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SUBSTITUTED UREAS BASED ON 2,6-DIMETHYL-3,5-PYRIDINEDICARBOXYLIC ACID AZIDES

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Under Curtius rearrangement conditions, 2,6-dimethyl-3,5-pyridinedicarboxylic acid azides form the corresponding isocyanates which react in situ with ammonia, primary and secondary amines to form mono-, di-, and trisubstituted ureas. The reaction of the 5-ethoxycarbonyl-2,6-dimethylnicotinic acid azide with imidazole under these conditions gave symmetrical N,N'-bis[5-(ethoxycarbonyl)-2,6-dimethylpyridin-3-yl]ureas.

Keywords: acylazides, amines, ureas, Curtius rearrangement.

Ureas containing a pyridine fragment possess various pharmacological activities [1-5], including anticancer activity [1].

We have studied the formation of ureas of the pyridine series by the reaction of the azide of 5-ethoxycarbonyl-2,6-dimethylnicotinic acid (**1**) and the diazide of 2,6-dimethylpyridine-3,5-dicarboxylic acid (**2**) with various amines.

On heating in dry inert solvents (benzene, toluene), the azides **1** and **2** underwent the Curtius rearrangement to give the corresponding isocyanates **3** and **4**, which reacted quantitatively *in situ* with primary and secondary amines to give the corresponding ureas **5a-r**, **6a-d**, **6f**,**g**,**j**,**l-p**,**r**. It should be noted that the products of the reaction with primary amines **5a-o**, **6a-d**,**f**,**g**,**j**,**l-o** have low solubility in most organic solvents, whereas the trisubstituted ureas **5p**,**r**, **6p**,**r** obtained from secondary amines dissolve well in polar and nonpolar organic solvents (hexane, benzene, toluene, lower alcohols), which complicates their complete isolation and purification.

Depending on the amount of ammonia reacting with the isocyanates **3** and **4**, formation of different reaction products was observed. For example, a 20-30-fold excess of aqueous ammonia led to the ureas **5a** and **6a**, which gave a positive qualitative reaction with *p-N,N*-dimethylaminobenzaldehyde, characteristic of an unsubstituted urea group [6]. With a small excess of ammonia in the presence of 2-propanol the basic product of the reaction was the biuret **7** or a high-melting substance, probably with a polymeric structure. It should be noted that we did not isolate a urea containing an imidazole fragment when the azide **1** reacted with imidazole. The product obtained was characterized as the urea **8**, the formation of which as the main product of reaction we also observed on the interaction of azide **1** with *tert*-butanol [7].

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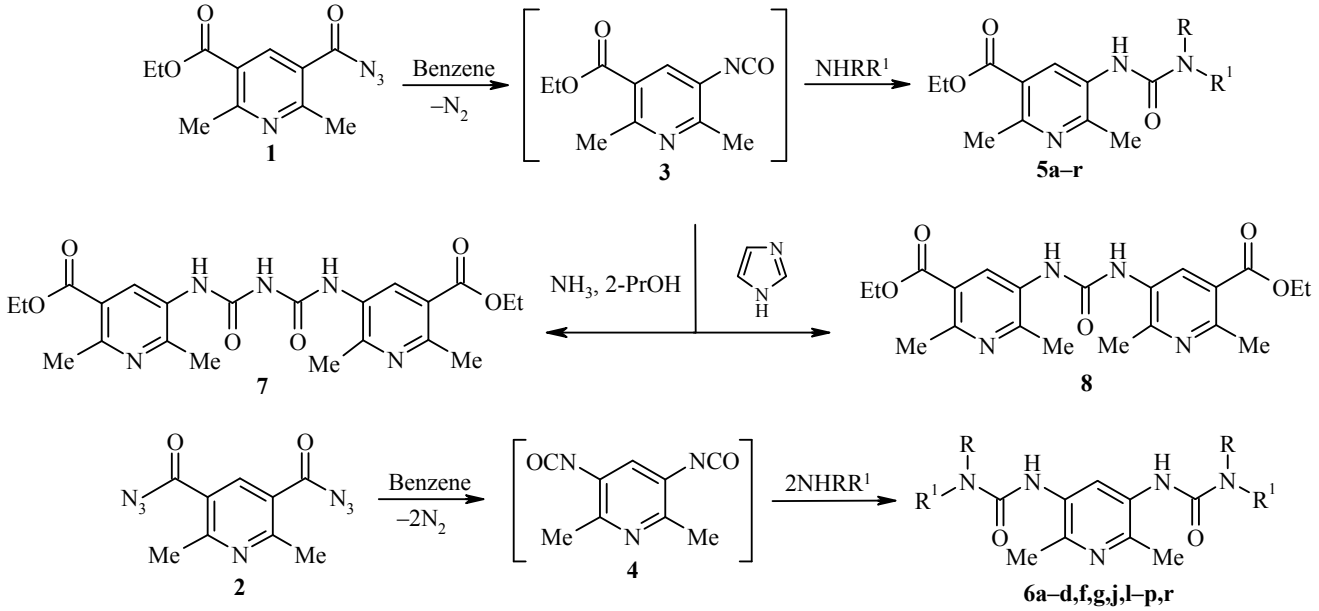
A decrease in the melting points was observed for the compounds **5a-r**, **6a-d**,**f**,**g**,**j**,**l-p**,**r** with increasing the degree of substitution at the nitrogen atom (Table 1). For example, the monoureas **5b-o** are high-melting substances (mp 170-220°C) in contrast to the ureas **5p-r** obtained from secondary amines (mp < 150°C). The diureas **6b**,**c**,**f**,**g**,**j**,**l-o**, containing primary amines, decompose at 280-320°C, whereas the diureas **6p**,**r**, containing the diethylamine and morpholine fragments, have mp < 200°C.



