The Synthesis of Optically Active 5-Phenylhydantoins (1)

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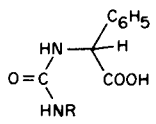
A number of reagents have been examined for effecting the conversion of an optically pure 2-phenylhydantoic acid to an optically active 5-phenylhydantoin. Trifluoroacetic anhydride (TFAA method) and dilute hydrochloric acid (acid-catalysis method) proved to be the reagents of choice. The dependence of the kinetics of racemization of the 5-phenylhydantoin system on temperature has been studied in dilute hydrochloric acid solution to support the conclusion that 5-phenylhydantoins prepared by the acid-catalysis method are nearly, if not entirely, optically uniform.

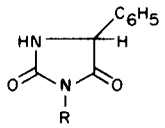
It has recently been shown that the racemic form of 3-ethyl-5-phenylhydantoin (**6**, ethotoin, Peganone) and of each of the related 5-phenylhydantoins, **2** and **4**, is converted metabolically by the dog to *R*(-)-2-phenylhydantoic acid (**1**) (2,3). An analogous stereospecific biotransformation by the dog of *N*-methyl-α-phenylsuccinimide (phensuximide, Milontin) has been reported more recently (4).

In the former study (3) in which the metabolic fate of 5-phenylhydantoin (**2**) itself was examined, it was found that somewhat more of the recovered drug and its principal metabolite, *R*(-)-**1**, appeared in the *R*-configuration than was administered as that configuration of the drug. In order to account for this finding, the suggestions were made that only the *R*-isomer of 5-phenylhydantoin (**2**) could serve as a substrate for the enzyme responsible for the ring-opening reaction and that the residual *S*-isomer of **2** underwent spontaneous and/or enzymatic *in vivo* racemization. In order to undertake *in vitro* racemization studies and to pursue certain enzymological aspects of the ring opening biotransformation, the pure (or nearly so) optical isomer(s) of a 5-phenylhydantoin, *e.g.*, **2**, **4** and/or **6** were required.

Optical isomers of compounds synthesized in this investigation are of the *R*(-)-configuration. *S*(+)-α-Amino-α-phenylacetic acid is available by resolution of its racemic material by the method of Holmes and Adams (5), and the synthetic procedures developed in the present study would be applicable as well to the preparation in the *S*-configuration of all compounds of the present study.



1, R = H
3, R = CH_3
5, R = CH_2CH_3



2, R = H
4, R = CH_3
6, R = CH_2CH_3

Results.

Studies of Synthetic Methods Applicable to the Conversion of *R*(-)-2-phenylhydantoic Acid and Its Derivatives to *R*(-)-5-phenylhydantoins of Apparent High Optical Purity.

In the present study the use of *N*-ethyl-5-phenylisoxazolium-3′-sulfonate (Woodward's Reagent K) (6), *N*,*N*-dicyclohexylcarbodiimide (7), or ethoxyacetylene (8) proved unsuitable for promoting the intramolecular coupling (cyclodehydration) of 2-phenylhydantoic acid (**1**) or of its 5-alkyl derivatives to 5-phenylhydantoins.

A reaction of ethyl chloroformate (cathyl chloride) (9) and *R*(-)-**1** in the presence of triethylamine furnished two crystalline products (*cf.* Experimental), but no 5-phenylhydantoin (2) was formed in this reaction as judged by tlc.

N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (10) was also found unsuitable for the cyclodehydration of a phenylhydantoic acid in trials where benzene and ethyl acetate were used as solvent mediums. When the reaction was carried out in tetrahydrofuran (THF), cyclodehydration with EEDQ of *R*(-)-**3** occurred at 25° and **4** was realized in consistent yields of 40% after workup. However, **4** was isolated in racemic condition.

Optically active 5-phenylhydantoins were obtained in adequate yields by cyclodehydration of *R*(-)-2-phenylhydantoic acid and of *R*(-)-5-alkyl-2-phenylhydantoic acids with trifluoroacetic anhydride (TFAA method). The

TABLE I

Cyclodehydration of *R*(-)-5-Substituted-2-phenylhydantoic Acids to *R*(-)-3-Substituted-5-phenylhydantoins by use of Trifluoroacetic Acid Anhydride (TFAA)

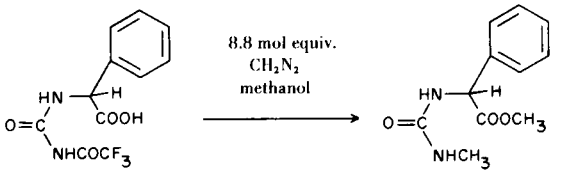
Cyclodehydration of *R*(-)-5-substituted-2-phenylhydantoic Acid Group R	Reaction Conditions temp (time) (a)	Recovered *R*(-)-3-substituted-5-phenylhydantoin Yield	$[\alpha]_D^{25}$ (b)
	°C (min)	%	deg.
H	0 (30); 25 (1440)	36	-32
CH_3	0 (25); 25 (45)	23	-111
CH_3	0 (45); 25 (25)	40	-108
Et	0 (45); 25 (30)	31	-88

