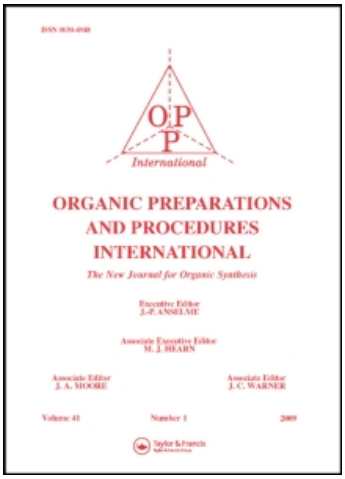

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OPPI BRIEFS

SYNTHESIS OF *bis*-ISOXAZOLYLNAPHTHOQUINONES

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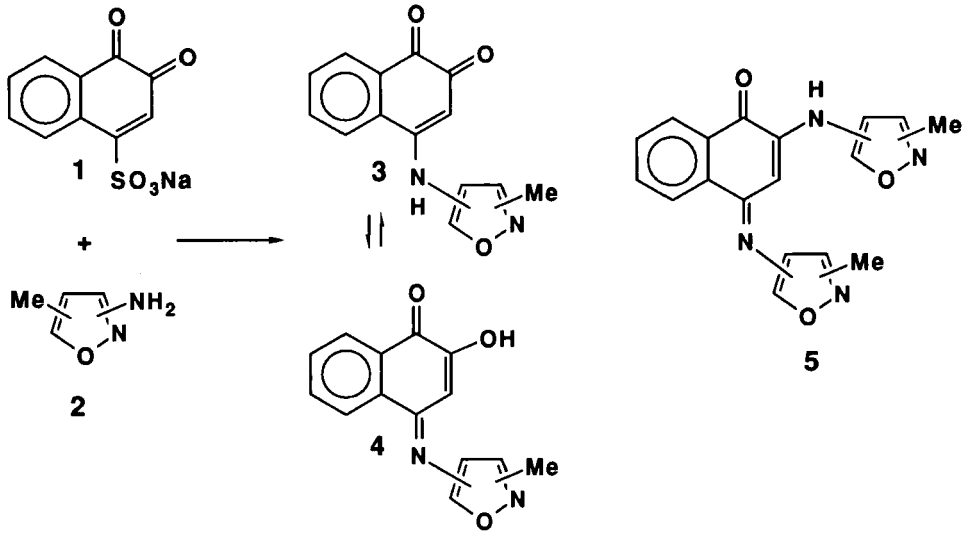
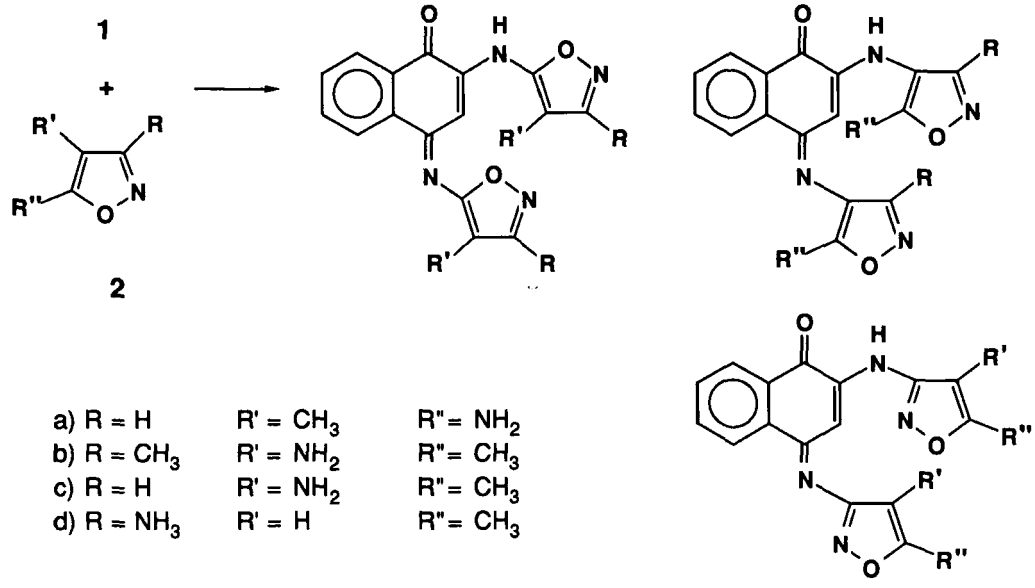
Previous results from our laboratory[1] have indicated that sodium 1,2-naphthoquinone-4-sulfonate (1) reacts with methyl substituted aminoisoxazoles (2) in aqueous solutions to give 4-(aminoisoxazolyl)-1,2-naphthoquinones (3) and 2-hydroxy-N-isoxazolyl-1,4-naphthoquinone-4-imines (4) as the major products, along with low yields of *bis*-isoxazolylnaphthoquinone (5) (Scheme 1). These compounds show trypanocidal activity against *T. cruzi* both *in vitro*[2] and *in vivo*.[3] Based on these findings and the widely known biological activity of many naphthoquinone and isoxazole derivatives,[4] we decided to focus our synthetic efforts towards compounds 5a-e which represent a relatively unexplored class of naphthoquinones[5] with an important potential biological function.



