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A New Pathway to Substituted 6-Chloro-2-pyridinecarboxylic Acid Derivatives from the Reaction of 4,6-Dichloro-2-oxa-5-aza-bicyclo[2.2.2]oct-5-en-3-ones with Nucleophiles.

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Dedicated to Professor Miha Tišler on the occasion of his 70th Birthday.

Abstract: Reaction of alcohols or amines with 4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones gives direct conversion into (3,(4,))5-substituted 6-chloro-2-pyridinecarboxylic acid derivatives via selective lactone cleavage followed by rapid elimination of HCl and H_2O in the presence of DBU.

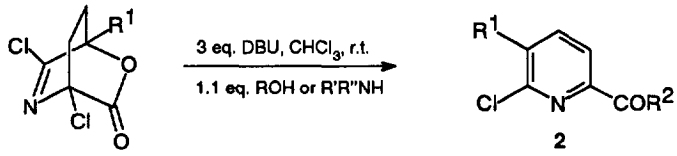
Methods for the generation of multisubstituted 6-chloro-2-pyridinecarboxylic acid derivatives are not always obvious and often of a narrow scope.[1] However they can be important precursors as many 6-substituted 2-pyridinecarboxylic acid derivatives are known to be useful compounds as pharmaceutics or as agrochemicals.[2] Recently we reported a general method for the generation of variably substituted 1,6-dihydro-6-oxo-2-pyridine-(and piperidine-) carboxylic acid derivatives by using (±)-4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones **1** and **3**.[3] Here we describe an adapted route for the generation of 6-chloro-2-pyridinecarboxylic acid derivatives applying the reaction of the cycloadducts **1** and **3** with alcohols or amines in the presence of DBU.

RESULTS AND DISCUSSION.

The 5-substituted 6-chloro-2-pyridinecarboxylic acid derivatives **2** were obtained from an one pot procedure by using the easily accessible Diels-Alder adducts **1**[4] of 6-substituted 3,5-dichloro-2*H*-1,4-oxazin-2-ones[5] and ethene (Scheme 1). Addition of 1.1 equivalent of ethanol at room temperature to a stirred reaction mixture of adduct **1a** and 3 equivalents of DBU in $CHCl_3$ (or THF) gave a new product that was isolated after 15 minutes reaction in 83 % yield. It was characterised as the ethyl 6-chloro-5-methyl-2-pyridinecarboxylate **2a** with an IR absorption for the ester group around 1720 cm^{-1}. The mass spectrum of **2a** with relative abundance of M^+, $[M+2]^+$ ions (3:1) pointed to the presence of one chlorine atom. In the ^1H NMR spectrum of **2a** two typical doublets were observed (7.43 ppm and 7.95 ppm) which could attributed to the pyridine protons in the 3 and 4 position; ^{13}C NMR absorptions were consistent with the assigned structure. Formation of a 1,6-dihydro-6-oxo-2-pyridinecarboxylate, as observed[3] when reacting **1a** with alcohols in neutral or acidic conditions followed by treatment of DBU, did not occur. Apparently a fast, selective attack of the alcohol (1.1 equivalents)

on the lactone function took place followed by rapid elimination of HCl and H_2O (under influence of DBU that serves as a base) without affecting the chlorimine function. As expected, similar reaction of **1a** with methanol and of **1b** with ethanol gave a good yield of the 2-pyridinecarboxylates **2b** and **2c**, respectively after 30 minutes reaction at room temperature (Scheme 1). The 6-chloro-2-pyridinecarboxamide **2d** (80 %) and **2e** (68 %) could be isolated after 30 minutes reaction of **1a** with propylamine or piperidine in the presence of DBU.

Scheme 1: Synthesis of 5-substituted 6-chloro-2-pyridinecarboxylic acid derivatives **2**.