(a) The denotation [0 (45); 25 (45)] is to indicate that the components were mixed and let stand at 0° for 45 minutes and then the reaction vessel was removed from the ice bath and kept at ambient temperature (25°) for an additional 45 minutes prior to workup (*i.e.*, quenching by pouring the TFAA solution onto ice). (b) c = 0.20 (absolute ethanol).

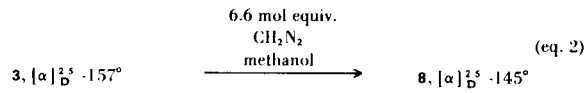
yields and optical properties of some 5-phenylhydantoins prepared by the TFAA method are summarized in Table I. In the TFAA conversion of *R*(-)-2-phenylhydantoic acid (**1**) to *R*(-)-5-phenylhydantoin (**2**), in which the product **2** had what proved to be a low specific rotation of -32°, the reaction required a period of 24 hours when carried out at 25°. Thin layer chromatography indicated that the mechanism of the cyclodehydration involved an intermediate, which was isolated and assigned structure **7**. In the TFAA conversions of *R*(-)-5-methyl- and of *R*(-)-5-ethyl-2-phenylhydantoic acid (**3** and **5**) to *R*(-)-3-methyl- and to *R*(-)-3-ethyl-5-phenylhydantoin (**4** and **6**), respectively, the reactions were complete within 1.5 hours. In these latter two reactions, no intermediate corresponding to **7** could be isolated or even observed by tlc.

Intermediate **7** was isolable in good yield, if the reaction were quenched 15 minutes after the solution of *R*(-)-**1** in TFAA was complete. The composition of **7** as a monotrifluoroacetyl derivative, $C_{11}H_9F_3N_2O_4$, was established on the basis of its elemental analyses and by the mass spectral evidence of accurate mass measurement of the apparent molecular ion. In a separate experiment, it was established that **7** was convertible to *R*(-)-**2**, $[\alpha]_D^{25}$ -47°, upon prolonged exposure to TFAA.

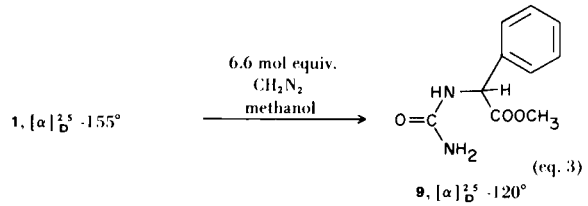
The structure of the monotrifluoroacetyl derivative **7** was suggested by the courses taken of **7** and of the known 2-phenylhydantoic acids, **1** and **3**, in their reactions with diazomethane. Upon treatment of its methanolic solution with excess diazomethane, the monotrifluoroacetyl derivative **7** formed **8**, incorporating two methyl groups and losing the trifluoroacetyl group. The identity of **8** was established as the methyl ester of *R*(-)-5-methyl-2-phenylhydantoic acid on the evidence of the formation of this same compound by diazomethane treatment of *R*(-)-5-methyl-2-phenylhydantoic acid (**3**) (*cf.* equation 2). The presence of the methyl ester group in these compounds was indicated by the ir spectral data and was firmly settled by a conversion of a sample of *R*(-)-**8** to *R*(-)-3-methyl-5-phenylhydantoin (**4**) under mild acidic conditions. The postulate that the trifluoroacetyl group is attached as shown in derivative **7** is consistent with the evidence of the introduction by diazomethane of the 5-methyl group, the acidity of the imide function, *i.e.* -$CONHCOCF_3$, accounting for the observed facile methylation at the 5-position (11). That diazomethane will not methylate under these conditions the 5-position of 2-



7, $[\alpha]_D^{25}$ -83° 8, $[\alpha]_D^{25}$ -148° (eq. 1)



3, $[\alpha]_D^{25}$ -157° 8, $[\alpha]_D^{25}$ -145° (eq. 2)



1, $[\alpha]_D^{25}$ -155° 9, $[\alpha]_D^{25}$ -120° (eq. 3)

phenylhydantoic acid without appropriate substitution to increase the acidity of that -NH- function is shown by the reaction described in equation 3, in which phenylhydantoic acid itself in the presence of excess methanolic diazomethane was found to form only its methyl ester, **9**.

