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STUDY OF THE ACYLATION REACTION OF 2,6-DIMETHYL-3,5-PYRIDINEDICARBOXYLIC ACID HYDRAZIDES

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Acylation of 3-ethoxycarbonyl-2,6-dimethyl-5-pyridinecarboxylic acid hydrazide and 2,6-dimethyl-3,5-pyridinedicarboxylic acid dihydrazide using aromatic acid chlorides gave the corresponding N-aroyl hydrazides. It was found that the hydrazinolysis of 3-ethoxycarbonyl-2,6-dimethyl-5-pyridine-dicarboxylic acid N-aroyl hydrazides occurred not at the ester group but as a rehydrazinolysis reaction at the dihydrazide fragment.

Keywords: aromatic acid halides, hydrazide, hydrazine hydrate, hydrazinolysis, X-ray analysis.

The studies [1, 2] demonstrated the possibility of a stepwise hydrazinolysis of the ester groups in diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate with subsequent formation of 3-ethoxycarbonyl-2,6-dimethyl-5-pyridine-carboxylic acid hydrazide (**1**) and 2,6-dimethyl-3,5-dipyridinedicarboxylic acid dihydrazide (**2**) and then the corresponding hydrazones using aromatic aldehydes. It was found that the free ester group in the case of the hydrazones obtained from the monohydrazide **1** does not participate in the hydrazinolysis reaction.

With the aim of investigating the chemical properties of the hydrazides **1** and **2** we have studied their acylation reaction with the aromatic acid halides **3a-h**. This reaction occurs under base catalysis conditions using dry, refluxing acetonitrile. The choice of solvent and the temperature conditions are limited by the solubility of the hydrazides **1, 2** in organic solvents.

The 3,5-pyridinedicarboxylic acid N-aroyl hydrazides **4, 5a-h** formed in the reaction are neutralized using aqueous alcoholic sodium bicarbonate solution to give the corresponding bases **6, 7a-h** (Tables 1-3). As is evident from the Table the most difficulty occurs in the reaction with 2-methoxybenzoyl chloride and this is evidently linked both with the lower electrophilicity of the reagent and with the steric hindrance generated by the *ortho*-methoxy group.

The N-aroyl hydrazides **6, 7a-h** are quite stable to acid and base hydrolysis but this occurs to give 2,6-dimethyl-3,5-pyridinedicarboxylic acid by refluxing for 6-10 h in 15% hydrochloric acid, virtually the same time being needed for the complete hydrolysis using a 2N aqueous alcohol solution of potassium hydroxide under reflux.

The ester group of the monohydrazide **1** readily takes part in a hydrazinolysis reaction to give the dihydrazide **2** [1]. We were interested in the possible hydrazinolysis of the ester group in the obtained N-aroyl hydrazides **6a-h**. It was found that prolonged reflux of both the bases **6a,b,e,f,h** and the hydrochlorides

