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Azines and Azoles: CXXV.[1] New Regioselective Synthesis of 1-Amino-6-methyluracils

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Abstract—Readily accessible 5-acetyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione reacts with substituted hydrazines and carboxylic acid hydrazides under mild conditions to give the corresponding hydrazones. Under severe conditions (heating in boiling dimethylformamide) the reaction is accompanied by extrusion of COS with formation of substituted 1-amino-6-methyluracils. Reactions of 5-acetyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione with monosubstituted alkyl- and arylhydrazines take different pathways, depending on the conditions. Heating of equimolar mixtures of the reactants in ethanol or propan-1-ol leads to the formation of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides rather than 1-amino-6-methyluracil derivatives.

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Among numerous known syntheses of 1-aminouracils, two approaches must be noted. The first of these includes reactions with semicarbazide derivatives [2–4], and the second is based on direct amination of uracil derivatives with such reagents as hydroxylamine *O*-sulfonic acid, which leads to mixtures of 1- and 3-aminosubstituted compounds [5]. As a rule, amination of 6-methyluracil involves almost exclusively the N^3 atom due to steric hindrances created by the 6-methyl group.

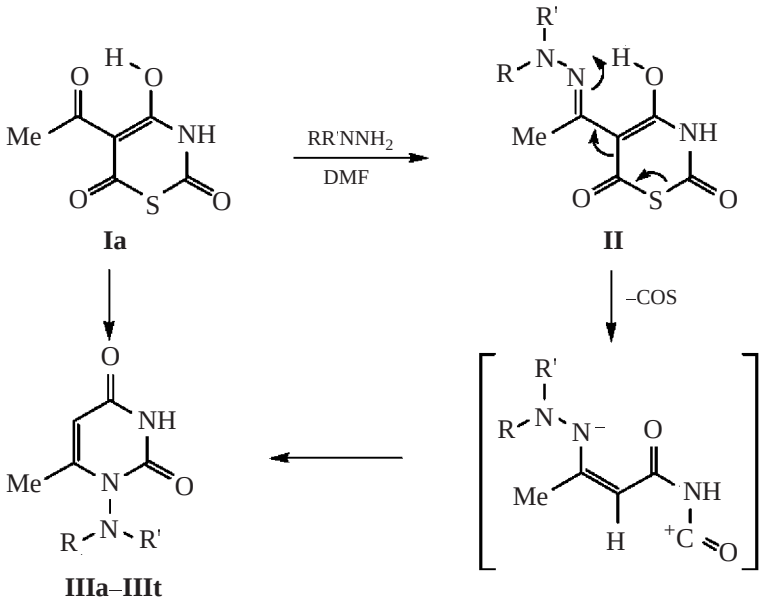
We recently developed a very simple and convenient procedure for the synthesis of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**) from malonic acid, potassium thiocyanate, and acetic anhydride in acetic acid [6, 7]. We showed that 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**) readily reacts under mild conditions with primary amines at the acetyl carbonyl group with formation of the corresponding Schiff bases without opening of the thiazine ring. The reaction under severe conditions (boiling dimethylformamide) is accompanied by extrusion of COS, and the products are 1-substituted 6-methyluracils [6, 8, 9].

Here we report on the reaction of thiazine **Ia** with substituted hydrazines and carboxylic acid hydrazides. We found that thiazine **Ia** very readily and quickly (within 5 min) reacts with hydrazines in dimethylformamide, dioxane, or diethyl ether to produce the corresponding hydrazones. Carboxylic acid hydrazides react similarly to give 90–95% of the corresponding acylhydrazones even at room temperature. For example, in 1–2 min after dissolution of 1 g of thiazine **Ia** and 0.9 g of 2-methoxybenzohydrazide in 8 ml of dimethylformamide at room temperature, the corresponding poorly soluble hydrazone quickly separates from the transparent solution.