In a previous study (3), we observed that *R*(-)-**1** underwent cyclodehydration to *RS*-**2** in the presence of 2 *N* hydrochloric acid under relatively mild conditions (48 hours, 25°). As will be discussed more thoroughly later, it was found during the present study that the isolation of *RS*-**2** after incubation of *R*(-)-**1** in dilute hydrochloric acid (48 hours, 25°) was not caused so much by the prolonged exposure to the acid medium as it was by the methodology of the isolation. Therefore, we have investigated this acid-catalyzed cyclodehydration reaction of *R*(-)-**1** as a function of the acid concentration and of the length of the heating period in search of conditions where the reaction would proceed nearly to completion and where acid-catalyzed racemization of the cyclodehydration product, *R*(-)-**2**, would remain minimal. It is seen from Table II, which summarizes a study of the

TABLE II

A Summary of the Acid-catalyzed Cyclodehydration Reactions of *R*(-)-2-Phenylhydantoic Acid (**1**) to *R*(-)-5-Phenylhydantoin (**2**)

Reaction conditions for cyclodehydration of 1 mmole of *R*(-)-**1** in 10 ml. of HCl at 94°		Recovered 5-Phenylhydantoin (**2**)	
[HCl]	time	Yield	$[\alpha]_D^{25}$ (c)
N	minutes	%	deg.
0.05	25	66 (a)	
0.10	40	65 (b)	
0.10	90	58	-89
0.30	25	71 (b)	
0.30	40	71	-112
0.60	25	63	-112
0.60	45	68	-101

(a) No cyclization occurred; material was phenylhydantoic acid as judged by thin layer chromatography. (b) Mixture of two materials, phenylhydantoic acid and 5-phenylhydantoin as judged by thin layer chromatography. (c) c = 0.20 (absolute ethanol).

acid-catalyzed cyclodehydration of *R*(-)-**1** under various conditions, that the minimal acid concentration and heating period required for an efficient production of *R*(-)-**2** of maximal specific rotation were, respectively, 0.30 *N* and 40 minutes. The heating period could be decreased to 25 minutes by use of 0.60 *N* hydrochloric acid without affecting the specific rotation of the product.

Studies were made also of the acid-catalysis method as applied to the cyclodehydrations of *R*(-)-5-methyl-2-phenylhydantoic acid (**3**) and of *R*(-)-5-ethyl-2-phenylhydantoic acid (**5**) to the *R*-forms, respectively, of 3-methyl-5-phenylhydantoin (**4**) and of 3-ethyl-5-phenylhydantoin (**6**, ethotoin, Peganone). The optical properties of these 3-alkyl-5-phenylhydantoins of the *R*-configuration are summarized in Table III and Table IV.

TABLE III

A Summary of the Acid-catalyzed Cyclodehydration Reactions of *R*(-)-5-Methyl-2-phenylhydantoic Acid (**3**) to *R*(-)-3-Methyl-5-phenylhydantoin (**4**)

Reaction conditions for cyclodehydration of 1 mmole of *R*(-)-**3** in 10 ml. of HCl at 94°		Recovered *R*(-)-3-methyl-5-phenylhydantoin (**4**)	
[HCl]	time	Yield	$[\alpha]_D^{25}$ (a)
N	minutes	%	deg.
0.10	60	76	-105
0.30	30	74	-108
0.60	20	70	-111
0.60	20	70	-108

(a) c = 0.20 (absolute ethanol).

TABLE IV

A Summary of the Acid-catalyzed Cyclodehydration Reactions of *R*(-)-5-Ethyl-2-phenylhydantoic Acid (**5**) to *R*(-)-3-Ethyl-5-phenylhydantoin (**6**, R(-)-ethotoin, *R*(-)-Peganone)

Reaction conditions for cyclodehydration of 1 mmole of *R*(-)-**5** in 10 ml. of HCl at 94°		Recovered *R*(-)-3-ethyl-5-phenylhydantoin (**6**)	
10 ml. HCl	time	Yield	$[\alpha]_D^{25}$ (a)
N	minutes	%	deg.
0.10	60	72	-84
0.30	30	74	-87
0.60	20	72	-88
0.60	20	76	-85

(a) c = 0.20 (absolute ethanol).

Some Studies of the Kinetics of Racemization of the 5-Phenylhydantoin System.

The rate constants of racemization of 5-phenylhydantoin and its 3-alkyl derivatives in 0.60 *N* hydrochloric acid solution were determined at different temperatures in the range of 70 to 85°. For each of the three 5-phenylhydantoins studied in this temperature range, the dependence of

observed rate constant of racemization on temperature followed the exponential Arrhenius equation,

$$k = A\, e^{-E_a/RT}$$

as evidenced by the apparent linear plot of the logarithm of the rate constant of racemization, k_{racem}, against 1/T (the temperature, T, in degrees Kelvin). A plot for each 5-phenylhydantoin is shown in Figure 1. Extrapolation of each curve in Figure 1 to the abscissa value corresponding to 94° permitted a rough assessment of k_{racem} for the temperature condition of 94° utilized in its preparation by the acid-catalysis method. These rate constants of racemization for the condition of 94° are summarized in a table at the base of Figure 1.

