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NOVEL ROUTE FOR THE TRANSFORMATION OF A PYRIMIDINE RING USING HYDRAZIDES

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It has been shown from X-ray structural analytical data that the reaction of 2-ethoxycarbonylmethyl-1,4,6-trimethylpyrimidinium iodide with carboxylic acid hydrazides gives pyrazolo[1,5-a]pyrimidine derivatives and not the isomeric triazolo[4,3-a]pyridines previously reported. This novel and previously unreported rearrangement of 1,2-dialkylpyrimidinium salts occurs via recyclization of the pyrimidine ring with inclusion of a fragment of the nucleophilic reagent into the transformation product.

Keywords: pyrimidinium iodide, pyrazolo[1,5-*a*]pyrimidine, Kost–Sagitullin rearrangement, recyclization, X-ray analysis.

The action of hydrazine and its derivatives on quaternary alkylpyrimidinium salts brings about an opening of the pyrimidine ring and subsequent inclusion of the nucleophile in the formed pyrazole or triazole ring [1, 2]. Primary amines with the same salts can also cause pyrimidine ring opening and subsequent closure but not by the reagent but by side amine or alkyl groups *via* Dimroth [3, 4] or Kost–Sagitullin [5, 6] rearrangements respectively. In the Kost–Sagitullin rearrangement the nucleophilic reagent can also enter position 2 of the formed pyridine ring to give the so called "transamination rearrangement" [7-9]. It should also be noted that, when pyrimidinium salts containing a primary amino group in positions 2 and 4 are treated with derivatives of hydrazine, aminoguanidine, and semicarbazide they give both pyrazole and triazole derivatives as well as the products of Dimroth rearrangement [1, 10, 11].

We have previously reported that the treatment of 2-ethoxycarbonylmethyl-1,4,6-trimethylpyrimidinium iodide (**1**) with the aminoguanidine (**2a**) and isoniazid (**2b**) (compounds containing a hydrazine fragment) gives 1,2,4-triazolo[4,3-*a*]pyridine derivatives **4a,b** [12]. It had been suggested that the formation of the bicyclic compound occurs *via* the intermediate adduct **3**, i.e. a transamination rearrangement and then subsequent cyclocondensation. It was also found that the product of demethylation of the starting salt **5** was formed and, in the reaction with the aminoguanidine the Kost–Sagitullin rearrangement product **6**. However, carrying out an X-ray investigation has since shown that the reaction of the isonicotinic acid hydrazide (**2b**) with iodide **1** does not give 4-ethoxycarbonyl-5,7-dimethyl-1-(4-pyridyl)-1,2,4-triazolo[4,3-*a*]pyridine **(4b)** but rather gives the structural isomer 3-ethoxycarbonyl-5,7-dimethyl-2-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidine (**7b**). It should be noted that, for a true proof of the structure of compound **7b**, the previously obtained ^{1}H NMR and mass spectroscopic data proved inadequate and insufficiently informative since they could be virtually identical for both structural isomers **4** and **7**.

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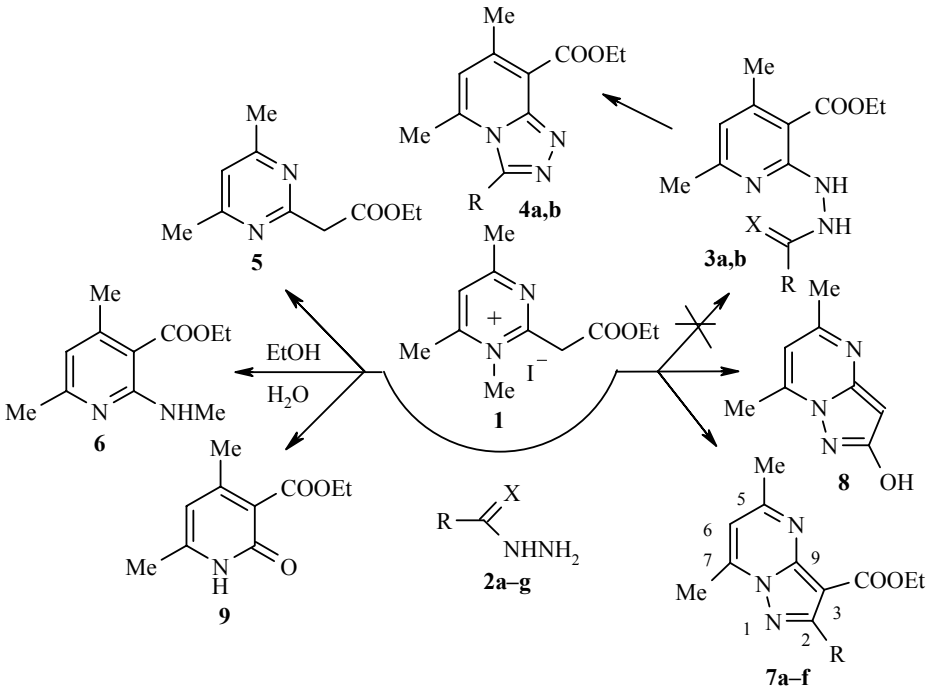

2-4,7 a R = NH_2, **b** R = 4-Py; **2,7 c** R = CH_2CN, **d** R = CH_2Ph, **e** R = (4,6-dimethylpyrimidin-2-yl)methyl, **f** R = Me; **2g** R = H; **2,3 a** X = NH, **b** X = O; **2c-g** X = O

In extending this investigation we have also studied the action of other carboxylic acid hydrazides on the iodide **1** (Tables 1 and 2).

In particular, it was found that heating the cyanoacetic acid hydrazide (**2c**) with salt **1** in absolute ethanol gives 2-cyanomethyl-3-ethoxycarbonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**7c**), the structure of which has been confirmed by X-ray structural analytical data.

