Monatshefte für Chemie 134, 1129–1136 (2003)
DOI 10.1007/s00706-003-0018-0

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Carboxamides of Dihydropyridin-2(1*H*)-ones

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Received December 16, 2002; accepted December 20, 2002
Published online June 2, 2003

Summary. 3-Carboxamides and 3-carboxanilides of 6-alkyl and 6-aryldihydropyridin-2(1*H*)-ones have been prepared *via* different reaction pathways. All synthesized amides show hydrogen bonds in their NMR spectra. The 4-hydroxy compounds were obtained as a mixture of tautomers. Their configurations were elucidated by NMR experiments.

Keywords. Carboxamides; Hydrogen bonds; Dihydropyridin-2-ones; Tautomerism; Tetrahydropyridine-3-carboxamides.

Introduction

Recently, we reported about the conversion of the 6-substituted dihydropyridin-2(1*H*)-one **1** to the 3-acetyl derivatives **2** and **3** [1]. In the sequel we attempted to synthesize the 3-carbamoyl analogues of the latter. Such compounds could be of pharmacological interest since the structurally related 1,8-naphthyridine **4** and quinoline-3-carboxamides **5** (Scheme 1) exhibit antiangiogenic [2], antiinflammatory [3–7], anthelmintic [8], immunomodulatory [9], or gastric antisecretory activity [10]. This paper deals with the preparation of 3-carboxamides of 6-alkyl and 6-aryldihydropyridin-2(1*H*)-ones which were afforded *via* two completely different reaction pathways.

Results and Discussion

Because carboxamides are readily available from the corresponding esters we synthesized the 2-oxo-6-phenylpyridine-3-carboxylate **7a** by *Dieckmann* condensation of the 4-azaheptanedioic acid ester **6** following a known procedure [11]. A mixture of the tautomeric amides **9a** and **10a** was obtained when ammonia was bubbled through a boiling solution of the ester **7a** in ethanol (Scheme 2). The corresponding anilides **9b** and **10b** were formed in moderate yields when we