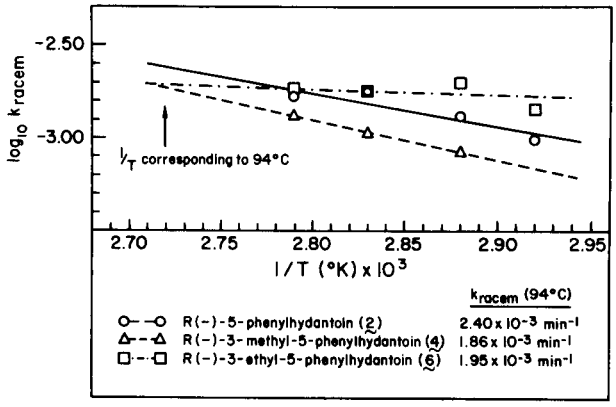


Figure 1. The relationship of the logarithm of the apparent first-order rate constant of racemization in 0.6 *N* hydrochloric acid solution of 5-phenylhydantoin (**2**), 3-methyl-5-phenylhydantoin (**4**), and of 3-ethyl-5-phenylhydantoin (**6**, ethotoin, Peganone) as a function of reciprocal temperature (in degrees Kelvin).

In another experiment, the rate constant of racemization of *R*(-)-**2** in 2 *N* hydrochloric acid at 37° was determined to be $3.3 \times 10^{-5}\,min^{-1}$.

Discussion.

By comparison of the specific rotations of the different preparations of *R*-(-)-**2** shown in Tables I and II, it is evident that the acid-catalysis method is superior to the TFAA method for the cyclodehydration of *R*(-)-**1** to *R*(-)-**2**. We find, however, that the TFAA method is as satisfactory as the acid-catalysis method for preparation of the 3-alkyl-5-phenylhydantoins, **4** and **6**, when optical purity is the criterion. This conclusion is based upon a comparison of the optical properties shown in Table I (TFAA method) with those properties shown in Tables III and IV (acid-catalysis method).

TABLE V

The Yields and Optical Properties of *R*(-)-2-Phenylhydantoic Acid and its 5-Alkyl Derivatives

$C_6H_5CH(NHCONHR)COOH$	$[\alpha]_D^{25}$ (a)	Yield %	M.p., °C
-H	-155	61	195-199
$-CH_3$	-157	89	175-179
$-C_2H_5$	-138	92	160-161

(a) c = 0.22 (absolute ethanol).

In the example in Table I where *R*(-)-2-phenylhydantoic acid (**1**) was converted by TFAA to *R*(-)-5-phenylhydantoin (**2**), it is likely that the accumulation of intermediate **7** is indirectly responsible for the low optical rotation of **2**. The trifluoroacetyl derivative **7** is sufficiently stable to the point of being isolable and storable, and its slow conversion to *R*(-)-**2** in the presence of TFAA (25°, 24 hours) is probably the rate limiting step in the overall reaction of *R*(-)-**1** to *R*(-)-**2**. The lengthy reaction period that is required for the completeness of the conversion of *R*(-)-**1** to *R*(-)-**2** may be the cause of the lower optical purity of *R*(-)-**2** in this method of preparation.

The smooth conversions of the 5-alkyl-2-phenylhydantoic acids, *R*(-)-**3** and *R*(-)-**5**, to 3-alkyl-5-phenylhydantoins and the lack of evidence for accumulation in either of these reactions of 5-acyl intermediate corresponding to **7** are factors which suggest the instability in TFAA medium of a 5-acyl-5-alkyl-2-phenylhydantoic acid such as **10**. Support for this concept may be found in the diazomethylation reaction of **7** in absolute methanol, in

C_6H_5-CH(NHCON(R)COCF$_3$)-COOH — **10** (R = CH_3 or CH_2CH_3)

C_6H_5-CH(NHCONHR)-COCOCF$_3$ — **11** (R = CH_3 or CH_2CH_3)

which the introduction into **7** of the 5-methyl group presumably elicits removal of the 5-trifluoroacetyl group by solvent (*cf.* **7** → **8**). In the TFAA cyclodehydration reactions of *R*(-)-**3** and *R*(-)-**5**, we believe the result of this instability factor is to favor the production of the corresponding mixed anhydride derivatives (*e.g.*, **11**), these intermediates being assumed to cyclize smoothly to 3-alkyl-5-phenylhydantoins.

