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New Dipyrrinonols Derived from 2,3-Dihydro-1*H*-pyrrol-3-ones

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Summary. The reaction of 2-aminomethylene-2,3-dihydropyrrol-3(1*H*)-ones with ethyl bromoacetate, chloroacetonitrile, or dilute HCl gave rise to a series of methine dyes, namely 1-aryl-2-[3-hydroxy-1-aryl-4,5-diphenyl-1*H*-pyrrol-2-yl]methylene-4,5-diphenyl-2,3-dihydropyrrol-3(1*H*)-ones.

Keywords. Dihydropyrroles; Oxonols; Dipyrrins.

Introduction

Almost a century ago, *Friedländer* reported that treatment of indoxylaldehyde with dilute hydrochloric acid leads to formation of the 2-(3-hydroxy-1*H*-indol-2-ylmethylene)-1,2-dihydroindol-3-one [1]. Similar results were obtained by the synthesis of oxygenated dipyrrins from the reaction of 3-hydroxypyrroles or 4-oxo-Δ^2-pyrrolines with triethyl orthoformate or formic acid [2–5]. Attempted hydrolysis of a 2-(dialkylamino)methylene-2,3-dihydropyrrol-2-one had also led to oxygenated dipyrrins [6]. While in the aforementioned cases dipyrrins were prepared from 3-hydroxypyrroles bearing no substituents at the N atoms, we want to report that *N*,*N*′-diaryldipyrrins may also be efficiently prepared from readily accessible *N*-aryl-2-aminomethylene-4,5-diphenyl-2,3-dihydropyrrol-3(1*H*)-ones **1a**–**1e**.

Results and Discussions

The preparation of the Δ^4-pyrrolinones **1a**–**1e** from diphenylcyclopropenone and glyoxal bisimines has been reported earlier [7]. Recently, we reported the formation of spiro[1,3-benzodioxole-2,2′-(2′,3′-dihydro-1′*H*-pyrrol-3′-ones)] and 3,4-dichloro-7-methoxy-5-(4-methoxyphenyl)-5,10-dihydrophenazine-1,2-dione from the reaction of Δ^4-pyrrolinones and 3,4,5,6-tetrachloro-1,2-benzoquinone [8]. We became interested in reacting **1a**–**1e** with reagents like α-haloesters or -nitriles

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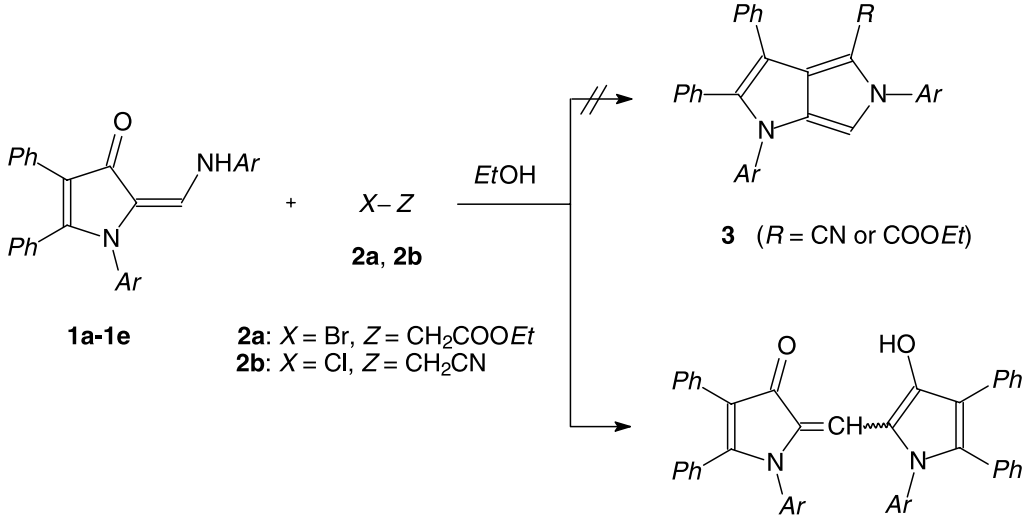
aimed at preparing 1,5-dihydropyrrolo[3,4-*b*]pyrroles **3**. Instead, we obtained the monomethine dyes **4a**–**4e** [9] in yields of 35–87% (based on converted starting material **1a**–**1e**) by warming **1a**–**1e** with ethyl bromoacetate (**2a**) or chloroacetonitrile (**2b**) in refluxing ethanol. *E.g.*, in the reaction mixture of **1b** with **2a**, *p*-toluidine as a coupled product is found as well as unreacted **1b** (18%) and **4b** (87%), whereas when **1b** was reacted with chloroacetonitrile (**2b**) the yield of **4b** was 68% with 20% of unreacted pyrrole. These values demonstrate that the yields are satisfactory in most cases (see Table 1).

