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Synthesis of Amino and Hydroxy Derivatives of 4,7-Phenanthroline

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Abstract — Nitro-, dinitro-, and hydroxynitrophenyl-substituted 4,7-phenanthrolines were reduced with tin(II) chloride in a mixture of acetic and nitric acids to obtain amino, diamino, and hydroxy derivatives of 4,7-phenanthroline. When heated with aromatic aldehydes, the products form azomethines of the 4,7-phenanthroline series.

Amino and hydroxy groups deserve special attention among functional substituents in heterocyclic compounds. Amino- and hydroxy-substituted heterocycles are interesting by their biological activity [1, 2] and as starting materials for synthesis of diverse and practically promising compounds, such as sulfamides, acetylamines, azomethines, esters, and azo dyes.

The synthesis of 4,7-phenanthrolines containing hydroxy groups has been reported in [3, 4]. These compounds are most commonly obtained by Conrad–Limpach and Knorr reactions, starting from 6-quinolylamine or *p*-phenylenediamine and esters of β-oxo- and β-dicarboxylis acids. Amino derivatives of 4,7-phenanthroline are less accessible. Mlochowski and Skrowarczewska managed to nitrate 4,7-phenanthroline to obtain 5-nitro-4,7-phenanthroline [5], but did not reduce the latter. 5-Amino-4,7-phenanthroline [6] was prepared by substitution of the halogen in 5-chloro- or 5-bromo-4,7-phenanthrolines under the action of concentrated ammonia in the presence of copper(II) acetate, and 5,6-diamino-4,7-phenanthroline [7], by a multistep procedure involving nitration of *p*-toluenesulfonyl derivative of 5-amino-4,7-phenanthroline, hydrolysis of the sulfamide group, and reduction of the 6-NO_2 group. Later on 5,6-diamino-3,8-dimethyl-4,7-phenanthroline was obtained by amination of 3,8-dimethyl-5-nitro-4,7-phenanthroline with hydroxylamine in the presence of alkali, but the product contained an admixture of 6-amino-5-nitro-4,7-phenanthroline [8]. No 4,7-phenanthrolines containing both amino and hydroxy groups have so far been reported.

Earlier [9, 10] we showed that acid-catalyzed reaction of azomethines of the 6-aminoquinoline series with acetophenone and substituted acetophenones gives rise to 1,3-diaryl-4,7-phenanthrolines. By varying substituents in the aldehyde moiety of the Schiff base and in the phenyl ring of the acetophenone one can obtain 4,7-phenanthrolines with desired substituents. In this way, by reacting (*p*-dialkylaminophenyl)methylene- and *o*- and *p*-hydroxyphenylmethylene-6-quinolylamines with acetophenone, as well as by reacting azomethines of the 6-aminoquinoline series with *p*-hydroxyacetophenone we synthesized *p*-dialkylaminophenyl- and hydroxyphenyl-substituted 4,7-phenanthrolines. However, this approach fails to provide 4,7-phenanthroline with a free amino group. The amino-substituted benzaldehyde required to prepare the corresponding Schiff base forms a polymer that does not react with 6-quinolylamine.

p-Aminoacetophenone, too, fails to undergo the catalytic condensation. The catalyst (conc. HCl) is primarily consumed for protonation of the amino group, thus decreasing the nucleophilic activity of the carbonyl group, its ability to protonation, and, as a consequence, CH-acidity of the methylketone.

Aiming at preparing previously unknown compounds of the 4,7-phenanthroline series, containing both an amino and a hydroxy groups in one molecule, we reduced nitro-, dinitro-, and hydroxynitro-substituted 4,7-phenanthrolines obtained by condensation of arylmethylene-6-quinolylamines, with acetophenone, *m*-nitro-, *p*-nitro-, and *p*-hydroxyacetophenone and 2-acetylquinoline.