It is plausible to assume that the extent of racemization of an optically active 5-phenylhydantoin is only slight during the periods of exposure to the conditions employed in preparations by the acid-catalysis method. These conditions are summarized in Tables II, III, and IV. This view is supported by the magnitude of the specific rotation (101°) of a sample of *R*(-)-**2** that was isolated after a

TABLE VI

The Yields, Optical Properties, and Physical Data of the Diazomethylation Products of *R*(-)-**7**, *R*(-)-**3**, and *R*(-)-**1**

Substrate (a)	Mmoles (b) CH_2N_2	Product	Yield	$[\alpha]_D^{25}$ (c)	M.p., °C		Analyses (d) C	H	N	M+
			mg.	deg.						
R(-)-**7**	8.8	ϕ-CH(COOCH$_3$)NHCONHCH$_3$)	107	-148	119-125	Found	59.21	6.18	12.82	222.1007
						Calcd.	59.43	6.35	12.61	222.1004
R(-)-**3**	6.6	ϕ-CH(COOCH$_3$)NHCONHCH$_3$)	158	-145	102-112	Found	59.48	6.36	12.68	222.1005
						Calcd.	59.43	6.35	12.61	222.1004
R(-)-**1**	6.6	ϕ-CH(COOCH$_3$)NHCONH$_2$)	168	-120	142-147	Found	57.57	5.79	13.52	208.0847
						Calcd.	57.66	5.80	13.46	208.0848

(a) 1 Mmole quantity of each substrate was employed. (b) Mmoles required for persistent yellow color. (c) c = 0.20 (absolute ethanol). (d) Materials were recrystallized from ethyl acetate prior to analyses.

heating period was employed longer than necessary for the completeness of the cyclodehydration reaction (*cf.* Table II). If one assumes a specific rotation of 112° for an optically pure enantiomer, a specific rotation of 101° for a sample of **2** would represent an enantiomeric ratio of 95:5. Substantial support for the assumption of high optical purities for the 5-phenylhydantoins prepared by the acid-catalysis method may be found in the evidence of the dependence of the observed rate constant of racemization, k_{racem}, on temperature. With the knowledge of k_{racem} at 94° for a given 5-phenylhydantoin, it is possible to evaluate with a reasonable degree of confidence the maximal extent of racemization that can occur within the time period utilized in the preparation of that particular 5-phenylhydantoin by the acid-catalysis method. For instance, in a 0.002 *M* solution of *R*(-)-5-phenylhydantoin (**2**) in 0.6 *N* hydrochloric acid, for which at 94° a k_{racem} of 1.94 x 10^{-3} min^{-1} was determined, only 5% of the initial concentration of the optically active material will be racemized during 25 minutes at 94°. If at time zero the 5-phenylhydantoin is 100% optically pure, the percent composition after 25 minutes at 94° of the *R*(-)- and *S*(+)- forms will be 97.5 and 2.5, respectively. We believe that these percentages would represent the maximal limits of composition of the optical forms of **2** present when 1 mmole of *R*(-)-phenylhydantoic acid (**1**) is cyclodehydrated under the conditions of solution in 0.60 *N* hydrochloric acid, a temperature of 94° and a reaction period of 25 minutes.

It is not known to what extent *R*(-)-phenylhydantoic acid (*i.e.*, **1**, **3**, or **5**) suffers racemization prior to cyclodehydration under the conditions of the acid-catalysis method. If racemization of a phenylhydantoic acid does occur under these conditions, we do not think its rate constant of racemization would exceed that of its 5-phenylhydantoin derivative. *R*(-)-α-Amino-α-phenylacetic acid, the amino acid from which were prepared the phenylhydantoic acids of the present study, did not racemize

TABLE VII

Effect of *p*H upon the Specific Rotation of *R*(-)-5-phenylhydantoin

*p*H (a)	Yield of *R*(-)-**2**	$[\alpha]_D^{25}$
	%	
6.0	37.5	-102°
7.0	40.5	-95°
8.0	43.0	-86°
9.0	48.4	-64°

(a) *p*H to which *R*(-)-**2** was exposed (3 minutes) prior to final adjustment of *p*H and workup.

to any observable extent when exposed to the conditions of the cyclodehydration reaction (0.6 *N* hydrochloric acid, 94°, 25 minutes).

