Non-bonded Aromatic–Amide Attraction in 5-Benzyl-3-arylhydantoins [1]

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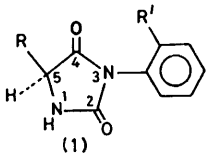
Proton and ^{13}C n.m.r. and *X*-ray diffraction evidence has been presented for non-bonded aromatic-amide attraction leading to a folded structure for hydantoin derivatives of phenylalanine in solution and in the solid state.

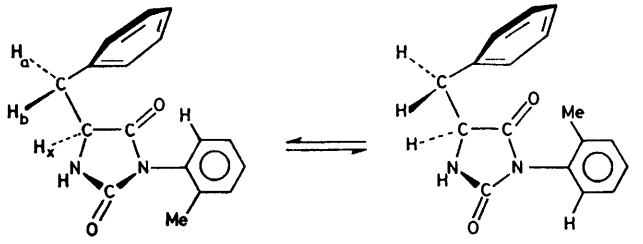
STERIC forces in aromatic substituted amides are of importance in understanding protein structure.[2] Steric interaction is generally synonymous with non-bonded repulsion. In certain amino-acid derivatives, however, there is compelling evidence for non-bonded attraction between the π-electron system and dipoles in the molecule.[3] Here we present proton and carbon-13 n.m.r. evidence for non-bonded aromatic–amide attraction in hydantoin derivatives (1) of phenylalanine in $(CD_3)_2SO$ and $CDCl_3$ solution.

The conformation of (1; R = $PhCH_2$) can be described by an appropriate combination of the three Newman projections (I), (II), and (III). On the basis of non-bonded repulsion due to crowding, one would expect limited contribution from conformation (III) in which the bulky phenyl ring is *gauche* to the larger groups (CO, NH) on the adjacent carbon atom. The preferred conformation would be expected to be (II) and (I) in which the phenyl group is near only one of the two larger groups. But, if for some reason the conformation (III) does make a major contribution, the preferred



(1)

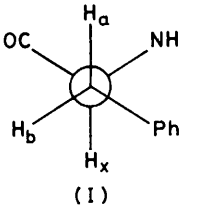
	R	R′		R	R′
a:	H	Me	f:	Pr^i	Me
b:	Me	Me	g:	*p*-$ClC_6H_4CH_2$	Me
c:	Ph	Me	h:	indol-2-ylmethyl	Me
d:	$PhCH_2$	Me	i:	$PhCH_2$	OMe
e:	$Ph(CH_2)_2$	Me			



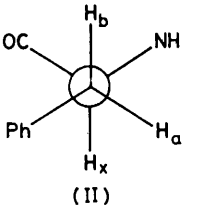
(2b) (2a)

position of the phenyl group would be over the hydantoin ring [as in (2)] instead of being away from this ring.

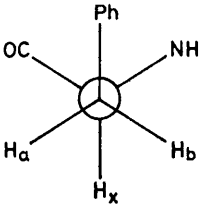
It is well known that the π-electron system of the phenyl ring produces a 'shielding cone' and a 'deshielding cone' which affect the n.m.r. spectra of protons within these cones: protons in the shielding cone are shifted upfield while protons in the deshielding cone are subjected to a downfield shift.



(I)



(II)



(III)

From a consideration of the to-scale molecular models of the hydantoin (1; R = $PhCH_2$), it became apparent that should the phenyl group be folded over the hydantoin ring in the preferred conformation (2), protons on the substituent at the 3-position of the hydantoin would be shifted upfield. This possibility provided a convenient way of examining the conformation of the hydantoin by studying the n.m.r. spectra of 3-tolylhydantoins. It can be seen from molecular models that the *o*-tolyl isomer is subject to restricted rotation about the *N*–aryl single bond and consists of the rotamers (2a) and (2b).

^1H *N.m.r. Studies.*—We have investigated the ^1H n.m.r. spectra of the series of compounds (1a—i). There is an obvious difference between the hydantoins derived from aliphatic amino-acids and those derived from aromatic amino-acids. As would be expected from considerations of symmetry, the glycine derivative (1a) shows a single peak for the methyl protons of the *o*-tolyl group. In the alanine and valine derivatives (1b) and (1f), two slightly separated methyl signals are observed. But in the hydantoins (1d), (1g), and (1h), there is clear evidence of upfield shielding of the methyl group due to the aromatic ring at C-5; the more downfield methyl signal appearing at a relatively fixed position can be ascribed to the rotamer (2b) while the higher field signal in varying positions is due to the rotamer (2a) (see Table 1).

