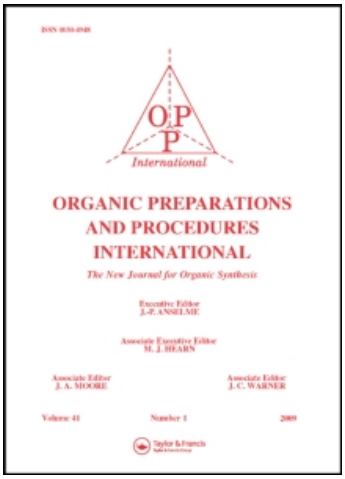


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# SYNTHESIS OF HALOGENATEDISOXAZOLYL NAPHTHOQUINONES

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# SYNTHESIS OF HALOGENATED ISOXAZOLYL NAPHTHOQUINONES

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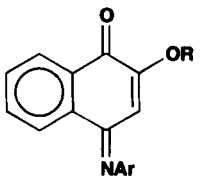
The synthesis of isoxazolyl naphthoquinone derivatives (**1a-3**) from sodium 1,2-naphthoquinone-4-sulfonate and 3,4-dimethyl-5-aminoisoxazole has been previously described;[1] **1a** exhibited significant biological activity against *T. cruzi*[2] and *S. aureus*.[3] As an extension of these investigations, the synthesis of **1b-d** was undertaken[4] in order to improve their physicochemical properties, and hopefully their biological activity. Taking into account the biological importance, and that some halogenated naphthoquinones have shown to possess antibacterial[5] and antitumoral[6] activity, we focused our attention on brominated and chlorinated derivatives of isoxazolyl naphthoquinones.

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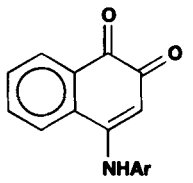


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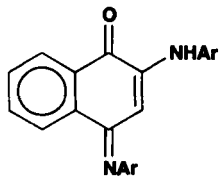
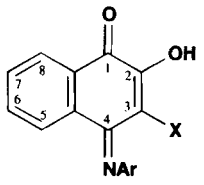



**3**

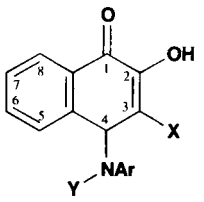
a) R = H b) R = $CH_3CO$ c) R = $CH_3(CH_2)_2CO$ d) R = $CH_3(CH_2)_6CO$
e) R = $CH_3(CH_2)_{14}CO$ f) R = p-$MeC_6H_4SO_2$ Ar = 3,4-dimethylisoxazolyl

The present work describes the preparation of new halogenated derivatives of **1a** and **2** (**4a** and **5b**) and an improved synthetic procedure for **4b**, a previously reported compound.[7] The by-product **5a** was isolated and characterized albeit in poor overall yield.

The preparation of bromine derivatives of isoxazolyl naphthoquinones (**4a** and **5a,b**) was carried out by reaction of **1a**[1] with N-bromosuccinimide (NBS) in dimethylformamide (DMF). When a 1:1.5 molar ratio of **1a**:NBS was used, a mixture of 65% of 3-bromo-2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (**4a**), 4% of 3-bromo-N-(3,4-dimethyl-5-isoxazolyl)-4-amine-1,2-naphthoquinone (**5a**) and 29% of 3-bromo-N-bromo-N-(3,4-dimethyl-5-isoxazolyl)-4-amine-1,2-naphthoquinone (**5b**) was obtained (Table 1). The separation of these compounds was achieved by preparative radial chromatography (PRC).




a) X = Br
b) X = Cl




a) X = Br, Y = H
b) X = Y = Br
c) X = Y = Cl

**4** Ar = 3,4-dimethylisoxazolyl **5**

Inspection of Table 1 reveals two important features. The first indicates that no starting material was detected when a molar ratio **1a**:NBS of 1:1.5 was used. The second observation is that as the NBS concentration is increased, the yield of monobrominated product **4a** gradually decreased and at a molar ratio of 1:2, the only product isolated was **5b** in 94% yield of pure material. Longer reactions time (30 and 60 min) did not affect the yield of products. These observations coupled with other halogenations,[8] suggest that bromination occurs first at position-3 to give **4a**, which then tautomerized to its ketonic form **5a**; **5a** is then brominated at the -NH group.[9] In addition, if **5b** remains in solution (ethanol, dimethyl sulfoxide, dichloromethane, chloroform), **4a** is formed spontaneously with little amounts of **5a**.