The observed rate constant of 3.3×10^{-5} min^{-1} for racemization of *R*(-)-**2** in 2 *N* hydrochloric acid at 37° now indicates that in our previous study (3) the isolation of *RS*-**2** after incubation of *R*(-)-**1** in 2 *N* hydrochloric acid (25°, 48 hours) was not due principally to racemization by acid of optically active **2** after its formation. In fact, one may calculate from this rate constant that after a prolonged exposure period of 48 hours to 2 *N* hydrochloric acid a sample of **2** initially optically pure would have an optical purity of 91%. It is evident from our present work that isolation of *RS*-**2** was an artifact of the methodology, the racemization of *R*(-)-**2** most likely occurring at alkaline *p*H during adjustment of the *p*H of the solution to the vicinity of neutrality prior to workup. We now recognize that rates of racemization of a 5-phenylhydantoin are significantly different within the *p*H range of 6.00-8.00, and we are currently investigating the effects of *p*H, different buffers, and different buffer concentrations on the rate of racemization in the hope of elucidating the actual mechanism(s) of racemization.

EXPERIMENTAL

Thin layer chromatograms were prepared by coating microscope slides with Silica Gel H. Suitable solvent systems were benzene:ethyl acetate:acetic acid in proportions, respectively, of 7:3:1 (solvent system A) and of 90:10:1 (solvent system B). Zones were visualized by spraying the eluted chromatograms with 5% phosphomolybdic acid in ethanol (PMA) and, then, baking the slide on the surface of a hot plate (zones were developed within minutes.

Micromelting points were taken on a Kofler hot stage microscope and are uncorrected.

Infrared spectra were measured with a Perkin-Elmer Model 257 instrument; samples were prepared in the form of pressed KBr disks.

Specific rotations at 589 nm (D-line) were measured on a Cary 60 spectropolarimeter.

Mass spectra (70 eV) were measured on a AEI-MS-902 spectrometer at the Research Triangle Institute Center for Mass Spectrometry. High resolution mass spectrographic measurements (peak matchings) were conducted by Mr. F. Williams (RTI Laboratory).

Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois.

Preparation of *R*(-)-2-phenylhydantoic Acid and its 5-Alkyl Derivatives.

RS- and *R*(-)-α-Amino-α-phenylacetic acid $[\alpha]_D^{25}$ -153° (c = 0.20 in 1 *N* hydrochloric acid) were purchased from a commercial source. A gram-ratio mixture of 1:1.2:10, respectively, of *RS*- or *R*(-)-α-amino-α-phenylacetic acid, potassium cyanate, and water in a covered evaporating dish was heated on the water bath for 90 minutes. The solution was filtered and the chilled filtrate was adjusted to *p*H 6.0, and a small amount of insoluble material was filtered off. The *p*H of the cold filtrate was lowered to 2, the heavy white precipitate of **1** being collected, washed with water, and recrystallized from water. The yield and optical properties of *R*(-)-phenylhydantoic acid (**1**), which was recrystallized to constant rotation, is included in Table V.

A molar ratio of 1.00:1.15:1.50, respectively, of *R*(-)-α-amino-α-phenylacetic acid, sodium hydroxide, and methyl (or ethyl) isocyanate was employed in preparation of the *R*(-)-enantiomer of 5-alkyl-2-phenylhydantoic acids, **3** and **5**. The quantity of water used as solvent was based upon the ratio of 15 ml. per gram of the amino acid. The reaction vessel was equipped with a mechanical stirrer.

To a vigorously stirred, cold (0-5°) sodium hydroxide solution of the amino acid was added dropwise the alkyl isocyanate, after which time the mixture was stirred vigorously at 0-5° for 2.5 hours. The cold solution was adjusted to *p*H 6, the insoluble material was filtered off, and the *p*H of the filtrate (5°) was slowly lowered to 2. The white precipitate was collected, washed, reprecipitated from dilute alkali, and vacuum dried (50°). The yields and optical properties of the *R*(-)-5-alkyl-2-phenylhydantoic acids, which were reprecipitated until constant rotations were obtained, are summarized in Table V.

Investigation of Woodward's Reagent K, *N,N*-Dicyclohexylcarbodiimide, and of Ethoxyacetylene as Intramolecular Coupling Agents for Conversion of 2-Phenylhydantoic Acid and its 5-Alkyl Derivatives to Hydantoins.

The reaction of one millimole quantities of each of *R*(-)-**1**, triethylamine, and *N*-ethyl-5-phenylisoxazolium-3′-sulfonate (Woodward's Reagent K) in cold (0-2°), dry acetonitrile contained after 42 hours only small amounts, if any, of **2**, as evidenced by tlc (solvent system A, three unidentified zones).

A reaction of *RS*-**1** (1.0 g.) and dicyclohexylcarbodiimide (1.2 g.) in a 5:2 mixture of dry tetrahydrofuran-acetonitrile (175 ml.) at room temperature showed by tlc (solvent system A) the formation within three hours of three unidentified materials in addition to **1** and **2**. The chromatographic properties of the reaction components did not appear to change over the next 27 hours.