The reduction of nitro groups was accomplished by heating at 100°C over the course of 2–3 h of a mixture of phenanthroline **Ia**–**Im**, tin(II) chloride, glacial acetis acid, and conc. HCl and resulted in preparation of amino-, diamino-, and hydroaminophenyl-substituted 1,3-diphenyl-4,7-phenanthrolines **IIa**–**IIl**, as well as 3-(3-aminophenyl)-1-(2-quinolyl)-

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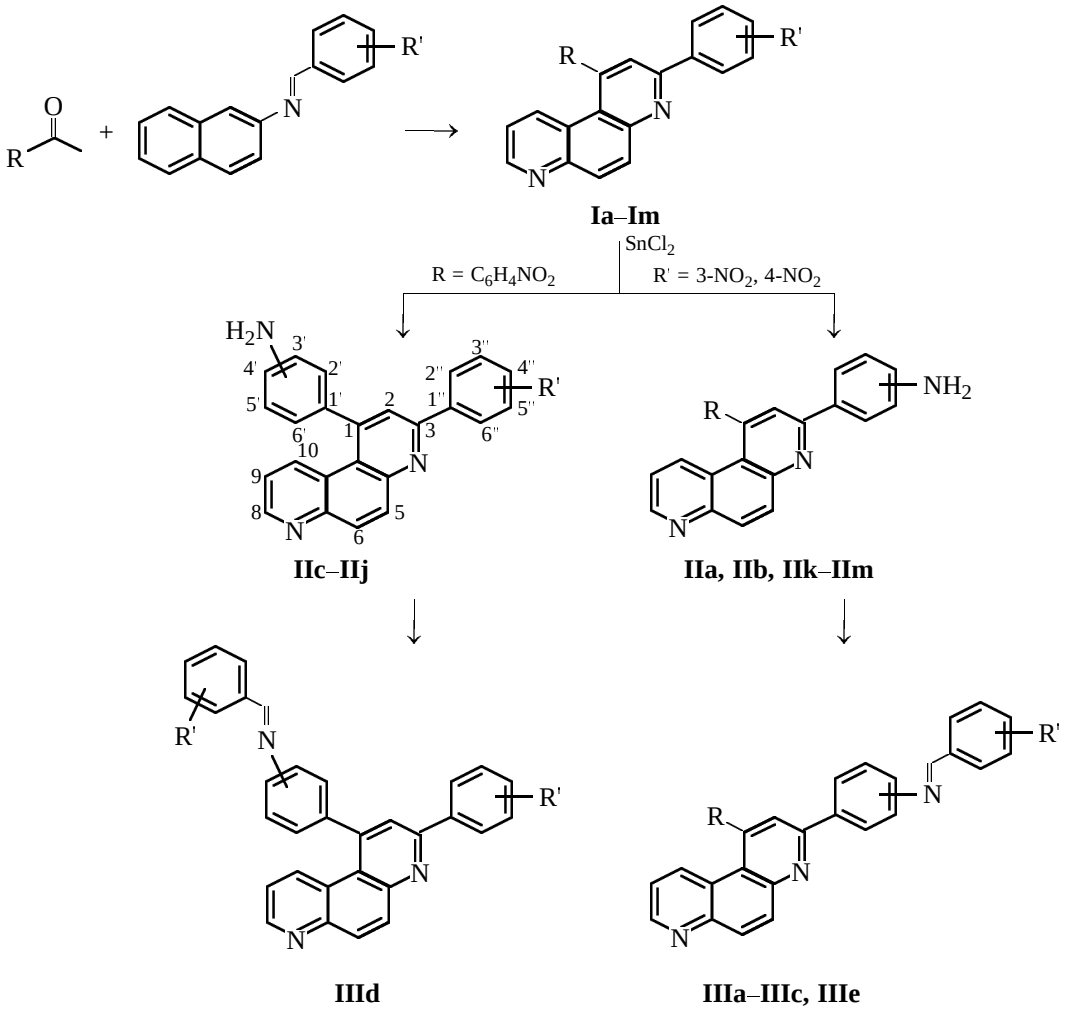