Details of the X-ray investigation and the crystallographic data for compounds **7b** and **7c** are given together in Table 3. The structure was solved by a direct method using the SHELXTL method [13]. Hydrogen atomic coordinates were determined from Fourier difference synthesis. In the final step the coordinates of all of the atoms, including the hydrogen atoms and anistropic thermal parameters for the non-hydrogen atoms, were refined together in a full matrix least squares analysis. The interatomic distances and valence and

TABLE 1. Data for the Reaction of Salt **1** with Hydrazides **2b-g**

Hydrazide	Solvent	Time, h	Yields of compounds, %				
			7	**8**	**5**	**6**	**9**
2b	Ethanol	50	37	—	19	—	—
	Water	30	27	—	10	—	23
2c	Ethanol	60	27	16	12	13	—
	Water	25	13	4	8	—	40
2d	Ethanol	20	21	18	12	10	—
2e	Ethanol	30	26	11	15	11	—
2f	Ethanol	27	10	31	15	9	—
	Water	40	—	15	9	—	50
2g	Ethanol	30	—	49	13	22	—

TABLE 2. Characteristics of the Compounds Synthesized **7b-f** and **8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*
		C	H	N		
7b	$C_{16}H_{16}N_4O_2$	64.62 / 64.86	5.34 / 5.40	18.84 / 18.92	153-154	0.63 (1:3)
7c	$C_{13}H_{14}N_4O_2$	60.37 / 60.46	5.41 / 5.43	21.78 / 21.70	168-169	0.62 (1:1)
7d	$C_{18}H_{19}N_3O_2$	69.81 / 69.60	6.10 / 6.15	13.58 / 13.59	109-110	0.54 (1:1)
7e	$C_{18}H_{21}N_5O_2$	63.69 / 63.72	6.17 / 6.19	20.63 / 20.65	145-146	0.55 (1:2)
7f	$C_{12}H_{15}N_3O_2$	61.33 / 61.80	6.28 / 6.44	18.13 / 18.02	124-125	0.59 (1:1)
8	$C_8H_9N_3O$	58.88 / 58.90	5.46 / 5.52	25.79 / 25.77	239-240 240-242°C [13]	0.59 (1:1)

* Eluent toluene–acetone.

conformational angles in the pyrazolo[1,5-*a*]pyrimidines **7b** and **7c** are given in Tables 4-6 and the molecular structures in Figs. 1 and 2. The interatomic distances and valence angles determined from the refined model structure agree with statistical mean data for the corresponding values.

Reaction of iodide **1** with carboxylic acid hydrazides gives compounds **5** and **6** but another pyrazolo[1,5-*a*]pyrimidine derivative 2-hydroxy-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**8**) was also formed. The presence in the ^{1}H NMR spectrum of signals for the two protons (H-3 and H-6) at 5.61 and 6.42 ppm respectively and the absence of signals for the ester group in conjunction with the ^{13}C NMR data (Tables 7

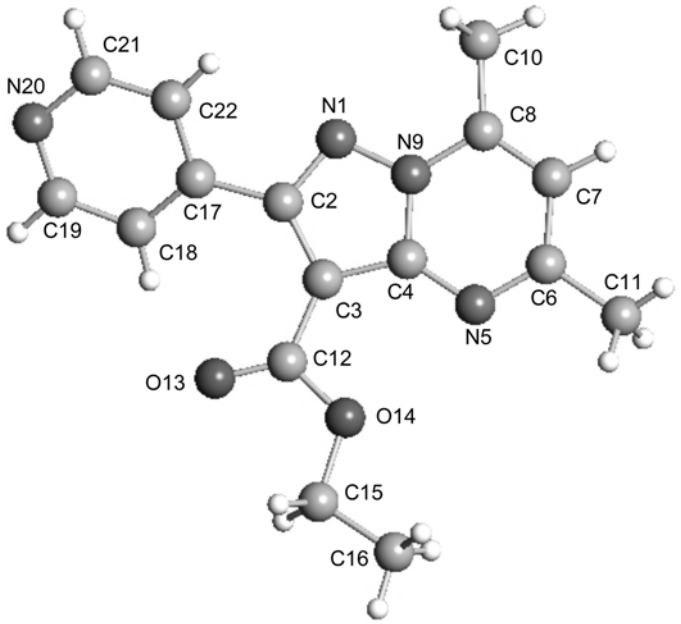

Fig. 1. Atomic structure of the 3-ethoxycarbonyl-5,7-dimethyl-2-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidine (**7b**) molecule with our atomic numbering

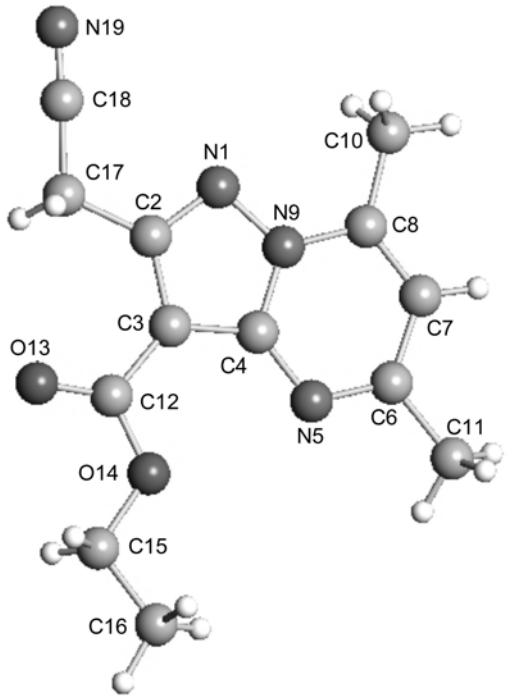

Fig. 2. Atomic structure of the 2-cyanomethyl-3-ethoxycarbonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**7c**) molecule with our atomic numbering.

and 8) and the mass spectra were in complete agreement with the structure for compound **8**. An additional argument in favor of this proposal is the counter synthesis of compound **8** from the hydrazide **2c** and acetylacetone [14] giving a compound with analogous physicochemical properties.

Obtaining the pyrazolo[1,5-*a*]pyrimidine derivatives led us to a new interpretation for this transformation. The scheme for formation of the pyrazolopyrimidines **7** and **8** can be represented in the following way:

