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SYNTHESIS OF NOVEL UNSYMMETRICALLY SUBSTITUTED 1,4-DIHYDROISONICOTINIC ACID AND ITS DERIVATIVES

I. Goba[1]*, B. Turovska[1], S. Belyakov[1], and E. Liepinsh[1]

The synthesis of new unsymmetrically substituted 1,4-dihydroisonicotinic acid bearing cyano and acetyl groups in positions 3 and 5 of the heterocycle has been developed. The methyl, ethoxycarbonylmethyl, and propionyloxymethyl esters of the acid have been obtained. The method of N-alkylation reaction of synthesized 1,4-dihydroisonicotinic acid esters has been elaborated.

Keywords: 1,4-dihydropyridines, unsymmetrical 1,4-dihydroisonicotinic acid, alkylation, esterification.

Derivatives of 4-aryl-substituted 1,4-dihydropyridines (1,4-DHP) are widely studied heterocycles that have been approved for use in cardiovascular medicine, such as amlodipine [1]. 1,4-DHP are mainly known as calcium mediators and possess also vasodilatory, hepatoprotective, neuromodulatory, memory enhancing, neuroprotective, antiatherosclerotic, antidiabetic, antioxidant, antimutagenic, and antitumor activity [2, 3].

In recent years, considerable attention has been paid to the synthesis of unsymmetrical 4-aryl-substituted 1,4-DHP [4]. It has been shown that the enantiomers of an unsymmetrically substituted 1,4-DHP may differ in biological activity [5-7], sometimes one opposite the other (calcium antagonist *vs.* calcium agonist; hypotensive *vs.* hypertensive activity) [8, 9].

At the same time, little attention has been paid to the unsymmetrical 1,4-DHP where, instead of the aryl group, the C-4 carbon of the heterocycle is substituted with different chemically active functional groups, e.g., carboxyl group [10, 11]. The biologically active symmetrical 1,4-dihydroisonicotinic acid derivatives gamma-pyrone and glutapyrone have been reported in the literature [12-15]. They differ from the classical 1,4-DHP compounds by their high water solubility and low toxicity [16].

There is only one report on the synthesis of unsymmetrically substituted 1,4-dihydroisonicotinic acid where 3-methoxycarbonyl-2,6-dimethyl-5-propoxycarbonyl-1,4-dihydropyridine-4-carboxylic acid was isolated as a minor product (yield 13%) besides the symmetrically substituted 1,4-dihydroisonicotinic acids [10].

The aim of the present work is to describe an efficient method for the synthesis of unsymmetrical 1,4-dihydroisonicotinic acid bearing cyano and acetyl groups in positions 3 and 5 of the heterocycle. Further eventual modifications of the chemically active carboxyl group at the stereogenic center of the heterocycle could lead to a novel class of potentially biologically active compounds.

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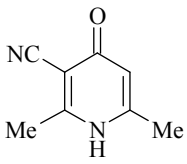
The Hantzsch reaction of glyoxylic acid with acetylacetonamine and 3-aminocrotonitrile (molar ratio 1:1:1) was carried out in glacial AcOH at 60°C, however the desired unsymmetrical 1,4-dihydroisonicotinic acid was not obtained. Instead 1,4-DHP **1** [17] and lactone **2** were isolated from the reaction media, and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy.



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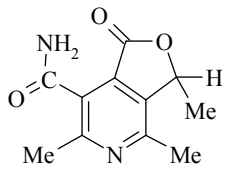
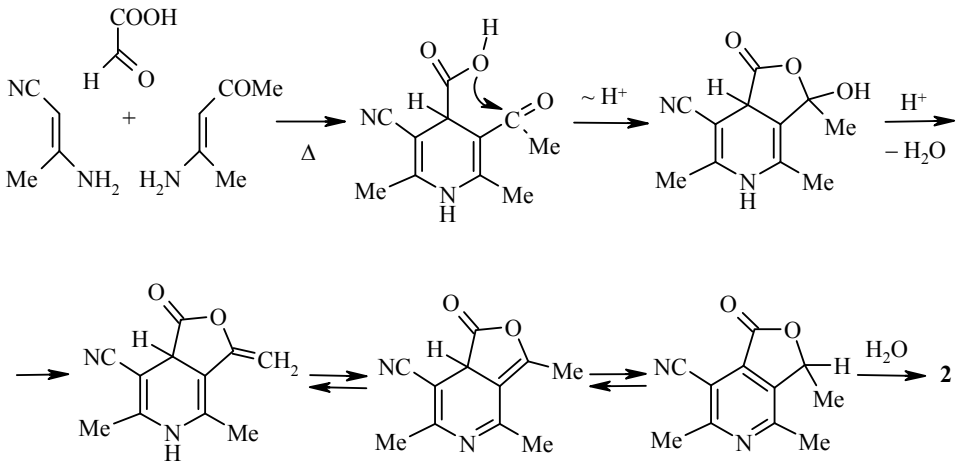