Under more severe conditions, surprising, much more interesting, and unpredictable pattern was observed. Heating of equimolar mixtures of thiazine **Ia** and substituted hydrazines in boiling DMF resulted in the formation of 67–86% of 1-amino-6-methyluracil derivatives **IIIa**–**IIIt**. The process was accompanied by evolution of carbonyl sulfide. With a view to determine the scope of this novel reaction, it was performed with various substituted hydrazines. 5-Acetylthiazine **Ia** reacted with alkyl-, aryl-, and hetarylhydrazines under analogous conditions to give 1-amino-6-methyluracil derivatives **IIIa**–**IIIj** (Table 1). Likewise, using carboxylic acid hydrazides we obtained 60–85% of 1-acylamino-6-methyluracils **IIIk**–**IIIs**. Presumably, in all cases the primary product is the corresponding hydrazone which loses COS molecule on heating, and open-chain intermediate thus formed undergoes intramolecular ring closure to 1-amino-6-methyluracil (Scheme 1). In the reaction of 4-aminobenzohydrazide with 2 equiv of

[1] For communication CXXIV see [1].

Scheme 1.



II, III, R = H, R' = Me (**a**), R = R' = Me (**b**), R = H, R' = $PhCH_2$ (**c**), Ph (**d**), 2-MeC_6H_4 (**e**), 4-$O_2NC_6H_4$ (**f**), 2,4,5-$Cl_3C_6H_2$ (**g**), R = R' = Ph (**h**), R = Ph, R' = $PhCH_2$ (**i**), RR'N = $Ph_2C{=}N$ (**j**), R = H, R' = Ac (**k**), R = R' = Ac (**l**), R = H, R' = PrCO (**m**), PhCO (**n**), 2-$MeOC_6H_4CO$ (**o**), 3-$MeOC_6H_4CO$ (**p**), 3-BrC_6H_4CO (**q**), 2-furylCO (**r**), 4-$ClC_6H_4OCH_2CO$ (**s**).

5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**), both amino groups in the former are involved, and the product is bis-uracil derivative **IIIt**. It should be noted that, following an analogous mechanism, thiazine **Ia** is converted into 6-methyl-2*H*-1,3-oxazine-2,4-dione (**IV**, yield 73%) on heating in pyridine.

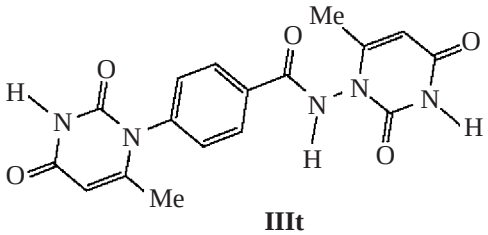
Table 1. Yields, melting points, R_f values, and elemental analyses of 1-amino-6-methyluracils **IIIa**–**IIIt**

Comp. no.	Yield, %	mp, °C	R_f (acetone–hexane, 1 : 1)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIIa	64	172–173	0.34	46.49	5.84	27.11	$C_6H_9N_3O_2$	46.45	5.85	27.08
IIIb	71	186–187	0.42	49.64	6.56	24.79	$C_7H_{11}N_3O_2$	49.70	6.55	24.84
IIIc	78	184–185	0.56	62.28	5.67	18.19	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17
IIId	84	271–273 (decomp.)	0.63	60.77	5.11	19.31	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.34
IIIe	71	285–287 (decomp.)	0.58	62.37	5.68	18.15	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17
IIIf	68	283–285 (decomp.)	0.66	50.45	3.84	21.41	$C_{11}H_{10}N_4O_4$	50.38	3.84	21.37
IIIg	66	275–277	0.46	41.18	2.51	13.12	$C_{11}H_8Cl_3N_3O_2$	41.21	2.52	13.11
IIIh	87	227–229	0.73 [a]	69.71	5.16	14.32	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
IIIi	83	233–235	0.52	70.39	5.57	13.69	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
IIIj	81	207–208	0.43	70.76	4.94	13.77	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76
IIIk	76	237–239	0.45 [a]	45.94	4.96	22.89	$C_7H_9N_3O_3$	45.90	4.95	22.94
IIIl	89	184–185	0.67 [a]	48.07	4.91	18.65	$C_9H_{11}N_3O_4$	48.00	4.92	18.66
IIIm	62	181–182	0.49 [a]	51.12	6.21	19.84	$C_9H_{13}N_3O_3$	51.18	6.20	19.89
IIIn	85	239–241	0.36 [a]	58.71	4.53	17.15	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.13
IIIo	82	265–267	0.29 [a]	56.79	4.75	15.28	$C_{13}H_{13}N_3O_4$	56.72	4.76	15.27

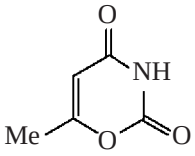
Table 1. (Contd.)