1 **3** **5a–r** **7** **8** **2** **4** **6a–d,f,g,j,l–p,r**

a–**o** R = H, **a** R^1 = H, **b** R^1 = Ph, **c** R^1 = 1-naphthyl, **d** R^1 = 2-MeC_6H_4, **e** R^1 = 3-MeC_6H_4, **f** R^1 = 4-MeC_6H_4, **g** R^1 = 2-$MeOC_6H_4$, **h** R^1 = 3-$MeOC_6H_4$, **i** R^1 = 4-$EtOC_6H_4$, **j** R^1 = 4-HOC_6H_4, **k** R^1 = 4-HO-2,6-$Me_2C_6H_2$, **l** R^1 = 4-BrC_6H_4, **m** R^1 = Bn, **n** R^1 = *c*-Hex, **o** R^1 = 2-Py; **p** R = R^1 = Et, **q** R+R^1 = $(CH_2)_5$, **r** R+R^1 = $(CH_2)_2O(CH_2)_2$

In the high-frequency region of the IR spectra of ureas **5a-r**, **6a-d**,**f**,**g**,**j**,**l-p**,**r**, the NH group stretching bands are observed in the 3350-3270 cm^{-1} range (Tables 2 and 3). The NH_2 group stretching bands at 3450-3400 cm^{-1} are observed in the spectra of ureas **5a** and **6a**. The presence of ester and urea groups in compounds **5a-r** is confirmed by the presence of intense absorption band in the 1760-1720 cm^{-1} (ethoxycarbonyl fragment) and 1690-1635 cm^{-1} regions (amide band I). Only the amide band I in the 1700-1640 cm^{-1} range was observed in the spectra of diureas **6a-d**,**f**,**g**,**j**,**l-p**,**r**.

Signals of the non-equivalent methyl groups in the positions 2 and 6 of the pyridine ring with chemical shifts of 2.36-2.56 and 2.50-2.71 ppm respectively are present in the ^1H NMR spectra of ureas **5a-r** (Tables 2 and 3). The position of the γ-H proton signal of the pyridine ring (a singlet in the 7.91-8.80 ppm range) depends on the electronic influence of the β-position substituent (Table 1). In the spectra of the ureas **5b-j**,**l-o**, which contain an aryl substituent at the nitrogen atom, this signal is shifted by 0.6-0.8 ppm to low field in comparison with the γ-proton position in the spectrum of the monosubstituted urea **5a.** In the spectra of ureas **5k**,**p-r** this signal is shifted by 0.6-0.7 ppm to high field, which is probably connected to the increased electron density on the pyridine ring due to the electron-donor substituents in the urea fragment. In the spectra of *N,N'*-disubstituted ureas, containing aromatic and pyridine fragments, the NH group proton signals appear as two singlets in the 7.29-9.64 ppm region, which is in agreement with literature data [3, 8, 9]. For *N,N,N'*-trisubstituted ureas **5p-r**, the NH group proton signal appears in the 7.65-8.25 ppm region, which permits the assignment of the more high-field NH proton signal in the spectra of *N,N'*-disubstituted ureas to the NH group attached to the pyridine ring (Table 2).

TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
5a	$C_{11}H_{15}N_3O_3$	55.75 / 55.69	6.48 / 6.37	17.85 / 17.71	145-147	55
5b	$C_{17}H_{19}N_3O_3$	65.25 / 65.16	6.28 / 6.11	13.35 / 13.41	185-186	99
5c	$C_{21}H_{21}N_3O_3$	69.75 / 69.41	5.68 / 5.82	11.65 / 11.56	180-182	70
5d	$C_{18}H_{21}N_3O_3$	66.15 / 66.04	6.58 / 6.47	12.75 / 12.84	220-221	93
5e	$C_{18}H_{21}N_3O_3$	66.11 / 66.04	6.38 / 6.47	12.95 / 12.84	175-177	95
5f	$C_{18}H_{21}N_3O_3$	66.19 / 66.04	6.61 / 6.47	12.95 / 12.84	178-180	94
5g	$C_{18}H_{21}N_3O_4$	62.75 / 62.96	6.28 / 6.16	12.35 / 12.24	173-175	92
5h	$C_{18}H_{21}N_3O_4$	62.83 / 62.96	6.03 / 6.16	12.13 / 12.24	160-162	96
5i	$C_{19}H_{23}N_3O_4$	63.97 / 63.85	6.56 / 6.49	11.85 / 11.76	198-200	98
5j	$C_{17}H_{19}N_3O_4$	62.09 / 62.00	5.68 / 5.81	12.84 / 12.76	272-275 (decomp.)	96
5k	$C_{19}H_{23}N_3O_4$	63.75 / 63.85	6.57 / 6.49	11.89 / 11.76	203-205	85
5l	$C_{17}H_{18}BrN_3O_3$	52.21 / 52.06	4.48 / 4.63	10.56 / 10.71	215-216	87
5m	$C_{18}H_{21}N_3O_3$	66.15 / 66.04	6.32 / 6.47	12.93 / 12.84	180-182	90
5n	$C_{17}H_{25}N_3O_3$	64.07 / 63.93	7.68 / 7.89	13.31 / 13.16	195-197	88
5o	$C_{16}H_{18}N_4O_3$	61.26 / 61.14	5.48 / 5.77	17.65 / 17.82	193-194	99
5p	$C_{15}H_{23}N_3O_3$	61.65 / 61.41	7.78 / 7.90	14.16 / 14.32	128-130	77
5q	$C_{16}H_{23}N_3O_3$	62.77 / 62.93	7.48 / 7.59	13.59 / 13.76	118-119	67
5r	$C_{15}H_{21}N_3O_4$	58.74 / 58.62	6.67 / 6.89	13.82 / 13.67	110-112	45
6a	$C_9H_{13}N_5O_2$	48.65 / 48.42	5.94 / 5.87	31.23 / 31.37	250 (subl.)	60
6b	$C_{21}H_{21}N_5O_2$	67.31 / 67.18	5.49 / 5.64	18.53 / 18.65	300-305 (decomp.)	95
6c	$C_{29}H_{25}N_5O_2$	73.41 / 73.25	5.45 / 5.30	14.59 / 14.73	295-300 (decomp.)	88
6d	$C_{23}H_{25}N_5O_2$	68.63 / 68.47	6.13 / 6.25	17.41 / 17.36	320-325 (decomp.)	90
6f	$C_{23}H_{25}N_5O_2$	68.65 / 68.47	6.38 / 6.25	17.21 / 17.36	280-282	93
6g	$C_{23}H_{25}N_5O_4$	63.58 / 63.44	5.87 / 5.79	15.87 / 16.08	315-320 (decomp.)	85
6j	$C_{21}H_{21}N_5O_4$	62.03 / 61.91	5.35 / 5.20	17.04 / 17.19	310-315 (decomp.)	70
6l	$C_{21}H_{19}Br_2N_5O_2$	47.21 / 47.30	3.72 / 3.59	12.97 / 13.13	275-280 (decomp.)	77
6m	$C_{23}H_{25}N_5O_2$	68.34 / 68.47	6.39 / 6.25	17.49 / 17.36	315-320 (decomp.)	80
6n	$C_{21}H_{33}N_5O_2$	65.19 / 65.09	8.35 / 8.58	18.21 / 18.07	280-282	83
6o	$C_{19}H_{19}N_7O_2$	60.32 / 60.47	5.16 / 5.07	26.06 / 25.98	289-291	91
6p	$C_{17}H_{29}N_5O_2$	60.99 / 60.87	8.63 / 8.71	20.68 / 20.88	198-200	65
6r	$C_{17}H_{25}N_5O_4$	56.32 / 56.19	7.05 / 6.93	19.12 / 19.27	205-207	67

