Synthesis of 5-Benzoyl-5-phenyl- and 5-Phenylhydroxymethyl-5-phenylhydantoins as Potential Anticonvulsants

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A series of 5-benzoyl-5-phenyl- and 5-phenyl-5-phenylhydroxymethylhydantoins have been synthesized from the reaction of urea, *N*-monosubstituted ureas and *sym-N,N*-disubstituted ureas with phenyltriketone hydrate, *via* a pinacol-pinacolone-type rearrangement mechanism. The compounds were evaluated for anticonvulsant activity in mice.

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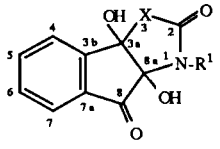
This communication describes the preparation and anticonvulsant properties of a number of 5,5-disubstituted hydantoins related to 5,5-diphenylhydantoin (phenytoin), and obtained from a novel molecular rearrangement reaction.

We have previously reported on the reaction of indane-1,2,3-trione hydrate (ninhydrin) with amides and ureas [2-4] to give 2,3,3a,8a-tetrahydro-3a,8a-dihydroxyindeno-[2,1-*b*]pyrrole-2,8-diones **1** and 2,3,3a,8a-tetrahydro-3,8a-dihydroxyindeno[2,1-*b*]imidazole-2,8-diones **2**, respectively. Interestingly, when the linear diphenyltriketone hydrate (**3**) was reacted with urea in refluxing benzene, the



1, X = CH_2
2, X = N-R^2

expected 4-benzoyl-2,3,4,5-tetrahydro-4,5-dihydroxy-5-phenylimidazol-2-one (**5**) was not obtained. The product, which was isolated in 68% yield, did not exhibit the expected -OH absorption bands in its ir spectrum, and elemental analysis indicated loss of a water molecule subsequent to product formation. Analysis of the product by ^{1}H-nmr spectroscopy revealed the presence of two deuterium oxide-exchangeable protons, and ^{13}C-nmr spectroscopy (Table 1) clearly showed that three carbonyl groups and one quaternary carbon atom were present in the molecule. These data, together with the unusually high wavenumber values for the carbonyl absorptions in the ir spectrum, suggested the presence of a hydantoin ring system in the molecule [5]. Mass spectral analysis of the product afforded a cracking pattern characteristic of that of a 5,5-disubstituted hydantoin derivative [6] showing ions at 280 (M^+), 175 ($M-C_6H_5CO$), 105 ($C_6H_5C\equiv O^+$), 104 ($C_6H_5C\equiv NH$), and 43 ($HN=C=O$) m/z (see Table 2 and Scheme 1), from which the identity of the product was determined to be 5-benzoyl-5-phenylhydantoin (**6a**). As can be seen in Scheme 1, the mass spectral fragmentation

Table 2

Mass Values of Fragments in the Electron Impact Mass Spectra of 5-Benzoyl-5-phenylhydantoin and its *N*-Substituted Derivatives