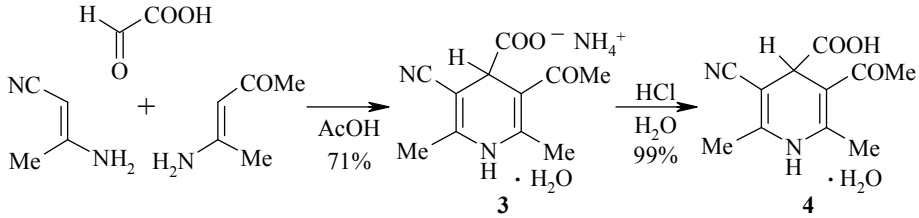
2

The formation of lactone **2** could proceed through the pyrolysis of 1,4-dihydroisonicotinic acid, obtained in the Hantzsch reaction. The proposed mechanism for lactone **2** involves intramolecular cyclization between carboxyl and acetyl groups, followed by the dehydration reaction and the hydrolysis of the cyano group.



A similar transformation due to pyrolysis of 1,4-dihydroisonicotinic acid to the lactones is known for the symmetrically substituted compounds at reflux temperature in various solvents [18-21].

In present work, it was found that an efficient three-component Hantzsch reaction can be realized at 0°C in glacial AcOH using glyoxylic acid, acetylacetonamine, and 3-aminocrotononitrile in the molar ratio 1:2:2, respectively. The ammonium salt of 3-acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid (**3**) was isolated as the primary product.



3 **4**

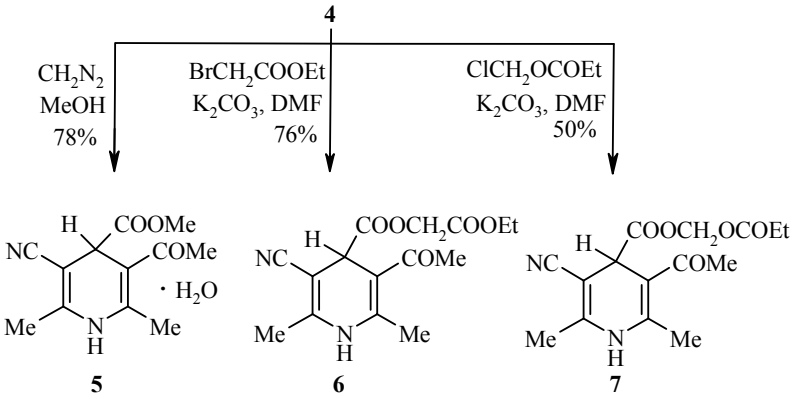
The structure of compound **3** was characterized with the ^{1}H and ^{13}C NMR spectroscopy data and unambiguously established by X-ray structural analysis (Fig. 1).

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid monohydrate (**4**) was obtained in 99% yield by the acidification of a concentrated solution of ammonium salt **3** in water with HCl. Compound **4** appears to be insoluble in water. The structure of compound **4** was confirmed by X-ray structural analysis (Fig. 2).

The esterification of the carboxylic acid was realized by the treatment of compound **4** with CH_2N_2, a method known for esterification of symmetrical 1,4-dihydropyridine-4-carboxylic acids [21] to yield 3-acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid methyl ester monohydrate (**5**). The structure of 1,4-DHP **5** was confirmed by NMR spectroscopy and X-ray structural analysis (Fig. 3).

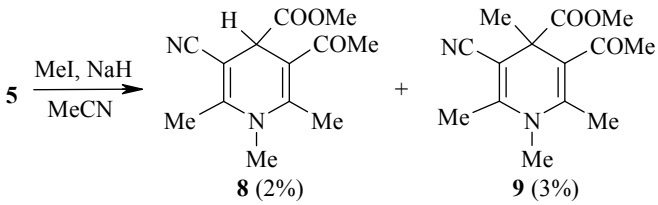
In this work the synthesis of ester derivatives differing in size was also developed; moreover, the similar esters could be used for lipase-catalyzed kinetic resolution of the racemic mixture into enantiomers [10].

The corresponding ethoxycarbonylmethyl ester **6** and propionyloxymethyl ester **7** of 1,4-dihydroisonicotinic acid **4** were synthesized using ethyl bromoacetate and propionyloxymethyl chloride in DMF.



Their structures were confirmed by ^1H and ^{13}C NMR spectroscopy. Additionally, the structure of 1,4-DHP **6** was confirmed by X-ray structural analysis (Fig. 4).

