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SYNTHESIS OF 6-BROMOMETHYL-SUBSTITUTED DERIVATIVES OF PYRIDIN-2(1H)-ONES AND THEIR REACTION WITH NUCLEOPHILES

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6-Bromomethyl-substituted derivatives of pyridin-2(1H)-ones were obtained by the bromination of 6-methyl-3,4-dihydropyridin-2(1H)-ones, and are the basis for the synthesis of thieno- and furo[3,4-b]-pyridin-2(1H)-ones and also for obtaining new amino derivatives in the pyridin-2(1H)-one series.

Keywords: amino derivatives of pyridin-2(1H)-ones, pyridin-2(1H)-ones, thieno- and furo[3,4-*b*]-pyridin-2(1H)ones, bromination.

Derivatives of pyridin-2(1H)-ones are of interest as compounds, depending on the structure, of significant biological activity. In this series cardiovascular preparations (amrinone, milrinone) [1,2], and compounds inhibiting HIV [3,4] were found and developed.

3,4-Dihydropyridin-2(1H)-ones **3a-c** are synthesized by the condensation of β-aminocrotonic acid methyl ester **1** with benzylidenecyanoacetamides **2** in a mixture of ethanol–acetic acid, 1:2. Judging by data of ^{1}H NMR spectra pyridones **3** are a mixture of *cis* and *trans* isomers. According to the data of [5], the signals with the greatest coupling constants (J_{34} = 7 Hz) correspond to the *cis*-isomer and with the least (J_{34} = 3 Hz) to the *trans*-isomer. The ratio of *cis* and *trans* isomers was 1:9.

Bromination of the synthesized pyridin-2(1H)-ones **3** has been carried out with the aim of obtaining furo- and thieno[3,4-*b*]pyridin-2(1H)-ones.

The use of N-bromosuccinimide as brominating agent (a specific reagent for brominating CH_3 groups in the allyl position) did not give the expected result. Bromo derivatives **5** were obtained by the interaction of pyridones **3** with bromine in acetic acid. According to the data of [6], the formation of the oxidized form **5** occurs as a result of fission of a molecule of HBr from the proposed intermediate dibromo compound **4**.

In a less polar solvent ($CHCl_3$) and on irradiation with a lamp (500 watt), it is evident that the radical mechanism dominates and bromination proceeds only at the methyl group. Unlike 6-bromomethylpyridin-2(1H)-ones **5**, the 6-bromomethyl-3,4-dihydropyridin-2(1H)-one **7** was difficult to obtain in the pure state, since on crystallizing lactonization occurs with the formation of 2,5-dioxo-4-phenyl-1,2,3,4,5,7-hexahydrofuro[3,4-*b*]-pyridine-3-carbonitrile (**8**). In the case of pyridin-2(1H)-ones **5** even after extended boiling in ethanol no lactonization with the formation of furo[3,4-*b*]pyridin-2(1H)-ones **6** was observed (Scheme 1).

A band is observed in the IR spectra of dihydropyridones **3** for the stretching vibrations of the nitrile group at 2260-2275 cm^{-1}, but in the case of pyridones **5** it is displaced in the direction of lower frequencies by 25-35 cm^{-1}, which indicates the presence of a more conjugated system.

