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INTERACTION OF 5-ACETYL-(ALKOXYCARBONYL)- 3-ALKOXYCARBONYL-6-METHYLPYRIDIN-2(1H)-ONES WITH PRIMARY AROMATIC AMINES AND HYDRAZINE HYDRATE

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5-Acetyl(alkoxycarbonyl)-3-alkoxycarbonyl-6-methylpyridin-2(1H)-ones have been obtained from enaminocarbonyl compounds. Their interactions with benzylamine, α-phenylethylamine, and hydrazine hydrate have been studied, as a result of which a series of amides, hydrazides, and hydrazones of 2(1H)-pyridones has been synthesized.

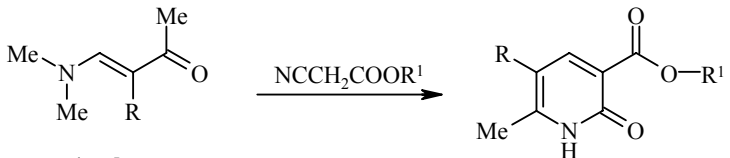
Keywords: amides, hydrazides, hydrazones, 2(1H)-pyridones.

The considerable attention paid to the synthesis and investigation of 2(1H)-pyridones is linked primarily with the broad spectrum of their biological activity. Among them are highly effective cardiotonics, tranquilizers, fungicides, antimicrobial preparations, etc. [1-4]. Certain functionally substituted pyridones proved to be inhibitors of the reverse transcriptase of HIV-1 [5], which opened new prospects for using them.

The introduction of such "pharmacophoric" fragments as hydrazide, hydrazone, and amide functions proved to have a significant effect on the biological activity of pyridones [2, 6]. The hydrazide of isonicotinic acid and its derivatives display high antitubercular activity [6]. Compounds have been discovered among the hydrazones of heterocyclic ketones, which possess high antitumor, antimicrobial, antitubercular, and other forms of activity [7].

In the present work the interaction has been studied of 3-alkoxycarbonyl-6-methylpyridin-2(1H)-ones, functionally substituted at position 5, with aromatic primary amines (benzylamine, α-phenylethylamine) and hydrazine hydrate, with the aim of synthesizing new derivatives of 2(1H)-pyridone, which are of interest as potential biologically active compounds.

The initial substituted pyridin-2(1H)-ones were obtained by reacting enaminocarbonyl compounds with cyanoacetic esters. We discovered previously that the substituted pyridones **2a,b** are formed on interacting ketone **1a** and keto ester **1b** with alkyl cyanoacetates [8].



1a–d **2a–e**

1, 2 a R = Me, **b** R = COOEt, **c** R = COOMe, **d** R = COMe;
2 e R = COMe; **2 a**,**c**,**d** R^1 = Me, **b**,**e** R^1 = Et

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Using this method we obtained in high yield and under mild conditions (40°C, 1 h) pyridone **2c** from keto ester **1c** and methyl cyanoacetate, and pyridones **2d,e** from diketone **1d** and alkyl cyanoacetates.

On heating (160-165°C, 30 min) pyridone **2a** with an excess of benzylamine amide **3a** is formed in 80% yield. In the case of pyridones **2b,c**, containing two alkoxycarbonyl groups in positions 3 and 5, only one group (that located at position 3) reacts with benzylamine or α-phenylethylamine under the same conditions, leading to the formation of amides **3b-e**.

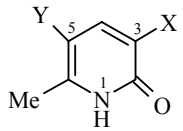
The structures of products **3a-e** were confirmed by the results of elemental analysis (Table 1) and by data of ^{1}H NMR and UV spectra (Table 2), and the structure of amide **3c** by the ^{13}C NMR spectrum as well (Table 2). The fact that the ester group in position 5 did not react was established, using amide **3c** as an example, with the aid of a 2D NOESY CH_3/CH_3O experiment.

