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Synthesis, spectroscopic and conformational analysis of 1,4-dihydroisonicotinic acid derivatives

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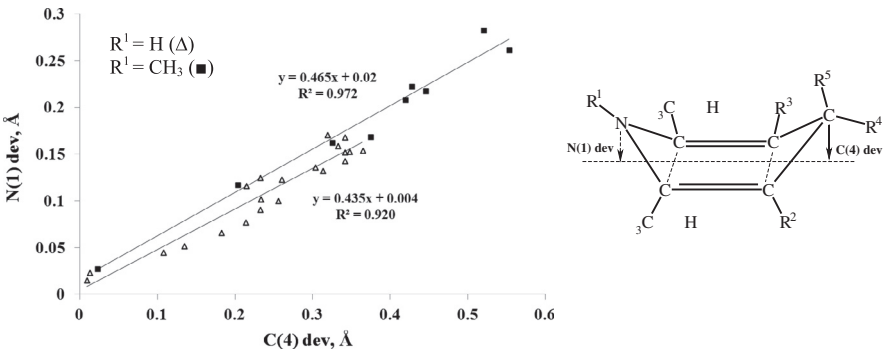
HIGHLIGHTS

- The present work offers methods for the synthesis of novel 1,4-DHINA derivatives.
- Crystals suitable for X-ray were obtained by slow evaporation from saturated solvents.
- Conformational properties have been investigated by X-ray, NMR and theoretical calculations.

GRAPHICAL ABSTRACT



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ABSTRACT

Structural and conformational properties of 1,4-dihydroisonicotinic acid derivatives, characterized by ester, ketone or cyano functions at positions 3 and 5 in solid and liquid states have been investigated by X-ray analysis and nuclear magnetic resonance and supported by quantum chemical calculations. The dihydropyridine ring in each of the compounds exists in flattened boat-type conformation. The observed ring distortions around the C(4) and N(1) atoms are interrelated. The substituent at N(1) has great influence on nitrogen atom pyramidality. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts and coupling constants are discussed in terms of their relationship to structural features such as character and position of the substituent in heterocycle, *N*-alkyl substitution and nitrogen lone pair delocalization within the conjugated system.

Introduction

1,4-Dihydroisonicotinic acid derivatives (1,4-DHINA) are important precursors for the synthesis of biologically active 1,4-dihydropyridines (1,4-DHPs). The parental compound, 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydroisonicotinic acid sodium salt, as well as 1,4-DHINA coupled with glutamic acid residue – glutapyrone, both possess antimutagenic properties [1–3]. Besides, glutapyrone shows a wide variety of pharmacological properties, amongst which the neuromodulatory one is the most pronounced [4,5]. Taurine derivative of 1,4-dihydroisonicotinic acid (tauropyrone) shows anti-platelet properties and is active as an anti-aggregant at concentrations that are six times lower than those for taurine [6].

Since the discovery of pharmacological effects of this class of substances, it has been of interest to know which conformation produces the optimum effect. The conformation of the dihydropyridine ring, the nature of the substituents and their mutual

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orientation play a key role for the biological activity of 1,4-DHPs [7]. A number of studies have been devoted to the conformational analysis of numerous 4-phenyl and 4-heteroaryl substituted 1,4-DHP derivatives [8–19], however the crystal structures of 1,4-DHINA derivatives are not analysed in literature until now.

In the course of studies on the chemistry of 1,4-DHINA we focused on conformation and spectroscopic properties of several symmetrically and unsymmetrically substituted derivatives (Table 1).

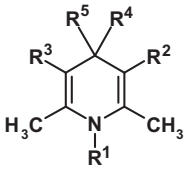
Experimental section

General information

Previously we have reported the synthesis and X-ray analysis of compounds **1d**–**1f** [20] and **5a**, **5b**, **5d** and **5e** [21]. The symmetrical 4-phenyl substituted 1,4-DHP derivatives **1c**–**3c** were synthesized at Latvian Institute of Organic Synthesis and obtained as stable solids with good yields.