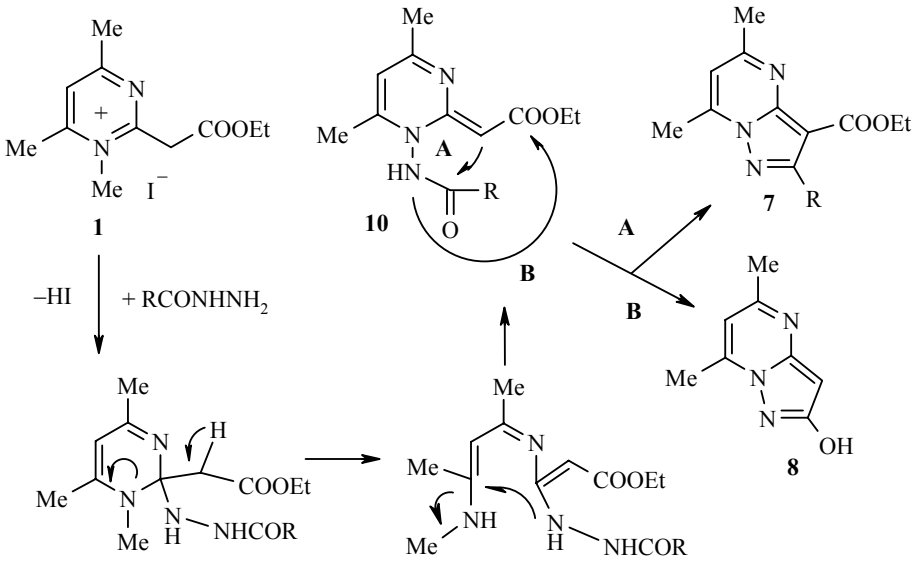

TABLE 3. Experimental X-ray Data

	Compound **7b**	Compound **7c**
Formula	$C_{16}H_{16}N_4O_2$	$C_{13}H_{14}N_4O_2$
Molecular weight	296.33	258.28
Crystal system	Triclinic	Triclinic
Space group	*P*-1 (No.2)	*P*-1 (No.2)
Unit cell parameters		
a, Å	7.6408(15)	8.3450(17)
b, Å	9.845(2)	8.4703(17)
c, Å	11.337(2)	10.793(2)
α	108.03(3)	68.52(3)
β	91.22(3)	70.19(3)
γ	112.66(3)	86.55(3)
V, Å^3	738.7(4)	666.1(3)
Z	2	2
$D_{X\text{-}ray}$, g/cm^3	1.332	1.288
M (MoKα) mm^{-1}	0.091	0.091
F(000)	312	272
Crystal size, cm	0.025 × 0.03 × 0.03	0.03 × 0.023 × 0.03
	Data set	
Temperature, K	293	293
Radiation wavelength, Å	MoKα , λ = 0.71073	MoKα, λ = 0.71073
θ_{min}, θ_{max}	1.9, 30.0	2.0, 30.0
Indices	-10 < *h* < 10; -13 < *k* < 13; 0 < *l* < 15	-11 < *h* <11; -11 < *k* < 11; 0 < *l* < 15
Number of independent measurements, *R*(int)	4500, 4299, 0.022	4081, 3888, 0.008
Number of observed reflections, *I* > 2.0 σ (*I*)	2709	3192
	Refinement	
Number of reflection parameters	4299, 264	3888, 229
R, *w*R2, *S*	0.0509, 0.1381, 1.02	0.0485, 0.1459, 1.04
Max. and Av. Shift/Error	0.00, 0.00	0.00, 0.00
$\Delta\rho_{min}$	-0.21	-0.20
$\Delta\rho_{max}$, e/Å^3	0.23	0.29

Evidently, attack of the hydrazine fragment at position 2 of the pyrimidine [15] and subsequent recyclization gives the intermediate **10** which can then recycle in two ways to form compounds **7a-f** (route **A**) or **8** (route **B**).

Competitive with this transformation is the Kost–Sagitullin rearrangement leading to compound **6**. In the case of attack at the methyl group of the quaternized nitrogen atom the demethylation product **5** is formed. In fact, salt **1** is transformed by four competitive routes.

It should be noted that, for the acetic **2f** and formic **2g** acid hydrazides the basic reaction product is compound **8** which is not formed at all in the case of the aminoguanidine **2a** and isoniazid **2b**. We were unable to separate compound **7g** in the reaction with hydrazide **2g**.

When the reaction was carried in aqueous medium, as in the case of the rearrangement of the same salt using aqueous amine solutions [16], pyridone **9** was formed instead of the normal Kost–Sagitullin rearrangement product.

TABLE 4. Bond Lengths (*l*) in the 3-Ethoxycarbonyl-5,7-dimethyl-2-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidine (**7b**) and 2-Cyanomethyl-3-ethoxycarbonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**7c**) Molecules

Compound **7b**		Compound **7c**	
Bond	*l*, Å	Bond	*l*, Å
$O_{(13)}$–$C_{(12)}$	1.205(2)	$O_{(13)}$–$C_{(12)}$	1.213(18)
$O_{(14)}$–$C_{(12)}$	1.328(2)	$O_{(14)}$–$C_{(12)}$	1.323(16)
$O_{(14)}$–$C_{(15)}$	1.444(3)	$O_{(14)}$–$C_{(15)}$	1.451(19)
$N_{(1)}$–$N_{(9)}$	1.361(2)	$N_{(1)}$–$N_{(9)}$	1.371(14)
$N_{(1)}$–$C_{(2)}$	1.341(2)	$N_{(1)}$–$C_{(2)}$	1.332(16)
$N_{(5)}$–$C_{(4)}$	1.348(2)	$N_{(5)}$–$C_{(4)}$	1.344(15)
$N_{(5)}$–$C_{(6)}$	1.325(2)	$N_{(5)}$–$C_{(6)}$	1.324(17)
$N_{(9)}$–$C_{(4)}$	1.383(2)	$N_{(9)}$–$C_{(4)}$	1.386(14)
$N_{(9)}$–$C_{(8)}$	1.373(2)	$N_{(9)}$–$C_{(8)}$	1.370(16)
$N_{(20)}$–$C_{(19)}$	1.331(3)	$N_{(19)}$–$C_{(18)}$	1.134(2)
$N_{(20)}$–$C_{(21)}$	1.332(3)	$C_{(2)}$–$C_{(3)}$	1.406(16)
$C_{(2)}$–$C_{(3)}$	1.423(2)	$C_{(2)}$–$C_{(17)}$	1.500(2)
$C_{(2)}$–$C_{(17)}$	1.485(2)	$C_{(3)}$–$C_{(4)}$	1.402(17)
$C_{(3)}$–$C_{(4)}$	1.410(2)	$C_{(3)}$–$C_{(12)}$	1.456 (17)
$C_{(3)}$–$C_{(12)}$	1.468(2)	$C_{(6)}$–$C_{(7)}$	1.417(18)
$C_{(6)}$–$C_{(7)}$	1.410(3)	$C_{(6)}$–$C_{(11)}$	1.492(2)
$C_{(6)}$–$C_{(11)}$	1.500(3)	$C_{(7)}$–$C_{(8)}$	1.361(17)
$C_{(7)}$–$C_{(8)}$	1.358(3)	$C_{(8)}$–$C_{(10)}$	1.486(18)
$C_{(8)}$–$C_{(10)}$	1.480(3)	$C_{(15)}$–$C_{(16)}$	1.468(3)
$C_{(15)}$–$C_{(16)}$	1.495(3)	$C_{(17)}$–$C_{(18)}$	1.457(2)
$C_{(17)}$–$C_{(18)}$	1.382(2)	$C_{(7)}$–$H_{(7)}$	0.93(17)
$C_{(17)}$–$C_{(22)}$	1.392(2)	$C_{(10)}$–$H_{(10A)}$	0.94(2)
$C_{(18)}$–$C_{(19)}$	1.384(3)	$C_{(10)}$–$H_{(10B)}$	1.00(3)
$C_{(21)}$–$C_{(22)}$	1.380(3)	$C_{(10)}$–$H_{(10C)}$	0.98(3)
$C_{(7)}$–$H_{(7)}$	0.97(2)	$C_{(11)}$–$H_{(11A)}$	0.96(3)
$C_{(10)}$–$H_{(10A)}$	0.94(3)	$C_{(11)}$–$H_{(11B)}$	0.97(3)
$C_{(10)}$–$H_{(10B)}$	0.97(3)	$C_{(11)}$–$H_{(11C)}$	0.99(3)
$C_{(10)}$–$H_{(10C)}$	0.96(3)	$C_{(15)}$–$H_{(15A)}$	0.99(3)
$C_{(11)}$–$H_{(11A)}$	0.96(4)	$C_{(15)}$–$H_{(15B)}$	0.92(3)
$C_{(11)}$–$H_{(11B)}$	0.99(4)	$C_{(16)}$–$H_{(16A)}$	1.05(2)
$C_{(11)}$–$H_{(11C)}$	0.91(4)	$C_{(16)}$–$H_{(16B)}$	0.90(4)
$C_{(15)}$–$H_{(15A)}$	0.99(3)	$C_{(16)}$–$H_{(16C)}$	1.09(4)
$C_{(15)}$–$H_{(15B)}$	1.05(3)	$C_{(17)}$–$H_{(17A)}$	0.98(3)
$C_{(16)}$–$H_{(16A)}$	0.96(3)	$C_{(17)}$–$H_{(17B)}$	0.97(3)
$C_{(16)}$–$H_{(16B)}$	0.97(3)		
$C_{(16)}$–$H_{(16C)}$	0.96(3)		
$C_{(18)}$–$H_{(18)}$	0.94(2)		
$C_{(19)}$–$H_{(19)}$	0.94(3)		
$C_{(21)}$–$H_{(21)}$	1.00(2)		
$C_{(22)}$–$H_{(22)}$	0.94(2)		