The acidic properties of 1,4-DHP are weakly expressed, and a strong alkaline agent is therefore required for *N*-alkylation. The reaction is promoted by polar aprotic solvents [22]. The *N*-alkylation of 1,4-dihydroisonicotinic acid methyl ester **5** by treatment with NaH and methyl iodide in acetonitrile resulted in inseparable reaction mixture, with the yield of isolated *N*-methyl substituted 1,4-DHP **8** only 2%. Unexpectedly, 4,4-disubstituted 1,4-DHP **9** was also isolated from the reaction medium.



This means that the presence of strong electron acceptors in the heterocycle increases not only the acidity of NH but also that of 4-CH. To our knowledge, this is the first example of the alkylation of the stereogenic center of 1,4-DHP. The structures of both compound **8** and **9** were confirmed by NMR spectroscopy and X-ray structural analysis (Fig. 5).

The *N*-alkylation of 1,4-DHP **5** was repeated using NaOH and methyl iodide in acetone, a method known for *N*-alkylation of 1,2-DHP [23]. These conditions of the alkylation reaction were more successful, and 3-acetyl-5-cyano-1,2,6-trimethyl-1,4-dihydropyridine-4-carboxylic acid methyl ester (**8**) was obtained in 65% overall yield.

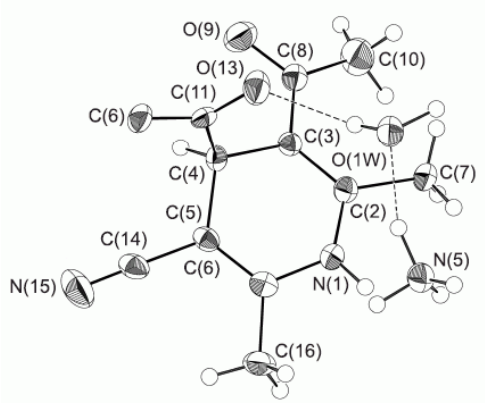


Fig. 1. Crystal structure of compound **3**.
Thermal ellipsoids are shown at the 50% probability level.

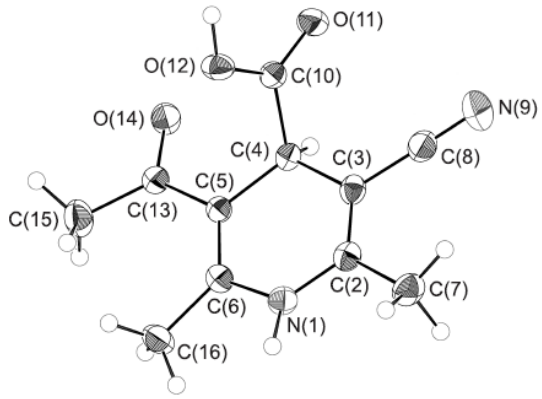


Fig. 2. Crystal structure of compound **4**.
Thermal ellipsoids are shown at the 50% probability level.

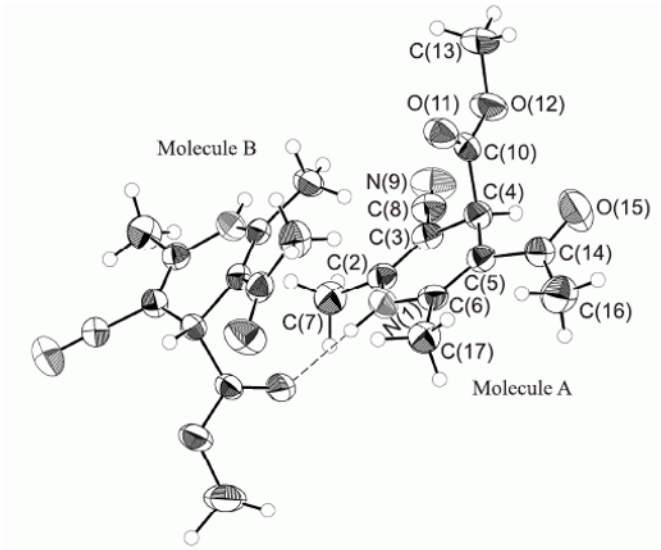


Fig. 3. Crystal structures of compound **5**.
Thermal ellipsoids are shown at the 50% probability level.

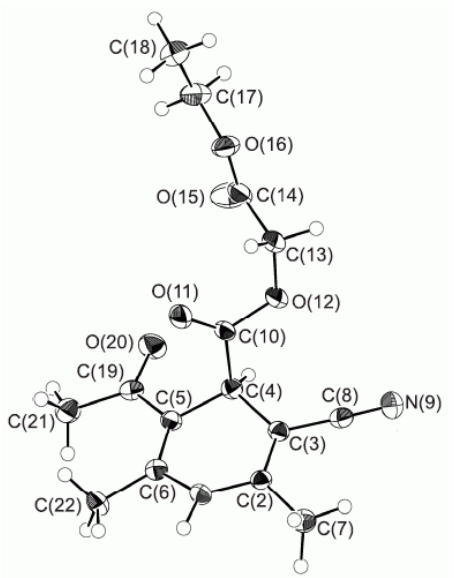


Fig. 4. Crystal structures of compound **6**.
Thermal ellipsoids are shown at the 50% probability level.

