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SYNTHESIS AND STRUCTURE ELUCIDATION OF 1-ARYL-SUBSTITUTED TETRAHYDROPYRIDONE DERIVATIVES

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*A series of 1-aryl-1,4,5,6-tetrahydro-4(1H)-pyridones having substituents in 2,3- and 2,3,5-positions was prepared from N-aryl-β-alanines and ethyl acetoacetate or 2,4-pentanedione. Twelve tentative biologically active compounds were identified by the combination of ^{1}H, ^{13}C and $^{1}H/^{13}C$ NMR spectroscopy. The extensive interest has been focused on the influence of substituents as well as on the number, attachment position, and the nature of the substituents. The unknown shielding of the heterocyclic ring on the aromatic carbon atoms was determined and the averaged chemical shift increments were successfully used for the assignment of the aromatic moiety of the studied compounds. The presence of two chiral elements in compounds **16, 17, 20-21** resulted in the mixture of diastereomers and double sets of the resonances in NMR spectra.*

Keywords: N-aryl-β-alanines, tetrahydropyridones, NMR spectroscopy.

N-Aryl-β-alanines and their derivatives possess a wide spectrum of biological activity [1-3]. The compounds under study are intermediate products in the synthesis of azetidinone, dihydroquinolone, benzodiazepine, imidazole, and dihydropyrimidinedione derivatives [4-8].

In this paper we report a synthesis of 1-aryl-substituted tetrahydropyridones from N-aryl-β-alanines.

N-Aryl-β-alanines **1**-**12** were used as starting compounds. These compounds were obtained from the corresponding arylamines and unsaturated acids by the method previously developed in our laboratory [5, 7].

1-Aryl-3-ethoxycarbonyl-1,4,5,6-tetrahydro-4(1H)-pyridones **13**-**21** and 3-acetyl-1-aryl-1,4,5,6-tetrahydro-4(1H)-pyridones **22**-**24** were prepared from the corresponding N-aryl-β-alanines and ethyl acetoacetate or 2,4-pentanedione in refluxing toluene in the presence of a catalytic amount of hydrochloric acid. It is possible that condensation of NH group in β-alanine with 1,3-diketo compound takes place first, and then the intermediate compound undergoes cyclization resulting in the respective hydropyridone **13**-**24**. The yield of the target compounds was not high, however the formed products were crystalline substances and were obtained from the reaction mixture easily.

The products obtained were analyzed by NMR spectroscopy. The NMR spectral assignments have been made by the comparison of the spectra between themselves and with the related fragments, assuming the validity of the additivity of the substituent effects, their general characteristics and the signal intensities [9-10].

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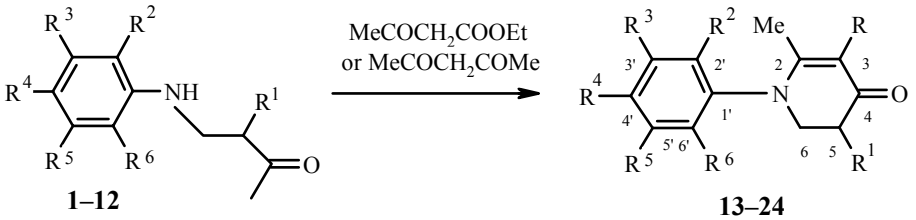

1-8, **13-20** R = COOEt, **9-12**, **21-24** R = COMe; **1**, **13** $R^1 = R^2 = R^3 = R^5 = R^6 = H$, $R^4 = OMe$;
2, **14** $R^1 = R^3 = R^5 = R^6 = H$, $R^2 = R^4 = Me$; **3**, **15** $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = R^6 = Me$;
4, **16** $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = H$; **5**, **17** $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = R^6 = H$;
6, **18** $R^1 = R^3 = R^5 = Me$, $R^2 = R^4 = R^6 = H$; **7**, **19** $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = R^6 = H$;
8, **20** $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = R^6 = H$; **9**, **21** $R^1 = R^2 = R^5 = Me$, $R^3 = R^4 = R^6 = H$;
10, **22** $R^1 = R^2 = R^3 = R^5 = R^6 = H$, $R^4 = Br$; **11**, **23** $R^1 = R^3 = R^4 = R^5 = R^6 = H$, $R^2 = Me$;
1, **24** $R^1 = R^3 = R^4 = R^6 = H$, $R^2 = R^5 = Me$