On interacting a large excess of hydrazine hydrate with pyridones **2b,c** (80°C, 30 min, *i*-PrOH) the monohydrazides **4a,b** were formed in 90% yield. Bishydrazides were not obtained on more extended heating (10 h) of the reactants.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_9H_{11}NO_3$	—	—	—	215-216 [8]	70
2b	$C_{12}H_{15}NO_5$	—	—	—	185-187 [8]	73
2c	$C_{10}H_{11}NO_5$	53.02 / 53.33	4.78 / 4.92	6.31 / 6.22	199-201	80
2d	$C_{10}H_{11}NO_4$	57.27 / 57.41	5.18 / 5.30	6.78 / 6.70	208-209	74
2e	$C_{11}H_{13}NO_4$	58.84 / 59.18	5.99 / 5.87	6.38 / 6.28	170-171	76
3a	$C_{15}H_{16}N_2O_2$	69.97 / 70.29	6.31 / 6.29	10.86 / 10.93	212-213	81
3b	$C_{16}H_{16}N_2O_4$	63.85 / 64.00	5.14 / 5.34	9.21 / 9.34	258-260	90
3c	$C_{17}H_{18}N_2O_4$	65.30 / 64.95	5.80 / 5.77	8.98 / 8.91	253-255	80
3d	$C_{17}H_{18}N_2O_4$	65.02 / 64.95	5.69 / 5.77	9.01 / 8.91	255-256	89
3e	$C_{18}H_{20}N_2O_4$	65.76 / 65.84	6.13 / 6.14	8.84 / 8.53	198-200	80
4a	$C_9H_{11}N_3O_4$	47.77 / 48.00	4.91 / 4.92	19.06 / 18.66	>260	90
4b	$C_{10}H_{13}N_3O_4$	49.82 / 50.20	5.76 / 5.48	17.58 / 17.57	>260	90
5a	$C_{17}H_{18}N_2O_3 \cdot H_2O$	64.58 / 64.70	6.51 / 6.34	8.92 / 8.89	203-204	87
5b	$C_{18}H_{20}N_2O_3 \cdot H_2O$	65.33 / 65.44	6.70 / 6.71	8.97 / 8.48	169-170	90
6	$C_{23}H_{23}N_3O_2$	73.78 / 73.97	6.43 / 6.21	11.51 / 11.25	165-166	65
7	$C_9H_{11}N_3O_3$	51.74 / 51.67	5.32 / 5.30	19.90 / 20.09	246-247	86
8	$C_9H_{13}N_5O_2$	48.64 / 48.42	6.00 / 5.87	31.29 / 31.38	260-261	85

TABLE 2. Spectral Characteristics of the Synthesized Compounds



2–**8**

Com-pound	UV spectrum (EtOH), λ_{max}, nm (ε)	^{1}H NMR spectrum, δ, ppm*				
		H-1 (1H, br. s)	H-4 (1H, s)	6-CH_3 (3H, s)	X	Y
1	2	3	4	5	6	7
2a	208 (9300), 243 (7760) 345 (9100)	13.40	8.10	2.55	3.90 (3H, s, CH_3)	2.15 (3H, s, CH_3)
2b	210 (15200), 263 (16700), 330 (8450)	13.05	8.80	2.82	4.38 (2H, q, CH_2); 1.40 (3H, t, CH_3)	4.38 (2H, q, CH_2); 1.40 (3H, t, CH_3)
2c	210 (14050), 263 (16850), 330 (8450)	12.50	8.50	2.60	3.78 (3H, s, CH_3)	3.80 (3H, s, CH_3)
2d	212 (18200), 280 (21800), 335 (11800)	12.95	8.75	2.85	3.95 (3H, s, CH_3)	2.55 (3H, s, CH_3)
2e	212 (18500), 283 (21400), 338 (11900)	13.10	8.70	2.85	4.40 (2H, q, CH_2); 1.40 (3H, t, CH_3)	2.55 (3H, s, CH_3)
3a	208 (21800), 240 (12800), 335 (16800)	12.10	8.20	2.30	10.20 (1H, t, NH); 4.55 (2H, d, CH_2); 7.20-7.40 (5H, m, C_6H_5)	2.10 (3H, s, CH_3)
3b	208 (29400), 260 (16200), 325 (11100)	12.70	8.76	2.68	9.73 (1H, t, NH); 4.55 (2H, d, CH_2); 7.20-7.40 (5H, m, C_6H_5)	3.85 (3H, s, CH_3)

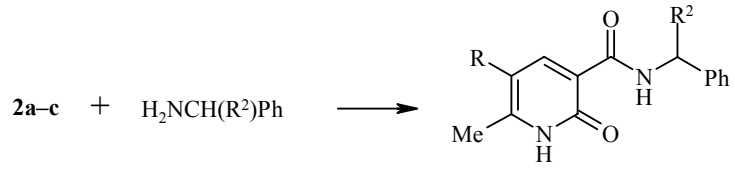
TABLE 2 (continued)