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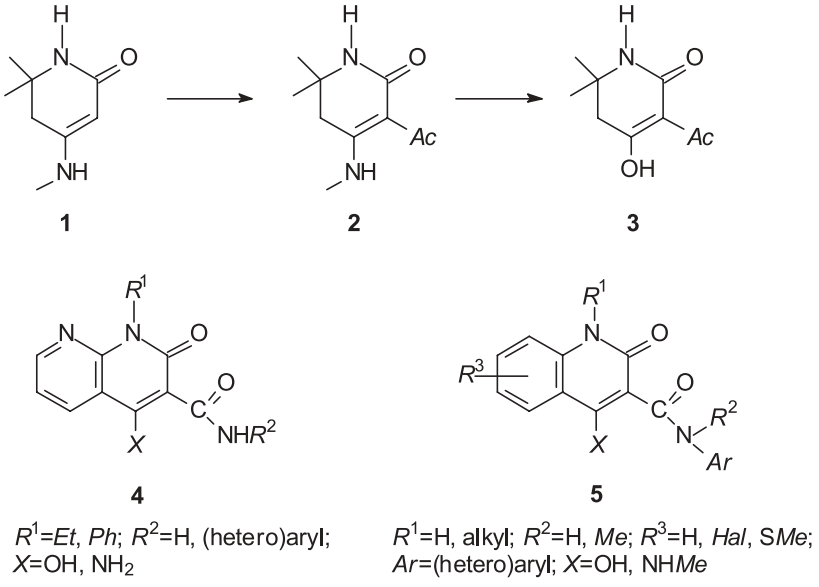
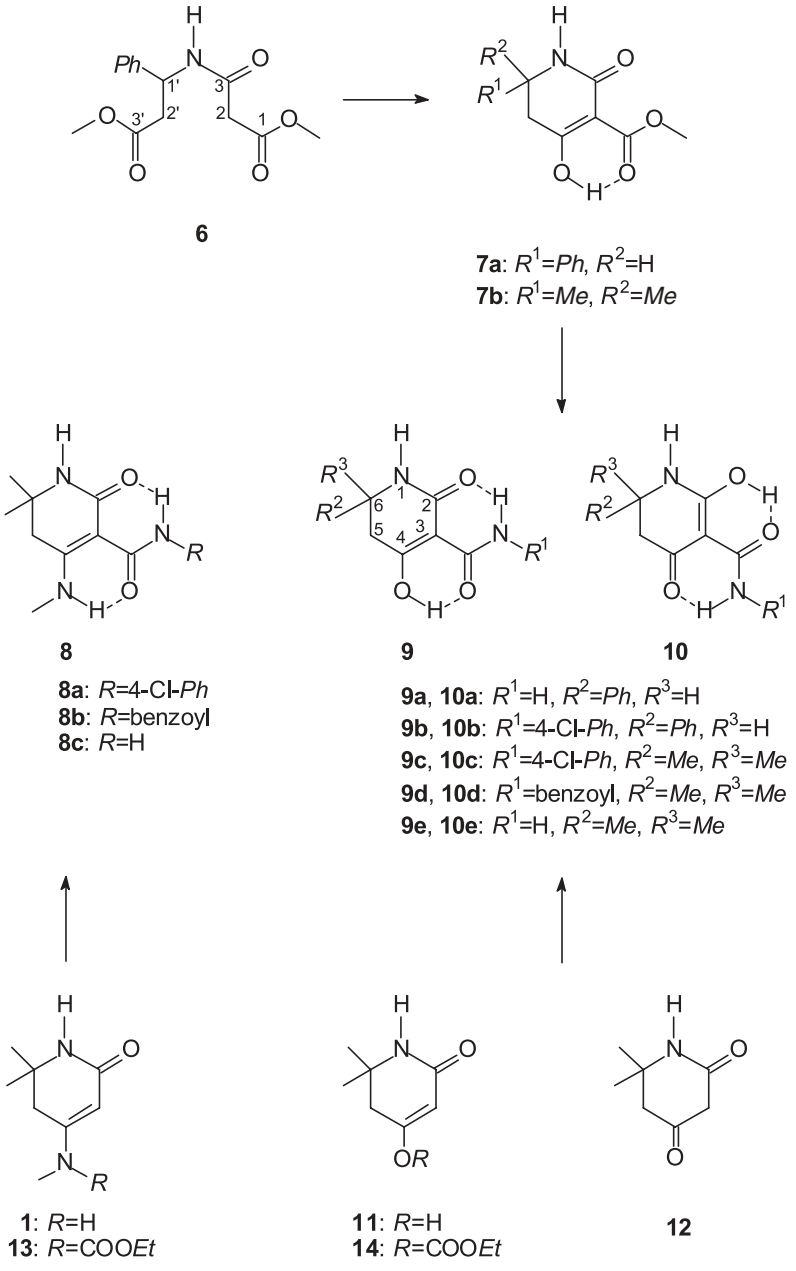


Scheme 1

refluxed **7a** with 4-chloroaniline in *DMF* following a reported procedure [12]. However, almost quantitative amounts were obtained when the compounds were fused together.

The synthesis of the 6,6-dimethyl analogues was accomplished *via* quite a different pathway since the 6,6-dimethylpyridine-3-carboxylate **7b** is not available in acceptable yields by the above-mentioned method. Therefore, we tried to introduce an alkoxycarbonyl substituent in ring position 3 of the readily available tautomers **11**, **12** [13], or **1**. The 3-acetyl-4-hydroxypyridin-2-one **3** had to be prepared by hydrolysis of its 4-methylamino analogue **2**. It was not accessible from compounds **11** and **12** because they were preferably O-acylated. In contrast, the 4-methylamino analogue **2** has been prepared selectively from **1** under *Friedel-Crafts* reaction conditions [1]. However, when **1** was treated with ethyl chloroformate in a similar procedure we were not able to detect the formation of a carboxylated product. Consequently, we changed the reaction conditions, but the carbamic acid derivative **13** was the main product in each case. Evidence that the carboxylation had taken place at the 4-amino nitrogen of **1** was given by a long-range coupling from the methylamino protons to the carbonyl carbon of the ester in the *HMBC* spectrum of **13**. As expected compounds **11** and **12** gave selectively the carboxylic acid ester **14**. Saturation of the methyl groups in ring position 6 of compound **14** led to an *NOE* at the NH proton. In this way the possible formation of an 1-acyl product was ruled out.

