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Absolute Configuration of (+)-5-(3-Hydroxyphenyl)-5-phenylhydantoin, the Major Metabolite of 5,5-Diphenylhydantoin in the Dog

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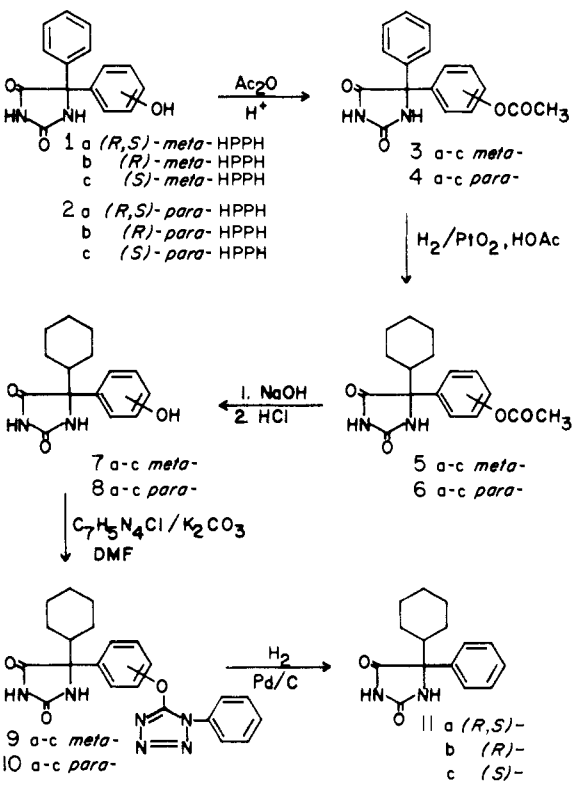
5-(3-Hydroxyphenyl)-5-phenylhydantoin (*m*-HPPH) has been resolved by crystallization of the brucine salts. The (+) enantiomer has been converted to (−)-5-cyclohexyl-5-phenylhydantoin, a compound previously demonstrated to have the *R* configuration.[3] The *R* configuration can accordingly be assigned to (+)-*m*-HPPH, the principal metabolite of 5,5-diphenylhydantoin (phenytoin) in the dog.

The metabolism of 5,5-diphenylhydantoin (phenytoin, DPH) has been studied in several species of animals. Reports published through the year 1971 have been reviewed by Chang and Glazko.[1] In all species examined with the exception of the dog, the principal metabolite is 5-(4-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH), which appears in urine largely conjugated with glucuronic acid. As DPH is a prochiral molecule, the two phenyl rings are spatially distinguishable and are not equivalent in enzymatic reactions. Introduction of a hydroxyl group in one of the phenyl rings creates a chiral center at carbon-5 of the hydantoin ring, and stereoselectivity of hydroxylation is reflected in optical activity of phenolic metabolites. In *p*-HPPH released by β-glucuronidase from its conjugate in human urine there was about a 10:1 preponderance of the levorotatory isomer relative to the dextrorotatory.[2] In enzymatically released *p*-HPPH from dog urine, the preponderance of the levorotatory isomer was about 2:1.

The amount of 5-(3-hydroxyphenyl)-5-phenylhydantoin (*m*-HPPH) in human urine is so small that isolation has not as yet been accomplished, and its stereoisomeric constitution is unknown. In the dog, on the other hand, *m*-HPPH is the major metabolite of DPH. Enzymatically released *m*-HPPH from dog urine was dextrorotatory in ethanol and alkaline aqueous solution and had the properties of an essentially pure optical isomer.[2]

Interest in the stereoselectivity and regioselectivity of the metabolism of the prochiral DPH molecule has directed attention to the absolute configurations of the phenolic metabolites. The assignment of the *S* configuration to (−)-*p*-HPPH (**2c** of Scheme I), the major metabolite of DPH in man, was accomplished by application of the "rule of shift" (Poupaert et al.[3]) and confirmed through X-ray crystallographic examination of the camphorsulfonate of (+)-*p*-HPPH (**2b**) (Koch et al.[4]). By conversion of **2b** to (−)-5-cyclohexyl-5-phenylhydantoin (**11b**), it was possible to make an assignment of the absolute configuration of the latter compound.[3]