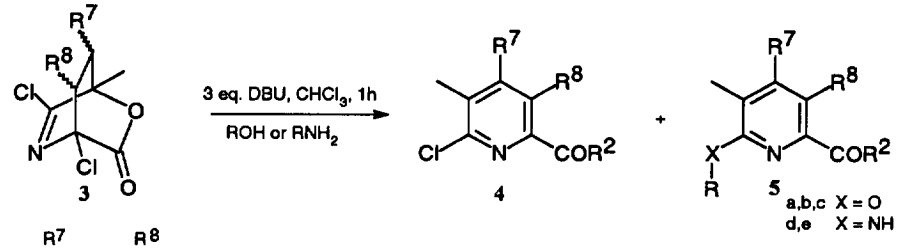
1a R^1 = Me
1b R^1 = Ph

2

2	R^1	R^2	Time, min	Yield **2** (%
a	Me	OEt	15	83
b	Me	OMe	30	79
c	Ph	OEt	30	70
d	Me	NHPr	30	80
e	Me	1-piperidinyl	30	68

Futhermore the method could also be applied to the crude cycloadducts[4] of the 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one and mono- or disubstituted alkene compounds (such as styrene, ethyl vinyl ether, allyl phenyl ether, cyclopentene and 4,7-dihydro-1,3-dioxepin) (Scheme 2). In a typical experiment the 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one[5] was reacted with 3 equivalents of dienophile in refluxing $CHCl_3$. After completion of the cycloaddition and evaporation of the solvent, 3 equivalents of DBU were added to the unpurified adduct in $CHCl_3$.[6] After five minutes of stirring at room temperature ethanol or propylamine (1.1 eq. or 3 eq.) was added slowly. Moderate yields (38 - 61 %) of the 3(,4),5-substituted 6-chloropyridines **4a-e** were isolated along with a low amount (9 - 26 %) of products of type **5** in some cases. Probably, functionalisation of the chlorimine function competes with lactone cleavage due to the sterical hindrance of the substituent in the (7 and) 8 position of the adduct. The mass spectra of compounds **4** showed M^+, $[M+2]^+$ peaks with relative abundance 3:1 indicating the presence of one chlorine atom. In the ^1H NMR spectra of **4a-c** a singlet was observed (7.25 ppm - 8.02 ppm) which could be attributed to the pyridine proton in the 4 position. Absorptions corresponding to two ethyl groups (**5a**) or propyl groups (**5d**) were observed in the ^1H NMR spectra of **5a,d** showing functionalisation of the chlorimine function by ethanol or propylamine. Cycloadducts with electron withdrawing groups in the (7 and) 8 position (e.g. COOEt or CONPhCO[4]) gave tarry products on reaction with ethanol and DBU (or Et_3N) and the expected pyridine derivatives could not be observed.

Scheme 2: Synthesis of 3(,4),5-substituted 6-chloro-2-pyridinecarboxylic acid derivatives **4**.



	R^7	R^8
3a	H	Ph
3b	H	OEt
3c	H	CH_2OPh
3d		$-(CH_2)_3-$
3e		$-CH_2OCH_2OCH_2-$

4, 5[a]	R^2	R^7	R^8	4[b], (%)	5[b], (%)
a	OEt	H	Ph	54	26
b	OEt	H	OEt	59	*f*[c]
c	OEt	H	CH_2OPh	55	*f*[c]
d	NHPr		$-(CH_2)_3-$	38	9
e	NHPr		$-CH_2OCH_2OCH_2-$	61	*f*[c]

[a] Crude adduct from the reaction of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one and the corresponding dienophile has been used.
[b] Yield calculated from the amount of crude adduct **3**.
[c] Only traces, if any, of the 6-ethoxy or 6-propylamino-pyridine were observed.

In conclusion we can state that the unsubstituted bicyclic adducts **1** and the (7,)8-substituted adducts **3** can be efficiently transformed into (3,(4,))5-substituted 6-chloro-2-pyridinecarboxylic acid derivatives **2** and **4** by an easy one pot procedure using alcohols or amines in the presence of DBU. The desired substitution pattern of the 6-chloro-2-pyridinecarboxylic acid derivative can be realised by choosing the appropriate cycloadduct and nucleophile. However electron withdrawing groups could not be introduced directly into the 3 and 4 position. This problem can be overcome by deprotection and subsequent oxidation of the alcohol function(s) in the pyridine **4c** or in the [1,3]dioxepino[5,6-*c*]pyridine **4e**. If required, further functionalisation of the 6-chloro-pyridine moiety would be possible.[7]

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier transform spectrometer. ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^1H and ^{13}C chemical shifts are reported in ppm relative to TMS or the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram Sil G/UV_{254}) and 70-230 mesh silica gel 60 (E.M. Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106. Synthesis and spectroscopic data of all the mentioned cycloadducts except **3c** and **3e** are described in a previous article.[4]