Another suitable way for the insertion of the carboxamido group in ring position 3 of anellated 4-hydroxypyridin-2-ones is their addition to isocyanates [6, 8, 14]. The reaction of 4-chlorophenyl isocyanate with **1** gave the 3-carboxanilide **8a**. The synthesis of the corresponding primary amide succeeded in a two-step procedure. Compound **1** was refluxed with benzoyl isocyanate, which has been prepared



Scheme 2

by the method of *Weikert et al.* [15] giving the imide **8b**. Acid hydrolysis of the latter afforded the amide **8c** in good yields.

Analogous reactions with compounds **11** and **12** yielded mixtures of tautomers in each case. The reaction with 4-chlorophenyl isocyanate gave the anilides **9c** and **10c**. The imides **9d** and **10d** were obtained upon treatment with benzoyl isocyanate and their alkaline hydrolysis afforded the tautomers **9e** and **10e**.

The resonances of all compounds were assigned with the aid of 1D and 2D NMR spectra. Special attention was directed to the distinction of the 3–8 NH and

OH signals in the ^{1}H NMR spectra of compounds **7**–**10**. The signals of their protons in ring position 1 were indicated by *NOE*s which were observed upon irradiation of the methyl groups in ring position 6. The resonances of the NH protons of the methylamino groups of compounds **8** were identified from their ^3J coupling with the methyl protons. Due to the hydrogen bonds in compounds **7**–**10** the signals of the concerning NH protons were shifted to 9–14 ppm and those for OH protons to about 17 ppm. The shift difference of 3–4 Hz of the resonances for the two geminal protons of the primary amides **8c**, **9a**, **9e**, **10a**, and **10e** made their distinction feasible.

When measured in $CDCl_3$ the tautomers **9** and **10** predominantly exist in the 4-hydroxy form, whereas in *DMSO*-d_6 the 2-hydroxy compound is the main constituent in ratios of about 7:3. They were discriminated by means of *HMBC* experiments. The OH protons of compounds **9** and **10** showed long-range couplings to the adjacent ring carbons 2 and 4. Those were undoubtedly discernible from the cross-peaks of 5-H to C-4 in their *HMBC* spectra.

The present paper provides an access to 3-carboxamides of 6-alkyl- and 6-aryldihydropyridin-2-ones *via* two different reaction pathways. The structures of the obtained tautomers were determined by NMR experiments.

Experimental

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). NMR spectra: Varian Inova 400 (298 K) 5 mm tubes, *TMS* as internal standard. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their results agreed favourably with the calculated values. Column chromatography (CC): silica gel 60 (Merck 70–230 mesh, pore diameter 60 Å). Thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200 × 200 mm).

(RS)-(±)-N-(2-(Methoxycarbonyl)-1-phenylethyl)malonamic acid methylester (**6**, $C_{14}H_{17}NO_5$)

Modified procedure [11]: Triethylamine (0.02 mol) was added dropwise to a suspension of 0.02 mol of methyl 3-amino-3-phenylpropionate hydrochloride in 40 cm^3 of CH_2Cl_2 at 0°C. Then 5 cm^3 of HCl_{conc} were added to a solution of the potassium salt of 0.06 mol of monomethyl malonate in 25 cm^3 of H_2O. The mixture was extracted repeatedly with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solution was concentrated to about 50 cm^3 and added dropwise at 0°C to the solution of the aminoacid ester. Likewise a solution of 0.02 mol of *DCC* in 10 cm^3 of CH_2Cl_2 was added. The mixture was stirred for 2 h at room temperature, then the precipitated *N*,*N*′-dicyclohexyl urea was filtered off. The filtrate was concentrated to 50 cm^3, washed with soda, H_2O, and dried. Then the solvent was removed *in vacuo* and the residue was recrystallized from ligroin yielding 5.52 g (99%) of **6**, mp 65°C (Ref [11] 52–53°C); IR (KBr): $\bar{\nu} = 3288$ (s), 3092 (w), 2953 (w), 2931 (w), 1741 (s), 1652 (s), 1557 (s), 1439 (s), 1276 (s), 1224 (s), 1057 (m), 1029 (m), 852 (m), 710 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.85$, 2.94 (2dd, $J = 15.5$, 6.0 Hz, 2 2′-H), 3.33, 3.38 (2d, $J = 17.8$ Hz, 2 2-H), 3.63 (s, OCH_3-C3′), 3.76 (s, OCH_3-C1), 5.46 (ddd, $J = 8.0$, 6.0, 6.0 Hz, 1′-H), 7.25–7.36 (m, 5 aromatic H), 8.08 (d, $J = 8.0$ Hz, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 40.12$ (C-2′), 40.91 (C-2), 49.72 (C-1′), 51.84 (OCH_3-C3′), 52.47 (OCH_3-C1), 126.23, 127.68, 128.73, 140.22 (aromatic C), 164.13 (C-1), 169.79 (C-3), 171.27 (C-1′) ppm.