Table 1. Isolated yields of dipyrrins **4a**–**4e**

Entry	*Ar*	*Z*	*X*	Method	Time (h)	Compound	Yield (%)
1	4-*Me*C_6H_4	CH_2CO_2Et	Br	A	24	**4b**	87
2	4-*Me*C_6H_4	CH_2CN	Cl	A	32	**4b**	68
3	4-*Me*OC_6H_4	CH_2CO_2Et	Br	A	15	**4c**	77
4	*Ph*	CH_2CO_2Et	Br	A	16	**4d**	50
5	4-*Me*OC_6H_4	–	–	B	2	**4c**	28
6	2-*Me*C_6H_4	–	–	B	4	**4a**	53
7	2-*Me*C_6H_4	CH_2CO_2Et	Br	A	6	**4a**	13
8	4-HOC_6H_4	–	–	B	4	**4e**	14
9	4-HOC_6H_4	CH_2CO_2Et	Br	A	30	**4e**	35

Method A: An excess of $BrCH_2$ CO_2Et or $ClCH_2CN$ in refluxing ethanol; *Method B*: 0.1 *N* HCl in refluxing ethanol



1, **4**	**a**	**b**	**c**	**d**	**e**
Ar	2-*Me*C_6H_4	4-*Me*C_6H_4	4-*Me*OC_6H_4	*Ph*	4-HOC_6H_4

Scheme 1

The structural assignments of **4a**–**4e** are based on the following findings: In the ^{13}C NMR spectra a medium intense to weak signal at $\delta = 167.3$–167.6 ppm was generally assigned to the carbonyl carbon atom and a signal between $\delta = 149.3$–149.6 ppm was assigned to C-3′ bearing the hydroxyl group. ^{13}C-135/90-DEPT spectra exhibited only signals with positive amplitude, a weak signal between $\delta = 114.9$–115.7 ppm confirmed the presence of a central methine carbon atom. Whereas the structures of **4a**–**4e** as a whole are clearly not symmetrical, the ^{13}C signal intensities are highly varying, indicating that minute shift differences of ''nearly equivalent'' carbon atoms in the aryl and phenyl groups attached to the different pyrrole rings cannot be resolved by the 75 MHz instrument used. In **4a** the 2-tolyl groups lack an internal vertical plane of symmetry (which is, however, present in all phenyl groups and *N*-aryl groups of **4b**–**4e**), so the spectrum of **4a** is more complex than spectra of **4b**–**4e**. The latter four compounds show their methine carbon signals in the range of $\delta = 115.4$–115.7 ppm and uniformly 8 aryl-*C*H signals. Two of them are of medium intensity at 125.5–125.8 and 128.5–128.6 ppm, whereas all other aryl-CH-signals are relatively intense and probably represent four carbon atoms each. Compounds **4b**–**4e** also show uniformly seven signals for quaternary sp^2-carbon atoms besides the carbonyl signal.

Special attention has been devoted to the magnitude of the ^3J(C,H) coupling of the carbonyl C-atom with the methine proton. From a ^{1}H coupled ^{13}C spectrum of **4b** at 125 MHz, a value of 6.2 Hz could be extracted. A ^{1}H inversely correlated HMBC experiment [10] did confirm both the signal assignments and the low ^3J(C,H) value found in the proton coupled spectrum. These findings will be discussed below.