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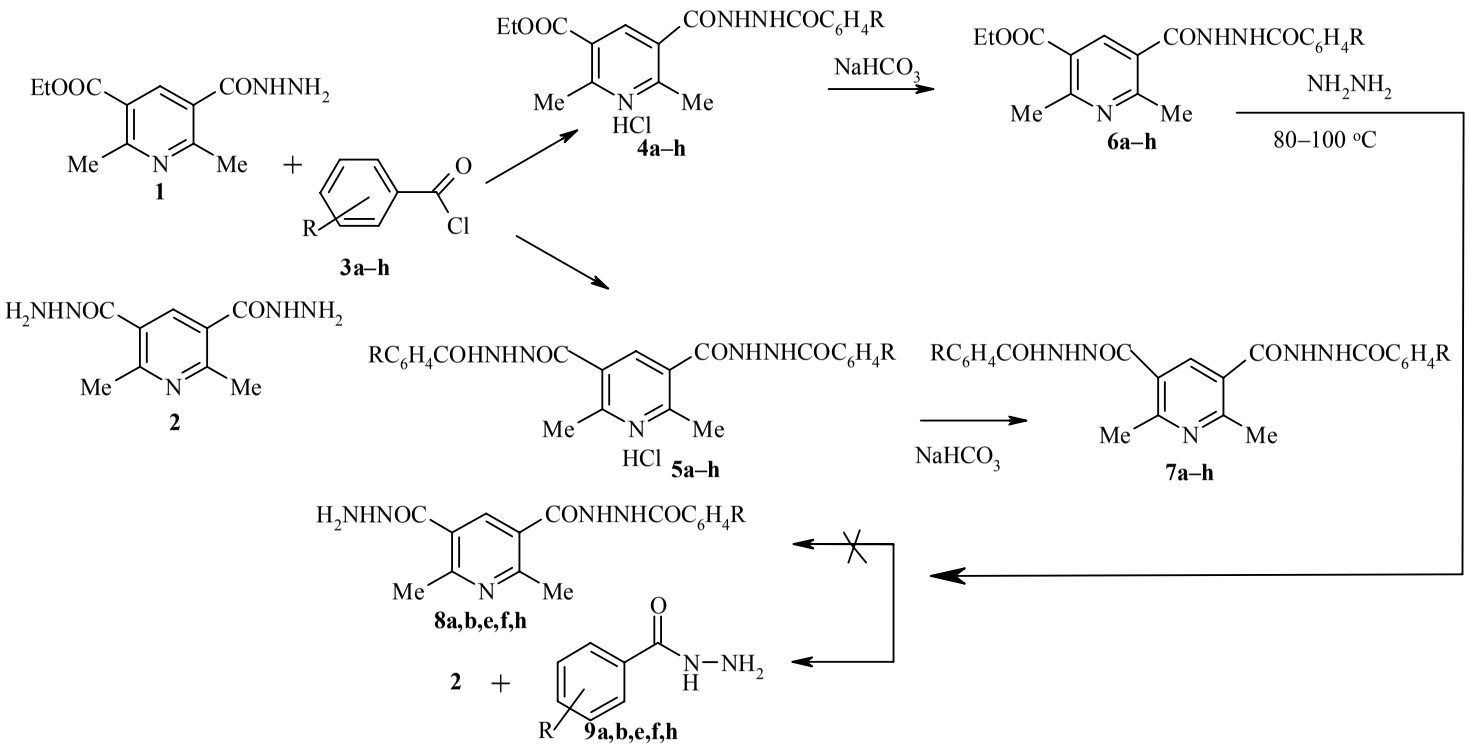

a R = H; **b** R = 4-*t*-Bu; **c** R = 4-Ph; **d** R = 2-OMe; **e** R = 3-NO_2; **f** R = 4-NO_2; **g** R = 2-Cl, 4-NO_2; **h** R = 2-F

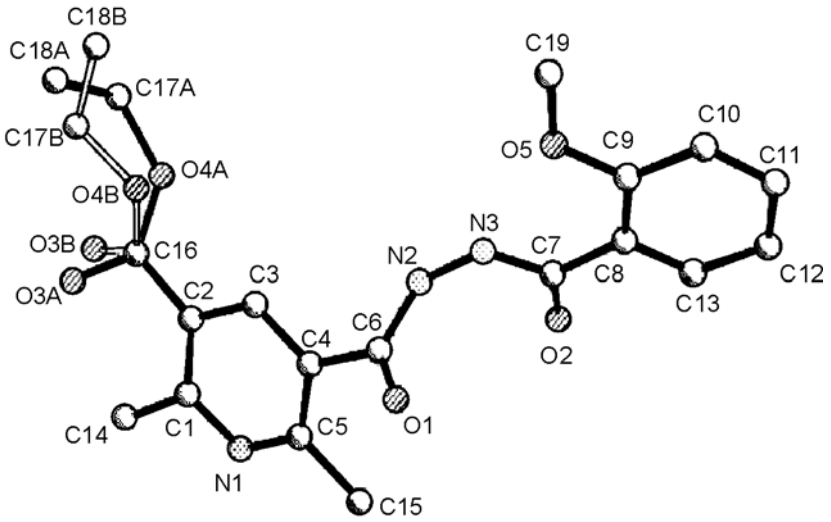

Fig. 1. Structure of compound **6d** derived from X-ray investigation

4a,b,e,f,h with an excess of hydrazine hydrate in medium of different polarity (methanol, butanol, 2-propanol, or acetonitrile) or in hydrazine hydrate (98%) without solvent gave the corresponding benzoic acid hydrazide **9a,b,e,f,h** and dihydrazide **2** and not compounds **8a,b,e,f,h**. Chromatographic monitoring of the course of the reaction did not reveal the formation of intermediate products.

Similar behavior for the free ester group has been reported before [3] in attempts to hydrazinolyze the hydrazones of the monohydrazide **1**. It is possible that the N-aroyl hydrazide fragment in compounds **6a-h** experiences steric hindrance towards the attack of the ester group similarly to the 4 substituent in diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate, the presence of which completely blocks the hydrazinolysis of the 3,5-ester groups (as shown in [2]).