Scheme I



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Application of the rule of shift based on comparison of optical rotation of (−)-*p*-HPPH and (+)-*m*-HPPH in ethanol and alkaline aqueous solutions permitted the inference that these two compounds were probably of opposite absolute configurations. With acceptance of the assignment of the previous investigators[3,4] of the *S* configuration to (−)-*p*-HPPH, the tentative assignment of the *R* configuration to (+)-*m*-HPPH, the major metabolite of DPH in the dog, was suggested.[2]

Assignment of the absolute configurations of the *m*-HPPH enantiomers can be established by conversion of either isomer of *m*-HPPH to an isomer of 5-cyclohexyl-5-phenylhydantoin by a sequence of reactions (Scheme I) similar to those employed by Poupaert et al. with (*R*)-(+)-*p*-HPPH. The present report describes the chemical studies leading to such assignments and discusses the significance of the configuration assigned to (+)-*m*-HPPH in relation to the present understanding of the stereospecificity of metabolism of DPH.

Results

Resolution of racemic *m*-HPPH (**1a**) was achieved by fractional crystallization of the brucine salts from ethyl acetate. The rotations of the individual enantiomers (**1b** and **1c**) as obtained in this way were $[\alpha]^{27}_D$ +88.3° and $[\alpha]^{26}_D$ −85.9° (*c* 1.0, 0.1 N NaOH), respectively.

Attempted direct reduction of **1a** to 5-cyclohexyl-5-(3-hydroxyphenyl)hydantoin (**7a**) under a variety of conditions gave multiple products as revealed by thin-layer chromatography (TLC). Such products included 5-cyclohexyl-5-phenylhydantoin (**11a**) and 5,5-dicyclohexylhydantoin (DCH) in addition to the desired product, **7a**, indicative of partial reduction of the phenolic aromatic system under all the conditions tested. Chemical modification of the phenolic group was accordingly resorted to in an effort to eliminate the undesired reduction of the phenolic substituent of **1a**. Acetylation of **1a** gave 5-(3-acetoxyphenyl)-5-phenylhydantoin (**3a**), which was readily reduced in high yield to 5-(3-acetoxyphenyl)-5-cyclohexylhydantoin (**5a**, Scheme I). The influence of a phenolic substituent in activating the reduction of a benzene nucleus has been described.[5] Acetylation evidently eliminates that activating influence, thereby allowing preferential reduction of the least substituted benzene ring. Subsequent saponification of **5a** gave the desired product, **7a**. The phenolic group was removed through the same reactions used by Poupaert et al.[3] with the corresponding para compound, **7a** being converted to the tetrazole ether, **9a**, which on hydrogenolysis[6] yielded **11a**.

Repetition of this reaction sequence (Scheme I) with (+)-*m*-HPPH (**1b**) gave (−)-5-cyclohexyl-5-phenylhydantoin, which had been shown by Poupaert et al. to be of the *R* configuration. This allows the assignment of the *R* configuration to (+)-*m*-HPPH.

Supporting evidence for the assignment of the *R* configuration to (+)-*m*-HPPH (**1b**) was obtained by subjecting (−)-*p*-HPPH (**2c**) to the same sequence of reactions in Scheme I. The previous assignment[3,4] of the *S* configuration to **2c** was confirmed, as **2c** was converted to (*S*)-(+)-5-cyclohexyl-5-phenylhydantoin (**11c**). Two of the intermediates in this conversion, **8c** and **10c**, had higher degrees of optical purity than reported for their respective enantiomers, **8b** and **10b**.[3] Repetition of the direct reduction of **2a** as described by Poupaert et al.[3] and examination of the crystallized product with TLC indicated that **8a** was contaminated with **11a** and DCH. Such contamination of **8b** could account for decreased optical purities of **8b** and **10b**. No such contamination of **8c** was observed when this compound was prepared by way of reduction of **4c**.