All chemicals were purchased from commercial sources (Sigma–Aldrich and Acros) and used without further purification. Reactions were monitored using analytical TLC plates (Merck, silica gel 60 F_{254}), and visualized with ultraviolet light (254 nm). Column chromatography was carried out using Acros silica gel (particle size 0.035–0.070 mm). IR spectra were recorded on a IRPrestige-21 Shimadzu spectrometer in Nujol. Melting points were determined with a SRS Stanford Research Systems OptiMelt Automated Melting Point System instrument. Elemental analysis was carried out on EA 1106 (Carlo Erba Instruments) automatic analyzer.

Table 1
Chemical structures for 1,4-DHP derivatives.



1,4-DHP	R^1	R^2	R^3	R^4	R^5
1a	H	$COOCH_3$	$COOCH_3$	H	COOH
1b	H	$COOCH_3$	$COOCH_3$	H	$COOCH_3$
1c	H	$COOCH_3$	$COOCH_3$	H	C_6H_5
1d	CH_3	$COOCH_3$	$COOCH_3$	H	$COOCH_3$
1e	CH_3	$COOCH_3$	$COOCH_3$	CH_3	$COOCH_3$
1f	CH_3	$COOCH_3$	$COOCH_3$	$CH(CH_3)_2$	$COOCH_3$
2a	H	$COCH_3$	$COCH_3$	H	COOH
2b	H	$COCH_3$	$COCH_3$	H	$COOCH_3$
2c	H	$COCH_3$	$COCH_3$	H	C_6H_5
2d	CH_3	$COCH_3$	$COCH_3$	H	$COOCH_3$
3a	H	CN	CN	H	COOH
3b	H	CN	CN	H	$COOCH_3$
3c	H	CN	CN	H	C_6H_5
3d	CH_3	CN	CN	H	$COOCH_3$
3e	CH_3	CN	CN	CH_3	$COOCH_3$
4a	H	$COOCH_3$	CN	H	COOH
4b	H	$COOCH_3$	CN	H	$COOCH_3$
4c	H	$COOCH_3$	CN	H	C_6H_5
4d	CH_3	$COOCH_3$	CN	H	$COOCH_3$
5a	H	$COCH_3$	CN	H	COOH
5b	H	$COCH_3$	CN	H	$COOCH_3$
5c	H	$COCH_3$	CN	H	C_6H_5
5d	CH_3	$COCH_3$	CN	H	$COOCH_3$
5e	CH_3	$COCH_3$	CN	CH_3	$COOCH_3$
6a	H	$COOCH_3$	$COCH_3$	H	COOH
6b	H	$COOCH_3$	$COCH_3$	H	$COOCH_3$
6c	H	$COOCH_3$	$COCH_3$	H	C_6H_5
6d	CH_3	$COOCH_3$	$COCH_3$	H	$COOCH_3$

Synthesis

2,6-Dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylic acid 3,5-dimethyl ester (1a) was synthesized by the procedure given in literature [22]. Yield 38%, colourless solid, mp 233–234 °C (from MeOH). ^{1}H NMR δ 2.22 (s, 6H, 2,6-CH_3), 3.60 (s, 6H, 3,5-$COOCH_3$), 4.58 (s, 1H, 4-H), 8.93 (s, 1H, NH), 11.95 (s, 1H, 4-COOH). ^{13}C NMR 17.85, 39.16, 50.79, 96.98, 146.17, 167.24, 174.42. Found: C, 53.52; H, 5.54; N, 5.16. Calc. for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20%. IR spectrum, ν_{max}/cm^{-1}: 3346 (NH), 1700 (CO), 1662 (CO).

2,6-Dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylic acid trimethyl ester (1b) was synthesized by the procedure given in literature [23]. Yield 93%, colourless solid, mp 158–159 °C (from MeOH). ^{1}H NMR δ 2.23 (s, 6H, 2,6-CH_3), 3.50 (s, 3H, 4-$COOCH_3$), 3.62 (s, 6H, 3,5-$COOCH_3$), 4.69 (s, 1H, 4-H), 9.01 (s, 1H, NH). ^{13}C NMR 17.89, 39.38, 50.89, 51.75, 96.30, 146.83, 166.97, 173.35. Found: C, 55.17; H, 5.98; N, 4.82. Calc. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94%. IR spectrum, ν_{max}/cm^{-1}: 3338 (NH), 1709 (CO), 1647 (CO).