Thus the result obtained not only broaden concepts of recyclization of pyrimidinium salts but also open up a novel route to synthesizing pyrazolo[1,5-*a*]pyrimidines.

TABLE 5. Valence Angles (ω) in the Molecules **7b** and **7c**

Compound **7b**				Compound **7c**			
Angle	ω, deg.	Angle	ω, deg.	Angle	ω, deg.	Angle	ω, deg.
1	2	3	4	5	6	7	8
$C_{(12)}$–$O_{(14)}$–$C_{(15)}$	117.15(16)	$C_{(2)}$–$C_{(17)}$–$C_{(22)}$	118.39(15)	$C_{(12)}$–$O_{(14)}$–$C_{(15)}$	118.07(12)	$C_{(6)}$–$C_{(7)}$–$H_{(7)}$	117.8(10)
$N_{(9)}$–$N_{(1)}$–$C_{(2)}$	104.54(13)	$C_{(18)}$–$C_{(17)}$–$C_{(22)}$	117.07(16)	$N_{(9)}$–$N_{(1)}$–$C_{(2)}$	103.63(9)	$C_{(8)}$–$C_{(7)}$–$H_{(7)}$	121.4(10)
$C_{(4)}$–$N_{(5)}$–$C_{(6)}$	116.77(15)	$C_{(17)}$–$C_{(18)}$–$C_{(19)}$	118.91(17)	$C_{(4)}$–$N_{(5)}$–$C_{(6)}$	116.87(10)	$C_{(8)}$–$C_{(10)}$–$H_{(10A)}$	111.9(14)
$N_{(1)}$–$N_{(9)}$–$C_{(4)}$	113.04(14)	$N_{(20)}$–$C_{(19)}$–$C_{(18)}$	124.62(18)	$N_{(1)}$–$N_{(9)}$–$C_{(4)}$	112.90(10)	$C_{(8)}$–$C_{(10)}$–$H_{(10B)}$	111.8(12)
$N_{(1)}$–$N_{(9)}$–$C_{(8)}$	124.09(14)	$N_{(20)}$–$C_{(21)}$–$C_{(22)}$	123.98(17)	$N_{(1)}$–$N_{(9)}$–$C_{(8)}$	124.75(10)	$C_{(8)}$–$C_{(10)}$–$H_{(10C)}$	109.0(12)
$C_{(4)}$–$N_{(9)}$–$C_{(8)}$	122.82(14)	$C_{(17)}$–$C_{(22)}$–$C_{(21)}$	119.47(17)	$C_{(4)}$–$N_{(9)}$–$C_{(8)}$	122.35(10)	$H_{(10A)}$–$C_{(10)}$–$H_{(10B)}$	108(2)
$C_{(19)}$–$N_{(20)}$–$C_{(21)}$	115.92(17)	$C_{(6)}$–$C_{(7)}$–$H_{(7)}$	119.1(11)	$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	113.48(11)	$H_{(10A)}$–$C_{(10)}$–$H_{(10C)}$	108(2)
$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	112.41(15)	$C_{(8)}$–$C_{(7)}$–$H_{(7)}$	120.2(11)	$N_{(1)}$–$C_{(2)}$–$C_{(17)}$	120.56(11)	$H_{(10B)}$–$C_{(10)}$–$H_{(10C)}$	108(2)
$N_{(1)}$–$C_{(2)}$–$C_{(17)}$	114.68(14)	$C_{(8)}$–$C_{(10)}$–$H_{(10A)}$	112.2(16)	$C_{(3)}$–$C_{(2)}$–$C_{(17)}$	125.95(12)	$C_{(6)}$–$C_{(11)}$–$H_{(11A)}$	113.2(17)
$C_{(3)}$–$C_{(2)}$–$C_{(17)}$	132.91(16)	$C_{(8)}$–$C_{(10)}$–$H_{(10B)}$	111.7(19)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	104.75(10)	$C_{(6)}$–$C_{(11)}$–$H_{(11B)}$	115.7(12)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	104.44(14)	$C_{(8)}$–$C_{(10)}$–$H_{(10C)}$	111.2(13)	$C_{(2)}$–$C_{(3)}$–$C_{(12)}$	126.15(12)	$C_{(6)}$–$C_{(11)}$–$H_{(11C)}$	110.8(16)
$C_{(2)}$–$C_{(3)}$–$C_{(12)}$	129.49(15)	$H_{(10A)}$–$C_{(10)}$–$H_{(10B)}$	104(2)	$C_{(4)}$–$C_{(3)}$–$C_{(12)}$	129.06(11)	$H_{(11A)}$–$C_{(11)}$–$H_{(11B)}$	101(2)
$C_{(4)}$–$C_{(3)}$–$C_{(12)}$	125.89(14)	$H_{(10A)}$–$C_{(10)}$–$H_{(10C)}$	106(3)	$N_{(5)}$–$C_{(4)}$–$N_{(9)}$	121.91(11)	$H_{(11A)}$–$C_{(11)}$–$H_{(11C)}$	104(2)
$N_{(5)}$–$C_{(4)}$–$N_{(9)}$	121.29(15)	$H_{(10B)}$–$C_{(10)}$–$H_{(10C)}$	111(2)	$N_{(5)}$–$C_{(4)}$–$C_{(3)}$	132.87(11)	$H_{(11B)}$–$C_{(11)}$–$H_{(11C)}$	111(2)
$N_{(5)}$–$C_{(4)}$–$C_{(3)}$	133.14(16)	$C_{(6)}$–$C_{(11)}$–$H_{(11A)}$	110(2)	$N_{(9)}$–$C_{(4)}$–$C_{(3)}$	105.22(10)	$O_{(14)}$–$C_{(15)}$–$H_{(15A)}$	110.5(13)
$N_{(9)}$–$C_{(4)}$–$C_{(3)}$	105.58(13)	$C_{(6)}$–$C_{(11)}$–$H_{(11B)}$	113(2)	$N_{(5)}$–$C_{(6)}$–$C_{(7)}$	122.68(12)	$O_{(14)}$–$C_{(15)}$–$H_{(15B)}$	106.7(14)
$N_{(5)}$–$C_{(6)}$–$C_{(7)}$	123.15(16)	$C_{(6)}$–$C_{(11)}$–$H_{(11C)}$	113(2)	$N_{(5)}$–$C_{(6)}$–$C_{(11)}$	117.22(12)	$C_{(16)}$–$C_{(15)}$–$H_{(15A)}$	112.2(12)

