DOI 10.1007/s10600-023-04098-1
Chemistry of Natural Compounds, Vol. 59, No. 4, July, 2023

CARBAMIDE DERIVATIVES OF LAPPACONITINE

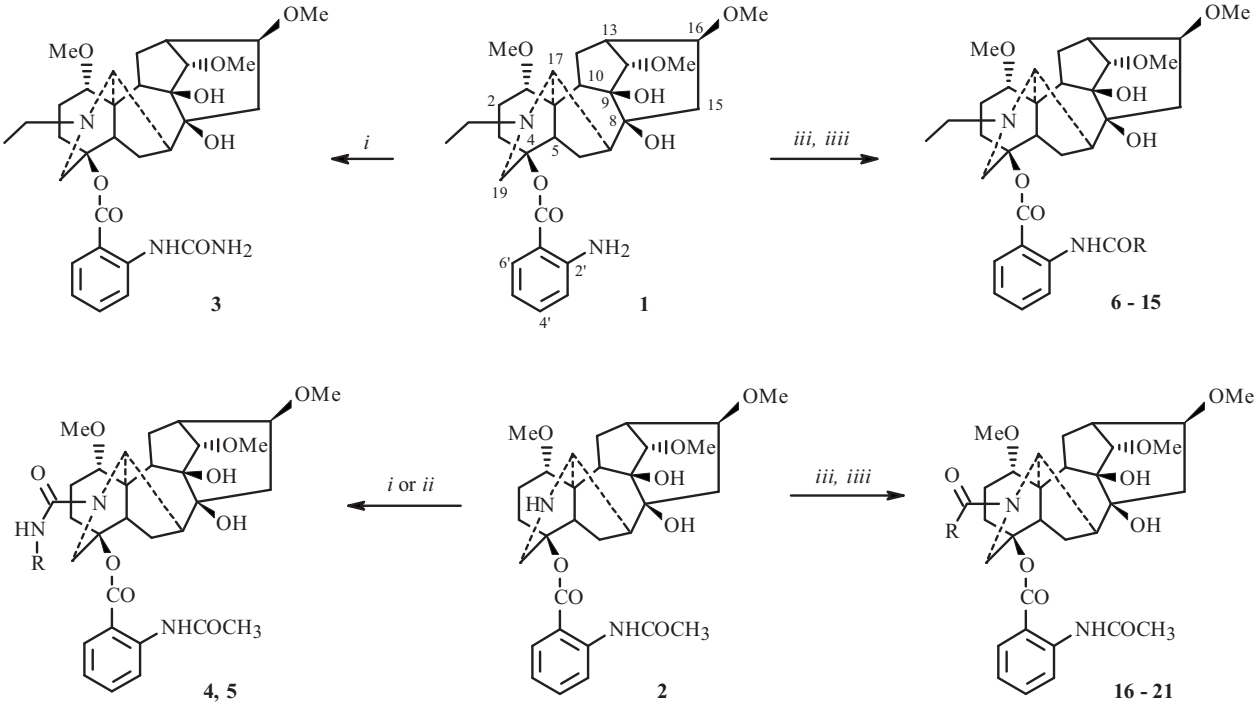
E. M. Tsyrlina,* T. M. Gabbasov, A. N. Lobov, and M. S. Yunusov

Carbamide derivatives of lappaconitine were prepared via reactions of N-*deacetyllappaconitine and* N-*20-norlappaconitine with potassium isocyanate, phenylisocyanate, or triphosgene followed by treatment with various amines.*

Keywords: *N*-deacetyllappaconitine, *N*-20-norlappaconitine, potassium isocyanate, phenylisocyanate, triphosgene, amines, carbamide derivatives of lappaconitine.

Urea derivatives are important structural platforms in medicinal chemistry that are used to develop antitumor, antibacterial, anticonvulsive, anti-HIV, and antidiabetic agents and other drugs [1].

The traditional methods for synthesizing urea derivatives include reactions of amines with phosgene, carbon monoxide, or isocyanates.



R = H (**4**); Ph (**5**); NHPh (**6**); NEt_2 (**7**, **16**); NH-*i*-Pr (**8**, **17**); 4-methylpiperazin-1-yl (**9**, **18**); 4-benzylpiperidin-1-yl (**10**); morpholin-4-yl (**11**, **19**); pyrrolidine-1-yl (**12**); NH-benzyl (**13**); trimetazidin-1-yl (**14**, **20**); cytisine-12-yl (**15**, **21**)

i. KNCO–AcOH–H_2O; *ii*. PhNCO–DMF; *iii*. triphosgene, DIPEA, CH_2Cl_2; *iiii*. amine, DIPEA

Ufa Institute of Chemistry, Ufa Federal Research Center, Russian Academy of Sciences, 71 Prosp. Oktyabrya, Ufa, 450054, Russian Federation, fax: 7 (347) 235 60 66, e-mail: tsirlina@anrb.ru. Translated from *Khimiya Prirodnykh Soedinenii*, No. 4, July–August, 2023, pp. 610–615. Original article submitted December 12, 2022.