3,5-Diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid (2a) was synthesized by the procedure given in literature [22]. Yield 25%, yellow solid, mp 173–174 °C (from MeOH) (lit. [22], 170 °C). ^{1}H NMR δ 2.23 (s, 6H, 2,6-CH_3), 2.27 (s, 6H, 3,5-$COCH_3$), 4.61 (s, 1H, 4-H), 8.91 (s, 1H, NH), 12.11 (s, 1H, 4-COOH). ^{13}C NMR 18.75, 29.65, 40.47, 107.67, 144.84, 174.41, 196.42. Found: C, 60.55; H, 6.36; N, 5.80. Calc. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%. IR spectrum, ν_{max}/cm^{-1}: 3318 (NH), 1715 (CO), 1601 (CO).

3,5-Diacetyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid methyl ester (2b) was synthesized by the procedure given in literature [21]. Yield 2.4 g (63%), yellow solid, mp 151–153 °C (from MeOH). ^{1}H NMR δ 2.24 (s, 6H, 2,6-CH_3), 2.28 (s, 6H, 3,5-$COCH_3$), 3.50 (s, 3H, 4-$COOCH_3$), 4.74 (s, 1H, 4-H), 9.03 (s, 1H, NH). ^{13}C NMR 18.78, 29.74, 40.36, 51.75, 107.18, 145.43, 173.32, 196.06. Found: C, 61.87; H, 6.82; N, 5.52. Calc. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%. IR spectrum, ν_{max}/cm^{-1}: 3307 (NH), 1728 (CO), 1675 (CO).

3,5-Diacetyl-1,2,6-trimethyl-1,4-dihydropyridine-4-carboxylic acid methyl ester (2d). To a stirred solution of compound **2b** (1.0 g, 0.004 mol) in anhydrous CH_3CN (20 mL) at r.t. was added sodium methoxide (0.3 g, 0.005 mol), as a result of which a vigorous reaction with hydrogen evolution was observed, and strongly colored anion, which gives characteristic orange fluorescence, was formed. At the end of hydrogen evolution CH_3I (1.2 mL, 0.02 mol) was added. Reaction mixture was stirred for 12 h and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (CH_2Cl_2-petroleum ether-acetone, 9:7:1) to give compound **2d**. Yield 0.6 g (57%), yellow solid, mp 106–108 °C (from CH_2Cl_2). ^{1}H NMR δ 2.31 (s, 6H, 2,6-$COCH_3$), 2.36 (s, 6H, 2,6-CH_3), 3.18 (s, 3H, N—CH_3), 3.51 (s, 3H, 4-$COOCH_3$), 4.73 (s, 1H, 4-H). ^{13}C NMR 16.27, 29.94, 33.97, 40.47, 51.89, 109.62, 148.99, 172.86, 196.77. Found: C, 63.42; H, 7.32; N, 5.21. Calc. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28%. IR spectrum, ν_{max}/cm^{-1}: 1736 (CO), 1649 (CO).

3,5-Dicyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid monohydrate (3a) was synthesized by the procedure given in literature [22]. Yield 64%, colourless solid, mp 189–190 °C (from MeOH) (lit. [24], 190 °C). ^{1}H NMR δ 2.03 (s, 6H, 2,6-CH_3), 4.02 (s, 1H, 4-H), 9.62 (s, 1H, NH), 13.09 (s, 1H, 4-COOH). ^{13}C NMR 17.71, 40.57, 78.00, 119.03, 148.42, 172.01. Found: C, 54.21; H, 4.89; N, 18.86. Calc. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 5.01; N, 18.99%. IR spectrum, ν_{max}/cm^{-1}: 3245 (NH), 2211 (CN), 1714 (CO).

3,5-Dicyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid methyl ester monohydrate (3b) was synthesized by the procedure given in literature [23]. Yield 3.2 g (86%), colourless solid, mp 176–178 °C (from MeOH) (lit. [24], 184 °C). ^{1}H NMR δ 2.04 (s, 6H, 2,6-CH_3), 3.70 (s, 3H, 4-$COOCH_3$), 4.24 (s, 1H, 4-H), 9.72 (s,