X-ray analysis of compound **6d** showed (Fig. 1, Tables 4, 5) that the N-aroyl hydrazide fragment has an *ap-ac-ap* conformation (torsional angles $C_{(4)}$–$C_{(6)}$–$N_{(2)}$–$N_{(3)}$ 172.7(2)°, $C_{(6)}$–$N_{(2)}$–$N_{(3)}$–$C_{(7)}$ 99.8(3)°, and $N_{(2)}$–$N_{(3)}$–$C_{(7)}$–$C_{(8)}$ -179.5(2)° which is apparently typical of N,N'-bis(2-arylcarbonyl)hydrazines. This is supported by the results of X-ray analysis of 1,2-dibenzoylhydrazine [4] and N,N'-bis(2-pyridinocarbonyl)hydrazine [5] in which a similar conformation of the C–C(=O)–NH–NH–C(=O)–C fragment is observed. The $C_{(7)}$–$O_{(2)}$ carbonyl group lies virtually in the plane of the benzene ring (torsional angle $O_{(2)}$–$C_{(7)}$–$C_{(8)}$–$C_{(13)}$ -6.1(4)°. Such an orientation is likely due to the formation of an intramolecular hydrogen bond $N_{(3)}$–H···$O_{(5)}$ (H···O 1.91 Å, N–H···O 135°). The rotation of the carbonyl group $C_{(6)}$–$O_{(1)}$ relative to the pyridine ring is in all likelihood associated with unfavored nonvalence interactions between the $O_{(1)}$ and $C_{(15)}$ atoms as evidenced by the deformation of the torsional angle $C_{(6)}$–$C_{(4)}$–$C_{(5)}$–$C_{(15)}$ to -7.3(4)°. The methoxy group lies in the $C_{(8)}$–$C_{(13)}$ ring plane (torsional angle $C_{(7)}$–$C_{(8)}$–$C_{(9)}$–$O_{(5)}$ 0.3(4)°).

With the exception of $C_{(16)}$ the atoms of the ester substituent are randomized into two conformations A and B with a population of 0.35: 0.65 as a consequence of free rotation around the $C_{(2)}$–$C_{(16)}$ and $O_{(4)}$–$C_{(17)}$ bonds (torsional angles $C_{(1)}$–$C_{(2)}$–$C_{(16)}$–$O_{(3)}$ 39.8(5)° (A), -18.2(4)° (B) and $C_{(16)}$–$O_{(4)}$–$C_{(17)}$–$C_{(18)}$ 77.0(6)° (A), -170.7(2)° (B). In both conformations the $C_{(2)}$, $O_{(4)}$, $C_{(16)}$, and $C_{(17)}$ atoms are coplanar (torsional angles $C_{(17)}$–$O_{(4)}$–$C_{(16)}$–$C_{(2)}$ -179.2(2)° (A), 180.0(2)° (B)). The $O_{(1)}$, $O_{(3)}$, and $O_{(4)}$ oxygen atoms form the attractive, shortened contacts $O_{(1)}$···$H_{(15B)}$ 2.70 (C–H···O 116°), $O_{(3)}$···$H_{(17B)}$ 2.09 (A), 2.39 Å (B) (C–H···O 125 (A), 110° (B)), and $O_{(4A)}$···$H_{(3)}$ 2.37(A), 2.44 Å (B) (C–H···O 99°) (sum of van der Waal radii 2.46 Å [4]).

TABLE 1. Characteristics of Compounds **6a-h, 7a-h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
6a	$C_{18}H_{19}N_3O_4$	63.14 / 63.33	5.47 / 5.61	12.09 / 12.31	183-184	55
7a	$C_{23}H_{21}N_5O_4$	64.35 / 64.03	4.72 / 4.91	16.33 / 16.23	282-283	60
6b	$C_{22}H_{27}N_3O_4$	66.67 / 66.48	6.57 / 6.85	10.41 / 10.57	175-176	82
7b	$C_{31}H_{37}N_5O_4$	68.72 / 68.49	6.49 / 6.86	12.93 / 12.88	244-245	55
6c	$C_{24}H_{23}N_3O_4$	69.23 / 69.05	5.32 / 5.55	10.28 / 10.07	214-215	94
7c	$C_{35}H_{29}N_5O_4$	72.36 / 72.03	5.28 / 5.01	12.26 / 12.00	351-352	70
6d	$C_{19}H_{21}N_3O_5$	61.74 / 61.45	5.51 / 5.70	11.57 / 11.31	170-171	14
7d	$C_{25}H_{25}N_5O_6$	61.28 / 61.09	5.46 / 5.13	14.61 / 14.25	264-265	20
6e	$C_{18}H_{18}N_4O_6$	56.21 / 55.96	4.53 / 4.70	14.27 / 14.50	230-231	77
7e	$C_{23}H_{19}N_7O_8$	52.83 / 52.98	3.83 / 3.67	18.55 / 18.80	318-320	80
6f	$C_{18}H_{18}N_4O_6$	55.65 / 55.96	4.91 / 4.70	14.72 / 14.50	225 (dec.)	95
7f	$C_{23}H_{19}N_7O_8$	52.61 / 52.98	3.74 / 3.67	18.49 / 18.80	275 (dec.)	81
6g	$C_{18}H_{17}ClN_4O_6$	51.59 / 51.38	4.22 / 4.07	13.38 / 13.31	204-205	94
7g	$C_{23}H_{17}Cl_2N_7O_8$	46.62 / 46.80	2.67 / 2.90	12.42 / 12.01	281-282	96
6h	$C_{18}H_{18}FN_3O_4$	60.34 / 60.16	5.32 / 5.05	11.61 / 11.69	253-254	72
7h	$C_{23}H_{19}F_2N_5O_4$	59.46 / 59.10	4.23 / 4.10	14.74 / 14.98	292-293	60