Examination of ^{13}C NMR spectra was complicated due to the lack of published information about the influence of the heterocyclic ring on the aromatic carbons. Therefore, this unknown influence was determined during the present investigation. The ^{13}C NMR spectra of compounds **13**, **19**, and **20** were potentially suitable for detection of the desirable influence. It was derived from the spectral data of the aromatic moiety of these compounds taking into account the influence of OMe, Me and Br as *para*-substituents on the aromatic carbon atoms, signal intensities, and general features of the additivity effects of substituents. Averaged chemical shift increments induced by the heterocyclic ring on the aromatic carbon atoms are shown in Table 1. The increments obtained were further used successfully for the assignment of the resonances of the aromatic ring moiety of other aryl-substituted compounds studied.

In the present work, $^1H/^{13}C$ 2D (HETCOR) NMR experiments [11, 12] were used to test, improve and extend the ^1H and ^{13}C NMR assignments of the resonances of tetrahydropyridone derivatives under study. The $^1H/^{13}C$ 2D NMR spectrum of compound **14** is presented in Fig. 1. The analysis was started from already known assignments. The correlations of this experiment confirmed the 1D assignments and exhibited some unexpectedness as well. Two of the cross-peaks of the methyl group resonances were pointed evidently to the nonlinear relationship of the ^1H and ^{13}C NMR spectral data. The resonance of the more shielded methyl group carbon atom located in C-2' position was correlated with the resonance of the more deshielded protons, although the resonance of the more deshielded methyl group carbon atom in position C-2 coincided with the resonance of the more shielded protons. The assignments of the corresponding resonances of other hydropyridone derivatives were evaluated with no difficulty.

TABLE 1. ^{13}C NMR Chemical Shift Increments (Δδ) Induced by the Heterocyclic Group on the Aromatic Carbon Atoms

Compounds	Δδ, ppm			
	C-*i*	C-*o*	C-*m*	C-*p*
13	15.90	-1.61	0.63	-1.45
19	17.16	-1.15	1.16	-0.50
22	16.17, 16.21*	-1.12, -1.03*	0.95, 1.04*	-1.66, -1.54*
Average values	16.36	-1.23	0.95	-1.29

* The data from ^{13}C NMR spectra, obtained using Bruker DRX 500 spectrometer operating at 125 MHz.

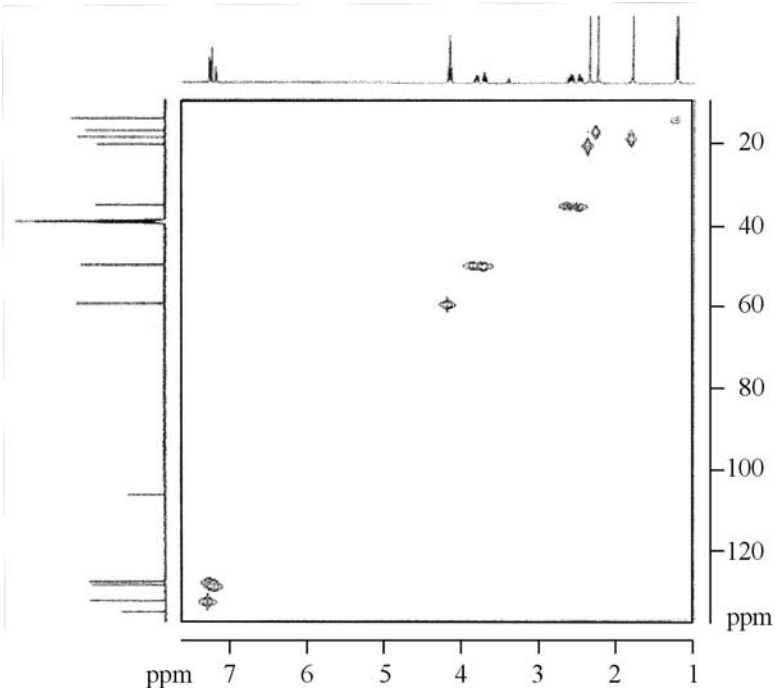

Fig. 1. HETCOR spectrum of compound **14** by Bruker DRX 500, at 500.130 MHz in $CDCl_3$.

