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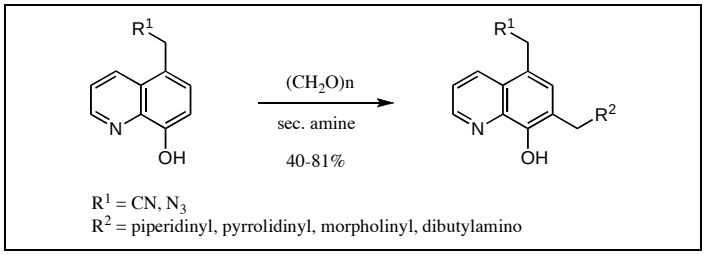

Seven new 5,7-disubstituted oxine derivatives have been synthesized *via* a Mannich reaction between a sec. amine (*e.g.* piperidine, pyrrolidine, morpholine, or dibenzylamine,) and 5-cyano or 5-azidomethyl-8-hydroxyquinoline, which were respectively obtained by nucleophilic displacement of 5-chloromethyl-8-hydroxyquinoline by cyanide or azide anions. In all cases, a single product was isolated in medium to fair yield and characterized on the basis of ^{1}H and ^{13}C-NMR, MS and IR spectrometric data. The X-ray structure of the product obtained from 5-cyanomethyl-8-hydroxyquinoline and piperidine is also reported.

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INTRODUCTION

The present work is connected to our previous contributions in the field of 8-hydroxyquinoline (= oxine) derivatives and their use as biologic or complexing tools [1]. It is well known that oxine is an excellent metal ion chelator [2]. However, unsubstituted oxine is too much water-soluble for practical liquid-liquid extraction. Therefore high lipophilic substituted oxines [3] have been synthesized to obviate this problem: for example, sparingly water-soluble but highly soluble in organic media 7-substituted derivatives of oxine, such as Kelex 100™ and aminoethylenes, have demonstrated superior extraction behaviors and are thoroughly used in hydrometallurgy and for analytical chemistry purposes [4]. Additionally some of these compounds are endowed with interesting biological activities when associated with metals or as metal-free chelators [5]. We report here about the synthesis of novel 5,7-disubstituted derivatives of oxine using the Mannich reaction.

RESULTS AND DISCUSSION

5-Cyanomethyl-8-hydroxyquinoline **2a** was synthesized according to the method reported by Warner *et al.* [5a]. 5-Chloromethyl-8-hydroxyquinoline hydrochloride **1** [6] underwent rapid and exothermic nucleophilic displacement by an excess of potassium cyanide in dimethylsulfoxide

Table 1

^{1}H-nmr data of oxines **2a** and **2b** (in DMSO-d_6).

oxine	R^1	H-2	H-3	H-4	H-6	H-7	CH_2R^1
2a	CN	8.92 (dd, $J_{2\text{-}3}$ 4.3 Hz)	7.65 (dd, $J_{3\text{-}4}$ 8.7 Hz)	8.43 (dd, $J_{2\text{-}4}$ 1.4 Hz)	7.54 (d, 1H)	7.15 (d ,1H)	4.35 (s, 2H)
2b	N_3	8.95 (dd, $J_{2\text{-}3}$ 4.4 Hz)	7.66 (dd, $J_{3\text{-}4}$ 8.8 Hz)	8.53 (dd, $J_{2\text{-}4}$ 1.5 Hz)	7.51 (d, 1H)	7.18 (d, 1H)	4.84 (s, 2H)

Table 2

^{13}C-nmr data of oxines **2a** and **2b** (in DMSO-d_6)*.

oxine	**C-2**	**C-3**	**C-4**	**C-4a**	**C-5**	**C-5a**	**C-6**	**C-7**	**C-8**	**C-8a**
2a	148.2	119.1	132.1	128.0	126.4	19.3	122.1	110.6	153.4	138.7
2b	148.3	121.5	132.8	129.7	127.2	51.0	122.3	110.4	154.1	138.9