In the ^{1}H NMR spectra methine proton signals were located at $\delta = 5.90$ and 5.92 ppm for **4a** and between 6.35 and 6.49 ppm (one signal only) for **4b**–**4e**, in addition, low field OH proton signals were found between 13.12 and 13.50 ppm. This chemical shift range is at the low field edge of that expected for COO*H* and indeed compounds **4** may be envisaged as doubly vinylogous carboxylic acids. An intramolecular hydrogen bridge might also contribute to the high chemical shift but it would have to involve an eight-membered ring. While 6H-singlets are observed at 3.76 for 4-OCH$_3$ in **4c** and 2.29 ppm for 4-CH$_3$ in **4b**, the signal for the 2-CH$_3$-groups in **4a** is slightly split by less than 2 Hz (1.74 and 1.75 ppm) and shifted upfield due to the diamagnetic shielding by the non-coplanar 5-phenyl groups. Thus **4a** probably exists as a mixture (4:3 as estimated from ^{1}H NMR integrals) of diastereomers and/or stable rotational isomers.

In the IR- and UV/Vis-spectra **4a**–**4e** show characteristic broad hydroxyl absorptions centered around 3430–3456 cm^{-1} and carbonyl bands around 1595 cm^{-1} (for more details see the experimental part). UV/Vis absorptions are compiled in Table 2. In one case (**4b**) it was demonstrated that the spectra are both solvent and *pH*-dependent, but the effects are not dramatic. All spectra show pronounced minima at 340–350 nm.

The results from the elemental analyses and the mass spectra are in accordance with the assigned structures **4a**–**4e**. Thus the mass spectra display the calculated molecular ions (except for **4e**, which most likely is pyrolyzed too fast to give a meaningful MS).

Table 2. Absorption maxima of the UV/Vis spectra of **4a**–**4e**

Compound	Solvent	λ_{max}/nm (log ε)
4a	Acetonitrile	507 (4.46), 444 (4.50), 264 (4.45)
4b	Acetonitrile	501 (4.46), 437 (4.46), 262 (4.50)
	Ethanol	501 (4.57), 446 (4.54), 265 (4.53)
	Ethanol (0.2 *N* NaOH)	550[a] (4.32), 510 (4.51), 445 (4.47), 262.5 (4.62)
	Ethanol (1.0 *N* HCl)	500 (4.69), 450[a] (4.53), 265 (4.53)
4c	Acetonitrile	502 (4.26), 438 (4.36), 262 (4.36)
4d	Acetonitrile	504 (4.37), 439.6 (4.37), 263.7 (4.37)
4e	Acetonitrile	504 (4.12), 437.5 (4.18), 266.6 (4.17), 225[a] (4.12)