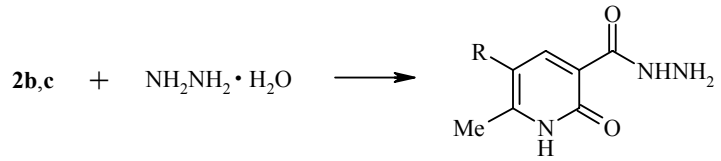
1	2	3	4	5	6	7
3c*[2]	210 (33000), 263 (16000), 328 (12950)	12.65	8.70	2.65	9.80 (1H, d, NH); 5.10 (1H, m, CH); 1.45 (3H, d, CH_3); 7.20-7.40 (5H, m, C_6H_5)	3.80 (3H, s, CH_3)
3d	210 (28600), 260 (18900), 324 (12800)	12.75	8.75	2.65	9.75 (1H, t, NH); 4.52 (2H, d, CH_2); 7.20-7.40 (5H, m, C_6H_5)	4.28 (2H, q, CH_2); 1.30 (3H, t, CH_3)
3e	210 (33200), 262 (19300), 325 (13100)	12.75	8.70	2.65	9.80 (1H, d, NH); 5.15 (1H, m, CH); 1.50 (3H, d, CH_3); 7.20-7.40 (5H, m, C_6H_5)	4.25 (2H, q, CH_2); 1.30 (3H, t, CH_3)
4a	210 (17300), 263 (14100), 325 (10000)		8.68	2.62	10.15 (1H, s, NH)	3.80 (3H, s, CH_3)
4b	210 (21800), 260 (17900), 325 (12800)		8.70	2.65		4.25 (2H, q, CH_2); 1.30 (3H, t, CH_3)
5a	210 (18900), 275 (20200), 330 (10750)		8.48	2.58	3.80 (3H, s, CH_3)	2.45 (3H, s, CH_3); 3.75 (2H, s, CH_2); 7.10-7.30 (5H, m, C_6H_5)
5b	210 (18800), 275 (20700), 328 (11300)		8.45	2.60	4.22 (2H, m, CH_2); 1.25 (3H, d, CH_3)	2.35 (3H, s, CH_3); 3.75 (2H, s, CH_2); 7.10-7.40 (5H, m, C_6H_5)
6	210 (82000), 255 (41000), 335 (36000)	12.45	8.40	2.50	10.00 (1H, br. s, NH); 7.10-7.40 (10H, m, 2 C_6H_5)*[3]; 4.55 (2H, d, CH_2)	4.60 (2H, s, CH_2); 2.25 (3H, s, CH_3)
7	210 (17200), 270 (16200), 325 (11300)		8.70	2.6	10.20 (1H, br. s, N<u>H</u>NH_2)	2.45 (3H, s, CH_3)
8	208 (11400), 255 (13400), 340 (8950)	12.10	8.17	2.30	5.70 (2H, br. s, NH_2); 10.40 (1H, br. s, N<u>H</u>NH_2)	1.95 (3H, s, CH_3); 4.80 (2H, br. s, NH_2)

* Spectra were taken in $CDCl_3$ (compounds **2a,b,d,e**) and DMSO-d_6 (compounds **2s, 3a-e**, **4a,b**, **5a,b**, **6-8**). In all cases when the signal was d, t, or q, J ~7 Hz.

*[2] ^{13}C NMR spectrum (DMSO-d_6): 18.80 ($\underline{C}H_3$-$C_{(6)}$); 22.57 ($\underline{C}H_3$–CH); 48.11 ($\underline{C}$H–NH); 51.80 (CH_3); 107.64 ($C_{(5)}$); 116.81 ($C_{(3)}$); 125.84 (*o*-C_{Ph}); 126.84 (*p*-C_{Ph}); 128.43 (*m*-C_{Ph}); 143.94 (C_6H_5); 144.04 ($C_{(4)}$); 156.82 ($C_{(6)}$); 161.62 (CONH); 162.55 ($C_{(2)}$); 164.33 ($COCH_3$).

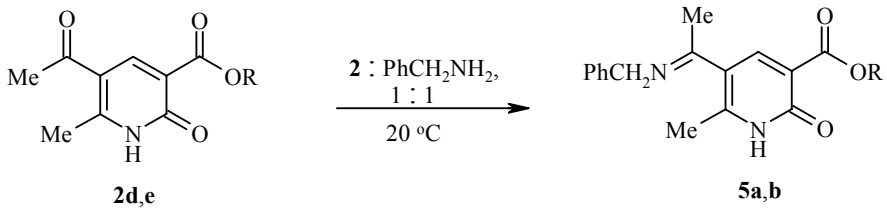
*[3] Signals of the C_6H_5 group protons in substituents X and Y were superimposed, forming an aggregate multiplet.