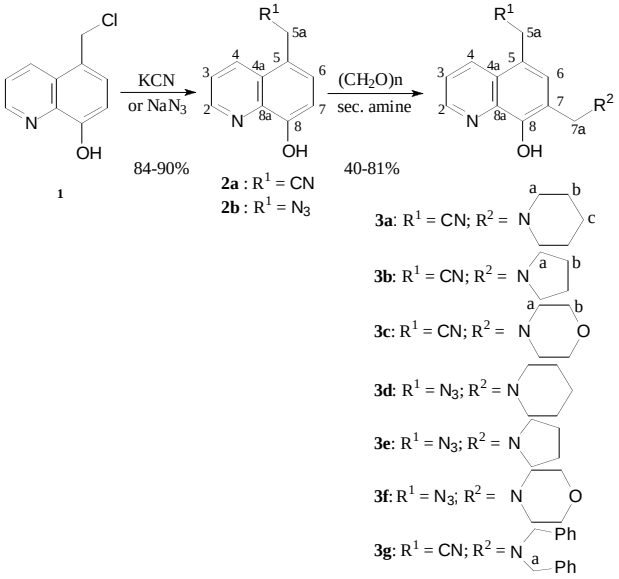
* For omitted CN signal see experimental details

(DMSO) at 90°C to give **2a** in good yield. The IR-spectra of the purified product exhibits the characteristic C≡N stretching vibration at 2260 cm^{-1}. As depicted in Table 1, the ^{1}H-NMR spectrum displays a characteristic singlet at 4.35 ppm integrating for the two benzylic protons, two signals at 7.15 and 7.54 ppm for H-6 and H-7 respectively, and a broad signal around 10 ppm attributed to the phenolic proton. The ^{13}C-NMR spectra, displays the expected nitrile peak at 116.9 ppm and one up-field resonance at 19.3 ppm assigned to the vicinal benzylic carbon.

5-Azidomethyl-8-hydroxyquinoline **2b** was isolated in good yield from **1** *via* a classical azide displacement in refluxing acetone [7]. The IR-spectra of **2b** exhibits the intense characteristic N_3-stretching vibration at 2090 cm^{-1} and the ^{1}H-NMR spectrum displays the expected singlet integrating for two benzylic protons at 4.8 ppm and 2 signals at 7.18 and 7.51 ppm for H-6 and H-7 respectively. Compared to precursor **2a**, the benzylic carbon is down-shielded to 51.0 ppm in **2b**. The pharmaceutical activities of **2a** and **2b** following oral administration in mice were investigated [8]. The complexing ability of **2b** towards Zn(II) has been recently evaluated elsewhere [9].

As outlined in Scheme 1, the reaction of phenols **2a** and **2b** with different secondary amines (*i.e.* piperidine, pyrrolidine, morpholine, and dibutylamine) under the conditions of the Mannich reaction in refluxing ethanol yields seven new products **3a-g**. The structure of these solely ortho-substituted products isolated in medium to fair yield was established on the basis of their spectroscopic data and furthermore fully ascertained by the X-ray molecular structure of **3a**. All IR-spectra display the expected set of characteristic bands in the region 2800-2980 cm^{-1} corresponding to the C-*H* valence stretching vibrations of the benzylic protons on C-5a and C-7a, and those of the amine. The H-7 doublet, around 7.2 ppm for the precursors **2a** and **2b** disappeared whereas the H-6 doublet turned into a singlet around 7.4 ppm in all ^{1}H NMR spectra of the products. NMR-data of the target compounds **3a-g** are summarized in Table 3 and 4.

Scheme 1



Aminomethylation of adducts **2a** & **2b** by secondary amines.

Table 3

^{1}H-nmr data of products **3a**-**g** (in DMSO-d_6 except **3g** in $CDCl_3$).