From a solution of 208 mg. (1.0 mmole) of *R*(-)-5-methyl-2-phenylhydantoic acid (**3**) and four molar equivalents of ethoxyacetylene in 30 ml. of ethyl acetate, which had been heated under reflux for 5 hours, there was isolated a dark oil (tlc, two zones, solvent system A) which furnished a 14% yield of *RS*-(**4**), m.p. 166-169° (from absolute ethanol).

Reaction of Ethyl Chloroformate (Cathyl chloride) and *RS*-Phenylhydantoic Acid (**1**).

To a stirred suspension formed from the reaction of 1.9 g. of *RS*-**1** and 1.0 g. of triethylamine in 225 ml. of dry THF at 0° was added during 15 minutes a solution of 1.1 g. of cathyl chloride in 25 ml. of THF. The suspension was stirred at 0° for 8.5 hours. By workup and by preparative thick layer chromatography of residues, two apparent homogeneous substances of m.p. 208-212° (164 mg.), and m.p. 150-155° and 195-202° (dimorphic, 103 mg.) have been isolated. No *RS*-**2** was formed in this reaction, as evidenced by tlc and the establishment of structures of the isolated materials was not pursued.

Conversion by EEDQ of *R*(-)-**1** to *R*(-)-Ethyl-2-phenylhydantoate.

A solution of 194 mg. (1.0 mmole) of *R*(-)-**1** and 272 mg. (1.1 mmole) of EEDQ in 10 ml. of 1:1 benzene-ethanol was stirred at room temperature for 19 hours. The solution was evaporated and the oil so obtained was crystallized from ether, giving 118 mg., m.p. 161-175° of *R*(-)-ethyl 2-phenylhydantoate. An analytical sample of m.p. 172-177° and $[\alpha]_D^{25}$ -124° (c = 0.2, absolute

ethanol) was prepared by recrystallization from ethyl acetate-petroleum ether.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.28; H, 6.32; N, 12.62.

Cyclodehydration by EEDQ of *R*(-)-**3** to *RS*-3-Methyl-5-phenylhydantoin (**4**).

A solution of 208 mg. (1.0 mmole) of *R*(-)-**3** and 272 mg. (1.1 mmole) of EEDQ in 50 ml. of dry THF was stirred at room temperature for 46 hours. The solvent was removed under reduced pressure, and the vacuum-dried solid was dissolved in 15 ml. of ethyl acetate. The organic solution was washed successively with 5 ml. portions of 0.005 *M* phosphate buffer of *p*H 6 and water. The organic phase was dried (sodium sulfate) and stripped, and the residue was recrystallized from 4 ml. of absolute ethanol to give 81 mg. of *RS*-**4**, m.p. 166-167° and $[\alpha]_D^{25} = 0$ (c = 0.42 absolute ethanol).

TFAA Method: Cyclodehydration Reactions in Trifluoroacetic Anhydride (TFAA) of 2-Phenylhydantoic Acid and its Derivatives to 5-Phenylhydantoins.

The hydantoic acid (1.0 g.) was added to ice-cold TFAA (8 ml.), and the mixture was stirred at 0° for the time designated in Table I. The reaction was allowed to attain room temperature and was then stirred at 25° for the time designated in Table I. The clear solution was poured over 80 ml. of cracked ice and this mixture was stirred until the precipitate was a filtrable solid (less than 30 minutes). In conversion of **4** to **6**, the precipitated gum was isolated with the aid of ether. After workup the solid (or gum) was washed with cold water, dried *in vacuo* and recrystallized from ethyl acetate-hexane. The yields and optical properties of 5-phenylhydantoins obtained by this method are summarized in Table I.

R(-)-5-Trifluoroacetyl-2-phenylhydantoic Acid (**7**).

To 8 ml. of cold TFAA was added 1.0 g. of *R*(-)-**1**, $[\alpha]_D^{25}$ -155° (c = 0.20, absolute ethanol), and the thick paste was stirred at 0° for 30 minutes. The mixture was then allowed to warm to room temperature, a clear solution resulting 15 minutes after removal of the ice bath. The solution was poured over cracked ice (80 ml.) and the chromatographically uniform precipitate so formed (1.15 g.), m.p. 210-215°, was collected, washed with water, and dried; $[\alpha]_D^{25}$ -83° (c = 0.218, absolute ethanol); ir: 3320, 3140, 1755, 1720, and 1687 cm^{-1}; mass spectrum, Calcd. for $C_{11}H_9F_3N_2O_4$, 290.0519. Found, 290.0519. For analysis a sample was recrystallized from ethyl acetate-hexane, m.p. 204-208°.