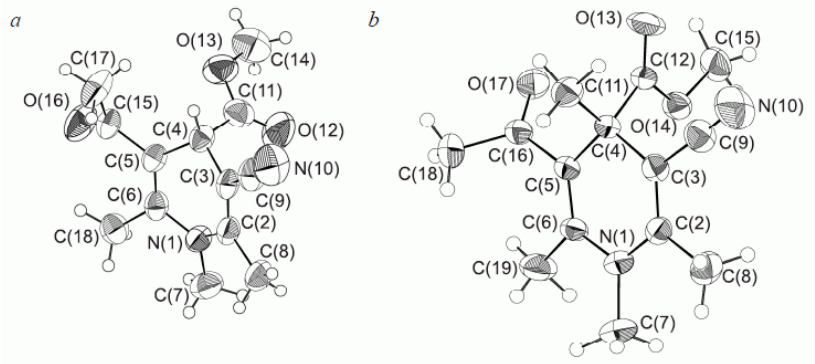


Fig. 5. Crystal structures of compounds **8** (*a*) and **9** (*b*).
Thermal ellipsoids are shown at the 50% probability level.

In the X-ray structures of compounds **3**-**6**, **8**, and **9** (Fig. 1-5), the 1,4-DHP ring adopts a flattened boat conformation. Atoms N(1) and C(4) show small displacements from the base of the boat plane defined by C(2)–C(3)–C(5)–C(6). As already observed in other 1,4-DHP structures [24-27], as well as in the present crystal structures, N(1) shows a smaller deviation from that plane compared to C(4) (Table 1).

The sum of the absolute values of the ring internal torsion angles (*P*) is a quantitative measure suggested for the evaluation of the flatness of the six-membered ring [28]. These values range from 14.7 (compound **9**) to 131.3 (compound **8**) (Table 1), indicating a significant amount of flattening from the ideal boat conformation.

Compounds **3**-**6**, **8**, and **9** form crystals as racemates as a result of the centrosymmetric space groups ($P2_1/a$, $P2_1/n$, $C2/c$ and $P\bar{1}$) in which they crystallize. Examination of ϕ in Table 1 reveals that the acetyl group remains nearly coplanar with the plane of the dihydropyridine ring and shows a preference for the *s-trans* conformation with respect to the double bond, except for 1,4-DHP **8**, which exists as the *s-cis* conformer (Fig. 5*a*).

TABLE 1. Geometric Parameters for the 1,4-Dihydropyridine Ring in Compounds **3**-**6**, **8**, and **9**

Compound	N(1) dev*, Å	C(4) dev*, Å	P^{*2}, deg.	ϕ, deg. C(2)–C(3)–C(8)–O(9)
3	0.119(4)	0.323(5)	92.8(4)	–173.7(6)
4	0.023(3)	0.012(4)	14.9(3)	–174.5(5)
5 (molecule A)	0.077(3)	0.213(3)	61.4(4)	–172.2(5)
5 (molecule B)	0.136(3)	0.303(3)	89.8(4)	–168.4(5)
6	0.117(2)	0.278(2)	82.2(3)	179.5(4)
8	0.218(3)	0.445(3)	131.3(4)	–33.3(4)
9	0.028(3)	0.022(3)	14.7(3)	–134.1(4)

* Deviation from the least square plane defined by C(2)–C(3)–C(5)–C(6).
*[2]Sum of the absolute values of the ring internal torsion angles of the 1,4-dihydropyridine ring.

It is worth noting that in the crystal structure of compound **3** a water molecule has been found (Fig. 1) that forms a hydrogen bond system with 1,4-DHP anions and ammonium cations. The lengths of these hydrogen bonds lie in the interval of 2.698(4)-2.811(4) Å.

Intermolecular NH···O=C hydrogen bonds between the 1,4-DHP NH group and the ester carbonyl O atom interlink two molecules of compound **5** (Fig. 3). The length of N(1)···O(11) is 2.957(3) Å (H···O(11) 2.03 Å, N(1)–H···O(11) 178°).

In summary, the present work offers a method for the synthesis of novel unsymmetrical 1,4-dihydroisonicotinic acid and its derivatives. The evaluation of the biological properties of the racemic 3-acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acid and its synthetic modifications, as well as the separation of the enantiomers, is currently in progress.