Comp. no.	Yield, %	mp, °C	R_f (acetone–hexane, 1 : 1)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIIp	80	271–272	0.30 [a]	56.66	4.77	15.29	$C_{13}H_{13}N_3O_4$	56.72	4.76	15.27
IIIq	76	249–251	0.32 [a]	44.48	3.12	24.63	$C_{12}H_{10}BrN_3O_3$	44.47	3.11	24.65
IIIr	69	263–265	0.25 [a]	51.09	3.87	17.85	$C_{10}H_9N_3O_4$	51.07	3.86	17.87
IIIs	62	239–240	0.38 [a]	50.38	3.92	11.44	$C_{13}H_{12}ClN_3O_4$	50.42	3.91	11.45
IIIt	54	275–276	0.16 [a]	55.25	4.08	18.97	$C_{17}H_{15}N_5O_5$	55.28	4.09	18.96

[a] Benzene–acetic acid, 10 : 1.



IIIt



IV

The structure of compounds **III** was confirmed by elemental analyses (Table 1) and ^{1}H and ^{13}C NMR, UV, IR, and mass spectra. 1-Amino-6-methyluracil derivatives **IIIa**–**IIIt** showed in the mass spectra (Table 2) the molecular ion peaks and peaks of fragment ions resulting from cleavage of the N–N bond; the latter are often the most abundant ions.

The ^{1}H NMR spectra of compounds **IIIa**–**IIIt** in DMSO-d_6 (Table 3) contain three singlets at δ 11.08–11.76, 5.39–5.74, and 1.87–2.28 ppm from the N^{3}H, 5-H, and 6-CH_3 protons, respectively. The 1-NH proton signal in the spectra of 1-amino-6-methyluracils obtained from monosubstituted hydrazines appears as a singlet at δ 10.42–11.37 (R = acyl) or

Table 2. Mass spectra of 1-amino-6-methyluracils **IIIa**–**IIIt**

Comp. no.	*m/z* (I_{rel}, %)
IIIa	155 M^+ (40), 126 (62), 112 (100), 97 (2), 83 (12), 84 (4), 70 (21), 69 (50), 54 (9), 43 (27), 41 (74)
IIIb	169 M^+ (9), 127 (11), 126 (57), 111 (29), 97 (20), 83 (24), 57 (11), 44 (100), 43 (49), 42 (54)
IIIc	231 M^+ (4), 196 (6), 141 (2), 127 (8), 126 (10), 106 (50), 91 (100), 83 (3), 77 (3), 65 (5), 51 (4), 39 (6)
IIId	217 M^+ (100), 174 (90), 145 (8), 132 (15), 126 (8), 105 (38), 92 (45), 91 (75), 77 (68), 65 (45), 51 (10), 39 (37)
IIIe	231 M^+ (80), 188 (27), 171 (5), 160 (5), 146 (11), 145 (10), 132 (12), 119 (30), 118 (15), 107 (14), 106 (100), 105 (26), 104 (25), 92 (14), 91 (34), 84 (14), 69 (19), 68 (15), 67 (24), 65 (15), 51 (15)
IIIf	262 M^+ (52), 246 (10), 219 (100), 177 (14), 150 (26), 138 (17), 136 (26), 126 (14), 122 (29), 90 (17), 83 (10), 76 (11), 65 (16), 54 (15), 42 (24)
IIIg	323 M^+ (19), 321 M^+ (41), 319 M^+ (45), 278 (28), 276 (28), 243 (38), 241 (57), 211 (10), 209 (36), 207 (36), 198 (32), 197 (26), 196 (96), 195 (47), 194 (100), 193 (30), 181 (13), 179 (14), 171 (9), 169 (28), 167 (29), 160 (13), 158 (15), 145 (7), 133 (5), 124 (8), 109 (10), 107 (8), 97 (11), 88 (10), 82 (9), 74 (8), 67 (10)
IIIh	293 M^+ (60), 250 (13), 233 (4), 201 (5), 180 (3), 168 (100), 167 (44), 125 (3), 115 (3), 91 (4), 77 (22), 51 (12)
IIIi	307 M^+ (8), 182 (30), 181 (86), 180 (19), 173 (18), 126 (3), 115 (3), 105 (6), 106 (4), 104 (8), 91 (100), 77 (60), 65 (11), 51 (10)
IIIj	305 M^+ (100), 262 (40), 261 (95), 247 (6), 233 (4), 221 (8), 195 (10), 185 (20), 180 (60), 165 (42), 152 (3), 144 (5), 139 (6), 131 (8), 118 (4), 104 (3), 84 (13), 77 (80), 67 (12), 54 (10), 51 (30)
IIIk	183 M^+ (22), 141 (96), 98 (59), 70 (11), 43 (100)