 0009-3130/23/5904-0730

TABLE 1. ^{1}H and ^{13}C NMR Spectral Data for Products **3** and **6**–**9** ($CDCl_3$, δ, ppm)*

C atom	**3**		**6****		**7**		**8**		**9*****	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	83.9	3.18	83.5	3.05	84.1	3.20	81.4	3.16	84.2	3.18
2	26.5	2.14	26.4	2.12	26.6	2.15	26.7	2.18	26.8	2.15
		2.27		2.29		2.28		2.28		2.28
3	31.7	1.85	31.4	1.88	31.6	1.82	31.8	1.82	31.8	1.83
		2.60		2.45		2.63		2.60		2.58
4	84.2	–	83.8	–	83.9	–	84.2	–	84.4	–
5	48.0	2.44	47.1	2.51	48.1	2.42	48.3	2.41	48.3	2.42
6	24.1	1.58	24.0	1.55	24.0	1.60	24.1	1.58	24.1	1.57
		2.69		2.70		2.68		2.68		2.66
7	47.6	2.17	47.5	2.18	47.5	2.17	47.6	2.15	47.5	2.15
8	75.6	–	75.4	–	75.6	–	75.6	–	75.6	–
9	78.6	–	78.4	–	78.5	–	78.5	–	78.6	–
10	49.9	2.09	49.6	2.08	49.8	2.11	49.8	2.09	49.8	2.09
11	51.0	–	50.8	–	50.9	–	50.9	–	50.9	–
12	26.3	1.99	26.3	1.98	26.3	1.98	26.2	1.96	26.2	1.96
		2.43		2.47		2.44		2.47		2.48
13	36.4	2.38	36.4	2.37	36.3	2.37	36.3	2.36	36.2	2.36
14	90.1	3.44	89.9	3.45	90.1	3.43	90.1	3.43	90.1	3.43
15	44.7	2.06	44.5	2.09	44.8	2.03	44.8	2.02	44.8	2.01
		2.37		2.35		2.39		2.38		2.38
16	82.9	3.29	82.8	3.27	82.9	3.31	82.9	3.30	82.9	3.29
17	61.5	3.02	61.5	3.02	61.6	3.02	61.5	3.00	61.5	2.99
19	55.8	2.58	56.0	2.56	55.6	2.53	55.6	2.56	55.5	2.54
		3.59		3.57		3.60		3.55		3.52
1-OMe	56.6	3.28	56.6	3.25	56.5	3.29	56.5	3.28	56.6	3.28
14-OMe	58.0	3.40	58.0	3.39	57.9	3.40	57.9	3.40	57.9	3.39
16-OMe	56.2	3.30	56.2	3.29	56.1	3.30	56.1	3.30	56.1	3.30
$N\underline{CH_2}Me$	49.1	2.57	49.2	2.57	49.1	2.58	49.0	2.52	49.0	2.50
		2.61		2.65		2.60		2.58		2.56
$NCH_2\underline{Me}$	13.3	1.13	13.1	1.13	13.4	1.12	13.5	1.11	13.3	1.11
OCO	167.7	–	167.5	–	168.0	–	167.9	–	168.1	–
1′	115.2	–	115.1	–	115.0	–	114.4	–	115.0	–
2′	142.9	–	142.8	–	143.7	–	143.5	–	143.4	–
3′	119.7	8.42	120.0	8.43	119.6	8.52	119.3	8.48	119.5	8.45
4′	134.3	7.45	134.3	7.43	134.2	7.43	134.3	7.43	134.3	7.44
5′	121.0	6.92	121.0	6.91	120.3	6.88	120.3	6.88	120.7	6.90
6′	131.0	7.85	130.9	7.82	130.8	7.86	131.0	7.85	131.0	7.87
$NH\underline{C}O$	155.7	–	152.8	–	154.6	–	154.3	–	154.5	–
$N\underline{H}CO$	–	10.32	–	10.45	–	10.57	–	10.25	–	10.73
NH_2	–	5.01	–	–	–	–	–	–	–	–
$N\underline{H}Ph$	–	–	–	7.94	–	–	–	–	–	–
$N\underline{H}CH(Me)_2$	–	–	–	–	–	–	–	4.66	–	–
$NH\underline{CH}(Me)_2$	–	–	–	–	–	–	42.3	3.97	–	–
$NHCH(\underline{Me})_2$	–	–	–	–	–	–	23.2	1.20	–	–
$N(\underline{CH_2}Me)_2$	–	–	–	–	41.6	3.40	–	–	–	–
$N(CH_2\underline{Me})_2$	–	–	–	–	13.7	1.22	–	–	–	–

* From HSQC data; ** NHPh δ_C, ppm: 138.6 (C-1″), 120.3 (C-2″, 6″), 128.9 (C-3″, 5″), 123.4 (C-4″); δ_H, ppm: 7.50 (H-2″, 6″), 7.28 (H-3″, 5″), 7.04 (H-4″); ***4-methylpiperazin-1-yl δ_C, ppm: 43.4 (C-2″, 6″), 54.6 (C-3″, 5″), 45.9 (Me); δ_H, ppm: 3.63 (H_2-2″), 3.63 (H_2-6″), 2.53 (H_2-3″), 2.53 (H_2-5″), 2.37 (Me).

Lappaconitine can be used as starting material to prepare new derivatives although its structure contains two *N*-containing groups, i.e., an aromatic *N*-acetylamine and a tertiary N atom in a heterocycle. While transformations of the aromatic amine are often used to produce new lappaconitine derivatives [2–8], modifications involving the heterocyclic N atom are rare [9, 10].

