Synthesis, Absolute Configuration, and Molecular Modeling Study of Etoxadrol, a Potent Phencyclidine-like Agonist

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Etoxadrol (**2a**), one of the eight possible optical isomers of 2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane, was synthesized from (*S,S*)-1-(2-piperidyl)-1,2-ethanediol, which was obtained from cleavage of dexoxadrol (**1a**, (*S,S*)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane). The absolute configuration of etoxadrol hydrochloride, a phencyclidine-like compound biologically, was determined to be 2*S*, 4*S*, and 6*S* at its three chiral centers by single-crystal X-ray analysis. Epietoxadrol (**2b**), epimeric with etoxadrol at the C-2 center, was also obtained from the synthesis. This much less potent enantiomer has the 2*R*,4*S*,6*S* configuration. The affinity of etoxadrol to the phencyclidine binding site was found to be comparable to that of phencyclidine itself and was 35 times more potent than its epimer, epietoxadrol. Three diastereomeric mixtures were prepared that had low affinity for the phencyclidine site. In studies of the discriminative stimulus properties of these compounds, it was found that only etoxadrol substituted for the phencyclidine stimulus. With use of computer-assisted molecular modeling techniques, a hypothetical phencyclidine binding site model has been developed that, unlike our former hypothesis based on Dreiding models, correctly predicts the higher affinity of etoxadrol and the lesser affinity of epietoxadrol for the phencyclidine site.

The medical usefulness of phencyclidine (PCP) and ketamine as anesthetics for humans was obviated or curtailed, respectively, by their undesirable side effects. The contemporary illicit use of PCP has exacerbated urban law enforcement problems, and overdose cases are a concern in major city medical centers. Only cocaine abuse rivals the abuse of PCP in many cities in the U.S. However, the recent observation[1] that MK-801, a potent phencyclidine-like agonist, possesses neuroprotective properties has prompted new interest in different structural classes of phencyclidine-like compounds.[2,3]

Recent interest in the (2-piperidyl)-1,3-dioxolane class of phencyclidine-like agonists has been spurred by the finding that one of the compounds in this class, dexoxadrol (**1a**, Scheme I), a dissociative anesthetic that is about equipotent with phencyclidine in its affinity for the phencyclidine binding site, and its relatively inactive enantiomer, levoxadrol (**1b**), are among the best pairs of enantiomeric ligands for demonstrating separation of PCP-like effects in behavioral and biochemical evaluations.[4] Dreiding molecular models have been used[4] to show complete overlap of the piperidine rings in PCP and dexoxadrol and simultaneous overlap of the aromatic ring of PCP with one of the aromatic rings of dexoxadrol, in two possible conformations of dexoxadrol based on its absolute configuration.[4] If this overlap of the two major areas (the piperidine and aromatic rings) in PCP-like molecules is essential for interaction with the phencyclidine binding site, then etoxadrol (2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane (**2a**), closely related both chemically and in its in vivo effects to dexoxadrol, would be expected to have a 2*R*,4*S*,6*S* configuration, based on (1) the known absolute configuration of dexoxadrol (*S,S*) from which it was synthesized and (2) a prediction of an *R* configuration at C-2, the third center of asymmetry, from the Dreiding model studies.

Two of the four possible diastereomeric mixtures of 2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane were originally prepared by Hardie et al.[5] (**2a** + **2b** (2*S*,4*S*,6*S* + 2*R*,4*S*,6*S*), and **3a** + **3b** (2*R*,4*R*,6*R* + 2*S*,4*R*,6*R*)) and tested for their local anesthetic, spasmolytic, and central nervous system activity. One particular enantiomer, etoxadrol (**2a**), was subsequently prepared[6] and found to act as a dissociative anesthetic.[7] We resynthesized these two mixtures as well as the remaining two diastereomeric mixtures (**4a** + **4b** (2*S*,4*R*,6*S* + 2*R*,4*R*,6*S*) and **5a** + **5b** (2*S*,4*S*,6*R* +

Table I. Binding Affinities and Behavioral Potencies of Isomeric 2-Ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolanes

isomer	binding affinity: K_i,[a] nM	behavioral potency: ED50,[b] μM
etoxadrol (**2a**)	107	2.4
epietoxadrol (**2b**)	3700	
2*R*,4*R*,6*R* (**3a**):2*S*,4*R*,6*R* (**3b**) (93:7)	2300	>100
2*S*,4*R*,6*S*:2*R*,4*R*,6*S*[c] (**4a** + **4b**)	40 000	>100
2*S*,4*S*,6*R*:2*R*,4*S*,6*R*[c] (**5a** + **5b**)	38 000	>100
dexoxadrol (**1a**)	104	
levoxadrol (**1b**)	12 300	

[a] Determined by displacement of [^{3}H]TCP from tissue homogenate preparation of whole rat brain minus cerebellum. The K_i values were determined from displacement data run in triplicate. [b] From rats trained to discriminate phencyclidine from saline in a two-lever drug discrimination procedure. The ED50 values were calculated from dose–effect curves that were fit by linear regression. [c] A 73:27 mixture of the two compounds (by GC). The absolute configuration at C-2 was unassigned.

