Synthesis of New 4-Nitrosophenyl-1,4-dihydropyridines of Pharmacological Interest

I. P. Santander-G.,* Luis J. Núñez-Vergara, J. A. Squella, P. A. Navarrete-Encina*

Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas, Casilla 233, Santiago 1, Chile
Fax 56(2)6782868; E-mail: paosang@vtr.net

Received 28 July 2003; revised 16 September 2003

Abstract: The synthesis and characterization of a series of 4-nitrosophenyl-1,4-dihydropyridines derived from the respective nitro compounds of pharmacological interest is described. The complete synthetic pathway is based on the classical Hantzsch 1,4-dihydropyridine synthesis to obtain the nitrophenyl 1,4-dihydropyridines in a first step, followed by chemical reduction of the nitro compound to the corresponding hydroxylamine and further oxidation to the nitroso derivative. The synthesis and characterization of the compounds is described.

Key words: Hantzsch synthesis, pyridines, reductions, drugs, nitroso compounds

1,4-Dihydropyridines have been broadly studied because of their relevant therapeutic uses[1]. They were synthesized for the first time by Arthur Hantzsch in 1882[2] and successive structural modifications involving additions, reductions and condensations, mainly in the 1, 2 and 6 positions of the dihydropyridine ring were performed. Later in 1977, modifications in positions 1, 3, 4 and 5, resulted in the Bayer[3] group synthesizing the drug Nifedipine, revolutionizing the pharmaceutical market due to its antihypertensive properties. The structural modifications continued until, in 1980, the Kellogg group reported the first crown ether with a dihydropyridine integrated inside the macrocycle with the purpose of mimicking the behavior of the natural coenzyme NADH.[3]

Recently, new compounds related to the 1,4-dihydropyridines have been synthesized in the search for new pharmacological properties.[4–7] A nice example of the effects of the replacement of the *o*-nitrophenyl group of Nifedipine by a xanthone group was reported by Rampa.[8] The presence of a xanthone group in the C-4 position in the 1,4-dihydropyridines ring produced potent and selective derivatives with a chronotropic negative activity. These modifications opened new perspectives in the search for more effective drugs for controlling cardiac arrhythmias.

From the redox point of view, nitroaryl 1,4-dihydropyridines exhibit two redox centers, i.e. the nitrophenyl group capable of being reduced, and the 1,4-dihydropyridine ring capable of being oxidized. In both cases, redox intermediates showing potential toxic properties can be generated. Concerning the electrochemical characterization of this type of compound, several works have been published by our laboratory.[9–11] Those reports document the feasibility of free-radical formation and its reactivity with different biological targets, such as endobiotics (gluthatione, DNA bases, RNA bases) or xenobiotic (*N*-acetylcysteine, captopril).[12–16] Furthermore, considering the above described characteristics, the effects of several 1,4-dihydropyridines on epimastigotes of *T. cruzi* have been tested.[17–20] Results indicated a causal relationship between reduction peak potentials and the effects on culture growth and oxygen consumption by the parasites. On the other hand, drugs derived from nitrophenyl 1,4-dihydropyridine derivatives degrade to nitroso compounds by exposure to light, and up to now, these redox intermediaries have not been well studied and little is known about their potential toxicity. Nevertheless, we have found that a photoproduct from Nifedipine, the nitrosopyridine derivative, gives rise to a free-radical formation.[21–23] Little evidence on the potential activity of the nitroso compounds or its related reduction products on parasites and neoplastic cells exist. It is important to consider that the nitroso group is reduced at lower cathodic potential than the nitro group, thus it will be easy to generate cytotoxic intermediaries from nitroso compounds.[24]

In the present paper, we have attempted the synthesis of nitroso-substituted derivatives of 1,4-dihydropyridine (Figure 1) to search for new compounds with potential toxic effects on parasites or tumoral cells.

The synthetic pathway was based on the classical Hantzsch synthesis of 1,4-dihydropyridines[25–27] using nitrobenzaldehyde as starting material and a subsequent reduction of the nitro group (see Scheme 1).

