Absolute Configuration of the Major Metabolite of 5,5-Diphenylhydantoin, 5-(4'-Hydroxyphenyl)-5-phenylhydantoin

Jacques H. Poupaert, Robert Cavalier, Michel H. Claesen,* and Pierre A. Dumont

Department of Medicinal Chemistry, School of Pharmacy, University of Louvain, B-3000 Louvain, Belgium. *Received May 5, 1975*

Chemical conversions, optical comparisons, and chiroptical measurements (CD) were employed to determine the absolute configuration of the enantiomers of 5-(4'-hydroxyphenyl)-5-phenylhydantoin (HPPH) (**1b** and **1c**). Studies on a key intermediate, (−)-2-cyclohexyl-2-phenylglycine (**5b**), led to the reexamination of the well-known rule of Clough–Lutz–Jirgensons. Optical comparisons by means of derivatization into hydantoins and 3-phenyl-2-thiohydantoins (application of Freudenberg's rule of shift) gave conclusions which were consistent with chiroptical measurements on the above compounds. Thus, (−)-HPPH (**1c**), the major metabolite of 5,5-diphenylhydantoin in man, has the *S* configuration. This assignment was confirmed by X-ray single-crystal structure analysis of (+)-HPPH 10-(+)-camphorsulfonate (**18b**).

The biologic fate of the widely used anticonvulsant, 5,5-diphenylhydantoin, has received considerable attention.[1] The main pathway of biotransformation appears to be hydroxylation by the liver microsomal enzyme systems[2] of one of the two phenyl substituents to give 5-(4'-hydroxyphenyl)-5-phenylhydantoin (HPPH, **1**). This process leads to the creation of an asymmetry center from a prochiral molecule. Levorotatory HPPH, $[\alpha]^{28}D$ −16° (EtOH), was isolated by Butler[1a] from human urine and it was inferred that this material was the optically pure enantiomer. In dogs, HPPH was found to be slightly dextrorotatory[1a] while a specific rotation, $[\alpha]^{28}D$ −13.5° (EtOH), was reported by Gorvin and Brownlee[1b] for HPPH excreted by rabbits. No quantitative conclusion about the stereoselectivity of the hydroxylation reaction could be drawn since the resolution of the synthetic racemic compound was not achieved. Furthermore, as a part of an investigation in progress in this laboratory on the determination of the stereoselectivity of the hepatic cytochrome P-450 mixed function oxygenases system by means of substrates such as 5,5-diphenylhydantoin, it was of interest to reinvestigate the possibility of preparing the pure enantiomers of HPPH and to assess their absolute configuration.

Hydantoins are α-amino acid derivatives. In spite of numerous studies concerned with absolute configuration of α-amino acids, asymmetric 2,2-diaryl-2-amino acids have not yet been investigated. Fortunately, the configuration of 2-methyl- and 2-ethyl-2-phenylglycine and the corresponding 3-phenyl-2-thiohydantoins (PTH) has been reported.[3] So, after resolving the pure enantiomers of HPPH (**1b** and **1c**), we converted **1b** into the corresponding 2-cyclohexyl-2-phenylglycine (**5b**), which was investigated with respect to configuration by classical optical methods (rule of molecular rotation shift and CD measurements).

Chemistry. HPPH (**1a**) was synthesized by demethylation of 5-(4'-methoxyphenyl)-5-phenylhydantoin;[4] this method proved to be very efficient for large-scale preparation and gave higher yields than the direct Bücherer synthesis.[4]

By fractional crystallization of the diastereoisomeric brucine salts of **1a** in absolute ethanol, both enantiomers [**1b**, $[\alpha]^{25}_{546}$ +107.3° [*c* 1, 0.5 *N* NaOH), and **1c**, $[\alpha]^{25}_{546}$ −107.3° (*c* 1, 0.5 *N* NaOH)] were recovered with the same specific rotation. Catalytic hydrogenation of **1b** with platinum oxide afforded (−)-5-cyclohexyl-5-(4'-hydroxyphenyl)hydantoin (**2b**). The removal of the phenolic hydroxyl group was achieved by formation of a tetrazole ether derivative **3b** and subsequent hydrogenolysis over palladium on charcoal.[5] Thus, (−)-5-cyclohexyl-5-phenylhydantoin (**4b**) was obtained. On the other hand, racemic **4a**[6] was hydrolyzed with a solution of sodium hydroxide to 2-cyclohexyl-2-phenylglycine (**5a**) which was subjected to N-formylation giving **6a**. The brucine salt of **6a** was repeatedly crystallized from water. Refluxing with dilute sulfuric acid led to the isolation of (−)-2-cyclohexyl-2-phenylglycine (**5b**) which on fusion with urea afforded **4b** (Scheme I).