EXPERIMENTAL

IR spectra were recorded on an IR Prestige-21 Shimadzu spectrometer in nujol. ^{1}H NMR spectra were recorded on Varian Mercury (200 MHz) and Varian 400-MR (400 MHz) spectrometers and ^{13}C NMR spectra on a Varian 400-MR (100 MHz) spectrometer using TMS as internal standard. Elemental analysis was carried out on an EA 1106 (Carlo Erba Instruments) automatic analyzer. Melting points were determined with an SRS Stanford Research Systems OptiMelt Automated Melting Point System instrument. 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). All chemicals were purchased from commercial sources (Sigma-Aldrich and Acros) and used without further purification.

2,6-Dimethyl-4-oxo-1,4-dihydropyridine-3-carbonitrile (1) and 3,4,6-Trimethyl-1-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carboxamide (2). Glyoxylic acid monohydrate (4.8 g, 0.05 mol) solution in glacial AcOH (20 ml) was added to a stirred solution of acetylacetonamine (5.2 g, 0.05 mol) and 3-aminocrotononitrile (4.3 g, 0.05 mol) in glacial AcOH (40 ml) at 100°C, and the reaction mixture was stirred for 8 h. Then the solvent was removed under reduced pressure and treated with acetone (40 ml), filtered, and dried to afford compound **1**. The crude product was purified by crystallization from MeOH. Yield 2.2 g (29%), yellowish solid, mp 302304°C (mp 299°C [17]). IR spectrum, ν, cm^{-1}: 2217, 1662. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 2.21 (3H, s, 2-CH_3); 2.38 (3H, s, 6-CH_3); 6.17 (1H, s, H-3); 12.26 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.2 (2-CH_3); 20.0 (6-CH_3); 91.0 (C-5); 116.2 (5-CN); 116.4 (C-3); 150.5 (C-2); 154.9 (C-6); 161.6 (C-4). Found, %: C 64.58; H 5.34; N 18.63. $C_8H_8N_2O$. Calculated, %: C 64.85; H 5.44; N 18.91. The filtrate was concentrated to yield compound **2**. The crude product was purified by

crystallization from acetone. Yield 0.3 g (3%), colorless solid, mp 256-258°C. IR spectrum, ν, cm^{-1}: 3423, 1764, 1654. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.57 (3H, d, *J* = 6.4, 3-CH_3); 2.51 (3H, s, 4-CH_3); 2.55 (3H, s, 6-CH_3); 5.84 (1H, q, *J* = 6.4, 3-CH); 7.76 (1H, s) and 7.90 (1H, s, 7-$CONH_2$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.9 (3-CH_3); 21.1 (4-CH_3); 21.2 (6-CH_3); 76.6 (C-3); 126.7 (C-7); 129.5 (C-7a); 140.2 (C-3a); 152.5 (C-4); 154.1 (C-6); 166.5 (C-1); 167.2 (7-$CONH_2$). Found, %: C 59.94; H 5.39; N 12.89. $C_{11}H_{12}N_2O_3$. Calculated, %: C 59.99; H 5.49; N 12.72.

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic Acid Ammonium Salt Monohydrate (3). Glyoxylic acid monohydrate (4.8 g, 0.05 mol) solution in glacial AcOH (20 ml) was added to astirred solution of acetylacetonamine (11.9 g, 0.10 mol) and 3-aminocrotononitrile (9.8 g, 0.10 mol) in glacial AcOH (40 ml) at 0°C . Then the reaction mixture was stirred for 12 h at room temperature, and the solvent was removed under reduced pressure. The mixture was treated with $CHCl_3$ (50 ml), filtered, and dried. The crude product was purified by crystallization from MeOH. Yield 9.5 g (71%), yellow solid, mp >130°C (decomp.). IR spectrum, ν, cm^{-1}: 3400, 3170, 2211, 1655, 1584. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 1.97 (3H, s, 6-CH_3); 2.11 (3H, s, 2-CH_3); 2.14 (3H, s, 3-$COCH_3$); 3.75 (1H, s, 4-CH); 8.83 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 17.3 (6-CH_3); 18.8 (2-CH_3); 29.3 (3-CO$\underline{C}H_3$); 43.1 (C-4); 82.7 (C-5); 108.2 (C-3); 120.9 (5-CN); 141.9 (C-2); 145.7 (C-6); 174.6 (4-COO^-); 197.8 (3-COMe). Found, %: C 51.76; H 6.68; N 16.30. $C_{11}H_{17}N_3O_4$. Calculated, %: C 51.75; H 6.71; N 16.46.