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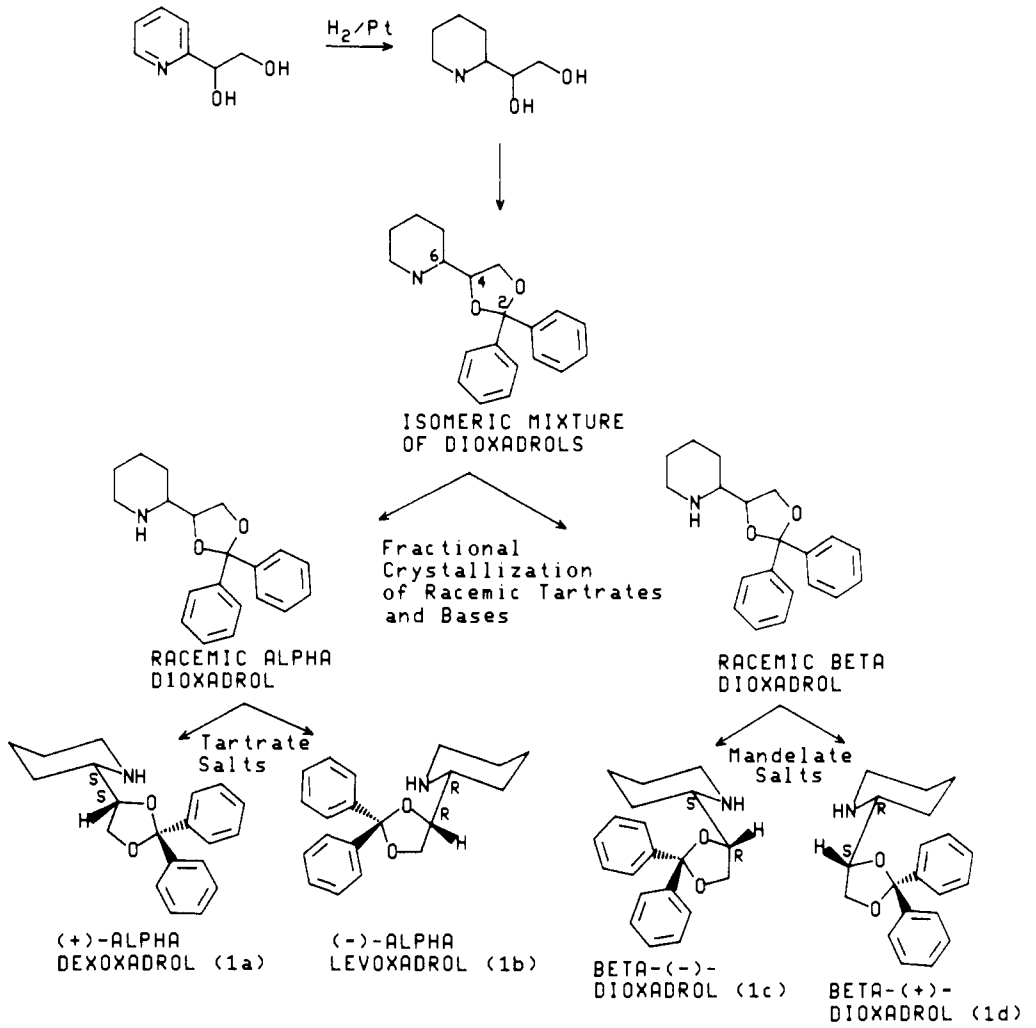
(1) Iversen, L. L.; Woodruff, G. N.; Kemp, J. A.; Foster, A. C.; Gill, R.; Wong, E. H. F. In *Sigma and Phencyclidine Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 757–766, and references therein.
(2) Jacobson, A. E.; Thurkauf, A.; Mattson, M. V.; Rice, K. C.; Koek, W.; Williams, A.; Woods, J. H. In *Sigma and Phencyclidine Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 35–45.
(3) Thurkauf, A.; Mattson, M. V.; Jacobson, A. E.; Rice, K. C. In *Sigma and Phencyclidine Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 47–54.
(4) Jacobson, A. E.; Harrison, E. A., Jr.; Mattson, M. V.; Rafferty, M. G.; Rice, K. C.; Woods, J. H.; Winger, G.; Solomon, R. E.; Lessor, R. A.; Silverton, J. V. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 110.
(5) Hardie, W. R.; Hidalgo, J.; Halberstadt, I. F.; Allen, R. E. *J. Med. Chem.* **1966**, *9*, 127.
(6) Hsi, R. S. P. *J. Labelled Compd.* **1974**, *10*, 381.
(7) Wilson, R. D.; Traber, D. L.; Barratt, E.; Creson, D. L.; Schmitt, R. C.; Allen, C. R. *Anesthesia Analgesia* **1970**, *49*, 236.

Scheme I



2*R*,4*S*,6*R*)). We determined, after evaluating the phencyclidine binding affinity (Table I) of these four diastereomeric mixtures (derived from **1a**, **1b**, **1c**, and **1d**, Scheme II), that in vitro PCP-like activity is present only in that mixture which was synthetically derived from dexoxadrol (**1a**) (i.e., 4*S*,6*S*). This diastereomeric mixture, therefore, was separated to give etoxadrol (**2a**) and its C-2 epimer, epietoxadrol (**2b**). We describe herein the preparation, purification, and binding affinity of **2a**, the biologically active enantiomer, as well as **2b**. The discriminative stimulus properties of **2a** and three diastereomeric mixtures have also been determined. The absolute configuration of etoxadrol was obtained by single-crystal X-ray diffraction.

Chemistry

Dexoxadrol (**1a**, *S*,*S*) and levoxadrol (**1b**, *R*,*R*) were obtained[5] from racemic α-dioxadrol (nomenclature of Hardy et al.)[5] (Scheme I) through recrystallization of their tartrate salts. Separation of racemic β-dioxadrol, by resolution of their mandalate salts, gave the β-(−)-dioxadrol (**1c**, *R*,*S*) and β-(+)-dioxadrol (**1d**, *S*,*R*) enantiomers. Their absolute configuration was established by a single-crystal X-ray analysis of **1c** (data not shown).[8]

Each of these four 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane optical isomers (**1a**, **1b**, **1c**, **1d**, Scheme II) was used to prepare the 2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane diastereomers **2a** + **2b**, **3a** + **3b**, **4a** + **4b**, and **5a** + **5b**, through the piperidinediol intermediates shown in Scheme II. Thus, acidic hydrolysis of dexoxadrol (Scheme II) provided the (*S*,*S*)-1-(2-piperidyl)ethanediol which was condensed with propiophenone dimethyl ketal to give a mixture of etoxadrol (**2a**, its 2*S*,4*S*,6*S* configuration determined by the single-crystal X-ray analysis; vide infra) and its epimer, epietoxadrol (**2b**, with a 2*R*,4*S*,6*S* configuration). Similarly, the diastereomers **3a** (2*R*,4*R*,6*R*) + **3b** (2*S*,4*R*,6*R*), were derived from levoxadrol (**1b**). Their absolute configurations were obtained from the known or deduced absolute configurations of their precursor and the reaction sequence (Scheme II). The **4a** and **4b** diastereomeric mixture was derived from β-(−)-dioxadrol (**1c**) and the **5a** and **5b** mixture from β-(+)-dioxadrol (**1d**).