It may be noted that conversion of (−)-*p*-HPPH and of (+)-*m*-HPPH to 5-cyclohexyl-5-phenylhydantoins of opposite rotations provides unequivocal demonstration that the two phenolic compounds are of opposite configurations, a demonstration that is wholly independent of knowledge of the absolute configuration of any compound involved.

Discussion

Resolution of *m*-HPPH through crystallization of the diastereomeric brucine salts has allowed determination of the maximum specific rotation of a pure isomer, $[\alpha]^{27}_D$ +88.3° (*c* 1, 0.1 N NaOH) and $[\alpha]^{25}_D$ +9.0° (*c* 0.5, EtOH) for (+)-*m*-HPPH (**1b**). The rotations of *m*-HPPH as isolated without crystallization from the urine of two dogs were $[\alpha]^{28}_D$ +8.3 and 8.0° (EtOH).[2] These rotations are lower than that of the chemically resolved isomer by somewhat more than the experimental error. These lower rotations could be due to the presence of a small amount of the levorotatory isomer or to contamination with unrelated materials. If due entirely to the opposite isomer, the composition of the isolate of the lower rotation would be 94% (+):6% (−). The reported rotation of the urinary product in 0.1 N NaOH ($[\alpha]^{26}_D$ +84°) is 95% of that of the synthetic isomer. Since the material from urine had been crystallized several times before that measurement was made, it could scarcely have contained any of the levorotatory isomer, and the lower rotation must have been due to chemical contamination. Without a technique that would permit a more accurate assessment of the optical purity of urinary *m*-HPPH, it is not possible to conclude with certainty whether the metabolic product from the dog consists wholly of a single isomer or whether there is a small amount of the other enantiomer. If any (−)-*m*-HPPH is produced at all, the amount is certainly very small relative to that of (+)-*m*-HPPH.

The conversion of (+)-*m*-HPPH (**1b**) to (*R*)-(−)-5-cyclohexyl-5-phenylhydantoin (Scheme I) has allowed assignment of the *R* configuration to **1b**. This assignment has confirmed the earlier suggestion[2] that **1b** is formed in the dog by a stereospecific metabolic oxidation of the pro-*R* phenyl substituent of DPH. The major enantiomer of metabolic *p*-HPPH produced in man from DPH has previously been identified[3,4] as (*S*)-(−)-*p*-HPPH (**2c**) formed by oxidation of the pro-*S* phenyl substituent. The *S* configuration of **2c** has also been confirmed in the present study, in which it was converted to (*S*)-(+)-5-cyclohexyl-5-phenylhydantoin through the same sequence of reactions used with **1b**.

Differences between the dog and man in their metabolism of DPH have been discussed by Butler et al.[2] A minimum of two functional types of hydroxylating enzymes must be postulated. The predominant type in man attacks principally if not exclusively the pro-*S* phenyl group, hydroxylating it in the para position. The predominant enzymatic type in the dog, on the other hand, attacks the pro-*R* phenyl group with complete or almost complete stereospecificity. The major product is (*R*)-(+)-*m*-HPPH.

Whether meta hydroxylation by the dog is direct or by way of an arene oxide intermediate is not certain, but there seems from available evidence to be some reason to favor the concept of an arene oxide pathway.[2] If the initial product were the 3,4-oxide, this could rearrange to yield a mixture of (*R*)-(+)-*m*-HPPH and (*R*)-(+)-*p*-HPPH. The former predominates, but (*R*)-(+)-*p*-HPPH is formed in larger amounts by the dog than by man, and it may well arise through the same enzymatic mechanism producing

the major product, (*R*)-(+)-*m*-HPPH. The same arene oxide could be the precursor of the 3,4-dihydrodiol metabolite, which has been identified in the urine of dogs as well as some other species.[1] The absolute configuration of this dihydrodiol metabolite has not been determined, but the following indirect evidence indicates that it is probably of the *R* configuration.[2] When urine is heated with acid to release the phenolic metabolites, this process would also convert the dihydrodiol metabolite to a mixture of *m*-HPPH and *p*-HPPH. When the proportions of metabolites yielded by acid treatment of dog urine are compared with those yielded by β-glucuronidase treatment, it is found that the acid treatment gives a higher proportion of (*R*)-(+)-*p*-HPPH relative to (*S*)-(−)-*p*-HPPH but does not give detectable amounts of (*S*)-(−)-*m*-HPPH. This suggests that additional amounts of (*R*)-(+)-*p*-HPPH and (*R*)-(+)-*m*-HPPH were produced from a dihydrodiol of the *R* configuration. The (*R*)-dihydrodiol as well as the (*R*)-arene oxide could be a precursor of both (*R*)-(+)-*m*-HPPH and (*R*)-(+)-*p*-HPPH.