Anal. Calcd. for $C_{11}H_9F_3N_2O_4$: C, 45.52; H, 3.13; N, 9.66. Found: C, 45.86; H, 3.11; N, 9.58.

A sample of *R*(-)-**7** (0.50 g.) in 4 ml. of cold TFAA was stirred for 15 minutes at 0° and then for 24 hours at room temperature. The usual workup gave *R*(-)-**2** (0.12 g.), m.p. 185-187° and $[\alpha]_D^{25}$ -47° (c = 0.40, absolute ethanol).

Diazomethylation Reactions of *R*(-)-**7**, *R*(-)-**3**, and *R*(-)-**1**.

To 1 mmole of the phenylhydantoic acid in 30 ml. of absolute methanol at 0° was added standardized ethereal diazomethane until the solution acquired a persistent faint yellow color (*cf.* Table VI). The yellow color was discharged by addition of 1 drop of glacial acetic acid, and the solution was evaporated to a semi-solid under reduced pressure. The residue was dissolved in the minimum quantity of ethyl acetate (2-10 ml.) and reprecipitated by addition of hexane. The yields of the crude but chromatographically pure (tlc) products so obtained by this procedure are summarized below in Table VI. The identity of *R*(-)-methyl 5-methyl-2-phenylhydantoate (**8**), obtained in this methylation reaction from both *R*(-)-**7** and *R*(-)-**3**, was confirmed also by a comparison of ir and mass spectra.

Acid Catalysis Method: Cyclodehydration Reactions in Dilute Hydrochloric Acid Solution of 2-Phenylhydantoic Acid and its Derivatives to 5-Phenylhydantoins.

A suspension of 200 mg. of the 2-phenylhydantoic acid derivative in 10 ml. of dilute hydrochloric acid was incubated at 94° for the time specified in Tables II, III, and IV. The nearly clear solution was filtered while hot, and the filtrate was chilled in an ice-water bath for 30 minutes. The crystalline solid was filtered off, washed with cold water, and vacuum dried (25°) overnight. The yields and optical properties of the 5-phenylhydantoins so obtained are summarized in Tables II, III, and IV.

Temperature Study of the Kinetics of Racemization.

The change in optical rotation was monitored by a synchronous scan at 280 nm on a Cary 60 Recording Spectropolarimeter. The cuvette was housed in the instrument in a thermostattable cell holder (No. 6040070) manufactured by Cary Instruments.

The stock solution of the optically active 5-phenylhydantoin in absolute ethanol (5.00 mg./ml.) was stored in a Teflon sealed glass tube at 5° prior to use. Hydrochloric acid solutions were prepared from Fisher Scientific Co. certified 1 *N* solution. For preparation of a sample, 2.80 ml. of 0.60 *N* hydrochloric acid preheated to the temperature of the experiment was pipeted into a 1.0 cm cuvette, the cuvette was returned to the thermostattable cell holder, and a baseline was recorded after ample time was given for thermal equilibration. The cuvette was removed, 0.20 ml. of the stock 5-phenylhydantoin solution was injected at the base of the acid solution at time zero, and, after stoppering and mixing, the cuvette was returned to the thermostatted cell holder. The change in optical rotation was followed for 1-2 hours. The optical changes during the first 15 minutes were not utilized in calculation of rate constants owing to the possibility of incomplete thermal equilibration.

The integrated rate expression for the rate of change of optical rotation of solutions of *R*(-)-5-phenylhydantoin (**2**) is

$$\ln \frac{\alpha_t}{\alpha_o} = -2k_{int}\, t$$

where k_{int} is the first-order rate constant for interconversion of either optical form of 5-phenylhydantoin to its enantiomer. In the present study $k_{racem} = 2k_{int}$.

Effect of *p*H on Racemization of Optically Active 5-Phenylhydantoin (**2**).

Each of four samples (200 mg.) of *R*(-)-**2** was suspended in 30 ml. of 2 *N* hydrochloric acid, each suspension was briefly warmed to effect solution, and each solution was let stand for 72 hours at room temperature. The *p*H of the four samples was adjusted, respectively, with sodium hydroxide solution to 6, 7, 8, and 9. Each sample was kept at the adjusted *p*H condition for exactly 3 minutes and those adjusted to *p*H 7, 8, and 9 were readjusted to *p*H 6. A sample was extracted with 2 x 30 ml. of ether, and the combined ether extract was dried and stripped to give chromatographically pure (tlc) 5-phenylhydantoin (**2**). The yields and optical properties of **2** are summarized in Table VII.

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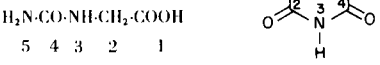
(2) The correct numberings for the hydantoic acid and hydantoin systems are shown below.



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