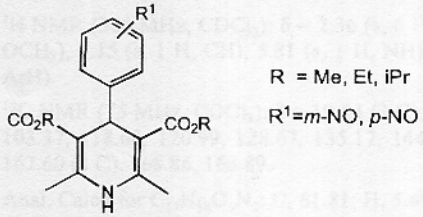
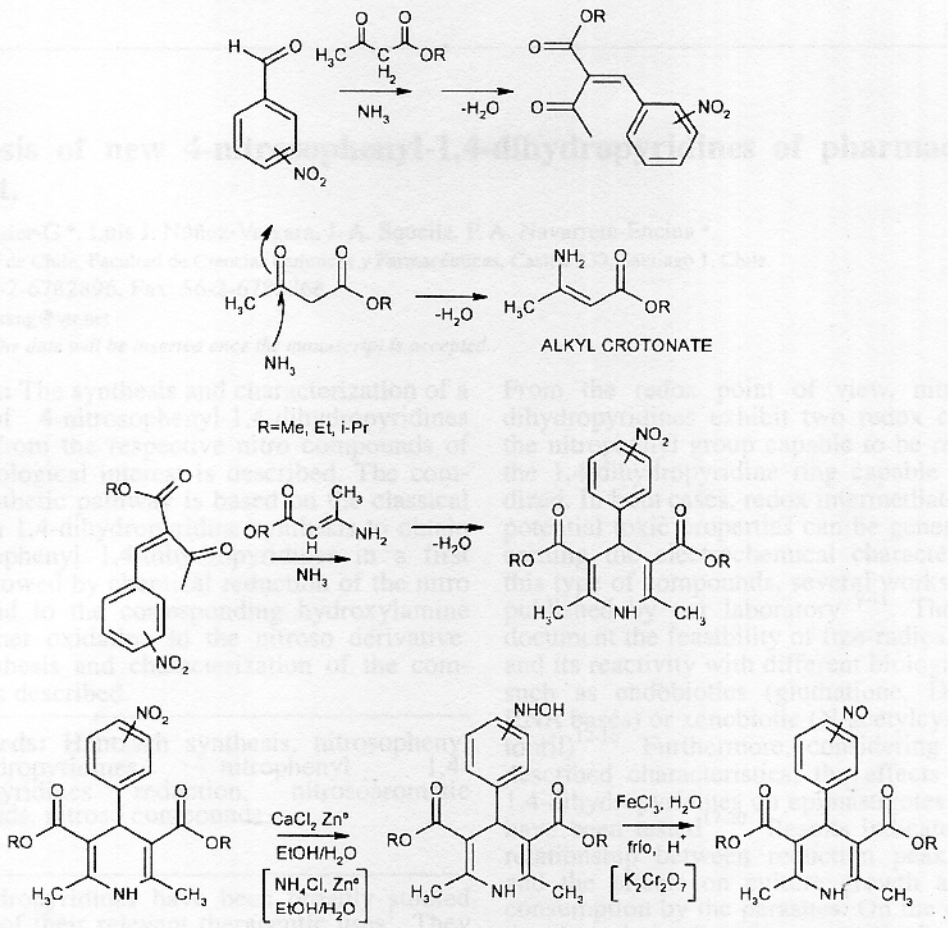


Figure 1 General structure of the synthesized compounds.

Reagents were purchased for Merck Laboratories (Santiago, Chile). All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy using a 300 MHz spectrometer (Bruker, WM 300), infrared spectroscopy (FT-IR Paragon Spectrometer, 100PC) and Elemental analysis (Perkin–Elmer, 240 B).The DHP nitroso de-

SYNTHESIS 2003, No. 18, pp 2781–2784
Advanced online publication: 23.10.2003
DOI: 10.1055/s-2003-42453; Art ID: M03203SS



Scheme 1 General scheme of the nitroso compounds synthesis.

rivatives are extremely labile compounds so it is difficult to maintain them in their pure state and this fact may account for the differences in their elemental analysis.

Nitroso compounds; General Procedure

4-(3- or 4-Nitrophenyl)-2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridine (2.1×10^{-2} mol) was dissolved in absolute EtOH (50 mL) in a round-bottom flask. Calcium chloride (3 g) previously dissolved in the minimum amount of distilled water was added. To the stirred solution was added Zn powder (2 g) in small portions. This takes about 5 min and the solution turns orange, corresponding to a solution of the hydroxylamine compound. Once all the Zn had been added, the system was maintained at a gentle reflux for 15 min with vigorous stirring. The warm solution was filtered to remove the ZnO formed. The filtered and cold solution was added as fast as possible to an ice-cold H_2O solution containing $FeCl_3$ (7 g) previously prepared. The resulting mixture was maintained at 0 °C for 10 min and a green precipitate was formed corresponding to the crude nitroso compound. The precipitate was filtered and dried in a vacuum dessicator. Toluene (10–20 mL) was added to the anhyd precipitate and stirred to form a homogeneous paste. The paste was poured into a chromatographic column (silica gel 60, 20 cm; toluene–EtOAc, 9:1). The eluted greenish portion was collected and concentrated until the appearance of green crystals. The solution was then cooled and stored for 24 h protected from the light and in an argon atmosphere to prevent decomposition of the compound. The crystals were filtered, dried and stored in a receptacle protected from the light and in an argon atmosphere.

