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7-(IMIDAZOLIDIN-1-YLMETHYL)QUINOLIN-8-OL: AN UNEXPECTED PRODUCT FROM A MANNICH-TYPE REACTION IN BASIC MEDIUM

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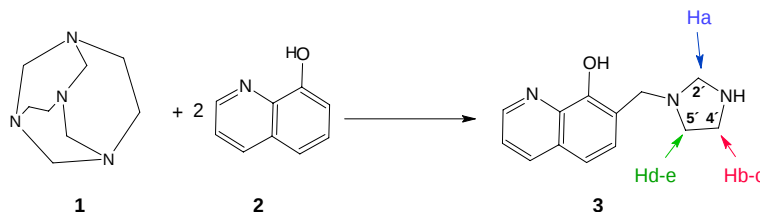
Abstract – 7-(Imidazolidin-1-ylmethyl)quinoline-8-ol, an *N*-substituted imidazolidine, was synthesized in a one-step reaction between 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) and 8-hydroxyquinoline. Obtaining this substance enhanced the scope of possibilities in the synthesis of unsymmetrically *N,N*-disubstituted imidazolidines. ¹H-NMR spectral studies revealed that this type of substance does not undergo ring-chain tautomerism.

In the course of our research into Mannich-type reactions in basic medium between macrocyclic amins and nucleophiles, we developed an *ortho*-regioselective method for preparing 1,3-bis(2'-hydroxy-5'-substitutedbenzyl)imidazolidines (BISBIAs) from 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) (**1**) and phenols,¹ using the concept of inter- and intramolecular hydrogen bonding to explain the *ortho*-regioselectivity of this reaction.

In order to analyze the effect of intramolecular hydrogen-bonding acceptor sites, we decided to carry out some reactions between **1** not only with 8-hydroxyquinoline (**2**) and 2-substituted phenols with hydrogen bond acceptor groups, such as *o*-nitrophenol, salicylaldehyde and 2-hydroxy-4-methoxy-acetophenone, but also with oxine π -isoelectronic systems, such as α - and β -naphthol. Intramolecular hydrogen bond formation in **2** and in the above mentioned phenols is of special interest, because this hydrogen bond induces important changes in their reactivity.

In this paper we report on the exclusive and preferential reaction between **1** and **2** to give an unsymmetrical imidazolidine (**3**) (Scheme 1). Although many methods have been described in the literature for obtaining symmetrically *N,N*-disubstituted imidazolidines there are few reports concerning the synthesis of unsymmetrical substituted imidazolidines²⁻⁶ and only one on *N*-monobenzylimidazolidines.⁷ It is noteworthy that the development of mild and efficient methods to obtain this heterocyclic systems has been

attracting much attention due not only to its pharmacological potential,²⁻⁸ but also to its use as a chiral support in asymmetric synthesis and as a component in many drugs.⁹



Scheme 1

Compound (3) could be the key to further synthetic reactions, mainly electrophilic substitution on the *N*-H group, leading to the construction of desired libraries of larger size using a variety of alkyl halides, acyl chlorides, isocyanates or carbonyl compounds. Besides, 3 is a potentially useful intermediate for the synthesis of heterocyclic compounds containing the quinoline ring system. Quinoline derivatives represent the effective moiety in several antimalarial drugs,¹⁰ some of which in addition exhibit strong cytotoxic or antimicrobial properties.^{11,12}

A close inspection of the ¹H-NMR spectrum of the crude reaction between 1 and 2 revealed that the reaction was producing unsymmetrical imidazolidines as indicated by the A₂B₂ splitting pattern of the ethylene residue, similar to that reported by Perillo *et al.*² for unsymmetrical *N,N*-dibenzylimidazolidines. According to our experience concerning the Mannich reaction in basic medium of phenols with 1, unsymmetrical *N,N*-disubstituted imidazolidines cannot be formed because of the high *ortho*-regioselectivity of this reaction. After isolating and purifying the main reaction product (56% yield), it was established that its structure corresponded to 3. The molecular structure of 3 became evident from NMR spectral measurements in CDCl₃. Thus, four signals were presented in the aliphatic region of the ¹H-NMR spectrum where three signals usually appear. Signals were unequivocally assigned to protons of the imidazolidine ring and to benzylic methylene, based on chemical shifts and correlation in 2D-COSY spectrum. Signals for aminallic and benzylic methylenes were single peaks indicating an average signal for all possible conformations, due to rapid conformational exchange (on the NMR spectral time scale), having ring inversion in both nitrogens and free rotation throughout the *N*-CH₂-Ar moiety. However, the ethylenediamine moiety (Hb-e hydrogens) proton signals were not isochronous and their signals presented an A₂B₂ system which is characteristic of unsymmetrically *N,N*-disubstituted imidazolidines.²