The molecules in the crystal are bound in an infinite chain by hydrogen bonding with $N_{(3)}$–H···$O_{(1)'}$ (1 - *x*, *y*, 1.5 - *z*) (H···O 1.83 Å, N–H···O 129°) and $N_{2)}$–H···$O_{(2)'}$ (0.5 - *x*, 0.5 - *y*, 1 - *z*) (H···O 2.00 Å, N–H···O 162°), the formation of which leads to lengthening of the $C_{(6)}$–$O_{(1)}$ and $C_{(7)}$–$O_{(2)}$ bonds to 1.226(3) and 1.233(3) Å respectively (mean value 1.210 Å [5]). It should be noted that the H($N_{(3)}$) atom takes part in simultaneous formation of two hydrogen bonds.

The IR spectra of the obtained compounds **6a-h, 7a-h** (Table 3) confirm the presence of associated and free NH groups. According to data in [6, 7] the absorption bands in the region 3210-3170 cm^{-1} are assigned to vibrations of associated NH group whereas a nonassociated NH group absorbs at 3540-3310 cm^{-1}. One broad, strong band is observed for the absorption of the NH–NH fragment in the case of the N-benzoyl dihydrazide **7a** (Table 3) and points to a strong association of the NH groups, however the presence of a substituent in the benzoyl fragment causes a decrease in the association and the spectrum of compounds **7g** shows only a narrow stretching band for a free NH group. As a rule the presence in the IR spectra for compounds **6a-h** of two absorption bands for the ester group agrees with the X-ray data (see Fig. 1) as regards the presence of the two conformations A and B while compounds **6b-f** show a strong bathochromic shift of the ester band when compared with that of the monohydrazide **1** (1740 cm^{-1}) [1]. Exchange of the ester group in compounds **6a-h** for a hydrazide fragment leads to an increase in the electron density in the pyridine ring as supported by the shift to high field for the pyridine ring H-4 proton signal in the ^{1}H NMR spectra when going from the hydrazides **6a-h** to **7a-h** (Table 3). For compounds containing the *o*-F and *o*-OMe groups this shift is minimal (0.04 and 0.10 ppm respectively) but in going from the monohydrazide **1** (8.12 ppm) to the dihydrazide **2** (7.65 ppm) it is

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm. (*J*, Hz)						
	4-H-Py (s, 1H)	CH_3 (3H, s)	OCH_2CH_3 (3H, t)	OCH_2CH_3 (2H, q)	NH (1H, s)	H arom	R
1	2	3	4	5	6	7	8
6a	8.20	2.72, 2.87	1.35 (*J* = 6.9)	4.32 (*J* = 6.9)	10.44, 10.55	7.92 (2H, d, *J* = 7.4); 7.51 (3H, m)	
7a	8.00	2.65	—	—	10.39, 10.55	7.96 (4H, d); 7.49 (6H, m)	
6b	8.16	2.62, 2.73	1.37 (*J* = 6.9)	4.31 (*J* = 6.9)	10.33, 10.41	7.48 (2H, d, *J* = 9.8); 7.85 (2H, d, *J* = 9.8)	1.35 (9H, s, $(CH_3)_3$)
7b	7.92	2.64	—	—	10.31, 10.48	7.48 (4H, d, *J* = 6.0); 7.88 (4H, d, *J* = 6.0)	1.34 (18H, s, $(CH_3)_3$)
6c	8.23	2.67, 2.76	1.38 (*J* = 6.9)	4.34 (*J* = 6.9)	10.44, 10.59	7.37-7.47 (3H, m); 7.61 (2H, d, *J* = 8.0); 7.68 (2H, d, *J* = 8.0); 8.02 (2H, d, *J* = 8.0)	
7c	7.98	2.69	—	—	10.37, 10.67	7.39–7.49 (6H, m); 7.71 (4H, d, *J* = 10.0); 7.80 (4H, d, *J* = 10.0); 8.15 (4H, d, *J* = 10.0)	
6d	8.22	2.67, 2.80	1.40 (*J* = 6.0)	4.34 (*J* = 6.0)	10.05, 10.69	7.08 (1H, t, *J* = 4.0); 7.17 (1H, d, *J* = 8.0); 7.52 (1H, t, *J* = 4.0); 7.83 (1H, d, *J* = 8.0)	3.98 (3H, s, OCH_3)
7d	8.12	2.73	—	—	10.12, 10.70	7.11 (2H, t, *J* = 5.0); 7.19 (2H, d, *J* = 7.0); 7.54 (2H, t, *J* = 5.0); 7.90 (2H, d, *J* = 7.0)	3.40 (6H, s, OCH_3)