The following nitroso compounds were synthesized following the above-described general procedure.

4-(3-Nitrosophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine

Yield: 40%; mp 246 °C.

IR (KBr): 3355, 1701, 1649, 1485, 1436, 1384, 1125, 1019 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 6 H, CH_3), 3.64 (s, 6 H, OCH_3), 5.15 (s, 1 H, CH), 5.81 (s, 1 H, NH), 7.61–7.68 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.64 (2 C), 29.67, 39.49, 51.10, 103.37, 118.60, 120.99, 128.67, 135.17, 144.82, 149.32, 166.84, 167.60 (2 C), 168.86, 168.89.

Anal. Calcd for $C_{17}H_{18}O_5N_2$: C, 61.81; H, 5.49; N. 8.48. Found: C, 62.30; H, 5.74; N, 8.58.

4-(3-Nitrosophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine

Yield: 40%; mp 118–119 °C.

IR (KBr): 3334, 2998, 1700, 1651, 1489, 1371, 1300, 1213, 1102, 1020 cm^{-1}.

Synthesis of new 4-nitrosophenyl-1,4-dihydropyridines of pharmacological interest.

I.P. Santander-G.*, Luis J. Núñez-Vergara, J. A. Squella, P. A. Navarrete-Encina *.
Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas, Casilla 233, Santiago 1, Chile.
Phone: 56-2-6782896, Fax: 56-2-6782868.
E-mail: paosang@vtr.net
Received: The date will be inserted once the manuscript is accepted..

Abstract: The synthesis and characterization of a series of 4-nitrosophenyl-1,4-dihydropyridines derived from the respective nitro compounds of pharmacological interest is described. The complete synthetic pathway is based on the classical Hantzsch 1,4-dihydropyridine synthesis to obtain the nitrophenyl 1,4-dihydropyridines in a first step, followed by chemical reduction of the nitro compound to the corresponding hydroxylamine and further oxidation to the nitroso derivative. The synthesis and characterization of the compounds is described.

Key words: Hantzsch synthesis, nitrosophenyl 1,4-dihydropyridines, nitrophenyl 1,4-dihydropyridines reduction, nitrosoaromatic compounds, nitroso compounds

1,4-dihydropyridines have been broadly studied because of their relevant therapeutic uses[1]. They were synthesized for the first time by Arthur Hantzsch in 1882[2] and successive structural modifications involving additions, reductions and condensations, mainly in the 1, 2 and 6 positions of the dihydropyridine ring were performed. Later in 1977, modifications in the positions 1, 3, 4 and 5, resulted in the Bayer[3] group synthesizing the drug Nifedipine, revolutionizing the pharmaceutical market due to its antihypertensive properties. The structural modifications continued, until in 1980, the Kellogg group reported the first crown ether with a dihydropyridine integrated inside the macrocyclic with the purpose of mimicking the behavior of the natural coenzyme NADH [3].

Until today, new compounds related to the 1,4-dihydropyridines looking for new pharmacological properties have been synthesized [4-7]. A nice example on the effects of the replacement of the *o*-nitrophenyl group of nifedipine by a xanthone group was reported by Rampa [8]. The presence of a xanthone group in C-4 position in the 1,4-dihydropyridines ring produced potent and selective derivatives with a chronotropic negative activity. These modifications opened new perspectives in the search for more effective drugs for controlling cardiac arrhythmias.