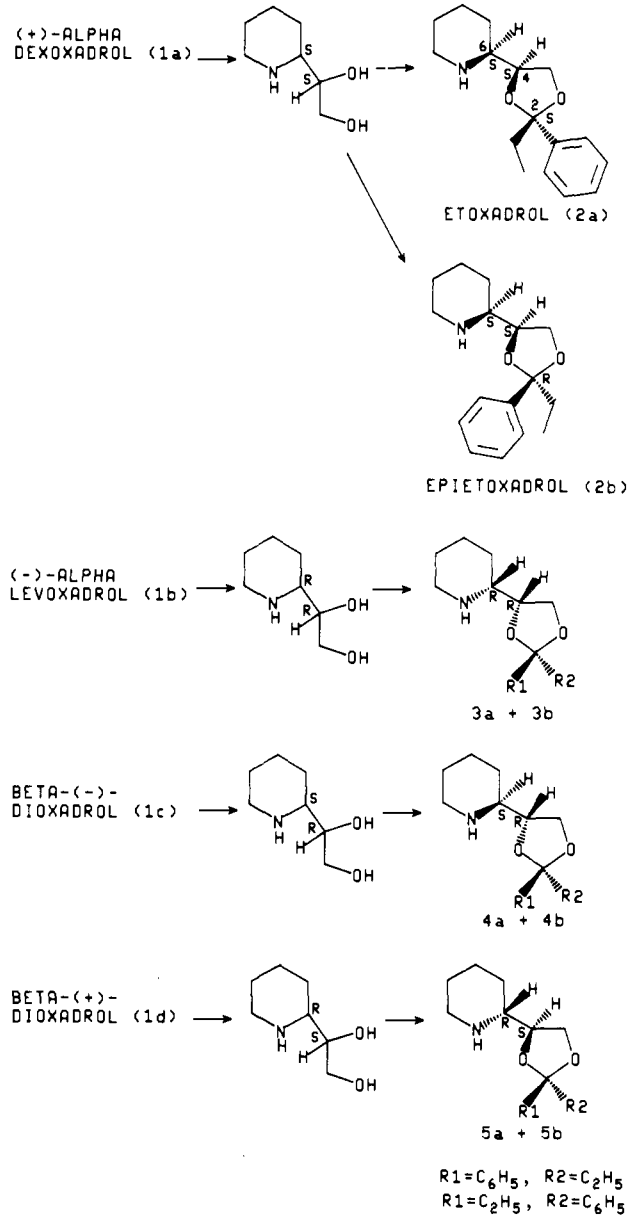
Etoxadrol (**2a**) and epietoxadrol (**2b**) were isolated and purified by chromatography after binding studies of the ketal mixtures indicated that only the ketal mixture derived from dexoxadrol had affinity for the phencyclidine binding site. Isomeric purity of **2a** and **2b** was determined by GC, HPLC, and NMR analysis.

Single-Crystal X-ray Analysis of Etoxadrol Hydrochloride (2a)

X-ray crystallographic data for etoxadrol hydrochloride, $C_{16}H_{23}NO_2 \cdot HCl$, fw = 297.82, were obtained from a clear colorless crystal, 0.08 × 0.12 × 0.55 mm^3. Least-squares refinement gave the orthorhombic $P2_12_12_1$ cell, a = 7.311 (1) Å, b = 11.622 (2) Å, c = 19.758 (3) Å, Z = 4 and D_{calcd} = 1.178 g cm^{-3}. A total of 2368 reflections were measured to $2\theta_{max}$ = 112° with a computer-controlled diffractometer

(8) Zenk, P. C.; May, E. L. Unpublished results.

Scheme II



(Nicolet R3m/v, Cu Kα radiation, λ = 1.541 78 Å), with an incident beam graphite monochromator. There were 1877 unique data and 74 unobserved data ($F_o < 3\sigma|F_o|$). The data were collected in the $\theta/2\theta$ mode with a scan width of $(2.0 + \Delta_{\alpha 1 \alpha 2})$, and the scan rate was a function of the count rate, 8.0°/min minimum, and 30.0°/min maximum. An empirical adsorption correction was applied to the data. The structure was solved by direct methods with the aid of the program SHELXS[9] and refined with use of the full-matrix least-squares program SHELXSL.[9] The 192 parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen bonded atoms. Hydrogen atoms were all located in Fourier difference maps and then allowed to ride on covalently bonded atoms with C–H = 0.96 Å, and isotropic thermal parameters set to 1.1 U_{eq} (C). Hydrogens bonded to nitrogen were refined isotropically. The maximum excursions for the final Fourier difference map were 0.16 and –0.26 e Å^{-3}. The final R factors for the 1803 observed reflections ($F_o > 3\sigma|F_o|$), including 643 Fridel equivalents, were R = 0.030 and R_w = 0.036, and R = 0.046 and R_w = 0.060 for the two possible enantiomers. The absolute configuration was determined by the Hamilton ratio test[10] to be the model with the lowest R values. The ratios of R values, 1.533 and 1.667 respectively for R and R_w, are both well above the value of 1.082 required for a significance level of 0.005 by the Hamilton ratio test. In Figure 1, drawn from experimentally determined coordinates, the asymmetric carbons are 2*S*, 4*S*, and 6*S*. The "hand" chosen also agrees with that determined to be the absolute configuration of dexoxadrol,[4] derived from the same 1-(2-piperidyl)ethanediol, which differs only by the substitution of an additional phenyl at C-2. Bond lengths and angles are normal, and as expected, the C–N bonds are long for the quadrivalent nitrogen atom.[11] The piperidine and the dioxolane ring conformations are chair and half-chair, respectively. There are hydrogen bonds linking the ions in infinite chains. N–H···Cl hydrogen bond parameters are N···Cl (3.085 (3), 3.121 (3) Å), H···Cl (2.15 (2), 2.19 (2) Å), and the angle N–H···Cl (178 (1), 164 (1)°). There are also several contacts shorter than the normal H···Cl van der Waals contacts[12] of 2.95 Å, H(6)···Cl (1.0 + x, y, z) = 2.73 (2) and H(4)···Cl (0.5 + x, 0.5 - y, -z) = 2.72 (2). Tables of coordinates and bond distances and angles have been deposited with the Crystallographic Data Center, Cambridge CB2 1EW, England.

