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

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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. They were synthesized for the first time by Arthur Hantzsch in 1882 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 group synthesizing the drug Nifedipine, revolutionizing the pharmaceutical market due to its antihypertensive properties. A nice example of the effects of modifications opened new perspectives in the search for new compounds related to 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.

Recently, new compounds related to the 1,4-dihydropyridines have been synthesized in the search for new pharmacological properties. A nice example of the effects of the replacement of the o-nitrophenyl group of Nifedipine by a xanthone group was reported by Rampa. 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. 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). Furthermore, considering the above described characteristics, the effects of several 1,4-dihydropyridines on epimastigotes of T. cruzi have been tested. 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. 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.

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

Reagents were purchased for Merck Laboratories (Santiago, Chile). All the synthesized compounds were characterized by 1H NMR, 13C 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-
derivatives 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 ($2.1 \times 10^{-2}$ 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$_2$O solution containing FeCl$_3$ (7 g) previously prepared. The resulting mixture was maintained at 0 ºC 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.

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 ºC.
IR (KBr): 3355, 1701, 1649, 1485, 1436, 1384, 1125, 1019 cm$^{-1}$.
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_5$N$_2$: 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 ºC.
IR (KBr): 3334, 2998, 1700, 1651, 1489, 1371, 1304, 1230, 1102, 1020 cm$^{-1}$.

Scheme 1 General scheme of the nitroso compounds synthesis.
1H NMR (300 MHz, CDCl3): δ = 1.20 (t, 6 H, J = 7.2 Hz, CH2CH3), 2.36 (s, 6 H, RCH3), 4.10 (q, 4 H, J = 3.8 Hz, CH2CH3), 5.10 (s, 1 H, CH), 5.70 (s, 1 H, NH), 7.67–7.70 (m, 4 H, ArH).

13C NMR (75 MHz, CDCl3): δ = 13.23 (2 C), 18.58 (2 C), 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.

Anal. Calcd for C19H22O5N2: C, 63.68; H, 6.19; N, 7.82. Found C, 64.59, 155.74 (2 C), 165.63, 167.18.

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

Yield: 40%; mp 131 °C.

IR (KBr): 3348, 2980, 1700, 1648, 1489, 1370, 1296, 1216, 1105, 1020 cm−1.

The procedure is almost the same as the described general procedure with the following modifications. The ethanolic solution of hydroxylamine formed was evaporated to dryness, and the crude compound was dissolved in acetic anhydride. This solution was then poured in the aq solution of FeCl3 followed by the rest of the workup.

References

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Synthesis 2003, No. 18, 2781–2784 © Thieme Stuttgart · New York


