Stereochemical Studies on Medicinal Agents. 18.[1] Absolute Configuration and Analgetic Potency of Trimeperidine Enantiomers

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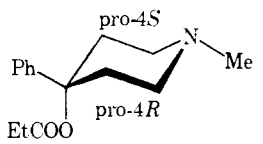
Enantiomers of tripmeperidine were prepared and the absolute configuration was determined by degradation of piperidinol [(+)-7] to (*R*)-3-dimethylamino-2-methylpropiophenone. The analgetic potency of the 2*S*,4*S*,5*R* isomer, (+)-13, is approximately equal to morphine and nine times that of its enantiomer. The absolute stereoselectivity of trimeperidine and that reported for α-prodine is qualitatively the same and the conformational features of the more potent enantiomers are also very similar. The results suggest that the antipodal stereoselectivity of trimeperidine is controlled primarily by the configuration and conformation of groups attached to the C-4 and C-5 chiral centers and that the 2-Me group plays a relatively minor role in the drug-receptor interaction. The present study lends further support to an earlier proposal that potency differences between enantiomeric 4-phenylpiperidines are due to the ability of the receptor to discriminate between the enantiotopic edges of the piperidine ring and to conformational factors.

Several recent publications[1-5] in this series have dealt with the antipodal stereoselectivity of 1-methyl-4-phenyl-4-propionoxypiperidine (1) substituted with alkyl groups on the pro-4*R* and pro-4*S* edges of the piperidine ring. On the basis of these studies it appears that a 3-alkyl group attached to the pro-4*S* edge is more favorable for analgetic activity than an identical substitution on the pro-4*R* edge. Two effects have been suggested to give rise to the observed antipodal stereoselectivity: (1) a pure configurational effect related to the ability of the receptor to discriminate between the enantiotopic edges (pro-4*R* and pro-4*S*) of the molecule, and (2) a conformational effect determined by the ability of an alkyl substituent (vicinal to C-4) to induce a chiral orientation of the phenyl or ester group and thereby influence drug-receptor association. Such studies have emphasized that configuration and conformation are inseparable features which must be considered together when analyzing structure-activity relationships of strong analgetics.



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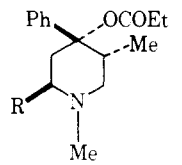
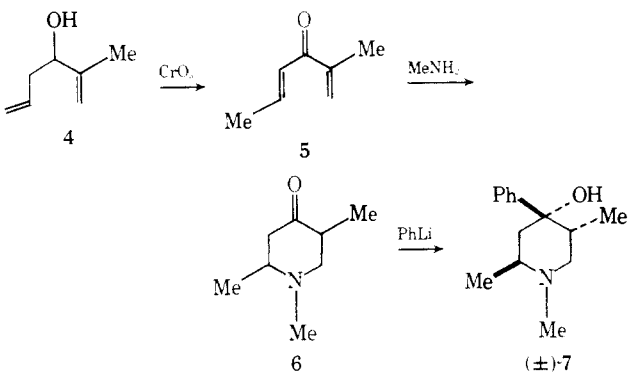
In an effort to acquire further information on the role of conformation and configuration in the action of such compounds, we have investigated the γ diastereomer of 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine (**2**,[6,7] trimeperidine). The relative stereochemistry of this potent analgetic recently has been determined by means of X-ray crystallography[8] and ^{13}C nmr[9] and is in accord with the *t*-2-Me, *c*-5-Me, *r*-4-OCOEt stereochemistry proposed previously by Prostakov and Mikheeva.[7] If the absolute stereochemical requirements for trimeperidine closely parallel those for α-prodine (**3**), this would provide additional support for our earlier conclusions[3,4] regarding the role played by a Me group in the C-3 or C-5 position. Further, the study of trimeperidine is of interest because it would allow us to evaluate the effect of a 2-Me group on the ability of analgetic receptors to distinguish between the enantiotopic edges of the piperidine ring. The present paper describes the preparation, biological evaluation, and absolute configurational determination of (+)- and (−)-trimeperidine as an approach to investigating this problem.



(±)-2, R = Me
(±)-3, R = H

Chemistry. The synthesis of the racemic piperidinol 7 was accomplished by a modification of the reported[6] procedure. Oxidation of 2-methyl-1,5-hexadien-3-ol (4) and concomitant isomerization of the double bond afforded ketone **5** which was allowed to undergo Michael condensation with methylamine without prior isolation. The resultant piperidine **6** was treated with phenyllithium to give a mixture of diastereomeric alcohols which contained a major quantity of the desired γ isomer **7**.



