Synthesis of novel unsymmetrically substituted 1,4-dihydropyridines and separation of the enantiomers of racemic 1,4-dihydropyridine containing isothioureiido group

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Abstract
Unsymmetrical 1,4-dihydropyridine esters 3a and 3d-h were synthesized from the symmetrical precursors 1a-c through the intermediacy of 2-bromomethyl derivatives 2a-c. Chiral acid o,ó-dibenzoyl-L-tartaric acid was used to separate the enantiomers of racemic 1,4-dihydropyridine 3a.

Keywords: 1,4-Dihydropyridines, calcium channel blockers, enantiomer separation

1. Introduction

The 1,4-dihydropyridine Ca$^{2+}$ channel blockers are clinically significant antihypertensive drugs$^{1-3}$ and have been immensely valuable as molecular tools with which probe structural and functional aspects of Ca$^{2+}$ channel function.$^{4,5}$

Most of the 1,4-dihydropyridines were prepared via the Hantzsch procedure.$^6$ This procedure is simple, and isolation of the product is generally straightforward but it works moderately well for symmetrical dihydropyridines, and the yield of the desired products decreases very rapidly for asymmetrically substituted dihydropyridines.$^7$ Symmetrically substituted dihydropyridines such as nifedipine are achiral compounds. Different substituents in compounds of the second-generation such as amlodipine, nitrendipine and nicardipine lead to chiral derivatives whose enantiomers differ in their pharmacological effects. In the case of the calcium antagonists, the differences are quantitative. However, the introduction of certain substituents in position 3 or 5 can lead to calcium agonists. The enantiomers exhibit opposite activity, one of them acting as agonist, the other as an antagonist. In this work we synthesized some new derivatives of unsymmetrically substituted 1,4-dihydropyridine rings. The compounds 3a and 3d-h were synthesized by using nucleophilic attack of thiourea, 2-mercapto-4,6-dimethyl
pyrimidine, 3,5-dimethylPyrazol, ammonium thiocyanate and sodium azide on the 2-bromomethyl-1,4-dihydropyridines 2a-c.

In view of chirality to pharmacological activity, the present article will describe the separation of the enantiomers of S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl) 1,4-dihydropyridin-2-yl)-methyl]-isothiourea.

2. Results and Discussion

Synthesis was started by Hantzsch reaction of ethyl acetoacetate with appropriate aldehyde and ammonia in refluxing ethanol, which afforded the 1,4-dihydropyridines 1a-c. Reaction of 1,4-dihydropyridines 1a-c with 1.1 equivalents of pyridinium bromide perbromide in dichloromethane/pyridine at -20 °C for 45 minutes afforded the crude products 2a-c as a yellow gum. We have published before the synthesis of 2a [2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine] in high yield by modifying the literature methods. Without further purification these brominated adducts were coupled with a range of nucleophiles at different conditions to give 2-substituted 1,4-dihydropyridines 3a and 3d-h (see table 1).

In the reaction of 2a with thiourea in refluxing ethanol for 5h, evaporation of solvent and recrystallization from EtOAc/Hex, isothiouronium salt 3a is formed. Transformation of isothiouronium salt 3a into its isothioure 3b, as free base, carried out by treatment of 3a in CH2Cl2/H2O with Na2CO3 with vigorous stirring, at room temperature. The C-4 carbon atom of 1,4-dihydropyridines is a prochiral atom. When at least one of the substituents, bound to the C-2 and C-3 carbon atoms, is different from those on the symmetric C-6 and C-5 positions of ring, the C-4 carbon atom is chiral and the compounds are racemates. Meanwhile compound 3b with different substituents at C-2 and C-6 is a racemic mixture. In order to prepare the diastereomeric salts of 3b, the mixture of 3b and (1S)-(−)-camphor-10-sulfonic acid in CH3CN was refluxed for 4h, but the product obtained was the thiol derivative 3c. However, Optical resolution of (+)-3b by salification with o,o′-dibenzoyl-L-tartaric acid and recrystallization of diastereomeric salts, then hydrolysis of crystallized diastereomer (−)-4 in CH2Cl2/H2O with NaHCO3 gave (−)-3b with 65% yield. On the other hand, reaction of isothiouronium salt (−)-4 with allyl bromide in the presence of base produces S-alkylated derivative (−)-3i (Scheme 1).
Table 1. Compounds 3

![Structural formula of 3](image)