**TABLE 1.** Bromination of 2-Hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (**1a**) with N-bromosuccinimide (NBS).

| | Ratio | Compounds (%) | | | |
|---|---|---|---|---|---|
| Reaction | 1a:NBS | **1a** | **4a** | **5a** | **5b** |
| 1 | 1:1 | 52 | 46 | – | – |
| 2 | 1:1.5 | – | 65 | 4 | 29 |
| 3 | 1:1.6 | – | 44 | 4 | 49 |
| 4 | 1:1.7 | – | 34 | 4 | 59 |
| 5 | 1:1.9 | – | 7 | 3 | 90 |
| 6 | 1:2 | – | – | – | 94 |

Taking into account the low yields of **5a** (3-4%), this compound might be an intermediate in the forward and reverse reactions. It is thus possible that the disappearance rate of these species could be greater than their appearance.

Recently, we described the synthesis of **5c** in high yields by chlorination of **1a** in acetic acid at 25°; **4b** was found in low yields as by-product.[7] All attempts to obtain **4b** as main product were unsuccessful, **5c** being obtained in all cases as the main product. For this reason, we examined the reaction of **1a** (1 equiv.) and 3-chloro-5,5-dimethylhydantoin (1 equiv.) in dimethylformamide for 30 min. at 25° gave a 51% yield of **4b**, with a 46% recovery of starting material. However, if the reaction is carried out with 1.5 equiv. of the chlorinating reagent, a mixture of **1a** (29%), **4b** (43%) and **5c** (27%) was formed, while **4b** (44%) and **5c** (54%) were formed with a molar ratio of 1:2. As can be observed, this new method improves the synthesis of **4b**, going from 4% to 51% yield. The fact that

the corresponding diketonic monochloride derivative was not observed, is consistent with the above proposed mechanism for halogenated compounds. Spectroscopic data of **4a,b** and **5a,b** are given in Table 2.

**TABLE 2.** Physical Properties Halogenated Isoxazolyl Naphthoquinones

| Cmpd | $^1$H NMR (ppm)[a] | | | | | | IR ($cm^{-1}$)[b] | | | | UV (nm)[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Me | OH | NH | H-5 | H-6,7 | H-8 | C=O | OH | NH | C=N | $\lambda_{max}$ |
| **4a** | 1.64 (s, 3H) 2.06 (s, 3H) | 7.69 (br, 1H) | – | 8.15 (m, 1H) | 7.49 (m, 2H) | 7.90 (m, 1H) | 1645 | 3324 | – | 1514 | 239.6 277.2 505.8 |
| **4b** | 1.67 (s, 3H) 2.08 (s, 3H) | Sno[d] | – | 8.11 (m, 1H) | 7.65 (m,2H) | 7.80 (m, 1H) | 1654 | 3325 | – | 1514 | 241.6 506.2 |
| **5a** | 2.60 (s, 3H) 2.93 (s, 3H) | – | 8.46 (m, 1H) | 8.46 (m, 1H) | 8.26 (m, 2H) | 8.02 (m, 1H) | 1727[e] 1662[f] | – | 3439 | 1531 | 260.0 444.0 |
| **5b** | 2.22 (s, 3H) 2.30 (s, 3H) | – | – | 7.48 (m, 1H) | 7.71 (m, 2H) | 8.01 (m, 1H) | 1736[e] 1664[f] | – | – | 1539 | 258.6 440.0 |

a) DMSO-$d_6$; b) KBr (pellets); c) ethanol; d) signal not observed; e) position-2; f) position-1



The $^1$H NMR spectra of the halogenated compounds in DMSO-$d_6$ are in accordance with those of **1a** and **2**.[1,4] In the spectra of **4a** and **4b**, the signal at δ 7.72 corresponding to the H-3 of the quinone ring in **1a** was not observed. The signal at δ 5.8 (H-3 in **2**) were not present in the spectra of **5a** and **5b** and the spectrum of **5b** did not exhibit the signal at δ 9.45 (NH). The chemical shifts of aromatic protons (H-5 to H-8) are in agreement with those previously reported.[1,4,7] Therefore, $^1$H NMR analyses revealed that in **4a**, **4b** and **5a** one halogen atom (bromine or chloride) was incorporated into position-3 while in **5b** the second bromine atom exchanges the proton of the NH group. The mass spectra of **5a** and **5b** confirm the proposed structures, since characteristic isotopic clusters[10] appeared in their molecular ions (**5a**, m/z 346,348 and **5b**, m/z 424,426,428) and in all fragments containing a bromine or chlorine atom. The mass spectra of **4a** and **4b** could not be determined because they decompose at temperatures higher than 229° and 184° respectively which was confirmed by thermal analyses (see Experimental Section).