(RS)-(±)-Methyl 1,2,5,6-tetrahydro-4-hydroxy-6-phenylpyridine-3-carboxylate (**7a**, $C_{12}H_{13}NO_4$)

7a was prepared according to Ref. [11]. From 5.02 g (0.018 mol) of **6** we obtained 2.04 g (48%) of **7a** after recrystallization from benzene, mp 138°C (Ref [11] 128–130°C); IR (KBr): $\bar{\nu} = 3223$ (m), 3095 (w), 2954 (w), 1677 (s), 1601 (s), 1448 (s), 1400 (s), 1340 (s), 1238 (s), 1217 (s), 1092 (s), 930 (s), 698 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.84$ (dd, $J = 17.4$, 5.5 Hz, 5-H), 2.92 (dd, $J = 17.4$, 10.6 Hz, 5-H), 3.93 (s, OCH_3), 4.71 (dd, $J = 10.6$, 5.5 Hz, 6-H), 5.58 (s, NH), 7.33–7.41 (m, 5 aromatic H), 14.10 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.14$ (C-5), 52.56 (C-6), 52.71 (OCH_3), 97.40 (C-3), 126.29, 128.71, 129.14, 139.48 (aromatic C), 168.28 (C-2), 172.03 (COO), 183.30 (C-4) ppm.

4′-Chloro-1,2,5,6-tetrahydro-6,6-dimethyl-4-methylamino-2-oxopyridine-3-carboxanilide (**8a**, $C_{15}H_{18}ClN_3O_2$)

4-Chlorophenyl isocyanate (0.03 mol) was added to a suspension of 0.02 mol of **1** in 50 cm^3 of acetonitrile. The mixture was heated on an oil-bath at 120°C for 16 h, cooled, and filtered with suction. The residue was triturated with propan-2-ol, filtered, and recrystallized from propan-2-ol giving 5.42 g (88%) of **8a**, mp 306°C; IR (KBr): $\bar{\nu} = 3228$ (w), 2964 (m), 1648 (m), 1606 (s), 1581 (s), 1539 (s), 1493 (m), 1475 (m), 1401 (s), 1307 (m), 1286 (m), 1225 (m), 838 (m), 812 (m) cm^{-1}; ^1H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.20$ (s, $(CH_3)_2$), 2.66 (s, 2 5-H), 2.99 (d, $J = 4.8$ Hz, NCH_3), 7.20 (s, N-H), 7.30 (d, $J = 8.8$ Hz, 2 m-aromatic H), 7.55 (d, $J = 8.8$ Hz, 2 o-aromatic H), 11.19 (d, $J = 4.8$ Hz, N*H*CH_3), 12.81 (s, NH*Ar*) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 28.02$ ($(CH_3)_2$), 29.85 (NCH_3), 37.48 (C-5), 48.25 (C-6), 87.32 (C-3), 120.90, 125.77, 128.80, 138.51 (aromatic C), 168.12, 168.27, 168.39 (C-2, C-4, *Ar*CO) ppm.

N-Benzoyl-1,2,5,6-tetrahydro-6,6-dimethyl-4-methylamino-2-oxopyridine-3-carboxamide (**8b**, $C_{16}H_{19}N_3O_3$)