Similar evidence for an arene oxide pathway in the para hydroxylation of the pro-*S* phenyl group is lacking, inasmuch as (*S*)-(−)-*m*-HPPH and the (*S*)-dihydrodiol have not been identified as metabolites. It had been suggested[2] that this hydroxylation may be direct. On the other hand, the experiments of Tomaszewski et al.[7] with deuterated DPH in the rat were interpreted as consistent with an arene oxide pathway in the production of (*S*)-(−)-*p*-HPPH (**2c**). Previous studies had shown *p*-HPPH of this configuration to be the principal metabolite of DPH in the rat.[1] Examination of the *p*-HPPH isolated from urine of rats given an equal mixture of deuterated and nondeuterated DPH failed to show a significant isotope effect. However, it seems likely that the experimental conditions were such that any possible isotope effect influencing rates of oxidative metabolism would have been obscured. Although information as to the rate of disappearance from the rat of doses of DPH as high as that of 160 mg/kg used by Tomaszewski et al.[7] has not been found in the literature, it is possible by use of extrapolations based on data from experiments of Gerber et al.[8] with smaller doses to infer that nearly all of the DPH would have been metabolized in the 24-h period during which urine was collected after dosage. If, as appears likely, the metabolism of both isotopic forms of DPH was almost complete during the urine collection period, the two isotopic forms of *p*-HPPH would be in nearly equal amounts in urine, and the isotopic compositions of *p*-HPPH isolated from urine would fail to reflect any difference that there might have been in rates of production. These experiments accordingly contribute no evidence as to the mechanism of oxidative attack.

The lack of direct chemical evidence for an arene oxide pathway in the hydroxylation of the pro-*S* phenyl group does not, however, preclude the possibility of that mechanism of metabolic attack. It is conceivable that the (*R*)- and (*S*)-3,4-oxides of DPH might undergo dissimilar fates, the former rearranging to a mixture of *m*- and *p*-phenol and undergoing enzymatic hydration and the latter rearranging exclusively or almost exclusively to the *p*-phenol.

The amount of *m*-HPPH present in urine of human DPH patients is so small that it does not appear feasible to determine its configuration by isolation and direct measurement of rotation. Efforts are presently being directed toward chromatographic separation of covalent diastereomers of *m*-HPPH, a technique that could allow determination of the optical constitution of very small samples of *m*-HPPH. If the *m*-HPPH in human urine, like the much larger amounts in dog urine, should prove to be of the *R* configuration, this might point to the (*R*)-3,4-arene oxide as the common precursor of this compound as well as of the small amount of (*R*)-(+)-*p*-HPPH. While attack on the pro-*R* phenyl group of DPH represents a very minor metabolic pathway in man, it may be of significance in that the unstable arene oxide is a reactive electrophilic compound capable of reaction with protein to produce antigens that could give rise to hypersensitivity reactions. A technique for assessing small quantities of (*R*)-(+)-*m*-HPPH and (*R*)-(+)-*p*-HPPH in urine would make possible the survey of large numbers of patients to reveal whether unusual patterns of metabolism of the pro-*R* ring are associated with adverse reactions.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are corrected. Infrared spectra (KBr pellets) were obtained on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet spectra were obtained on a Beckman Model 25 spectrophotometer. Optical rotations were measured in a 1-cm cell at 546 and 589 nm (D line) with a Cary Model 60 spectropolarimeter. Thin-layer chromatography (TLC) was conducted on microscope slides coated with silica gel H. Chromatograms were developed in a solvent system consisting of benzene–ethyl acetate–acetic acid (9:1:1). Zones were visualized by spraying the chromatograms with 5% phosphomolybdic acid in ethanol, followed by heating of the slide on the surface of a hot plate. The PtO_2 and Pd/C catalysts were obtained commercially (Matheson Coleman and Bell). Microanalyses were performed by Micro-Tech Laboratories, Skokie, IL. Analytical results are indicated by the symbols of the elements and are within 0.25% of the calculated values.