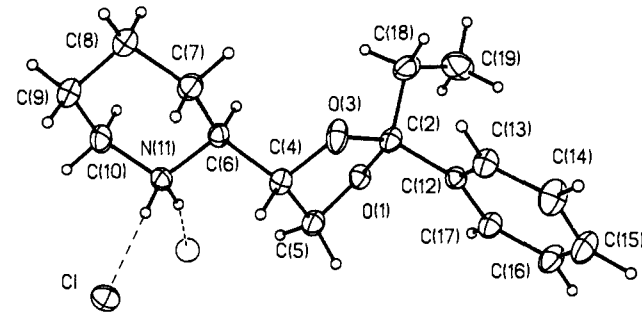


Figure 1. Absolute configuration of etoxadrol hydrochloride (**2a**).

Molecular Modeling Studies

In preparation for a molecular mechanics examination of etoxadrol (**2a**),[13] a computer model of the molecule as the free amine was constructed from phenyl, 1,3-dioxolane, and piperidine subunits found in the SYBYL fragment library. These fragments were linked by bonds of average C–C bond length and valence angle as provided by the SYBYL parameter set. A model of the structure of etoxadrol hydrochloride as determined by X-ray crystallography was also generated with the experimentally determined atomic coordinates.

The first goal of the molecular mechanics study of etoxadrol was to determine the lowest energy conformation of this conformationally mobile compound. The conformational analysis was treated in two parts: (1) the effect of pseudorotation of the dioxolane ring and (2) the conformational interaction of the freely rotating phenyl, ethyl, and piperidinyl substitutents. A systematic conformational search was performed on the dioxolane ring by using the "SEARCH" option of SYBYL. The lowest energy ring

(9) Sheldrick, G. M. SHELXTL80. Minicomputer Programs for Structure Determination, University of Gottingen, 1980.

(10) Hamilton, W. C. In *Statistics in Physical Sciences*; Ronald Press Co.; New York, 1964.

(11) Birnbaum, G. *Acta Crystallogr.* **1967**, *23*, 526.

(12) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(13) Carroll, F. I.; Brine, G. A.; Boldt, K. G.; Mascarella, S. W.; Moreland, C. G.; Sumner, S. J.; Burgess, J. P.; Stejskal, E. O. In *Sigma and Phencyclidine Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J. M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 91–106.

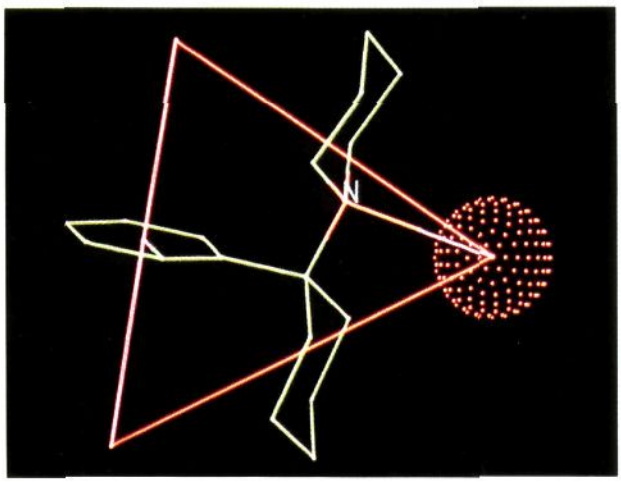


Figure 2. Axial phenyl conformer of PCP (green) with hypothetical location of PCP binding group(s) indicated by a 1-Å diameter dot sphere 2.8 Å in the direction of the nitrogen lone pair vector. Hydrogen atoms were removed for clarity.

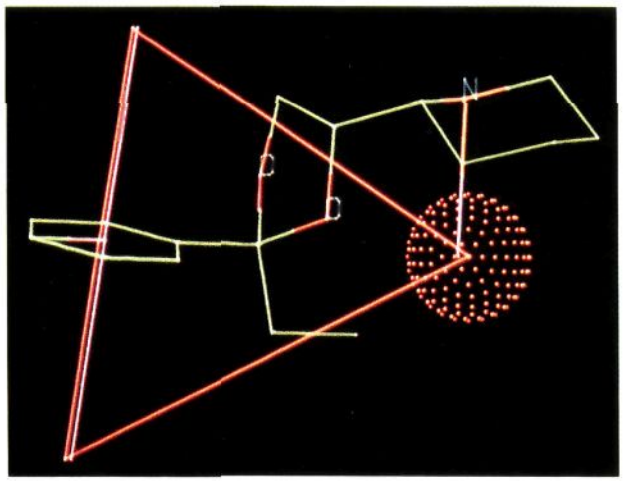


Figure 3. Least-squares superimposition of etoxadrol (green) on the proposed PCP pharmacophore (red triangle) containing the 1-Å dot sphere.