Models show that in (1c) the phenyl group cannot be as much over the hydantoin ring as in (1d) or (1g).

TABLE 1

Proton and carbon-13 n.m.r. spectra of hydantoins in $(CD_3)_2SO$ (δ in p.p.m. from $SiMe_4$)

Compound	R	R^1	o-Me_d [a]	o-Me_u [a]	o-H_d [b]	o-H_u [b]	Population IMe_u	Ratio [d] IMe_u/IMe_d
(1a)	H	Me	2.13		7.23			
			17.70					
(1b)	Me	Me	2.14	2.10	7.23		0.55	0.45
			17.91	*17.69*				
(1c)	Ph	Me	2.21	2.07	7.27		0.63	0.37
			17.34	*17.07*				
(1d)	$PhCH_2$	Me	2.07	1.36	7.05	6.29	0.60	0.40
			17.59	*16.83*				
(1e)	$Ph(CH_2)_2$	Me	(2.20) [c]		(7.10) [c]			
(1f)	Pr^i	Me	(2.12) [c]		(7.13) [c]			
			18.02	*17.80*				
(1g)	p-$ClC_6H_4CH_2$	Me	2.10	1.43	7.10	6.37	0.62	0.38
			17.70	*16.83*				
(1h)	$C_8H_6NCH_2$	Me	2.08	1.11	7.00	6.03	0.62	0.38
			17.26	*15.97*				
(1i)	$PhCH_2$	OMe	3.73	3.57	6.87	6.37	0.40	0.60
			(*55.89*)					

[a] Subscripts d and u stand for the downfield and upfield methyl resonance, respectively. [b] Subscripts d and u stand for the downfield and upfield o-proton resonance, respectively. [c] Values in parentheses indicate single peaks of the accidentally superimposed resonance. [d] The ratio was obtained by comparing the area under the upfield methyl (IMe_u) peak with the area under the downfield methyl (IMe_d) peak. [e] Italic values indicate carbon-13 chemical shifts from TMS.

Consequently, the two methyl peaks are closer together in (1c) than in (1d). In the case of (1e) the CH_2–CH_2 link allows multiple conformations some of which place the aromatic ring in close proximity to the amide groups of the hydantoin without being directly over the hydantoin ring. This accounts for the observation that only a single peak is seen for the methyl protons of the o-tolyl group in (1e). Kopple *et al.* observed a similar effect in dioxopiperazines.[4b]

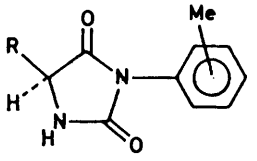
In the case of the hydantoin (1h) derived from tryptophan, the large separation between the methyl signals must be due to the stronger diamagnetic field of the indole ring in comparison to that of the phenyl ring in (1d). The o-proton of the tolyl ring shows chemical shifts (Table 1) consistent with the shielding due to aromatic ring-amide bond interaction.

In (1i) the small difference between the chemical shift of the methyl group in the two rotamers can be easily explained if the methyl protons fall outside the shielding cone of the phenyl ring. It may be noted that the o-proton in the two rotamers of (1i) shows considerable differences (0.5 p.p.m.) in chemical shift indicating that the phenyl ring is indeed folded over the hydantoin ring. Table 2 shows that the methyl protons of the m-tolyl- and p-tolyl-hydantoins derived from phenylalanine are not affected by the phenyl ring in the side-chain because they are outside the shielding cone of the folded phenyl ring. The o-proton, however, is shifted 0.4 p.p.m. upfield (see Table 2) indicating the folded conformation for all the 3-aryl-5-benzylhydantoins studied.