I. General procedure for the 5-substituted 6-chloro-2-pyridinecarboxylates and -carboxamides 2a-e.
A mixture of adduct **1a** or **1b** (5 mmol) in $CHCl_3$ (10 ml) and DBU (15 mmol) was stirred for 5 min at r.t.. On addition of the alcohol or amine (5.5 mmol) an exothermic reaction took place and after 15 - 30 min the solvent was removed under reduced pressure. Chromatography on silica gel with CH_2Cl_2/EtOAc (8:2) as eluent afforded compounds **2a-e** (yield: 68-83 %, Table 1). Analytical samples were obtained by recrystallisation in *n*-Hex/CH_2Cl_2 (**2b,c**) or by bulb to bulb distillation (**2a,d,e**).

Ethyl 6-chloro-5-methyl-2-pyridinecarboxylate 2a.
oil, bp: 135 °C, 2 mm Hg; IR (NaCl plates) cm^{-1}: 1720 (s), 1563 (m); ^1H NMR ($CDCl_3$) δ: 1.42 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.45 (s, 3H, 5-CH_3), 4.45 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 7.43 (dq, 1H, J ≈ 7.5 Hz, 1 Hz, H-4), 7.95 (d, 1H, J = 7.5 Hz, H-3); ^{13}C NMR ($CDCl_3$): 13.9 (CH_3), 19.5 (5-CH_3), 61.5 (CH_2), 123.4 (C-3), 136.5 (C-5), 139.6 (C-4), 145.6 (C-2), 151.5 (C-6), 163.5 (CO); m/z (%): 199 (M^+, 7), 155 (26), 127 (100); exact mass calcd for $C_9H_{10}ClNO_2$: 199.0400; found: 199.0401; anal cald for $C_9H_{10}ClNO_2$: C 54.15, H 5.05, N 7.02; found: C 54.35, H 4.91, N 6.79

Methyl 6-chloro-5-methyl-2-pyridinecarboxylate 2b.
m.p.: 77 °C (*n*-Hex/CH_2Cl_2); IR (KBr) cm^{-1}: 1736 (s), 1560 (m); ^1H NMR ($CDCl_3$) δ: 2.47 (s, 3H, 5-CH_3), 3.98 (s, 3H, CH_3), 7.73 (d, 1H, J = 7.5 Hz, H-4), 8.07 (d, 1H, J = 7.5 Hz, H-3); ^{13}C NMR ($CDCl_3$): 19.8 (5-CH_3), 52.8 (CH_3), 123.8 (C-3), 137.1 (C-5), 139.8 (C-4), 145.6 (C-2), 151.6 (C-6), 164.6 (CO); m/z (%): 185 (M^+, 10), 155 (20), 127 (100); exact mass calcd for $C_8H_8ClNO_2$: 185.0244; found: 185.0247; anal cald for $C_8H_8ClNO_2$: C 51.77, H 4.34, N 7.55; found: C 51.87, H 4.06, N 7.46

Ethyl 6-chloro-5-phenyl-2-pyridinecarboxylate 2c.
m.p.: 85 °C (*n*-Hex/CH_2Cl_2); IR (KBr) cm^{-1}: 1720 (s); ^1H NMR ($CDCl_3$) δ: 1.53 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 4.59 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 7.55 (s, 5H, H_{arom}), 7.88 (d, 1H, J = 7.5 Hz, H-4), 8.17 (d, 1H, J = 7.5 Hz, H-3); ^{13}C NMR ($CDCl_3$): 14.1 (CH_3), 62.0 (CH_2), 123.7 (C-3), 128.3, 128.6, 129.0 (C_{arom}), 136.7 (C_{ipso}), 140.2 (C-4), 140.4 (C-5), 146.9 (C-2), 149.6 (C-6), 163.8 (CO); m/z (%): 261 (M^+, 24), 217 (11), 189 (100), 153 (30); exact mass calcd for $C_{14}H_{12}ClNO_2$: 261.0556; found: 261.0558; anal cald for $C_{14}H_{12}ClNO_2$: C 64.25, H 4.62, N 5.35; found: C 64.25, H 4.44, N 5.30