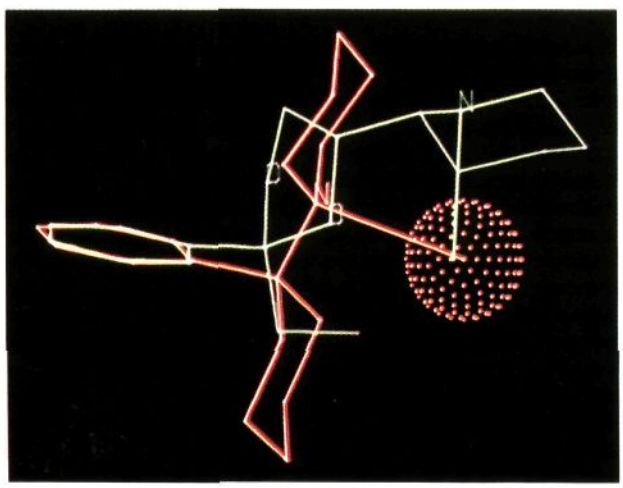


Figure 4. Computer-generated overlay of etoxadrol (green) and PCP (red).

conformer was determined to be a half-chair form of the ring. This was found to closely match the conformation of the dioxolane ring observed in the X-ray crystallographic structure. With this conformer of the dioxolane ring, the remaining rotatable bonds were subjected to a systematic conformational search. The lowest energy conformer of etoxadrol, as calculated by the conformational search, had torsional angles of the phenyl and ethyl substituents relative to the dioxolane ring that were very similar to those found by X-ray crystallography. However, there was a significant difference between the calculated and observed torsional angle between the dioxolane and piperidine rings. There is, of course, no a priori reason why the crystal structure determined by X-ray crystallography must match the energy-minimized structure determined by molecular mechanics. Obviously, crystal packing in the solid state may provide a low-energy conformer, but this conformer need not be among the lowest energy conformers calculated in a vacuum.[14]

In the X-ray crystallographic structure the dioxolane-to-piperidine angle (measuring the N–C–C–O angle) is 178.7° while the calculated lowest energy conformer has an angle of −61.6° between those two rings. The −62° calculated rotomer was found to be 0.75 kcal/mol lower in energy than the 179° rotomer found in the X-ray analysis. As a final step in the refinement of the structure, the lowest energy conformer of etoxadrol was optimized by the MAXIMIN2 minimization module of SYBYL.

An optimized model of an etoxadrol diastereomer epimeric at the acetal (C-2) carbon, epietoxadrol (2b), was generated by the procedure outline above for etoxadrol. The dioxolane-to-piperidine angle (-60.5°) in the energy-minimized conformer of epietoxadrol was essentially the same as that in etoxadrol itself. Also, the dioxolane ring was calculated to have conformation very close to that of the model and the experimentally determined structure of etoxadrol. Hence, the principal difference between etoxadrol and epietoxadrol is simply the position of the phenyl and ethyl substituents on the dioxolane ring. Finally, a second series of systematic conformational searches was performed to identify specifically any conformers of etoxadrol or epietoxadrol that could mimic PCP.

(14) Differences can also arise because the crystallographic determination was conducted on etoxadrol in salt form, and the computer-assisted molecular modeling that we used does not have parameterization for quaternary amines. Only the base form of the amines were used in the calculations; it is unknown whether they are protonated when interacting with the binding site.

Binding Studies

Binding sites were performed as previously described by Jacobson et al.,[4] using a tissue homogenate preparation of fresh whole rat brain minus cerebellum. Incubation was carried out at 5 °C with [^{3}H]TCP as the radioligand. Rapid filtration was done through filters presoaked in 0.03% polylysine. The inhibition constant (K_i) for determination of the affinity of the compound for the PCP binding site was calculated from the Cheng–Prusoff equation[15] with our predetermined K_d for TCP (16.5 nM) from Scatchard analysis. Experiments were performed in triplicate, and 10 μM TCP was used for determination of the nonspecific binding.

Drug Discrimination Studies

Nine rats were trained to discriminate 1.25 mg/kg PCP from saline in a two-lever drug discrimination procedure as has previously been described.[16] Etoxadrol (**2a**) and

(15) Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

(16) Slifer, B. L.; Balster, R. L. *Subst. Alcohol Actions/Misuse* **1984–1985**, *5*, 273.

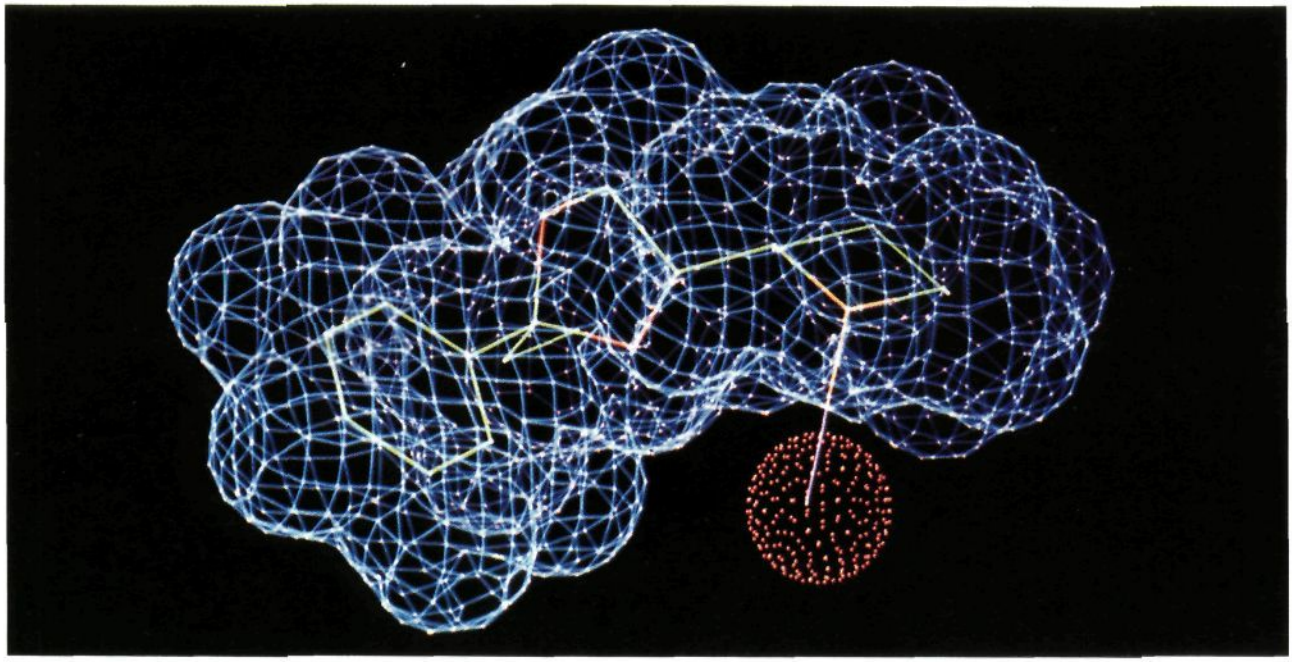


Figure 5. Molecular volume of etoxadrol generated at the van der Waals radii (blue) with the 1-Å diameter dot sphere 2.8 Å in the direction of the nitrogen lone pair vector of the axial phenyl PCP conformer.