TABLE 2. Spectroscopic Characteristics of Compounds **5a-r**

Compound	IR spectrum (KBr), ν, cm^{-1}			^{1}H NMR spectrum (DMSO-d_6+CCl_4), δ, ppm (*J*, Hz)							
	ν_{NH}	$\nu_{OC=O}$	$\nu_{NHC=O}$	COOEt		2,6-CH_3 (3H, s) and (3H, s)		H-4 (1H, s)	NH (1H, s)	NH (1H, s)	Other protons
				CH_3 (3H, t)	CH_2 (2H, q)						
1	2	3	4	5	6	7	8	9	10	11	12
5a	3400*, 3280	1760	1690	1.33 (*J* = 7.2)	4.31	2.54	2.71	8.06	9.64	—	4.55 (2H, s, NH_2)
5b	3300	1750	1660	1.39 (*J* = 7.1)	4.32	2.45	2.61	7.91	8.66	8.79	6.89 (1H, t, *J* = 7.2, H-4'); 7.21 (2H, t, *J* = 7.2, H-3',5'); 7.43 (2H, d, *J* = 7.2, H-2',6')
5c	3300	1755	1660	1.32 (*J* = 6.9)	4.30	2.56	2.64	8.75	8.59	9.22	7.47-7.69 (4H, m, H-5',6',7',8'); 7.95 (1H, d, *J* = 8.0, H-4'); 7.99 (1H, d, *J* = 8.0, H-3'); 8.17 (1H, d, *J* = 8.0, H-2')
5d	3290	1745	1660	1.32 (*J* = 7.0)	4.30	2.47	2.62	8.65	8.07	8.22	2.27 (3H, s, $ArCH_3$); 6.87 (1H, t, *J* = 7.2, H-5'); 7.04-7.10 (2H, m, H-3',4'); 7.82 (1H, d, *J* = 7.2, H-6')
5e	3300	1750	1660	1.38 (*J* = 7.1)	4.32	2.48	2.61	8.68	7.97	8.82	2.30 (3H, s, $ArCH_3$); 6.70 (1H, d, *J* = 6.4, H-4'); 7.05 (1H, t, *J* = 6.4, H-5'); 7.15 (1H, d, *J* = 6.4, H-6'); 7.32 (1H, s, H-2')
5f	3320, 3270	1750	1660	1.38 (*J* = 7.1)	4.33	2.47	2.62	8.67	7.87	8.72	2.27 (3H, s, $ArCH_3$); 6.98 (2H, d, *J* = 6.7, H-3',5'); 7.28 (2H, d, *J* = 6.7, H-2',6')
5g	3260	1750	1660	1.38 (*J* = 6.9)	4.31	2.49	2.62	8.65	8.58	8.59	3.94 (3H, s, OCH_3); 6.76–6.87 (3H, m, H-3',4',5'); 8.15 (1H, d, *J* = 7.1, H-6')
5h[*2]	3290	1755	1650	1.41 (*J* = 6.8)	4.36	2.50	2.63	8.68	7.88	8.78	3.78 (3H, s, OCH_3); 6.44 (1H, d, *J* = 6.4, H-6'); 6.84 (1H, d, *J* = 6.4, H-4'); 7.07 (1H, t, *J* = 6.4, H-5'); 7.20 (1H, s, H-2')
5i	3310	1750	1660	1.38 (*J* = 6.7)	4.32	2.47	2.62	8.69	7.79	8.58	1.42 (3H, t, *J* = 7.0, 4'-$CH_2C\underline{H}_3$); 3.96 (2H, q, *J* = 7.0, 4'-$C\underline{H}_2CH_3$); 6.73 (2H, d, *J* = 8.0, H-3',5'); 7.29 (2H, d, *J* = 8.0, H-2',6')
5j	3390*[3], 3300	1720	1650	1.31 (*J* = 6.9)	4.29	2.50	2.61	8.67	8.08	9.11	6.70 (2H, d, *J* = 9.0, H Ar) 7.23 (2H, d, *J* = 9.0, H Ar); 8.83 (1H, s, OH)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
5k	3280	1755	1650	1.30 (J = 6.6)	4.27	2.46	2.61	7.91	8.21	8.65	2.12 (6H, s, 2',6'-CH_3); 6.48 (2H, s, H-3',5'); 9.18 (1H, s, OH)
5l	3330	1740	1660	1.32 (J = 6.9)	4.31	2.48	2.62	8.64	8.31	9.37	7.46 (4H, s, H Ar)
5m*2	3330	1720	1640	1.37 (J = 7.0)	4.25-4.36*4	2.40	2.60	8.66	6.94*5	7.81	4.25-4.36 (2H, m, CH_2Ph); 7.18-7.25 (1H, m, H Ph); 7.28-7.35 (4H, m, H Ph);
5n	3310	1745	1650	1.39 (J = 6.8)	4.29	2.40	2.60	8.68	6.20-6.28*4	7.48	1.10-1.29 (4H, m, $2CH_2$ cyclohexyl); 1.55-1.82 (6H, m, $3CH_2$ cyclohexyl); 3.48–3.56 (1H, m, 1-CH cyclohexyl)
5o*2	3225	1720	1690	1.39 (J = 7.6)	4.33	2.49	2.50	8.80	9.82	11.10	6.92-6.98 (1H, m, H-5'); 7.27 (1H, d, J = 8.0, H-3'); 7.64-7.72 (1H, m, H-4'); 8.23 (1H, d, J = 4.8, H-6')
5p*2	3250	1720	1635	1.37 (J = 7.4)	4.29	2.38	2.67	7.95	7.84	—	1.16 (6H, t, J = 6.8, $2CH_3$); 3.32 (4H, q, J = 6.8, $2CH_2$)
5q	3250	1740	1650	1.31 (J = 6.6)	4.28	2.36	2.64	7.95	8.25	—	1.43-1.65 (6H, m) and 3.37-3.46 (4H, m, $(CH_2)_5$)
5r	3240	1725	1645	1.39 (J = 6.7)	4.32	2.38	2.67	7.98	8.05	—	3.38–3.46 (4H, m) and 3.59–3.66 (4H, m, $4CH_2$ morpholine)