TABLE 5 (continued)

1	2	3	4	5	6	7	8
$N_{(5)}–C_{(6)}–C_{(11)}$	116.13(18)	$H_{(11A)}–C_{(11)}–H_{(11B)}$	107(3)	$C_{(7)}–C_{(6)}–C_{(11)}$	120.09(12)	$C_{(16)}–C_{(15)}–H_{(15B)}$	113.0(14)
$C_{(7)}–C_{(6)}–C_{(11)}$	120.72(18)	$H_{(11A)}–C_{(11)}–H_{(11C)}$	107(3)	$C_{(6)}–C_{(7)}–C_{(8)}$	120.80(12)	$H_{(15A)}–C_{(15)}–H_{(15B)}$	107(2)
$C_{(6)}–C_{(7)}–C_{(8)}$	120.68(18)	$H_{(11B)}–C_{(11)}–H_{(11C)}$	107(3)	$N_{(9)}–C_{(8)}–C_{(7)}$	115.38(11)	$C_{(15)}–C_{(16)}–H_{(16A)}$	112.3(13)
$N_{(9)}–C_{(8)}–C_{(7)}$	115.24(16)	$O_{(14)}–C_{(15)}–H_{(15A)}$	109.6(14)	$N_{(9)}–C_{(8)}–C_{(10)}$	118.27(11)	$C_{(15)}–C_{(16)}–H_{(16B)}$	120.7(19)
$N_{(9)}–C_{(8)}–C_{(10)}$	118.40(16)	$O_{(14)}–C_{(15)}–H_{(15B)}$	109.6(13)	$C_{(7)}–C_{(8)}–C_{(10)}$	126.34(13)	$C_{(15)}–C_{(16)}–H_{(16C)}$	92.4(18)
$C_{(7)}–C_{(8)}–C_{(10)}$	126.32(17)	$C_{(16)}–C_{(15)}–H_{(15A)}$	113.7(13)	$O_{(13)}–C_{(12)}–O_{(14)}$	123.53(13)	$H_{(16A)}–C_{(16)}–H_{(16B)}$	116(2)
$O_{(13)}–C_{(12)}–O_{(14)}$	122.95(17)	$C_{(16)}–C_{(15)}–H_{(15B)}$	114.2(12)	$O_{(13)}–C_{(12)}–C_{(3)}$	124.12(12)	$H_{(16A)}–C_{(16)}–H_{(16C)}$	103(2)
$O_{(13)}–C_{(12)}–C_{(3)}$	125.95(16)	$H_{(15A)}–C_{(15)}–H_{(15B)}$	103(2)	$O_{(14)}–C_{(12)}–C_{(3)}$	112.34(11)	$H_{(16B)}–C_{(16)}–H_{(16C)}$	108(3)
$O_{(14)}–C_{(12)}–C_{(3)}$	111.10(15)	$C_{(15)}–C_{(16)}–H_{(16A)}$	111.6(15)	$O_{(14)}–C_{(15)}–C_{(16)}$	107.18(17)	$C_{(2)}–C_{(17)}–H_{(17A)}$	105.3(14)
$O_{(14)}–C_{(15)}–C_{(16)}$	106.9(2)	$C_{(15)}–C_{(16)}–H_{(16B)}$	108.2(15)	$C_{(2)}–C_{(17)}–C_{(18)}$	113.91(14)	$C_{(2)}–C_{(17)}–H_{(17B)}$	109.9(15)
$C_{(2)}–C_{(17)}–C_{(18)}$	124.47(15)	$C_{(15)}–C_{(16)}–H_{(16C)}$	109.2(19)	$N_{(19)}–C_{(18)}–C_{(17)}$	177.2(2)	$C_{(18)}–C_{(17)}–H_{(17A)}$	106.7(13)
$H_{(16A)}–C_{(16)}–H_{(16B)}$	108(2)	$C_{(18)}–C_{(19)}–H_{(19)}$	117.8(13)	$C_{(18)}–C_{(17)}–H_{(17B)}$	106.2(12)	$H_{(17A)}–C_{(17)}–H_{(17B)}$	115(2)
$H_{(16A)}–C_{(16)}–H_{(16C)}$	111(3)	$N_{(20)}–C_{(21)}–H_{(21)}$	117.0(16)				
$H_{(16B)}–C_{(16)}–H_{(16C)}$	109(3)	$C_{(22)}–C_{(21)}–H_{(21)}$	119.0(16)				
$C_{(17)}–C_{(18)}–H_{(18)}$	121.0(12)	$C_{(17)}–C_{(22)}–H_{(22)}$	120.5(12)				
$C_{(19)}–C_{(18)}–H_{(18)}$	120.1(12)	$C_{(21)}–C_{(22)}–H_{(22)}$	119.9(12)				
$N_{(20)}–C_{(19)}–H_{(19)}$	117.6(13)						