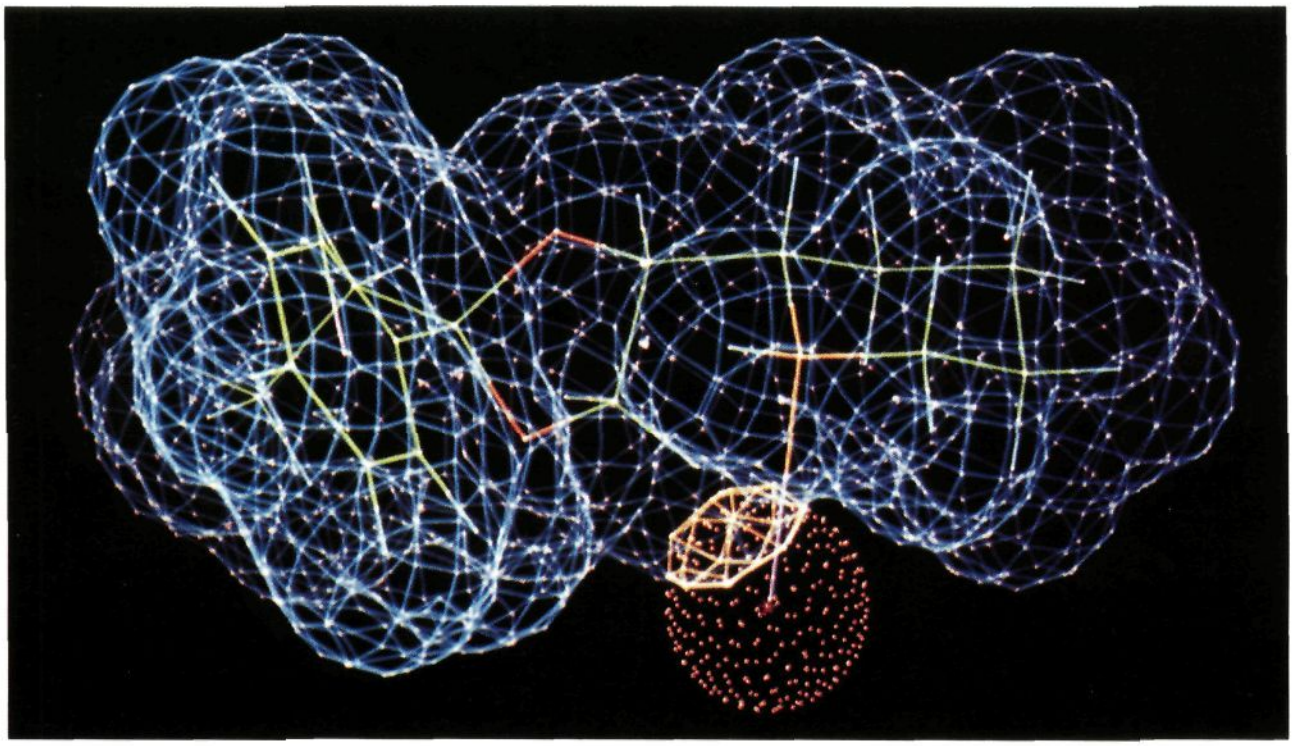


Figure 6. Molecular volume of epietoxadrol generated at the van der Waals radii (blue) with the 1-Å diameter sphere 2.8 Å in the direction of the nitrogen lone pair vector of the axial phenyl PCP conformer.

three of the diastereomeric mixtures (**3a** + **3b**, **4a** + **4b**, and **5a** + **5b**), suspended in an emulphor/ethanol/saline vehicle, were tested for their ability to substitute for the PCP stimulus. The latter compounds were tested at doses up to 30 mg/kg. The dose–effect curve for the active compound was fit by linear regression, and doses expected to result in 50% PCP-lever selection were calculated.

Results and Discussion

The ratio of propiophenone ketal epimers obtained from (*S*,*S*)- and (*R*,*R*)-1-(2-piperidyl)ethanediol (from dexoxadrol and levoxadrol, respectively) was 93:7, as determined by GC analysis. The ratio of epimers obtained from the *S*,*R* and *R*,*S* diols (from β-(−)- and β-(+)-dioxadrol, respectively) was found to be 73:27 (Scheme I). The affinities of these ketal mixtures for the PCP binding site are listed in Table I. Significant binding was observed only in that set of epimers derived synthetically from dexoxadrol. Separation of these epimers, followed by determination of their binding affinity, showed that only the major isomer in this mixture, etoxadrol (**2a**), was PCP-like in its binding characteristics. A similar result was found in the

drug-discrimination studies. Of the compounds tested, only etoxadrol substituted for the PCP stimulus (Table I). Its potency relative to PCP closely paralleled the 2-fold potency difference in binding. The other diastereomeric mixtures failed to substitute for PCP at any dose tested, consistent with their lesser affinity for the phencyclidine site. Previous research has demonstrated the stereospecificity of the dioxadrol enantiomers for discriminative stimulus effects, where only dexoxadrol (**1a**) substitutes for ketamine or PCP.[4,17]

The absolute configuration of etoxadrol hydrochloride was determined to be 2*S*, 4*S*, and 6*S* by de novo X-ray analysis. The configuration assignment of 4*S* and 6*S* for etoxadrol is in agreement with the known absolute configuration of dexoxadrol from which it was derived.[4] The configuration of 2*S* for the chiral ketal carbon of etoxadrol (**2a**) places the phenyl group in a position that does not overlap with the phenyl moiety in PCP, in Dreiding molecular models, when the piperidine rings are aligned. Epietoxadrol (**2b**), the much less potent epimer, has a 2*R* configuration. This compound, which interacts weakly with the phencyclidine site, has its phenyl ring in the "correct" position for overlap with the phenyl ring in PCP, when the piperidine rings are aligned in Dreiding molecular models. Both dexoxadrol and etoxadrol bind to the phencyclidine site with affinities similar to that of PCP. While the possibility exists that dexoxadrol and etoxadrol bind to the PCP site in radically different ways, their similarity in structure, binding affinity, and behavioral effects lends doubt to this idea. These data render our former hypothesis,[4] based on Dreiding molecular models, untenable since it does not correctly predict the higher affinity of etoxadrol and the lesser affinity of epietoxadrol for the phencyclidine binding site.