***N*-Propyl-6-chloro-5-methyl-2-pyridinecarboxamide 2d.**
oil, bp: 145 °C, 2 mm Hg; IR (NaCl plates) cm^{-1}: 1680 (s), 1527 (s); ^1H NMR ($CDCl_3$) δ: 1.01 (t, 3H, J = 7 Hz, $N(CH_2)_2C\underline{H}_3$), 1.70 (sext, 2H, J = 7 Hz, $NHCH_2C\underline{H}_2CH_3$), 2.42 (s, 3H, 5-$CH_3$), 3.43 (q, 2H, J = 7 Hz, $NC\underline{H}_2CH_2CH_3$), 7.69 (d, J = 7.5 Hz, 1H, H-4), 7.88 (br s, 1H, NH), 8.02 (d, J = 7.5 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$): 11.1 (CH_3), 19.4 (5-CH_3), 22.6 (CH_2), 40.9 (NCH_2), 120.7 (C-3), 135.2 (C-5), 140.1 (C-4), 147.9 (C-2), 149.6 (C-6), 162.7 (CO); m/z (%): 212 (M^+, 31), 183 (72), 154 (100), 126 (80); exact mass calcd for $C_{10}H_{13}ClN_2O$: 212.0716; found: 212.0715; anal cald for $C_{10}H_{13}ClN_2O$: C 56.47, H 6.16, N 13.17; found: C 56.22, H 6.12, N 12.96

***N*-Piperidinyl-6-chloro-5-methyl-2-pyridinecarboxamide 2e.**
oil, bp: 145 °C, 2 mm Hg; IR (NaCl plates) cm^{-1}: 1640 (s), 1550 (m); ^1H NMR ($CDCl_3$) δ: 1.25 (m, 2H, $(CH_2)_2C\underline{H}_2(CH_2)_2$), 1.68 (m, 4H, $C\underline{H}_2CH_2NCH_2C\underline{H}_2$), 2.41 (s, 3H, 5-$CH_3$), 3.47 en 3.70 (m, 4H, $C\underline{H}_2NC\underline{H}_2$), 7.45 (d, 1H, J = 8 Hz, H-4), 7.66 (d, 1H, J = 8 Hz, H-3); ^{13}C NMR ($CDCl_3$): 19.3 (5-CH_3), 24.1, 25.1, 26.0 (CH_2), 43.0, 47.9 (CH_2NCH_2), 121.8 (C-3), 133.1 (C-5), 139.8 (C-4), 149.6 (C-2), 151.8 (C-6), 165.6 (CO); m/z (%): 238 (M^+, 8), 154 (10), 126 (22), 84 (100); exact mass calcd for $C_{12}H_{15}ClN_2O$: 238.0873; found: 238.0874; anal cald for $C_{12}H_{15}ClN_2O$: C 60.38, H 6.33, N 11.74; found: C 60.07, H 6.30, N 11.53

II. Synthesis and spectroscopic data of cycloadducts 3c and 3e.
Allyl phenyl ether or 4,7-dihydro-1,3-dioxepin (0.017 mmol, 3 equiv) was added at once to a stirred solution of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one[5] (1.0 g, 5.6 mmol) in $CHCl_3$ (5 ml). After reflux for 6 hours the solvent was evaporated and the crude reaction mixture purified by chromatography (silica gel, eluent: 5 % EtOAc/$CHCl_3$) **3c** (60 %, for the other regioisomer see ref 3) or by crystallisation by adding 2 ml of diisopropyl ether **3e** (82 %).

(±)-*Endo* 4,6-dichloro-1-methyl-8-phenoxymethyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one 3c.
m.p.: 105 °C (CCl_4); IR (KBr) cm^{-1}: 1780 (s), 1610 (s); ^1H NMR ($CDCl_3$) δ: 1.75 (s, 3H, 1-CH_3), 1.90 - 3.00 (m, 3H, H-7*endo*, H-7*exo*, H-8*exo*), 3.95 and 4.41 (m, 2H, CH_2O), 6.91 - 7.32 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$): 20.4 (1-CH_3), 36.0, 42.4 (C-7 and C-8), 66.4 (CH_2O), 83.0 (C-4), 86.8 (C-1), 114.8, 121.8, 129.8 (Ar-C), 158.0 (C-*ipso*), 163.6 (C-6), 164.6 (C-3); $J_{C6\text{-}CH_3}$ = 5 Hz, $J_{C6\text{-}H7exo}$ = 9 Hz, $J_{C6\text{-}H7endo}$ ≈ 1 Hz, $J_{C3\text{-}}$