TABLE 6. Torsional Angles (δ) in the Molecules **7b** and **7c**

Compound **7b**		Compound **7c**	
Angle	δ, deg	Angle	δ, deg
$C_{(15)}–O_{(14)}–C_{(12)}–O_{(13)}$	-0.4(3)	$C_{(15)}–O_{(14)}–C_{(12)}–O_{(13)}$	-0.4(2)
$C_{(12)}–O_{(14)}–C_{(15)}–C_{(16)}$	-179.5(2)	$C_{(12)}–O_{(14)}–C_{(15)}–C_{(16)}$	-175.24(18)
$N_{(9)}–N_{(1)}–C_{(2)}–C_{(3)}$	-0.11(19)	$C_{(2)}–N_{(1)}–N_{(9)}–C_{(4)}$	0.29(13)
$C_{(2)}–N_{(1)}–N_{(9)}–C_{(8)}$	-177.39(16)	$N_{(9)}–N_{(1)}–C_{(2)}–C_{(3)}$	0.53(14)
$C_{(6)}–N_{(5)}–C_{(4)}–N_{(9)}$	0.2(3)	$C_{(4)}–N_{(5)}–C_{(6)}–C_{(11)}$	179.51(12)
$C_{(4)}–N_{(5)}–C_{(6)}–C_{(11)}$	-179.41(19)	$C_{(6)}–N_{(5)}–C_{(4)}–N_{(9)}$	0.36(17)
$C_{(4)}–N_{(9)}–C_{(8)}–C_{(7)}$	2.3(3)	$N_{(1)}–N_{(9)}–C_{(4)}–N_{(5)}$	178.62(11)
$C_{(8)}–N_{(9)}–C_{(4)}–N_{(5)}$	-2.1(3)	$C_{(8)}–N_{(9)}–C_{(4)}–N_{(5)}$	-0.85(18)
$N_{(1)}–N_{(9)}–C_{(4)}–C_{(3)}$	-0.2(2)	$C_{(4)}–N_{(9)}–C_{(8)}–C_{(7)}$	0.82(17)
$N_{(1)}–N_{(9)}–C_{(8)}–C_{(10)}$	1.8(3)	$N_{(1)}–N_{(9)}–C_{(8)}–C_{(7)}$	-178.59(12)
$C_{(21)}–N_{(20)}–C_{(19)}–C_{(18)}$	0.3(4)	$C_{(3)}–C_{(2)}–C_{(17)}–C_{(18)}$	-177.57(14)
$N_{(1)}–C_{(2)}–C_{(17)}–C_{(18)}$	150.45(19)	$C_{(17)}–C_{(2)}–C_{(3)}–C_{(4)}$	177.57(13)
$C_{(17)}–C_{(2)}–C_{(3)}–C_{(4)}$	-179.15(18)	$C_{(17)}–C_{(2)}–C_{(3)}–C_{(12)}$	-4.2(2)
$C_{(3)}–C_{(2)}–C_{(17)}–C_{(22)}$	152.6(2)	$C_{(12)}–C_{(3)}–C_{(4)}–N_{(5)}$	3.5(2)
$C_{(3)}–C_{(2)}–C_{(17)}–C_{(18)}$	-30.4(3)	$C_{(4)}–C_{(3)}–C_{(12)}–O_{(14)}$	-0.50(19)
$C_{(2)}–C_{(3)}–C_{(4)}–N_{(9)}$	0.09(18)	$C_{(4)}–C_{(3)}–C_{(12)}–O_{(13)}$	178.94(14)
$C_{(2)}–C_{(3)}–C_{(12)}–O_{(13)}$	2.4(3)	$C_{(2)}–C_{(3)}–C_{(12)}–O_{(14)}$	178.27(12)
$C_{(2)}–C_{(3)}–C_{(12)}–O_{(14)}$	177.14(17)	$C_{(11)}–C_{(6)}–C_{(7)}–C_{(8)}$	-179.47(13)
$C_{(4)}–C_{(3)}–C_{(12)}–O_{(13)}$	176.80(18)	$C_{(6)}–C_{(7)}–C_{(8)}–C_{(10)}$	178.74(13)
$N_{(5)}–C_{(6)}–C_{(7)}–C_{(8)}$	-0.9(3)	$C_{(15)}–O_{(14)}–C_{(12)}–C_{(3)}$	179.03(12)
$C_{(6)}–C_{(7)}–C_{(8)}–N_{(9)}$	-0.9(3)	$C_{(2)}–N_{(1)}–N_{(9)}–C_{(8)}$	179.74(12)
$C_{(2)}–C_{(17)}–C_{(18)}–C_{(19)}$	-178.27(19)	$N_{(9)}–N_{(1)}–C_{(2)}–C_{(17)}$	-178.23(12)
$C_{(2)}–C_{(17)}–C_{(22)}–C_{(21)}$	177.4(2)	$C_{(4)}–N_{(5)}–C_{(6)}–C_{(7)}$	0.09(18)
$N_{(20)}–C_{(21)}–C_{(22)}–C_{(17)}$	1.2(4)	$C_{(6)}–N_{(5)}–C_{(4)}–C_{(3)}$	179.80(13)
$C_{(15)}–O_{(14)}–C_{(12)}–C_{(3)}$	179.22(17)	$N_{(1)}–N_{(9)}–C_{(4)}–C_{(3)}$	-0.96(13)
$N_{(9)}–N_{(1)}–C_{(2)}–C_{(17)}$	179.21(14)	$C_{(4)}–N_{(9)}–C_{(8)}–C_{(10)}$	-178.38(12)
$C_{(2)}–N_{(1)}–N_{(9)}–C_{(4)}$	0.2(2)	$N_{(1)}–N_{(9)}–C_{(8)}–C_{(10)}$	2.21(18)
$C_{(4)}–N_{(5)}–C_{(6)}–C_{(7)}$	1.3(3)	$C_{(8)}–N_{(9)}–C_{(4)}–C_{(3)}$	179.57(11)
$C_{(6)}–N_{(5)}–C_{(4)}–C_{(3)}$	-179.18(19)	$N_{(1)}–C_{(2)}–C_{(3)}–C_{(4)}$	-1.11(15)
$C_{(8)}–N_{(9)}–C_{(4)}–C_{(3)}$	177.43(16)	$N_{(1)}–C_{(2)}–C_{(3)}–C_{(12)}$	177.10(12)
$C_{(4)}–N_{(9)}–C_{(8)}–C_{(10)}$	-175.52(19)	$N_{(1)}–C_{(2)}–C_{(17)}–C_{(18)}$	1.0(2)
$N_{(1)}–N_{(9)}–C_{(4)}–N_{(5)}$	-179.66(16)	$C_{(2)}–C_{(3)}–C_{(4)}–N_{(9)}$	1.17(13)
$N_{(1)}–N_{(9)}–C_{(8)}–C_{(7)}$	179.66(18)	$C_{(2)}–C_{(3)}–C_{(4)}–N_{(5)}$	-178.34(13)
$C_{(19)}–N_{(20)}–C_{(21)}–C_{(22)}$	-1.4(4)	$C_{(12)}–C_{(3)}–C_{(4)}–N_{(9)}$	-176.97(12)
$C_{(17)}–C_{(2)}–C_{(3)}–C_{(12)}$	-3.9(3)	$C_{(2)}–C_{(3)}–C_{(12)}–O_{(13)}$	1.2(2)
$N_{(1)}–C_{(2)}–C_{(3)}–C_{(12)}$	175.31(17)	$N_{(5)}–C_{(6)}–C_{(7)}–C_{(8)}$	-0.1(2)
$N_{(1)}–C_{(2)}–C_{(3)}–C_{(4)}$	0.0(2)	$C_{(6)}–C_{(7)}–C_{(8)}–N_{(9)}$	-0.38(19)
$N_{(1)}–C_{(2)}–C_{(17)}–C_{(22)}$	-26.6(2)		
$C_{(12)}–C_{(3)}–C_{(4)}–N_{(9)}$	-175.43(16)		
$C_{(12)}–C_{(3)}–C_{(4)}–N_{(5)}$	4.0(3)		
$C_{(2)}–C_{(3)}–C_{(4)}–N_{(5)}$	179.50(19)		
$C_{(4)}–C_{(3)}–C_{(12)}–O_{(14)}$	-2.8(2)		
$C_{(11)}–C_{(6)}–C_{(7)}–C_{(8)}$	179.8(2)		
$C_{(6)}–C_{(7)}–C_{(8)}–C_{(10)}$	176.8(2)		
$C_{(22)}–C_{(17)}–C_{(18)}–C_{(19)}$	-1.2(3)		
$C_{(18)}–C_{(17)}–C_{(22)}–C_{(21)}$	0.2(3)		
$C_{(17)}–C_{(18)}–C_{(19)}–N_{(20)}$	1.0(4)		