Some hydantoins and PTH derivatives were synthesized for the purpose of optical comparisons. According to Dudley,[7] (*R*)-(−)-5-phenylhydantoin was prepared from (*R*)-(−)-2-phenylglycine; catalytic hydrogenation over platinum oxide afforded (*R*)-(+)-5-cyclohexylhydantoin, which was also obtained from (*R*)-(−)-2-cyclohexylglycine.[8] The optically active PTH's were obtained by Edman's method,[9] with the exception of 5-cyclohexyl-3,5-diphenyl-2-thiohydantoin (**7b** and **7c**), which was prepared from the ester and phenyl isothiocyanate. The cyclic derivatives bearing a hydrogen in the 5 position are probably racemized to some extent,[10,11] but this does not preclude the assignment of absolute configuration by optical methods.

Results and Discussion

Optical Comparisons. The Rule of Shift. The rule of shift was used according to the following proposal. When two "similar" compounds A and B are subjected to identical chemical transformations into A' and B' and the differences of molecular rotations, $\Delta[\Phi](A' - A)$ and $\Delta[\Phi](B' - B)$, are found to have the same sign, A and B possess the same relative configuration.

The principal application of this rule allows the assignment of the absolute stereochemistry of α-amino acids from the sign of the difference of molecular rotation† in acidic and neutral solutions: $\Delta[\Phi]_{CLJ} = [\Phi]_D^{H^+} - [\Phi]_D^{H_2O}$ is positive to α-amino acids having the L_S configuration (rule of Clough–Lutz–Jirgensons[12,13]). In order to apply the present statement, the "comparable" character of the amino acid 2-substituents had to be demonstrated. As shown in Table I, both (*R*)-2-cyclohexylglycine (**13**) and (*R*)-2-phenylglycine (**15**) give a negative shift, $\Delta[\Phi]_{CLJ}$. However, a slightly positive value, $\Delta[\Phi]_{CLJ} + 6$, was recorded for **5b**. Taking into account this observation and the rather similar size of the two substituents in **5b**, it seemed worthwhile to test the validity of the Clough–Lutz–Jirgensons rule. Hence the $\Delta[\Phi]_{CLJ}$ values of α-amino acids which are shown in Table I were compared with those of two other molecular rotation shifts, i.e., $\Delta[\Phi]_{Hyd} = [\Phi]_D^{Hyd} - [\Phi]_D^{H_2O}$ (with $[\Phi]_D^{Hyd}$ = molecular rotation of their hydantoin derivatives) and $\Delta[\Phi]_{PTH} = [\Phi]_D^{PTH} - [\Phi]_D^{H_2O}$ (with $[\Phi]_D^{PTH}$ = molecular rotation of their derivatives into 3-phenyl-2-thiohydantoins).

Comparisons of these shifts, $\Delta[\Phi]_{CLJ}$, $\Delta[\Phi]_{Hyd}$, and

† Most of the experimental specific rotations were measured at 546 or 579 nm; the [Φ] values observed at these wavelengths were close to those at the sodium D line and the resulting Δ[Φ] values did not endanger the stereochemical conclusions.