4 5 6 (±)-7

Optical resolution of (±)-7 was achieved through fractional crystallization of the 3′-nitrotartranilate salts. The (+)- and (−)-3′-nitrotartranilic acids were prepared either by reacting tartaric acid with 3-nitroaniline in the presence of DCC or by going through the diacetyltartaric anhydride intermediate.

The degradative sequence for determining the absolute configuration of (+)-7 is illustrated in Scheme I. Conversion of (+)-7 to methiodide **8** followed by a Hoffmann elimination procedure afforded a 60:40 mixture of olefins **9** and **10**. It is noteworthy that no elimination occurred on the pro-4*S* edge of the piperidine ring, and this presumably is related to the absence of a trans-coplanar arrangement between the onium group and β hydrogen.[4,10] Hydroxylation of olefin **9** with OsO_4 followed by *in situ* cleavage of triol **11** with $NaIO_4$ gave (−)-**12** which was isolated as the HCl salt[11] in 94% optical purity.

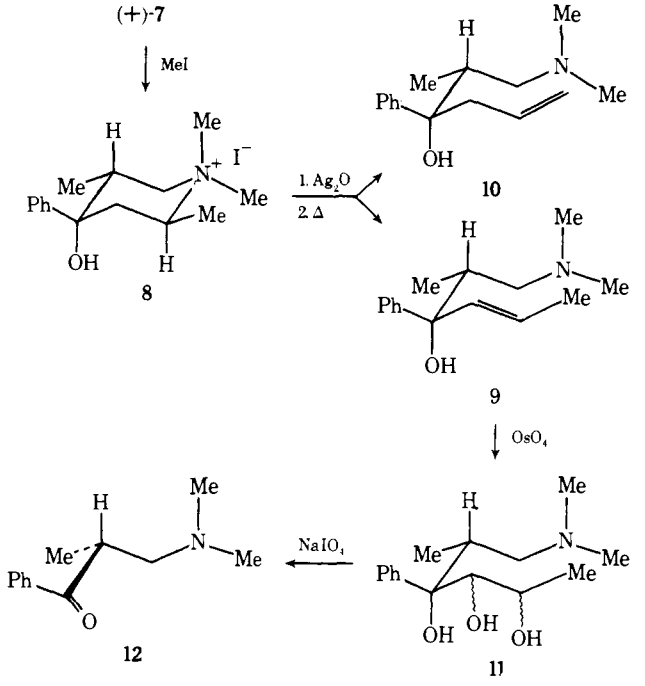
By virtue of the known relative stereochemistry of 7,[7-9] and on the basis that (−)-**12** is known to possess the *R*

Table I. Analgetic Potencies of Trimeperidine and Its Enantiomers

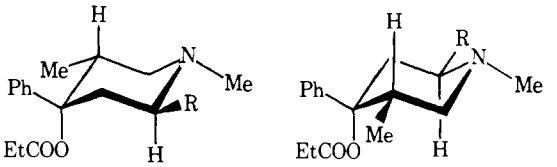
Compd[a]	Configuration	ED_{50}, mg/kg[b]	Onset[c]	Peak[d]	Duration[e]
(+)-**13**	2*S*,4*S*,5*R*	0.94 (0.75–1.19)[f]	3.7	18.0	131
(−)-**13**	2*R*,4*R*,5*S*	8.8 (7.0–11.0)	4.4	19.1	149
2		0.92 (0.70–1.20)	3.5	20.5	126
Morphine		1.2[g]			

[a] Tested as the HCl salts. [b] Tested sc in mice by the hot-plate procedure.[12] [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).

Scheme I



configuration,[11] it follows that the absolute stereochemistry of (+)-7 is 2*S*,4*S*,5*R*. Esterification of (+)- and (−)-7 with propionyl chloride afforded the corresponding propionate esters as the HCl salts. Since esterification does not alter the stereochemistry at C-4, the absolute configurations are as depicted in perspective formulas (+)- and (−)-**13**.