Two spin-spin coupling systems (AB and ABX) were identified in the aromatic region. The AB system was assigned to the protons in the carbocyclic ring system, whilst the second system corresponded to that of the "pyridine" ring. HMBC and HMQC heteronuclear correlation experiments as well as signal integrals ratio led us to establish unequivocally the imidazolidine ring. Figure 1 shows the ³J heteronuclear correlation of aminallic hydrogens (δ=3.65) to carbons 4' and 5'. A ³J is also shown between Hd-e hydrogens (δ=2.82) and

the benzylic carbon ($\delta=54.5$). Compound (**3**) was identified as the imidazolidine-7-(imidazolidin-1-ylmethyl)quinolin-8-ol. The M^+ peak in LR EI-MS at 229 and elemental analysis further confirmed the structure.

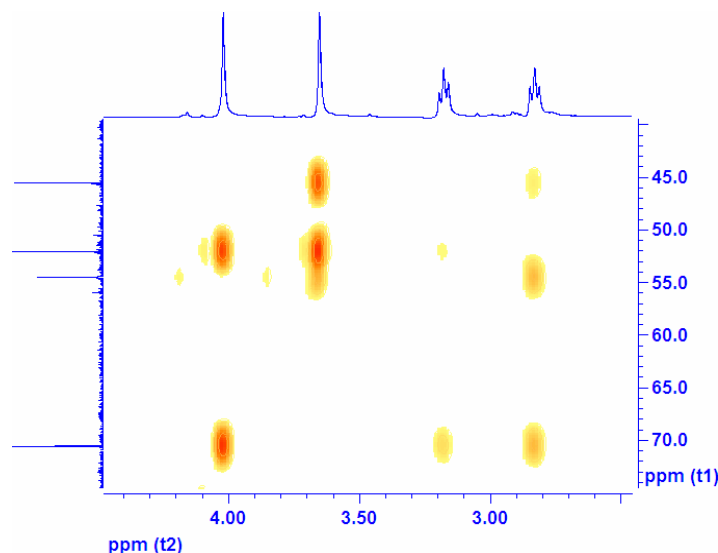
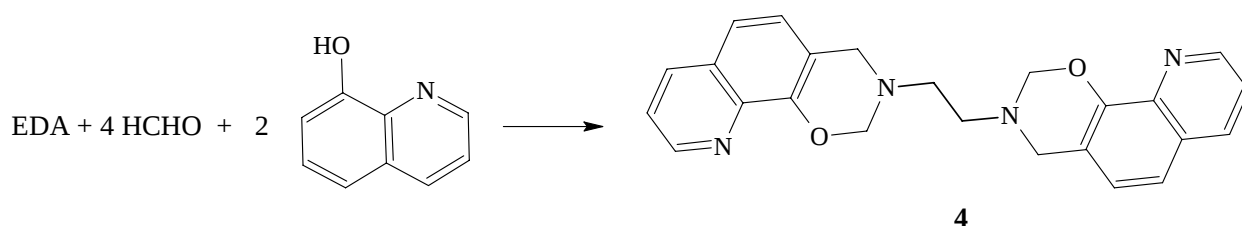