R = C_6H_5 (**Ia, Ib, IIa, IIb, IIIa, IIIb**), 3-$NO_2C_6H_4$ (**Ic**–**If**), 4-$NO_2C_6H_4$ (**Ig**–**Ij**), 4-HOC_6H_4 (**Ik, Il, IIk, IIl, IIIe**), 2-quinolyl (**Im, IIm**), 4-$C_6H_5CH{=}NC_6H_4$ (**IIIc**), 2-OH (**IIId**); R' = 3-NO_2 (**Ia, Ic, Ig, Ik, Im**), 4-NO_2 (**Ib, Id, Ih, Il**), 2-OH (**Ie, Ii, IIe, IIi, IIId, IIIe**), 4-OH (**If, Ij, IIf, IIj**), 3-NH_2 (**IIc, IIg**), 4-NH_2 (**IId, IIh**), 4-Br (**IIIa**), 4-Cl (**IIIb**), H (**IIIc**); positions of amino groups and azomethine bonds in phenyl rings: 3 (**IIa, IIc**–**IIf, IIk, IIm, IIIb, IIId**), 4 (**IIb, IIh**–**IIj, IIl, IIIa, IIIc, IIId**).

4,7-phenanthroline (**IIm**). Characteristics of compounds **IIa**–**IIm** are given in the table.

The IR spectra of compounds **IIa**–**IIm** lack stretching vibration bands of nitro groups at 1540–1510 and 1350–1340 cm^{-1}, characteristic of the starting nitro derivatives **Ia**–**Im**. Band at 3420–3210 cm^{-1} appear, assignable to stretching vibrations of amino groups.

The mass spectra of aminophenanthrolines **IIa**–**IIm** show a base molecular ion peak and a number of low-intensity fragment ions $[M - C_6H_5NH_2]^+$, $[M - C_6H_5OH]^+$, and $[M - HCN]^+$. There are double-charged molecular $[M]^{2+}$ and fragment $[M - HCN]^{2+}$ ion peaks, which is characteristic of fused heteroaromatic compounds.

The UV spectra of amino-4,7-phenanthrolines **IIa**–**IIm** (see table) in band positions (Clar β-, ρ-, and α-bands [11]) are similar to those of 1,3-diaryl-4,7-phenanthrolines [12]. The presence in the phenyl ring of a *meta*-amino group not conjugated with the phenanthroline nucleus has almost no effect on band positions and intensities, whereas a *para*-amino group in the phenyl ring strongly enhances the long-wave α-band, as is the case with *p*-dialkylaminophenyl-substituted 4,7-phenanthrolines [12].

In the ^1H NMR spectra of compounds **IIa**–**IIm**, amino protons appear as broadened singlets at 5.30–5.75 ppm. The *para*-hydroxy group of the phenyl ring gives a singlet at 9.50–9.80 ppm, and the *ortho*-hydroxy group, a singlet at 13.10–14.15 ppm. Phenan-

Yields, melting points, UV spectra, and elemental analyses of 4,7-phenanthroline derivatives **IIa**–**IIm** and **IIIa**–**IIIe**