(+)-**13**, R = Me
(+)-**14**, R = H
(−)-**13**, R = Me
(−)-**14**, R = H

Pharmacology. The analgetic potencies of trimeperidine [(±)-**2**] and its enantiomers were determined by the hot-plate procedure[12] after sc administration in mice (Table I). The (+) isomer is approximately nine times more potent than its enantiomer and slightly more active than morphine. It is noteworthy that (±)-**2** and (+)-**13** are equipotent, an observation that is difficult to explain but is not without precedent.[13] The similar onset, peak, and duration of action of the enantiomers suggest that their difference in potency is a reflection of receptor-related events rather than differential access into the CNS. Indeed, this has been shown to be the case with the α-prodine enantiomers **14**.[5]

Stereostructure–Activity Relationship. The chiral

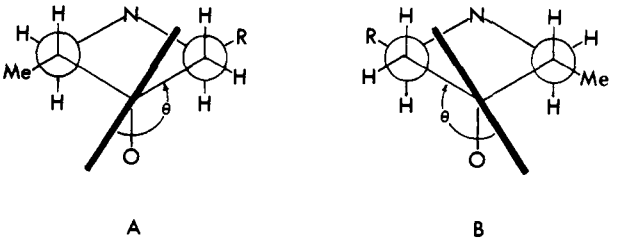
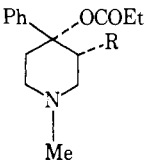


Figure 1. Projection formulas of trimeperidine (R = Me) and α-prodine (R = H) illustrating the relationship between the sign of the torsion angle, θ, and the more potent (A) and less potent enantiomers (B).

centers common to the more potent enantiomers of trimeperidine [(+)-**13**] and α-prodine [(+)-**14**][4] are of identical configuration. Moreover, X-ray[8,14] and ^{13}C nmr[9,15] studies suggest that trimeperidine and α-prodine assume very similar conformations. Analysis of the X-ray[8] data together with our absolute configurational assignment reveals that the torsion angle between the phenyl group and piperidine ring in (+)-**13** is of identical sign and similar magnitude to the more potent α-prodine enantiomer, (+)-**14**.[4] The projection formulas illustrating this are shown in Figure 1. A similar relationship has been found for other closely related analgetics as well.[3,4]

The results suggest that the antipodal stereoselectivity of trimeperidine is controlled primarily by the configuration and conformation of groups attached to the C-4 and C-5 chiral centers and that the 2-Me group plays a relatively minor role.

It may be significant that the potency ratio, (+)-**13**/(−)-**13** ~ 9, differs from the ratios (~25) found for α-prodine [(+)-**14**/(−)-**14**][4] and its 2-ethyl and 2-propyl homologs **15** and **16**.[1] Even after taking into account the possible low-



15, R = Et
16, R = Pr

ering of the enantiomeric potency ratio due to the likelihood of incomplete resolution, the calculated ratio,† (+)-**13**/(−)-**13** = 12, still differs substantially from that of α-prodine. While differential distribution and metabolism of the enantiomers cannot be excluded as a possibility, it seems unlikely that this can account for the lower ratio since (+)- and (−)-**13** possess very similar time courses of action. Moreover, several studies[5,16-19] have shown that there is no significant difference between the brain levels of enantiomeric analgetics.

Since the presence of an equatorial 2-Me group does not appear to affect the magnitude and sign of the torsion

† This is based on the presence of a maximum of 3% enantiomeric impurity.

angle between the phenyl and piperidine ring, the lower enantiomeric potency ratio of trimeperidine (relative to that of α-prodine) could arise either by the 2-Me substituent sterically interfering with drug-receptor association in (+)-**13** or by enhancing association in (−)-**13**. Further investigation would be required to clarify this point.

The results of the present study are in accord with the earlier proposal[3,4] that substitution of a methyl group vicinal to a 4-phenyl group gives rise to antipodal stereoselectivity by a combination of two mechanisms: firstly, by determining the absolute sign of a torsion angle between the phenyl or ester group and piperidine ring; this would allow more facile association of one enantiomer [(+)-**13**] with the receptor. Secondly, the 5-Me group attached to the pro-4*R* enantiotopic edge of the piperidine ring [(−)-**13**] sterically interferes with receptor binding, while identical substitution on the pro-4*S* edge offers no such interference.

Finally, as was pointed out in earlier studies,[3] the correlation between geometry and antipodal stereoselectivity does not necessarily imply that the more potent analgetic ligands bind to the receptor in conformation A (Figure 1). The important feature of the correlation 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 conformation of the ligand when in the complexed state.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by MHW 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 the Perkin-Elmer 237B spectrophotometer as liquid films or KBr disks. Nmr data (δ) were recorded with a Varian A-60D spectrometer in $CDCl_3$ (Me_4Si) or D_2O (DSS). All ir and nmr spectra were consistent with assigned structures. Gc analyses were performed on the Varian Aerograph Model 700 or Perkin-Elmer Model 900 gas chromatographs. Optical rotations were taken in a 1-dm cell utilizing a Perkin-Elmer Model 141 polarimeter.