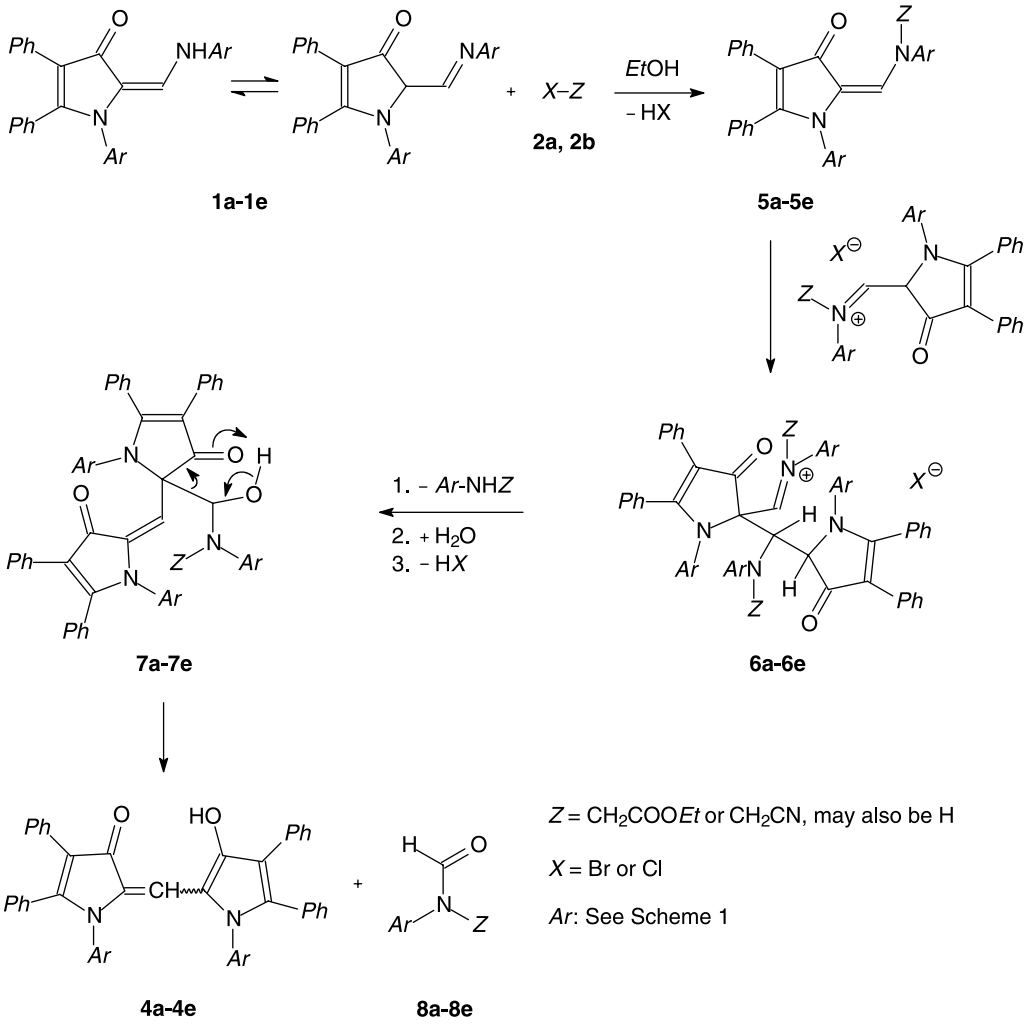
[a] Shoulder

The formation of dipyrrins **4a**–**4e** may be rationalized as a hydrolysis of the starting 2-(aminomethylene)-3-pyrrolinones under slightly acidic conditions (0.1 *N* aqueous HCl) to the corresponding 3-hydroxypyrrole-2-carbaldehyde. Replacement of the formyl group in one half of that material to generate the 1,2-dihydro-3*H*-pyrrol-3-one was assumed to be followed by condensation of the latter with the remaining aldehyde to form a dipyrrin [6].

While **2a** releases HBr in refluxing ethanol (which would provide the true reagent for a closely analogous pathway to convert **1a**–**1e** into **4a**–**4e**), chloroacetonitrile is stable under the same conditions. On the other hand, both reactants **2a** and **2b** would release hydrogen halide upon their reaction with **1a**–**1e**. Hydrolysis of **1a**–**1e** in the way outlined above may thus be assisted by acid and/or **2a**, **2b**. Moreover, liberation of the amine need not happen in the beginning of the reaction sequence, it may take place also at a later stage. Since **2b** brings about the reaction as well we are inclined to suggest a rationale as given in Scheme 2: the imine tautomer of **1a**–**1e** is either alkylated by the electrophilic carbon of **2a**, **2b** or protonated and the resulting intermediate **5** attacks the corresponding iminium ion to generate **6a**–**6e** which is condensed to **7a**–**7e**. The latter undergoes a retro-aldol like cleavage to afford ultimately **4a**–**4e**. The anilides **8a**–**8e** were not isolated from the reaction mixtures, at least for $Z = H$ they could be hydrolyzed under the reaction conditions to the corresponding amine and formic acid. Alternatively, an acid catalyzed liberation of amine followed by loss of formic acid or its ethyl ester cannot be excluded.

Finally, the question whether compounds **4** exist in the (*E*) or (*Z*) configuration needs to be tackled. While it is tempting to rationalize the high downfield chemical shift of the OH protons with an intramolecular hydrogen bridge to the carbonyl oxygen (which would be possible only in the (*E*) configuration), the carboxylic acid-like nature of the hydroxyl group serves to explain this large paramagnetic shift as well. On the other hand, the magnitude of ^3J(C,H) of the carbonyl-C with the methine proton (6.2 Hz) rather points to a *cis* vicinal orientation of the carbonyl group and the proton. For several α,β-unsaturated carbonyl compounds the values for *cis* vicinal couplings of the carbonyl C and a proton are found in the range of 7.4 to 9.7 Hz, whereas the corresponding ^3J values for a *trans* orientation fall into the range 11 to 15.2 Hz [11]. A vicinal *cis* orientation of C=O and methine C–H at the central double bond in turn means that the (*Z*) configuration has to be assigned (with all necessary caution!) to **4b** and by analogy also to **4a** and **4c**–**4e**. Earlier works on related compounds either did not attempt a configurational assignment [4, 5] or suggested an (*E*) configuration without backing it up with additional experiments [6].

