Synthesis of novel unsymmetrically substituted 1,4-dihydropyridines and separation of the enantiomers of racemic 1,4-dihydropyridine containing isothioureido 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 substituens 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.**

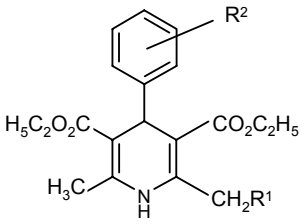
In view of chirality to pharmacological activity, the present article will describe the separation of the enantiomers of S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl) 1,4-dihydropyridin-2-yl)-methyl]-isothiourea.

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[8] by modifying the literature methods.[7,9,10] 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).

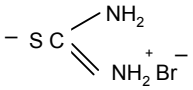
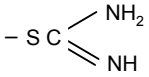
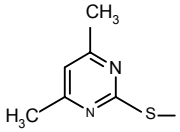
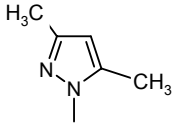
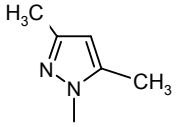
In the reaction of **2a** with thiourea in refluxing ethanol for 5h, evaporation of solvent and recrystallization from EtOAc/Hex, isothiouronium salt **3a** is formed. Transformation of isothiouronium salt **3a** into its isothiourea **3b**, as free base, carried out by treatment of **3a** in CH_2Cl_2/H_2O with Na_2CO_3 with vigorous stirring, at room temperature.[11] The C-4 carbon atom of 1,4-dihydropyridines is a prochiral atom. When at least one of the sunstituents, 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 diasteromeric salts of **3b**, the mixture of **3b** and (1S)-(+)-camphor-10-sulfonic acid in CH_3CN was refluxed for 4h, but the product obtained was the thiol derivative **3c**. However, Optical resolution of **(±)-3b** by salification with *o,ó*-dibenzoyl-L-tartaric acid and recrystallization of diastereomeric salts, then hydrolysis of crystallized diastereomer **(-)-4** in CH_2Cl_2/H_2O with $NaHCO_3$ 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).

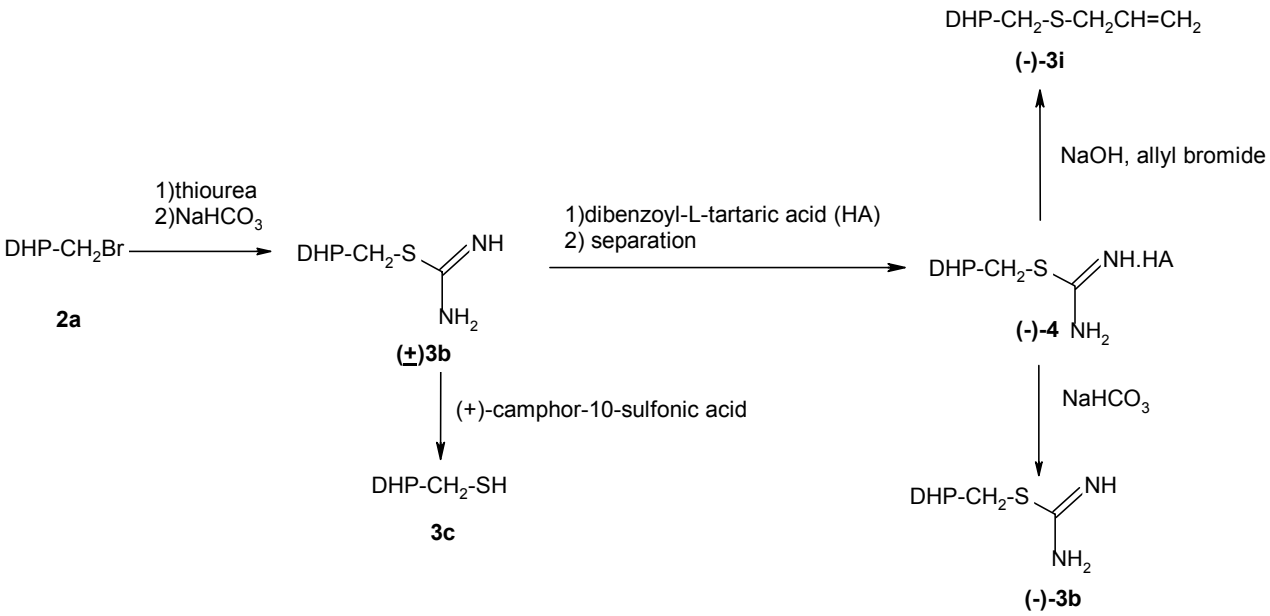
Table 1. Compounds **3**



(DHP-CH_2-R^1)