From the redox point of view, nitroaryl 1,4-dihydropyridines exhibit two redox centers, i.e. the nitrophenyl group capable to be reduced and the 1,4-dihydropyridine ring capable to be oxidized. In both cases, redox intermediates showing potential toxic properties can be generated. Concerning the electrochemical characterization of this type of compounds, several works have been published by our laboratory [9-11]. Those reports document the feasibility of free-radical formation and its reactivity with different biological targets, such as endobiotics (gluthatione, DNA bases, RNA bases) or xenobiotic (N-acetylcysteine, captopril)[12-16]. Furthermore, considering the above described characteristics, the effects of several 1,4-dihydropyridines on epimastigotes of T. cruzi have been tested[17-20]. Results indicated a causal relationship between reduction peak potentials and the effects on culture growth and oxygen consumption by the parasites. On the other hand, drugs derived from nitrophenyl 1,4-dihydropyridine derivatives degrade to nitroso compounds by exposition to light, and up to date, these redox intermediaries are not well studied and little is known about their potential toxicity. Nevertheless, we have found that a photoproduct from nifedipine, the nitrosopyridine derivative, gives rise to a free-radical formation[21-23]. Little evidence on the potential activity of the nitroso compounds or its related reduction products on parasites and neoplastic cells exist. It is important to consider that the nitroso group is reduced at lower cathodic potential than nitro group, thus it will be easy to generate cytotoxic intermediaries from nitroso compounds [24].

In the present paper, we have attempted the synthesis of nitroso substituted derivatives of 1,4-dihydropyridine to search new potential compounds with toxic effects on parasites or tumoral cells.

The synthetical pathway was based on the classical Hantzsch synthesis of 1,4-dihydropyridines[25-27] using nitrobenzaldehyde as starting material and a subsequent reduction of the nitro group (see Scheme 1).

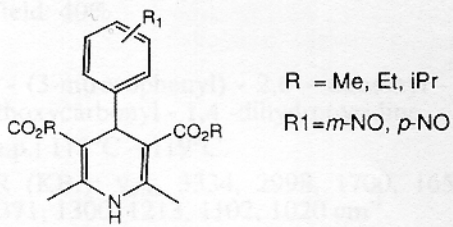
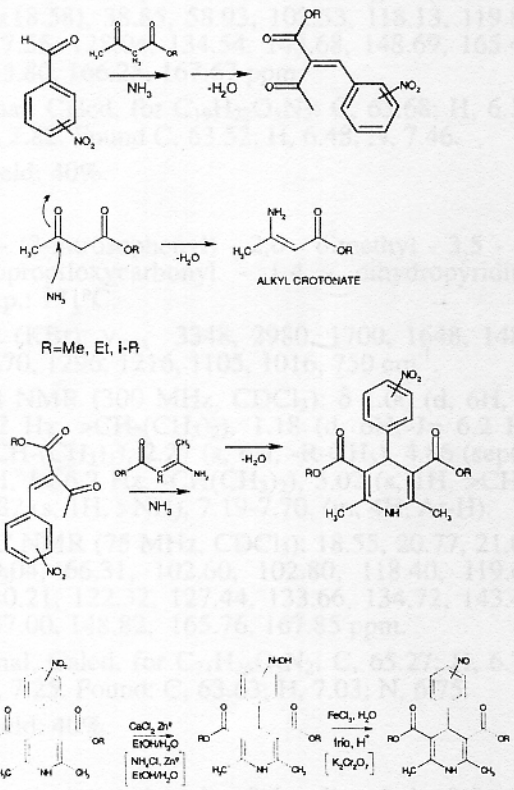


Figure 1 General structure of the synthesized compounds.



Scheme 1. General scheme of the nitroso compounds synthesis

All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR spectroscopy using a 300 MHz spectrometer (Bruker, WM 300), infrared spectroscopy (FT-IR Paragon Spectrometer, 100PC) and Elemental analysis (Perkin Elmer, 240 B).

Experimental Section

General procedure for the synthesis of some of the nitroso compounds.

4-(3 or 4-nitrophenyl) - 2,6 - dimethyl - 3,5 – dialkoxycarbonyl - 1,4 - dihydropyridine (2.1x 10^{-2} mol) are dissolved in absolute EtOH (50 mL) in a round bottom flask. Calcium chloride (3g) previously dissolved in the minimum amount of distilled water is added. To the stirred solution is added Zn in powder (2g) in small portions. This takes about 5 minutes and the solution turns orange, corresponding to a solution of the hydroxylamine compound. Once all the Zn has been added, the system is maintained at a gently reflux for 15 minutes with vigorous stirring. The warm solution is filtered to take off the ZnO formed. The filtered and cold solution is added as fast as possible to an ice cold water solution containing $FeCl_3$ (7g) previously prepared. The resulting mixture is maintained at 0 °C for 10 minutes and a green precipitate is formed corresponding to the crude nitroso compound. The precipitate is filtered and dried in a vacuum dessicator. Toluene (10-20 mL) is added to the dry precipitate and stirred to form an homogeneous paste. The paste is poured into a 20 cm silica gel 60 chromatographic column (mobile phase: toluene: ethyl acetate 9:1). The eluted greenish portion is collected and concentrated until the apparition of green crystals. The solution is then cooled and left in repose for 24 hours protected from the light and in an argon atmosphere to prevent decomposition of the compound. The crystals are filtered, dried and stored in a recipient protected from the light and in an argon atmosphere.