The aryl group at the 3-position of hydantoin is not essential for the non-bonded attractive force. Thus, upfield shift was observed for the alkyl substituents at 3-position in 5-benzyl-3-propylhydantoin. That this attractive force is quite strong was demonstrated by the observation that this upfield shift did not disappear until the temperature was raised to *ca.* 150 °C (see Table 3). A temperature dependence study of the ^1H n.m.r. spectrum of (1d) was carried out (see Figure 1). The two separate methyl peaks seen at room temperature, broadened, and coalesced at *ca.* 110 °C and then a single peak appeared as the temperature was raised further.

TABLE 2

Proton and carbon-13 n.m.r. spectra of hydantoins (δ in p.p.m. from $SiMe_4$) in $(CD_3)_2SO$



	R	Me	aryl-Me	(o)H
(2a)	H	*meta*	2.34	7.20
			(21.26)	
(2b)	$C_6H_5CH_2$	*meta*	2.25	6.83
			(21.26)	
(3a)	H	*para*	2.34	7.26
			(21.04)	
(3b)	$C_6H_5CH_2$	*para*	2.28	6.87
			(21.04)	

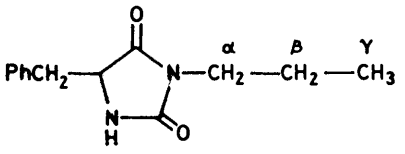
[a] Carbon-13 resonance for aryl-Me in $(CD_3)_2SO$ are given in parentheses.

Rotamer Population.—The relative proportion of the rotamers (2a) and (2b) for various hydantoins can be determined by integration of the area under the two o-methyl peaks or the two o-proton peaks (see Table 1). It is interesting to note that the rotamer (2a) in which the o-methyl group is facing the substituent (aliphatic or aromatic) at C-5 is preferred over the rotamer (2b) in which the o-methyl group is far away from the C-5 substituent. But, the reverse situation prevails in the case of (1i), the only difference here being the substitution of an OMe group for Me.

^{13}C *N.m.r. Studies.*—^{13}C N.m.r. is known to be more sensitive to structural changes than ^1H n.m.r. Thus, for (1f), the ^{13}C n.m.r. spectrum showed two peaks separated by *ca.* 0.22 p.p.m., on the other hand, when a 270 MHz ^1H n.m.r. spectrum of the same compound was recorded, the methyl signal was unresolved. In the ^{13}C

TABLE 3

Temperature study of the ^1H n.m.r. spectra for 5-benzyl-3-propylhydantoin



[$(CD_3)_2SO$]

Temperature (°C)	Chemical shifts and coupling contants (H_z from $SiMe_4$)							
	α-CH_2	β-CH_2	CH_3	$PhCH_2$	J_{av}	CH	Ph	NH
40	188.3	72.0	34.5	179.5	4.8	260.5	432	483
60	189.0	73.5	36.0	179.0	5.1	258.0		
80	189.2	75.0	37.0	179.0		255.8		
100	189.5	76.0	38.0	178.5	5.2	256.6		
120	190.7	77.5	39.0	179.0	5.3	255.6		457
150	190.5	79.0	40.3	178.5	5.6	253.0	429.5	
Δ	2.2	7.0	5.8	−1.0		−7.5	−2.5	

n.m.r. spectrum of (1d), (1g), and (1h), the separation between the signals for the tolyl methyl group was much larger (0.76, 0.87, and 1.29 p.p.m., respectively), than in the case of hydantoins from aliphatic amino-acids.

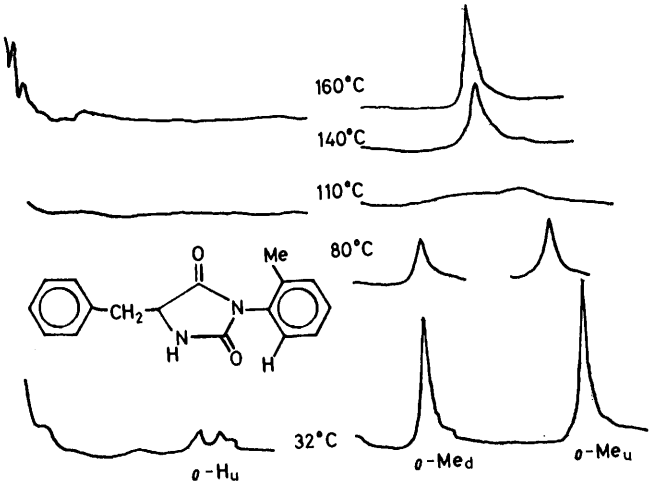


FIGURE 1 Temperature dependent ^1H n.m.r. spectra of 5-benzyl-3-(*o*-tolyl)hydantoin in $(CD_3)_2SO$