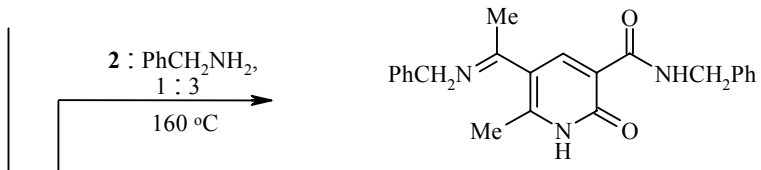


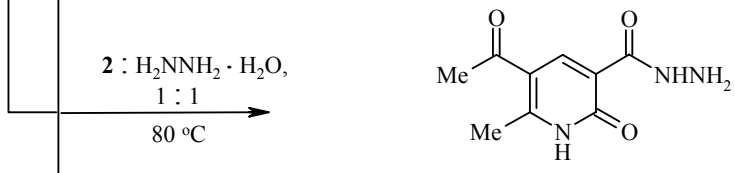


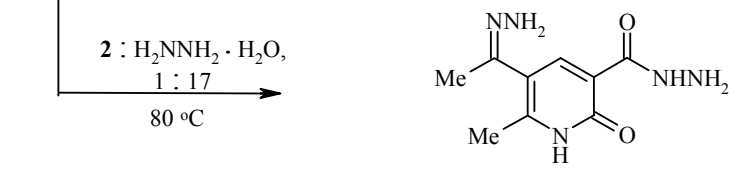
3 a R = Me, R^2 = H, **b** R = COOMe, R^2 = H, **c** R = COOMe, R^2 = Me,
d R = COOEt, R^2 = H, **e** R = COOEt, R^2 = Me, **4 a** R = COOMe, **b** R = COOEt

We discovered that the structure of the products of the interaction of benzylamine and hydrazine hydrate with pyridones **2d,e**, containing an acetyl group in position 5, depends on the reaction conditions when interacting equivalent quantities of pyridones **2d,e** and benzylamine. At 20°C azomethines **5a,b** are formed in 87-90% yield.









5 a R = Me, **b** R = Et

On heating pyridone **2d** with an excess of benzylamine (160°C, 20 min) the reaction proceeds at both the acetyl and ester groups and leads to amide **6** in 65% yield. From equimolar quantities of hydrazine hydrate and pyridone **2d** or **2e** hydrazide **7** is formed in 86% yield on boiling in *i*-PrOH solution (1 h). Under the same conditions, but using a large excess of hydrazine hydrate, the hydrazidohydrazone **8** is formed in 85% yield.

The structures of products **5-8** were confirmed by data of elemental analysis (Table 1) and of ^{1}H NMR and UV spectra (Table 2).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) instrument, and the ^{13}C NMR spectrum (62 MHz) and the 2D NOESY experiment on a Bruker DRX-500 instrument. The UV spectra were taken on a Specord UV-vis instrument in ethanol.

Esters **2a,b** were obtained by the known method of [8].

3,5-Dimethoxycarbonyl-6-methylpyridin-2(1H)-one (2c). A mixture of 2-acetyl-3-dimethylaminoacrylic acid methyl ester (**1c**) (10 g, 5.9 mmol) and methyl cyanoacetate (5.8 g, 5.9 mmol) was maintained for 1 h 30 min at 40°C and 1 day at room temperature. Dry ether was then added to the copious yellow precipitate, the solid was filtered off, washed with ether, and recrystallized from methanol. Product **2c** (10.5 g) was obtained.

5-Acetyl-3-methoxycarbonyl-6-methylpyridin-2(1H)-one (2d). A mixture of 3-(dimethylamino-methylene)pentane-2,4-dione (**1d**) (3 g, 2 mmol), methyl cyanoacetate (2.8 g, 2.8 mmol), and absolute methanol (7 ml) was maintained for 1 h at 40°C, then for 1 day at room temperature. The bright-yellow solid (3.5 g) was filtered off, washed with methanol, and recrystallized from methanol. Product **2d** (3.1 g) was obtained as a snow-white solid.

5-Acetyl-3-ethoxycarbonyl-6-methylpyridin-2(1H)-one (2e) was obtained analogously to pyridone **2d** from diketone **1d** (2 g, 1.3 mmol), ethyl cyanoacetate (2 g, 1.8 mmol), and absolute ethanol (5 ml). Compound **2e** was recrystallized from ethanol.

3-Benzylcarbamoyl-5-ethoxycarbonyl-6-methylpyridin-2(1H)-one (3d). A mixture of pyridone **2b** (1 g, 4 mmol) and benzylamine (1.3 g, 12 mmol) was heated on an oil bath. At 130-140°C the reaction mixture became homogeneous, it was heated to 160-170°C and maintained at this temperature for 15 min. After cooling, absolute ether was added to the copious colorless solid, the solid was filtered off, and washed thoroughly with absolute ether, and with methanol. Amide **3d** (1.1 g) was obtained.