* $\nu_{(NH_2)}$.

*2 Solvent DMSO-d_6.

*3 $\nu_{(OH)}$.

*4 Multiplet.

*5 Broad singlet.

TABLE 3. Spectroscopic Characteristics of Compounds **6a-d**,**f**,**g**,**j**,**l-p**,**r**

Compound	IR spectrum (KBr), ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)				
	ν_{NH}	$\nu_{NH-C=O}$	2,6-CH_3 (6H, s)	H-4 (1H, s)	2NH (2H, s)	2NH (2H, s)	Other protons
6a*	3450*[2] 3320	1700	2.25	8.26	7.71	—	5.95 (4H, s, $2NH_2$)
6b	3290	1655	2.35	8.50	7.77	8.66	6.87 (2H, t, *J* = 6.7, 2H-4'); 7.19 (4H, t, *J* = 6.7, 2H-3',5'); 7.41 (4H, d, *J* = 6.7, 2H-2',6')
6c	3305	1650	2.46	8.74	8.22	9.12	7.47-7.63 (8H, m, 2H-5',6',7',8'); 7.96 (2H, d, *J* = 8.1, 2H-4'); 8.01 (2H, d, *J* = 8.1, 2H-3'); 8.20 (2H, d, *J* = 8.1, 2H-2')
6d	3280	1655	2.37	8.37	7.92	8.15	2.29 (6H, s, $2ArCH_3$); 6.83–6.89 (2H, m, 2H-5'); 7.00-7.12 (4H, m, 2H-3',4'); 7.82 (2H, d, *J* = 6.6, 2H-6')
6f	3290	1660	2.32	8.47	7.52	8.52	2.25 (6H, s, $2ArCH_3$); 6.97 (4H, d, *J* = 6.8, 2H-3',5'); 7.28 (4H, d, *J* = 6.8, 2H-2',6')
6g	3350 3280	1665	2.37	8.38	8.16	8.42	3.91 (6H, s, $2OCH_3$); 6.80–6.95 (6H, m, 2H-3',4',5'); 8.13 (2H, d, *J* = 7.6, 2H-6')
6j	3300	1660	2.34	8.58	7.85	8.66	6.68 (4H, d, *J* = 9.0, H Ar); 7.23 (4H, d, *J* = 9.0, H Ar); 9.07 (2H, s, 2OH)
6l	3280	1655	2.36	8.57	8.08	9.16	7.45 (8H, s, H Ar)
6m	3310	1650	2.31	8.36	6.61	7.49	4.32 (4H, s, $2CH_2Ph$); 7.12-7.25 (2H, m, H Ph); 7.27-7.35 (8H, m, H Ph)
6n	3300	1655	2.24	8.39	6.25*[3]	7.43	1.05-1.90 (20H, m) and 3.35-3.50 (2H, m, $2C_6H_{11}$)
6o	3225	1695	2.46	8.93	9.83	10.89	7.0-7.06 (2H, m, 2H-5'); 7.32 (2H, d, *J* = 8.4, 2H-3'); 7.68-7.83 (2H, m, 2H-4'); 8.28 (2H, d, *J* = 6.2, 2H-6')
6p	3340	1660	2.31	7.61	7.35	—	1.05-1.25 (12H, m, $4CH_2C\underline{H}_3$); 3.31-3.39 (8H, m, $4C\underline{H}_2CH_3$)
6r	3245	1640	2.30	7.41	7.95	—	3.41-3.43 (8H, m) and 3.55-3.67 (8H, m, $8CH_2$ morpholine)