In conclusion, this study shows that the mild conditions in the reaction of 2-aminomethylene-Δ^4-pyrrolinones with an α-bromoester or chloroaceto-nitrile



Scheme 2

and/or just acid can be used for the synthesis of new monomethine dipyrrinonol dyes for which a (*Z*)-configuration may be suggested from NMR evidence.

Experimental

The uncorrected melting points were determined on a Reichert Thermovar hot stage microscope. Elemental analyses were obtained on a Carlo Erba 1106 CHN analyzer; these values agreed favourably with the calculated ones. The IR (KBr) spectra were recorded on a Perkin Elmer 983 spectrophotometer. The 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were observed on a Bruker WM 300 instrument with *TMS* as internal standard and $CDCl_3$ as solvent. In addition, a Bruker DRX 500 instrument was used to record a proton coupled ^{13}C spectrum and a HMBC experiment on compound **4b**. The ^{13}C signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on an AMD 604 instrument. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of silica gel Merck PF_{254} and toluene:ethyl acetate (10:1) as developing solvent. Zones were eluted with acetone or ethyl acetate.

*General Procedure for the Preparation of **4a–4e***

Method A: Samples of 100 mg of Δ^4-pyrrolinones **1a–1e** were heated with an excess of ethyl bromoacetate (**2a**) or chloroacetonitrile (**2b**) (1.12 mmol) in 5 cm^3 of ethanol for 15–32 h. After cooling, red crystals of **4a–4e** precipitated, which were filtered off and recrystallized from ethanol. The filtrate was concentrated, dissolved in ethyl acetate (in case of the reaction of **1b** with **2a** a colorless precipitate was collected and identified as *p*-toludine.HCl) and subjected to plc. Two zones were extracted with ethyl acetate. The faster moving zone contained additional **4a–4e**, which was crystallized from ethanol, whereas the slower zones contained unreacted **1a–1e**.

Method B: When 100 mg of Δ^4-pyrrolinone **1a–1e** in 5 cm^3 of ethanol were heated with 2 cm^3 of 0.1 *N* HCl at reflux for 2–3 h, red crystals of **4a–4e** precipitated upon cooling. For yields see Table 1.

2-{[3-Hydroxy-1-(2-methylphenyl)-4,5-diphenyl-1H-pyrrol-2-yl]-methylene}-1-(2-methylphenyl)-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (**4a**, $C_{47}H_{36}N_2O_2$)

Yield 40 mg (53%), mp 293–295°C, scarlet red crystals (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.74$ and 1.75 (2s, $2CH_3$), 5.90 and 5.92 (2s, methine-H), several m at 6.88–7.39 (28Ar–H), 13.70 (broadened s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.1$ and 17.2 (2s, $2CH_3$), 114.9 and 115.0 (methine-*C*H), 125.7, 126.5, 127.8, 128.0, 128.6, 128.7, 129.7, 130.0, 130.1, 130.2, 130.4, 130.7, 130.8 (aryl-*C*H), 115.4, 115.5, 124.8, 130.7, 132.5, 135.8, 135.8, 137.4, 149.5, 149.6 (qu. *C*), 167.3 (*C*=O) ppm; IR (KBr): $\bar{\nu} = 3450$ (broad, OH), 1595 (C=O) cm^{-1}; MS (70 eV): $m/z = 660$ (M^+, 56), 644 (56), 643 (M^+-OH, 100), 336 (18), 330 (12), 194 (13), 178 (21), 128 (15), 91 (20).