<table>
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<th>Entry</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
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<td>3-NO₂</td>
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<tr>
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<td>3b</td>
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<td>3c</td>
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<td>3d</td>
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<td>5</td>
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<td>-SCN</td>
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<tr>
<td>7</td>
<td>3g</td>
<td>-</td>
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<tr>
<td>8</td>
<td>3h</td>
<td>-</td>
<td>3-NO₂</td>
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<tr>
<td>9</td>
<td>3i</td>
<td>-SCH₂CH=CH₂</td>
<td>3-NO₂</td>
<td>45</td>
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3. Experimental Section

2-[(4,6-Dimethylpyrimidin-2-yl)thio]-methyl-3,5-dicarboethoxy-6-methyl-4-(2-methoxyphenyl)-1,4-dihydropyridine (3d). A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(2-methoxyphenyl)-1,4-dihydropyridine 2c (obtained from 1.39 mmol of 1c), 2-mercapto-4,6-dimethyl pyrimidine (0.21 g, 1.53 mmol) and ethanol (20 ml) was heated to reflux for 2 h and then evaporated. The residue was partitioned between CH$_2$Cl$_2$ (30 ml) and saturated Na$_2$CO$_3$ solution, and the organic layer washed with water, dried over Na$_2$SO$_4$ and evaporated. Recrystallization of crude product from 2-propanol furnished 3d (0.38 g, 57%) as yellow crystals. M.p. 142 °C, IR (KBr) $\tilde{\nu}$ = 3423 (br. m), 3060 (w), 2977-2927 (m), 1686 (s), 1643 (m), 1585 (s), 1489 (s), 1310 (s), 1288 (m), 1103 (s), 747 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.17 (t, $J$ = 6.47 Hz, 3H, CH$_3$ ester), 1.20 (t, $J$ = 6.12 Hz, 3H, CH$_3$ ester), 2.21 (s, 3H, CH$_3$-6), 2.47 (s, 6H, 2×CH$_3$ pyrimidine), 3.72 (s, 3H, O-CH$_3$), 3.99-4.09 (m, 4H, 2×CH$_2$ ester), 4.49 (AB quartet, $J$ = 14.34 Hz, 2H, CH$_2$-2), 5.27 (s, 1H, C(4)-H), 6.76-7.82 (m, 3H, Ar-H, H-5 pyrimidine), 7.09 (dt, $J_1$ = 7.74 Hz, $J_2$ = 1.46 Hz, 1H, Ar-H), 7.24 (dd, $J_1$ = 7.91 Hz, $J_2$ = 1.64 Hz, 1H, Ar-H), 8.55 (s, 1H, NH) ppm; anal. calcd for C$_{26}$H$_{31}$N$_3$O$_5$: C, 62.75; H, 6.27; N, 8.44. Found: C, 62.92; H, 6.05; N, 8.36.

2-Azidomethyl -3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine (3e). A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine 2b (obtained from 1.37 mmol of 1b), sodium azide (0.10 g, 1.15 mmol) and ethanol (20 ml) was heated to reflux for 24 h and then evaporated. The residue was partitioned between CH$_2$Cl$_2$ (20 ml) and 2M HCl solution, and the organic layer washed with water, dried over Na$_2$SO$_4$ and
evaporated. Recrystallization of crude product from EtOH furnished \(3e\) (0.22 g, 35%) as yellow crystals.

IR (KBr) \(\bar{\nu} = 3312\) (s), 3078 (w), 2976-2901 (m), 2115 (m), 1699 (s), 1509 (s), 1249 (s), 1204 (s), 1095 (s), 753 (s) cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.06\) (t, \(J=7.12\) Hz, 3H, CH\(_3\) ester), 1.24 (t, \(J=7.02\) Hz, 3H, CH\(_3\) ester), 2.32 (s, 3H, CH\(_3\)-6), 3.71 (q, \(J=7.02\) Hz, 2H, CH\(_2\) ester), 3.97 (q, \(J=7.10\) Hz, 2H, CH\(_2\) ester), 4.53 (s, 2H, CH\(_2\)-2), 5.37 (s, 1H, C(4)-H), 7.08 (dt, \(J_1=7.59\) Hz, \(J_2=1.68\) Hz, 1H, Ar-H), 7.18 (dt, \(J_1=7.48\) Hz, \(J_2=1.12\) Hz, 1H, Ar-H), 7.26 (dd, \(J_1=2.89\) Hz, \(J_2=1.27\) Hz, 1H, Ar-H), 8.12 (s, 1H, NH) ppm.