Product	H-2	H-3	H-4	H-6	CH_2R^1	CH_2R^2	H-a	H-b	H-c
3a	8.97 (dd, J_{2-3} 4.3 Hz)	7.56 (dd, J_{3-4} 8.7 Hz)	8.38 (dd, J_{2-4} 1.4 Hz)	7.49 (s, 1H)	4.43 (s, 2H)	3.72 (s, 2H)	2.42 (s, 4H)	1.48 (s, 4H)	1.39 (s, 2H)
3b	8.96 (dd, J_{2-3} 4.4 Hz)	7.57 (dd, J_{3-4} 8.8 Hz)	8.49 (dd, J_{2-4} 1.5 Hz)	7.58 (s, 1H)	4.42 (s, 2H)	3.78 (s, 2H)	2.55 (s, 4H)	1.76 (s, 4H)	-
3c	8.94 (dd, J_{2-3} 4.5 Hz)	7.58 (dd, J_{3-4} 8.9 Hz)	8.45 (dd, J_{2-4} 1.6 Hz)	7.56 (s, 1H)	4.48 (s, 2H)	3.72 (s, 2H)	3.61 (s, 4H)	2.47 (s, 4H)	-
3d	8.95 (dd, J_{2-3} 4.2 Hz)	7.53 (dd, J_{3-4} 8.6 Hz)	8.44 (dd, J_{2-4} 1.4 Hz)	7.29 (s, 1H)	4.44 (s, 2H)	3.73 (s, 2H)	2.45 (s, 4H)	1.48 (s, 4H)	1.35 (s, 2H)
3e	8.88 (dd, J_{2-3} 4.4 Hz)	7.67 (dd, J_{3-4} 8.8 Hz)	8.43 (dd, J_{2-4} 1.5 Hz)	7.57 (s, 1H)	4.46 (s, 2H)	3.89 (s, 2H)	2.55 (s, 4H)	1.32 (s, 4H)	-
3f	8.94 (dd, J_{2-3} 4.3 Hz)	7.49 (dd, J_{3-4} 8.7 Hz)	8.35 (dd, J_{2-4} 1.4 Hz)	7.34 (s, 1H)	4.63 (s, 2H)	3.88 (s, 2H)	3.77 (s, 4H)	2.63 (s, 4H)	-
3g	8.93 (dd, J_{2-3} 4.4 Hz)	7.49 (dd, J_{3-4} 8.8 Hz)	8.13 (dd, J_{2-4} 1.5 Hz)	7.27 (s, 1H)	4.02 (s, 1H)	3.91 (s, 1H)	3.69 (s, 4H)	-	-

Table 4

^{13}C-nmr selected data of products **3a-c** (in DMSO-d_6) and **3f-g** (in $CDCl_3$)*.

Product	C-2	C-3	C-4	C-4a	C-5	C-5a	C-6	C-7	C-8	C-8a
3a	148.4	119.5	132.2	125.5	116.4	19.5	129.1	121.8	151.8	138.7
3b	148.3	119.5	132.2	125.4	116.4	19.5	129.2	121.8	151.2	138.7
3c	148.4	119.2	132.3	125.5	116.6	19.5	129.6	121.9	151.4	138.6
3f	148.9	121.0	132.1	126.6	116.6	52.3	129.7	121.9	153.3	139.5
3g	149.0	121.9	130.8	125.8	117.7	20.7	128.5	118.7	153.1	139.4

* For omitted signals see experimental details

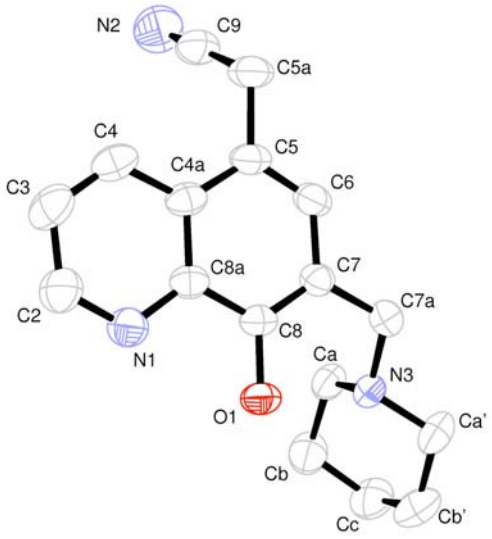


Figure 1. Molecular configuration and atom numbering scheme for **3a** showing 50% probability ellipsoids.