*[1] Solvent DMSO-d_6.

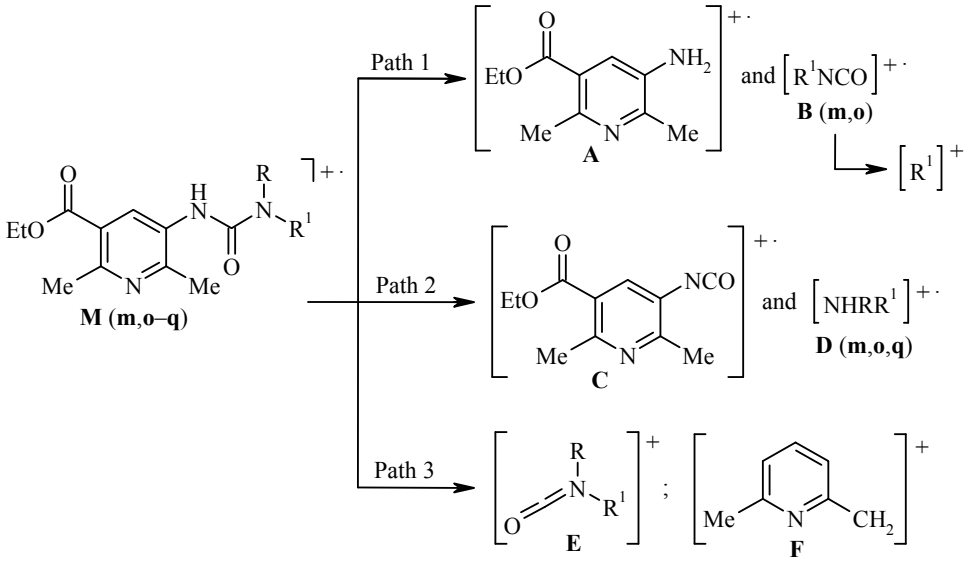
*[2] $\nu_{(NH_2)}$.

*[3] Broad singlet.

Substitution of ester group by urea in compounds **6a-d**,**f**,**g**,**j**,**l-p**,**r** leads to an upfield shift by 0.09-0.16 ppm of the methyl group proton signals at the positions 2 and 6 of the pyridine ring; the signal of the γ-proton on the pyridine ring is shifted upfield by 0.1-0.3 ppm due to the presence of aryl substituents in the compounds **6a-d**,**f**,**g**,**j**,**l**, and by 0.4-0.6 ppm in the case of compounds **6p**,**r** containing a diethylamine and morpholine fragment, respectively. The signals of the protons of the NH groups are also shifted upfield by 0.1-0.4 ppm, in comparison with the positions of these protons in the spectra of the corresponding monoureas **5a-d**,**f**,**g**,**j**,**l-p**,**r**.