Comp. no	Yield, %	mp, °C	UV spectrum, λ_{max}, nm (log ε)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIa	36	222–223	237 (4.56), 291 (4.57), 358 (3.83)	82.91	4.88	11.79	$C_{24}H_{17}N_3$	83.00	4.90	12.10
IIb	37	243–244	235 (4.56), 261 (4.47), 292 (4.46), 345 (4.48)	82.79	4.91	11.94	$C_{24}H_{17}N_3$	83.00	4.90	12.10
IIc	49	284–285	236 (4.52), 259 (4.46), 290 (4.56), 337 (3.90), 357 (3.81)	79.58	4.63	15.21	$C_{24}H_{18}N_4$	79.56	4.97	15.47
IId	58	290–291	239 (4.50), 291 4.49), 348 (4.45)	79.37	4.81	15.11	$C_{24}H_{18}N_4$	79.56	4.97	15.47
IIe	47	271–272	238 (4.41), 292 (4.46), 353 (4.11)	79.41	4.73	11.38	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
IIf	42	279–280	237 (4.49), 293 (4.47), 356 (3.97)	79.17	4.59	11.46	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
IIg	56	287–288	243 (4.52), 291 (4.45), 349 sh (3.90)	79.24	4.75	15.31	$C_{24}H_{18}N_4$	79.56	4.97	15.47
IIh	47	264–265	243 (4.60), 291 (4.43), 340 (4.52)	79.55	4.83	15.41	$C_{24}H_{18}N_4$	79.56	4.97	15.47
IIi	36	268–270	234 (4.35), 258 (4.40), 293 (4.43), 339 (4.21), 352 sh (4.08)	79.48	4.73	11.46	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
IIj	45	297–298	239 (4.43), 260 (4.39), 292 (4.40), 347 (4.49)	79.31	4.55	11.37	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
IIk	44	291–293	238 (4.41), 290 (4.39), 351 sh (3.79)	79.19	4.60	11.43	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
III	49	289–290	240 (4.47), 259 (4.45), 291 (4.48)	79.22	4.59	11.19	$C_{24}H_{17}N_3O$	79.34	4.68	11.57
IIm	34	209–210	238 (4.51), 292 (4.50), 353 sh (3.82)	81.37	4.26	13.84	$C_{27}H_{18}N_4$	81.41	4.52	14.07
IIIa[a]	72	248–249	231 (4.52), 262 (4.45), 293 (4.47), 344 (4.43), 363 sh (4.40)	72.32	3.57	7.84	$C_{31}H_{20}BrN_3$	72.37	3.89	8.17
IIIb[b]	64	185–186	232 (4.38), 264 (4.52), 291 (4.66), 358 sh (3.94)	79.14	4.09	8.74	$C_{31}H_{20}ClN_3$	79.23	4.26	8.95
IIIc	69	357–359	232 (4.49), 289 (4.38), 334 (4.37)	89.58	4.66	10.33	$C_{38}H_{26}N_4$	84.76	4.83	10.41
IIId	77	299–300	237 (4.59), 292 (4.48), 341 (4.40), 357 sh (4.09)	79.69	4.49	8.64	$C_{31}H_{21}N_3O_2$	79.66	4.50	8.99
IIIe	79	249–250	238 (4.67), 264 (4.60), 289 (4.58), 352 sh (3.78)	79.41	4.23	8.75	$C_{31}H_{21}N_3O_2$	79.66	4.50	8.99

[a] Found Br, %: 15.24. Calculated Br, %: 15.56. b Found Cl, %: 7.22. Calculated Cl, %: 7.56.

throline proton signals (7.20–8.90 ppm) are at positions expected from the spectra of 1,3-diaryl-4,7-phenanthrolines [9]. The anisotropic effect of the hydroxy and amino groups extends mostly to protons of the phenyl rings (6.35–8.10 ppm) bearing these groups. In the spectra of phenanthrolines **IIc**–**IIj** amino-substituted in the phenanthroline 1-Ph ring, we observe a downfield shift of the signal of H^{10} which comes under the cone of phenyl ring current forces. Probably, amino substitution in the phenyl ring disturbes its acoplanarity, thus attenuating its shielding effect. If there is an *ortho*-hydroxy substituent in the phenanthroline 3-Ph ring, the signal of the H^2 proton closest to this phenyl group shifts downfield (8.07–8.10 ppm).

To assess the reactivity of the amino groups in 4,7-phenanthrolines, we have studied condensation of compounds **IIa**, **IIb**, **IIh**, **IIi**, and **IIk** with aromatic aldehydes. Since the amino group in 1,3-diaryl-4,7-phenanthrolines is a constituent part of the aniline moiety, to react compounds **IIa**, **IIb**, **IIh**, **IIi**, and **IIk** with aldehydes requires the same conditions as to condense the latter with aniline, i.e. to heat the reactants in alcoholic toluene (toluene is added in view of the poor solubility of aminophenanthrolines in alcohols). The reactions with amines **IIa** and **IIb** give azomethines **IIIa** and **IIIb**, while diamine **IIh** provides bisazomethine **IIIc**. Aminohydroxy-substituted phenanthrolines **IIi** and **IIk** react with salicylaldehyde to form bisphenol azomethines of the 4,7-phenanthroline series **IIId** and **IIIe**. The yields of condensation peroducts **IIIa**–**IIIe** (see table) suggest a fairly high reactivity of the amino groups toward aldehydes.

The IR spectra of compounds **IIIa**–**IIIe** lack bands at 3420–3210 cm^{-1}, characteristic of NH_2 stretching vibrations. A band characteristic of N=CH stretching vibrations appears at 1635–1630 cm^{-1}. The mass spectra contain molecular ion peaks $[M]^+$ (I 50–70%). Peaks of $[M - C_6H_4R']^+$, $[M - CH - C_6H_4R']^+$, and $[M - HCN]^+$ fragment ions and $[M]^{2+}$, $[M - HCN]^{2+}$, and $[M - CH - C_6H_4R']^{2+}$ double-charged ions are also present.