TABLE 2. ^{1}H and ^{13}C NMR Spectral Data for Products **10**–**14** ($CDCl_3$, δ, ppm)*

C atom	**10****		**11*****		**12******		**13*******		**14********	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	84.2	3.20	84.1	3.19	84.3	3.18	84.0	3.17	84.3	3.19
2	26.8	2.17	26.7	2.15	26.8	2.16	26.6	2.16	26.8	2.18
		2.30		2.28		2.28		2.29		2.28
3	31.8	1.83	31.8	1.86	31.8	1.83	31.8	1.83	31.8	1.83
		2.60		2.60		2.59		2.60		2.60
4	84.2	–	84.4	–	84.1	–	84.2	–	84.3	–
5	48.3	2.43	48.2	2.46	48.4	2.42	48.1	2.44	48.4	2.42
6	24.1	1.59	24.1	1.58	24.1	1.59	24.1	1.59	24.1	1.58
		2.68		2.68		2.66		2.70		2.66
7	47.6	2.16	47.6	2.16	47.6	2.15	47.6	2.17	47.6	2.16
8	75.7	–	75.6	–	75.6	–	75.6	–	75.7	–
9	78.6	–	78.6	–	78.6	–	78.6	–	78.6	–
10	49.8	2.10	49.8	2.10	49.8	2.09	49.8	2.09	49.8	2.09
11	51.0	–	51.0	–	51.0	–	50.9	–	51.0	–
12	26.3	1.98	26.3	1.97	26.3	1.95	26.3	2.00	26.3	1.98
		2.48		2.48		2.50		2.47		2.50
13	36.4	2.37	36.4	2.37	36.4	2.37	36.4	2.38	36.3	2.37
14	90.2	3.44	90.2	3.43	90.2	3.43	90.1	3.45	90.2	3.43
15	44.9	2.03	44.9	2.02	44.8	2.01	44.7	2.08	44.9	2.03
		2.39		2.38		2.39		2.40		2.39
16	83.0	3.31	82.9	3.30	82.9	3.31	82.9	3.31	82.9	3.30
17	61.6	3.01	61.5	3.01	61.5	2.99	61.5	3.03	61.6	3.00
19	55.6	2.53	55.6	2.57	55.6	2.53	55.7	2.57	55.5	2.54
		3.56		3.54		3.54		3.58		3.53
1-OMe	56.6	3.30	56.5	3.29	56.6	3.28	56.5	3.30	56.6	3.29
14-OMe	58.0	3.41	57.9	3.40	57.9	3.39	58.0	3.42	57.9	3.41
16-OMe	56.2	3.31	56.2	3.30	56.1	3.30	56.2	3.33	56.1	3.31
N$\underline{C}H_2$Me	49.0	2.52	49.0	2.54	49.0	2.51	49.1	2.56	49.0	2.50
		2.58		2.58		2.57		2.59		2.58
$NCH_2\underline{Me}$	13.5	1.12	13.5	1.12	13.6	1.11	13.4	1.14	13.6	1.11
OCO	168.1	–	168.1	–	168.0	–	167.9	–	168.1	–
1′	115.0	–	115.1	–	114.8	–	114.6	–	114.9	–
2′	143.7	–	143.3	–	143.7	–	143.4	–	143.6	–
3′	119.6	8.47	119.5	8.48	119.3	8.56	119.4	8.56	119.5	8.49
4′	134.2	7.44	134.4	7.46	134.2	7.43	134.4	7.47	134.3	7.44
5′	120.4	6.89	120.8	6.92	120.3	6.88	120.6	6.93	120.5	6.90
6′	130.9	7.87	131.0	7.88	130.9	7.86	131.0	7.88	130.9	7.87
NH$\underline{C}$O	154.7	–	154.8	–	154.0	–	154.9	–	154.7	–
N$\underline{H}$CO	–	10.65	–	10.73	–	10.45	–	10.42	–	10.69

*From HSQC data; **4-benzylpiperidin-1-yl δ_C, ppm: 44.4 (C-2″, 6″), 32.0 (C-3″, 5″), 38.3 (C-4″), 43.1 ($\underline{C}H_2$Ph), 140.2 (C-1‴), 129.1 (C-2‴, 6‴), 128.3 (C-3‴, 5‴), 126.0 (C-4‴); δ_H, ppm: 2.83, 4.19 (H_2-2″), 2.83, 4.19 (H_2-6″), 1.26, 1.74 (H_2-3″), 1.26, 1.74 (H_2-5″), 1.76 (H-4″), 2.57 (C$\underline{H}_2$Ph), 7.15 (H-2‴, 6‴), 7.28 (H-3‴, 5‴′), 7.20 (H-4‴); ***morpholin-4-yl δ_C, ppm: 66.6 (C-2″, 6″), 44.0 (C-3″, 5″); δ_H, ppm: 3.75 (H_2-2″), 3.75 (H_2-6″), 3.55 (H_2-3″), 3.55 (H_2-5″); ****pyrrolidin-1-yl δ_C, ppm: 45.8 (C-2″, 5″), 25.6 (C-3″, 4″); δ_H, ppm: 3.50 (H-2″, 5″), 1.96 (H-3″, 4″); *****NH-benzyl δ_C, ppm: 138.9 (C-1″), 127.8 (C-2″, 6″), 128.7 (C-3″, 5″), 127.4 (C-4″), 44.4 ($\underline{C}H_2$Ph); δ_H, ppm: 7.38 (H-2″, 6″), 7.34 (H-3″, 5″), 7.29 (H-4″), 4.49 (C$\underline{H}_2$Ph), 5.37 (N$\underline{H}$CH_2Ph); ******trimetazidin-1-yl δ_C, ppm: 43.9 (C-2″, 6″), 52.7 (C-3″, 5″), 56.5 ($\underline{C}H_2$Ph), 123.7 (C-1‴), 152.7 (C-2‴), 142.4 (C-3‴), 153.0 (C-4‴), 107.0 (C-5‴), 125.2 (C-6‴), 61.3 (2‴-OMe), 60.8 (3‴-OMe), 56.0 (4‴-OMe); δ_H, ppm: 3.58 (H_2-2″), 3.58 (H_2-6″), 2.55 (H_2-3″), 2.55 (H_2-5″), 3.54 (C$\underline{H}_2$Ph), 6.65 (H-5‴), 7.01 (H-6‴), 3.90 (2‴-OMe), 3.88 (3‴-OMe), 3.86 (4‴-OMe).