## EXPERIMENTAL SECTION

Ultraviolet absorption spectra (UV) were carried out on a Shimadzu UV-260 spectrophotometer. The $^1$H NMR spectra were recorded on a 80.13 MHz and a 200.13 MHz Bruker spectrometers, with tetramethylsilane as internal standard. IR spectra were obtained from potassium bromide discs on a

Nicolet 5 SXC FT-IR. The mass spectra were recorded on a Finnigan Model 3300 F-I00 Quadrupole Mass Spectrometer. Melting points were determined on a Büchi 510 Melting point apparatus and were uncorrected. TG-DTG-DTA measurements were made with a Netzsch simultaneous thermal analyzer 429 (CIMM, Córdoba, Argentina), in nitrogen atmosphere. Chromatotron Model 7924T was used for preparative radial chromatography (PRC). Analyses were performed by UMYMFOR Laboratories, Buenos Aires, Argentina. All chemicals and reagents were of analytical grade. 2-Hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine **1a**[1] and 3-chloro-5,5-dimethylhydantoin[11] were prepared as previously reported. Precoated Silica gel (Merck) was used for tin layer chromatography (TLC).

**General Procedure for Synthesis of Bromo Derivatives.**- To a solution of **1a** in N,N-dimethylformamide (DMF) was added dropwise at 25°, a solution of NBS in DMF. The reaction mixture was stirred at room temperature for five minutes. The progress of the reaction was monitored by TLC (EtOAc/EtOH 9:1). Then 100 mL of cooled water (0-5°) were added and the resulting precipitate was filtered, washed with water and dried.

**3-Bromo-2-hydroxy-3,4-dimethyl-(5-isoxazolyl)-1,4-naphthoquinone-4-imine (4a)**.- Following the general procedure, the reaction between **1a** (578.2 mg, 2.16 mmoles) in 20 mL of DMF and NBS (580.2 mg, 3.3 mmol) in 5 mL of DMF afforded up to 776.0 mg of a precipitate, which by PRC (EtOAc/acetone 5:5) yielded 481.5 mg (65%) as dark red crystals of **4a**. Since melts were not observed in the melting point apparatus, TG-DTG-DTA analyses were performed showing that **4a** decomposed with an onset and peak temperatures of 229° and 234° respectively. **4a** decomposed into the mass spectrometer.

*Anal.* Calcd. for $C_{15}H_{11}BrN_2O_3$: C, 52.02; H, 3.18; Br, 22.83; N, 8.09
Found: C, 51.73; H, 3.39; Br, 23.04; N, 8.17

**3-Bromo-N-(3,4-dimethyl-5-isoxazolyl)-4-amino-1,2-naphthoquinone (5a)**.- From the previous reaction, an orange solid was obtained by PRC ($Cl_3CH$/EtOAc 9:1) which after washing with 10 mL of hot ethanol under reduced pressure yielded 31.3 mg (4%) of pure **5a**, mp: 181-182°. MS(70 eV) m/z(%): $M^+$, 348(16.6)-346(18.3), 198(33.9), 130(41.2), 102 (29.7), 76(23.7), 68(73.5), 43(100).

*Anal.* Calcd. for $C_{15}H_{11}BrN_2O_3$: C, 52.02; H, 3.18; Br, 22.83; N, 8.09
Found: C, 51.87; H, 3.47; Br, 23.05; N, 8.20

**3-Bromo-N-bromo-N-(3,4-dimethyl-5-isoxazolyl)-4-amino-1,2-naphthoquinone (5b)**.- Following the general procedure, the reaction between **1a** (107.7 mg, 0.40 mmol) in 4 mL of DMF and NBS (160.0 mg, 0.90 mmol) in 2 mL of DMF yielded **5b** as an orange solid (160.4 mg, 94%) . mp: 169-170°. MS (70 eV) m/z (%): $M.^+$, 428 (1.7)-426 (2.6)-424 (1.7), 348 (22.9), 346 (21.1), 267 (38.5, 198 (100), 96 (30.1), 68 (36.9).