Figure 1

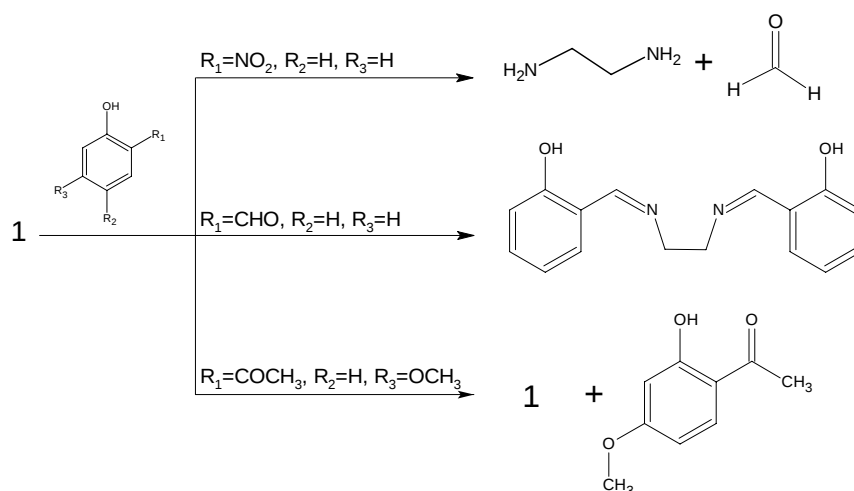
On the other hand, **3** is also an aminomethylphenol (*ortho*-Mannich base) able to form O–H $\cdots$ N intramolecular hydrogen bonds. The strength of these intramolecular hydrogen bonds has been studied.^{13,14} Other studies of their spectral properties^{15,16} have shown that this is a strong interaction producing additional stabilization for the Mannich base. The impact of the H-bond in these Mannich bases so formed is well reflected in ^1H -NMR spectra in which the benzylic hydrogens are shifted to lower field ($\Delta\delta > 0.25$ ppm)¹ compared to other benzylimidazolidines which cannot form this type of H-bond.² Besides, a very broad absorption in the IR spectrum of **3** corroborates the proton transfer process in this *ortho*-Mannich base.¹⁵ Then, it was expected that this H-bond induces ring-chain tautomerism. In order to establish if **3** undergoes ring-chain tautomerism, ^1H -NMR experiments were carried out using DMSO-*d*₆ which stimulates ring-chain tautomerism equilibrium.¹⁷ Our results showed that only the cyclic form was present, because the spectra did not show the signal corresponding to aldiminic hydrogens near 7.00 ppm¹⁸ and the characteristic signal of an aminated methylene always appeared at 3.65 ppm.

Next, in order to check another additional possibility to obtain **3** we decided to carry out the reaction using the method described by Burke.¹⁹ Thus, a mixture of ethylenediamine, 8-hydroxyquinoline and 37% aqueous formaldehyde in a 1:2:4 ratio at room temperature with continuous stirring for 4 h afforded 3,3'-ethane-1,2-diylbis-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*h*]quinoline (**4**) in 92% yield (Scheme 2). Neither **3** nor phenol-formaldehyde polymers containing 8-hydroxyquinoline residues²⁰ were detected in the reaction mixture.