(*RS*)-5-(3-Hydroxyphenyl)-5-phenylhydantoin (1a). The method of Butler et al.[2] was used to prepare **1a** from 3-hydroxybenzophenone. Recrystallization from ethanol–benzene gave white crystals: mp 216.5–218 °C (lit.[9] mp 217–218 °C); R_f 0.24.

(*R*)-(+)- and (*S*)-(−)-5-(3-Hydroxyphenyl)-5-phenylhydantoin (1b and 1c). Anhydrous brucine (7.36 g, 18.7 mmol) was added to a solution of **1a** (5.00 g, 18.7 mmol) in 80 mL of hot ethyl acetate. After all brucine had dissolved, the solution was set aside to cool at room temperature. Crystals were rapidly deposited and were collected after 1.5 h to give 9.48 g of brucine salt A. A was recrystallized from 250 mL of ethyl acetate to give 5.78 g of brucine salt B. Decomposition of a sample of B with 1 N HCl and extraction of the *m*-HPPH with diethyl ether gave a material having $[\alpha]^{27}_D$ +60° (*c* 1.0, 0.1 N NaOH). B was recrystallized from 225 mL of ethyl acetate, giving 3.15 g of brucine salt C. Decomposition of C gave 1.25 g of **1b**, $[\alpha]^{26}_D$ +77°. Recrystallization of **1b** from ethanol–benzene gave two crops of crystals (250 mg, $[\alpha]^{27}_D$ +88.5°; 637 mg, $[\alpha]^{27}_D$ +86.4°). An additional crystallization of these combined crops gave pure **1b** as white needles: mp 218.5–220.5 °C (lit.[2] mp 219–220 °C); $[\alpha]^{27}_{546}$ +107°, $[\alpha]^{27}_D$ +88.3° (*c* 1.0, 0.1 N NaOH), $[\alpha]^{25}_D$ +9.0° (*c* 0.5, EtOH). No further improvement of the specific rotations was observed with additional recrystallizations. The brucine salt recovered from the filtrate of C was decomposed, and the hydantoin (950 mg) was recrystallized from ethanol–benzene (50 mL final volume). This procedure gave an initial crop (440 mg) of white powder, $[\alpha]^{25}_D$ +22°. Subsequent concentration of the filtrate (30 mL final volume) gave an additional 241 mg of **1b**, $[\alpha]^{26}_D$ +88.0°.

The filtrates A and B were combined, and the brucine salts were decomposed to give 2.81 g of the hydantoin, $[\alpha]^{26}_D$ −55°. Crystallization from ethanol–benzene (100 mL final volume) gave 678 mg of white powder, $[\alpha]^{26}_D$ −17°. Further concentration of the filtrate (75 mL final volume) gave 1200 mg of 1c, $[\alpha]^{26}_D$ −67°. Additional crystallizations of a 250-mg sample gave 105 mg of **1c**: mp 218.5–220 °C; $[\alpha]^{26}_{546}$ −103°, $[\alpha]^{26}_D$ −85.9° (*c* 1.0, 0.1 N NaOH); IR spectrum identical with that of **1b**.

(*R*)-(−)- and (*RS*)-5-(3-Acetoxyphenyl)-5-phenylhydantoin (3b and 3a). A suspension of **1b** (400 mg, 1.49 mmol) in 5 mL of acetic anhydride was magnetically stirred while 2 drops of concentrated H_2SO_4 was added. The resulting solution was stirred

for 30 min and then poured over 25 g of crushed ice. The precipitate was filtered off, washed with water, and recrystallized from ethanol–water to give 314 mg (68%) of white crystals (**3b**): mp 214.5–216.5 °C; R_f 0.34; $[\alpha]^{26}_{546}$ −17.5°, $[\alpha]^{26}_{D}$ −11.9° (*c* 0.482, EtOH). Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