All resonances of the compounds studied have been assigned unambiguously. The ^{13}C and ^{1}H NMR spectral data for the compounds **13-24** under study are presented in Tables 2-4.

The resonances of the heterocyclic ring moiety carbon atoms revealed the characteristic effects due to the influence of the present substituents. The resonances of C-2 atoms in compounds **22-24** were shifted downfield by 4.5 ppm in respect to those in **13-21**, while their chemical shifts predicted by the additivity rule showed the opposite trend. The signals of C-3 atoms in both groups of compounds were found to resonate according to the usual substituent effects.

The methyl group attached to position-5 in compounds **16-21** caused about 3-4 ppm downfield shift for the C-4 atoms, while the β-influence of methyl group on the C-6 atoms reached about 6 ppm. It was interesting to notice that the chiral centre at C-5 arose due to the methyl group in the compounds mentioned above, consequently the ABX spin system of hydrogens attached to C-6 and C-5 atoms, was present in ^{1}H NMR spectra. ^{1}H NMR studies of the tentative hydropyridones provided a part of the reliable and necessary information on their structures.

On the other hand, the methyl substituents attached to the benzene ring afforded valuable information about structural features of the molecules of the studied compounds. Compounds **16**, **17**, **20**, **21** possessing the asymmetrical axis due to the asymmetrical substituted benzene ring existed as diastereoisomers [13] and were detected as two separate isomers in their NMR spectra. Two sets of the resonances were observed in the NMR spectra of the compounds mentioned above. The intensities of the pairs of resonances measured from ^{1}H spectra showed the ratio of 4:6.

Analysis of NMR spectra showed that there were no double sets of the resonances in compounds **14**, **23**, **24**, which possess asymmetrical substituted benzene ring but have no 5-methyl substituent in heterocycle ring. Similar effect was observed for compounds **16**, **17**, which possess 5-methyl substituent in the heterocycle ring, but have symmetrically substituted benzene ring. Moreover, compounds **13**, **15**, **20**, owing to the presence of the symmetrically substituted benzene ring and absence of the 5-methyl substituent in the heterocycle ring, had no double resonances.

TABLE 2. ^{13}C NMR Spectral Data of Compounds **13-18**

Carbon	Chemical shifts, δ, ppm					
	13	**14**	**15**	**16**	**17**	**18**
C-2	161.83	162.38	162.46	161.51, 161.28	163.61, 163.47	162.54
C-3	106.74	106.10	105.52	105.44, 105.37	106.02	106.70
C-4	186.55	186.55	186.26	189.46, 189.25	190.36, 190.25	190.52
C-5	35.43	35.43	35.34	37.79, 37.63	38.49, 38.40	38.75
C-6	51.35	50.08	48.48	55.99, 55.68	57.28, 57.08	58.06
C-1'	136.69	140.03	138.68	142.38, 142.27	142.81, 142.75	144.05
C-2'	127.93	138.02	134.69	134.98, 134.74	133.7, 133.64	124.11
C-3'	114.71	131.82	129.44	131.32, 131.25	139.25, 139.20	139.87
C-4'	158.45	134.49	137.73	128.55, 128.46	130.17, 130.11	129.75
C-5'	114.71	128.02	129.44	127.51, 127.44	127.08, 127.00	139.87
C-6'	127.93	127.21	134.69	127.90, 127.18	125.15, 124.44	124.11
2-CH_3	19.20	18.81	17.95	18.65,18.60, 18.50,18.45	19.33, 19.17	
$COOCH_2CH_3$	167.16; 59.48; 14.10	167.16; 59.52; 14.18	167.02; 59.40; 14.12	167.25; 59.49,58.47; 14.12,14.08	168.03, 167.99; 60.49; 14.41	168.06; 60.16; 14.63
5-CH_3				13.05,12.99, 12.36,12.31	12.88, 13.19	12.99
2'-CH_3		17.13	17.30	17.24,17.21, 17.13,17.17	14.21, 14.25	
3'-CH_3					20.48, 20.36	21.20
4'-CH_3 (OCH_3)	55.35	20.57	20.41			
5'-CH_3						21.20
6'-CH_3			17.30			