The slow evaporation of a saturated solution of **3a** in ethanol at 4°C in the dark yielded single crystals suitable for X-ray diffraction. The measurements were carried out on a Bruker Nonius Kappa CCD area diffractometer at room temperature. The structure solved by direct methods [10] and refined by full-matrix least squares [11] is given in Figure 1 (*vide supra*). The colorless crystals are monoclinic, space group $P2_1/c$ with 4 formula units per unit-cell. The crystal data and details of the X-ray analysis are listed in Table 5. One hydrogen-bonding association exists in the solid-state crystal structure between the phenolic OH and the pyridine nitrogen atom (**N1**). The bond lengths are 1.004 Å and 1.715 Å for O1 H1 and N1 H1 respectively and the O1 H1 N1 angle is 147.7°. The crystallographic-information-file (CIF) has been deposited with the *The Cambridge Crystallographic Data Centre* as supplementary data under the reference CCDC 680528. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5

Crystal data and structure refinement of **3a**

Empirical formula	$C_{17}H_{19}N_3O$
Formula weight	281.35
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	
a (Å)	12.6714 (3)
b (Å)	11.8221 (2)
C (Å)	10.7275 (2)
β (°)	111.481 (8)
Volume (Å^3)	1495.38 (5)
Z	4
Calculated density	1.25
Absorbtion coefficient	0.160
F(1000)	934
Crystal size (mm)	0.20 × 0.18 × 0.16
θ Range for data collection	2.44-29.04 θ
Reflection collected / unique	9679
Completeness to θ = xx.yy	99.76%
Refinement method	Full-matrix least-square on F^2
Data / restraints /parameters	3982 / 0/ 266
Goodness-of-fit on F^2	1.046
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0468
R indices (all data)	0.0757

CONCLUSION

During this work, we succeeded in synthesizing seven new 8-hydroxyquinoline derivatives by a Mannich reaction from 5-cyano and 5-azidomethyl-8-hydroxyquinoline with piperidine, pyrrolidine, morpholine or dibenzylamine. In all cases, a single product was isolated in medium to fair yield and characterized by suitable spectroscopies. The molecular structure of one of these *C*-ortho-substituted phenol (**3a**) could be fully ascertained by X-ray diffraction. These new compounds are currently evaluated for their complexing and biological properties as antibacterial or fungicide agents.

EXPERIMENTAL

Melting points were measured with a Buchi 510 apparatus and are uncorrected. Nmr spectra were recorded in DMSO-d_6 or $CDCl_3$ using a Bruker AC200 spectrometer operating at 200

MHz for ^{1}H and 50 MHz for ^{13}C. Assignments of the various protons were supported by successive irradiations. IR spectra were recorded on a Perkin Elmer 577 spectrometer, solid products being palletized in KBr. Elemental analyses were carried out by the 'Service de Microanalyse' of the 'Institut de Chimie des Substances Naturelles' in Gif-sur-Yvette, France. Esi$^+$-HRMS were performed on a QTOF micro Waters MS-spectrometer at the University Blaise Pascal in Clermont Ferrand, France and ms-IE$^+$ on a Polaris thermo-electron MS-spectrometer at the UATRS/CNRS in Rabat, Morocco.