The UV spectra of azomethines **IIIa**–**IIIe** (see table) are similar to those of the starting amines **IIa**, **IIb**, **IIh**, **IIi**, and **IIk** in terms of band positions and

relative intensities. The spectra of phenanthrolines **IIIb** and **IIIe** with the azomethine bond in the *meta* position of the phenyl ring show an additional band at 264 nm, that partially overlaps with the *p*-band (291–293 nm) of the phenanthroline nucleus. This band (264 nm) can be assigned to the π,π* transition in the ArCH=N group [13] that is not conjugated with the phenanthroline nucleus and acts as an independent chromophore. In *p*-arylmethyleneamino-substituted phenanthrolines, the azomethine moiety is incorporated into the common conjugation system.

The ^{1}H NMR spectra of azomethines **IIIa**–**IIIe** lack amino proton sinals. The azomethine proton appears as a singlet at 9.10–9.15 ppm. In the group of aromatic proton signals (6.35–8.90 ppm), additional aldehyde proton signals appear. Arylmethylene substitution in the phenanthroline 1-Ph ring enhances shielding of H^{10} and shifts its signal upfiled (7.90–7.95 ppm) with respect to the same proton signal in the starting amino derivatives **IIg**–**IIj** (8.10–8.15 ppm).

EXPERIMENTAL

The mass spectra were recorded on a Varian MAT-311 with direct inlet, ionizing energy 70 eV. The IR spectra were measured on a Nicolet Protege-460 Fourier spectrometer. The 1H NMR spectra were obtained on a Tesla BS-567 spectrometer (100 MHz) in DMSO-d_6, internal reference TMS. The UV spectra were obtained on a Specord UV-Vis spectrophotometer for ethanol solutions (c 10^{-4} M). The melting points were measured on a Kofler hot stage.

Nitro-substituted 1,3-diphenyl-4,7-phenanthrolines **Ia**, **Ib**, and **Ih** were prepared as described in [9], hydroxynitrophenanthrolines **Ie**, **If**, and **Ii**–**Il**, as described in [10], and 1-(2-quinolyl)-3-(3-nitrophenyl)-4,7-phenanthroline (**Im**), as described in [14].

1,3-Bis(3-nitrophenyl)-4,7-phenanthroline (Ic). A mixture of 1.4 g of 3-nitrophenylmethylene-6-quinolylamine, 0.8 g of 3-nitroacetophenone, 20 ml of 1-butanol, and 0.5 ml of conc. HCl was refluxed for 2 h. The precipitate that formed was filtered off, treated with aqueous NH_4OH, and recrystallized for ethanol–toluene (1 : 1). Yield 0.75 g (36%), mp 294–295°C. IR spectrum, ν, cm^{-1}: 1530, 1350 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 422 $[M]^+$ (100), 392 (10), 376 (11), 300 (20), 278 (18). ^{1}H NMR spectrum, δ, ppm: 7.13 d.d (H^9), 7.83 s (H^2), 7.90 d (H^{10}), 8.30 m ($H^{5,6}$), 8.85 d.d (H^8), 7.47–7.60 m, 8.35 s, 8.44 m ($8H_{arom}$). Found, %: C 68.10; H 3.19; N 13.08. $C_{24}H_{14}N_4O_4$. Calculated, %: C 68.25; H 3.32; N 13.26.