TABLE 2 (continued)

1	2	3	4	5	6	7	8
6e	8.20	2.58, 2.70	1.35 (J =7.8)	4.31 (J = 7.8)	10.55, 10.98	7.80 (1H, t, J = 8.2); 8.35 (1H, d, J = 8.2); 8.42 (1H, d, J = 8.2); 8.75 (1H, s)	
7e	8.09	2.78	—	—	10.65, 11.08	7.91 (2H, t, J = 5.2); 8.50 (2H, d, J = 5.2); 8.58 (2H, d, J = 5.2); 8.88 (2H, s)	
6f	8.19	2.62, 2.72	1.32 (J = 7.9)	4.31 (J = 7.9)	10.71*	8.11 (2H, d, J = 9.8); 8.33 (2H, d, J = 9.8)	
7f	7.82	2.67	—	—	10.55, 10.91	8.14 (4H, d, J = 8.0); 8.36 (4H, d, J = 8.0)	
6g	8.18	2.61, 2.71	1.32 (J = 7.9)	4.28 (J = 7.9)	10.46*	7.79 (1H, s); 8.24 (1H, d, J = 9.8); 8.31 (1H, d, J = 9.8)	
7g	7.91	2.62	—	—	10.65*	7.82 (2H, d, J = 8.5); 8.31 (2H, d, J = 8.5); 8.4 (2H, s)	
6h	8.19	2.69, 2.75	1.32 (J = 7.9)	4.31 (J = 7.9)	10.45*	7.30 (2H, t, J = 8.0); 7.51-7.79 (2H, m)	
7h	8.15	2.75	—	—	10.45, 10.65	7.34 (4H, t, J = 7.8); 7.60-7.79 (4H, m)	

* Broad singlet with intensity of 2H.

TABLE 3. IR Spectra of the Synthesized Compound

Compound	ν, cm^{-1}				
	ν_{NH} free	ν_{NH} assoc.	$\nu_{C=O}$	amide I band and ($\nu_{C=O}$)	amide II band and (δ_{NH})
6a	3420	3230	1740, 1720	1660	1570, 1550
7a	3450*	3200		1670*, 1610	1565
6b		3340, 3205	1720, 1700	1655, 1610	1555
7b	3450	3280		1700, 1670, 1640, 1610	1565, 1545
6c	3450*	3190	1710	1665	1525
7c	3540	3270		1660, 1650	1540
6d	3380, 3340	3250	1710	1680, 1650-1630	1570
7d	3430	3340, 3270		1675-1650	1550
6e	3420	3210	1720	1650	1540
7e		3190		1610	1540
6f	3400	3200	1710*	1690-1660	1530
7f	3510*, 3410	3280, 3230		1650, 1610	1540-1530
6g	3410	3210	1725, 1700	1650, 1610	1540
7g	3400			1630	1540
6h	3450	3220	1740, 1720*	1660, 1630	1570-1550
7h	3450	3250*		1670-1650	1560-1510

* Shoulder on main band.