3-Benzylcarbamoyl-5-methoxycarbonyl-6-methylpyridin-2(1H)-one (3b) was obtained analogously to amide **3d** from diester **2c** (0.9 g, 4 mmol) and benzylamine (1.3 g, 12 mmol) with a yield of 1.05 g.

3-Benzylcarbamoyl-5,6-dimethylpyridin-2(1H)-one (3a) was obtained analogously to compounds **3b,d** from pyridone **2a** (0.3 g, 1.7 mmol) and benzylamine (0.27 g, 2.5 mmol) with a yield of 0.34 g.

5-Methoxycarbonyl-6-methyl-3-(1-phenylethyl)carbamoylpyridin-2(1H)-one (3c). A mixture of pyridone **2c** (3 g, 12 mmol) and α-phenylethylamine (4.4 g, 36 mmol) was maintained at 160-165°C for 20 min. After cooling, the solid was filtered off, and washed with ether. Methanol was added to it, the mixture was boiled for 5-10 min, and cooled. The solid was filtered off, washed with methanol, and with dry ether. Amide **3c** (3 g) was obtained.

5-Ethoxycarbonyl-6-methyl-3-(1-phenylethyl)carbamoylpyridin-2(1H)-one (3e). A mixture of pyridone **2b** (1 g, 4 mmol) and α-phenylethylamine (1.5 g, 12 mmol) was maintained at 160-165°C for 35 min, then cooled, absolute ether was added, and the solid separated. Absolute ethanol was added to the solid, and the mixture boiled for 5-10 min. The solid was separated, washed with absolute ether, and amide **3e** (1.05 g) was obtained.

3-Carbazoyl-5-methoxycarbonyl-6-methylpyridin-2(1H)-one (4a). A mixture of diester **2c** (0.9 g, 4 mmol), hydrazine hydrate (3 ml), and 2-propanol (5 ml) was boiled for 30 min. After cooling, the solid was filtered off, washed with methanol, and with ether. Product **4a** (0.8 g) was obtained.

3-Carbazoyl-5-ethoxycarbonyl-6-methylpyridin-2(1H)-one (4b) was obtained analogously to pyridone **4a** from diester **2b**.

5-(1-Benzyliminoethyl)-3-methoxycarbonyl-6-methylpyridin-2(1H)-one (5a). A mixture of pyridone **2d** (0.21 g, 1 mmol) and benzylamine (0.11 g, 1 mmol) was stirred vigorously at room temperature and maintained at the same temperature for 1 day. Absolute ether was then added, the precipitate was filtered off, and washed with absolute ether. Azomethine **5a** (0.26 g) was obtained as the hydrate.

5-(1-Benzyliminoethyl)-3-ethoxycarbonyl-6-methylpyridin-2(1H)-one (5b) was obtained analogously to azomethine **5a** from pyridone **2a,** as the hydrate.

3-Benzylcarbamoyl-5-(1-benzyliminoethyl)-6-methylpyridin-2(1H)-one (6). A mixture of ester **2d** (0.63 g, 3 mmol) and benzylamine (1.0 g, 9 mmol) was maintained at 160°C for 20 min. The liquid reaction mixture was evaporated in vacuum, ether was added to it, the solid was filtered off, and boiled in acetone for 5-10 min. After cooling, the solid was filtered off, washed with acetone, and product **6** (0.72 g) was obtained.

5-Acetyl-3-carbazoyl-6-methylpyridin-2(1H)-one (7). A mixture of pyridone **2d** (0.21 g, 1 mmol) and hydrazine hydrate (0.05 g, 1 mmol) in 2-propanol (0.85 ml) was boiled for 1 h. After cooling, the solid was filtered off, washed with methanol, and with ether, and boiled for 5-10 min in acetone. The solid was then filtered off, washed with acetone, with ether, and hydrazide **7** (0.18 g) was obtained. The same hydrazide **7** was obtained analogously from pyridone **2e**.

3-Carbazoyl-5-(1-hydrazonoethyl)-6-methylpyridin-2(1H)-one (8). A mixture of pyridone **2d** (0.21 g, 1 mmol), hydrazine hydrate (1 ml, 17 mmol), and 2-propanol (1.5 ml) was boiled for 1 h, cooled, the slightly yellowish solid was separated, and was thoroughly washed with absolute methanol, then with absolute ether. Compound **8** (0.19 g) was obtained.

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