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic Acid Monohydrate (4). Conc. HCl (1.0 ml) was added to a solution of compound **3** (1.0 g, 0.004 mol) in H_2O (15 ml). The yellow precipitate formed was filtered, washed with H_2O, and dried to afford compound **4**. Yield 0.9 g (99%), yellow solid, mp 138-140°C. Crystals of compound **4** for X-ray structural analysis were obtained by crystallization from MeOH. IR spectrum, ν, cm^{-1}: 3421, 2208, 1701, 1662. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.04 (3H, s, 6-CH_3); 2.21 (3H, s, 3-$COCH_3$); 2.22 (3H, s, 2-CH_3); 4.16 (1H, s, 4-CH); 9.21 (1H, s, NH); 12.54 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 17.4 (6-CH_3); 19.1 (2-CH_3); 29.9 (3-CO$\underline{C}H_3$); 41.0 (C-4); 79.4 (C-5); 106.3 (C-3); 119.6 (5-CN); 145.0 (C-2); 148.3 (C-6); 173.3 (4-COOH); 196.2 (3-COMe). Found, %: C 55.52; H 5.79; N 11.82. $C_{11}H_{14}N_2O_4$. Calculated, %: C 55.46; H 5.92; N 11.76.

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic Acid Methyl Ester Monohydrate (5). A freshly prepared solution of CH_2N_2 in diethyl ether (prepared from diazogen according to the protocol given in the literature [29]) was added to a stirred solution of compound **4** (3.1 g, 0.01 mol) in MeOH (135 ml). Then the solvent was removed under reduced pressure, and the obtained solid was purified by crystallization from MeOH. Yield 2.4 g (78%), yellow crystals, mp 150-152°C. Crystals of compound **5** for X-ray structural analysis were obtained by crystallization from CH_2Cl_2. IR spectrum, ν, cm^{-1}: 3312, 2202, 1747, 1696. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.04 (3H, s, 6-CH_3); 2.23 (3H, s, 3-$COCH_3$); 2.25 (3H, s, 2-CH_3); 3.60 (3H, s, 4-$COOCH_3$); 4.27 (1H, s, 4-CH); 9.30 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 17.4 (6-CH_3); 19.2 (2-CH_3); 30.2 (3-CO$\underline{C}H_3$); 41.2 (C-4); 52.0 (4-COO$\underline{C}H_3$); 78.9 (C-5); 106.2 (C-3); 119.2 (5-CN); 145.7 (C-2); 148.8 (C-2); 172.2 (4-$\underline{C}OOCH_3$); 195.9 (3-COMe). Found, %: C 57.23; H 6.45; N 11.22. $C_{12}H_{16}N_2O_4$. Calculated, %: C 57.13; H 6.39; N 11.10.

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic Acid Ethoxycarbonylmethyl Ester (6). K_2CO_3 (0.9 g, 0.007 mol) was added at room temperature to a solution of compound **4** (1.0 g, 0.004 mol) in dry DMF (2 ml), and the reaction mixture was stirred for 2 h, after which ethyl bromoacetate (0.8 ml, 0.007 mol) was added. Then the reaction mixture was stirred overnight at room temperature. The mixture was treated with H_2O (10 ml), and the precipitate was filtered off and dried to afford compound **6**. Yield 1.1 g (76%), colorless solid, mp 158-159°C. Crystals of compound **6** for X-ray structural analysis were obtained by crystallization from CH_2Cl_2. IR spectrum, ν, cm^{-1}: 3270, 2205, 1749, 1659. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.06 (3H, s, 6-CH_3); 2.23 (3H, s, 3-$COCH_3$); 2.25 (3H, s, 2-CH_3); 4.10 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.41 (1H, s, 4-CH); 4.66 (2H, s, OCH_2CO); 9.36 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.9 ($CH_2\underline{C}H_3$); 17.4 (6-CH_3); 19.2 (2-CH_3); 30.0 (3-CO$\underline{C}H_3$); 40.9 (C-4); 60.8 ($\underline{C}H_2CH_3$); 61.2 (O$\underline{C}H_2CO$); 78.5 (C-5); 105.1 (C-3); 119.2 (5-CN); 146.0 (C-2); 149.0 (C-6); 167.3

(COOEt); 171.2 (4-<u>C</u>OOCH$_2$); 195.9 (3-COMe). Found, %: C 58.68; H 5.85; N 9.04. $C_{15}H_{18}N_2O_5$. Calculated, %: C 58.82; H 5.92; N 9.15.