TABLE 4. Bond Lengths (*l*) in the Structure **6d**

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$O_{(1)}$–$C_{(6)}$	1.226(3)	$N_{(1)}$–$C_{(5)}$	1.331(4)	$C_{(5)}$–$C_{(15)}$	1.520(5)
$O_{(2)}$–$C_{(7)}$	1.233(3)	$N_{(2)}$–$C_{(6)}$	1.330(3)	$C_{(7)}$–$C_{(8)}$	1.491(3)
$O_{(3A)}$–$C_{(16)}$	1.218(4)	$N_{(2)}$–$N_{(3)}$	1.390(3)	$C_{(8)}$–$C_{(9)}$	1.385(4)
$O_{(3B)}$–$C_{(16)}$	1.225(3)	$N_{(3)}$–$C_{(7)}$	1.333(3)	$C_{(8)}$–$C_{(13)}$	1.386(4)
$O_{(4A)}$–$C_{(16)}$	1.347(4)	$C_{(1)}$–$C_{(2)}$	1.395(4)	$C_{(9)}$–$C_{(10)}$	1.389(4)
$O_{(4A)}$–$C_{(17A)}$	1.460(4)	$C_{(1)}$–$C_{(14)}$	1.515(4)	$C_{(10)}$–$C_{(11)}$	1.371(5)
$O_{(4B)}$–$C_{(16)}$	1.317(3)	$C_{(2)}$–$C_{(3)}$	1.396(3)	$C_{(11)}$–$C_{(12)}$	1.368(6)
$O_{(4B)}$–$C_{(17B)}$	1.458(4)	$C_{(2)}$–$C_{(16)}$	1.448(4)	$C_{(12)}$–$C_{(13)}$	1.389(4)
$O_{(5)}$–$C_{(9)}$	1.369(3)	$C_{(3)}$–$C_{(4)}$	1.369(4)	$C_{(17A)}$–$C_{(18A)}$	1.528(4)
$O_{(5)}$–$C_{(19)}$	1.431(3)	$C_{(4)}$–$C_{(5)}$	1.377(4)	$C_{(17B)}$–$C_{(18B)}$	1.519(4)
$N_{(1)}$–$C_{(1)}$	1.329(4)	$C_{(4)}$–$C_{(6)}$	1.502(3)		

0.47 ppm. In most cases the proton signals for the NH–NH fragment appear as sharp singlets but for compounds **6, 7f-h** with strong electron acceptor substituents in the aroyl fragment they are seen as a broadened singlet, evidently as a result of their closeness in chemical shift values.

Hence the impossibility of hydrazinolysis of the ester group in compounds **6a-h** is difficult to explain in terms of the unavailability of the electron center due to steric factors and also the electronic effect of the hydrazide fragment in the *meta*-related position in the pyridine ring. Evidently the reason must be looked for in features of the mechanism of the hydrazinolysis reaction.

TABLE 5. Valence Angles (ω) in the Structure **6d**

Angle	ω, deg	Angle	ω, deg
$C_{(16)}$–$O_{(4A)}$–$C_{(17A)}$	124.7(4)	$O_{(2)}$–$C_{(7)}$–$N_{(3)}$	121.6(2)
$C_{(16)}$–$O_{(4B)}$–$C_{(17B)}$	112.4(3)	$O_{(2)}$–$C_{(7)}$–$C_{(8)}$	120.4(2)
$C_{(9)}$–$O_{(5)}$–$C_{(19)}$	120.6(2)	$N_{(3)}$–$C_{(7)}$–$C_{(8)}$	118.0(2)
$C_{(1)}$–$N_{(1)}$–$C_{(5)}$	119.6(3)	$C_{(9)}$–$C_{(8)}$–$C_{(13)}$	118.4(3)
$C_{(6)}$–$N_{(2)}$–$N_{(3)}$	121.0(2)	$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	125.7(2)
$C_{(7)}$–$N_{(3)}$–$N_{(2)}$	119.8(2)	$C_{(13)}$–$C_{(8)}$–$C_{(7)}$	116.0(3)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	121.8(2)	$O_{(5)}$–$C_{(9)}$–$C_{(8)}$	117.3(2)
$N_{(1)}$–$C_{(1)}$–$C_{(14)}$	114.8(3)	$O_{(5)}$–$C_{(9)}$–$C_{(10)}$	121.8(3)
$C_{(2)}$–$C_{(1)}$–$C_{(14)}$	123.4(3)	$C_{(8)}$–$C_{(9)}$–$C_{(10)}$	120.9(3)
$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	117.2(3)	$C_{(11)}$–$C_{(10)}$–$C_{(9)}$	119.3(3)
$C_{(1)}$–$C_{(2)}$–$C_{(16)}$	122.7(2)	$C_{(12)}$–$C_{(11)}$–$C_{(10)}$	121.2(3)
$C_{(3)}$–$C_{(2)}$–$C_{(16)}$	120.0(3)	$C_{(11)}$–$C_{(12)}$–$C_{(13)}$	119.2(3)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	120.8(3)	$C_{(8)}$–$C_{(13)}$–$C_{(12)}$	121.0(3)
$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	117.6(2)	$O_{(3B)}$–$C_{(16)}$–$O_{(4B)}$	117.4(3)
$C_{(3)}$–$C_{(4)}$–$C_{(6)}$	119.8(3)	$O_{(3A)}$–$C_{(16)}$–$O_{(4A)}$	130.3(5)
$C_{(5)}$–$C_{(4)}$–$C_{(6)}$	122.6(3)	$O_{(3A)}$–$C_{(16)}$–$C_{(2)}$	113.6(5)
$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	122.9(3)	$O_{(3B)}$–$C_{(16)}$–$C_{(2)}$	126.4(3)
$N_{(1)}$–$C_{(5)}$–$C_{(15)}$	116.0(3)	$O_{(4B)}$–$C_{(16)}$–$C_{(2)}$	116.1(2)
$C_{(4)}$–$C_{(5)}$–$C_{(15)}$	121.0(3)	$O_{(4A)}$–$C_{(16)}$–$C_{(2)}$	112.3(2)
$O_{(1)}$–$C_{(6)}$–$N_{(2)}$	123.7(2)	$O_{(4A)}$–$C_{(17A)}$–$C_{(18A)}$	113.2(6)
$O_{(1)}$–$C_{(6)}$–$C_{(4)}$	122.4(2)	$O_{(4B)}$–$C_{(17B)}$–$C_{(18B)}$	102.0(3)
$N_{(2)}$–$C_{(6)}$–$C_{(4)}$	113.8(2)		