Etoxadrol and the mixture containing the enantiomer of etoxadrol (**3a + 3b**) do not show quite as large a difference in binding affinity as the dexoxadrol–levoxadrol pair of enantiomers (Table I). There was a 21-fold difference in affinity in the former pair; the latter pair had a 118-fold difference in affinity. Etoxadrol and its epimer epietoxadrol (**2b**) showed a 35-fold difference in binding affinity, and much greater differences in affinity were noted between etoxadrol and the remaining epimeric mixtures (355–374-fold differences). Insufficient quantities of the three other mixtures (**3a + 3b** (2*R*,4*R*,6*R* + 2*S*,4*R*,6*R*), **4a + 4b** (2*S*,4*R*,6*S* + 2*R*,4*R*,6*S*), and **5a + 5b** (2*S*,4*S*,6*R* + 2*R*,4*S*,6*R*)) were obtained for separation of the epimeric compounds, and the absolute configurations at C-2 in the latter two pairs of compounds were unassigned. Although these mixtures were relatively impotent in vitro and in vivo (Table I), the separation of these compounds will be the subject of future work.

Recently, a computer-assisted molecular modeling technique was reported to distinguish between compounds that interact with the phencyclidine and the σ binding site.[18] That work indicated that the aromatic ring, the nitrogen atom, and a spatial vector from the nitrogen atom essentially overlapped in phencyclidine-like compounds. The compounds that were chosen for that study were structurally very similar to PCP.

In addition, a pharmacophore hypothesis for the phencyclidine binding site was developed in a recent study by Carroll et al.,[13] based on ligand-binding structure–activity relationship data from PCP and its analogues reported by Kamenka and Geneste.[19] A representation of this is shown in Figure 2 with PCP itself. In this hypothesis an aromatic binding site pocket extends ca. 3.5 Å above and below the plane of the aromatic ring and a hydrogen bonding site ca. 2.8 Å along the vector of the nitrogen lone pair. These three points defined the triangle shown in Figure 2 (the side of the triangle passing through the aromatic ring is 7.0 Å and the remaining sides are 6.7 and 7.7 Å). It was also hypothesized that the area close to the hydrogen-bonding binding site is sterically inaccessible to the ligand. The region is represented by the dot volume in Figure 2. In this study we chose to use the latter hypothesis and to examine the dioxolane compounds, which are structurally quite different from PCP, but which retain the biological similarity. The computer-generated lowest energy conformer of etoxadrol (**2a**) was fitted to the PCP pharmacophore (Figure 3), by a least-squares regression analysis (FIT) of two points defining the center and plane of the phenyl rings (represented by dummy atoms above and below the plane of each ring) and a point 2.8 Å along the direction of the nitrogen lone pair vector. The fit of etoxadrol to PCP in its pharmacophoric conformation gave a root mean square (RMS) fit of 0.12 Å, indicating a close overlap (Figure 4). It should be noted that this pharmacophore hypothesis does not require an atom-for-atom overlay of the two structures. The pharmacophore only requires that the nitrogen lone pair vectors point at the same point in space and that the phenyl rings be coplanar and concentric. Besides fitting the PCP pharmacophore, the van der Waals volume of etoxadrol does not interfere with the volume determined to be essential for the binding site (Figure 5). In contrast, the low-energy conformer of epietoxadrol gave an RMS of 0.89 when fitted to the PCP pharmacophore, indicating a poor overlay. In fact, no conformer of epietoxadrol was identified that could satisfy both the geometric and steric requirements of the PCP pharmacophore. In order to obtain a close fit of epietoxadrol to the PCP pharmacophore geometry, it was necessary to rotate the phenyl and piperidinyl rings away from their optimal angles. This torsional adjustment resulted in an energy increase of >0.5 kcal/mol and more significantly also resulted in a prohibitively large overlap of the dioxolane ring with the essential H-bonding volume of the binding site model (Figure 6). Thus, although both etoxadrol and epietoxadrol possess the prerequisite phenyl and amino groups necessary for binding to the PCP site, their difference at a third center of asymmetry (at C-2) caused a profound effect on the relative spatial relationship of their phenyl and amino groups and their interaction with the phencyclidine site. We are currently attempting to test this pharmacophore hypothesis through the synthesis and evaluation of other compounds structurally dissimilar to PCP.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian XL-300 instrument. Mass spectra (CI) were obtained on a Finnigan 1015D instrument. Gas chromatographic (GC) analysis was performed on a Hewlett-Packard 5880 instrument equipped with a 25-m SE-30 capillary column and a flame-ionization detector. Optical rotations were obtained on the

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(19) Kamenka, J. M.; Geneste, P. In *Phencyclidine and Related Arylcyclohexylamines: Present and Future Application*; Kamenka, J. M., Domino, E. F., Geneste, P., Eds.; NPP Books: Ann Arbor, MI, 1983; pp 1–12.
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free bases with a Perkin-Elmer Model 241 polarimeter. Where elemental analyses are indicated only by symbols of those elements, analytical results obtained are within ±0.4% of the theoretical values. These combustion analyses were obtained at Galbraith Laboratories, Inc., Knoxville, TN, or at Atlantic Microlaboratories, Inc., Atlanta, GA. Molecular models were constructed with a molecular modeling system (an Evans and Sutherland PS330 graphics system linked to a Digital Equipment Corp. microVAX work station). Software employed was the SYBYL program (version 5.05) from Tripos Associates, St. Louis, MO.