The following nitroso compounds were synthesized following the above described general procedure.

4 - (3-nitrosophenyl) - 2,6 – dimethyl - 3,5 – dimethoxycarbonyl - 1,4-dihydropyridine.

m.p.: 246 °C.

IR (KBr): ν_{max} 3355, 1701, 1649, 1485, 1436, 1384, 1125, 1019 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H, -CH_3), 3.64 (s, 6H, -O-CH_3), 5.15 (s, 1H, >CH-), 5.81 (s, 1H, >NH), 7.61-7.68 (m, 4H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): (2x19.64), 29.67, 39.49, 51.10, 103.37, 118.60, 120.99, 128.67, 135.17, 144.82, 149.32, 166.84, (2x167.60), 168.86, 168.89 ppm.

Anal. Calcd. for $C_{17}H_{18}O_5N_2$: C, 61.81; H, 5.49; N. 8.48. Found: C, 62.30; H, 5.74; N, 8.58.

Yield: 40%.

4 - (3-nitrosophenyl) - 2,6 – dimethyl - 3,5 - diethoxycarbonyl - 1,4 -dihydropyridine.

m.p.: 118°C – 119°C.

IR (KBr): ν_{max} 3334, 2998, 1700, 1651, 1489, 1371, 1300, 1213, 1102, 1020 cm^{-1}.

^{1}H-NMR (300MHz, $CDCl_3$): δ1.20 (t, 6H, J= 7.2 Hz, -CH_2CH_3), 2.36 (s, 6H, R-CH_3), 4.10 (q, 4H, J=3.8 Hz, -CH_2CH_3), 5.10(s, 1H, >CH-), 5.70(s, 1H, >NH), 7.67-7.70(m, 4H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): (2x13.23), (2x18.58), 38.85, 58.93, 102.53, 118.13, 119.82, 127.55, 128.04, 134.54, 143.68, 148.69, 165.46, 165.80, 166.25, 167.67 ppm.

Anal. Calcd. for $C_{19}H_{22}O_5N_2$: C, 63.68; H, 6.19; N, 7.82. Found C, 63.52; H, 6.48; N, 7.46.

Yield: 40%.

4 - (3-nitrosophenyl) - 2,6 - dimethyl - 3,5 - diisopropiloxycarbonyl - 1,4 - dihydropyridine.
m.p.: 131°C.

IR (KBr): ν_{max} 3348, 2980, 1700, 1648, 1489, 1370, 1296, 1216, 1105, 1016, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 6H, J= 6.2 Hz, >CH-$(CH_3)_2$), 1.18 (d, 6H, J= 6.2 Hz, >CH-$(CH_3)_2$), 2.27 (s, 6H, -R-CH_3), 4.86 (septet, 2H, J= 6.2 Hz, -$CH(CH_3)_2$), 5.02 (s, 1H, >CH-), 5.82 (s, 1H, >NH), 7.19-7.70, (m, 4H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): 18.55, 20.77, 21.08, 39.04, 66.31, 102.60, 102.80, 118.40, 119.66, 120.21, 122.32, 127.44, 133.66, 134.72, 143.47, 147.00, 148.82, 165.76, 167.85 ppm.

Anal. Calcd. for $C_{21}H_{26}O_5N_2$: C, 65.27; H, 6.78; N, 7.25. Found: C, 63.63; H, 7.03; N, 6.75.

Yield: 40%.

4 - (4-nitrosophenyl) - 2,6 – dimethyl - 3,5 – diethoxycarbonyl - 1,4-dihydropyridine.

m.p.: 87 °C – 88 °C.

IR (KBr) : ν_{max} 3342, 2998, 1672, 1487, 1369, 1303, 1217, 1120, 1020, 810 cm^{-1}.