EXPERIMENTAL

Crystals of **6d** are monoclinic, $C_{19}H_{21}N_3O_5$, at 20°C a = 18.676(4), b = 15.851(4), c = 15.825(3) Å; β = 124.35(1)°; V =3868(2) Å^3; M_r = 371.39; Z = 8; space group $C2/c$; d_{calc} = 1.276 g/cm^3; μ(MoKα) = 0.094 mm^{-1}, F(000) = 1568. Unit cell parameters and intensities for 3627 reflections (3386 independent, R_{int} = 0.026) were measured on an automatic, four circle Siemens P3/PC diffractometer (MoKα, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by a direct method using the SHELXTL program package [8]. The positions of the hydrogen atoms were revealed from electron density difference synthesis and were refined using the "riding" model with $U_{iso} = nU_{eq}$ for the non-hydrogen atom bonded to the given hydrogen atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). In the refinement limits were set for the bond lengths in the randomized fragment: $C_{(16)}$–$O_{(3)}$ 1.202(5), $C_{(16)}$–$O_{(4)}$ 1.337(5), $O_{(4)}$–$C_{(17)}$ 1.452(5), and $C_{(17)}$–$C_{(18)}$ 1.530(5) Å. The structure was solved by an F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms with the exclusion of the randomized atoms which were refined isotropically. The final difference parameters were wR_2 = 0.222 for 3356 reflections (R_1 = 0.068 for 1327 reflections with $F > 4\sigma(F)$, S = 0.933). The bond lengths and valence angles are given in Tables 4 and 5 respectively.

IR spectra were recorded on a UR-20 instrument for KBr tablets (0.25%) and ^{1}H NMR spectra on a Varian 300VXR spectrometer (300 MHz) using DMSO-d_6 solvent and TMS internal standard. Monitoring of the reaction course and the product purity was carried out using TLC on Silufol UV-254 plates in the system benzene–ethyl acetate–methanol (10:7:1) and revealed using iodine vapor.

Acylation Reaction of the Hydrazides 1, 2 (General Method). The acid chloride (0.001 mol for each hydrazide group) was added to a solution of the corresponding hydrazide (**1** or **2**) (0.001 mole) in acetonitrile (25 ml). The reaction mixture was refluxed for 1 h. The corresponding precipitated hydrochloride **4, 5a-h** was filtered off, dissolved in methanol, and a two-fold excess of saturated, aqueous sodium bicarbonate was added. The precipitate obtained was recrystallized from acetonitrile or a mixture of acetonitrile and water.

Hydrazinolysis of 3-Ethoxycarbonyl-2,6-dimethylpyridine-5-carboxylic Acid 2-Benzoyl Hydrazide (6a). Hydrazine hydrate (98%, 2 ml) was added to a solution of **6a** (0.34 g, 0.001 mol) in methanol (10 ml) and refluxed for 6 h. The precipitated dihydrazide **2** was filtered off and the solution was evaporated to dryness in vacuo. The benzoic acid hydrazide **9a** obtained was crystallized from ethanol. Yield 48%; mp 116-117°C (ethanol) (mp 116.5-117.5°C [9]). The compound prepared did not give a depression in melting point with a sample obtained by method [9] from ethyl benzoate and hydrazine hydrate.