1,2,5-Trimethyl-4-piperidinone (6). A mixture of Et_2O (60 ml) and H_2O (40 ml) containing 20 g (0.18 mol) of **4** (Chemical Samples Co., Columbus, Ohio) was stirred under N_2 while a 6 *M* solution of CrO_3 (110 ml) was added over a 30-min period. The mixture was refluxed for 1 hr over a steam bath and cooled, and the organic layer was separated. The aqueous phase was extracted with Et_2O, the combined Et_2O extracts were dried (Na_2SO_4), and the solvent volume was reduced to about 50 ml *in vacuo*. The mixture was refluxed with 20 ml of aqueous $MeNH_2$ (40%) for 4 hr, cooled, acidified (10% HCl), and extracted with Et_2O. The aqueous phase was made basic (20% NaOH) and was extracted with $CHCl_3$. Removal of solvent from the $CHCl_3$ extract followed by vacuum distillation afforded 3.4 g (13.7%) of **6**, bp 53–55° (3.5 mm) [lit.[6] bp 73–75° (7 mm)].

(±)-γ-1,2,5-Trimethyl-4-phenyl-4-piperidinol (7). A solution of **6** (10 g, 0.071 mol) in dry THF (50 ml) was slowly added to 50 ml of a 2.3 *M* (benzene—Et_2O, 70:30) solution of phenyllithium. Addition was carried out under dry N_2 with the temperature maintained below 5°. The reaction mixture was allowed to stir at room temperature for 4 hr and then was quenched with H_2O (100 ml). The organic layer was separated and the aqueous phase extracted (Et_2O). The Et_2O extract and organic phase were combined and the solvent was removed. The residual oil was distilled *in vacuo* to yield a mixture of the diasteromeric alcohols (8.2 g, 53%), bp 90–130° (0.5 mm), from which the pure γ isomer **7** (2.01 g), mp 106–107° (lit.[6] 107–108°), was obtained after several recrystallizations from petroleum ether (bp 30–60°).

(+)- and (−)-3′-Nitrotartranilic Acid. Procedure a. Diacetyl-*d*-tartaric anhydride[20] (21.6 g, 0.10 mol) and *m*-nitroaniline (15.3 g, 0.11 mol) were refluxed in dry CH_2Cl_2 (200 ml) for 6 hr. The reaction mixture was cooled and extracted with 1 *N* KOH (2 × 50 ml) followed by extraction with H_2O (100 ml). The combined extracts were stirred at 25° for 2 hr, made acidic (20% HCl), and cooled (ice bath). The white solid which precipitated was collected by filtration and recrystallized (H_2O) to yield 17.2 g (60%) of (+)-3′-nitrotartranilic acid: mp 205–207° dec; $[\alpha]^{23}D$ +93.4° (*c* 0.5, H_2O). *Anal.* ($C_{10}H_{10}O_7N_2$) C, H, N. (−)-3′-Nitrotartranilic acid was prepared from (−)-diacetyl-*l*-tartaric anhydride by the same procedure: mp 207–209° dec; $[\alpha]^{23}D$ −90.5° (*c* 0.2, H_2O). *Anal.* ($C_{10}H_{10}O_7N_2$) C, H, N.

Procedure b. A solution of *m*-nitroaniline (2.0 g, 0.0145 mol) and (+)-tartaric acid (2.15 g, 0.0143 mol) in dry THF (50 ml) was allowed to stand under N_2 for 18 hr at 25° in the presence of 3.0 g of dicyclohexylcarbodiimide. The dicyclohexylurea which formed was removed by filtration and the filtrate was made basic with 10% NaOH and extracted with C_6H_6 (3 × 10 ml). The basic solution was acidified with HCl (5%) and on cooling (ice bath) 1.52 g (30%) of the tartranilate was obtained. Recrystallization (H_2O) and drying gave the pure (−)-3′-nitrotartranilic acid: mp 207–208°; $[\alpha]^{22}D$ +93.8° (*c* 0.5, H_2O). Ir and nmr spectra of (+)-3′-nitrotartranilic acid prepared by the two synthetic procedures were identical in all respects.