Two lappaconitine derivatives, *N*-deacetyllappaconitine (**1**) and *N*-20-norlappaconitine (**2**) [11, 12], have been used as platforms to introduce a carbamide motif.

TABLE 3. ^{1}H and ^{13}C NMR Spectral Data of Products **4**, **5**, and **15**–**17** ($CDCl_3$, δ, ppm)*

C atom	**4**		**5****		**15*****		**16**		**17**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	81.5	3.28	81.9	3.37	84.3	3.20	82.9	3.25	81.8	3.24
2	26.2	1.61	26.4	1.67	26.9	2.19	25.9	1.85	26.2	1.58
		2.28		2.33		2.30		2.22		2.28
3	31.4	1.81	31.3	1.87	31.9	1.88	31.5	1.88	31.5	1.79
		2.65		2.65		2.51		2.65		2.67
4	82.7	–	82.6	–	84.4	–	83.5	–	83.0	–
5	47.3	2.52	47.8	2.59	48.2	2.46	47.9	2.53	47.8	2.50
6	24.3	1.74	24.3	1.83	24.1	1.57	24.1	1.78	24.2	1.73
		2.81		2.86		2.65		2.75		2.77
7	53.6	2.04	53.7	2.12	47.6	2.16	53.9	2.00	53.6	2.00
8	75.3	–	75.6	–	75.6	–	75.5	–	75.4	–
9	77.8	–	78.0	–	78.6	–	78.2	–	78.0	–
10	49.6	2.18	49.7	2.22	49.9	2.10	49.9	2.16	49.7	2.16
11	50.4	–	50.8	–	51.0	–	50.9	–	50.3	–
12	25.5	2.00	25.7	2.06	26.3	2.05	26.3	2.02	25.6	1.96
		2.37		2.46		2.50		2.48		2.45
13	36.3	2.42	36.7	2.44	36.4	2.37	36.8	2.38	36.8	2.39
14	89.8	3.46	89.9	3.49	90.2	3.43	89.9	3.44	89.9	3.46
15	44.3	2.05	44.4	2.04	44.8	2.02	44.3	2.03	44.3	2.02
		2.63		2.62		2.39		2.55		2.64
16	82.5	3.39	82.8	3.38	82.9	3.30	82.8	3.33	82.7	3.38
17	56.1	4.28	57.0	4.34	61.5	3.00	59.4	3.98	55.8	4.33
19	49.2	3.47	49.3	3.51	55.7	2.56	50.5	3.52	49.1	3.35
		4.30		4.47		3.49		4.10		4.19
1-OMe	56.2	3.28	56.1	3.27	56.6	3.30	56.1	3.26	56.0	3.27
14-OMe	58.0	3.41	58.0	3.42	57.9	3.40	58.0	3.40	57.9	3.40
16-OMe	56.3	3.32	56.3	3.37	56.2	3.30	56.3	3.30	56.4	3.31
N$\underline{CH_2}$Me	–	–	–	–	49.0	2.52	–	–	–	–
						2.57				
NCH$_2$$\underline{Me}$	–	–	–	–	13.6	1.13	–	–	–	–
OCO	167.5	–	167.4	–	168.0	–	167.3	–	167.5	–
1′	115.0	–	115.1	–	115.1	–	115.4	–	115.1	–
2′	141.9	–	141.9	–	143.1	–	141.8	–	141.8	–
3′	120.3	8.66	120.4	8.68	119.6	8.26	120.3	8.66	120.3	8.67
4′	134.9	7.51	134.8	7.52	134.2	7.38	134.6	7.50	134.8	7.51
5′	122.4	7.02	122.4	7.04	120.8	6.87	122.3	7.02	122.4	7.03
6′	131.0	7.90	131.0	7.93	130.9	7.82	131.0	7.92	131.0	7.92
NH$\underline{C}$O	169.1	–	169.1	–	154.9	–	169.1	–	169.1	–
NHCO$\underline{Me}$	25.6	2.22	25.6	2.23	–	–	25.5	2.20	25.6	2.23
N$\underline{H}$CO	–	10.94	–	10.98		10.61	–	11.03	–	11.00
NCO	165.9	–	155.0	–	–	–	164.1	–	156.8	–
NH$_2$	–	4.91	–	–	–		–	–	–	–
N$\underline{H}$CH(Me)$_2$	–	–	–		–	–	–	–	–	4.48
NH$\underline{CH}$(Me)$_2$	–	–	–	–	–	–	–	–	42.4	3.98
NHCH($\underline{Me}$)$_2$	–	–	–	–	–	–	–	–	23.8	1.17
N($\underline{CH_a}$Me)$_2$	–	–	–	–	–	–	42.5	3.08	–	–
N($\underline{CH_b}$Me)$_2$	–	–	–	–		–	42.5	3.47	–	–
N(CH$_2$$\underline{Me}$)$_2$	–	–	–	–	–	–	13.6	1.11	–	–

* From HSQC data; ** NHPh δ_C, ppm: 139.4 (C-1″), 119.6 (C-2″, 6″), 123.0 (C-3″, 5″), 120.0 (C-4″); δ_H, ppm: 7.32 (H-2″, 6″), 7.28 (H-3″, 5″), 7.03 (H-4″); ***cytisin-12-yl δ_C, ppm: 163.4 (C-2″), 117.5 (C-3″), 138.7 (C-4″), 105.5 (C-5″), 148.7 (C-6″), 34.6 (C-7″), 26.0 (C-8″), 27.4 (C-9″), 49.1 (C-10″), 50.2 (C-11″), 51.3 (C-13″); δ_H, ppm: 6.38 (H-3″), 7.23 (H-4″), 6.09 (H-5″), 3.12 (H-7″), 1.97 (H_a-8″), 2.03 (H_b-8″), 2.59 (H-9″), 3.91 (H_a-10″), 4.16 (H_b-10″), 3.18 (H_a-11″), 4.30 (H_b-11″), 3.18 (H_a-13″), 4.28 (H_b-13″).