Hydrazinolysis of 3-Ethoxycarbonyl-2,6-dimethylpyridine-5-carboxylic Acid 2-(*p*-*tert*-Butyl-benzoyl) Hydrazide (6b). Hydrazine hydrate (85%, 6 ml) and ethanol (2 ml) were added to the hydrazine **6b** (0.39 g, 0.001 mol). The mixture was refluxed for 10 h, and the solution was evaporated to dryness in vacuo. The precipitate obtained was extracted with refluxing methanol. The methanol solution was evaporated and the residue was recrystallized from 2-propanol. Yield of *p*-*tert*-butylbenzoyl hydrazide (**9b**) 43%; mp 117-118°C (2-propanol) (mp 118-120°C [10]). The compound prepared did not give a depression in melting point with a sample obtained by method [10] from ethyl *p*-*tert*-butylbenzoate and hydrazine hydrate (85%). The precipitate insoluble in methanol is the dihydrazide **2**.

Hydrazinolysis of 3-Ethoxycarbonyl-2,6-dimethylpyridine-5-carboxylic Acid 2-(*m*-Nitrobenzoyl) Hydrazide (6e) was carried out similarly to the hydrazinolysis of the hydrazide **6b** over 5 h. Yield of *m*-nitrobenzoyl hydrazide **9e** 52%; mp 152-154°C (ethanol) (mp 154°C [9]).

Hydrazinolysis of 3-Ethoxycarbonyl-2,6-dimethylpyridine-5-carboxylic Acid 2-(*p*-Nitrobenzoyl) Hydrazide (6f) was carried similarly to the hydrazinolysis of **6b** over 3 h. Yield of *p*-nitrobenzoyl hydrazide **9f** 67%; mp 209-210°C (water) (mp 210°C [11]). The compound prepared did not give a depression in melting point with a sample obtained by method [11] from ethyl *p*-nitrobenzoate and hydrazine hydrate (98%).

Hydrazinolysis of 3-Ethoxycarbonyl-2,6-dimethylpyridine-5-carboxylic Acid 2-(*o*-Fluorobenzoyl) Hydrazide (6h) was carried out similarly to the hydrazinolysis of **6a** over 13 h. Yield of *o*-fluorobenzoyl hydrazide **9h** 27%; mp 71-73°C (cyclohexane) (mp 72-73°C [12]). The compound prepared did not give a depression in melting point with a sample obtained by method [12] from ethyl *o*-fluorobenzoate and hydrazine hydrate (85%).

REFERENCES

1. E. Yu. Nesterova, A. V. Samukha, and M. V. Voevudsky, *Reports of Dnepropetrovsk University* [in Russian], No. 6, 83 (2001).
2. E. Yu. Nesterova, A. V. Samukha, M. V. Voevudsky, and V. N. Goncharuk, *Aspects of Chemistry and Chemical Technology* [in Russian], No. 6, 47 (2003).
3. E. Yu. Nesterova, M. V. Voevudsky, and A. V. Samukha, *Reports of Dnepropetrovsk University* [in Russian], No. 7, 75 (2002).
4. S. S. S. Raj, B. M. Yamin, A. M. A. Boshaala, M. T. H. Tarafder, K. A. Crouse, and H.-K. Fun, *Acta Crystallogr.*, **C56**, 1011 (2000).
5. S. Shao, D. Zhu, Y. Song, X. Z. You, S. S. Raj, and H.-K. Fun, *Acta Crystallogr.*, **C55**, 1841 (1999).
6. E. V. Titov, A. P. Grekov, V. I. Rybal'chenko, and V. V. Shevchenko, *Teor. Eksp. Khim.*, **4**, 742 (1968).
7. E. V. Titov and V. I. Rybal'chenko, *Teor. Eksp. Khim.*, **7**, 212 (1971).

8. G. M. Sheldrick, *SHELXTL PLUS PC Version, A System of Computer Programs for the Determination of Crystal Structure from X-ray Diffraction Data,* Rev. 5.1 (1998).
9. A. P Grekov and M. S. Solov'eva, *Ukr. Khim. Zh.*, **27**, 384 (1961).
10. H. L. Yale, K. Losee, J. Martins, M. Holsing, F. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
11. A. P. Grekov, O. P. Shvaika, and L. M. Egupova, *Zh. Obshch. Khim.*, **29**, 2027 (1959).
12. E. L. Bennett and C. Niemann, *J. Amer. Chem. Soc.*, **72**, 1800 (1950).