3

Entry	Product	R^1	R^2	Yield (%)
1	3a		3-NO_2	80
2	3b		3-NO_2	60
3	3c	- SH	3-NO_2	45
4	3d		2-OCH_3	57
5	3e	-N_3	2-Cl	35
6	3f	-SCN	2-Cl	45
7	3g		2-Cl	49
8	3h		3-NO_2	35
9	3i	-S CH_2CH= CH_2	3-NO_2	45



Scheme 1

3. Experimental Section

2-[(4,6-Dimethylpyrimidin-2-yl)thio-]-methyl-3,5-dicarboethoxy-6-methyl-4-(2-methoxy-phenyl)-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_2Cl_2 (30ml) and saturated Na_2CO_3 solution, and the organic layer washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of crude product from 2-propanol furnished **3d** (0.38 g, 57%) as yellow crystals. M.p. 142 ºC, IR (KBr) $\overline{\nu} = 3423$ (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}; ^1H NMR (400 MHz, $CDCl_3$): δ= 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 $C_{26}H_{31}N_3O_5$: 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_2Cl_2 (20ml) and 2M HCl solution, and the organic layer washed with water, dried over Na_2SO_4 and

evaporated. Recrystallization of crude product from EtOH furnished **3e** (0.22 g, 35%) as yellow crystals.

IR (KBr) $\overline{\nu}$ = 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, $CDCl_3$): δ = 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), 7.28 (dd, J_1=3.24 Hz, J_2=1.43 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_2Cl_2 (20ml) and 2M HCl solution, and the organic layer washed with water, dried over Na_2SO_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) $\overline{\nu}$ = 3351 (s), 3057 (w), 2979-2937 (m), 2156 (s), 1686(s), 1651 (m), 1625 (m), 1504 (s), 1281 (s), 1208 (s), 1095 (s), 1048 (s), 757(s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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 $C_{21}H_{24}N_2O_5S$: 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_2Cl_2 and HCl 2M, the organic layer washed with saturated Na_2CO_3 solution and water, dried over Na_2SO_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) $\overline{\nu}$ = 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, $CDCl_3$): δ = 1.21 (t, *J*=7.09 Hz, 3H, CH_3 ester), 1.25 (t, *J*=7.13 Hz, 3H, CH_3 ester), 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 $C_{25}H_{31}N_3O_5$: C, 62.94; H, 6.16; N, 9.17. Found: C, 62.92; H, 6.51; N, 9.19.

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 ºC, IR (KBr) $\overline{\nu}$ = 3293 (m), 3100 (w), 2980-2850 (m), 1687 (s), 1652 (m), 1620 (m), 1528 (s), 1499 (s) ,1350 (s), 1273 (s), 1203(s), 1102(s), 715 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (m, 6H, 2×CH_3 ester), 2.22-2.62(m, 9H, 2×CH_3 pyrazol and CH_3-6), 4.06-4.20(m, 4H, 2×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 $C_{24}H_{28}N_4O_6$: C, 61.53; H, 5.98; N, 11.96. Found: C, 61.73; H, 6.07; N, 12.01.

***S*-[(6-Methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-methyl]-isothiouronium *o,ó*-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,ó*-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 ºC for 24 h. Recrystallization of the obtained crystalls from EtOAc/Hex furnished (-)-S-[(6-methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4- yl)-methyl]-isothiouronium *o,ó*-dibenzoyl-L-tartarate (0.03 g, 30%) , m.p. 162-163 ºC, $[\alpha]_{578}$=-29.13º (c=1.3 ,MeOH) as yellow crystals.

(-)- S-[(6-methyl)-3,5-dicarboethoxy-4-(3-nitrophenyl)1,4-dihydropyridin-2-yl)-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_2Cl_2/H_2O (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_2SO_4 and evaporated. Recrystallization of crude product from Et_2O furnished **(-)-3b** (0.03 g, 65%), mp. 119-120 ºC, $[\alpha]_{578}$ = -10.53º (c=1.9 , CH_2Cl_2).

(-)- 2-(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 ºC, $[\alpha]_{578}$ = -7.35º (c=2, CH_2Cl_2); IR(KBr) $\overline{\nu}$ = 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}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J*=7.12 Hz, 6H, 2×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×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 $C_{22}H_{26}N_2O_6S$: C, 59.19; H, 5.83; N, 6.27. Found: C, 58.83; H, 5.89; N, 6.42.

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