TABLE 7. ^{1}H NMR spectra of Compounds **7b-f** and **8** in DMSO-d_6

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)					
	$OCH_2\underline{CH_3}$, t, *J* = 7.1	5-CH_3, s	7-CH_3, s	OCH_2, q, *J* = 7.1	H-6, s	R
7b	1.27	2.62	2.79	4.32	6.99	7.72 (2H, d. *J* = 6.8, H-2",6"); 8.74 (2H, d, *J* = 6.8, H-3", H-5")
7c	1.44	2.68	2.82	4.44	6.78	4.23 (2H, s, CH_2CN)
7d	1.38	2.62	2.77	4.30	6.83	4.41 (2H, s, 2-CH_2); 7.08-7.29 (5H, m, C_6H_5)
7e	1.19	2.61	2.72	4.14	6.84	2.35 (6H, s, H-4',6'); 4.55 (2H, s, 2-CH_2); 6.86 (H, s, H-5')
7f	1.29	2.59	2.71	4.34	6.82	2.57 (3H, s, 2-CH_3)
8	—	2.44	2.54	—	6.42	5.61 (H, s, H-3); 10.37 (H, br. s, OH)

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer (300, 76 MHz respectively) used in the frames of US CRDF RESC 17-5 program with DMSO-d_6 solvent and TMS internal standard. X-ray analysis was carried out on an Enraf-Nonius CAD-4 refractometer. Mass spectra were recorded on an MK-1321 spectrometer with direct introduction of the sample into the ion source and ionization energy of 70 eV. TLC was carried out on Silufol UV-254 plates and revealed using iodine vapor and the Ehrlich reagent. Preparative separations were carried out by column chromatography on L 5/40 silica gel. Compounds **5** (R_f 0.67, toluene–acetone, 1:1), **6** (R_f 0.62, toluene–acetone, 4:1), and **9** (R_f 0.52, toluene–acetone, 1:2) were identical in melting point and ^{1}H NMR spectrum with known samples and the hydrazides **2b-d,f,g** were prepared similarly to the method for synthesizing compound **2e**. The characteristics and ^{1}H NMR and ^{13}C NMR spectroscopic data for compounds **7b-f** and **8** are given in Tables 2, 7, and 8.

4,6-Dimethyl-2-pyrimidinylacetic Acid Hydrazide (2e). A mixture of ethyl 4,6-dimethyl-2-pyrimidinylacetate (1.94 g, 0.01 mol) and hydrazine hydrate solution (85%, 1 ml, 0.02 mol) was heated in ethanol (10 ml) for 18 h. The solvent and excess hydrazine were distilled off in vacuo and the residue was recrystallized from absolute ethanol (10 ml). Crystals were filtered off and washed with hot hexane to give the hydrazide **2e** (1.69 g, 94%); mp 135-137°C. ^{1}H NMR spectrum, δ, ppm: 2.41 (6H, s, 4- and 6-CH_3); 3.32 (2H, br. s, NH_2); 3.60 (2H, s, CH_2); 6.95 (1H, s, H-5); 9.03 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 23.16 (4- and 6-CH_3); 44.12 (CH_2); 117.15 ($C_{(5)}$); 164.26 ($C_{(2)}$); 165.58 ($C_{(4)}$ and $C_{(6)}$), 167.45 (C=O).

Reaction of Salt 1 with Isonicotinic Acid Hydrazide (2b) in Absolute Ethanol. A mixture of salt **1** (5.1 g, 0.015 mol) and hydrazide **2b** (4.1 g, 0.03 mol) in absolute ethanol (20 ml) was heated for 50 h at ~100°C. Solvent was distilled off and the residue was dissolved in water (10 ml) and extracted with toluene (4 × 10 ml). The toluene extracts were dried using $MgSO_4$ and evaporated in vacuo. The residue was separated on a column (toluene–acetone, 3:1) to give compound **7b** (1.64 g, 37%) and compound **5** (0.55 g, 19%).