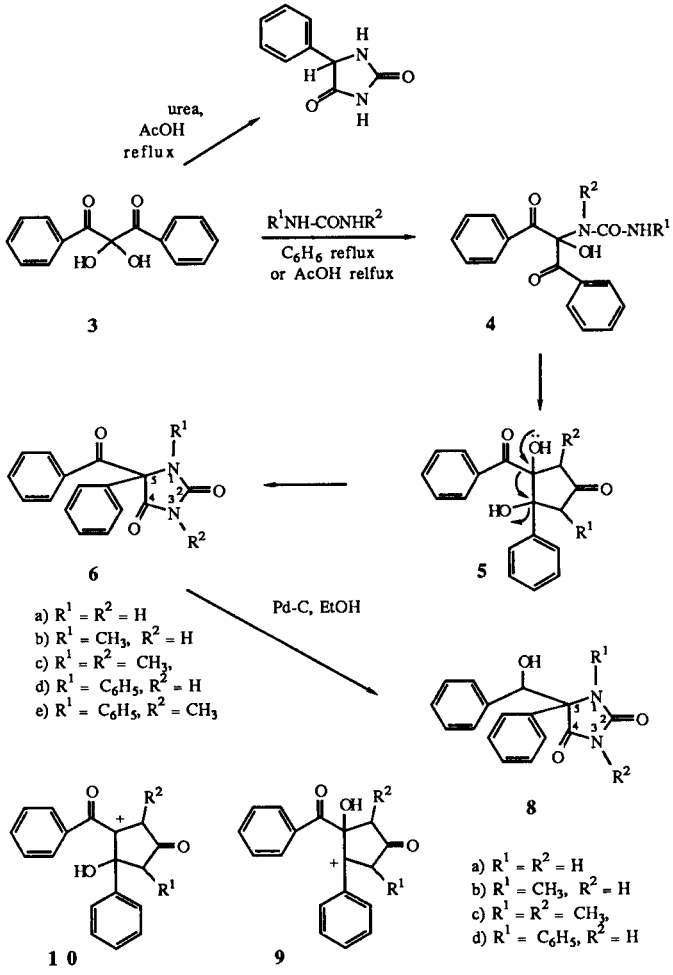
Compound	m/z			
	M+	Fragment A	Fragment B	Fragment C
6a	280	175	104	43
6b	294	189	118	43
6c	308	203	118	57
6d	356	251	180	43
6e	370	265	180	57

Table 1

Carbon-13 Chemical Shifts [a] of 5-Benzoyl-5-phenylhydantoin Derivatives

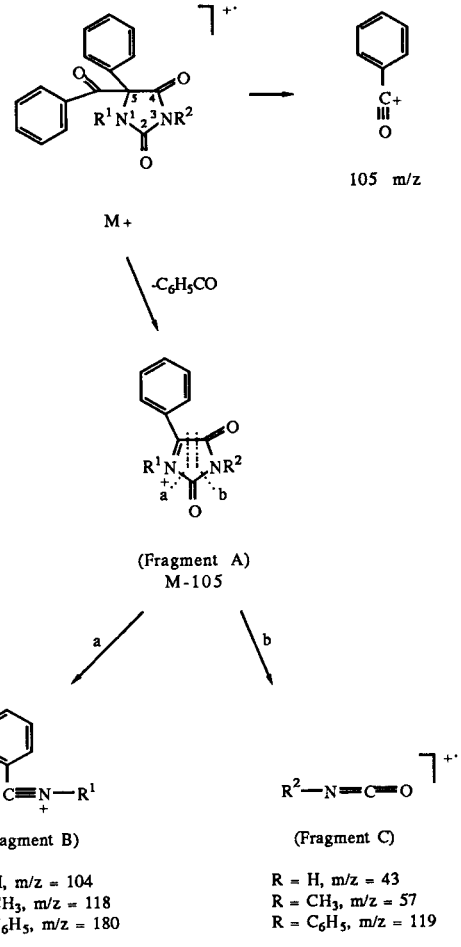
Compound	δ (ppm) [b]					
	Ar-*C*=O	C-2	C-4	C-5	N-1-CH_3	N-3-CH_3
6a	192.49 s	156.70 s	170.90 s	75.70 s	-	-
6b	191.79 s	155.26 s	169.69 s	80.98 s	25.99 q	-
6c	191.40 s	154.87 s	168.32 s	80.00 s	25.35 q	26.39 q
6d	192.08 s	154.75 s	168.38 s	74.48 s	-	-

[a] Spectra were proton coupled and were run in DMSO-d_6 at 310° K using TMS as internal standard. [b] Abbreviations are: s (singlet), and q (quartet).



Scheme 1

Mass Spectral Fragmentation of 5-benzoyl-5-phenylhydantoins



pathway for these 5,5-disubstituted hydantoins also provides a diagnostically useful means for determining the *N*-substitution pattern in the molecule.

N-Methylurea, *sym*-*N,N*-dimethylurea, and *N*-phenylurea all reacted with **3** in a similar manner to urea, to give the corresponding *N*-substituted 5-benzoyl-5-phenylhydantoins, **6b**, **6c**, and **6d**, respectively (see Tables 1 and 2 for ^{13}C-nmr and mass spectral data). *Sym*-Diphenylurea, however, failed to react with **3**.