Resolution of (±)-γ-1,2,5-Trimethyl-4-phenyl-4-piperidinol (7). A solution of 2.00 g (0.0092 mol) of **7** in MeOH (10 ml) was added to a solution of (+)-3′-nitrotartranilic acid (2.43 g, 0.0090 mol) in H_2O (50 ml) which was heated on a steam bath. When dissolution had taken place, the solution was filtered and the solvent removed from the filtrate to give a residue which was dissolved in 20 ml of MeOH–Me_2CO (1:1). After storage at 5° for 10 hr the salt which crystallized was collected and dried *in vacuo* to give 1.53 g (70%) of (−)-**7** (+)-3′-nitrotartranilate: mp 140–141°; $[\alpha]^{22}D$ +51° (*c* 1, MeOH). *Anal.* ($C_{24}H_{31}N_3O_8$) O, H, N. Further recrystallization (MeOH) of this material failed to change the melting point or $[\alpha]D$. The (−) free base was generated by addition of NH_4OH (2 ml) to the salt and extraction with Et_2O (3 × 10 ml). The Et_2O extracts were dried (Na_2SO_4) and decolorized (charcoal), and the solvent was removed. Crystallization of the residue from petroleum ether (bp 30–60°) gave (−)-**7** (0.510 g, 51%): mp 105–106°; $[\alpha]^{22}D$ −29.1° (*c* 1, MeOH).

Partially resolved (+)-**7** was recovered from the resolution mother liquor by addition of base (10% NaOH) and extraction with $CHCl_3$ (3 × 10 ml). Solvent was removed from the extract *in vacuo* to give 1.2 g (0.0055 mol) of crude (+)-**7**: $[\alpha]^{22}D$ +11.1°. This base was combined with (−)-3′-nitrotartranilic acid (1.35 g, 0.0050 mol) and treated as described above to afford (+)-**7** (−)-3′-nitrotartranilate (1.72 g): mp 139–141°; $[\alpha]^{22}D$ −52.5° (*c* 1, MeOH). *Anal.* ($C_{24}H_{31}N_3O_8$) C, H, N. Isolation of the free base as described for the antipode gave 0.550 g (55%) of (+)-**7**: mp 106–107°; $[\alpha]^{22}D$ +29.5°.

γ-1,2,5-Trimethyl-4-phenyl-4-piperidinol Methiodide (8). A mixture of (+)-**7** (0.08 g, 0.0036 mol) and 1 ml of MeI in Et_2O (5 ml) were stirred for 10 hr. The salt which formed was collected, washed (Et_2O), and dried *in vacuo* to yield **8** (0.121 g, 97%): mp 223–225°; $[\alpha]^{23}D$ −5.5° (c 1, H_2O). *Anal.* ($C_{15}H_{24}NOI$) C, H, N.

(+)-6-Dimethylamino-5-methyl-4-phenyl-4-hydroxy-2-hexene (9). Freshly prepared Ag_2O (0.0006 mol, prepared according to Cope and Trumbull)[13] and **8** (0.120 g, 0.0003 mol) were stirred in H_2O (10 ml) in the dark for 2 hr. The reaction mixture was filtered and the filtrate (which gave a negative iodide test) was concentrated to a clear oil by removal of solvent *in vacuo*. After the oil was heated (200°) neat for 10 min under N_2, the mixture was cooled and extracted with 5% HCl. The extract was basified with NaOH (10%), extracted with Et_2O (3 × 5 ml), dried (Na_2SO_4), and evaporated to afford 0.042 g (60%) of a yellow oil. An nmr spectrum of this oil showed it to be a mixture of olefins **9** (allylic methyl doublet δ 1.72) and **10** (*gem*-alkene multiplet δ 5.08). Separation of the olefinic mixture by preparative gc (0.32 cm × 6 m OV-17; 200°; flow, 200 ml/min) gave pure **9** (R_t = 14 min) and **10** (R_t = 12 min) in a 3:2 ratio. The yield of **9**, $[\alpha]^{22}D$ +2.8° (*c* 1, MeOH), was 0.020 g. *Anal.* ($C_{15}H_{23}NO$) C, H, N.