More detailed investigations of the structural features of studied compounds **13-24** were carried out by the combination of NMR spectral and computer molecular modeling data analysis. Molecular modeling was based on CS MM2 5.0 and CS MOPAC 5.0 by using molecular mechanics and semiempirical quantum-mechanical methods, respectively. The geometry of the molecules of the compounds under studies was optimized to the global minimum of steric energy summary. Molecular modeling analysis showed that the sterical arrangement of the optimized molecular models changed due to the different methylsubstitution of both rings of molecules of the compounds under studies. Investigations on rotation of benzene and heterocycle rings around the (C-1')–(N-1) bond showed significant energetic barriers. The largest value of the hindered rotation barrier was estimated for compounds **16**, **17**, **20**, **21**.

TABLE 3. ^{13}C NMR Spectral Data of Compounds **19-24**

Carbon	Chemical shifts, δ, ppm					
	19	**20**	**21**	**22**	**23**	**24**
C-2	161.16	162.06, 161.85	162.64, 162.41	165.69	166.96	167.24
C-3	108.05	105.70	106.40	114.00	113.01	112.93
C-4	189.88	189.75, 189.57	190.54, 190.35	189.29	189.11	189.09
C-5	39.42	38.56, 38.14	38.75, 38.59	35.73	35.75	35.75
C-6	58.69	56.45, 56.14	57.02, 56.70	51.05	49.88	49.94
C-1'	142.86	140.27, 140.17	143.28, 143.17	143.09	142.51	140.04
C-2'	127.35	138.29, 138.20	132.62, 132.41	128.98	134.37	133.92
C-3'	130.96	132.07	132.14, 132.08	132.65	131.34	131.80
C-4'	138.30	134.90, 134.66	130.23, 130.24	121.04	128.72	128.04
C-5'	130.96	128.37, 128.28	138.03, 137.97	132.65	127.04	138.17
C-6'	127.35	127.94, 127.22	129.23, 128.47	128.98	127.56	126.72
2-CH_3	19.24	18.96, 18.81	19.54, 19.39	20.12	19.71	19.73
$COOCH_2CH_3$	168.11; 60.16; 14.63	167.63; 59.80; 14.47	168.36; 60.42; 5.03			
$COCH_3$				198.52; 32.33	197.89; 32.33	197.94; 32.32
5-CH_3			13.87, 13.29			
2'-CH_3		13.39, 12.75	17.70, 17.59		17.06	16.98
4'-CH_3	20.96	17.50, 17.38				
5'-CH_3			21.16			20.48

TABLE 4. ^{1}H NMR Spectra of Compounds **13-24**

Com-pound	Chemical shifts, δ, ppm (coupling constants, *J*, Hz)
1	2
13	1.20 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.85 (3H, s, 2-CH_3); 2.42-2.53 (2H, m, $COCH_2$); 3.80 (3H, s, OCH_3); 3.71-3.86 (2H, m, NCH_2); 4.15 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 6.95-7.35 (4H, m, Ar)
14	1.15 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.75 (3H, s, 2-CH_3); 2.18 (3H, s, 2'-CH_3); 2.27 (3H, s, 4'-CH_3); 2.36-2.58 (2H, m, $COCH_2$); 3.58-3.80 (2H, m, NCH_2); 4.08 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.08-7.20 (3H, m, Ar)
15	1.20 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.75 (3H, s, 2-CH_3); 2.18 (6H, s, 2',6'-CH_3); 2.25 (3H, s, 4'-CH_3); 2.44-2.53 (2H, m, $COCH_2$); 3.60-3.75 (2H, m, NCH_2); 4.10 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.00 (2H, s, Ar-3', 5')
16	1.00, 1.04 (3H, 2d, *J* = 6.8, 5-CH_3); 1.15 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.74 (3H, s, 2-CH_3); 2.23, 2.28 (3H, 2s, 2'-CH_3); 2.55-2.67 (1H, m, COCH); 3.50-3.72 (2H, m, NCH_2); 4.06 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.26-7.46 (4H, m, Ar)
17	1.24 (3H, d, *J* = 6.8, 5-CH_3); 1.39 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.96 and 1.98 (3H, 2s, 2-CH_3); 2.19 and 2.25 (3H, 2s, 2'-CH_3); 2.33 and 2.34 (3H, 2s, 3'-CH_3); 2.60-2.82 (1H, m, COCH); 3.42-3.70 (2H, m, CH_2N); 4.30 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 6.90-7.30 (3H, m, Ar)