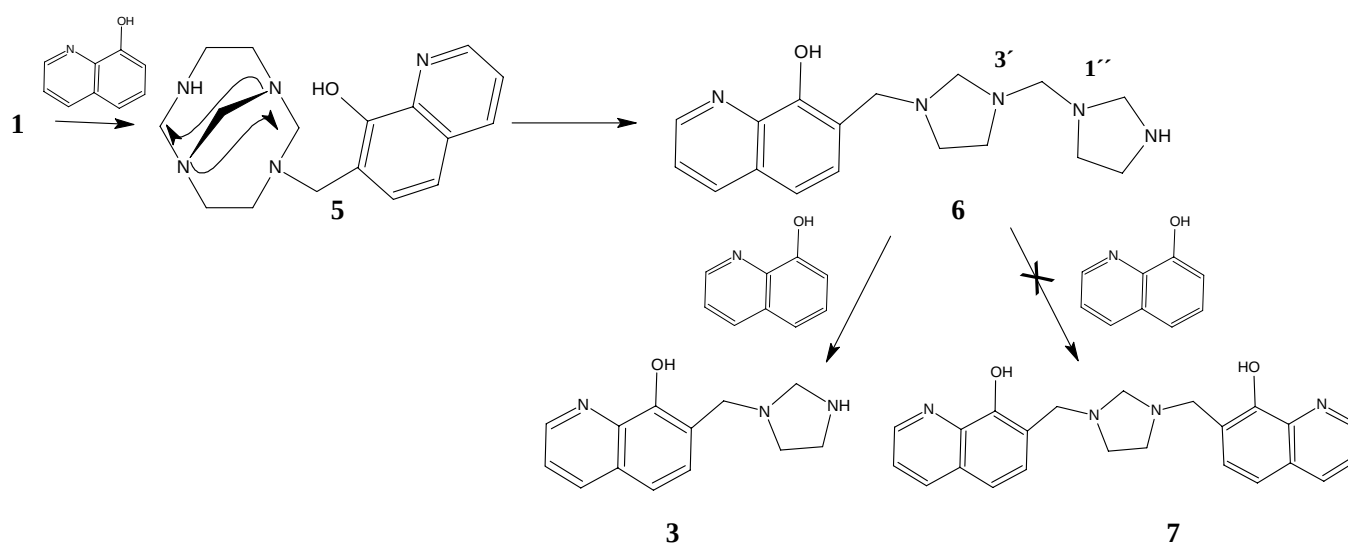
Scheme 2

In order to explore the generality of the reaction, we chose three phenols, which also form an intramolecular hydrogen bond, which were subject to the same reaction conditions to obtain **3**. Nevertheless, the reaction using these phenols never afforded *N*-monobenzylimidazolidines. As shown in Scheme 3, ethylenediamine and formaldehyde were obtained owing to the decomposition of TATD with *o*-nitrophenol; reaction with salicylaldehyde gave *N,N'*-ethylenebis(salicylaldehydeimine) as the major product (62%), whilst starting reagents were quantitatively recovered when 2-hydroxy-4-methoxy-acetophenone was used.



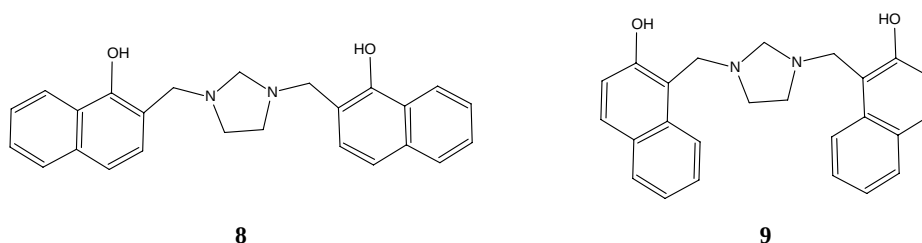
Scheme 3

Based on these preliminary results, where undesired products were obtained, we concluded that formation of *N*-monosubstituted imidazolidines from **1** is restricted to **2**. According to the above experimental results, we assume that compound (**3**) formation should have a different pathway from that reported previously.¹ Then, we proposed a mechanism for the synthesis of **3**, as shown in Scheme 4, in which the intermediate (**5**) undergoes an intramolecular rearrangement to **6** before the attack of a second molecule of oxine can occur. We assume that a subsequent regioselective cleavage of the *N*₃'-CH₂-*N*₁' moiety in **6** furnishes the products. The intermolecular hydrogen bond interaction between **2** and *N*₃' to form **3** is more favourable than that on *N*₁' to form **7**, which was not detected in the reaction mixture, because the introduction of the heteroatom (quinolinic nitrogen) in **6** influences the hydrogen bond ability of *N*₃' through electronic factors.



Scheme 4

These facts strongly suggest that the introduction of the heteroatom (quinolinic nitrogen) forces the reaction to give 3. In support of this assumption, we found that the reaction of 1 with α - and β -naphthol under the same conditions afforded the corresponding symmetrical imidazolidines (8 and 9). Thus, it is concluded that the introduction of a further hydrogen bonding acceptor site in 2 is the main factor responsible for the observed selective production.



EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Paragon FT-IR system FT-IR instrument. NMR spectra were performed in CDCl_3 at rt on a Bruker AMX 400 Avance. Melting points were taken with an Electrothermal apparatus and are uncorrected. Elemental analysis was done on a Carlo Erba instrument.