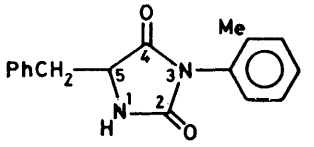
The conclusion drawn from ^1H n.m.r. spectra are thus in accord with the deductions from the ^{13}C n.m.r. spectra.

Solvent and Concentration Effect.—The ^1H n.m.r. spectrum of (1d) was slightly different in the highly polar solvent [$^2H_6$]dimethyl sulphoxide than in $CDCl_3$ (see Table 4). The concentration of the solution too affected the spectrum. Some proton peaks of (1d) shifted downfield while others moved upfield with increasing dilution of the chloroform solution. In particular, the upfield *o*-methyl and *o*-proton peaks moved downfield rapidly on dilution but the downfield *o*-methyl signal remained unchanged.

The dilution studies were made on (1d) primarily to determine whether the non-bonded attraction was intermolecular or intramolecular. With increasing dilution the higher field methyl peak moved to lower field but even in very dilute solutions there was a sizeable separation (22.5 Hz) between the two methyl signals. Hence, in chloroform solution there is evidence for intermolecular effects although the intramolecular part of the effect is of major consequence in influencing the n.m.r. resonances. In $(CD_3)_2SO$ solution the concentration effect was minimal, indicating thereby that almost all the attractive force was intramolecular. The concentration studies made on 5-benzyl-3-ethyl-2-thiohydantoin and 5-benzyl-3-(*m*-tolyl)hydantoin in $CDCl_3$ solution (see Table 5) showed that the attractive force was essentially intramolecular. In $(CD_3)_2SO$ solution the spectra of these hydantoins were unaffected upon dilution.

TABLE 4

The concentration effect of 5-benzyl-3-(*o*-tolyl)hydantoin



Concentration (M)	Chemical shifts (Hz from $SiMe_4$)					
	5-CH	$PhCH_2$	*o*-Me_d	*o*-Me_u	*o*-H_u	NH
0.418	259.5	185.0	132.0	97.0	384.0	430.0
0.0206	263.5	187.2	132.0	100.0	390.0	408.0
0.103	265.0	189.5	132.5	104.0		408.0
0.052	265.0	189.5	132.0	105.5	412.0	374.5
0.026	266.0	190.5	132.0	108.0		
0.013		191.0	132.0	109.0		
0.007			132.0	109.5		
			In $(CD_3)_2SO$			
0.400	277.0	187.5	126.0	83.5	283.5	474.0
0.048	276.0	184.0	124.5	81.0		474.0
0.024	276.0	184.5	125.0	81.0		474.0

u and d stand for the upfield and downfield peaks, respectively.

X-Ray Diffraction Studies.—The *X*-ray crystal structure of (1g) was determined and showed the same folded conformation as found in the solution n.m.r. studies (Figure 2).[5] The distance between the methyl carbon and the plane of the benzyl ring is 3.56 Å, while Bovey's

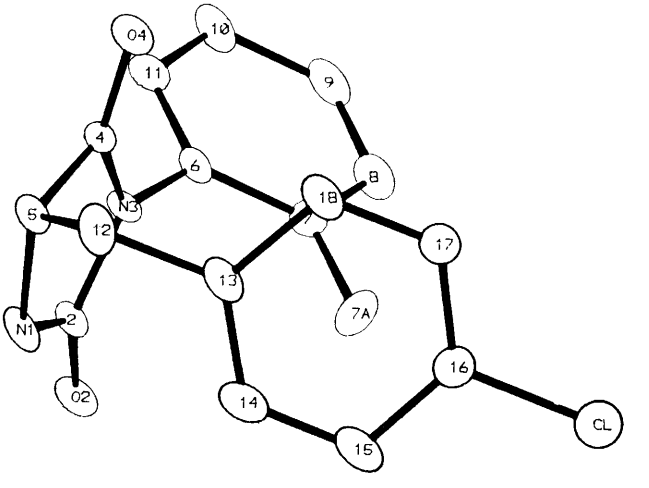
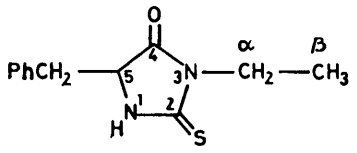