Scheme 1

Extensive studies of the medium, time and temperature effects on the course of these reactions allowed us to select the best reaction conditions to direct the synthesis towards the formation of 5. This paper reports an improved synthetic procedure for the previously reported[1] 5a and the new compounds 5b-d (Scheme 2).

When the reaction between 1 and 2a was carried out in aqueous solution of 3 N HCl at reflux, the disubstituted naphthoquinone 5a was isolated in 60% yield. When 1 reacted with 2b-c in aqueous solution of 2 N HCl at room temperature, a mixture of products was obtained. Compounds 5b-c were isolated from the crude products by extraction with ethyl acetate, followed by chromatography on silica gel, in 27 and 21% yield respectively. The best results were obtained from the reaction of 1 with 2d in aqueous solution of 2N HCl at room temperature which afforded 5d, free of by-products, in 70% yield (Table 1). These compounds were characterized by IR, MS



Scheme 2

TABLE 1. Reaction Conditions for *bis*-Isoxazolylnaphthoquinones

Compound	Experimental Conditions HCl (N)	(°C)	Yield (%)	mp. (°C)
5a	3.0	reflux	60	183-184
5b	2.0	25	27	193-194
5c	2.0	25	21	165-166
5d	2.0	25	70	215-216

TABLE 2. ^{1}H NMR of *bis*-Isoxazolylnaphthoquinones (δ)

Compound	H-3	H-5	H-6	H-7	H-8	Errors (Hz)
5a	7.690	8.580	7.756	7.658	8.172	0.057
5b	5.620	8.535	7.753	7.656	8.229	0.157
5c	6.050	7.531	7.692	7.646	8.206	0.054
5d	7.920	8.538	7.749	7.650	8.228	0.093

and ^1H NMR. The chemical shifts and coupling constants, calculated by LAOCOON III program, are summarized in Tables 2 and 3 respectively.

TABLE 3. Coupling Constants of *bis*-Isoxazolylnaphthoquinones (Hz)

Compound	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}
5a	8.123	1.447	0.661	6.921	1.631	8.016
5b	8.103	1.307	0.507	6.867	1.349	7.914
5c	7.446	1.809	0.153	6.632	1.145	8.517
5d	8.623	1.037	0.436	6.879	1.457	7.753

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 melting point apparatus and were uncorrected. The IR spectra were recorded from potassium bromide discs with a Nicolet 5-SXC FT-IR spectrophotometer. ^1H NMR spectra were obtained in $CDCl_3$ on a Bruker WP 80 SY at 80.13 MHz. Chemical shifts are reported in δ units. The mass spectra were recorded on a Finningan Model 3300 F-100 Quadrupole Mass Spectrometer. Data were collected and processed with an INCOS Data System using a Nova III computer. Column chromatography was performed on silica gel 60 (Macherey Nagel 0.05-0.2 mm). Analyses were performed by UMYMFOR Laboratories, Buenos Aires, Argentina.

2-(4-Methyl-5-isoxazolylamino)-N-(4-methyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (5a).- A solution of 0.196 g (0.002 mol) of 5-amino-4-methylisoxazole in 30 ml of 3 N HCl was added to a solution of 0.260 g (0.001 mol) of sodium 1,2-naphthoquinone-4-sulfonate in 10 ml of water. The reaction mixture was stirred for 30 min at room temperature and then boiled at reflux for 10 min. The insoluble red material was collected, dried and recrystallized from benzene-CCl_4, mp. 183-184°. Its spectral data are in accordance with those previously reported.[1] IR (KBr): 3495 (O-H); 1661 (C=O); 1641 (C=N); 2643 (N-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3); 2.19 (s, 3H, CH_3); 7.66 (m, 1H, H-7); 7.69 (m, 1H, H-3); 7.73 (m, 1H, N-H); 7.76 (m, 1H, H-6); 8.11 (s, 1H, H-3'); 8.15 (s, 1H, H-3'); 8.17 (m, 1H, H-8); 8.58 (m, 1H, H-5). MS (25 eV): m/e (%) 334 (100); 253 (50); 199 (30); 211 (15).

Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.19; N, 16.77

Found: C, 64.66; H, 4.25; N, 16.57

2-(3,5-Dimethyl-4-isoxazolylamino)-N-(3,5-dimethyl-4-isoxazolyl)-1,4-naphthoquinone-4-imine (5b).- To a solution of 0.260 g (0.001 mol) of sodium 1,2-naphthoquinone-4-sulfonate in 10 ml of water, a solution of 0.224 g (0.002 mol) of 4-amino-3,5-dimethylisoxazole in 20 ml of 2N HCl was added. The reaction mixture was stirred for 30 min at room temperature. The insoluble product was collected and washed with water. Then it was suspended in ethyl acetate and extracted with an aqueous solution of NaOH (pH 11-12). The organic phase was washed with water and dried over

Na_2SO_4. The solvent was then removed and the residue was chromatographed on silica gel. Elution with benzene gave N-(3,5-dimethyl-4-isoxazolyl)-4-amino-1,2-naphthoquinone 3b (the less polar compound) as the minor component (0.014 g, 3.90%), mp. 167-168°. The more polar product 5b (0.098 g, 27%) was eluted with benzene-chloroform (1:4), mp. 193-194° after recrystallization from benzene. IR (KBr): 3327 (N-H); 1608 (C=N); 1662 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, CH_3); 2.15 (s, 3H, CH_3); 2.17 (s, 3H, CH_3); 2.27 (s, 3H, CH_3); 5.62 (s, 1H, H-3); 6.48 (br, 1H, N-H); 7.66 (m, 1H, H-7); 7.75 (m, 1H, H-6); 8.23 (m, 1H, H-8); 8.54 (m, 1H, H-5). MS (25 eV): m/e (%) 362 (4); 319 (35); 211 (16); 195 (100).

Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38

Found: C, 65.72; H, 5.23; N, 15.19

2-(5-Methyl-4-isoxazolylamino)-N-(5-methyl-4-isoxazolyl)-1,4-naphthoquinone-4-imine (5c).-A solution of 0.196 g (0.002 mol) of 4-amino-5-methylisoxazole in 40 ml of 2N HCl was added to a stirred solution of 0.260 g (0.001 mol) of sodium 1,2-naphthoquinone-4-sulfonate in 10 ml of water. The mixture was stirred at room temperature for 30 min. The insoluble product was collected, washed with water and dried in vacuum. Then it was suspended in ethyl acetate and extracted with an aqueous solution of NaOH (pH 11-12). The organic layer was washed with water and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel. Elution with ethyl acetate-acetone (1:4) gave 5c (0.071 g, 21%), mp. 165-166° after recrystallization from acetone. IR (KBr): 3328 (NH); 1658 (C=O); 1604 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 6.05 (s, 1H, H-3); 6.62 (br, 1H, N-H); 7.65 (m, 1H, H-7); 7.69 (m, 1H, H-6); 8.06 (s, 1H, H-3'); 8.21 (m, 1H, H-8); 8.23 (m, 1H, H-3'); 8.53 (m, 1H, H-5). MS (25 eV): m/e (%) 334 (7); 319 (2); 291 (69); 195 (100).

Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.22; N, 16.76

Found: C, 64.45; H, 3.99; N, 16.58

2-(5-Methyl-3-isoxazolylamino)-N-(5-methyl-3-isoxazolyl)-1,4-naphthoquinone-4-imine (5d).-A solution of 0.196 g (0.002 mol) of 3-amino-5-methylisoxazole in 40 ml of 2 N HCl was added rapidly to a stirred solution of 0.260 g (0.001 mol) of sodium 1,2-naphthoquinone-4-sulfonate in 10 ml of water. The reaction was completed after stirring for 30 min at room temperature. The insoluble product was collected and recrystallized from acetone giving a yellow product 5d, mp. 232-233°. IR (KBr): 3534 (O-H); 1661 (C=O); 1634 (C=N); 2667 (N-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3); 2.49 (s, 3H, CH_3); 5.86 (s, 1H, H-4'); 6.03 (s, 1H, H-4'); 7.65 (m, 1H, H-7); 7.69 (m, 1H, N-H); 7.75 (m, 1H, H-6); 7.92 (s, 1H, H-3); 8.23 (m, 1H, H-8); 8.54 (m, 1H, H-5). MS (70 eV): m/e (%) 334 (28); 319 (100); 211 (68); 43 (70).

Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.19; N, 16.77

Found: C, 64.98; H, 4.51; N, 16.90

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