Compound **1** (5 mmol) was dried twice by azeotropic removal of H_2O with benzene and dissolved in 90 cm^3 of benzene in an Ar atmosphere at 100°C. Then a solution of 15 mmol of benzoyl isocyanate in 10 cm^3 of benzene was added dropwise. The mixture was refluxed for 3 h and the solvent removed *in vacuo*. The residue was suspended in CH_2Cl_2 and filtered. The filtrate was concentrated and purified by CC. The fractions containing **8b** were collected, the solvent was evaporated, and the residue was recrystallized from ethanol/ethyl acetate giving 1.14 g (76%) of **8b**, mp 253°C; IR (KBr): $\bar{\nu} = 3235$ (m), 2964 (m), 1710 (s), 1599 (s), 1501 (s), 1468 (s), 1417 (s), 1280 (s), 1206 (s), 840 (m), 711 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (s, $(CH_3)_2$), 2.61 (s, 2 5-H), 3.05 (d, $J = 5.2$ Hz, NCH_3), 5.91 (s, N1-H), 7.45 (t, $J = 8.0$ Hz, 2 m-aromatic H), 7.51 (t, $J = 8.0$ Hz, p-aromatic H), 8.02 (d, $J = 8.0$ Hz, 2 o-aromatic H), 11.79 (d, $J = 5.2$ Hz, N*H*CH_3), 13.87 (s, NH(CO)$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.52$ ($(CH_3)_2$), 30.16 (NCH_3), 38.05 (C-5), 48.81 (C-6), 88.79 (C-3), 127.82 (o-aromatic C), 128.51 (m-aromatic C), 132.07 (p-aromatic C), 134.64 (i-aromatic C), 165.35 (*Ph*CO), 168.57, 168.69, 168.76 (C-2, C-4, CONH) ppm.

1,2,5,6-Tetrahydro-6,6-dimethyl-4-methylamino-2-oxopyridine-3-carboxamide (**8c**, $C_9H_{15}N_3O_2$)

Compound **8b** (0.4 mmol) and 0.01 g of toluene-4-sulphonic acid were refluxed in 100 cm^3 of ethanol for 4 h. The mixture was cooled and the solvent evaporated. The residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with H_2O and dried. The solvent was evaporated and the residue recrystallized from ethanol/ethyl acetate giving 0.057 g (72%) of **8c**, mp 252°C; IR (KBr): $\bar{\nu} = 3348$ (m), 3248 (w), 3184 (w), 1628 (s), 1596 (s), 1559 (s), 1462 (m), 1415 (m), 1391 (s), 1378 (s), 1276 (m), 816 (w) cm^{-1}; ^1H

NMR (400 MHz, *DMSO*-d_6): $\delta = 1.17$ (s, $(CH_3)_2$), 2.55 (s, 2 5-H), 2.92 (d, $J = 4.8$ Hz, NCH_3), 6.51 (d, $J = 4.4$ Hz, 1 $CONH_2$), 6.76 (s, N1-H), 9.37 (d, $J = 4.4$ Hz, 1 $CONH_2$), 11.39 (d, $J = 4.8$ Hz, N*H*CH_3) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 27.93$ $(CH_3)_2$, 29.26 (NCH_3), 37.09 (C-5), 47.94 (C-6), 87.44 (C-3), 167.06 (C-4), 168.04 (C-2), 171.85 ($CONH_2$) ppm.

(RS)-(±)-1,2,5,6-Tetrahydro-4-hydroxy-2-oxo-6-phenylpyridine-3-carboxamide (**9a**) *and (RS)-(±)-1,4,5,6-tetrahydro-2-hydroxy-4-oxo-6-phenylpyridine-3-carboxamide* (**10a**, $C_8H_{12}N_2O_3$)

A stream of NH_3 was bubbled through a boiling solution of 0.4 mmol of **7a** in 60 cm^3 of dry *Et*OH for 10 h. The mixture was cooled and the solvent was removed *in vacuo*. The colourless residue was triturated with *Et*OH/H_2O and recrystallized from *Et*OH yielding 0.076 g (82%) of **9a** and **10a**, mp 186°C; IR (KBr): $\bar{\nu} =$ 3355 (m), 3224 (m), 2963 (w), 1636 (s), 1594 (s), 1581 (s), 1321 (m), 1085 (m), 792 (m), 765 (m), 698 (s) cm^{-1}.

9a (main component): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.74$–2.92 (m, 2 5-H), 4.69–4.76 (m, 6-H), 5.56 (s, N1-H), 5.69 (s, 1 $CONH_2$), 7.35–7.41 (m, 5 aromatic H), 9.31 (s, 1 $CONH_2$), 17.27 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.89$ (C-5), 52.92 (C-6), 94.00 (C-3), 126.28, 128.72, 129.17, 139.90 (aromatic C), 168.39 (C-2), 173.16 ($CONH_2$), 186.73 (C-4) ppm.