Scheme I

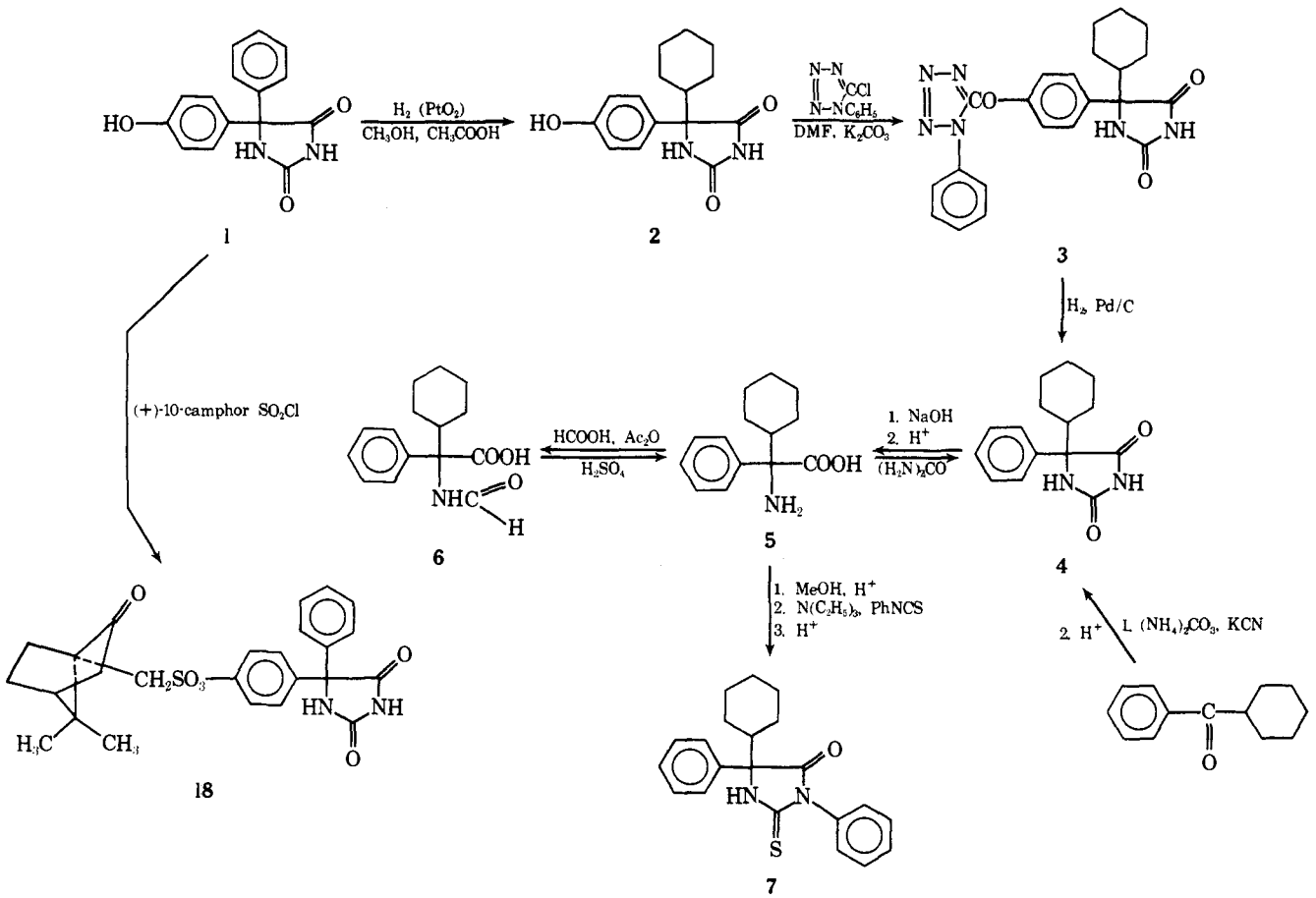
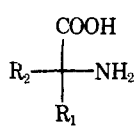


Table I. Molecular Rotation Differences for α-Amino Acids and Their Corresponding Derivatives. Δ[Φ] Values Calculated for the *R* Series



No.	R_1	R_2	$\Delta[\Phi]_{CLJ}$[a]	$\Delta[\Phi]_{Hyd}$[b]	$\Delta[\Phi]_{PTH}$[c]
8	CH_3	H	−11.4[d]	+49.6[e]	+50[f]
9	C_2H_5	H	−11.6[d]		
10	$CH(CH_3)CH_3$	H	−26.5[d]	+140.6[e]	+48.8[g]
11	$CH_2CH(CH_3)CH_3$	H	−35.4[d]	+79.6[e]	
12	$CH(CH_3)CH_2CH_3$	H	−35.5[d]	+115.3[e]	
13	$c\text{-}C_6H_{11}$	H	−45.3[d]	+186.3[h]	+95[f]
14	$CH_2C_6H_5$	H	−49.6[d]	+125[e]	+57.1[f]
15	C_6H_5	H	−81.6[d]	−30.2[i]	
16	C_6H_5	CH_3	−51[j]	−94.2[k]	−61.9[j]
17	C_6H_5	C_2H_5	−16[j]	−208.7[l]	−82.3[j]
5b	C_6H_5	$c\text{-}C_6H_{11}$	+6[m]	−351.4[n]	−417[o]

[a] 2 or 5 *N* HCl and H_2O. [b] EtOH. [c] CH_3OH. [d] See ref 13. [e] T. Suzuki, K. Igarashi, K. Hase, and K. Tuzimura, *Agric. Biol. Chem.*, 37, 411 (1973). [f] See Experimental Section, optically active 3-phenyl-2-thiohydantoin derivatives. [g] C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry, and B. Sjöberg, *Acta Chem. Scand.*, 15, 903 (1961). [h] See Experimental Section, (*R*)-(+)-5-cyclohexylhydantoin. [i] See ref 7. [j] See ref 3. [k] L. M. Long, U.S. Patent 2561284 (July 17, 1951). The solvent was not indicated. [l] H. Sobotka, M. F. Holzman, and J. Kahn, *J. Am. Chem. Soc.*, 54, 4697 (1932). [m] See Experimental Section, **5b**. [n] See Experimental Section, **4b**. [o] See Experimental Section, **7b**.

$\Delta[\Phi]_{PTH}$, for the α-amino acids **8–14** showed a consistent behavior. A negative shift $\Delta[\Phi]_{CLJ}$ and positive shifts, $\Delta[\Phi]_{Hyd}$ and $\Delta[\Phi]_{PTH}$, were recorded in the *R* series. Nevertheless, some irregularities were observed for the (*R*)-2-phenyl-2-amino acids **15–17** and **5b**; increasing negative values of $\Delta[\Phi]_{Hyd}$ and $\Delta[\Phi]_{PTH}$ were obtained in contrast to the above 2-alkyl-2-amino acids **8–14**, whereas $\Delta[\Phi]_{CLJ}$ showed decreasing negative values, with a slightly positive shift for **5b**.