The mechanism of formation of **6a** most likely procedes *via* initial generation of the ureide, **5**, in a two-step manner analogous to the formation of **2** from the reaction of urea with ninhydrin [4]. Failure to isolate **5** probably results from its spontaneous conversion to **6a**, *via* a pinacol-pinacolone type molecular rearrangement. This rearrangement most likely involves formation of carbocation **9**, rather than the alternative, less stable carbocation **10**, with migration of the benzoyl group to give **6a**. From nmr and mass spectral analysis of the product from the reaction of *N*-methylurea with **3**, only the N-1-CH_3 product, **6b**, was formed; none of the isomeric N-3-CH_3 compound was detected in the reaction mixture. The structural assignment was based upon the δ-value of N-CH_3 group resonance (δ 2.68), which is indicative of a -C-N(CH_3)-CO- moiety, rather than a -CO-N(CH_3)-CO- moiety [7], and also upon the presence of an intense ion of m/z 118, attributable to the $C_6H_5C\equiv N^+$-CH_3 fragment (route a, Scheme 1), and the absence of an ion of m/z 57 in the mass spectrum. Thus, if the rearrangment mechanism suggested above is operating, the ureide **4** (R^1 = H, R^2 = CH_3), and not **4** (R^1 = CH_3, R^2 = H), is formed initially, prior to cyclization and rearrangement.

Reaction of *N*-phenylurea with **3** similarly afforded an *N*-phenyl derivative of **6a**; mass spectral analysis of the product showed a strong ion of m/z 180 ($C_6H_5C\equiv N^+$-C_6H_5) but no ion of m/z 119 (C_6H_5-N=C=O) was observed. In addition, the compound could be *N*-methylated with diazomethane to form **6e**, which exhibited an *N*-methyl resonance at δ 3.09 (-CO-N(CH_3)-CO-) in its ^{1}H-nmr spectrum, and showed ions of m/z 180 and m/z 57 (CH_3-N=C=O) in its mass spectrum. These data prove conclusively

that phenyl substitution is at N-1 in the above compounds.

Compounds **6b**, **6c** and **6d** could also be prepared by the reaction of the appropriate *N*-substituted urea with **3** in refluxing glacial acetic acid. Although in some cases, yields of products using this method were lower than those obtained in refluxing benzene, the decreased reaction time in the former case (12 minutes compared to 18 hours) may be an advantage. Surprisingly, the reaction of urea with **3** in refluxing glacial acetic acid did not afford **6a**, but gave 5-phenylhydantoin (**7**) and benzoic acid; these products presumably result from facile acid-catalyzed C-debenzoylation of the initially generated **6a**.

Catalytic hydrogenation of compounds **6a-6d** with palladium-on-charcoal in ethanol afforded the corresponding 5-phenyl-5-phenylhydroxymethylhydantoins, **8a-8d**, in good yield (68-90%). These compounds were considered to be interesting analogues of the pharmacologically active 5,5-diphenylhydantoin, with potential as anticonvulsant agents. In each case the reduction products were obtained as mixtures of the two possible diastereomeric alcohols, which were not separated. Compound **8b** could also be prepared by hydrogenation of **6b** with palladium-on-charcoal in glacial acetic acid-perchloric acid media, and from the reaction of **6b** with diborane in THF, but yields were comparatively low (*i.e.* 57% and 16%, respectively).