TABLE 4. ^{1}H and ^{13}C NMR Spectral Data of Products **18**–**21** ($CDCl_3$, δ, ppm)*

C atom	18**		19***		20****		21*****	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	82.9	3.26	82.7	3.26	82.9	3.23	83.0	3.18
2	26.1	1.79	26.1	1.75	26.0	1.81	25.6	1.42
		2.24		2.24		2.22		2.09
3	31.4	1.86	31.4	1.86	31.5	1.85	31.4	1.88
		2.63		2.63		2.63		2.30
4	83.3	–	83.2	–	83.4	–	82.9	–
5	47.8	2.53	47.8	2.57	47.9	2.54	46.9	2.57
6	24.1	1.77	24.1	1.76	24.1	1.76	23.7	1.62
		2.76		2.77		2.75		2.65
7	54.1	1.97	54.0	1.98	54.1	1.99	53.5	1.89
8	75.3	–	75.3	–	75.4	–	75.4	–
9	78.1	–	78.0	–	78.1	–	78.0	–
10	49.8	2.16	49.8	2.18	49.8	2.16	49.8	2.11
11	50.7	–	50.6	–	50.8	–	50.6	–
12	26.2	2.03	26.2	2.03	26.2	2.02	26.2	2.01
		2.38		2.37		2.37		2.32
13	36.5	2.41	36.4	2.42	36.5	2.40	36.5	2.37
14	89.8	3.44	89.7	3.45	89.8	3.44	89.8	3.41
15	44.3	2.04	44.3	2.04	44.3	2.03	44.3	1.98
		2.52		2.54		2.54		2.48
16	82.8	3.37	82.9	3.34	82.7	3.39	82.8	3.32
17	59.9	3.87	59.7	3.91	59.8	3.90	58.1	3.84
19	50.4	3.54	50.5	3.54	50.4	3.54	51.0	3.31
		4.07		4.09		4.07		3.45
1-OMe	56.1	3.25	56.1	3.25	56.1	3.24	56.4	3.28
14-OMe	58.0	3.40	58.0	3.40	58.0	3.41	58.0	3.38
16-OMe	56.3	3.34	56.3	3.33	56.3	3.36	56.3	3.32
OCO	167.3	–	167.3	–	167.3	–	166.9	–
1′	115.3	–	115.3	–	115.4	–	115.3	–
2′	141.8	–	141.8	–	141.8	–	141.8	–
3′	120.3	8.66	120.3	8.66	120.3	8.66	120.4	8.65
4′	134.6	7.49	134.6	7.50	134.6	7.49	134.6	7.49
5′	122.3	7.01	122.3	7.02	122.3	7.02	122.3	7.03
6′	131.0	7.91	131.0	7.91	131.0	7.91	131.0	7.85
NHCOMe	169.0	–	169.1	–	169.1	–	169.4	–
NHCOMe	25.5	2.19	25.6	2.20	25.5	2.20	25.6	2.29
NHCO	–	11.02	–	11.03	–	11.03	–	11.01
NCO	164.0	–	164.2	–	164.3	–	162.7	–

* From HSQC data; **4-methylpiperazin-1-yl δ_C, ppm: 46.8 (C-2″, 6″), 54.9 (C-3″, 5″), 45.9 (Me); δ_H, ppm: 3.38, 3.49 (H_2-2″), 3.38, 3.49 (H_2-6″), 2.50, 2.57 (H_2-3″), 2.50, 2.57 (H_2-5″), 2.36 (Me); ***morpholin-4-yl δ_C, ppm: 66.9 (C-2″, 6″), 47.8 (C-3″, 5″); δ_H, ppm: 3.69, 3.75 (H_2-2″), 3.69, 3.75 (H_2-6″), 3.26, 3.43 (H_2-3″), 3.26, 3.43 (H_2-5″); ****trimetazidin-1-yl δ_C, ppm: 47.3 (C-2″, 6″), 53.2 (C-3″, 5″), 56.7 ($\underline{C}H_2$Ph), 123.9 (C-1‴), 152.6 (C-2‴), 142.4 (C-3‴), 153.0 (C-4‴), 107.1 (C-5‴), 125.0 (C-6‴), 61.2 (2‴-OMe), 60.8 (3‴-OMe), 56.0 (4‴-OMe); δ_H, ppm: 3.28 (H_a-2″, 6″), 3.42 (H_b-2″, 6″), 2.48 (H_a-3″, 5″), 2.53 (H_b-3″, 5″), 3.48 ($C\underline{H}_2$Ph), 6.64 (H-5‴), 6.98 (H-6‴), 3.87 (2‴-OMe), 3.86 (3‴-OMe), 3.85 (4‴-OMe); *****cytisin-12-yl δ_C, ppm: 163.3 (C-2″), 117.3 (C-3″), 138.4 (C-4″), 105.5 (C-5″), 149.3 (C-6″), 35.4 (C-7″), 26.5 (C-8″), 27.8 (C-9″), 49.0 (C-10″), 51.7 (C-11″), 54.7 (C-13″); δ_H, ppm: 6.48 (H-3″), 7.25 (H-4″), 5.99 (H-5″), 3.00 (H-7″), 1.96 (H_a-8″), 2.02 (H_b-8″), 2.47 (H-9″), 3.84 (H_a-10″), 4.47 (H_b-10″), 3.04 (H_a-11″), 4.01 (H_b-11″), 3.20 (H_a-13″), 4.01 (H_b-13″).