Some comments can be made about the variations of $\Delta[\Phi]_{CLJ}$. Branching in the alkyl chain (R^1) or introduction of a phenyl ($R_1 = CH_2C_6H_5$, C_6H_5) residue leads to larger $\Delta[\Phi]_{CLJ}$ for α-amino acids **8–15**, whereas opposition of an alkyl (R_2) and a phenyl (R_1) leads to smaller $\Delta[\Phi]_{CLJ}$ for α-amino acids **16, 17, and 5b**. As a matter of fact, $\Delta[\Phi]_{CLJ}$ do not vary in an uniform way, but increase (**8–15**) with a maximum for 2-phenylglycine (**15**) and decrease with finally an inversion of the observed sign for (−)-2-cyclohexyl-2-phenylglycine (**5b**).

Chiroptical Measurements. Knabe et al.[3] have published the ORD and CD curves of (*R*)-(−)-5-methyl- and 5-ethyl-3,5-diphenyl-2-thiohydantoins, which are characterized by a negative Cotton effect around 270 nm. In our hands, (+)-5-cyclohexyl-3,5-diphenyl-2-thiohydantoin (**7c**) prepared from **5c** showed in CD a positive Cotton effect around 270 nm, which indicated an *R* configuration for (−)-2-cyclohexyl-2-phenylglycine (**5b**).

X-Ray Diffraction. Owing to the discrepancy mentioned above in the optical comparisons, it was considered desirable to confirm the previous results by X-ray analysis of a derivative prepared from a compound with an asym-

metric center of known absolute configuration. Since the absolute configuration of (+)-10-camphorsulfonic acid is available from the literature,[14] the (+)- and (−)-HPPH (+)-10-camphorsulfonate (**18b,c**) were prepared by reaction of 10-camphorsulfonyl chloride and **1b,c** in dioxane–pyridine solution. Only (+)-HPPH (+)-10-camphorsulfonate (**18b**) yields the required single crystals in ethyl acetate. According to crystal data[15] of **18b** the *R* configuration can be definitively assigned to **1b**.

Conclusions

The results presented in Table I clearly demonstrate that 2-cyclohexyl-2-phenylglycine (**5b**) does not follow the Clough–Lutz–Jirgensons rule. A similar exception has been previously reported for isovaline.[13] In both cases, the sizes of the substituents are similar and the $\Delta[\Phi]_{CLJ}$ values small. It would thus appear that these factors preclude a configurational assignment based on the Clough–Lutz–Jirgensons rule. On the other hand, the highly negative values of $\Delta[\Phi]_{Hyd}$ and $\Delta[\Phi]_{PTH}$ observed with **5b** allow one to assess the *R* configuration for this amino acid. Additional support is given by the 270-nm positive Cotton effect which is observed with **7c**. Consequently (+)-HPPH (**1b**), having the same stereochemistry as **5b**, has an *R* configuration and (−)-HPPH (**1c**), the major metabolite of 5,5-diphenylhydantoin in man, has an *S* configuration. The present finding establishes that the enzymatic hydroxylation undergone by only one of the two phenyl substituents preferably occurs on the pro-*S* phenyl group. Work is currently in progress on the preparation from optically pure labeled HPPH enantiomers of the corresponding 5-(2′-^{2}H-phenyl)- and 5-(2′-^{3}H-phenyl)-5-phenylhydantoin to investigate with microsomal preparations the degree of stereoselectivity of this hydroxylation reaction.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 237 infrared spectrometer. The NMR spectra were recorded on a Perkin-Elmer R24 (60-MHz) instrument. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra were obtained from a LKB 9000 S apparatus (70 eV). CD measurements were performed using a Cary 61 spectropolarimeter. Elemental analyses are indicated only by symbols of the elements and are within 0.4% of the theoretical values. Precoated silica gel 60 F_{254} plates (Merck) were used for TLC with the following systems: I, $CHCl_3$–MeOH–benzene–25% NH_4OH (66:22:11:1); II, butanol–AcOH–H_2O (40:20:40); III, $CHCl_3$–acetone–benzene–AcOH (60:20:20:5). The spots were detected by uv light or iodine vapor.

(*R,S*)-5-(4′-Hydroxyphenyl)-5-phenylhydantoin (1a). To a stirred warm (60°) solution of 5-(4′-methoxyphenyl)-5-phenylhydantoin[4] (58 g, 0.23 mol) in acetic acid (500 ml) was added 48% hydrobromic acid (500 ml). The mixture was refluxed for 3 hr, cooled, and diluted with water (2 l.). The products were filtered off, washed with water, and crystallized from ethanol or water–dioxane 70:30 (v/v): yield 48.75 g (80.5%); mp 305–307° dec; R_f 0.50 (I).