FIGURE 2 Structure of (1g)

TABLE 5

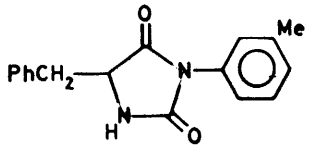
Concentration studies (^{1}H n.m.r. spectra in $CDCl_3$)

5-Benzyl-3-ethyl-2-thiohydantoin



Concentration (M)	Chemical shifts (H_2 from $SiMe_4$) β-CH_3	α-CH_2	5-CH	Ph	NH
0.158	64.5	226	257.5	434	450
0.079	66.0	227	257.0		
0.040	66.5	228.5	258.0	435	
0.020	66.5	229.0		435	380

3-*m*-Tolyl-5-benzyl hydantoin



Concentration (M)	Chemical shifts (Hz from $SiMe_4$) (*m*)CH_3	5-CH	(*o*)H	NH
0.158	140	257	415	400
0.079	141.5	258	416	380
0.040	141.3	260	418	360
0.020	142.0		420	345
0.010	142.5		420	

Z and *P* co-ordinates are 2.56 and 0.36 respectively.[6] This places the *o*-tolyl methyl group in the shielding cone of the phenyl ring. According to Bovey's Tables this should lead to 1.0 p.p.m. difference in chemical shift between the two conformations. The observed difference of 0.71 p.p.m. in solution shows that there is a substantial preferred orientations of phenyl ring over the dipolar region of the hydantoin.

Conformation of 5-Benzylhydantoins in Solution.—The n.m.r. studies reported here give clear indication for a folded conformation (2) for 5-benzylhydantoins in solution. The findings from *X*-ray diffraction studies too provide support for this conformation. To explain the concentration effect observed in $CDCl_3$ solution but not in $(CD_3)_2SO$ solution it is suggested that hydrogen bonding involving the NHCO group in the hydantoin ring creates a 'dipolar pocket' as shown in Figure 3. Non-bonded attraction between the π-electrons in the 5-benzyl group and this 'dipolar pocket' becomes important in concentrated solution. In dilute solutions this attraction disappears but the aromatic ring of the benzyl group is still folded over the hydantoin ring because of the intramolecular non-bonded interaction between the π-electrons and the dipole of the ring system.

The observed relative proportion of rotamers (2a) and (2b) are not easily accounted for. It is possible that (2a) is favoured over (2b) because of hydrophobic interaction between the *o*-methyl group and the benzyl group. In the case of (1i), it then becomes necessary to assume that the proximity of the hydrophilic oxygen of the OMe group changes the rotamer population in favour of (2b).

It has been noted earlier that there is no chemical-shift difference in the ^{1}H n.m.r. spectrum of (1d) in $(CD_3)_2SO$ solution upon dilution. The amide proton (NH) peak appears at *ca.* δ 7.90 as a broad peak, thereby indicating considerable hydrogen bonding. It is suggested that the CONH group of the hydantoin ring is hydrogen bonded to the solvent, thus excluding the intramolecular hydrogen bonding postulated for $CDCl_3$ solution. A probable conformation of the solvated hydantoin is shown in Figure 3.

The folded structure for phenylalanine hydantoins is in agreement with an earlier suggestion by Robinson and Jencks,[7] based on activity coefficient studies of peptide solutions, that there should be an intramolecular aromatic ring-amide attraction in solution. From a consideration of the vicinal couplings of the methylene protons of [^{15}N, 1-^{13}C] phenylalanine and a hydantoin derived from it, Bose and Tavares [8] concluded that one rotamer was preferred because of non-bonded attraction.