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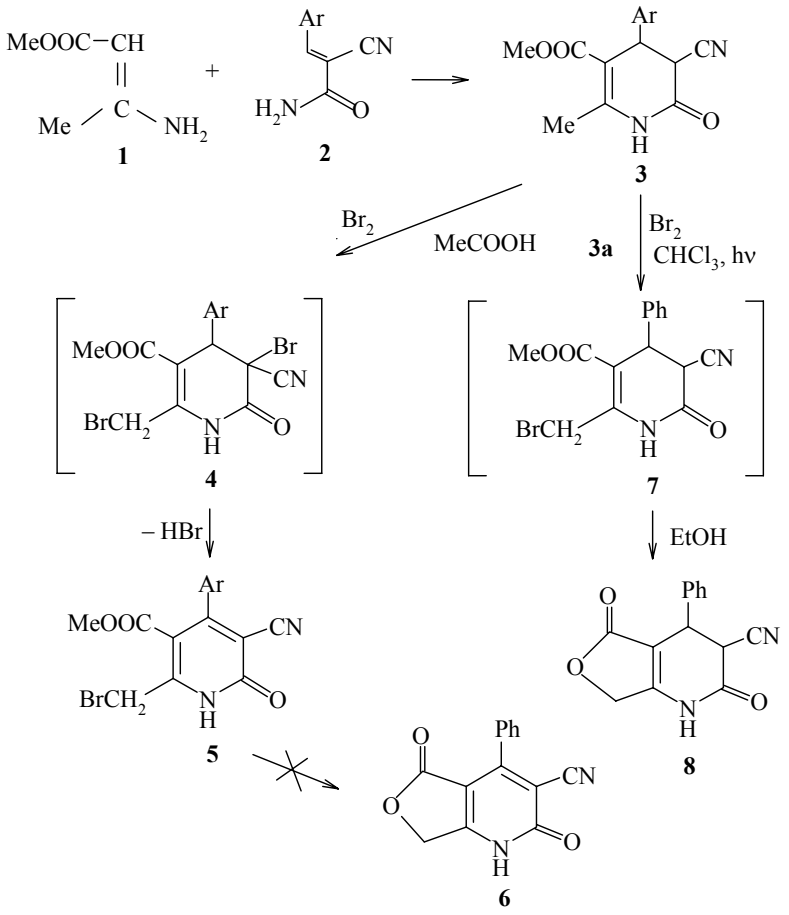
Scheme 1



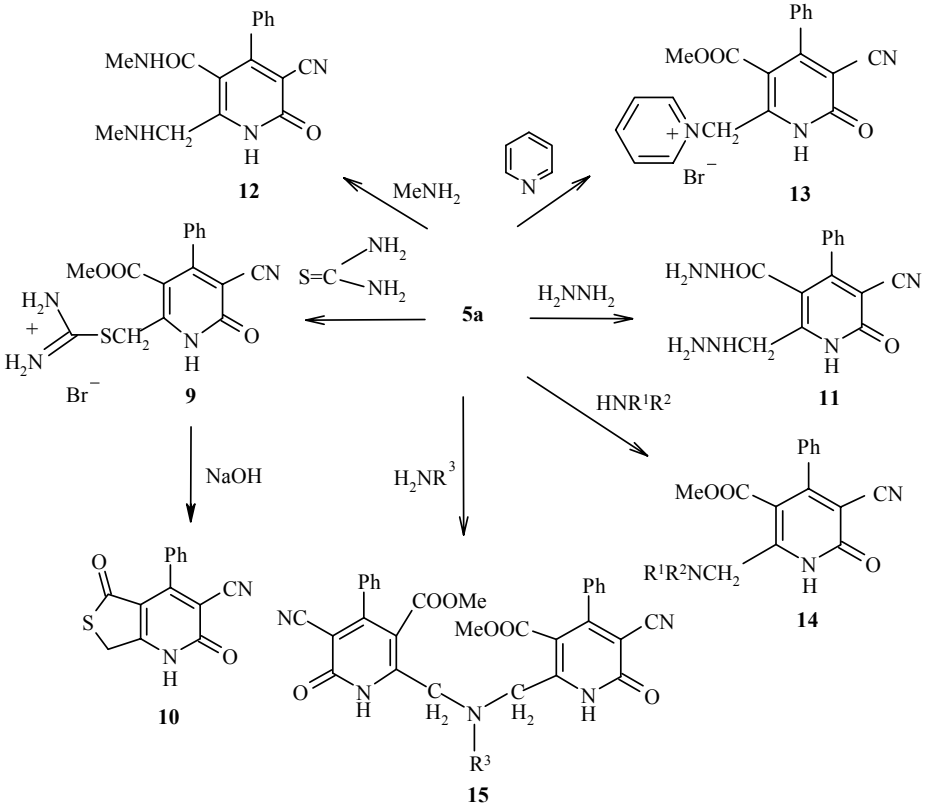
2, **3**, **5** **a** Ar = Ph, **b** Ar = *m*-$NO_2C_6H_4$, **c** Ar = *p*-$NO_2C_6H_4$

Doublet signals are displayed in the ^{1}H NMR spectra of the dihydro derivatives **3** for the H-3 and H-4 protons, which disappear from the spectra of pyridones **5**. On interacting pyridone **5a** with thiourea initially thiouronium salt **9** is formed, which in strongly alkaline medium is cyclized into 2,5-dioxo-4-phenyl-1,2,5,7-tetrahydrothieno[3,4-*b*]pyridine-3-carbonitrile (**10**).