(*R*)-(+)- and (*S*)-(−)-5-(4′-Hydroxyphenyl)-5-phenylhydantoin (1b and 1c). Anhydrous brucine (225 g) was added to a stirred hot solution of **1a** (100 g) in absolute ethanol (4 l.). After 24 hr at room temperature and 24 hr in a refrigerator, pellets of the resulting salt were collected (230 g). Decomposition of a sample of this salt with 2 *N* hydrochloric acid afforded **1c**, $[\alpha]^{25}_{546}$ −27° (*c* 1, 0.5 *N* NaOH). After five further crystallizations from absolute ethanol and decomposition of the brucine salt, 24 g of **1c** was recovered; $[\alpha]^{25}_{546}$ −71.5°. Three crystallizations of the free hydantoin furnished 9 g of **1c**: $[\alpha]^{25}_{546}$ −107.3 ± 0.8° (*c* 1, 0.5 *N* NaOH); $[\alpha]^{25}_{546}$ −25.7° (*c* 0.43, CH_3OH). The dextrorotatory mother liquors were concentrated and additional amounts of **1c** were isolated until the filtrate had a specific rotation of approximately +60°. The filtrate was evaporated to dryness and treatment with 2 *N* HCl afforded 28 g of **1b**: $[\alpha]^{25}_{546}$ +60°. Three crystallizations from ethanol yielded 9.5 g of **1b**, $[\alpha]^{25}_{546}$ +107 ± 0.8° (c 1, 0.5 *N* NaOH).

(*R,S*)- and (*R*)-(−)-5-(4′-Hydroxyphenyl)-5-cyclohexylhydantoin (2a and 2b). To a solution of **1b** (2.68 g, 10 mmol) in methanol (150 ml)–acetic acid (50 ml) was added platinum oxide (400 mg). The hydrogenation was performed at a pressure of 60 psi in a Parr apparatus. After 2 hr, the hydrogen uptake was 3.7 equiv. The catalyst was filtered off and the solvent evaporated to dryness. The residue was dissolved in boiling acetone (150 ml); water was added to a total volume of 400 ml. After 1 day at room temperature, 2.36 g (86% yield) was recovered. Three additional crystallizations from acetone–water gave analytical samples: R_f 0.55 (I); mp 325–332° dec; $[\alpha]^{25}_{546}$ −111.5° (*c* 0.22, EtOH); ir (KBr pellet) 3280 (broad, OH and NH), 3020, 2930, 2850, 1760–1705 (C=O), 1610, 1510, 760, 725 cm^{-1}; NMR (Me_2SO-d_6) δ 9.35 (1 H, s, NH), 6.45–6.80 (2 H, m), 7.0–7.50 (2 H, m), 2–0.5 (11 H, m, c-C_6H_{11}); mass spectrum *m/e* molecular ion 274. Anal. ($C_{15}H_{18}N_2O_3$) C, H, N. In the same way, from **1a** was obtained **2a**: mp 305–307° dec. Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

Phenyltetrazole Ether of 5-(4′-Hydroxyphenyl)-5-cyclohexylhydantoin (3a and 3b). To a stirred solution of **2b** (900 mg, 3.28 mmol) in DMF (7 ml) were added anhydrous potassium carbonate (1500 mg, 10.85 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (592 mg, 3.28 mmol) in two portions over 1 hr. The mixture was stirred for 4 hr and then left for 16 hr at room temperature. After dilution with water, the precipitate was filtered off and washed with water, yielding 860 mg (56.4%). The crude product was crystallized from ethanol–water: mp 235–238°; R_f 0.68 (III); $[\alpha]^{25}_{546}$ +85° (*c* 1.28, EtOH); mass spectrum *m/e* 418 (M^+), 390, 308, 236, 192, 176, 135, 120, 118, 104, 91, 77. In the same way from **2a** was obtained **3a**: mp 220–223°.

(*R,S*)-5-Cyclohexyl-5-phenylhydantoin (4a). A solution of cyclohexyl phenyl ketone (60 g, 0.319 mol) and potassium cyanide (30 g, 0.46 mol) in a mixture of DMF, water, and ethanol (270:75:50 ml) was placed in a 500-ml pressure bottle. After addition of ammonium carbonate (100 g), the bottle was warmed in an oil bath at 100° for 68 hr and at 123° for an additional 48 hr. After cooling, hot water was added and the turbid mixture was acidified to pH 2 with concentrated hydrochloric acid, cooled, and filtered. The crude product was dissolved in 10% NaOH and the resulting mixture was extracted with ether. The aqueous layer was acidified to pH 2 and filtered. **4a** was crystallized from ethanol with a yield of 78.9 g (95%): mp 269–270°;[6] R_f 0.82 (I); 0.65 (II). Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