Synthesis of 7-(imidazolidin-1-ylmethyl)quinolin-8-ol (3): To a solution of 1 (168 mg, 1 mmol) in water (2 mL) was dropwise added a solution of 2 (290 mg, 2 mmol) in dioxane (3 mL) at rt and the mixture was stirred for 24 h, when a yellow precipitate appeared. The product (257 mg, 56%) was filtered off and washed with water and benzene. Recrystallization from ethanol gave a yellow solid: mp 134-135 °C; IR (KBr) 3447, 3070-2200, 3053, 2979, 2925, 2837, 1560, 1450, 1375, 1230; $^1\text{H-NMR}$

(CDCl₃) δ 2.82(t, J = 7.2 Hz, 2H), 3.17(t, J = 7.2 Hz, 2H), 3.65(s, 2H), 4.01(s, 2H), 4.15(bs, 1H), 7.27(d, J = 7.2 Hz, 1H), 7.33(d, J = 7.2 Hz, 1H), 7.40(dd, J = 8.4, 4.6 Hz, 1H), 8.10(dd, J = 8.4, 1.6 Hz, 1H), 8.85(dd, J = 4.6, 1.6 Hz, 1H). ¹³C NMR (CDCl₃) δ 45.5, 52.1, 54.5, 70.6, 117.5, 119.1, 121.4, 127.9, 128.2, 134.9, 138.4, 148.7, 152.2. Anal. Calcd for C₁₃H₁₅N₃O: C, 68.10; H, 6.59; N, 18.32. Found: C, 68.06; H, 6.67; N, 18.33. LR EI-MS: m/z 229 (M⁺).

Synthesis of 3,3'-ethane-1,2-diylbis-3,4-dihydro-2H-[1,3]oxazino[5,6-*h*]quinoline (4): Under vigorous stirring a mixture of ethylenediamine (0.34 mL, 5 mmol) and 8-hydroxyquinoline (1.5 g 10 mmol) was dissolved in dioxane (10 mL) and formaldehyde (1.5 mL, 20 mmol) was slowly added. Stirring was continued for 4 h at rt until a precipitate appeared. The solid was filtered off and washed with water (1.83 g, 92%). Recrystallization from ethanol gave a white solid: mp 175-176 °C. IR (KBr) 3030, 2930, 2860, 1480, 1435, 1250; ¹H NMR(CDCl₃) δ 3.13(s, 4H), 4.22(s, 4H), 5.21(s, 4H), 7.14(d, J = 8.4 Hz, 2H), 7.33(d, J = 8.4 Hz, 2H), 7.39(dd, J = 8.3, 4.2 Hz, 2H), 8.09(dd, 2H), 8.90(dd, J = 8.3, 1.7 Hz, 2H). ¹³C NMR (CDCl₃) δ 50.2, 50.1, 50.7, 83.6, 119.1, 121.2, 126.1, 128.2, 135.9, 136.1, 139.4, 149.5, 149.6. Anal. Calcd for C₂₄H₂₂N₄O₂: C, 72.34; H, 5.56; N, 14.06. Found: C, 72.38; H, 5.27; N, 14.07.

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REFERENCES AND NOTES

1. A. Rivera, G. I. Gallo, M. E. Gayón, and P. Joseph-Nathan, *Synth. Commun.*, 1993, **23**, 2921.
2. I. A. Perillo, C. de los Santos, and A. Salerno, *Heterocycles*, 2003, **60**, 89.
3. A. R. Katritzky, K. Suzuki, and H.-Y. He, *J. Org. Chem.*, 2002, **67**, 3109.
4. J. Zhao, V. Pattaropong, Y. Jiang, and L. Hu, *Tetrahedron Lett.*, 2003, **44**, 229.
5. I. Coldham, R. C. B. Copley, T. F. N. Haxell, and S. Howard, *Org. Lett.*, 2001, **3**, 3799.
6. J. B. Lambert, D. E. Husenland, and G.-T. Wang, *Synthesis*, 1986, 657.
7. B. Li, R. Bemish, R. A. Buzon, C. K.-F. Chiu, S. T. Colgan, W. Kissel, T. Le, K. R. Leeman, L. Newell, and J. Roth, *Tetrahedron Lett.*, 2003, **44**, 8113.
8. I. A. Perillo, E. Repetto, M. C. Caterina, R. Massa, G. Gutkind, and A. Salerno, *Eur. J. Med. Chem.*, 2005, **40**, 811 and references cited therein.