5-Cyanomethyl-8-hydroxyquinoline (2a). 5-Chloromethyl-8-hydroxyquinoline·HCl **1** [6] (4.60 g, 20 mmoles) were carefully added over 15 min into a solution of KCN (3.9 g, 3.0 eq) in dry DMSO (50 mL) at 90°C under Ar under an efficient fume board. The mixture was stirred under 95°C for 1 hour, allowed to cool to rt, poured onto 100 mL of chilled water. The precipitate was filtered on a sintered glass and thoroughly washed with cold water, dried *in vacuo* to yield the nitrile **2a** (3.12 g, 84%) as a brown solid used without further purification for the Mannich reaction; mp 179-180°C (benzene, Litt. [5a] 178-180°C); IR: 2260 cm^{-1}; ^{1}H and ^{13}C nmr, see Table 1 & 2. Other ^{13}C nmr signal: 116.9 (*C*N). EI$^+$-ms: m/z 184.06 (44) [M]$^+$, 183.09 (26), 155.11 (54), 130.15 (30), 79.09 (100), 61.12 (20).

5-Azidomethyl-8-hydroxyquinoline (2b). A mixture of 5-chloromethyl-8-hydroxyquinoline·HCl **1** (4.60 g, 20 mmoles) and NaN_3 (7.84 g, 3 eq) in abs. acetone (100 mL) was refluxed for 20 hours under controlled atmosphere (N_2). After cooling, the solvent was evaporated under reduced pressure and the residue partitioned between $CHCl_3$/H_2O (150 mL, 1:1). The organic phase was isolated, washed with water (3×20 mL), dried (Na_2SO_4), and finally concentrated *in vacuo* to yield the azide **2b** as a grey solid (3.12 g, 90%) used without further purification for the Mannich reaction; mp 110°C (benzene); IR: 2090 cm^{-1}; ^{1}H and ^{13}C nmr, see Table 1 & 2. *Anal.* Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.04; H, 3.93; N, 27.36. EI$^+$-ms: m/z 200.97 (14) [M+H]$^+$, 158.05 (92), 156.91 (100), 130.14 (20), 79.06 (82), 61.07 (26).

General procedure for the Mannich reaction. An equimolar mixture of the substrate (**2a** or **2b**), paraformaldehyde, and the sec. amine in abs. EtOH (30 mL) was refluxed for 4 hours under controlled atmosphere (N_2). After cooling, the solvent was evaporated under reduced pressure and the resulting solid isolated on a sintered glass, washed with cold ether (*ca*. 30 mL), and finally dried *in vacuo*. When possible, analytical samples were obtained by crystallization from EtOH.

5-Cyanomethyl-7-piperidinomethyl-8-hydroxyquinoline 3a was obtained as a brown solid in 78% yield (620 mg from 2.7 mmoles of **2a**); mp 150°C; IR: 2270 cm^{-1} (C≡N stretching); ^{1}H nmr, see Table 3; ^{13}C nmr, see Table 4; other ^{13}C nmr signals: 119.4 (*C*N), 57.5 (C7a), 53.9 (Ca), 25.6 (Cb), 23.9 (Cc). *Anal.* Calcd. for $C_{16}H_{17}N_3O$: C, 72.57; H, 6.81. N, 14.94. Found: C, 72.53; H, 6.71; N, 14.87. ESI$^+$-hrms: m/z 282.1609 (13) [M+H]$^+$, 197.0697 (100) [M-$C_5H_{10}N$]$^+$, 158.9972 (5).

5-Cyanomethyl-7-pyrrolidinomethyl-8-hydroxyquinoline 3b was obtained as a brown solid in 69% yield (620 mg from 2.7 mmoles of **2a**); mp 110°C; IR: 2252 cm^{-1} (C≡N stretching); ^{1}H nmr, see Table 3; ^{13}C nmr, see Table 4; other ^{13}C nmr signals: 119.4 (*C*N), 53.9 (C7a), 53.6 (Ca), 23.3 (Cb). EI$^+$-ms: m/z 267.99 (22) [M+H]$^+$, 198.05 (16), 156.93 (42), 130.12 (12), 86.14 (14), 84.13 (18), 79.07 (100), 70.18 (82), 61.15 (18); ESI$^+$-hrms: m/z 268.1442 [M+H]$^+$; X-ray structure, see Fig. 1.