α-(*S*,*S*)-1-(2-Piperidyl)-1,2-ethanediol Hydrochloride. Dexoxadrol ((4*S*,6*S*)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane, 10 g, 32.4 mmol) was dissolved in 100 mL of MeOH and 20 mL of 1.0 N HCl solution. This mixture was warmed to 40 °C. After 10 h, H_2O (50 mL) was added and the mixture extracted with ether (300 mL). The organic layer was discarded and the aqueous layer lyophilized to give (4*S*,6*S*)-1-(2-piperidyl)-1,2-ethanediol (5.8 g, 100%), as a white powder; mp 125 °C, $[\alpha]^{25}_D$ −8.66° (*c* = 5.2, H_2O).

Etoxadrol ((2*S*,4*S*,6*S*)-2-Ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane, 2a). To a refluxing solution of (4*S*,6*S*)-1-(2-piperidyl)-1,2-ethanediol hydrochloride (2.0 g, 11.0 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) in 25 mL of dry nitromethane was added a solution of propiophenone dimethyl acetal (2.57 g, 14.3 mmol, 1.3 equiv) in 5 mL of dry nitromethane. After 10 min the reaction mixture was cooled in an ice bath and poured into a separatory funnel containing 50 mL of 1 N NaOH solution and 50 mL of ether. The organic layer was removed, dried ($MgSO_4$), and concentrated to give 2.62 g (91%) of a mixture of **2a** and **2b**. GC analysis showed a 91:7 ratio of acetal isomers. The major isomer (**2a**) was isolated from the mixture by crystallization of the HCl salt from 2-propanol. The minor isomer, epietoxadrol ((2*R*,4*S*,6*S*)-2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane, **2b**) was separated from the free base of the mother liquor by chromatography (silica gel, Et_2O (99%)/NH_4OH (1%)) followed by preparation of the HCl salt and recrystallization from 2-propanol.

Etoxadrol (2a) hydrochloride: mp 220–221 °C (lit.[6] mp 222–224 °C), $[\alpha]^{25}_D$ +14.1° (*c* = 4.4, MeOH) (lit.[20] $[\alpha]^{25}_D$ +16.6°); mass spectrum (CI, NH_3), 262 (M + 1); ^1H NMR ($CDCl_3$) δ 7.38 (d, *J* = 6.6 Hz, 2 H), 7.2 (m, 3 H), 4.17 (dd, *J* = 6.9, 5.0 Hz, 1 H), 3.99 (d, *J* = 5.0 Hz, 1 H), 3.71 (dd, *J* = 7.4, 7.4 Hz, 1 H), 3.27 (d, *J* = 11.0 Hz, 1 H), 2.9 (m, 1 H), 2.72 (dd, *J* = 5.0, 5.0 Hz, 1 H), 1.86 (q, *J* = 7.3 Hz, 2 H), 1.3–1.8 (m, 6 H), 0.84 (t, *J* = 7.3 Hz, 3 H, Me). Anal. ($C_{16}H_{23}NO_2$·HCl) C, H, N.

Epietoxadrol (2b) hydrochloride: mp 218–220 °C; $[\alpha]^{25}_D$ −13.0° (*c* = 0.2, $CHCl_3$); mass spectrum (CI, NH_3), 262 (M + 1); ^1H NMR ($CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2 H), 7.30 (m, 3 H), 4.00 (dd, *J* = 6.2, 6.2 Hz, 1 H), 3.8 (m, 1 H), 3.71 (dd, *J* = 6.2, 6.2 Hz, 1 H), 3.12 (d, *J* = 11.1 Hz, 1 H), 2.82 (ddd, *J* = 10.9, 4.0, 4.0 Hz, 1 H), 2.65 (ddd, *J* = 11.7, 11.7, 2.3 Hz, 1 H), 1.91 (dq, *J* = 7.1, 1.1 Hz, 2 H), 1.0–1.8 (m, 6 H), 0.90 (t, *J* = 7.1 Hz, 3 H, Me). Anal. ($C_{16}H_{23}NO_2$·HCl) C, H, N.

Resolution of β-(±)-Dioxadrol (1c + 1d). A mixture of 0.5 g (3.2 mmol) of (*S*)-(+)-mandelic acid and 1.0 g (3.2 mmol) of the racemic β-dioxadrols was brought to solution in 15 mL of boiling EtOAc. The mixture was then allowed to stand at room temperature for 4 h. The resulting crystalline material (0.65 g) was filtered and washed with ice-cold EtOAc (10 mL). The crystals were dissolved in 4 mL of MeOH, diluted with 8 mL of acetone, and concentrated on a hot plate to a final volume of 4 mL. After cooling to room temperature over 5 h, the crystalline (*S*)-(+)-mandelate salt of β-(+)-dioxadrol (**1d**) (0.45 g, mp 181–182 °C) was isolated by filtration.

The filtrate from the original crystallization was evaporated to dryness and the residue partitioned between 1 N NH_4OH solution and ether. The dried (Na_2SO_4) organic layer was concentrated to give crude free base, which was dissolved in EtOAc (15 mL) and treated with (*R*)-(−)-mandelic acid (0.25 g). Isolation and recrystallization as described above gave β-(−)-dioxadrol (**1c**) (0.47 g, mp 177–180 °C).

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Registry No. **1a**, 4741-41-7; **1b**, 4792-18-1; **1c**, 117178-67-3; **1d**, 117178-68-4; **1d** (*S*)-(+)-mandelate, 117178-69-5; **2a**, 28189-85-7; **2a**·HCl, 23239-37-4; **2b**, 117019-61-1; **2b**·HCl, 117019-54-2; **3a**, 117019-55-3; **3b**, 117019-56-4; **4a**, 117019-57-5; **4b**, 117019-58-6; **5a**, 117019-59-7; **5b**, 117019-60-0; (4*S*,6*S*)1-(2-piperidyl)-1,2-ethanediol hydrochloride, 116928-44-0; (±)-β-dioxadrol, 47255-57-2; propiophenone dimethyl acetal, 25310-92-3.