(*R*)-(−)-5-Cyclohexyl-5-phenylhydantoin (4b). (a) From 3b. A solution of **3b** (440 mg, 1.05 mmol) in absolute ethanol was submitted to hydrogenolysis[5] (50 psi) in a Parr apparatus at 50° for 6 hr over 5% palladium on charcoal (400 mg). After filtering, fresh catalyst (200 mg) was added and hydrogenolysis was continued for a further 18 hr. The catalyst was filtered off and washed with hot ethanol and the solution was evaporated to dryness. The residue was dissolved in 1.25 *N* NaOH (40 ml); the insoluble fraction was discarded and the filtrate gave after acidification crude **4b**, which was filtered and washed with ethanol: 80 mg (29.4%). The product was crystallized three times from absolute ethanol, yielding a sample identical (melting point, TLC, ir) with **4b** obtained from **5b**: $[\alpha]^{25}_{546}$ −152° (*c* 0.135, EtOH).

(b) From 5b. A mixture of **5b** (2 g, 8.58 mmol) and urea (20 g) was warmed at 145° for 2 hr. To the hot solution was added 0.5 *N* hydrochloric acid (50 ml) and the resulting mixture was boiled for 2–3 min. After cooling, the product was filtered off, washed with water, and dried over P_2O_5 with a yield of 1.61 g (73%). After three crystallizations from ethanol, the product had mp 307–309° dec: $[\alpha]^{25}_{546}$ −158.6° (*c* 0.28, EtOH). The ir and the TLC behavior of **4b** was identical with **4a**: mass spectrum *m/e* 258 (M^+), 176, 147, 132, 104, 77.

(*R,S*)-2-Cyclohexyl-2-phenylglycine (5a). A hot (90°) solution of **4a** (30 g, 0.116 mol) in 20% NaOH (300 ml) was placed in a pressure bottle and warmed at 160° for 12 hr. After cooling, the pasty mass was dissolved in hot water (800 ml) and acidified to pH 6.5 with hydrochloric acid. The precipitate was filtered off, washed with water, extracted with boiling ethanol, and dried yielding 18 g (73%): mp 260–265° dec; R_f 0.72 (II); mass spectrum *m/e* 188, 186, 150, 132, 104; ir (KBr pellet) 3060, 2940, 2860, 1640, 1595 (sh), 1530, 1500 (sh), 1450, 1370, 1115, 730, 690 cm^{-1}.

(*R,S*)-*N*-Formyl-2-cyclohexyl-2-phenylglycine (6a). The amino acid **5a** (18 g, 0.077 mol) was dissolved at room temperature in formic acid (98–100%, 50 ml). To the cooled (−10°) stirred solution was added acetic anhydride (75 ml) in three portions over 0.5 hr. The mixture was allowed to come to room temperature. After 2 hr, ice–water (500 ml) was added. The precipitate was filtered off, washed with water, and dried. The yield of **6a** was 14.5 g (71.4%): mp 195–196°; R_f 0.50 (III). Crystallization from ethanol–water did

not improve the melting point. Prolonged boiling of a methanol solution of **6a** decomposed the product: mass spectrum *m/e* 243, 216, 161, 133, 104: ir (KBr) 3280, 2930, 2860, 1750, 1725 (C=O), 1610, 1510 cm^{-1}. Anal. ($C_{15}H_{19}O_3N \cdot \frac{1}{3}H_2O$) C, H, N.

(*R*)-(−)- and (*S*)-(+)-*N*-Formyl-2-cyclohexyl-2-phenylglycine (6b and 6c). The *N*-formylamino acid **6a** (10 g, 38.4 mmol) and brucine·$4H_2O$ (23 g, 49.4 mmol) were dissolved in boiling water (1200 ml). By successive concentration to around 200 ml, 9.2 g of the brucine salt of the dextrorotatory acid was obtained. The specific rotation of each fraction was measured on a sample obtained by treatment of a small amount of the salt with 0.5 *N* NaOH, extraction of brucine with $CHCl_3$, and precipitation of the acid with 0.5 *N* HCl. Three crystallizations from water and decomposition of the salt afforded **6c**: $[\alpha]^{25}_{546}$ +68.4° (*c* 0.4, 0.5 *N* NaOH). By subsequent concentration of the above mother liquor (200 ml), 8 g of the salt of the levorotatory acid was isolated. Two crystallizations from water and decomposition of the salt afforded **6b**: $[\alpha]^{25}_{546}$ −69.3° (*c* 0.4, 0.5 *N* NaOH).