10a (minor constituent): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.68$–2.88 (m, 2 5-H), 4.69–4.76 (m, 6-H), 5.69 (s, 1 $CONH_2$), 5.75 (s, N1-H), 7.35–7.41 (m, 5 aromatic H), 9.66 (s, 1 $CONH_2$), 17.74 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.19$ (C-5), 53.57 (C-6), 86.60 (C-3), 126.23, 128.66, 129.19, 139.82 (aromatic C), 173.18 ($CONH_2$), 174.57 (C-2), 189.57 (C-4) ppm.

(RS)-(±)-4′-Chloro-1,2,5,6-tetrahydro-4-hydroxy-2-oxo-6-phenylpyridine-3-carboxanilide (**9b**) *and (RS)-(±)-4′-chloro-1,4,5,6-tetrahydro-2-hydroxy-4-oxo-6-phenylpyridine-3-carboxanilide* (**10b**, $C_{18}H_{15}ClN_2O_3$)

Compound **7a** (0.2 mmol) and 0.24 mmol of 4-chloroaniline were triturated with a pestle in a mortar. The mixture was given in a round bottom flask and melted with agitation at 170°C on an oil-bath for 3 h. The mixture was allowed to cool and the residue was recrystallized from *Et*OH/H_2O giving 0.064 g (94%) of **9b** and **10b**, mp 228°C; IR (KBr): $\bar{\nu} =$ 3192 (m), 3111 (w), 3069 (w), 3033 (w), 1651 (s), 1594 (s), 1548 (s), 1491 (s), 1405 (s), 1226 (m), 1092 (m), 1012 (m), 834 (m), 701 (m) cm^{-1}.

9b (minor constituent): ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 2.80$–3.18 (m, 2 5-H), 4.73–4.83 (m, 6-H), 7.29–7.63 (m, 9 aromatic H), 8.31 (s, NH), 12.26 (s, NHAr), 16.35 (s, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 36.90$ (C-5), 50.41 (C-6), 95.14 (C-3), 122.30, 126.52, 127.92, 128.87, 129.16, 135.97, 141.28 (aromatic C), 167.55 (C-2), 169.05 (*Ar*CO), 184.44 (C-4) ppm.

10b (main component): ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 2.68$–2.85 (s, 2 5-H), 4.81–4.91 (m, 6-H), 7.29–7.63 (m, 9 aromatic H), 9.41 (s, NH), 11.97 (s, NHAr), 17.50 (s, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 42.62$ (C-5), 51.34 (C-6), 86.44 (C-3), 122.30, 126.52, 128.06, 128.87, 129.16, 136.32, 140.44 (aromatic C), 169.42 (*Ar*CO), 173.46 (C-2), 189.11 (C-4) ppm.

4′-Chloro-1,2,5,6-tetrahydro-4-hydroxy-6,6-dimethyl-2-oxopyridine-3-carboxanilide (**9c**) *and 4′-chloro-1,4,5,6-tetrahydro-2-hydroxy-6,6-dimethyl-4-oxopyridine-3-carboxanilide* (**10c**, $C_{14}H_{15}ClN_2O_3$)

4-Chlorophenyl isocyanate (0.02 mol) was added to a suspension of 0.02 mol of **11**/**12** in 50 cm^3 of acetonitrile. After the addition of 0.3 cm^3 of triethylamine the mixture was heated on an oil-bath at 120°C over night. It was cooled and filtered with suction and the residue was triturated with propan-2-ol, filtered, and recrystallized from propan-2-ol giving 5.35 g (91%) of **9c** and **10c**, mp 202°C; IR (KBr): $\bar{\nu} =$ 3163 (m), 3117 (m), 3058 (m), 3025 (m), 2973 (m), 1655 (s), 1595 (s), 1557 (s), 1491 (s), 1427 (s), 1301 (m), 1261 (m), 1087 (m), 1009 (m), 825 (s), 798 (s) cm^{-1}.