^{1}H-NMR : δ1.21 (t, 6H, J=7.1 Hz, CH_2CH_3), 2.36 (s, 6H, R-CH_3), 4.10 (q, 4H, J= 7.1 Hz, -CH_2-CH_3), 5.10 (s, 1H, R-CH), 5.70 (s, 1H, >NH), 7.50 (d, 2H, J = 8.3 Hz, Ar-H), 7.70 (d, 2H, J= 8.3 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): (2x14.24), 19.66, 21.44, 40.44, (2x59.98), 103.10, 121.11, 125.29, 128.21, 128.86, 129.03, 144.59, (2x155.74), 165.63, 167.10 ppm.

Anal. Calcd. for $C_{19}H_{22}O_5N_2$: C, 63.68; H, 6.19; N, 7.82. Found C, 66.20; H, 6.55; N, 6.96.

Yield: 35%.

4 - (4-nitrosophenyl) - 2,6 – dimethyl - 3,5 - diisopropiloxycarbonyl - 1,4-dihydropyridine.

m.p.: 101 °C.

IR (KBr): ν_{max} 3309, 2982, 1700, 1649, 1489, 1345, 1301, 1218, 1104, 1016, 833 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, 6H, J= 6.2 Hz, -CH-$(CH_3)_2$), 1.26 (d, 6H, J= 6.2 Hz, -CH-$(CH_3)_2$), 2.35 (s, 6H, -R-CH_3), 4.96 (septet, 2H, J= 6.2 Hz, -$CH(CH_3)_2$), 5.07 (s, 1H, >CH-), 5.85 (s, 1H, -R-NH), 7.48 (d, 2H, J= 8.8 Hz, Ar-H); 8.11 (d, 2H, J= 8.8 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): 19.69, 21.87, 21.12, 40.29, 67.40, 103.27, 103.42, 121.06, 123.19, 128.24, 129.10, 144.45, 146.14, 155.34, 165.66, 166.64, 166.70 ppm.

Anal. Calcd. for $C_{21}H_{26}O_5N_2$: C, 65.27; H, 6.78; N, 7.25. Found: C, 66.87; H, 6.96; N, 6.99.

Yield: 40%.

4 - (4-nitrosophenyl) - 2,6 – dimethyl - 3,5 – dimethoxycarbonyl - 1,4-dihydropyridine.

The procedure is almost the same just described general procedure with the following modification: The ethanolic solution of hydroxylamine formed is evaporated to dryness and the crude compound is dissolved in acetone. This solution is then poured in the aqueous solution of $FeCl_3$ followed by the remaining of the workup.

m.p. 147 °C.

IR (KBr): ν_{max} 3335, 2951, 1704, 1650, 1488, 1435, 1020 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 6H, R-CH_3), 3.65 (s, 6H, -O-CH_3), 5.10 (s, 1H, >CH-), 5.86 (s, 1H, >NH), 7.52 (d, 2H, J= 8.6 Hz, Ar-H), 7.79 (d, 2H, J= 8.6 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): (2x18.33), 19.56, 40.01, 51.07, (2x58.38), 102.73, (2x121.18), (2x128.45), 144.87, (2x155.32), 165.47, 167.44 ppm.

Anal. Calcd. for $C_{17}H_{18}O_5N_2$: C, 61.81; H, 5.49; N. 8.48. Found: C, 62.22; H, 5.63; N, 8.61.

Yield. 30%.

The *meta-* and *para*-nitroso derivatives may be stored in the mentioned conditions for a period of about one month without appreciable decomposition. The *ortho-* derivative was very unstable and it was not possible to isolate it in pure form from the above mentioned conditions.

Acknowledgements:

We thank supporting from FONDECYT 2010029 and FONDECYT 8000016

References

(1) *Drug of the Future*, **1988**, *13* (3), 207.
(2) Hantzsch, A., *Justus Liebigs Ann. Chem.* **1882**, *1*, 215
(3) Stout, D., Meyers, A. *Chem.Rev.* **1982**, *82*, 223.
(4) Hilgeroth, A., Billich, A., Lilie, H. Eu. J.*Med.Chem.*, **2001**, *36* (4), 367.
(5) Bhavik, B., Dinesh, D., Yogesh, Y., Anamik, A., Anil A. K., *Bioorg.Med.Chem.*, **2001**, *9* (8), 1993.
(6) Yamada, S., Misono, T, Ichikawa, M., Morita, C. *Tetrahedron*, **2001**, *57* (43), 8939.
(7) Jhy-Chong, J.C, Jwu-Lai, J.L., Chia-Sui, C.S., Shwu-Fen, S. F., Chie-Ho, C.H., Ing-Jun, I.J. Bioorg.Med.Chem., **2002**, *10* (23), 719.
(8) Rampa, A, Chiarine,A., Bisi, A., Budriese, R., Valenti, P. Drug. Res. **1991**, *41* (7) 705.
(9) Squella., J.A.,. Huerta., M., Bollo, S, Pessoa, H., Núñez-Vergara, L. J. Electrochimica Acta. **1997**, *42* (15) 2305
(10) Díaz-Araya, G, Godoy, L., Naranjo, L., Squella., J.A., Letelier, M.E., Núñez-Vergara, L. J. Gen. Pharmacol.. **1998**, *31* (3), 385.
(11) Núñez-Vergara, L. J., .Díaz-Araya, G, Olea-Azar, C., Atria, A.M., Bollo-Dragnic, S., Squella, J.A. Pharmaceutical Research. **1998**, *15* (11), 1690.
(12) Núñez-Vergara, L. J., Navarrete-Encina, P.A., Ortiz, M.E., Bollo, S., Squella, J.A. Chem. Biol.. Int., **1996**, *101*, 89.
(13) Núñez-Vergara, L. J., Guíñez-Castro, J.E., Bollo, S., Squella, J.A. *Bol. Soc. Chil. Quím.* **1996**, *41*, 363.
(14) Núñez-Vergara, L. J., Ortiz, M.E., Bollo, S., Squella, J.A. Che. Biol. Int..**1997**, *106*, 1.
(15) Núñez-Vergara, L. J., Bollo-Dragnic, S., Olea-Azar, C., Santander, P., Gunckel, S., Squella, J.A. Bol. Soc. Chil. Quím. **1998**, 43, 231-239
(16) Núñez-Vergara, L.J, Sturm, J.C., Olea-Azar, C., Navarrete-Encina, P., Bollo, S., Squella, J.A. , Free Rad. Res. **2000**, *32*: 399.
(17) Núñez-Vergara, L. J., Squella, J.A., Bollo-Dragnic, S., Morello, A., Repetto, Y., Aldunate, J., Letelier, M. Comp. Biochem. Phys., **1997**, *118*, 105.
(18) Núñez-Vergara, L. J., Squella, J.A., Bollo-Dragnic, S., Marín-Catalán, R., Pino, L. Díaz, G, Letelier, M.E. Gen. Pharmacol., **1998**, *30* (1),85.
(19) Maya, J.D., Morello, A., .Repetto, Y., Tellez, R., Rodriguez, A., Zelada, O., Puebla, P., Caballero, E., .Medarte, M., Núñez-Vergara, L.J, Squella, J.A., .Bontá, M., .Bollo, S., San Feliciano, A. Comp. Biochem. Phys. Part C, **2000**, *125*, 103.
(20) Maya, J.D., .Morello, A., .Repetto, Y., Rodríguez, A., Puebla, P., Caballero, E., Medarde, M., Núñez-Vergara, L. J, Squella, J.A., Ortiz, M.E., Fuentealba, J., San Feliciano, A. Exp. Parasitol., **2001**, *99*, 1.
(21) Alvarez-Lueje, A., Naranjo, L., Núñez-Vergara, L. J , Squella, J.A. J. Pharm.Biomed. Anal. **1998**, *16*, 853.
(22) Sturm, J.C., Núñez-Vergara, L. J, de la Fuente, J., Castro, C., Navarrete-Encina, P., Squella, J.A. .J. Electrochem. Soc. **2001**, *148* (10), 1.
(23) Núñez-Vergara, L. J, Bollo, S., Fuentealba, J., Sturm, J.C., Squella, J.A. Pharmaceutical Research, **2002**, *19* (4) 522.
(24) Hoffmann, D., Rivenson, A., Wynder, E.L., Hecht, S.S.. Chemistry and Biochemistry. ACS Symposium Series 553, **1992**, 267.
(25) Holleck, L., Schindler, R. Electrochem. **1956**, *60*, 1138,.
(26) Maurin, M.B., Vickery, R.D., Ma, P., Manalo, J., Hussain, M.A. *Pharm.* **1992**, .Res. *9* (11), 1518.
(27) Fax, H.H., Lewis, J.I., Wenner, W. *J. Org. Chem.* **1951**, *16*, 1259.