1-(3-Nitrophenyl)-3-(4-nitrophenyl)-4,7-phenanthroline (Id) and 1-(4-nitrophenyl)-3-(3-nitrophenyl)-4,7-phenanthroline (Ig) were prepared in a similar way from the corresponding azomethine (3- or 4- nitrophenylmethylene-6-quinolylamine) and 3- or 4- nitroacetophenone. Compound **Id**, yield 39%, mp 298–299°C. IR spectrum, ν, cm^{-1}: 1530, 1355 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 422 $[M]^+$ (100), 392 (8), 376 (10), 300 (29). ^{1}H NMR spectrum, δ, ppm: 7.10 d.d (H^9), 7.80 s (H^2), 7.88 d (H^{10}), 8.26 d, 8.30 m ($H^{5,6}$), 8.88 d.d (H^8), 7.59 m, 8.20 s, 8.36 d, 8.46 d ($8H_{arom}$). Found, %: C 68.21; H 3.36; N 12.93. $C_{24}H_{14}N_4O_4$. Calculated, %: C 8.25; H 3.32; N 13.26. Compound **Ig**, yield 44%, mp 301–302°C. IR spectrum, ν, cm^{-1}: 1535, 1362 (NO_2). Mass spectrum, *m/z* (I_{rel}, %): 422 $[M]^+$, 300 (18). ^{1}H NMR spectrum, δ, ppm: 7.11 d.d (H^9), 7.86 s (H^2), 7.79 d (H^{10}), 8.29 m ($H^{5,6}$), 8.87 d.d (H^8), 7.49 m, 8.08 d, 8.18 s, 8.38 d ($8H_{arom}$). Found, %: C 67.96; H 3.19; N 13.23. $C_{24}H_{14}N_4O_4$. Calculated, %: C 68.25; H 3.32; N 13.26.

3-(3-Aminophenyl)-1-phenyl-4,7-phenanthroline (IIa). A hot solution of 7 g of $SnCl_2 \cdot 2H_2O$ in 40 ml of conc. HCl was added with stirring to a suspension of 1.6 g of 3-(3-nitrophenyl)-1-phenyl-4,7-phenanthroline (**Ia**) in 40 ml of glacial acetic acid. The mixture was heated for 2h at 100°C, cooled, and neutralized with 20% aqueous NaOH. The precipitate that formed was filtered off and dried. Compound **IIa** was extracted with toluene in a Soxhlet apparatus.

Aminophenanthrolines **IIb**–**IIm** were prepared in a similar way. With compounds **IIc**, **IId**, **IIg**, and **IIh**, the reaction mixture was heated for 3 h. With compounds **IIb**–**IId**, **IIi**, and **IIk**, after heating, a precipitate formed and was filtered off, washed with glacial acetic acid, and neutralized; further workup was performed as described above. Hydroxyamine **IIi** was recrystallized from toluene and its isomer **IIk**, from DMF.

^{1}H NMR spectrum of diaminophenanthroline **IIh**, δ, ppm (J, Hz): 5.45 s (NH_2), 5.60 s (NH_2), 6.65 d ($H^{3',5'}$, ^3J 8.0), 6.72 d ($H^{3'',5''}$, ^3J 7.8), 7.12 d ($H^{2',6'}$, ^3J 8.0), 7.22 d (H^9, ^3J 8.2, ^4J 4.1), 7.76 s (H^2), 8.04 d ($H^{2'',6''}$, ^3J 7.8), 8.11 m ($H^{5,6,10}$), 8.80 d.d (H^8, ^3J 4.1, ^4J 1.8).

3-[4(4-Bromobenzylidene)aminophenyl]-1-phenyl-4,7-phenanthroline (IIIa). A solution of 0.5 g of *p*-bromobenzaldehyde in 20 ml of ethanol was added to a solution of 0.9 g of 3-(4-aminophenyl)-1-phenyl-4,7-phenanthroline (**IIb**) in 30 ml of toluene. The mixture was refluxed for 10 min. The precipitate that formed was filtered off and recrystallized from ethanol–toluene (2 : 1).

Azomethines **IIIb**–**IIIe** were synthesized in a similar way. Compounds **IIIb**, **IIIc**, and **IIIe** were isolated after removal of the solvent and purified by recrystallization from 2-propanol (**IIIb**, **IIIc**) or toluene (**IIId**, **IIIe**). ^{1}H NMR spectrum of compound **IIId**, δ, ppm (*J*, Hz): 6.95–7.80 m ($12H_{arom}$), 7.92 d (H^{10}, ^3J 7.9), 8.24–8.40 m ($4H_{arom}$), 8.90 d.d (H^8, ^3J 4.8, ^4J 2.1), 9.15 s (CH=N), 13.0 s (OH), 14.15 s (OH).

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