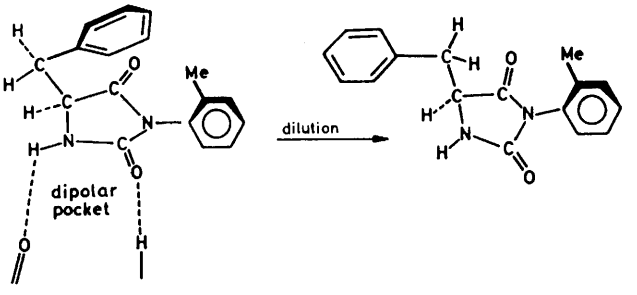


FIGURE 3 A non-bonded attractor

In case of aromatic cyclic dipeptides, both in solution and in the solid, Kopple *et al.*[4,9] and some other groups [10] have shown that the phenyl ring is folded over the diketopiperazine ring. The present study adds a new class of compounds to those that show evidence for non-bonded aromatic-amide attraction.

The non-bonded attraction between aromatic systems and suitably disposed dipoles (such as peptide bonds) can be expected to influence the conformation of peptides containing aromatic amino-acids. Such attraction may modify the structure of proteins and affect substrate–enzyme binding.

EXPERIMENTAL

The ^{13}C n.m.r. spectra were recorded as a pulsed Fourier transformed n.m.r. (22.6 MHz; Brucker HX-90) applied with broad bond proton decoupling and the deuterium signal lock. The samples were mostly dissolved in $(CD_3)_2SO$ and $SiMe_4$ added as an internal standard in a 10 mm n.m.r. tube.

The assignment of carbon resonance was undertaken by the off-resonance decoupling method. Proton n.m.r. spectra were recorded on a Varian HA-60 spectrometer with $SiMe_4$ as an internal standard. Mass spectral measurements were made on an Hitachi–Perkin-Elmer RMU-7 spectro-

TABLE 6

Spectral data of hydantoins

Compd.	R	R′	X	Yield (%)	M.p. (°C)	m^+/e	I.r. (ν/cm^{-1})	δ[(CD$_3$)$_2$SO]
(1a)	H	C$_6$H$_4$Me-*o*	O	82	153	190	1 698	8.40 (1 H, s), 6.95—7.40 (4 H, m), 4.08 (2 H, s), 2.13 (3 H, s)
(1b)	Me	C$_6$H$_4$CH$_3$-*o*	O	36	112—113	204	1 701	8.40 (1 H, s), 7.18—7.38 (4 H, m), 4.35 (1 H, q), 2.14 (1.4 H, s), 2.10 (1.6 H, s), 1.35 (3 H, d)
(1e)	Ph	C$_6$H$_4$Me-*o*	O	63	198—199	266	1 709	9.82 (1 H, s), 7.20—7.48 (9 H, m), 5.54 (0.4 H, s), 5.42 (0.6 H, s), 2.21 (1.2 H, s), 2.07 (1.8 H, s)
(1e)	Ph(CH$_2$)$_2$	C$_6$H$_4$Me-*o*	O	2	110	294	1 695	8.50 (1 H, s), 7.00—7.40 (9 H, m), 4.18 (1 H, t), 2.75 (2 H, t), 1.80—2.40 (2 H, m), 2.20 (3 H, s)
(1f)	Pr^i	C$_6$H$_4$Me-*o*	O	54	182—183	232	1 709	8.83 (1 H, s), 7.10—7.38 (4 H, m), 4.20 (1 H, d), 2.50 (1 H, m), 2.12 (3 H, s), 1.08 (3 H, d), 0.90 (3 H, d)
(1g)	*p*-ClC$_6$H$_4$CH$_2$	C$_6$H$_4$Me-*o*	O	48	141—143	314	1 709	8.50 (1 H, s), 7.15—7.38 (7.6 H, m), 6.37 (0.4 H, d), 4.60 (1 H, t)
				(Found: C, 66.0; H, 4.75; N, 8.91%)				8. C$_{17}$H$_{15}$N$_2$O$_2$Cl requires C, 65.10; H, 4.77; N,
(1h)	C$_8$H$_5$NCH$_2$ (Indole methylene)	C$_6$H$_4$Me-*o*	O	25	209—210	309	1 709	8.42 (1 H, d), 6.80—7.70 (9.6 H, m), 6.03 (0.4, d), 4.60 (1 H, t), 3.25 (2 H, d), 2.08 1.2 H, s), 1.11 (1.8 H, s)
(1i)	PhCH$_2$	C$_6$H$_4$OMe-*o*	O	63	164—165	296	1 709	8.37 (1 H, s), 7.30 (5 H, s), 6.80—7.30 (3.4 H, m), 6.35 (0.6 H, d), 4.52 (1 H, t), 3.73 (1.8 H, s), 3.57 (1.2 H, s), 3.08 (2 H, d)
(2a)	H	C$_6$H$_4$Me-*m*	O	78	119—120	190	1 695	8.25 (1 H, s), 7.05—7.50 (4 H, m), 4.06 (2 H, s), 2.35 (3 H, s)
(2b)	PhCH$_2$	C$_6$H$_4$Me-*m*	O	53	122	280	1 695	8.47 (1 H, s), 7.32 (5 H, s), 7.18~7.31 (2 H, m), 6.80 (2 H, broad s), 3.15 (2 H, d), 2.25 (3 H, s)
(3a)	H	C$_6$H$_4$Me-*p*	O	68	211—212	190	1 709	8.22 (1 H, s), 7.25 (4 H, s), 4.06 (2 H, s), 2.33 (3 H, s)
(3b)	PhCH$_2$	C$_6$H$_4$Me-*p*	O	68	131	280	1 701	8.50 (1 H, s), 7.28 (5 H, s), 7.20 (2 H, d), 6.85 (2 H, d), 4.52 (1 H, t), 3.06 (2 H, d), 2.26 (2 H, s)
(4) *	PhCH$_2$	Pr^n	O		143	232	1 695	8.05 (1 H, s), 7.20 (5 H, s), 4.34 (1 H, t), 2.99 (2 H, d), 1.20 (2 H, m), 0.58 (3 H, t)
(5)	PhCH$_2$	Et	S	74	148—149	234	1 739	8.05 (1 H, s), 7.30 (5 H. s), 4.64 (1 H, t), 3.56 (2 H, q), 3.10 (2 H, d), 0.75 (3 H, t)