The signals of the 5-methoxycarbonyl and amino groups present in the spectrum of bromide **9** disappear in the ^{1}H NMR spectra of thiolactone **10**. Since the electronegativity of the sulfur atom is less than that of oxygen then in the IR spectra of the thiolactones the carbonyl group vibrations are displaced from 1731 (for lactone **8**) to 1670 cm^{-1}.

On using hydrazine hydrate as the nucleophilic reagent not only is the bromine atom replaced by hydrazine but the hydrazine hydrate also reacts with the 5-methoxycarbonyl group with the formation of 5-carbazoyl-3-cyano-6-hydrazinomethyl-4-phenylpyridin-2(1H)-one (**11**). Signals are observed in the ^{1}H NMR spectra for the methylene protons at 4.10 ppm, signals for the OMe group protons are absent and there is a broadened singlet at 6.10 ppm which corresponds to 6 protons ($2H_2N$-NH).

The results of the interaction of the bromomethyl derivatives **5** depend on the character of the amine used.



14 a $R^1 + R^2 = -(CH_2)_5-$; **b** $R^1 = H$, $R^2 = CH_2CH_2Ph$; **c** $R^1 = H$, $R^2 = Ph$;
d $R^1 = H$, $R^2 = CH_2COOEt$; **15 a** $R^3 = (CH_2)_3COOEt$; **b** $R^3 = (CH_2)_3Me$

The amino derivatives **14** are obtained by the reaction of pyridin-2(1H)-one **5a** with piperidine, 2-phenylethylamine, aniline, and glycine ethyl ester hydrochloride. In the ^1H NMR spectra of amines **14a-d** the signals for the 6-CH_2 group protons are retained at 3.55-4.37 ppm.

TABLE 1. Characteristics of Compounds **3**, **5**, and **8-15**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, %
		C	H	N	Br	S		
1	2	3	4	5	6	7	8	9
3a	$C_{15}H_{14}N_2O_3$	66.72 / 66.65	5.03 / 5.22	10.29 / 10.36			174-176	57
3b	$C_{15}H_{13}N_3O_5$	57.35 / 57.14	3.95 / 4.16	13.28 / 13.33			187-189	60
3c	$C_{15}H_{13}N_3O_5$	57.37 / 57.14	4.01 / 4.16	13.39 / 13.33			190-193	52
5a	$C_{15}H_{11}BrN_2O_3$	51.40 / 51.89	2.90 / 3.19	7.80 / 8.07	23.20 / 23.02		182-184	42
5b	$C_{15}H_{10}BrN_3O_5$	45.69 / 45.94	2.32 / 2.57	10.47 / 10.71	20.92 / 20.37		168-170	43
5c	$C_{15}H_{10}BrN_3O_5$	46.01 / 45.94	2.22 / 2.57	10.55 / 10.71	19.74 / 20.37		170-172	45
8	$C_{14}H_{10}N_2O_3$	65.60 / 66.14	4.05 / 3.96	10.73 / 11.02			222-224	52
9	$C_{16}H_{15}BrN_4O_3S$	45.05 / 45.40	3.53 / 3.57	13.16 / 13.24		7.54 / 7.57	172-174	85