(*R,S*)- and (*R*)-(−)-2-Cyclohexyl-2-phenylglycine (5a and 5b). A suspension of **6b** (1.5 g, 5.7 mmol), $[\alpha]^{25}_{546}$ −68.4° (c 0.4, 0.5 *N* NaOH), in 10% sulfuric acid (25 ml) was refluxed for 6 hr. The hot solution was cooled, filtered, and brought to pH 1.3 with 20% sodium hydroxide yielding 0.566 g. Further neutralization to pH 4 afforded 0.503 g of additional material (80.5%): R_f 0.72 (II); mp 274–276° dec; $[\alpha]^{25}_{546}$ −26.25° (*c* 0.1295, H_2O); $[\alpha]^{25}_{546}$ −23.7° (c 0.135, 2 *N* HCl). In the same way, **6a** gave **5a** (0.984 g, 74%): mp 270–271° dec.

(*R*)-(+)-5-Cyclohexylhydantoin. A solution of (*R*)-(−)-5-phenylhydantoin[7] [$[\alpha]^{25}_{546}$ −115° (c 0.1, EtOH)] (7 g, 40 mmol) in methanol–acetic acid (200:50 ml) was hydrogenated under 40 psi over platinum oxide (250 mg) for 3.5 hr at room temperature in a Parr apparatus. The catalyst was filtered off. The filtrate gave white crystals on standing (4.42 g, 60.7%): mp 223–224° (EtOH); $[\alpha]^{25}_{546}$ +97° (c 0.2, EtOH). Anal. ($C_9H_{14}O_2N_2$) C, H, N. The melting point of the racemic compound[16] was 226–227°.

(*R*)-(−)- and (*S*)-(+)-5-Cyclohexyl-3,5-diphenyl-2-thiohydantoin (7b and 7c). A solution of **5b** [240 mg, 10.3 mmol, $[\alpha]^{25}_{546}$ −6.65° (*c* 1, 2 *N* HCl)] and 99% sulfuric acid (0.6 ml) in dry CH_3OH (15 ml) was refluxed for 10 days. The solvent was evaporated and to the residue were added triethylamine (2 ml) and phenyl isothiocyanate. After 0.5 hr, benzene (5 ml) was added. The mixture was refluxed for 0.5 hr, left overnight at room temperature, and evaporated to dryness. The residual oil was triturated with 2 *N* hydrochloric acid (10 ml) and the mixture was boiled for 10 min. The oil was separated and dissolved in hot ethanol. After cooling, white crystals of **7b** were collected and recrystallized from methanol: yield 80 mg (22%); mp 251–253°; R_f 0.90 (III); $[\alpha]^{25}_{579}$ −43° (c 0.5, CH_3OH); ir (KBr pellet) 3300, 3060, 2940, 2860, 1730 (C=O), 1595, 1500 cm^{-1}. Anal. ($C_{21}H_{22}N_2OS$) C, H, N. In the same way, from **5c**, $[\alpha]^{25}_{546}$ +22° (*c* 0.135, 2 *N* HCl), was obtained **7c**: mp 224–225°: $[\alpha]^{25}_{546}$ +136.5°; CD (*c* 3.23 × 10^{-5} g/ml, CH_3OH); $[\Phi]_{330}$ −810°, $[\Phi]_{300}$ 0°, $[\Phi]_{269}$ +26.000°, $[\Phi]_{248}$ +24.900°, $[\Phi]_{235}$ 0°, $[\Phi]_{215}$ +44.400°.

Optically Active 3-Phenyl-2-thiohydantoin Derivatives of Amino Acids (Table I). The procedure of Edman et al.[9] was applied. Cyclization of the 5-phenyl-4-thiohydantoic acids was performed by refluxing in 10% hydrochloric or sulfuric acid for 5–10 min. The PTH derivatives were crystallized from methanol or ethanol.

(*S*)-(−)-5-Methyl-3-phenyl-2-thiohydantoin: mp 174.5–175.5°; R_f 0.60 (III); $[\alpha]^{25}_{546}$ −23.5° (*c* 0.2, CH_3OH). Anal. ($C_{10}H_{10}N_2OS$) C, H, N.

(*S*)-(−)-5-Benzyl-3-phenyl-2-thiohydantoin: mp 172–174.5°; R_f 0.66 (III); $[\alpha]^{25}_{546}$ −40.4° (*c* 0.225, CH_3OH). Anal. ($C_{16}H_{14}N_2OS$) C, H, N.

(*R*)-(+)-5-Cyclohexyl-3-phenyl-2-thiohydantoin: mp 245–246°; R_f 0.77 (III); $[\alpha]^{25}_{546}$ +30.8° (c 0.2, CH_3OH). Anal. ($C_{15}H_{18}N_2OS$) C, H, N.