9. D. Lucet, T. Le Gall, and C. Mioskowski, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2580.
10. T. J. Egan, D. C. Ross, and P. A. Adams, *Febs Lett.*, 1994, **352**, 54.
11. K. Kamienska-Trela, L. Kania, J. Sitkowski, and L. Kaczmarek, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1617.
12. H. Z. Alkhathlan, *Synth. Commun.*, 1992, **22**, 2659.
13. A. Koll, S. M. Melikova, A. Karpfen, and P. Wolschann, *J. Mol. Struct.*, 2001, **559**, 127.
14. W. Schilf, A. Szady-Chelmieniecka, E. Grech, P. Przybylski, and B. Brzezinski, *J. Mol. Struct.*, 2002, **643**, 115.
15. M. Rospenk, L. Sobczyk, A. Rabold, and G. Zundel, *Spectrochim. Acta A*, 1999, **55**, 855.
16. A. Fedorowicz, J. Mavri, P. Bala, and A. Koll, *Chem. Phys. Lett.*, 1998, **289**, 457.
17. L. Lázár, A. Göblyös, F. Evanics, G. Bernáth, and F. Fülöp, *Tetrahedron*, 1998, **54**, 13639.
18. J. R. Pliego, A. F. C. Alcântara, D. P. Veloso, and W. B. Almeida, *J. Braz. Chem. Soc.*, 1999, **10**, 381 and references cited therein.
19. W. J. Burke and C. W. Stephens, *J. Am. Chem. Soc.*, 1952, **74**, 1518.
20. N. M. Salema, K. A. K. Ebraheemb, and M. S. Mubaraka, *React. Funct. Polym.*, 2004, **59**, 63.
21. **2,2'-[Imidazolidine-1,3-diyl]di(methylene)]di(1-naphthol) (8)**: 42%; mp 69-73 °C. IR (KBr) 3100-2650, 3050, 2819, 1634, 1597, 1577, 1277. ¹H NMR(CDCl₃) δ 3.08(s, 4H), 3.70(s, 2H), 4.10(s, 4H), 7.11(d, *J* = 9.0 Hz, 2H), 7.31(d, *J* = 9.0 Hz, 2H), 7.47-7.49 (m, 4H), 7.77(d, *J* = 8.4 Hz, 2H), 8.21(d, *J* = 8.3 Hz, 2H). ¹³C NMR (CDCl₃) δ 49.9, 50.5, 74.4, 113.4, 119.7, 121.0, 124.6, 125.1, 125.7, 126.8, 127.4, 133.1, 149.0. Anal. Calcd for C₂₅H₂₄N₂O₂: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.29; H, 6.31; N, 7.26. **2,2'-[Imidazolidine-1,3-diyl]di(methylene)]di(1-naphthol) (9)**: 88%; mp 152-153 °C. IR (KBr) 3080-2350, 3052, 2860, 1622, 1466, 1450, 1228. ¹H NMR(CDCl₃) δ 3.14(s, 4H), 3.76(s, 2H), 4.41(s, 4H), 7.14(d, *J* = 8.8 Hz, 2H), 7.32(t, *J* = 8.4 Hz, 2H), 7.45(t, *J* = 8.4 Hz, 2H), 7.67(d, *J* = 8.8 Hz, 2H), 7.74(d, *J* = 8.4 Hz, 2H), 7.81(d, *J* = 8.4 Hz, 2H). ¹³C NMR (CDCl₃) δ 51.9, 53.2, 75.1, 111.1, 119.0, 120.9, 122.6, 126.5, 128.5, 128.8, 129.5, 132.2, 156.2. Anal. Calcd for C₂₅H₂₄N₂O₂: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.02; H, 6.30; N, 7.30.