3-Acetyl-5-cyano-2,6-dimethyl-1,4-dihydropyridine-4-carboxylic Acid Propionyloxymethyl Ester (7). K_2CO_3 (0.9 g, 0.007 mol) was added at room temperature to a solution of compound **4** (1.0 g, 0.004 mol) in dry DMF (7 ml), and the reaction mixture was stirred for 2 h, after which propionyloxymethyl chloride (0.8 g, 0.007 mol) was added. The mixture was stirred overnight, diluted with $CHCl_3$ and washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude residue was chromatographed on silica gel with hexane–acetone, 2:1, to yield compound **7**. Yield 0.7 g (50%), yellow solid, mp 92-93°C. IR spectrum, ν, cm^{-1}: 3230, 2208, 1765, 1667. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$), δ, ppm (*J*, Hz): 1.03 (3H, t, *J* = 7.5, CH$_2$C<u>H</u>$_3$); 2.04 (3H, s, 6-CH$_3$); 2.23 (3H, s, 3-COCH$_3$); 2.25 (3H, s, 2-CH$_3$); 2.34 (2H, q, *J* = 7.5, C<u>H</u>$_2$CH$_2$); 4.27 (1H, s, 4-CH); 5.65 (1H, d, *J* = 5.9) and 5.72 (1H, d, *J* = 5.9, OCH$_2$O); 9.35 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d$_6$), δ, ppm: 8.6 (CH$_2$<u>C</u>H$_3$); 17.4 (6-CH$_3$); 19.2 (2-CH$_3$); 26.6 (<u>C</u>H$_2$CH$_3$); 30.2 (3-CO<u>C</u>H$_3$); 41.3 (C-4); 78.3 (C-5); 79.0 (OCH$_2$O); 105.9 (C-3); 118.8 (5-CN); 146.1 (C-2); 149.2 (C-2); 170.5 (4-<u>C</u>OOCH$_2$); 172.3 (<u>C</u>OCH$_2$CH$_3$); 195.6 (3-COMe). Found, %: C 58.64; H 5.77; N 9.19. $C_{15}H_{18}N_2O_5$. Calculated, %: C 58.82; H 5.92; N 9.15.

3-Acetyl-5-cyano-1,2,6-trimethyl-1,4-dihydropyridine-4-carboxylic Acid Methyl Ester (8). NaOH (0.4 g, 0.01 mol) was added to a solution of compound **5** (1.1 g, 0.004 mol) in acetone under argon atmosphere. The resulting solution was stirred for 10 min; then MeI (2 ml, 0.03 mol) was added. The reaction mixture was stirred at room temperature for an additional 10 min, and then the solvent was removed under reduced pressure. Then H_2O (10 ml) was added to the mixture, and the product was extracted with Et_2O (3×30 ml). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by crystallization from MeOH. Yield 0.7 g (65%), yellow crystals, mp 115-117°C. IR spectrum, ν, cm^{-1}: 2198, 1734, 1654. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm: 2.29 (3H, s, 6-CH$_3$); 2.32 (3H, s, 3-COCH$_3$); 2.37 (3H, s, 2-CH$_3$); 3.18 (3H, s, NCH$_3$); 3.69 (3H, s, 4-COOCH$_3$); 4.30 (1H, s, 4-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.9 (2-CH$_3$); 18.5 (6-CH$_3$); 29.8 (3-CO<u>C</u>H$_3$); 34.3 (NCH$_3$); 41.4 (C-4); 52.5 (4-COO<u>C</u>H$_3$); 81.6 (C-5); 108.9 (C-3); 119.7 (5-CN); 147.8 (C-2); 151.7 (C-6); 171.9 (4-COOMe); 197.9 (3-COMe). Found, %: C 62.82; H 6.54; N 11.24. $C_{13}H_{16}N_2O_3$. Calculated, %: C 62.88; H 6.49; N 11.28.

3-Acetyl-5-cyano-1,2,4,6-tetramethyl-1,4-dihydropyridine-4-carboxylic Acid Methyl Ester (9). Sodium hydride (0.5 g, 0.010 mol) was added to a solution of compound **5** (2.2 g, 0.009 mol) in anhydrous MeCN (80 ml). The resulting solution was stirred for 10 min; then MeI (4 ml, 0.06 mol) was added, and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the mixture was treated with H_2O (10 ml) and extracted with $CHCl_3$ (3×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was chromatographed on silica gel with CH_2Cl_2–ethyl acetate, 4:1. The obtained solid was purified by crystallization from MeOH. Yield 0.07 g (3%), yellow crystals, mp 158-160°C. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm: 1.46 (3H, s, 4-CH$_3$); 2.13 (3H, s, 2-CH$_3$); 2.24 (3H, s, 6-CH$_3$); 2.31 (3H, s, 3-COCH$_3$); 3.17 (3H, s, NCH$_3$); 3.74 (3H, s, 4-COOCH$_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.8 (2-CH$_3$); 19.2 (6-CH$_3$); 24.7 (4-CH$_3$); 32.1 (3-CO<u>C</u>H$_3$); 33.9 (NCH$_3$); 45.6 (C-4); 52.7 (4-COO<u>C</u>H$_3$); 87.9 (C-5); 117.6 (C-3); 118.5 (5-CN); 147.9 (C-2); 149.8 (C-6); 173.9 (4-COOMe); 200.9 (3-COMe). Found, %: C 63.91; H 6.95; N 10.67. $C_{14}H_{18}N_2O_3$. Calculated, %: C 64.11; H 6.92; N 10.68.