It should be noted that in compounds **5o** and **6o,** obtained with 2-aminopyridine, the proton signal of one of the urea NH groups is strongly shifted downfield and appears at 11.10 and 10.89 ppm, respectively. This may be connected to the formation of intramolecular hydrogen bond between the nitrogen atom of the pyridine ring substituent and the proton of the NH group of the urea group, analogous to the hydrogen bond in *N*,*N*'-dipyridylureas [2], which leads to a considerable downfield shift of one of the NH group signals.

Ureas with different degrees of substitution at the nitrogen atom have different disintegration patterns under the influence of electron impact [10]. The most characteristic for *N*,*N*'-disubstituted aryl-containing ureas is the formation of the corresponding isocyanate and amine fragments, capable of forming the particular urea (paths 1 and 2). In *N*,*N*,*N*'-trisubstituted ureas decomposition proceeds with the formation of *N*,*N*-disubstituted isocyanate fragments (path 3).



In the mass spectra of *N*,*N*'-disubstituted ureas **5m**,**o** and **8** (Table 4), molecular ion peaks with intensity 12-15% are present, the fragmentation of which is linked to decomposition of the urea fragment (paths 1 and 2) in agreement with [10, 11]. The main direction of decomposition in the case of compounds **5m** and **8** is the formation of the ion of the ethyl ester of 5-amino-2,6-dimethylnicotinic acid (**A**, *m/z* 194), which exhibits the strongest peak in the spectra of these compounds, whereas in the spectra of compound **5o** the 2-aminopyridine peak (**D**$_{o}$, *m/z* 94, path 2) is the strongest. Apparently this is connected to the charge localization on the amino group nitrogen atom, which in better stabilized by resonance at the α-position of the pyridine nucleus, rather than in the β-position. The peaks of the benzylisocyanate ion (**B**$_{m}$, *m/z* 133) and 2-pyridylisocyanate ion (**B**$_{o}$, *m/z* 120) are present in the spectra of these compounds with intensities of 29 and 23% respectively. In the spectra of compound **5m**, the subsequent fragmentation of the ion **B**$_{m}$ probably leads to the appearance of the intense ion peak of the resonance stabilized benzyl ion **R**$^{1}_{m}$ (*m/z* 91, 70%). In the spectrum of compound **5o**, the pyridinium cation peak intensity **R**$^{1}_{o}$ (*m/z* 78, 33%) is lower by almost a half (Table 4).

TABLE 4. Mass Spectra of Ureas **5m**,**o-q** and **8**

Compound	$[M]^{+\bullet}$	*m/z* (I_{rel}, %)						
		A 194	**B**	**R**[1]	**C** 220	**D**	**E**	**F** 106
5m	327 (15)	(100)	133 (29)	91 (70)	(19)	107 (26)	—	(40)
5o	314 (15)	(32)	120 (23)	78 (32)	(4)	94 (100)	—	—
5p	293 (7)	—	—	—	—	—	100 (100)	(26)
5q	305 (20)	—	—	—	(12)	84 (16)	112 (100)	—
8	414 (12)	(100)	—	—	(30)	194 (100)	—	(12)

In the mass spectra of the *N*,*N*,*N*'-trisubstituted ureas **5p**,**q**, there are molecular ion peaks with intensities of 7 and 20%, respectively, the fragmentation of which most probably leads to the formation of disubstituted isocyanate ions **E(p**,**q)** (path 3), which appear in the spectra as the peaks $\mathbf{E_p}$ (*m/z* 100) and $\mathbf{E_q}$ (*m/z* 112) with intensities of 100% (Table 4). The 2,6-dimethylpyridine fragment **F** (*m/z* 106) is present in the spectra of ureas **5m**,**p** and **8** as peaks of medium and low intensity.

Therefore, the azides of 2,6-dimethylpyridine-3,5-dicarboxylic acid and its monoethyl ester react with primary amines, secondary amines and ammonia under the conditions of Curtius rearrangement, to give the corresponding ureas, decomposition of which under electron impact is in agreement with the generally accepted disintegration scheme for this class of compounds.

EXPERIMENTAL

IR spectra of KBr pellets were recorded with a Specord 75IR spectrometer. ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer in a 4:1 mixture of DMSO-d_6 and CCl_4 with TMS as internal standard. Chromato-mass spectrometry was carried out on a Varian 1200L gas chromatograph with a mass spectrometer as detector (0.25 mm×50 m column with SE-30 stationary phase (polymethylsiloxane + 5% phenylsiloxane), helium carrier gas, evaporator temperature 300°C, EI ionization 70 eV). Elemental analysis was carried out with a Vario EL III instrument (Elementar). Melting points were determined in open capillary with an apparatus for melting point determination (PTP). The course of reactions and the purity of the reaction products were monitored by TLC on Sorbfil PTSKh-AF-A plates with iodine vapor visualization.