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
10	$C_{14}H_8N_2O_2S\times$ $\times 1/2H_2O$	60.74 / 60.64	2.96 / 3.27	10.33 / 10.10		11.79 / 11.56	152-154	40
11	$C_{14}H_{14}N_6O_2$	56.37 / 56.17	4.73 / 4.72	28.11 / 28.12			180-182	71
12	$C_{16}H_{16}N_4O_2$	64.67 / 64.85	5.33 / 5.24	18.88 / 18.91			275-277	78
13	$C_{20}H_{16}BrN_3O_3$	56.45 / 56.35	3.85 / 3.78	9.68 / 9.86			182-184	65
14a	$C_{20}H_{21}N_3O_3\times$ $\times H_2O$	64.85 / 65.05	6.29 / 6.27	11.28 / 11.37			88-90	57
14b	$C_{23}H_{21}N_3O_3$	70.92 / 71.30	5.09 / 5.46	10.55 / 10.84			193-195	34
14c	$C_{21}H_{17}N_3O_3$	70.13 / 70.18	4.76 / 4.77	11.67 / 11.69			188-190	81
14d	$C_{19}H_{19}N_3O_5$	61.10 / 61.78	4.93 / 5.18	10.97 / 11.38			238-240	17
15a	$C_{36}H_{33}N_5O_8$	64.15 / 65.15	4.95 / 5.01	10.49 / 10.55			214-216	12
15b	$C_{34}H_{31}N_5O_6$	67.47 / 67.42	5.00 / 5.16	11.47 / 11.56			205-208	42

TABLE 2. Spectral Characteristics of Compounds **3**, **5**, and **8-15**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)*
	C=O	C≡N	NH	
1	2	3	4	5
3a	1640, 1710	2260	3170, 3280	2.40 (0.3H, s, 6-CH_3, *cis*); 2.45 (2.7H, s, 6-CH_3, *trans*); 3.35 (3H, s, OCH_3); 4.45 (0.1H, d, *J* = 7, 3-H, *cis*); 4.22 (0.9H, d, *J* = 3.2, 3-H, *trans*); 4.95 (0.1H, d, *J* = 7.4, 4-H, *cis*); 4.58 (0.9H, d, *J* = 3.2, 4-H, *trans*); 7.26 (5H, m, C_6H_5); 10.48 (0.1H, s, NH, *cis*); 10.80 (0.9H, s, NH, *trans*)
3b	1645, 1715	2270	3180, 3280	2.35 (0.3H, s, 6-CH_3, *cis*); 2.37 (2.7H, s, 6-CH_3, *trans*); 3.53 (0.3H, s, OCH_3, *cis*); 3.55 (2.7H, s, OCH_3, *trans*); 4.28 (0.9H, d, *J* = 4, 3-H, *trans*); 4.60 (0.1H, d, *J* = 7.4, 3-H, *cis*); 4.72 (0.9H, d, *J* = 4.0, 4-H, *trans*); 4.95 (0.1H, d, *J* = 7.4, 4-H, *cis*); 7.40 (2H, d, C_6H_4); 8.10 (2H, d, C_6H_4); 10.50 (0.1H, s, NH, *cis*); 10.82 (0.9H, s, NH, *trans*)
3c	1645, 1715	2275	3185, 3270	2.32 (0.3H, s, 6-CH_3, *cis*); 2.34 (2.7H, s, 6-CH_3, *trans*); 3.44 (3H, s, OCH_3); 4.24 (0.9H, d, *J* = 3.0, 3-H, *trans*); 4.48 (0.1H, d, *J* = 7.0, 3-H, *cis*); 4.55 (0.9H, d, *J* = 3.0, 4-H, *trans*); 4.85 (0.1H, d, *J* = 7.0, 4-H, *cis*); 7.33 (2H, m , C_6H_4); 8.33 (2H, m , C_6H_4); 10.44 (0.9H, s, NH, *cis*); 10.77 (0.1H, s, NH, *trans*)
5a	1650, 1750	2240	3160, 3220	3.38 (3H, s, OCH_3); 4.6 (2H, s, CH_2); 7.38 (5H, m, C_6H_5); 13.10 (1H, br. s, NH)
5b	1650, 1735	2240	3160, 3310	3.44 (3H, s, OCH_3); 4.25 (2H, s, CH_2); 7.97 (4H, m, C_6H_4); 13.42 (1H, br. s, NH)
5c	1658, 1735	2240	3160, 3310	3.45 (3H, s, OCH_3); 4.60 (2H, s, CH_2); 7.68 (2H, d, *J* = 8, C_6H_2); 8.32 (2H, d, *J* = 8, C_6H_2); 13.49 (1H, br. s, NH)
8	1678, 1731	2245	3180, 3220, 3280	4.3 (1H, d, *J* = 8, CH); 5.1 (1H, d, *J* = 8, CH); 4.95 (2H, s, CH_2); 7.35 (5H, s, C_6H_5); 11.37 (1H, s, NH)
9	1652, 1713	2222	3240, 3330	3.35 (3H, s, OCH_3); 4.44 (2H, s, CH_2); 7.19-7.63 (5H, m, C_6H_5); 9.29 (4H, br. s, H_2N–C=N^+H_2)