X-ray Structural Study of Compounds 3-6, **8**, **and 9** were collected on a Nonius Kappa CCD automatic diffractometer using graphite monochromated MoKα radiation (λ 0.71073 Å). The crystal structures of compounds **3-6**, **8**, and **9** were solved by the direct method and refined by full-matrix least squares.

*Crystallografic data for compound **3***: $C_{11}H_{17}N_3O_4$; monoclinic; *a*.2101(2), *b* 21.9161(9), *c* 9.8536(4) Å; β 98.7586(15)°; *V* 1279.68(9) Å^3; *Z* 4; μ 0.102 mm^{-1}; D_{calc} 1.325 g/cm^3; space group is $P2_1/a$. A total of 2922 independent reflection intensities were collected at rt. For structure refinement, 1742 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.0791.

*Crystallographic data for compound **3***: $C_{11}H_{17}N_3O_4$; monoclinic; *a* 7.2101(2), *b* 21.9161(9), *c* 9.0402(4) Å; β 98.7586(15)°; *V* 1279.68(9) Å^3; *Z* 4; μ 0.102 mm^{-1}; d_{calc} 1.325 g/cm^3, space group is $P2_1$/a. A total of 2922

independent reflection intensities was collected at room temperature. For structure refinement, 1742 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.0791.

Crystallographic data for compound ***4***: $C_{11}H_{12}N_2O_3$; monoclinic; *a* 7.6661(3), *b* 9.0402(4), *c* 15.1405(8) Å; β 90.865(2)°; *V* 1049.16(8) Å^3; *Z* 4; μ 0.103 mm^{-1}; d_{calc} 1.394 g/cm^3, space group is $P2_1/n$. A total of 2623 independent reflection intensities was collected at -80°C. For structure refinement, 1555 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.056.

Crystallographic data for compound ***5***: $C_{12}H_{14}N_2O_3$; monoclinic; *a* 18.9169(4), *b* 8.4317(2), *c* 29.7239(9) Å; β 92.6462(3); *V* 4735.96(19) Å^3; *Z* 16; μ 0.096 mm^{-1}; d_{calc} 1.314 g/cm^3; space group is C2/*c*. A total of 5823 independent reflection intensities was collected at room temperature. For structure refinement, 3259 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.062.

Crystallographic data for compound ***6***: $C_{15}H_{18}N_2O_5$; triclinic; *a* 7.3908(3), *b* 9.7183(4), *c* 11.4310(6) Å; α 107.853(2), β 92.714(2), γ 103.050(3)°; *V* 755.29(6) Å^3; *Z* 2; μ 0.102 mm^{-1}; d_{calc} 1.347 g/cm^3; space group is $P\bar{1}$. A total of 3817 independent reflection intensities was collected at -100°C. For structure refinement, 1835 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.046.

Crystallographic data for compound ***8***: $C_{13}H_{16}N_2O_3$; triclinic, *a* 8.3347(4), *b* 8.7044(5), *c* 9.4134(6) Å; α 84.218(2), β 77.323(2), γ 88.050(3)°; *V* 662.84(7) Å^3; *Z* 2; μ 0.089 mm^{-1}; d_{calc} 1.244 g/cm^3; space group is $P\bar{1}$. A total of 3364 independent reflection intensities was collected at room temperature. For structure refinement, 1718 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.084.

Crystallographic data for compound ***9***: $C_{14}H_{18}N_2O_3$; triclinic; *a* 8.8469(4), *b* 9.0310(3), *c* 9.8536(4) Å; α 85.9830(14), β 82.637(2), γ 63.8545(13)°; *V* 700.80(5) Å^3; *Z* 2; μ 0.088 mm^{-1}; d_{calc} 1.243 g/cm^3; space group is $P\bar{1}$. A total of 3424 independent reflection intensities was collected at room temperature. For structure refinement, 2238 reflections with $I \geq 2\sigma(I)$ were used. The final *R*-factor is 0.067.

Crystallographic data for compounds **3** (deposit CCDC 886198), **4** (deposit CCDC 886816), **5** (deposit CCDC 886199), **6** (deposit CCDC 885314), **8** (deposit CCDC 885313), and **9** (deposit CCDC 886197) have been deposited at the Cambridge Crystallographic Data Center.

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