The reactions of **1** and **2** with potassium isocyanate in an AcOH–H_2O mixture produced the corresponding carbamide derivatives **3** and **4** in yields of 54 and 50%, respectively.

The reaction of **1** with phenylisocyanate in DMF was unsuccessful while **2** (DMF, room temp., 24 h) gave **5** in 66% yield.

The presence of the carboxamide on the amine on the aromatic ring of **3** was confirmed by a shift of the resonance in the ^{15}N NMR spectrum for the Ar-NH group from δ_N 63.5 ppm for *N*-deacetyllappaconitine (**1**) to δ_N 102.9 ppm. Its presence on the heterocyclic N atom in **4** and **5** was confirmed by a weak-field shift of the H-17 resonance in the ^1H NMR spectra from δ 3.06 ppm for *N*-20-norlappaconitine (**2**) to δ 4.28 and 4.34 ppm (for **4** and **5**, respectively) and a shift of the N-20 resonance in the ^{15}N NMR spectra of **4** and **5** to δ_N 94.1 and 93.6 ppm, respectively, as compared to the starting resonance of **2** at δ_N 38.0 ppm.

Derivatives **6–15** (78–94% yields) were prepared using triphosgene followed by treatment with amines to produce the carbamide derivatives on the aromatic amine of **1**; derivatives **16–21** (46–81%), by using **2** as starting material.

Resonances of C atoms and the protons corresponding to them in ^1H and ^{13}C NMR spectra were completely assigned based on 2D NMR experiments for all products **3–21** (Tables 1–4). In all instances, additional resonances as compared to **1** and **2** appeared for the carbamide moiety in the range δ 152.8–165.9 ppm in the ^{13}C NMR spectra.

EXPERIMENTAL

Mass spectra using chemical ionization at atmospheric pressure (APCI) were measured in an LCMS-2010 EV quadrupole LC-MS (Shimadzu). ^1H, ^{13}C NMR, and ^{15}N NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III-500 pulsed spectrometer [500.13 MHz (^1H), 125.76 MHz (^{13}C)] with TMS internal standard and at 50.67 MHz (^{15}N) with liquid ammonia external digital standard. Methods for recording NMR spectra embedded in the spectrometer operating system (COSY, HSQC, HMBC, NOESY, ^{13}C-dept 135, dept 90) with full suppression of protons were used for accurate assignment of resonances in ^1H and ^{13}C NMR spectra. Chemical shifts (CSs) of protons were determined from 2D HSQC spectra; CSs of N atoms, from ^1H–^{15}N HMBC spectra. TLC monitoring used C_6H_6–MeOH (80:20 vol%). The spectral part of the research utilized equipment at the Khimiya CCU, UfIC, UFRC, RAS, and the Agidel′ RCCU, UFRC, RAS.

General Method for Preparing Carbamide Derivatives 3 and 4. A solution of *N*-deacetyllappaconitine (**1**) or *N*-20-norlappaconitine (**2**) (0.001 mol) in a mixture of AcOH (0.4 mL) and H_2O (4 mL) was treated slowly dropwise with a solution of KNCO (0.004 mol) in H_2O (8 mL). The mixture was stirred for 3 h at room temperature, made basic with saturated Na_2CO_3 solution to pH 9, and extracted with $CHCl_3$ (4 × 20 mL). The solvent was distilled off. The product was purified by column chromatography (CC) over SiO_2 using C_6H_6–MeOH (1–3 vol%).

***N*-Deacetyllappaconitine-*N*-carboxamide (3)**. Elution by C_6H_6–MeOH (1%) isolated starting **1** (0.093 g, 83% conversion); by C_6H_6–MeOH (2%), product **3** (0.262 g), yield 54% considering conversion; mp 152–153°C. Mass spectrum (APCI), *m/z* 586 $[M + H]^+$ (calcd for $C_{31}H_{44}N_3O_8$, 586.312). ^{15}N NMR (δ, ppm): 42.4 (N-20), 77.1 (Ar-NHC(O)$\underline{N}H_2$), 102.9 (Ar-NH).

***N*-20-Norlappaconitine-*N*-20-carboxamide (4)**. Elution by C_6H_6–MeOH (2%) isolated product **4** (0.108 g), 50% yield; mp 140–141°C. Mass spectrum (APCI), *m/z* 600 $[M + H]^+$ (calcd for $C_{31}H_{42}N_3O_9$, 600.291). ^{15}N NMR (δ, ppm): 73.1 ($C(O)NH_2$), 94.1 (N-20), 128.4 (Ar-NH).

***N*-20-Norlappaconitine-*N*-20-phenylcarboxamide (5)**. A mixture of *N*-20-norlappaconitine (**2**, 0.222 g, 0.4 mmol) and phenylisocyanate (0.13 mL, 1.2 mmol) was dissolved in DMF (3 mL) and stirred for 24 h at room temperature. The solvent was distilled off. The product was purified by column chromatography (CC) over SiO_2 using C_6H_6–MeOH (1–3 vol%). Elution by C_6H_6–MeOH (2%) isolated product **5** (0.178 g), 66% yield; mp 126–127°C. Mass spectrum (APCI), *m/z* 676 $[M + H]^+$ (calcd for $C_{37}H_{46}N_3O_9$, 676.323). ^{15}N NMR (δ, ppm): 93.6 (N-20), 104.6 (C(O)NH), 128.4 (Ar-NH).