9c (minor constituent): ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.26$ (s, $(CH_3)_2$), 2.67 (s, 2 5-H), 7.38-7.59 (m, 5 aromatic H), 7.88 (s, NH), 12.31 (s, NH*Ar*), 16.31 (s, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 28.18$ ($(CH_3)_2$), 41.89 (C-5), 49.15 (C-6), 94.13 (C-3), 122.16, 128.27, 129.11, 136.03 (aromatic C), 166.58 (C-2), 169.16 (*Ar*CO), 184.84 (C-4) ppm.

10c (main component): ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.26$ (s, $(CH_3)_2$), 2.49 (s, 2 5-H), 7.38–7.59 (m, 5 aromatic H), 8.99 (s, NH), 12.01 (s, NH*Ar*), 17.22 (s, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 27.29$ ($(CH_3)_2$), 48.07 (C-5), 50.38 (C-6), 85.20 (C-3), 122.16, 127.84, 129.11, 136.49 (aromatic C), 169.50 (*Ar*CO), 171.91 (C-2), 189.93 (C-4) ppm.

N-Benzoyl-1,2,5,6-tetrahydro-4-hydroxy-6,6-dimethyl-2-oxopyridine-3-carboxamide (**9d**) *and N-benzoyl-1,4,5,6-tetrahydro-2-hydroxy-6,6-dimethyl-4-oxopyridine-3-carboxamide* (**10d**, $C_{15}H_{16}N_2O_4$)

The tautomeric mixture **11**/**12** (5 mmol) was dried twice by azeotropic removal of H_2O with benzene and dissolved in 100 cm^3 of benzene in an Ar atmosphere at 100°C. Then a solution of 0.6 mmol of benzoyl isocyanate in 30 cm^3 of benzene was added dropwise. The mixture was refluxed for 3 h, allowed to cool, and filtered. The residue was recrystallized from benzene giving 0.643 g (47%) of **9d** and **10d**, mp 170°C; IR (KBr): $\bar{\nu} = 3257$ (m), 2966 (m), 1715 (s), 1663 (s), 1614 (s), 1583 (s), 1490 (s), 1283 (m), 1228 (m), 783 (m), 699 (m) cm^{-1}.

9d (main component): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (s, $(CH_3)_2$), 2.70 (s, 2 5-H), 5.79 (s, N1-H), 7.45–8.07 (m, 5 aromatic H), 13.37 (s, NH(CO)$_2$), 16.26 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.83$ ($(CH_3)_2$), 42.82 (C-5), 49.87 (C-6), 95.10 (C-3), 127.97 (o-aromatic C), 128.85 (m-aromatic C), 133.05 (p-aromatic C), 133.18 (i-aromatic C), 164.64 (*Ph*CO), 167.14 (C-2), 170.42 (CONH), 187.37 (C-4) ppm.

10d (minor constituent): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (s, $(CH_3)_2$), 2.59 (s, 2 5-H), 6.17 (s, N1-H), 7.45–8.07 (m, 5 aromatic H), 13.31 (s, NH(CO)$_2$), 17.40 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.06$ $(CH_3)_2$, 48.79 (C-5), 51.20 (C-6), 87.41 (C-3), 128.04 (o-aromatic C), 128.85 (m-aromatic C), 132.95 (p-aromatic C), 133.22 (i-aromatic C), 164.72 (*Ph*CO), 170.81 (CONH), 172.93 (C-2), 190.91 (C-4) ppm.

1,2,5,6-Tetrahydro-4-hydroxy-6,6-dimethyl-2-oxopyridine-3-carboxamide (**9e**) *and 1,4,5,6-tetrahydro-2-hydroxy-6,6-dimethyl-4-oxopyridine-3-carboxamide* (**10e**, $C_8H_{12}N_2O_3$)

Compounds **9d**/**10d** (1 mmol) were refluxed in 50 cm^3 of 2 *M* NaOH solution for 3 h. The mixture was cooled to 0°C and acidified with HCl_{conc}. Then the mixture was extracted repeatedly with CH_2Cl_2. The combined organic layers were washed with H_2O and dried. The solvent was evaporated and the residue was recrystallized from *Et*OH/H_2O giving 0.116 g (63%) **9e** and **10e**, mp 109°C; IR (KBr): $\bar{\nu} = 3269$ (s), 2972 (m), 1654 (s), 1599 (s), 1571 (s), 1260 (m), 1075 (m), 796 (m) cm^{-1}.