2-Thiocyanatomethyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine (3f). A mixture of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine \(2b\) (obtained from 1.37 mmol of \(1b\)), ammonium thiocyanate (0.12 g, 1.51 mmol) and ethanol (20 ml) was heated to reflux for 3 h and then evaporated. The residue was partitioned between CH\(_2\)Cl\(_2\) (20 ml) and 2M HCl solution, and the organic layer washed with water, dried over Na\(_2\)SO\(_4\) and evaporated. Recrystallization of crude product from dibuthyl ether furnished \(3f\) (0.33 g, 45%) as yellow crystals. M.p. 157 ºC, IR (KBr) \(\bar{\nu} = 3351\) (s), 3057 (w), 2979-2937 (m), 2156 (s), 1692 (s), 1651 (m), 1625 (m), 1504 (s), 1281 (s), 1208 (s), 1095 (s), 1048 (s), 757 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.22\) (t, \(J=7.01\) Hz, 6H, 2 × CH\(_3\) ester), 2.36 (s, 3H, CH\(_3\)-6), 4.05-4.14 (m, 6H, 2 × CH\(_2\) ester and CH\(_2\)-2), 5.43 (s, 1H, C(4)-H), 6.75 (s, 1H, NH), 7.09 (dt, \(J_1=7.58\) Hz, \(J_2=1.52\) Hz, 1H, Ar-H), 7.17 (dt, \(J_1=7.48\) Hz, \(J_2=1.09\) Hz, 1H, Ar-H), 7.26 (dd, \(J_1=7.57\) Hz, \(J_2=1.11\) Hz, 1H, Ar-H), 7.40 (dd, \(J_1=6.23\) Hz, \(J_2=1.52\) Hz, 1H, Ar-H) ppm; Anal. Calcd for C\(_{21}\)H\(_{24}\)N\(_2\)O\(_5\)S: C, 57.01; H, 5.02; N, 6.65. Found: C, 57.34; H, 5.41; N, 6.50.

2-(3,5-dimethyl Pyrazol-1-yl)-methyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine (3g). A solution of 2-bromomethyl-3,5-dicarboethoxy-6-methyl-4-(2-chlorophenyl)-1,4-dihydropyridine \(2b\) (obtained from 1.54 mmol of \(1b\)) in THF (15 ml) was added via a cannula, to a magnetically stirred solution of NaPz in THF at room temperature. NaPz was prepared in situ from PzH (3,5-dimethyl pyrazol) (0.15 g, 1.51 mmol) and NaH 80% (0.048 g, 1.60 mmol) in THF (15 ml) at room temperature under argon atmosphere. The mixture was stirred at room temperature for 3 h and then evaporated. The residue was partitioned between CH\(_2\)Cl\(_2\) (20 ml) and 2M HCl solution, and the organic layer washed with water, dried over Na\(_2\)SO\(_4\) and evaporated. Recrystallization of crude product from ethanol gives \(3g\) (0.31 g, 49%) as milky crystals. M.p. 103-104 ºC, IR (KBr) \(\bar{\nu} = 3270\) (s), 3095 (w), 2980-2950 (m), 1692 (s), 1652 (m), 1620 (m), 1551 (s), 1510 (s), 1280 (s), 1203 (s), 1097 (s), 752 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.22\) (t, \(J=7.01\) Hz, 6H, 2 × CH\(_3\) pyrazol), 2.20 (s, 3H, CH\(_3\) pyrazol), 2.22 (s, 3H, CH\(_3\) pyrazol), 2.29 (s, 3H, CH\(_3\)-6), 4.06-4.20 (m, 4H, 2 × CH\(_2\) ester), 5.38 (d, \(J=16\) Hz, 1H, CH\(_2\)-2), 5.46 (s, 1H, C(4)-H), 5.72 (d, \(J=16\) Hz, 1H, CH\(_2\)-2), 5.91 (s, 1H, NH), 7.05-7.37 (m, 5H, Ar-H, Pyrazol-H) ppm; Anal. Calcd for C\(_{25}\)H\(_{31}\)N\(_3\)O\(_5\): C, 62.94; H, 6.16; N, 9.17. Found: C, 62.94; H, 6.16; N, 9.17.