TABLE 2 (continued)

1	2	3	4	5
10	1655, 1670	2230	3140	4.5 (2H, s, CH_2); 7.23-7.60 (5H, m, C_6H_5); 11.7 (1H, br. s, NH)
11	1647, 1693	2210	3215, 3310	4.10 (2H, s, CH_2); 5.60-6.70 (6H, br. s, 2NH–NH_2); 7.35 (5H, s, C_6H_5)
12	1660, 1672	2218	3160	2.35 (3H, s, $CH_2NH\underline{CH_3}$); 2.82 (3H, s, $CONH\underline{CH_3}$); 4.02 (2H, s, CH_2); 7.35 (5H, s, C_6H_5)
13	1670, 1728	2210	3360	3.45 (3H, s, CH_3); 6.12 (2H, s, CH_2); 7.3-7.7 (5H, m, C_6H_5); 8.17-9.25 (5H, m, pyridinium)
14a	1645, 1693	2218	3260, 3370	1.40 (6H, br. s, $(-CH_2-)_3$); 2.38 (4H, m, $-CH_2-N-CH_2-$); 3.37 (3H, s, OCH_3); 3.55 (2H, s, CH_2); 7.20-7.58 (5H, m, C_6H_5)
14b	1640, 1730	2230	3100, 3330	2.73–3.40 (4H, m, $-CH_2-CH_2-$); 3.44 (4H, s, CH_3+NH); 4.10 (2H, s, CH_2); 7.15-7.73 (10H, m, $2C_6H_5$)
14c	1650, 1730	2220	3170, 3320, 3380	3.37 (4H, s, CH_3+NH amine); 4.37 (2H, s, CH_2); 6.47-7.60 (10H, m, $2C_6H_5$)
14d	1650, 1720, 1745	2230	3150, 3210	1.26 (3H, m, $CH_2-\underline{CH_3}$); 3.40 (4H, s, CH_3+NH amine); 3.60 (2H, s, $\underline{CH_2}-CO$); 4.22 (2H, q, $\underline{CH_2}-CH_3$); 4.3 (2H, s, CH_2); 7.40 (5H, s, C_6H_5)
15a	1645, 1735	2230	3140, 3210	1.26 (3H, m, $CH_2-\underline{CH_3}$); 2.00 (2H, m, 3-CH_2); 2.28 (4H, m, $2CH_2$); 2.84 (2H, m, CH_2); 3.45 (6H, s, $2OCH_3$); 3.96 (4H, s, CH_2); 4.06 (2H, q, $\underline{CH_2}-CH_3$); 7.36 (10H, m, $2C_6H_5$)
15b	1685, 1730, 1745	2230	3150, 3260	0.78 (3H, t, $CH_2-\underline{CH_3}$); 1.32 (4H, m, $\underline{CH_2}-\underline{CH_2}-CH_3$); 2.4 (2H, t, $\underline{CH_2}-CH_2-CH_2-CH_3$); 3.45 (6H, s, $2OCH_3$); 3.75 (4H, s, $N(CH_2)_2$); 7.25-7.62 (10H, m, $2C_6H_5$); 12.85 (2H, br. s, 2NH)

* The ^{1}H NMR spectra of compounds **14a** and **15a** were taken in $CDCl_3$.

On using aqueous methylamine solution under mild conditions (room temperature), besides replacement of bromine by a methylamino group, amidation of the ester group at position **5** also occurs with the formation of 5-cyano-2-methylaminomethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-(N-methyl)carboxamide (**12**).

In their turn the application of γ-aminobutyric acid ethyl ester and *n*-butylamine as nucleophiles leads to the formation of dimers **15**, in which one molecule of amine is linked to two molecules of pyridone. The integrated intensities of the proton signals of the pyridone ring substituents in the dimers **15** in the ^{1}H NMR spectra were doubled in comparison with the proton signals of the amine residue (R^3).

It is known that quaternized derivatives of pyridine are potential agents for gene transfection [7].

