

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

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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 uses¹. They were synthesized for the first time by Arthur Hantzsch in 1882² 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 Bayer³ 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 NADH³.

Until today, new compounds related to the 1,4-dihydropyridines looking for new pharmacological properties have been synthesized⁴⁻⁷. A nice example on the effects of the replacement of the *o*-nitrophenyl group of nifedipine by a xanthone group was reported by Rampa⁸. 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 laboratory⁹⁻¹¹. Those reports document the feasibility of free-radical formation and its reactivity with different biological targets, such as endobiotics (glutathione, 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 tested¹⁷⁻²⁰. 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 formation²¹⁻²³. 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 compounds²⁴.

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-dihydropyridines²⁵⁻²⁷ using nitrobenzaldehyde as starting material and a subsequent reduction of the nitro group (see Scheme 1).

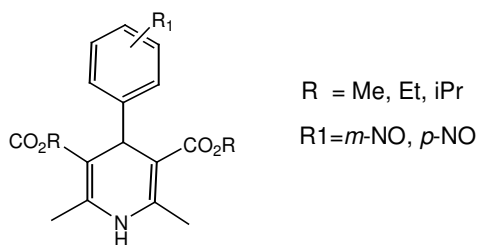
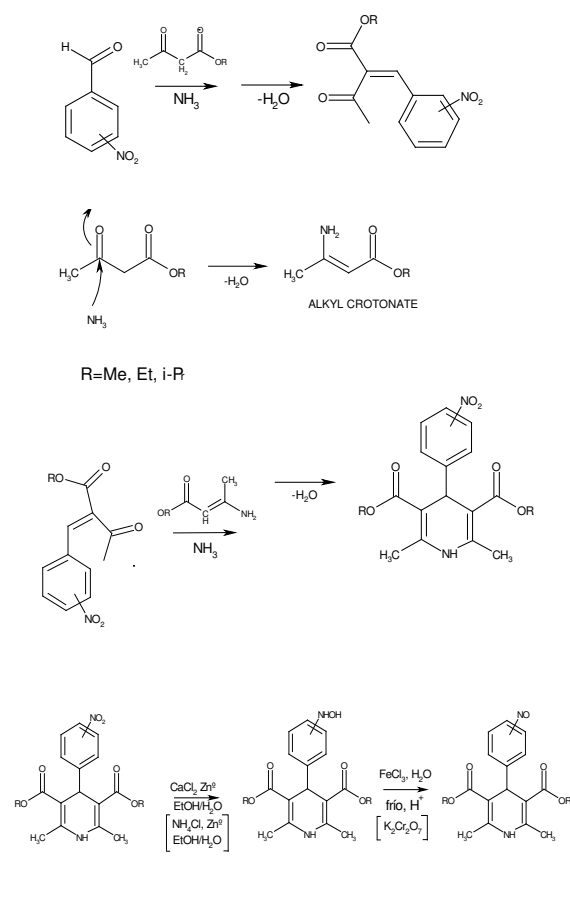


Figure 1 General structure of the synthesized compounds.



Scheme 1. General scheme of the nitroso compounds synthesis

All the synthesized compounds were characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ 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 (2.1×10^{-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 desiccator. 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} .

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

$^{13}\text{C NMR}$ (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 $\text{C}_{17}\text{H}_{18}\text{O}_5\text{N}_2$: 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} .

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ 1.20 (t, 6H, $J=7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 2.36 (s, 6H, R- CH_3), 4.10 (q, 4H, $J=3.8$ Hz, $-\text{CH}_2\text{CH}_3$), 5.10 (s, 1H, $>\text{CH-}$), 5.70 (s, 1H, $>\text{NH}$), 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 $\text{C}_{19}\text{H}_{22}\text{O}_5\text{N}_2$: 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} .

^1H NMR (300 MHz, CDCl_3): δ 1.00 (d, 6H, $J=6.2$ Hz, $>\text{CH}-(\text{CH}_3)_2$), 1.18 (d, 6H, $J=6.2$ Hz, $>\text{CH}-(\text{CH}_3)_2$), 2.27 (s, 6H, R- CH_3), 4.86 (septet, 2H, $J=6.2$ Hz, $-\text{CH}(\text{CH}_3)_2$), 5.02 (s, 1H, $>\text{CH-}$), 5.82 (s, 1H, $>\text{NH}$), 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 $\text{C}_{21}\text{H}_{26}\text{O}_5\text{N}_2$: 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} .

$^1\text{H-NMR}$: δ 1.21 (t, 6H, $J=7.1$ Hz, CH_2CH_3), 2.36 (s, 6H, R- CH_3), 4.10 (q, 4H, $J=7.1$ Hz, $-\text{CH}_2-\text{CH}_3$), 5.10 (s, 1H, R- CH), 5.70 (s, 1H, $>\text{NH}$), 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 $\text{C}_{19}\text{H}_{22}\text{O}_5\text{N}_2$: 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}

^1H NMR (300 MHz, CDCl_3): δ 1.11 (d, 6H, $J=6.2$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 1.26 (d, 6H, $J=6.2$ Hz, $-\text{CH}-(\text{CH}_3)_2$), 2.35 (s, 6H, R- CH_3), 4.96 (septet, 2H, $J=6.2$ Hz, $-\text{CH}(\text{CH}_3)_2$), 5.07 (s, 1H, $>\text{CH-}$), 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 $\text{C}_{21}\text{H}_{26}\text{O}_5\text{N}_2$: 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 - di-methoxycarbonyl - 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}

^1H NMR (300 MHz, CDCl_3): δ 2.37 (s, 6H, R- CH_3), 3.65 (s, 6H, $-\text{O}-\text{CH}_3$), 5.10 (s, 1H, $>\text{CH-}$), 5.86 (s, 1H, $>\text{NH}$), 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 $\text{C}_{17}\text{H}_{18}\text{O}_5\text{N}_2$: 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.

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