Reaction of Salt 1 with Hydrazide 2b in Water. A solution of iodide **1** (1.34 g, 0.004 mol) and hydrazide **2b** (1.1 g, 0.008 mol) in water (10 ml) was heated for 30 h at ~100°C and then extracted with chloroform (3 × 10 ml), dried using $MgSO_4$, and the solvent distilled off. The residue was separated on a column (toluene–acetone, 2:1) to give compound **7b** (0.27 g, 27%), compound **5** (0.075 g, 10%), and compound **9** (0.18 g, 23%).

TABLE 8. ^{13}C NMR Spectra of Compounds **7b-g** and **8**

Compound	Chemical shifts, δ, ppm											
	$OCH_2\underline{CH_3}$	5-CH_3	7-CH_3	O–CH_2	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(9)}$	C=O	R
7b	13.82	16.23	24.28	59.13	148.54	99.54	161.60	110.47	145.19	148.14	161.21	123.45 ($C_{(3')}$ and $C_{(5')}$); 139.90 ($C_{(4')}$); 153.94 ($C_{(1')}$ and $C_{(6')}$)
7c	14.03	16.24	24.80	59.17	149.36	98.53	162.04	110.61	145.62	147.55	161.56	17.80 (2-CH_2); 115.72 (CN)
7d	13.97	16.28	24.07	58.42	158.27	99.89	160.33	109.39	144.85	147.82	161.88	33.60 (2-CH_2); 125.22 ($C_{(4')}$); 127.34 ($C_{(2')}$ and $C_{(4')}$); 128.26 ($C_{(3')}$ and $C_{(5')}$); 138.58 ($C_{(1')}$)
7e	13.82	16.36	24.14	58.23	156.07	99.77	160.26	109.28	144.88	147.93	161.73	23.12 (4'- and 6'-CH_3); 116.6 ($C_{(5')}$); 166.83 ($C_{(2')}$); 165.32 ($C_{(4')}$ and $C_{(6')}$)
7f	14.12	16.28	24.10	58.37	156.26	95.36	162.10	109.20	144.67	147.91	160.26	14.55 (2-CH_3)
8	—	16.40	23.68	—	156.33	99.54	165.67	105.53	143.47	148.47	—	—

Reaction of Salt 1 with Cyanoacetic Acid Hydrazide (2c) in Absolute Ethanol. A mixture of salt **1** (4.08 g, 0.012 mol) and hydrazide **2c** (2.37 g, 0.024 mol) was heated for 50 h in absolute ethanol (15 ml). Solvent was distilled off and the residue was dissolved in water (10-12 ml) and extracted with toluene (3 × 15 ml). The toluene solution was dried using $MgSO_4$, solvent was distilled off, and the residue was separated on a column (toluene–acetone, 4:1) to give compound **7c** (0.85 g, 27%), compound **5** (0.28 g,12%), and compound **6** (0.32 g, 13%). Distillation of solvent from the aqueous solution and preparative separation on a column (toluene–acetone, 1:1) gave compound **8** (0.31 g, 16%). Mass spectrum of compound **8**, *m/z* (I_{rel}, %): 163 (100), 124 (10), 108 (16), 93 (11), 81 (10), 67 (9), 53 (7).

Reaction of Salt 1 with Hydrazide 2c in Water. A mixture of the salt **1** (4.08 g, 0.012 mol) and hydrazide **2c** (2.37 g, 0.024 mol) in water (15 ml) was heated for 25 h. After treatment by the method for compounds **1** and **2b** in ethanol the toluene solution gave compound **5** (0.21 g, 8%) and compound **7c** (0.4 g, 13%) and the aqueous gave compound **9** (0.93 g, 40%) and compound **8** (0.07 g, 4%).

Reaction of Salt 1 with 4,6-Dimethyl-2-pyrimidinylacetic Acid Hydrazide (2e) in Absolute Ethanol. A mixture of salt **1** (1.34 g, 0.004 mol) and hydrazide **2e** (1.44 g, 0.008 mol) in absolute ethanol (7 ml) was heated for 30 h at ~100°C. Solvent was distilled off and the residue was separated preparatively on a column (toluene–acetone, 1:1) to give compound **7e** (0.35 g, 26%), compound **5** (0.12 g, 15%), compound **6** (0.09 g, 11%), and compound **8** (0.07 g, 11%). Mass spectrum of **2e**, *m/z* (I_{rel}, %): 339 (64), 294 (44), 293 (100), 267 (12), 266 (15), 112 (13), 42 (14), 28 (18), 18 (37).

Reaction of Salt 1 with Phenylacetic Acid Hydrazide (2d) in Absolute Ethanol. A solution of salt **1** (2.04 g, 0.006 mol) and hydrazide **2d** (1.8 g, 0.012 mol) in absolute ethanol (10 ml) was heated for 20 h. Treatment similar to that of compounds **1** and **2e** in absolute ethanol gave compound **7d** (0.39 g, 21%), compound **5** (0.14 g, 12%), compound **6** (0.12 g, 10%), and compound **8** (0.18 g, 18%).

Reaction of Salt 1 with Acetic Acid Hydrazide (2f) in Absolute Ethanol. A mixture of salt **1** (1.02 g, 0.003 mol) and hydrazide **2f** (0.44 g, 0.006 mol) in absolute ethanol (8 ml) was heated for 27 h at ~100°C. Solvent was distilled off and the residue was successively washed with hexane and chloroform. Solvent was removed from the hexane extract and the residue was separated on a column (hexane–acetone, 4:1) to give compound **7f** (0.7 g, 10%), compound **5** (0.09 g, 15%), and compound **6** (0.55 g, 9%). Distillation of solvent from the chloroform extract and column chromatography of the residue (toluene–acetone, 2:1) gave compound **8** (0.15 g, 31%).

Reaction of Salt 1 with Hydrazide 2f in Water. A solution of the iodide **1** (1.34 g, 0.004 mol) and hydrazide **2f** (0.66 g, 0.008 mol) in water (10 ml) was heated for 40 h, extracted with hexane and chloroform, and worked up as for compounds **1** and **2f** in absolute ethanol to give compound **5** (0.07 g, 9%) from the hexane solution and compounds **8** (0.1 g, 15%) and **9** (0.39 g, 50%) from the chloroform solution.

Reaction of Salt 1 with Formic Acid Hydrazide 2g in Absolute Ethanol. A mixture of salt **1** (1.02 g, 0.003 mol) and hydrazide **2g** (0.44 g, 0.006 mol) in absolute ethanol (8 ml) was heated for 30 h at ~100°C. Solvent was distilled off and the residue was washed with chloroform and preparatively separated on a column (hexane–acetone, 3:1) to give compound **5** (0.1 g, 13%), compound **6** (0.18 g, 22%), and compound **8** (0.32 g, 49%).

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