We have shown the possibility of synthesizing quaternized derivatives in the pyridone series, using pyridine as an example. Pyridinium bromide **13** was obtained by the interaction of pyridone **3a** with pyridine. It is seen from the ^{1}H NMR spectra that compared with bromine the pyridinium cation displaces the signal of the methylene protons towards low field from 4.50 to 6.10 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 580B instrument in Nujol, the ^{1}H NMR spectra on a WH 90/DC (90 MHz) instrument, internal standard was TMS. A check on the progress of reactions and the homogeneity of substances was carried out by TLC on Silufol plates in acetone–hexane, 1:1.

The characteristics of the synthesized compounds are given in Tables 1 and 2.

5-Cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (3a). β-Aminocrotonic acid methyl ester **1** (1.15 g, 10 mmol) and benzylidenecyanoacetamide **2** (1.72 g, 10 mmol) were dissolved in a mixture (20 ml) of acetic acid–ethanol, 1:2. The solution obtained was boiled for 3 h and then maintained at 5-8°C for 24 h. The solid formed was filtered off, washed with ethanol, and crystallized from ethanol. Compound **3a** (1.6 g) was obtained.

Compounds 3b,c were obtained analogously.

2-Bromomethyl-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic Acid Methyl Ester (5a). Dihydropyridone **3a** (5 g, 18.5 mmol) was suspended in acetic acid (20 ml). Bromine (2 ml, 37 mmol) in acetic acid (10 ml) was added dropwise with vigorous stirring during 50 min to the obtained suspension. The clear solution obtained was left for 24 h at 20°C, and was then poured into water (800 ml) with vigorous stirring. The resulting solid was filtered off, washed with a large amount of water, and recrystallized from ethanol. Compound **5a** (2.7 g) was obtained

Compounds 5b,c were obtained analogously.

2-Bromomethyl-5-cyano-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (7) and 2,5-Dioxo-4-phenyl-1,2,3,4,5,7-hexahydro-furo[3,4-*b*]pyridine-3-carbonitrile (8). Compound **3a** (1.35 g, 5 mmol) was suspended in dry chloroform (12 ml) and a solution of bromine (0.88 g, 5.5 mmol) in dry chloroform (3 ml) was added dropwise while boiling and irradiating with a lamp (500 watt). After the addition of all the bromine, stirring and irradiation was continued for a further 10 min. The reaction mixture was then poured into water (100 ml) and unpurified compound **7** (0.73 g) was filtered off. Furopyridone **8** (0.66 g) was obtained after crystallization of compound **7** from ethanol.

S-[(5-Cyano-3-methoxycarbonyl-6-oxo-4-phenyl-1,6-dihydro-2-pyridyl)methyl]thiouronium Bromide (9). Compound **5a** (0.5 g, 1.44 mmol) was suspended in acetonitrile (7 ml), and thiourea (0.11 g, 1.44 mmol) was added. The mixture obtained was stirred at room temperature for 3 h. The solid formed was filtered off, and washed with acetonitrile (2 x 5 ml). Compound **9** (0.52 g) was obtained.

2,5-Dioxo-4-phenyl-1,2,5,7-tetrahydrothieno[3,4-*b*]pyridine-3-carbonitrile (10). Compound **9** (0.4 g, 0.93 mmol) was added to a solution of NaOH (0.15 g, 3.7 mmol) in water (20 ml). The mixture was stirred for 24 h, acidified to pH ~4-5 with hydrochloric acid, and stirring continued for a further 30 min. The resulting solid was filtered off, washed with water to a neutral reaction, and recrystallized from ethanol. Compound **10** (0.1 g) was obtained.

3-Carbazoyl-5-cyano-2-hydrazinomethyl-6-oxo-4-phenyl-1,6-dihydropyridine (11). Hydrazine hydrate (55%) (2 ml) was added to a suspension of pyridone **5a** (0.5 g, 1.44 mmol) in ethanol (7 ml), and the mixture boiled for 40 min. The resulting solid was filtered off, and recrystallized from ethanol. Compound **11** (0.3 g) was obtained.