H_{8exo} = 2.5 Hz, indicative for an 8-substituted *endo* structure[4,8]; m/z (%): 313 (M^+, 11), 236 (10), 107 (32), 94 (100); exact mass calcd for $C_{14}H_{13}N_1O_3Cl_2$: 313.0271; found 313.0268

(±)-*Endo* 4,6-dichloro-1-methyl-2,10,12-trioxa-5-azatricyclo[7.2.2.0^{7,8}]tridec-5-en-3-one 3e.

m.p.: 178 °C (CH_2Cl_2/Diisopropyl ether); IR (KBr) cm^{-1}: 1613 (s), 1785 (s); ^1H NMR ($CDCl_3$) δ: 1.82 (s, 3H, 1-CH_3), 2.67 (m, 2H, H-7*exo*, H-8*exo*), 3.83 and 4.29 (2 x br. s, 4H, $(CH_2O)_2$), 4.91 (br. d, 2H, OCH_2O); ^{13}C NMR ($CDCl_3$): 18.5 (1-CH_3), 47.7, 50.5 (C-7 and C-8), 64.4 and 68.9 (2 x CH_2O), 84.8 (C-4), 87.2 (C-1), 99.2 (OCH_2O), 163.0 (C-6), 164.8 (C-3); $J_{C6\text{-}CH_3}$ = 5 Hz, $J_{C6\text{-}H7exo}$ = 7 Hz, $J_{C3\text{-}H8exo} \approx$ 1 Hz, indicative for an 7,8-disubstituted *endo* structure[4,8]; m/z (%): 280 (MH^+, 1), 235 (1), 205 (4), 170 (35), 140 (44), 44 (100); exact mass calcd for $C_{10}H_{10}N_1O_4Cl_2$ [M^+-H]: 277.9986; found : 277.9994

III. General procedure for the synthesis of 3(,4-di)substituted 6-chloro-5-methyl-2-pyridinecarboxylates or -carboxamides 4 and the corresponding 6-ethoxy or 6-propylamino derivatives 5.

A stirred solution of 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one[5] (1 g, 5.5 mmol) and dienophile (16.5 mmol) in $CHCl_3$ (5 ml) is refluxed for 30 min - 6 h. Disappearance of the typical dark violet color (due to the 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one) under UV light (366 nm) on TLC (silica gel, CH_2Cl_2/EtOAc (8:2)) was indicative for completion of the reaction.[6] Evaporation of the solvent and dienophile gave the crude adducts which were dissolved in $CHCl_3$ (5 ml), DBU (16.5 mmol) was added and the mixture was stirred for 5 min at r.t.. To this solution EtOH (0.35 ml, 6.1 mmol, **3a-c**) or propylamine (0.50 ml, 18.3 mmol, **3d,e**) was added dropwise and the mixture stirred for 1 h at r.t. (**3a-c**) (reflux, **3d,e**). After removal of the solvent under reduced pressure, chromatography on silica gel with CH_2Cl_2/EtOAc (8:2) as eluent afforded **4a-e** and **5a,d** as pure compounds (Table 2). Analytical samples were obtained by recrystallisation.

Ethyl 6-chloro-5-methyl-3-phenyl-2-pyridinecarboxylate 4a.

m.p.: 90 °C (*n*-Hex/CH_2Cl_2); IR (KBr) cm^{-1}: 1736 (s), 1540 (w); ^1H NMR ($CDCl_3$) δ: 1.10 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.43 (s, 3H, 5-CH_3), 4.20 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 7.32 (m, 5H, H_{arom}), 7.59 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$): 13.6 (CH_3), 19.5 (5-CH_3), 61.6 (CH_2), 128.2, 128.3, 128.4 (C_{arom}), 134.6 (C-5), 136.2 (C-3), 137.1 (C_{ipso}), 141.4 (C-4), 146.3 (C-2), 149.8 (C-6), 165.6 (CO); m/z (%): 275 (M^+, 18), 230 (13), 203 (100), 168 (28); exact mass calcd for $C_{15}H_{14}ClNO_2$: 275.0713; found: 275.0710; anal cald for $C_{15}H_{14}ClNO_2$: C 65.34, H 5.12, N 5.08; found: C 64.99, H 5.00, N 4.99