By use of procedures similar to those described for the preparation of **3b**, **3a** was obtained from **1a** in 85% yield: mp 193–195 °C. Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

(*R*)-(−)- and (*RS*)-5-(3-Acetoxyphenyl)-5-cyclohexylhydantoin (5b and 5a). A sample of **3b** (250 mg, 0.806 mmol) was added to 25 mL of glacial acetic acid containing 100 mg of a prereduced PtO_2 catalyst. The reduction was carried out in a Parr hydrogenation apparatus at 25 °C with an initial pressure of 50 psi. After the calculated equivalents of H_2 had been consumed, the catalyst was filtered off and washed with ethanol. The filtrate was evaporated under reduced pressure and the residue was crystallized from ethanol–water to give 210 mg (82%) of white needles (**5b**): mp 291.5–294.5 °C; R_f 0.40; $[\alpha]^{25}_{546}$ −128°, $[\alpha]^{25}_{D}$ −106° (*c* 0.1, EtOH). Anal. ($C_{17}H_{20}N_2O_4$) C, H, N.

The racemic material, **5a**, was obtained from **3a** in 73% yield: mp 268.5–270 °C. Anal. ($C_{17}H_{20}N_2O_4$) C, H, N.

(*R*)-(−)- and (*RS*)-5-Cyclohexyl-5-(3-hydroxyphenyl)hydantoin (7b and 7a). A sample of **5b** (158 mg, 0.50 mmol) was suspended in 2 mL of 1 N NaOH and was warmed on a steam bath for 5 min. The warm mixture was acidified to pH 2 by addition of 6 N HCl and then cooled in an ice bath. The precipitate was filtered off, washed with water, and recrystallized from ethanol–water to give 118 mg (86%) of a white powder (**7b**): mp 277–279 °C dec; R_f 0.31; $[\alpha]^{26}_{546}$ −146°, $[\alpha]^{26}_{D}$ −121° (*c* 0.268, EtOH); IR 3430, 3320, 2935, 2855, 1760–1750, and 1730–1710 cm^{-1}; UV (0.1 N NaOH) 216 nm (ε 12 800), 231 (11 900), and 293 (3880). Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

Similarly, **7a** was prepared from **5a** in 89% yield. The analytical sample was recrystallized from ethyl acetate–hexane: mp 219.5–222 °C. Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

(*R*)-(−)- and (*RS*)-5-Cyclohexyl-5-[3-(1-phenyl-5-tetrazolyloxy)phenyl]hydantoin (9b and 9a). A mixture of **7b** (100 mg, 0.365 mmol) and finely ground K_2CO_3 (150 mg, 1.09 mmol) was added to 1.5 mL of dry DMF. The suspension was stirred while 5-chloro-1-phenyl-1*H*-tetrazole (66 mg, 0.365 mmol) was added in two equal portions over a period of 1 h. After 18 h of stirring, the suspension was poured into 30 mL of water. Acidification (pH 6) of the mixture with 6 N HCl gave a white precipitate, which was filtered off, washed with water, and recrystallized from ethanol–water to give 87 mg (57%) of **9b**: mp 190.5–191.5 °C; R_f 0.40; $[\alpha]^{26}_{546}$ −100°, $[\alpha]^{26}_{D}$ −83.7° (*c* 0.098, EtOH). Anal. ($C_{22}H_{22}N_6O_3$) C, H, N.

The racemic material, **9a**, was prepared from **7a** in 61% yield: mp 230.5–231.5 °C. Anal. ($C_{22}H_{22}N_6O_3$) C, H, N.