9e (main component): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (s, $(CH_3)_2$), 2.58 (s, 2 5-H), 5.29 (s, N1-H), 5.63, 9.32 (2s, $CONH_2$), 17.14 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.95$ ($(CH_3)_2$), 43.20 (C-5), 49.64 (C-6), 93.28 (C-3), 167.17 (C-2), 173.11 ($CONH_2$), 186.55 (C-4) ppm.

10e (minor constituent): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (s, $(CH_3)_2$), 2.49 (s, 2 5-H), 5.44 (s, N1-H), 5.63, 9.58 (2s, $CONH_2$), 17.79 (s, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.49$ ($(CH_3)_2$), 48.91 (C-5), 50.54 (C-6), 85.53 (C-3), 173.03, 173.11 (C-2, $CONH_2$), 190.14 (C-4) ppm.

Ethyl N-methyl-N-(1,2,3,6-tetrahydro-2,2-dimethyl-6-oxopyridin-4-yl)carbamate (**13**, $C_{11}H_{18}N_2O_3$)

Compound **1** (1 mmol) was dried twice by azeotropic removal of H_2O with benzene and was dissolved in 20 cm^3 of *THF* and 0.5 cm^3 of *HMPA* in an Ar atmosphere. The solution was cooled to -78°C, then

2 cm^3 of a 1.5 *M* solution of lithium diisopropylamide monotetrahydrofuran in cyclohexane were added through a dropping funnel. The mixture was allowed to reach room temperature and was stirred for 1 h. Then ethyl chloroformate was added dropwise at $-78°C$ and the mixture was again allowed to warm up. After addition of 15 cm^3 of H_2O the mixture was repeatedly extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O to remove *HMPA*, dried, and the solvent was evaporated. The mixture was purified by CC eluting with CH_2Cl_2:*Me*OH = 29:1. Recrystallization from benzene/*n*-heptane gave 0.176 mg (78%) of **13**, mp 133°C, IR (KBr): $\bar{\nu} = 3176$ (w), 2966 (w), 1716 (s), 1667 (s), 1605 (m), 1374 (s), 1324 (s), 1170 (s), 837 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (s, $(CH_3)_2$), 1.32 (t, $J = 7.0$ Hz, CH_3), 2.77 (s, 2 5-H), 3.21 (s, NCH_3), 4.22 (q, $J = 7.0$ Hz, OCH_2), 5.50 (s, 3-H), 6.64 (s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.25$ (CH_3), 28.34 (($CH_3)_2$), 35.80 (NCH_3), 41.03 (C-5), 51.44 (C-6), 62.36 (OCH_2), 107.31 (C-3), 153.34 (C-4), 153.99 (COO), 167.27 (C-2) ppm.

Ethyl (1,2,3,6-tetrahydro-2,2-dimethyl-6-oxopyridin-4-yl) carbonate (**14**, $C_{10}H_{15}NO_4$)

Compounds **11**/**12** (2 mmol) and 2 mmol of *DMAP* were dissolved in 50 cm^3 of CH_2Cl_2 in an Ar atmosphere. Ethyl chloroformate (2.2 mmol) was diluted with 5 cm^3 of CH_2Cl_2 and was added dropwise to the solution. The mixture was stirred over night and partitioned between H_2O and CH_2Cl_2. The aqueous layer was once extracted with CH_2Cl_2 and the combined organic layers were washed 5 times with H_2O, dried, and the solvent was removed *in vacuo*. The residue was recrystallized from benzene/*n*-heptane yielding 0.371 g (87%) of **14**, mp 94°C; IR (KBr): $\bar{\nu} = 3194$ (m), 2986 (m), 1770 (s), 1761 (s), 1666 (s), 1631 (s), 1402 (m), 1231 (s), 1046 (m), 865 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, CH_3), 1.29 (s, $(CH_3)_2$), 2.45 (s, 2 5-H), 4.20 (q, $J = 7.2$ Hz, Hz, OCH_2), 5.78 (s, 3-H), 7.44 (s, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.68$ (CH_3), 28.34 (($CH_3)_2$), 39.16 (C-5), 51.08 (C-6), 64.80 (OCH_2), 108.54 (C-3), 150.89 (COO), 159.33 (C-4), 166.65 (C-2) ppm.

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