2-{[3-Hydroxy-1-(4-methylphenyl)-4,5-diphenyl-1H-pyrrol-2-yl]-methylene}-1-(4-methylphenyl)-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (**4b**, $C_{47}H_{36}N_2O_2$)

Yield 65 mg (87%), mp 268–270°C, scarlet red crystals (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$ (s, $2CH_3$), 6.41 (s, methine-H), several m at 6.78–7.34 (28Ar–H), 13.34 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$ ($2CH_3$), 115.7 (methine-*C*H), 125.7, 127.7, 127.9, 128.4, 129.2, 129.4, 129.7, 130.4 (aryl-*C*H), 115.8, 125.6, 130.9, 132.5, 134.3, 137.6, 149.3 (qu. *C*), 167.4 (*C*=O) ppm; IR (KBr): $\bar{\nu} = 3456$ (broad, OH), 1595 (C=O) cm^{-1}; MS (70 eV): $m/z = 660$ (M^+, 53), 644 (54), 643 (M^+-OH, 100), 194 (14), 178 (10), 91 (14).

2-{[3-Hydroxy-1-(4-methoxyphenyl)-4,5-diphenyl-1H-pyrrol-2-yl]-methylene}-1-(4-methoxyphenyl)-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (**4c**, $C_{47}H_{36}N_2O_4$)

Yield 67 mg (77%), mp 318–320°C, scarlet red crystals (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.76$ (s, $2OCH_3$), 6.35 (s, methine-H), 6.63 (d, $^3J = 8.9$ Hz, 4Ar–H), 6.83 (d, $^3J = 8.0$ Hz, 4Ar–H), several m between 7.03–7.37 (20Ph–H), 13.50 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.3$ ($2OCH_3$), 115.7 (methine-*C*H), 114.0, 125.7, 127.8, 128.0, 128.5, 129.7, 130.4, 130.6 (aryl-*C*H), 115.7, 125.8, 129.6, 131.0, 132.5, 149.5, 158.9 (qu. *C*), 167.3 (*C*=O) ppm; IR (KBr): $\bar{\nu} = 3430$ (broad OH), 1597 (C=O) cm^{-1}; MS (70 eV): $m/z = 692$ (M^+, 61), 675 (M^+-OH, 100), 658 (6), 353 (14), 352 (13), 341 (13), 210 (17), 178 (14), 77 (12).

2-[(3-Hydroxy-1,4,5-triphenyl-1H-pyrrol-2-yl)methylene]-1,4,5-triphenyl-1,2-dihydro-3H-pyrrol-3-one (**4d**, $C_{45}H_{32}N_2O_2$)

Yield 38 mg (50%), mp 307–310°C, scarlet red crystals (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.49$ (s, methine-H), several m at 6.90–7.40 (30Ar–H), 13.12 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 115.4$ (methine-*C*H), 125.8, 127.8, 128.0, 128.6, 128.9, 129.5, 129.7, 130.4 (aryl-*C*H),

116.1, 125.6, 128.6, 130.8, 132.4, 137.0, 149.4 (qu. *C*), 167.7 (*C*=O) ppm; IR (KBr): $\bar{\nu} = 3455$ (broad, OH), 1592 (C=O) cm^{-1}; MS (70 eV): $m/z = 632$ (M^+, 41), 615 (M^+-OH, 100), 311 (14), 180 (17), 178 (15), 77 (22).

2-{[3-Hydroxy-1-(4-hydroxyphenyl)-4,5-diphenyl-1H-pyrrol-2-yl]-methylene}-1-(4-hydroxyphenyl)-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (**4e**, $C_{45}H_{32}N_2O_4$)

Yield 26 mg (35%), mp 324–325°C, scarlet red crystals (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.45$ (s, methine-H), 6.55 (d, $^3J = 8.5$ Hz, 4Ar–H), 6.85 (d, $^3J = 8.6$ Hz, 4Ar–H), several m at 7.05–7.22 (20Ph–H), 9.69 (broadened s, 2Aryl-O*H*), 13.37 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 115.6$ (methine-CH), 115.4, 125.5, 127.5, 127.9, 128.6, 129.0, 130.0, 130.2 (aryl-*C*H), 114.2, 125.0, 126.9, 130.7, 132.4, 149.9, 157.1 (qu. *C*), 166.2 (C=O); $\bar{\nu} = 3450$ and 3440 (broad OH), 1595 (C=O) cm^{-1}.

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