General Method for Preparing Carbamide Derivatives 6–21 [13]. A solution of triphosgene (0.37 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added slowly dropwise with stirring to a solution of **1** or **2** (1 mmol) and DIPEA (1.1 mmol) in CH_2Cl_2 (3.5 mL), held for 15 min after the addition, and treated with a solution of the appropriate amine (1 mmol) (aniline, diethylamine, isopropylamine, *N*-methylpiperazine, 4-benzylpiperidine, morpholine, pyrrolidine, benzylamine, trimetazidine, cytisine) and DIPEA (1.1 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 2–3 h (TLC monitoring), treated with CH_2Cl_2 (10 mL), rinsed with Na_2CO_3 solution, dried over Na_2SO_4, and evaporated. The product was purified by CC over SiO_2 using C_6H_6–MeOH (1–3 vol%).

***N*-Phenyl-*N*-deacetyllappaconitinecarboxamide (6)**. Elution by C_6H_6–MeOH (2%) isolated product **6** (0.595 g), 90% yield; mp 136–137°C. Mass spectrum (APCI), *m/z* 662 $[M + H]^+$ (calcd for $C_{37}H_{48}N_3O_8$, 662.343). ^{15}N NMR (δ, ppm): 41.9 (N-20), 105.6 (OC(O)-Ar-NH), 109.7 (NH-Ar).

***N′*,*N′*-Diethyl-*N*-deacetyllappaconitinecarboxamide (7)**. Elution by C_6H_6–MeOH (2%) isolated product **7** (0.497 g), 78% yield; mp 102–103°C. Mass spectrum (APCI), *m/z* 642 $[M + H]^+$ (calcd for $C_{35}H_{52}N_3O_8$, 642.375). ^{15}N NMR (δ, ppm): 41.8 (N-20), 100.8 (Ar-NH), 100.2 ($N(Et)_2$).

***N′-iso*-Propyl-*N*-deacetyllappaconitinecarboxamide (8)**. Elution by C_6H_6–MeOH (2%) isolated product **8** (0.593 g), 94% yield; mp 138–139°C. Mass spectrum (APCI), *m/z* 628 $[M + H]^+$ (calcd for $C_{34}H_{50}N_3O_8$, 628.359). ^{15}N NMR (δ, ppm): 41.9 (N-20), 102.9 (Ar-NH), 106.8 (NH-*i*-Pr).

Lappaconine-4-[2-(4-methylpiperazine-1-carboxamido)]benzoate (9). Elution by C_6H_6–MeOH (2%) isolated product **9** (0.580 g), 87% yield; mp 114–115°C. Mass spectrum (APCI), *m/z* 669 $[M + H]^+$ (calcd for $C_{36}H_{53}N_4O_8$, 669.386). ^{15}N NMR (δ, ppm): 37.8 ($N(C_2H_4)_2\underline{N}$-CH_3), 41.2 (N-20), 86.7 ($\underline{N}(C_2H_4)_2$N-CH_3), 100.9 (Ar-NH).

Lappaconine-4-[2-(4-benzylpiperidine-1-carboxamido)]benzoate (10). Elution by C_6H_6–MeOH (1%) isolated product **10** (0.688 g), 93% yield; mp 104–105°C. Mass spectrum (APCI), *m/z* 744 $[M + H]^+$ (calcd for $C_{43}H_{58}N_3O_8$, 744.422). ^{15}N NMR (δ, ppm): 42.6 (N-20), 101.7 (Ar-NH), 93.5 ($N(C_2H_4)_2$CH-Bn).

Lappaconine-4-[2-(morpholine-4-carboxamido)]benzoate (11). Elution by C_6H_6–MeOH (1.5%) isolated product **11** (0.603 g), 92% yield; mp 110–111°C. Mass spectrum (APCI), *m/z* 656 $[M + H]^+$ (calcd for $C_{35}H_{50}N_3O_9$, 656.354). ^{15}N NMR (δ, ppm): 41.8 (N-20), 86.4 ($N(C_2H_4)_2O$), 101.2 (Ar-NH).

Lappaconine-4-[2-(pyrrolidine-1-carboxamido)]benzoate (12). Elution by C_6H_6–MeOH (2%) isolated product **12** (0.575 g), 90% yield; mp 131–132°C. Mass spectrum (APCI), *m/z* 640 $[M + H]^+$ (calcd for $C_{35}H_{50}N_3O_8$, 640.359). ^{15}N NMR (δ, ppm): 41.7 (N-20), 104.2 (Ar-NH), 93.0 ($N(C_2H_4)_2$).

***N′*-Benzyl-*N*-deacetyllappaconitinecarboxamide (13)**. Elution by C_6H_6–MeOH (1.5%) isolated product **13** (0.562 g), 83% yield; mp 112–113°C. Mass spectrum (APCI), *m/z* 676 $[M + H]^+$ (calcd for $C_{38}H_{50}N_3O_8$, 676.359). ^{15}N NMR (δ, ppm): 42.2 (N-20), 91.2 (NH-Bn), 102.8 (Ar-NH).

Lappaconine-4-[2-(trimetazidine-1-carboxamido)]benzoate (14). Elution by C_6H_6–MeOH (1.5%) isolated product **14** (0.784 g), 94% yield; mp 101–102°C. Mass spectrum (APCI), *m/z* 835 $[M + H]^+$ (calcd for $C_{45}H_{63}N_4O_{11}$, 835.449). ^{15}N NMR (δ, ppm): 41.7 (N-20), 101.7 (Ar-NH), 89.4 ($C(O)\underline{N}(C_2H_4)_2N$), 49.0 ($C(O)N(C_2H_4)_2\underline{N}$).

Lappaconine-4-[2-(cytisine-12-carboxamido)]benzoate (15). Elution by C_6H_6–MeOH (2%) isolated product **15** (0.697 g), 92% yield; mp 148–149°C. Mass spectrum (APCI), *m/z* 759 $[M + H]^+$ (calcd for $C_{42}H_{55}N_4O_9$, 759.396). ^{15}N NMR (δ, ppm): 41.9 (N-20), 101.5 (Ar-NH), 82.1 (N-12″), 173.9 (N-1″).