5-Cyano-2-methylaminomethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-(N-methyl)carboxamide (12). Aqueous 30% methylamine solution (1 ml, 8.6 mmol) was added to a suspension of pyridone **5a** (0.3 g, 0.86 mmol) in ethanol (10 ml). The clear solution obtained was stirred at room temperature, and after 10 min a precipitate formed, which was filtered off next day, and washed with ethanol (10 ml). Compound **12** (0.2 g) was obtained.

1-[(5-Cyano-3-methoxycarbonyl-6-oxo-4-phenyl-1,6-dihydro-2-pyridyl)-methyl]pyridinium Bromide (13). Pyridone **5a** (0.94 g, 2.71 mmol) was dissolved with heating in acetone (75 ml) and pyridine (0.24 g, 2.71 mmol) was added. The solution obtained was stirred for 2 h at ~20°C, and the solvent evaporated in vacuum. The residue was dissolved in methanol and left for 24 h at ~20°C. The solid was filtered off and recrystallized from 2-propanol. Pyridinium bromide **13** (0.75 g) was obtained.

5-Cyano-6-oxo-4-phenyl-2-piperidinomethyl-1,6-dihydropyridine-3-carboxylic Acid Methyl Ester (14a). Piperidine (1.5 ml, 15.3 mmol) was added to a solution of pyridone **5a** (0.5 g, 1.44 mmol) in DMF (8 ml). The reaction mixture was stirred at 80°C for 1 h, cooled, and poured into water (15 ml). After a day the solid was filtered off, and crystallized from ethanol–ether, 1:3. Compound **14a** (0.3 g) was obtained.

5-Cyano-6-oxo-4-phenyl-2-[(2-phenylethyl)aminomethyl]-1,6-dihydropyridine-3-carboxylic Acid Methyl Ester (14b). 2-Phenylethylamine (0.35 g, 2.88 mmol) was added to a solution of pyridone **5a** (0.5 g, 1.44 mmol) in methanol (20 ml) . The solution obtained was boiled for 10 min, cooled, and poured into water (50 ml). The solid was filtered off, and crystallized from ethanol–ether, 1:1. Compound **14b** (0.19 g) was obtained.

2-Anilinomethyl-5-cyano-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic Acid Methyl Ester (14c). A solution of pyridone **5a** (0.5 g, 1.44 mmol) and aniline (0.27 g, 2.88 mmol) in DMF (5 ml) was stirred for 2 h at ~20°C, then poured into water (50 ml) acidified with hydrochloric acid (pH 4-5). The solid was filtered off, and crystallized from ethanol. Compound **14c** (0.42 g) was obtained.

5-Cyano-2-[(ethoxycarbonylmethyl)aminomethyl]-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic Acid Methyl Ester (14d). A solution of pyridone **5a** (0.5 g, 1.44 mmol) and glycine ethyl ester hydrochloride (0.41 g, 2.94 mmol) in DMF (5 ml) was stirred for 1 h 30 min at ~20°C, then poured into water (50 ml). The solid was filtered off and crystallized from ethanol–ether, 1:1. Compound **14d** (0.09 g) was obtained.

4-[Bis(5-cyano-3-methoxycarbonyl-6-oxo-4-phenyl-1,6-dihydro-2-pyridylmethyl)]aminobutyric Acid Ethyl Ester (15a). A solution of pyridone **5a** (0.5 g, 1.44 mmol), γ-aminobutyric acid ethyl ester hydrochloride (0.48 g, 2.86 mmol), and triethylamine (0.4 ml, 2.86 mmol) in methanol (5 ml) was stirred at ~20°C for 6 h, and left for a day. The reaction mixture was poured into acidified (pH ~2) water (50 ml). The solid was filtered off, and crystallized from ethanol–chloroform, 10:1. Compound **15a** (0.09 g) was obtained.

Bis(5-cyano-3-methoxycarbonyl-6-oxo-4-phenyl-1,6-dihydro-2-pyridyl-methyl)butylamine (15b). A mixture of pyridone **5a** (0.55 g, 1.58 mmol) and *n*-butylamine (0.31 ml, 3.14 mmol) in ethanol (35 ml) was boiled for 2 h, cooled, and poured into acidified (pH ~4-5) water (150 ml). The solid was filtered off, and crystallized from ethanol. Compound **15b** (0.4 g) was obtained.

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