Ethyl 6-chloro-3-ethoxy-5-methyl-2-pyridinecarboxylate 4b.

mp: 82 °C (*n*-Hex/CH_2Cl_2); IR (KBr) cm^{-1}: 1719 (s), 1588 (w); ^1H NMR ($CDCl_3$) δ: 1.45 (m, 6H, 2 x $CH_2C\underline{H}_3$), 2.40 (s, 3H, 5-CH_3), 4.12 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 4.44 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 7.25 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$): 14.1, 14.5 (CH_3), 20.0 (5-CH_3), 61.5, 65.3 (CH_2), 124.6 (C-4), 136.5 (C-2), 136.6 (C-5), 141.3 (C-6), 153.8 (C-3), 163.9 (CO); m/z (%): 243 (M^+, 23), 214 (67), 198 (35), 143 (100); exact mass calcd for $C_{11}H_{14}ClNO_3$: 243.0662; found: 243.0662; anal cald for $C_{11}H_{14}ClNO_3$: C 54.22, H 5.79, N 5.75; found: C 54.36, H 5.79, N 5.72

Ethyl 6-chloro-5-methyl-3-phenoxymethyl-2-pyridinecarboxylate 4c.

mp: 113 °C (*n*-Hex/CH_2Cl_2); IR (KBr) cm^{-1}: 1706 (s), 1596 (m), 1545 (w); ^1H NMR ($CDCl_3$) δ: 1.39 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.45 (s, 3H, 5-CH_3), 4.44 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 5.43 (s, 2H, $C\underline{H}_2OPh$), 7.00 and 7.30 (m, 5H, H_{arom}), 8.02 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$): 14.2 (CH_3), 19.8 (5-CH_3), 62.1 (CH_2), 65.9 (OCH_2Ph), 114.7, 121.4, 129.6 (C_{arom}), 135.1 (C-3), 136.5 (C-5), 138.9 (C-4), 142.4 (C-2), 149.8 (C-6), 158.1 (C_{ipso}), 164.8 (CO); m/z (%): 305 (M^+, 20), 259 (11), 212 (18), 184 (100); exact mass calcd for $C_{16}H_{16}ClNO_3$: 305.0819; found: 305.0816; anal cald for $C_{16}H_{16}ClNO_3$: C 62.85, H 5.27, N 4.58; found: C 62.95, H 5.07, N 4.55

***N*-Propyl-6,7-dihydro-3-chloro-4-methyl-5*H*-2-pyridine-1-carboxamide 4d.**

mp: 120 °C (Et_2O/Diisopropyl ether); IR (KBr) cm^{-1}: 1655 (s), 1523 (s); ^1H NMR ($CDCl_3$) δ: 1.00 (t, 3H, J = 7 Hz, $CH_2CH_2C\underline{H}_3$), 1.65 (sext, 2H, J = 7 Hz, $CH_2C\underline{H}_2CH_3$), 2.16 (pent, 2H, J = 7 Hz, $CH_2C\underline{H}_2CH_2$), 2.34 (s, 3H, 4-CH_3), 2.88 (t, 2H, J = 7 Hz, $C\underline{H}_2CH_2CH_2$), 3.41 (m, 4H, $CH_2CH_2C\underline{H}_2$ and $NHC\underline{H}_2CH_2CH_3$), 7.90 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 11.4 (CH_3), 16.4 (4-CH_3), 22.9, 24.7, 31.7, 32.2 (CH_2), 40.8 (NCH_2), 130.9 (C-4), 140.4 (C-7a), 141.8 (C-1), 147.2 (C-3), 158.6 (C-4a), 164.4 (CO); m/z (%): 252 (M^+, 76), 223 (51), 195 (16), 167 (100); exact mass calcd for $C_{13}H_{17}ClN_2O$: 252.1029; found: 252.1032; anal cald for $C_{13}H_{17}ClN_2O$: C 61.78, H 6.78, N 11.08; found: C 61.80, H 6.93, N 11.10