Compounds were submitted for anticonvulsant evaluation to the Antiepileptic Drug Development Program of the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke. Evaluations of compounds were carried out as suspensions in 30% polyethylene glycol (5-benzoyl-5-phenyl derivatives), or as solutions in methylene chloride (5-phenyl-5-phenylhydroxymethyl derivatives), in male mice (Carworth Farms, #1) at three dose levels (30, 100, and 300 mg/kg i.p.). Compounds were evaluated in the maximal electroshock seizure test (MES), and the subcutaneous pentylenetetrazol (Metrazol®) seizure threshold test (scMet); and for neurotoxicity in the rotorod test. Compounds **6c** and **8b** both showed activity at below 100 mg/kg in the above tests, but were toxic. Compound **6b** was active at < 100 mg/kg in all tests, and showed no neurotoxicity.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R24 Spectrometer and the ^{13}C-nmr spectra were recorded on a Bruker WP80 Spectrometer using tetramethylsilane as internal reference. Mass spectra (electron impact) were obtained on an A.E.I. MS12 Spectrometer operating at a probe temperature of 200° and an ionization voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer 237 grating Spectrophotometer. Catalytic hydrogenations were carried out at atmospheric pressure on a Gallenkampf all glass hydrogenator and at higher pressure on a Baskerville electromagnetically agitated autoclave. All melting points are uncorrected and were taken on a Reichert hot-stage microscope. Evaporations were carried out under reduced pressure on a rotary evaporator. Yields of solids refer to products obtained prior to recrystallization, unless otherwise stated.

5-Benzoyl-5-phenylhydantoin (**6a**).

Method A.

Finely powdered urea (0.60 g, 0.01 mole) was added to a solution of diphenyltriketone hydrate (**3**) (2.5 g, 0.01 mole) in benzene (200 ml) and the mixture heated under reflux for 18 hours. Water generated during the course of the reaction was removed using a Dean and Stark water trap. The resulting precipitate was filtered to afford 1.92 g (68%) of **6a** as a white crystalline powder, mp 189-191°; ir (liquid paraffin): 1790, 1725, 1690-1670 (C = O) cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 11.31 (bs, 1H, exchangeable with deuterium oxide, N-3-H), 9.50 (s, 1H, exchangeable with deuterium oxide, N-1-H), 7.82-7.09 (m, 10H, aromatic); ms: m/z (%) 280 (M$^+$) (4), 175 (77), 105 (10), 104 (100), 43 (35).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.52; H, 4.50; N, 9.81.

Method B.

A mixture of diphenyltriketone hydrate (2.56 g, 0.01 mole) and urea (0.60 g, 0.01 mole) was dissolved in glacial acetic acid (25 ml) and the solution heated at reflux temperature for 12 minutes. On cooling, a crystalline deposit was obtained, which was filtered to afford 1.06 g (61%) of 5-phenylhydantoin (**7**) as a white powder, mp 176-178° (lit 179-180° [8]; ir and ms spectra were identical to previously reported data [5,6]. The mother liquors from the reaction were evaporated and the residue treated with saturated sodium bicarbonate solution (10 ml). The resulting solution was washed with ethyl acetate (2 x 20 ml), acidified with hydrochloric acid (10% v/v, 20 ml) and extracted with diethyl ether (2 x 30 ml). The combined extracts were dried, filtered and evaporated to dryness, the residual solid was triturated with diethyl ether, and filtered to give benzoic acid (0.12 g, 60%).

5-Benzoyl-*N*-3-methyl-5-phenylhydantoin (**6b**).

The reaction of diphenyltriketone hydrate with *N*-methylurea *via* Method A above afforded 1.80 g (61%) of **6b** as a white crystalline compound, mp 194-196°; ir (liquid paraffin) 1778, 1725 (sh), 1710, 1690 (sh) cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 11.66 (bs, 1H, exchangeable with deuterium oxide, N-3-H), 8.11-7.01 (m, 10H, aromatic), 2.68 (s, 3H, N-1-CH$_3$); ms: m/z (%) 294 (M+, 10), 189 (34), 118 (99), 43 (9).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.80; N, 9.52. Found: C, 69.14; H, 4.80; N, 9.52.

Compound **6b** was also prepared in 51% yield from method B above.

5-Benzoyl-*N*-1,*N*-3-dimethyl-5-phenylhydantoin (**6c**).