Diethylcarbamoyl-*N*-20-norlappaconitine (16). Elution by C_6H_6–MeOH (1%) isolated product **16** (0.452 g), 69% yield; mp 195–196°C. Mass spectrum (APCI), *m/z* 656 $[M + H]^+$ (calcd for $C_{35}H_{50}N_3O_9$, 656.354). ^{15}N NMR (δ, ppm): 90.6 (N-20), 91.1 ($N(Et)_2$), 128.9 (Ar-NH).

Isopropylcarbamoyl-*N*-20-norlappaconitine (17). Elution by C_6H_6–MeOH (2%) isolated product **17** (0.487 g), 76% yield; mp 115–116°C. Mass spectrum (APCI), *m/z* 642 $[M + H]^+$ (calcd for $C_{34}H_{48}N_3O_9$, 642.338). ^{15}N NMR (δ, ppm): 89.5 (N-20), 102.1 (NH-*i*-Pr), 128.9 (Ar-NH).

***N*-20-Norlappaconitin-20-yl(4-methylpiperazin-1-yl)methanone (18)**. Elution by C_6H_6–MeOH (3%) isolated product **18** (0.550 g), 81% yield; mp 132–133°C. Mass spectrum (APCI), *m/z* 683 $[M + H]^+$ (calcd for $C_{36}H_{51}N_4O_9$, 683.365). ^{15}N NMR (δ, ppm): 38.4 ($N(C_2H_4)_2\underline{N}$-CH_3), 79.9 ($\underline{N}(C_2H_4)_2$N-CH_3), 91.3 (N-20), 128.9 (Ar-NH).

***N*-20-Norlappaconitin-20-yl(4-morpholin-4-yl)methanone (19)**. Elution by C_6H_6–MeOH (2%) isolated product **19** (0.534 g), 80% yield; mp 142–143°C. Mass spectrum (APCI), *m/z* 670 $[M + H]^+$ (calcd for $C_{35}H_{48}N_3O_{10}$, 670.333). ^{15}N NMR (δ, ppm): 79.2 ($N(C_2H_4)_2O$), 91.8 (N-20), 128.9 (Ar-NH).

***N*-20-Norlappaconitin-20-yl(trimetazidin-1-yl)methanone (20)**. Elution by C_6H_6–MeOH (1.5%) isolated product **20** (0.622 g), 73% yield; mp 95–96°C. Mass spectrum (APCI), *m/z* 849 $[M + H]^+$ (calcd for $C_{45}H_{61}N_4O_{12}$, 849.428). ^{15}N NMR (δ, ppm): 49.3 ($C(O)N(C_2H_4)_2\underline{N}$), 81.8 ($C(O)\underline{N}(C_2H_4)_2N$), 91.0 (N-20), 128.8 (Ar-NH).

***N*-20-Norlappaconitin-20-yl(cytisin-12-yl)methanone (21)**. Elution by C_6H_6–MeOH (2%) isolated product **21** (0.358 g), 46% yield; mp 178–179°C. Mass spectrum (APCI), *m/z* 773 $[M + H]^+$ (calcd for $C_{42}H_{53}N_4O_{10}$, 773.376). ^{15}N NMR (δ, ppm): 90.0 (N-20), 129.2 (Ar-NH), 137.1 (N-12''), 175.8 (N-1'').

ACKNOWLEDGMENT

The work was supported on topic No. 122031400260-7 "Synthesis of biologically active compounds based on natural compounds. Creation of ecologically clean materials and technologies."

REFERENCES

1. A. K. Ghosh and M. Brindisi, *J. Med. Chem.*, **63**, 2751 (2020).
2. S. A. Ross and S. W. Pelletier, *Heterocycles*, **32** (7), 1307 (1991).
3. N. V. Malykhina, S. A. Osadchii, M. M. Shakirov, E. E. Shul′ts, and G. A. Tolstikov, *Dokl. Chem.*, **394**, 16 (2004).
4. T. M. Gabbasov, E. M. Tsyrlina, and S. G. Yunusova, *Chem. Nat. Compd.*, **54**, 947 (2018).
5. T. M. Gabbasov, E. M. Tsyrlina, L. V. Spirikhin, and M. S. Yunusov, *Chem. Nat. Compd.*, **54**, 951 (2018).
6. T. M. Gabbasov, E. M. Tsyrlina, and M. S. Yunusov, *Chem. Nat. Compd.*, **57**, 594 (2021).
7. Liang Chengyuan, Tian Danni, Jia Minyi, Sun Han, Ju Weihui, and Pei Shaomeng, CN Patent No. 106632247A, May 10, 2017.
8. V. E. Romanov, E. E. Shul′ts, and G. A. Tolstikov, *Chem. Nat. Compd.*, **44**, 346 (2008).
9. N. A. Pankrushina, I. A. Nikitina, N. V. Anferova, S. A. Osadchii, M. M. Shakirov, E. E. Shults, and G. A. Tolstikov, *Russ. Chem. Bull.*, **52** (11), 2490 (2003).
10. L. Pang, C. Y. Li, G. H. Gong, and Z. S. Quan, *Acta Pharm. Sin. B*, **10** (4), 628 (2020).
11. T. M. Gabbasov, I. B. Chernikova, E. M. Tsyrlina, and M. S. Yunusov, *Chem. Nat. Compd.*, **57**, 727 (2021).
12. J. L. Wang, X. L. Shen, Q. H. Chen, G. Qi, W. Wang, and F. P. Wang, *Chem. Pharm. Bull.*, **57** (8), 801 (2009).
13. P. Majer and R. S. Randad, *J. Org. Chem.*, **59**, 1937 (1994).