanson, *ibid.*, **37**, 2784 (1972).
(7) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(8) P. S. Portoghese, *Annu. Rev. Pharmacol.*, **10**, 51 (1970).
(9) P. S. Portoghese and D. L. Larson, *J. Pharm. Sci.*, **57**, 711 (1968).
(10) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).
(11) P. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960).
(12) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963).
(13) A. C. Cope and E. Trumbull, *Org. React.*, **11**, 317 (1960).
(14) S. Archer, Abstracts of Papers, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p 4M.
(15) A. H. Beckett, A. F. Casy, and H. J. Harper, *Chem. Ind. (London)*, 485 (1959).
(16) G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **13**, 525 (1960).
(17) F. R. Ahmed and W. H. Barnes, *ibid.*, **16**, 1249 (1963).
(18) J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Med. Chem.*, 7, 57 (1964).
(19) D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1963, p 167.
(20) A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, 23, 1405 (1967).
(21) F. R. Ahmed, W. H. Barnes, and L. D. Masironi, *Acta Crystallogr.*, **16**, 237 (1963).
(22) F. N. Marshall, W. R. Jones, and L. C. Weaver, *Proc. Soc. Exp. Biol.*, **116**, 912 (1964).
(23) L. O. Randall and G. Lehman, *J. Pharmacol. Exp. Ther.*, **93**, 314 (1948).
(24) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, 9, 939 (1957).
(25) E. Kutter, A. Herz, H. Teschemacher, and R. Hess, *J. Med. Chem.*, **13**, 801 (1970).
(26) J. W. Miller and H. W. Elliott, *J. Pharmacol. Exp. Ther.*, **113**, 283 (1955).
(27) P. S. Portoghese, Z. S. D. Gomaa, D. L. Larson, and E. Shefter, *J. Med. Chem.*, 16, 199 (1973) (paper 13); P. S. Portoghese, Z. S. D. Gomaa, and D. L. Larson, 162nd National Meeting of the American Chemical Society, Abstracts, 1971, Medi-59.
(28) A. Goldstein, "Biostatistics," Macmillan, New York, N. Y., 1964.