*Anal.* Calcd. for $C_{15}H_{10}Br_2N_2O_3$: C, 42.45; H, 2.35; Br, 37.26; N, 6.60
Found: C, 42.70; H, 2.23; Br, 37.36; N, 6.70

**3-Chloro-2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (4b)**.- A solution of 3-chloro-5,5-dimethylhydantoin (46.7 mg; 0.29 mmol) in 1.5 mL of DMF was added dropwise at 25° to a solution of **1a** (64.4 mg; 0.24 mmol) in 3.5 mL of DMF. The mixture was stirred

for 30 min. and then the reaction mixture was poured into 100 mL of cooled solution (0-5°) of acetic acid (pH 5) and extracted three times with 50 mL of chloroform. The combined extracts were evaporated under reduced pressure at room temperature and the residue was purified by PRC (EtOAc/Acetone, 5:5) yielding 36.9 mg (51%) of **4b** as dark red crystals. Although melting could not be observed on the melting point apparatus, TG-DTG-DTA analyses proved that this compound decomposed with an onset and peak temperatures of 184° and 212° respectively; **4b** decomposed into the mass spectrometer.

*Anal.* Calcd. for $C_{15}H_{11}ClN_2O_3$: C, 59.60; H, 3.64; Cl, 11.59; N, 9.27
Found: C, 59.82; H, 3.95; Cl, 11.42; N, 8.99

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## REFERENCES

1. a)A. E. Fernández, M. M. de Bertorello and R. H. Manzo, *Anal. Asoc. Quím.. Argent.*, **70**, 49 (1982); *Chem. Abs.*, **97**, 6198v (1982); b) C. S. Ortiz, M. R. Longhi, M. M. de Bertorello and M. C. Briñón, *Org. Prep. Proc. Int.*, **23**, 181 (1991).

2. a) E. M. Pahn, M. P. Molina Portela and A. O. M. Stoppani, *Rev. Argent. Microbiol.*, **20**, 107 (1988); *Chem. Abs.*,**110**, 91920d (1989); b) M. N. Schwarcz de Tarlovsky, S. G. Goijman and A. O. M. Stoppani, *ibid.*, **20**, 183 (1988); *ibid.*,**111**, 36497s (1989); c) M. N. Schwarcz de Tarlovsky, S. G. Goijman, M. P. Molina Portela and A. O. M. Stoppani, *Experientia*, **46**, 502 (1990); d) P. Amuchástegui, E. Moretti, B. Basso, N. Sperandeo and M. M. de Bertorello, *Rev. Argent. Miorobiol.*, **22**, 199 (1990); *Chem. Abs.*, **116**, 169943j (1991).

3. P. Bogdanov, I. Albesa, N. R. Sperandeo and M. M. de Bertorello, *Rev. Argent. Microbiol.*, **25**, 119 (1993).

4. N. R. Sperandeo, M. M. de Bertorello and M. C. Briñón, *J. Pharm. Sci.*, **83**, 232 (1994).

5. a) D. E. Pisani, A. J. Elliot, D. R. Hinman, L. M. Aaronson and R. S. Pardini, *Biochem. Pharmacol.*, **35**, 3791 (1986); b) J. R. Ames, M. D. Ryan and P. Kovacic, *J. Free Radicals Biol. Med.*, **2**, 377 (1986).

6. A. J. Lin, B. J. Lillis and A. C. Sartorelli, *J. Med. Chem.*, **18**, 917 (1975).

7. V. G. Dabbene, M. C. Briñón and M. M. de Bertorello, *J. Pharm. Sci.*, Submitted for publication.

8. a) R. H. Thomson, *J. Org. Chem.*, **13**, 377 (1948); b) R. A. Thomson, *ibid.*, **17**, 1083 (1952).

9. E. W. C. W. Thomm and M. Wayman, *Can. J. Chem.*, **47**, 3289 (1969).

10. a) F. W. Mc Lafferty, *"Interpretation of Mass Spectra"* W. A. Benjamin, New York, NY ,1967; b) H. D. H. Budzikiewicz, C. Djerassi and D. H. Williams, *"Mass Spectrometry of Organic Compounds"*, Holden-Day Inc. San Francisco, 1967, and reference therein.

11. R. A. Corral and D. O. Orazi, *J. Org. Chem,* **28**, 1100 (1963).

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