***N*-Propyl-1,5-dihydro-8-chloro-9-methyl-[1,3]dioxepino[5,6-c]pyridine-6-carboxamide 4e.**

mp: 145 °C (CH_2Cl_2/Diisopropyl ether); IR (KBr) cm^{-1}: 1639 (s), 1542 (s); ^1H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J = 7 Hz, $NHCH_2CH_2C\underline{H}_3$), 1.62 (sext, 2H, J = 7 Hz, $NHCH_2C\underline{H}_2CH_3$), 2.33 (s, 3H, 9-$CH_3$), 3.35 (q, 2H, J = 7 Hz, $NHC\underline{H}_2CH_2CH_3$), 4.90 (s, 2H, CH_2O), 4.95 (s, 2H, CH_2O), 5.41 (s, 2H, OCH_2O), 7.82 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): 11.4 (CH_3), 15.5 (9-CH_3), 22.8 (CH_2), 41.1 (NCH_2), 66.7, 67.3 (CH_2O), 96.6 (OCH_2O), 131.0 (C-9), 136.2 (C-5a), 144.2 (C-6), 148.1 (C-8), 152.3 (C-9a), 164.4 (CO); m/z (%): 284 (M^+, 6), 254 (9), 226 (7), 197 (8), 169 (23), 141 (21), 58 (100); exact mass calcd for $C_{13}H_{17}ClN_2O_3$: 284.0928; found: 284.0929; anal calcd for $C_{13}H_{17}ClN_2O_3$: C 54.84, H 6.02, N 9.84; found: C 54.96, H 6.03, N 9.82

Ethyl 6-ethoxy-5-methyl-3-phenyl-2-pyridinecarboxylate 5a.

oil; IR (NaCl plates) cm^{-1}: 1736 (s), 1606 (m); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 1.32 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.15 (s, 3H, 5-CH_3), 4.03 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 4.38 (q, 2H, J = 7 Hz, $C\underline{H}_2CH_3$), 7.25 (m, 5H, H_{arom}), 7.35 (s, 1H, H-4); ^{13}C NMR ($CDCl_3$): 13.5, 14.5 (CH_3), 15.7 (5-CH_3), 60.9, 61.9 (CH_2), 123.1 (C-5), 127.1, 128.0, 128.2 (C_{arom}), 130.1 (C-3), 138.7 (C_{ipso}), 140.4 (C-4), 142.9 (C-2), 160.7 (C-6), 167.2 (CO); m/z (%): 285 (M^+, 100), 270 (60), 257 (51); exact mass calcd for $C_{17}H_{19}NO_3$: 285.1365; found: 285.1366

***N*-Propyl-6,7-dihydro-3-propylamino-4-methyl-5*H*-2-pyridine-1-carboxamide 5d.**

mp: 158 °C (CH_2Cl_2/Diisopropyl ether); IR (KBr) cm^{-1}: 3357 (m), 1657 (s), 1606 (m); ^1H NMR ($CDCl_3$) δ: 1.00 (m, 6H, 2 x $NHCH_2CH_2C\underline{H}_3$), 1.65 (m, 4H, 2 x $NHCH_2C\underline{H}_2CH_3$), 2.04 (pent, 2H, J = 7.5 Hz, $CH_2C\underline{H}_2CH_2$), 2.05 (s, 3H, 4-CH_3), 2.76 (t, 2H, J = 7.5 Hz, $C\underline{H}_2CH_2CH_2$), 3.32 (t, 2H, J = 7.5 Hz, $CH_2CH_2C\underline{H}_2$), 3.40 (m, 4H, 2 x -$NHC\underline{H}_2CH_2CH_3$), 4.15 (br s, 1H, NH), 8.16 (br s, 1H, CONH); ^{13}C NMR ($CDCl_3$): 11.4, 11.7 (2 x $NHCH_2CH_2\underline{C}H_3$), 13.2 (4-$CH_3$), 22.8, 23.0 (2 x $NHCH_2\underline{C}H_2CH_3$), 25.1 ($CH_2\underline{C}H_2CH_2$), 31.0, 31.8 ($\underline{C}H_2CH_2\underline{C}H_2$), 40.5, 43.9 (2 x $NH\underline{C}H_2CH_2CH_3$), 115.6 (C-4), 130.5 (C-7a), 138.7 (C-1), 153.9 (C-4a), 154.9 (C-3), 166.4 (CO); m/z (%): 275 (M^+, 76), 190(100), 159 (73); exact mass calcd for $C_{16}H_{25}N_3O_1$: 275.1997; found: 275.1996

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