TABLE 4 (continued)

1	2
18	1.18 (3H, d, *J* = 6.9, 5-CH_3); 1.34 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 2.00 (3H, s, 2-CH_3); 2.34 (6H, s, 3',5'-Ar); 2.53-2.72 (1H, m, COCH); 3.53-3.83 (3H, m, NCH_2); 4.28 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 6.77 (2H, s, 2',6'-CHAr); 6.99 (H, s, 4'-CHAr)
19	1.02 (3H, d, *J* = 6.9, 5-CH_3); 1.15 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.74 (3H, s, 2-CH_3); 2.23 (3H, s, 4'-CH_3); 2.40-2.80 (1H, m, COCH); 3.56-4.00 (2H, m, NCH_2); 4.06 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.21-7.53 (4H, m, Ar)
20	1.02 and 1.05 (3H, 2d, *J* = 6.9, 5-CH_3); 1.18 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.76 and 1.77 (3H, 2s, 2-CH_3); 2.19-2.24 (3H, 2s, 2'-CH_3); 2.32 (3H, s, 4'-CH_3); 2.49-2.70 (1H, m, COCH); 3.40-3.70 (2H, m, NCH_2); 4.09 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.10-7.30 (3H, m, Ar)
21	0.99 and 1.03 (3H, 2d, *J* = 6.9, 5-CH_3); 1.18 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 1.74 and 1.75 (3H, 2s, 2-CH_3); 2.14 and 2.19 (3H, 2s, 2'-CH_3); 2.47 and 2.49 (3H, 2s, 5'-CH_3); 2.45-2.53 (1H, m, COCH); 3.40-3.75 (2H, m, NCH_2); 4.06 (2H, q, *J* = 7.1, $COO\underline{CH_2}CH_3$); 7.00-7.30 (3H, m, Ar)
22	1.95 (3H, s, 2-CH_3); 2.35 (3H, s, $COCH_3$); 2.50-2.65 (2H, m, $COCH_2$); 3.82-3.93 (2H, m, NCH_2); 7.35-7.80 (4H, m, Ar)
23	1.90 (3H, s, 2-CH_3); 2.25 (3H, s, 2'-CH_3); 2.35 (3H, s, $COCH_3$); 2.45- 2.73 (2H, m, $COCH_2$); 3.66-3.90 (2H, m, NCH_2); 7.28-7.47 (4H, m, Ar)
24	1.90 (3H, s, 2-CH_3); 2.25 (3H, s, 2'-CH_3); 2.27 (3H, s, 5'-CH_3); 2.35 (3H, s, $COCH_3$); 2.40-2.68 (2H, m, $COCH_2$); 3.61-3.86 (2H, m, NCH_2); 7.08-7.22 (3H, m, Ar)

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded as solutions of 50 mg of each compound in 0.7 ml of DMSO-d_6 (**13-16**, **20-24**), $CDCl_3$ (**17**, **18**), acetone-d_6 (**19**). Chemical shifts are reported as δ (ppm) downfield from TMS. Samples were spun in 5 mm o.d. tubes at ambient temperature. ^{13}C NMR spectra were obtained at 50 MHz on a Varian Gemini-200 spectrometer and at 63 MHz on AC 250-P Bruker spectrometer operating in Fourier transform mode. $^1H/^{13}C$ 2D spectra were recorded on a Bruker DRX 500 spectrometer operating at 500 MHz (^1H) and 125 MHz (^{13}C), using standard software for data acquisition, processing and plotting.