5-(4′-Hydroxyphenyl)-5-phenylhydantoin 10-(+)-Camphorsulfonate (18a–c). To a stirred cooled (0°) solution of **1a** (5.38 g, 20 mmol) in pyridine (12 ml) and dioxane (100 ml) was added (+)-10-camphorsulfonyl chloride[17] (5.80 g, 23 mmol) over 1.5 hr. The mixture was allowed to come to room temperature. After 24 hr, water (500 ml) was added. The pasty mass was separated and dissolved in ether. The ether phase was filtered on aluminum oxide, and the filtrate on standing gave white needles of **18a** (2.5 g, 26%), which were crystallized from methanol: mp 217–219°; $[\alpha]^{25}_{546}$ +25° (*c* 0.57, MeOH); R_f 0.5 (III). Anal. ($C_{25}H_{26}O_6N_2S$) C, H, N. In the same way, from **1b** was obtained **18b**: mp 197–198°; $[\alpha]^{25}_{546}$ +4.9° (*c* 0.55, CH_3OH); R_f 0.5 (III). Anal. ($C_{25}H_{26}O_6N_2S$) C, H, N. Similarly, from **1c** was obtained **18c**: mp 194–195°; $[\alpha]^{25}_{546}$ +44.2° (*c* 0.095, CH_3OH); R_f 0.5 (III). Anal. ($C_{25}H_{26}O_6N_2S$) C, H, N. The NMR and ir spectra of **18a–c** were consistent with the proposed structure and were identical.

Acknowledgments. This study was supported by a grant from the "Fonds de la Recherche Fondamentale Collective. One of us (J.P.) is indebted to the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" for financial support. We thank Dr. M. Koch for X-ray single-crystal structure analysis, Mrs L. Frippiat for technical assistance, and Dr. P. Crooy (R.I.T.S.A., Genval, Belgium) for supplying microanalyses.

References and Notes

(1) (a) Th. C. Butler, *J. Pharmacol. Exp. Ther.*, **119**, 1 (1957); (b) J. H. Gorvin and G. Brownlee, *Nature (London)*, **179**, 1248 (1957); (c) E. W. Maynert, *J. Pharmacol. Exp. Ther.*, **130**, 275 (1960); (d) D. M. Woodbury, *Epilepsia*, **10**, 121 (1969); (e) A. J. Atkinson, Jr., J. Macgee, J. Strong, D. Garteiz, and Th. E. Gaffney, *Biochem. Pharmacol.*, **19**, 2483 (1970); (f) T. Chang, A. Savory, and A. J. Glazko, *Biochem. Biophys. Res. Commun.*, **38**, 444 (1970); (g) M. G. Horning, C. Stratton, A. Wilson, E. C. Horning, and R. M. Hill, *Anal. Lett.*, **4**, 537 (1971); (h) T. Chang and A. J. Glazko in "Antiepileptic Drugs", D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Ed., Raven Press, New York, N.Y., 1972, Chapter 14; (i) T. Chang, R. A. Okerholm, and A. J. Glazko, *Anal. Lett.*, **5**, 195 (1972); (j) O. Borgå, M. Garle, and M. Gutova, *Pharmacology*, **7**, 129 (1972); (k) T. Chang, R. A. Okerholm, and A. J. Glazko, *Res. Commun., Chem. Pathol. Pharmacol.*, **4**, 13 (1972).

(2) (a) H. Kutt and K. Verebely, *Biochem. Pharmacol.*, **19**, 675 (1970); (b) W. L. Gabler and G. L. Hubbard, *ibid.*, **21**, 3071 (1972).

(3) J. Knabe and C. Urbahn, *Justus Liebigs Ann. Chem.*, **750**, 21 (1971).

(4) H. R. Henze and A. F. Isbell, *J. Am. Chem. Soc.*, **76**, 4152 (1954).

(5) W. J. Musliner and J. W. Gates, *J. Am. Chem. Soc.*, 88, 4271 (1966).

(6) M. Tiffeneau, B. Tchoubar, and Saias-Lambert, *Bull. Soc. Chim. Fr.*, 445 (1947).

(7) K. H. Dudley and D. L. Bius, *J. Heterocycl. Chem.*, **10**, 173 (1973).

(8) H. Reihlen and L. Knöpfle, *Justus Liebigs Ann. Chem.*, **523**, 199 (1936).

(9) P. Edman, *Acta Chem. Scand.*, **4**, 277 (1950).

(10) H. Autenhoff and J. G. Hansen, *Pharmazie*, **250**, 336 (1970).

(11) T. Suzuki and K. Tuzimura, *Agric. Biol. Chem.*, **37**, 689–691 (1973).

(12) O. Lutz and B. Jirgensons, *Ber.*, **64**, 1221 (1931).

(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Wiley, New York, N.Y., 1961, pp 85–88.

(14) W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Chapman and Hall, London, 1974, pp 85–88.

(15) M. Koch, *Acta Crystallogr., Sect. B*, in press.

(16) J. Edelson, J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **80**, 2698 (1958).

(17) P. D. Bartlett and L. H. Knox in "Organic Syntheses", Collect. Vol. V, H. E. Baumgarten, Ed., Wiley, New York, N.Y., 1973, p 196.