The reaction of diphenyltriketone hydrate with *sym-N,N*-dimethylurea *via* method A above afforded 2.25 g (73%) of **6c** as a white crystalline powder, mp 101-104°; ir (liquid paraffin) 1772, 1725 (sh), 1715, 1690, cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 8.06-7.10 (m, 10H, aromatic), 2.98 (s, 3H, N-3-CH$_3$), 2.68 (s, 3H, N-1-CH$_3$); ms: m/z (%) 308 (M+, 12), 203 (76), 118 (100), 57 (63).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.22; H, 5.31; N, 9.10.

Compound **6c** was also prepared in 63% yield from method B above.

5-Benzoyl-*N*-1,5-diphenylhydantoin (**6d**).

The reaction of diphenyltriketone hydrate with *N*-phenylurea *via* method A above, afforded 1.12 g (31%) of **6d** as a white cyrstalline solid, mp 212-214°; ir (liquid paraffin): 1795, 1730, 1685 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.02 (bs, 1H, exchangeable with deuterium oxide, N-3-H), 8.09-7.10 (m, 15H, aromatic); ms: m/z (%) 356 (M+, 45), 251 (87), 180 (67), 105 (100), 43 (22).

Anal. Calcd. for $C_{22}H_{16}N_2O_3$: C, 74.14; H, 4.53; N, 7.86. Found: C, 74.10; H, 4.54; N, 7.91.

An improved yield (55%) of compound **6d** was obtained using the conditions in method B above.

5-Benzoyl-*N*-3-methyl-*N*-1,5-diphenylhydantoin (**6e**).

To a solution of 5-benzoyl-*N*-1,5-diphenylhydantoin (3.58 g, 0.1 mole) in dry THF (20 ml) was added dropwise, with stirring, an ethereal solution of diazomethane (generated from *N*-methyl-*N*-nitrosotoluene-4-sulfonamide [9]) until the reaction solution retained a permanent yellow coloration. Glacial acetic acid (~10 ml) was then added to destroy the excess diazomethane, and the solution was evaporated to dryness. The residual solid was crystallized from diethyl ether to afford white crystals of **6e**, 3.12 g (84%), mp 165-168°; ir (liquid paraffin): 1780, 1725 (sh), 1720, 1690 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.10-6.69 (m, 15H, aromatic), 3.09 (s, 3H, N-3-CH_3); ms: m/z (%) 370 (M+, 30), 265 (93), 180 (100), 57 (3).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 75.00; H, 4.95; N, 7.62.

5-Phenyl-5-phenylhydroxymethylhydantoin (**8a**).

To a solution of 5-benzoyl-5-phenylhydantoin (0.56 g, 0.02 mole) in absolute ethanol (50 ml) was added 5% palladium-on-charcoal (0.5 g) and the mixture hydrogenated at atmospheric pressure until no further uptake of hydrogen was observed. The catalyst was then removed by filtration, and the filtrate evaporated to dryness. The residual solid was crystallized from 96% ethanol to afford 0.51 g (90%) of **8a** as white crystals, mp 140-147°; ir (liquid paraffin): 3450, 3250 (-OH), 1742, 1720 (sh), 1710 (C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.78 (bs, 1H, exchangeable with deuterium oxide, N-3-H) 8.36 (s, 1H, exchangeable with deuterium oxide, N-1-H), 7.31-6.80 (m, 10H, aromatic), 6.08 (s, 1H, exchangeable with deuterium oxide, -OH), 5.14 (2 x s, 1H, diastereomeric C-H's); ^{13}C-nmr (DMSO-d_6): δ 175.21 and 174.11 (2 x s, diastereomeric C-4's), 155.78 and 156.04 (2 x s, diastereomeric C-2's), 76.82 and 76.17 (2 x d, diastereomeric C(OH)'s), 72.53 and 72.32 (2 x s, diastereomeric C-5's).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.35; H, 4.71; N, 10.20.

N-1-Methyl-5-phenyl-5-phenylhydroxymethylhydantoin (**8b**).

Method A.