Preparation of 1-Aryl-3-ethoxycarbonyl-1,4,5,6-tetrahydro-4(1H)-pyridones 13-21 and 3-Acetyl-1-aryl-1,4,5,6-tetrahydro-4(1H)-pyridones 22-24. To a mixture of corresponding N-aryl-β-alanine **1-12** (0.1 mol) and ethyl acetoacetate (or 2,4-pentanedione) (40 ml) in toluene (50 ml), concentrated hydrochloric acid (5 ml) were added and the mixture was heated under reflux for 15 h removing liberated water by Dean–Stark trap. The solvents were removed in vacuo, the residue suspended in 5 % Na_2CO_3 (150 ml) and extracted with diethyl ether (4 × 100 ml). The solvent was removed in vacuo, the oil was recrystallized from corresponding solvent to afford a white solid, or separated by flash chromatography.

3-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-methyl-1,4,5,6-tetrahydro-4(1H)-pyridone (13): mp 145-146°C (hexane), yield 11.5%. Found, %: C 66.71; H 6.43; N 4.69. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

1-(2,4-Dimethylphenyl)-3-ethoxycarbonyl-2-methyl-1,4,5,6-tetrahydro-4(1H)-pyridone (14): mp 122-123°C (hexane), yield 12.3%. Found, %: C 71.21; H 7.15; N 4.64. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87.

3-Ethoxycarbonyl-2-methyl-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (15): mp 95-97°C, yield 4.5% after purification by column chromatography (diethyl ether). Merk Kieselgel l60 silica gel (15-40 μm) was used for column chromatography. Found, %: C 71.56; H 7.78; N 4.46. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

3-Ethoxycarbonyl-2,5-dimethyl-1-(2-methylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (16): mp 90-91°C (heptane), yield 10.7%. Found, %: C 71.35; H 7.80; N 4.75. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87.

1-(2,3-Dimethylphenyl)-3-ethoxycarbonyl-2,5-dimethyl-1,4,5,6-tetrahydro-4(1H)-pyridone (17): mp 109-110°C (ethanol), yield 17.7%. Found, %: C 71.55; H 7.42; N 4.41. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

1-(3,5-Dimethylphenyl)-3-ethoxycarbonyl-2,5-dimethyl-1,4,5,6-tetrahydro-4(1H)-pyridone (18): mp 111-112°C (ethanol), yield 6.6%. Found, %: C 71.46; H 7.82; N 4.47. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

3-Ethoxycarbonyl-2,5-dimethyl-1-(4-methylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (19): mp 80-82°C (hexane), yield 27.7%. Found, %: C 71.53; H 7.85; N 4.55. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87.

1-(2,4-Dimethylphenyl)-3-ethoxycarbonyl-2,5-dimethyl-1,4,5,6-tetrahydro-4(1H)-pyridone (20): mp 102-103°C (heptane), yield 14.7%. Found, %: C 71.55; H 7.42; N 4.46. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

1-(2,5-Dimethylphenyl)-3-ethoxycarbonyl-2,5-dimethyl-1,4,5,6-tetrahydro-4(1H)-pyridone (21): mp 89-90°C (heptane), yield 14.7%. Found, %: C 71.46; H 7.21; N 4.51. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

3-Acetyl-1-(4-bromophenyl)-2-methyl-1,4,5,6-tetrahydro-4(1H)-pyridone (22): mp 73-75°C (ethanol), yield 18.7%. Found, %: C 54.33; H 4.36; N 4.78. $C_{14}H_{14}BrNO_2$. Calculated, %: C 54.56; H 4.58; N 4.55.

3-Acetyl-2-methyl-1-(2-methylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (23): mp 49-51°C (heptane), yield 54.9%. Found, %: C 74.32; H 6.89; N 5.87. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76.

3-Acetyl-2-methyl-1-(2,5-dimethylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (24): mp 67-68°C (heptane), yield 26.2%. Found, %: C 74.49; H 7.71; N 5.27. $C_{16}H_{19}NO_2$. Calculated, %: C 74.68; H 7.44; N 5.44.

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