5-Cyanomethyl-7-morpholinomethyl-8-hydroxyquinoline 3c was obtained as a beige solid in 77% yield (590 mg from 2.7 mmoles of **2a**); mp 138°C; IR: 2307 cm^{-1} (C≡N stretching); ^{1}H nmr, see Table 3; ^{13}C nmr, see Table 4; other ^{13}C nmr signals: 119.3 (*C*N), 56.7 (C7a), 66.3 (Ca), 53.3 (Cb). *Anal.* Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.75; H, 5.99; N, 14.77. EI$^+$-ms: m/z (26) 283.93 [M+H]$^+$, 275.76 (16), 198.06 (52), 156.94 (58), 130.14 (14), 88.11 (32), 79.08 (100), 61.15 (20).

5-Azidomethyl-7-piperidinomethyl-8-hydroxyquinoline 3d was obtained as an orange hygroscopic gum in 81% yield (1.2 g from 5.0 mmoles of **2b**); IR: 2096 cm^{-1} (N_3 stretching); ^{1}H nmr, see Table 3. ESI$^+$-ms: m/z 297.95 (2) [M+H]$^+$, 163.88 (22), 156.88 (100), 130.11 (10), 100.14 (10), 98.12 (16), 86.12 (48), 84.12 (76), 79.07 (58), 61.09 (14). ESI$^+$-hrms: m/z 298.1609 [M+H]$^+$.

5-Azidomethyl-7-pyrrolidinomethyl-8-hydroxyquinoline 3e was obtained as a dark hygroscopic gum in 60% yield (177 mg from 2.5 mmoles of **2b**); IR: 2106 cm^{-1} (N_3 stretching); ^{1}H-nmr, see Table 3. ESI$^+$-ms: m/z 283.05 (2) [M]$^+$, 172.06 (14), 159.05 (48), 156.93 (30), 130.12 (40), 117.12 (28), 89.10 (12), 79.07 (100), 61.09 (16). ESI$^+$-hrms: m/z 284.1507 [M+H]$^+$.

5-Azidomethyl-7-morpholinomethyl-8-hydroxyquinoline 3f was obtained as a yellow solid in 40% yield (300 mg from 2.5 mmoles of **2b**); mp 134°C; IR: 2097 cm^{-1} (N_3 stretching); ^{1}H nmr, see Table 3; ^{13}C nmr, see Table 4; other ^{13}C nmr signals: 59.7 (C7a), 66.9 (Ca), 53.2 (Cb). *Anal.* Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72, N, 23.40. Found: C, 60.14; H, 5.68, N, 23.26. EI$^+$-ms: m/z 257.1 (27) [M-N_3]$^+$, 202.1 (100).

5-Cyanomethyl-7-(*N*,*N*-dibutylamino)methyl-8-hydroxyquinoline 3g was obtained as pale yellow needles in 65% yield (640 mg from 2.5 mmoles of **2a**); mp 113°C; IR: 2102 cm^{-1} (C≡N stretching); ^{1}H nmr, see Table 3; ^{13}C nmr, see Table 4; other ^{13}C nmr signals: 137.4, 129.5, 128.7 (Ar.), 115.3 (*C*N), 58.3 (Ca), 54.9 (C7a). *Anal.* Calcd. for $C_{26}H_{23}N_3O$: C, 79.36; H, 5.89, N, 10.68. Found: C, 79.11; H, 5.79, N, 10.56. EI$^+$-ms: m/z 394.19 (52) [M+H]$^+$, 350.97 (64), 243.12 (100), 198.13 (93), 141.00 (28).

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