To a solution of 5-benzoyl-*N*-1-methyl-5-phenylhydantoin (0.59 g, 0.02 mole) in glacial acetic acid (50 ml) was added perchloric acid (70%, 0.5 ml) and 5% palladium-on-charcoal (0.5 g), and the mixture hydrogenated under slight pressure (0.25-0.5 atmosphere) until no further uptake of hydrogen was observed. The catalyst was then removed by filtration, the filtrate neutralized with sodium bicarbonate solution, and the resulting solution extracted with diethyl ether (3 x 50 ml). The combined extracts were dried over anhydrous magnesium sulfate and the solvent evaporated to dryness. The residue was crystallized from diethyl ether to afford 0.34 g (57%) of **8b** as a white crystalline solid, mp 163-170°; ir (liquid paraffin): 3460, 3390, 3180-3140, 3060, 1760, 1718 (sh), 1709, cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.85 (bs, 1H, exchangeable with deuterium oxide, N-3-H), 8.00-6.91 (m, 10H, aromatic), 6.12 (s, 1H, exchangeable with deuterium oxide, -OH), 5.73 (2 x s, 1H, diastereomeric C-H's), 2.47 (s, 3H, N-1-CH_3).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.54; H, 5.51; N, 9.60.

Method B.

To a solution of 5-benzoyl-*N*-1-methyl-5-phenylhydantoin (0.59 g, 0.02 mole) in absolute ethanol (50 ml) was added 5% palladium-on-charcoal (0.5 g) and the mixture was hydrogenated following the procedure described for the synthesis of **8a**, to afford **8b** in 83% yield.

Method C.

Diborane in THF (15 ml of a 1 molar solution) was added to 5-benzoyl-*N*-1-methyl-5-phenylhydantoin (0.59 g, 0.02 mole) under anhydrous conditions and the solution heated under anhydrous reflux for 19 hours. Hydrochloric acid solution (10% v/v) was then added dropwise until the effervescence ceased. The reaction mixture was then poured into water (50 ml) and extracted with diethyl ether (3 x 50 ml). The combined ether extracts were dried over magnesium sulfate, filtered and evaporated to dryness. The residual gum was triturated with dry diethyl ether to afford 0.09 g (16%) of **8b** as an off-white solid.

N-1,*N*-3-Dimethyl-5-phenyl-5-phenylhydroxymethylhydantoin (**8c**).

To a solution of 5-benzoyl-*N*-1,*N*-3-dimethyl-5-phenylhydantoin (0.62 g, 0.02 mole) in absolute ethanol (50 ml) was added 5% palladium-on-charcoal (0.5 g). The mixture was then hydrogenated following the procedure described for the synthesis of **8a**, to afford 0.52 g (84%) of **8c** as a white crystalline powder, mp 110-112°; ir (liquid paraffin): 3460 (sh) 3335, 1770, 1698 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.72-6.91 (m, 10H, aromatic), 6.18 (bs, 1H, exchangeable with deuterium oxide, -OH) 5.77 (2 x s, 1H, diastereomeric C-H's), 2.76 (2 x s, 3H, diastereomeric N-3-CH_3's), 2.64 (2 x s, 3H, diastereomeric N-1-CH_3's).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.44; H, 5.90; N, 9.01.

N-1,5-Diphenyl-5-phenylhydroxymethylhydantoin (**8d**).

To a solution of 5-benzoyl-N-1, 5-diphenylhydantoin (0.72 g, 0.02 mole) in absolute ethanol (50 ml) was added 5% palladium-on-charcoal (0.5 g). The mixture was then hydrogenated following the procedure described for the synthesis of **8a**, to afford 0.49 g (68%) of **8d** as a white crystalline solid, mp 165-169°; ir (liquid paraffin): 3490, 3265, 3160, 1765, 1725 (sh), 1710 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.22 (bs, 1H, exchangeable with deuterium oxide, N-3-H), 7.91-6.50 (m, 15H, aromatic), 6.15 (bs, 1H, exchangeable with deuterium oxide, -OH), 5.70 (2 x s, 1H, diastereomeric C-H's).

Anal. Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 74.01; H, 5.15; N, 7.82.

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