* This compound was kindly supplied by Dr. John Kryschuk.

meter at an ionization potential of 70 eV and the samples were introduced by a direct probe.

The i.r. spectra were recorded as Nujol mulls on a Hitachi–Perkin-Elmer model 247 grating spectrometer. The elemental analyses were undertaken at Alfred Bernhardt Mikro Laboratory in West Germany.

Formation of Hydantoin Derivatives.—Hydantoins were prepared following the method of Finkbeiner.[11] The synthesis of a typical hydantoin is described below.

5-Benzyl-3-o-tolylhydantoin (1d).—DL-Phenylalanine (4.15 g, 0.025 mol, Aldrich Chemical) was dissolved in an ice-cold solution of KOH (1.70 g, 0.03 mol) in water (45 ml). *o*-Tolyl isocyanate (4.0 g, 0.03 mol, Aldrich Chemical) was added to the amino-acid solution during 20 min. The reaction mixture was warmed to 60—70 °C for 2 h; the by-product, a urea derivative, was precipitated from the solution. The filtrate was acidified with enough concentrated hydrochloric acid to precipitate the hydantoic acid which was collected by filtration. The hydantoic acid derivative was suspended in dilute hydrochloric acid (1 : 1) (20 ml) and was refluxed until it dissolved (a few hours) effecting cyclization to the hydantoin. The hydantoin separated on cooling of the solution and was filtered off and recrystallized from absolute ethanol; yield 6.5 g (88%), m.p. 134—135 °C, mass spectrum: *m/e* 280; i.r. $\nu_{max.}$ 1 701 cm^{-1} (NHCO); ^{1}H n.m.r. δ 7.95 (1 H, s), 6.31—7.48 (9 H, m), 4.62 (1 H, t), 3.18 (2 H, d), 6.29 (1.2 H, s), and 7.05 (1.8 H, s) (Found: C, 72.9; H, 5.6; N, 10.1. C$_{17}$H$_{16}$N$_2$O$_2$ requires C, 72.98; H, 5.68; N, 10.05%).

Analytical and spectral data are summarized in Table 6.

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