2-(3,5-dimethyl Pyrazol-1-yl)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (3h). The compound (3h) was synthesized with 2-bromomethyl-3,5-
dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine 2a as above method. M.p. 157-158 °C, IR (KBr) \( \bar{\nu} = 3293 \) (m), 3100 (w), 2980-2850 (m), 1687 (s), 1652 (m), 1620 (s), 1499 (s), 1350 (m), 715 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.23 \) (m, 6H, 2\( \times \)CH\(_3\) ester), 2.22-2.62 (m, 9H, 2\( \times \)CH\(_3\) pyrazol and CH\(_3\)-6), 4.06-4.20 (m, 4H, 2\( \times \)CH\(_2\) ester), 5.12 (s, 1H, C(4)-H), 5.56 (AB quartet, \( J = 16 \) Hz, 2H, CH\(_2\)-2), 5.91 (s, 1H, NH), 7.37 (m, 1H, Ar-H), 7.37 (m, 1H, Ar-H), 7.49 (m, 1H, Ar-H), 7.61 (m, 1H, Ar-H), 8.08 (m, 1H, Ar-H) ppm; Anal. Calcd for C\(_{24}\)H\(_{28}\)N\(_4\)O\(_6\): C, 61.53; H, 5.98; N, 11.96. Found: C, 61.73; H, 6.07; N, 12.01.

\( S-[(6\text{-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)}\text{-methyl]-isothiouronium} \text{ } o,\bar{o}\text{-dibenzoyl-L-tartarate} \) (-)-4. A mixture of (±)-S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-methyl]-isothiourea 3b (0.12g, 0.26 mmol), \( o,\bar{o}\)-dibenzoyl-L-tartaric acid (0.04 g, 0.13 mmol) and isopropanol is heated to the reflux temperature for 2.5 h. After cooling at room temperature, the solution is cooled to 0 °C for 24 h. Recrystallization of the obtained crystals from EtOAc/Hex furnished (-)-S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-yl)-methyl]-isothiouronium \( o,\bar{o}\)-dibenzoyl-L-tartarate (0.03 g, 30%) , m.p. 162-163 °C, \( [\alpha]_{578} = -29.13^\circ \) (c=1.3, MeOH) as yellow crystals.

\( (-)- S-[(6\text{-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)}\text{-methyl]-isothioure} \) (-)-3b. Sodium bicarbonate (0.01 g, 0.12 mmol) was added to a suspension of the (-)-4 (0.1 g, 0.12 mmol) in a biphasic CH\(_2\)Cl\(_2\)/H\(_2\)O (2:1, 12 ml) mixture. The mixture was vigorously stirred for 0.5 h, then the organic phase was separated, washed with water, dried over Na\(_2\)SO\(_4\) and evaporated. Recrystallization of crude product from Et\(_2\)O furnished (-)-3b (0.03 g, 65%), mp. 119-120 °C, \( [\alpha]_{578} = -10.53^\circ \) (c=1.9, CH\(_2\)Cl\(_2\)).

\( (-)- 2\text{-(Allyl thio)-methyl-3,5-dicarboethoxy-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine} \) (-)-3i. An aqueous solution of NaOH (32%, 0.06 ml) was added to a stirred solution of (-)-4 (0.1g, 0.12 mmol) and allyl bromide (0.03 g, 0.29 mmol) in ethanol/water (1:1, 12 ml), under an argon atmosphere. After 1.5 h stirring at room temperature, the mixture was filtered. Recrystallization of the crude product from ethanol furnished compound (-)-3i as yellow needle crystals (0.02 g, 45%). mp. 118-119 °C, \( [\alpha]_{578} = -7.35^\circ \) (c=2, CH\(_2\)Cl\(_2\)); IR(KBr) \( \bar{\nu} = 3316\) (s), 3092 (w), 2964-2850 (m), 1675 (s), 1639 (m), 1527 (s), 1350 (s), 1288 (s), 1211 (s), 1101 (s), 802 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.22 \) (t, \( J=7.12 \) Hz, 6H, 2\( \times \)CH\(_3\) ester), 2.41 (s, 3H, CH\(_3\)-6), 3.11 (d, \( J=7.2 \) Hz, 2H, S-CH\(_2\)), 4.01-4.15 (m, 6H, 2\( \times \)CH\(_2\) ester, CH\(_2\)-2), 5.00-5.08 (m, 2H, = CH\(_2\)), 5.12 (s, 1H, CH-4), 5.74-5.82 (m, 1H, =CH), 6.97 (s,1H, NH), 7.38 (t, \( J=7.94 \) Hz, 1H, ArH) 7.63 (d, \( J=7.69 \) Hz, 1H, ArH), 8.01 (m, 1H, ArH), 8.12 (m, 1H, ArH) ppm. Anal. Calcd for C\(_{22}\)H\(_{26}\)N\(_2\)O\(_6\)S : C, 59.19; H, 5.83; N, 6.27. Found: C, 58.83; H, 5.89; N, 6.42.
References