(*R*)-(−)- and (*RS*)-5-Cyclohexyl-5-phenylhydantoin (11b and 11a). A solution of **9b** (60 mg, 0.144 mmol) in 50 mL of absolute ethanol was hydrogenated in a Parr apparatus over 60 mg of 10% Pd/C catalyst. The reduction was started with an initial pressure of 50 psi at 25 °C and was complete within 2 h as judged by TLC. The catalyst was filtered off and washed with ethanol. The filtrate was taken to dryness under reduced pressure. The residue was dissolved in hot ethanol, the solution was filtered, and the hot filtrate was diluted with an equal volume of hot water. The solution was allowed to stand for 18 h. This procedure gave 33 mg (89%) of white needles, which was homogeneous as determined by TLC. This sample was recrystallized from ethyl acetate–hexane to give the analytical sample (**11b**): mp 312–313 °C dec; R_f 0.51; $[\alpha]^{25}_{546}$ −154°, $[\alpha]^{25}_{D}$ −128° (*c* 0.145, EtOH). Data reported by Poupaert et al.:[3] mp 307–309 °C dec; $[\alpha]^{25}_{546}$ −152°, −158.6° (*c* 0.135, 0.28; EtOH). Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

A similar preparation of **11a** from **9a** was achieved with a yield of 67%: mp 267–268.5 °C (lit.[10] mp 269–270 °C). This sample was identical (IR, melting point, and R_f) with an authentic sample of **11a** prepared from cyclohexylphenyl ketone via the procedure described for the preparation of **1a**.[2]

Preparation of Compounds Derived from (*S*)-(−)-*p*-HPPH (2c). Compounds **4c**, **6c**, **8c**, **10c**, and **11c** were synthesized by the same procedures as those described, respectively, for the preparations of **3b**, **5b**, **7b**, **9b**, and **11b**.

(*S*)-(+)-5-(4-Acetoxyphenyl)-5-phenylhydantoin (4c). A 500-mg sample of **2c** that had been isolated from human urine,[2] $[\alpha]^{26}_{D}$ −90° (*c* 1.0, 0.1 N NaOH), was acetylated to give 398 mg (69%) of **4c**: mp 186–188.5 °C; R_f 0.40; $[\alpha]^{26}_{546}$ +17.2°, $[\alpha]^{26}_{D}$ +14.4° (*c* 0.25, EtOH). Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

(*S*)-5-(4-Acetoxyphenyl)-5-cyclohexylhydantoin (6c). Reduction of a 350-mg sample of **4c** gave 292 mg (82%) of a homogeneous white solid after purification by precipitation from ethanol–water. Attempted purification of this material by recrystallization gave gelatinous precipitates in a number of different solvent systems. The material was homogeneous by TLC (R_f 0.45) and displayed an IR spectrum consistent with the proposed structure; consequently, no further characterization of this compound was attempted.

(*S*)-(+)-5-Cyclohexyl-5-(4-hydroxyphenyl)hydantoin (8c). The 292-mg sample of crude **6c** was saponified, the alkaline solution was acidified, and the resulting white solid was recrystallized from acetone–water to give 215 mg (85%) of white powder (**8c**): mp 340–342 °C dec; R_f 0.28; $[\alpha]^{26}_{546}$ +148°, $[\alpha]^{26}_{D}$ +121° (*c* 0.155, EtOH). Data reported by Poupaert et al.[3] for **8b**: mp 325–332 °C dec; $[\alpha]^{25}_{546}$ −111.5° (*c* 0.22, EtOH). Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

(*S*)-(+)-5-Cyclohexyl-5-[4-(1-phenyl-5-tetrazolyloxy)phenyl]hydantoin (10c). A sample of **8c** (150 mg) was converted to **10c** (174 mg, 76%): mp 232–233.5 °C; R_f 0.38; $[\alpha]^{26}_{546}$ +100°, $[\alpha]^{26}_{D}$ +83.9° (*c* 0.495, EtOH). Data reported by Poupaert et al.[3] for **10b**: mp 235–238 °C; $[\alpha]^{25}_{546}$ −85° (*c* 1.28, EtOH). Anal. ($C_{22}H_{22}N_6O_3$) C, H, N.

(*S*)-(+)-5-Cyclohexyl-5-phenylhydantoin (11c). A sample of **10c** was hydrogenated to give **11c**, with a yield of 65%: mp 310–312 °C dec; $[\alpha]^{26}_{546}$ +158°, $[\alpha]^{26}_{D}$ +130° (*c* 0.152, EtOH); IR spectrum and R_f identical with those of **11b**.

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