(−)-(*R*)-3-Dimethylamino-2-methylpropiophenone Hydrochloride (12·HCl). Olefin **9** (0.0458 g, 0.196 mmol) was oxidized with OsO_4–$NaIO_4$ according to the procedure of Pappo, *et al.*[21] The olefin was dissolved in dioxane–H_2O (75:25, 10 ml) and OsO_4 (0.005 g) was added to the stirred mixture. To the reaction mixture (maintained under N_2) there was added divided portions of $NaIO_4$ (1.00 g) over 30 min. After stirring for an additional 1.5 hr the mixture was extracted with Et_2O (3 × 5 ml) and dried (Na_2SO_4), and the solvent was removed to afford 0.025 g of an oil. Dropwise addition of ethereal HCl to a solution (2 ml of Et_2O) of the oil afforded the HCl salt which was purified by crystallization (EtOAc–EtOH). There was obtained 0.015 g (35%) of **12**·HCl: mp 185–186°; $[\alpha]^{23}D$ −46.0° (*c* 1, H_2O). *Anal.* ($C_{12}H_{18}NOCl$) C, H, N. An authentic sample[11] of **12**·HCl, $[\alpha]^{23}D$ −49.0° (*c* 1, H_2O), mp 184–185°, gave an undepressed mixture melting point.

Trimeperidine Hydrochloride (2·HCl). A mixture of 0.50 g (0.0023 mol) of (±)-7 and 3 ml of propionyl chloride was allowed to stand at 25° for 3 days under N_2. Et_2O (5 ml) was added, the mixture filtered, and the solid washed two times with petroleum ether (5 ml) and crystallized (Me_2CO) two times to yield 0.42 g (60%) of 2·HCl: mp 201–202° (lit.[7] 198–199°). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

(+)-(2S,4S,5R)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(+)-13·HCl]. The procedure described for 2·HCl was employed using 0.100 g (0.00046 mol) of (+)-7 and 1 ml of propionyl chloride. The yield of (+)-13·HCl, mp 198–200°, $[\alpha]^{23}D$ +34.4° (c 0.5, EtOH), was 0.11 g (77%). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

(−)-(2R,4R,5S)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(−)-13·HCl]. This was prepared from (−)-7 using a procedure identical with that described above: mp 199–200°; $[\alpha]^{23}D$ −34.2° (c 0.5, EtOH). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

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A Structural Modification Study of the Antimalarial 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

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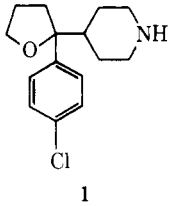
A structural modification study of the antimalarial 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran was conducted. This included: (a) modification of the tetrahydrofuran portion; (b) modification of the *p*-chlorophenyl portion; (c) modification of the piperidine portion; and (d) combined modifications. It was found that 4-[1-(*p*-chlorophenyl)-1-ethoxyethyl]piperidine displayed both prophylactic and therapeutic antimalarial activities. The corresponding *N*-methyl, *N*-methyl *N*-oxide, and the *N*-ethyl analogs also exhibited some activity. Prophylactic antimalarial activity of 4-[1-[2,8-bis(trifluoromethyl)-4-quinolinyl]-1-ethoxyethyl]piperidine was also observed. Compounds in this series, in general, have a rather narrow marginality for structural modification.

Among a series of substituted tetrahydrofuran derivatives synthesized by Marxer,[1-3] 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (**1**) was found to possess both causal prophylactic and therapeutic activity in experimental animals.[3,4] Since the structure–activity pattern of compounds of this class bears a close resemblance to that of another class of antimalarials, the amino alcohols,[5] a structural modification study of **1** was conducted in this laboratory. This included (1) modification of the tetrahydrofuran portion (compounds **4a,b, 7a–d, 9, 12, 14,** and **16**); (2) modification of the *p*-chlorophenyl portion (compounds **17–19**); (3) modification of the piperidine portion (compounds **24** and **25**); and (4) combined modifications (compounds **26a–h,j, 27, 28,** and **31**).



1

Chemistry. (1) Modification of the Tetrahydrofuran Portion. Since a tetrahydrofuran ring consists of five atoms, we can visualize that breaking the ring bonds one at a time would theoretically yield five compounds (the ethers **7b,c, 9,** and the alcohols **12** and **14**) isomeric with the parent compound **1,** while still retaining the original structural framework. For structure–activity comparison, other related compounds **4a,b** and **7a,d** were also prepared.

The alcohols **4a** and **4b** were prepared by treatment of 4-(*p*-chlorobenzoyl)pyridine (**2**) with the appropriate Grignard compound (to yield **3a** and **3b**) followed by hydrogenation. The yield of **3b** was much lower than of **3a,** owing to the fact that a side reaction—reduction of the ketone **2** in the presence of ethylmagnesium iodide to form α-(*p*-chlorophenyl)-4-pyridinemethanol—occurred simultaneously during the reaction. The ethers **7a–d** were obtained by alkylation of the alcohols **3a** and **3b** fol-