The 5-ethoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid azide (**1**) was synthesized by a known method [12], and the 2,6-dimethylpyridine-3,5-dicarboxylic acid diazide (**2**) by method [7].

Ethyl 5-[(Aminocarbonyl)amino]-2,6-dimethylnicotinate (5a). 35% Aqueous ammonia (15 ml) was added to monoazide **1**(1.5 g, 6 mmol), and the mixture was refluxed for 30 min. The precipitate which formed on cooling was filtered off, washed with a small amount of water, and crystallized from 2-PrOH.

Ureas 5b-r (General Method). A mixture of monoazide **1**(1.99 g, 8 mmol) and the corresponding amine (9 mmol) in dry benzene (10 ml) was refluxed for 1 h. The solution was cooled, the precipitate was filtered off and crystallized from 2-PrOH. Compounds **5p-r** were isolated by evaporating benzene from the reaction mixture in vacuum with subsequent recrystallization of the residue from 2-PrOH.

Diureas 6a-d,f,g,j,l-p,r (General Method). A mixture of diazide **2** (1.96 g, 8 mmol) and the corresponding amine (18 mmol) in dry benzene (10 ml) was refluxed for 1 h. The solution was cooled, the precipitate was filtered off and crystallized from EtOH. Compounds **6p**,**r** were isolated by evaporation of the benzene from the reaction mixture in vacuum and subsequent recrystallization of the residue from 2-PrOH.

Ethyl 5-({[({[5-(Ethoxycarbonyl)-2,6-dimethylpyridin-3-yl]amino}carbonyl)amino]carbonyl}-amino)-2,6-dimethylnicotinate (7). Dry benzene (50 ml) and a solution of 35% aqueous ammonia (2.5 ml) in

2-PrOH (12 ml) were added to monoazide **1** (5.0 g, 20 mmol). The mixture was refluxed for 1 h, the precipitate was filtered off, dried in air, and recrystallized from 2-PrOH. Yield 3.0 g (65%); mp 197-199°C. IR spectrum, ν, cm^{-1}: 3310, 3140 (ν_{NH}), 1740 (ν_{CO}), 1635 (ν_{NHCO}), 1550 (δ_{NH}), 1455 (δ_{CCH}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (6H, t, *J* = 6.9, $2CH_2C\underline{H}_3$);, 2.43 (6H, s, 2,2'-CH_3); 2.61 (6H, s, 6.6'-CH_3), 4.35 (4H, q, *J* = 6.9, $2C\underline{H}_2CH_3$); 8.60 (2H, s, H-4,4'); 8.72 (2H, s, 2NH); 9.13 (1H, s, NH). Found, %: C 57.91; H 6.08; N 15.18. $C_{22}H_{27}N_5O_6$. Calculated, %: C 57.76; H 5.95; N 15.31.

Ethyl 5-[({[5-(Ethoxycarbonyl)-2,6-dimethylpyridin-3-yl]amino}carbonyl)amino]-2,6-dimethylnicotinate (8). Benzene (25 ml) and imidazole (0.83 g, 12 mmol) were added to monoazide **1** (3 g, 12 mmol). The mixture was refluxed for 1 h. The solution was evaporated, the mixture formed was washed with water, the precipitate was filtered off, washed with water, and crystallized from 2-PrOH. Yield 0.97 g (39%); mp 230-232°C. IR spectrum, ν, cm^{-1}: 3300 (ν_{NH}), 1710 (ν_{CO}), 1550 (δ_{NH}), 1455 (δ_{CCH}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (6H, t, *J* = 7.0, $2CH_2C\underline{H}_3$); 2.52 (6H, s, 2,2'-CH_3); 2.70 (6H, s, 6,6'-CH_3); 4.08-4.76 (4H, m, $2C\underline{H}_2CH_3$); 8.64 (2H, s, H-4,4'); 9.26 (2H, s, 2NH). Found, %: C 61.01; H 6.43; N 13.44. $C_{21}H_{26}N_4O_5$. Calculated, %: C 60.86; H 6.32; N 13.52.

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