Table 2. (Contd.)

Comp. no.	*m/z* (I_{rel}, %)
IIIl	225 M^+ (22), 183 (50), 141 (96), 98 (59), 83 (6), 70 (11), 54 (7), 43 (100)
IIIm	211 M^+ (11), 142 (4), 141 (33), 98 (24), 71 (89), 43 (100), 41 (22)
IIIn	245 M^+ (6), 105 (100), 77 (40), 51 (14), 45 (12)
IIIo	136 (8), 135 (100), 120 (3), 105 (3), 92 (6), 77 (19), 64 (3), 51 (3), 39 (4)
IIIp	275 M^+ (4), 136 (11), 135 (100), 107 (20), 92 (9), 77 (11), 64 (5), 63 (3), 51 (3)
IIIq	325 M^+ (4), 323 M^+ (4), 185 (94), 183 (100), 157 (23), 155 (23), 105 (6), 104 (4), 76 (21), 75 (17), 50 (15)
IIIr	235 M^+ (12), 206 (2), 192 (3), 164 (1), 96 (5), 95 (100), 67 (4), 39 (10)
IIIs	311 M^+ (18), 310 M^+ (9), 309 M^+ (57), 182 (65), 168 (10), 154 (90), 143 (29), 142 (10), 141 (81), 128 (39), 127 (29), 126 (10), 113 (42), 111 (100), 99 (6), 83 (9), 77 (11), 75 (32), 54 (8), 51 (7)
IIIt	369 M^+ (3), 351 (4), 326 (4), 308 (5), 245 (11), 243 (16), 229 (100), 202 (10), 200 (24), 186 (89), 171 (9), 159 (15), 146 (33), 130 (14), 126 (35), 120 (87), 103 (13), 98 (27), 92 (22), 90 (23), 83 (20), 76 (12), 68 (29), 43 (47)

Table 3. UV, IR and ^{1} HNR spectra of 1-amino-6-methylurasils **IIIa**–**IIIt**

Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)				
			N^3H	C^5H	Me	R	R^1
IIIa	207 (0.93), 267 (0.81)	417, 500, 528, 630, 646, 735, 756, 837, 892, 976, 1033, 1070, 1132, 1167, 1197, 1212, 1378, 1400, 1442, 1510, 1580, 1653, 1701, 1717, 2590, 2995, 3100, 3176, 3320, 3448	11.26 s	5.40 s	2.18 s	5.79 q (1H, *J* 5.7)	2.54 d (3H, *J* 5.7)
IIIb	206 (1.29), 238 (1.51), 267 (1.25)	413, 450, 486, 525, 600, 637, 720, 759, 875, 924, 980, 1002, 1029, 1045, 1077, 1151, 1200, 1223, 1263, 1376, 1400, 1441, 1459, 1616, 1669, 1706, 1724, 2796, 2853, 2924, 2962, 3035, 3077, 3432	11.10 s	5.39 s	2.13 s	2.82 s (6H)	
IIIc	210 (1.30), 268 (1.01)	427, 482, 507, 526, 605, 632, 652, 702, 726, 744, 777, 800, 818, 858, 880, 921, 981, 1050, 1090, 1194, 1374, 1389, 1409, 1452, 1470, 1493, 1512, 1605, 1669, 1697, 1717, 2806, 2830, 2850, 2886, 2937, 2975, 3005, 3066, 3084, 3185, 3291, 3410	11.20 s	5.33 s	1.98 s	6.06 t (1H, *J* 4.9)	7.36–7.29 m (5H), 4.02 d (2H, *J* 4.9)
IIId	208 (1.63), 231 (1.46), 262 (1.42)	428, 492, 508, 530, 593, 618, 635, 692, 704, 758, 850, 872, 895, 965, 975, 1027, 1035, 1081, 1179, 1198, 1250, 1373, 1392, 1444, 1457, 1496, 1424, 1600, 1677, 1698, 1716, 2793, 2822, 2885, 3019, 3129, 3276, 3289, 3400	11.38 s	5.60 s	2.11 s	8.67 s (1H)	7.21 t (2H, *J* 7.3), 6.83 t (1H, *J* 7.3), 6.64 d (2H, *J* 7.3)

Table 3. (Contd.)

Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)				
			N^3H	C^5H	Me	R	R^1
IIIe	207 (1.63), 229 (0.88), 264 (0.93)	432, 511, 525, 546, 565, 593, 628, 639, 673, 719, 754, 784, 857, 935, 977, 1001, 1041, 1079, 1111, 1154, 1184, 1200, 1215, 1252, 1304, 1387, 1430, 1444, 1462, 1486, 1519, 1590, 1609, 1663, 1705, 1897, 1933, 1957, 2060, 2177, 2397, 2466, 2610, 2773, 2943, 2816, 3035, 3085, 3179, 3322, 3431	11.28 s	5.49 d (J 1.2)	2.10 s	7.93 s (1H)	7.04 d (2H, J 7.3), 7.00 d.t (1H, J 0.8, 7.8), 6.74 d.t (1H, J 0.7, 7.8), 6.30 d (1H, J 7.8), 2.16 s (3H)
IIIf	207 (1.79), 257 (0.96), 334 (1.26)	414, 431, 496, 516, 526, 554, 582, 628, 656, 693, 714, 753, 824, 850, 878, 978, 1000, 1049, 1081, 1112, 1181, 1204, 1216, 1279, 1311, 1343, 1377, 1390, 1405, 1426, 1459, 1491, 1501, 1546, 1594, 1672, 1725, 1923, 1958, 3081, 3146, 3292, 3434	11.53 s	5.66 s	2.08 s	9.70 s (1H)	8.11 d (2H, J 9.1), 6.83 d (2H, J 9.1)
IIIg	207 (2.16), 212 (1.95), 263 (0.81)	424, 454, 483, 527, 557, 567, 578, 630, 694, 719, 735, 749, 766, 798, 811, 826, 856, 883, 909, 982, 1004, 1041, 1080, 1140, 1182, 1214, 1231, 1258, 1272, 1383, 1404, 1449, 1462, 1503, 1569, 1609, 1680, 1728,1968, 2810, 2834, 2847, 2932, 3009, 3063, 3089, 3152, 3211, 3290, 3434	11.15 s	5.44 s	2.28 s	8.22 s (1H)	7.31 s (2H)
IIIh	207 (1.92), 267 (1.19)	422, 450, 508, 571, 622, 655, 691, 707, 750, 761, 826, 882, 893, 910, 919, 962, 980, 1000, 1030, 1037, 1050, 1169, 1181, 1079, 1156, 1222, 1272, 1323, 1368, 1377, 1390, 1421, 1439, 1459, 1493, 1589, 1625, 1686, 1712, 2975, 3074, 3217, 3406	11.57 s	5.51 s	2.09 s		7.32–7.37 m (4H), 7.05–7.10 m (6H)
IIIi	211 (1.93), 237 (1.75), 267 (1.32)	406, 433, 517, 536, 554, 574, 693, 704, 716, 754, 773, 821, 879, 898, 978, 1028, 1041, 1081, 1201, 1212, 1276, 1372, 1413, 1454, 1464, 1494, 1583, 1597, 1616, 1666, 1727, 1975, 2341, 2361, 2802, 2823, 2852, 2915, 3006, 3131, 3435	11.45 s	5.42 s	1.87 s	7.34–7.40 m (4H), 7.30–7.33 d.d (1H), 7.25–7.30 d.t (2H), 7.91 t (1H, J 7.5), 6.78 d (2H, J 7.5), 5.08 d (1H, J 11.8), 4.66 d (1H, J 11.8)	
IIIj	207 (2.45), 253 (1.13), 275 (1.31), 320 (0.39)	407, 425, 504, 533, 557, 573, 655, 667, 694, 727, 746, 767, 777, 795, 809, 843, 880, 970, 1001, 1038, 1080, 1175, 1303, 1320, 1373, 1406, 1431, 1444, 1463, 1490, 1561, 1653, 1711, 1969, 2343, 2362, 2787, 2854, 2925, 3029, 3176, 3423	11.08 s	5.52 s	2.23 s	7.59–7.64 t (3H), 7.43–7.52 m (5H), 7.22–7.26 d.d (2H)	

Table 3. (Contd.)

Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)				
			N^3H	C^5H	Me	R	R^1
IIIk	209 (2.19), 259 (2.75)	428, 492, 529, 556, 625, 652, 737, 753, 841, 897, 946, 982, 1000, 1014, 1027, 1043, 1089, 1111, 1228, 1243, 1278, 1370, 1400, 1435, 1466, 1519, 1627, 1686, 1708, 1970, 2195, 2300, 2419, 2451, 2496, 2812, 2839, 2897, 2923, 3005, 3095, 3274	11.22 s	5.42 s	2.04 s	10.44 s (1H)	2.01 s (3H)
IIIl	210 (2.01), 261 (2.65)	419, 442, 512, 559, 573, 598, 614, 636, 656, 687, 733, 755, 859, 895, 945, 975, 1003, 1032, 1043, 1057, 1084, 1198, 1236, 1293, 1370, 1383, 1406, 1439, 1460, 1493, 1626, 1672, 1724, 1736, 1954, 2092, 2181, 2410, 2832, 2890, 2934, 3029, 3453	11.76 s	5.74 s	2.02 s	2.35 s (6H)	
IIIm	208 (0.84), 259 (0.94)	426, 508, 528, 578, 652, 657, 734, 752, 789, 814, 849, 872, 902, 958, 984, 1010, 1036, 1050, 1086, 1115, 1186, 1236, 1279, 1376, 1396, 1456, 1504, 1625, 1671, 1731, 1967, 2192, 2249, 2295, 2419, 2632, 2789, 2873, 2932, 2963, 3210, 3448	11.39 s	5.54 s	1.99 s	10.57 s (1H)	2.23 m (2H), 1.58 m (2H), 0.91 t (3H, *J* 7.3)
IIIn	206 (2.09), 231 (1.59)	433, 540, 606, 690, 706, 796, 877, 908, 923, 932, 1001, 1030, 1075, 1120, 1160, 1284, 1308, 1449, 1487, 1536, 1579, 1605, 1632, 1671, 1805, 1902, 1960, 2999, 3052, 3160, 3201, 3426	11.50 s	5.64 s	2.08 s	11.22 s (1H)	7.93 d (2H, *J* 7.9), 7.65 t (1H, *J* 7.9), 7.56 d (2H, *J* 8.4)
IIIo	211 (2.07), 241 (1.11), 258 (1.31), 299 (0.42)	407, 427, 484, 526, 541, 565, 597, 632, 650, 668, 698, 721, 751, 788, 813, 826, 892, 915, 985, 1012, 1044, 1115, 1162, 1184, 1240, 1258, 1296, 1388, 1418, 1466, 1480, 1498, 1603, 1678, 1732, 2815, 2854, 2930, 2953, 3012, 3221, 3436	11.25 s	5.47 s	2.13 s	10.42 s (1H)	7.88 d.d (1H, *J* 7.9, 1.9), 7.50–7.54 m (1H), 7.12 d (1H, *J* 8.4), 7.06 t (1H, *J* 7.5), 3.98 s (3H)
IIIp	214 (2.20), 257 (1.58), 296 (0.36)	419, 447, 469, 507, 523, 553, 577, 628, 673, 685, 727, 743, 757, 781, 802, 836, 870, 887, 903, 928, 945, 968, 1040, 1086, 1096, 1229, 1298, 1322, 1382, 1398, 1435, 1454, 1484, 1507, 1580, 1610, 1629, 1667, 1685, 1726, 2406, 2600, 3070, 3212	11.32 s	5.50 s	2.11 s	11.04 s (1H)	7.52 d (1H, *J* 7.7), 7.47 d (1H, *J* 1.5), 7.39 t (1H, *J* 7.7), 7.11 d.d (1H, *J* 7.7, 1.5), 3.86 s (3H)

Table 3. (Contd.)

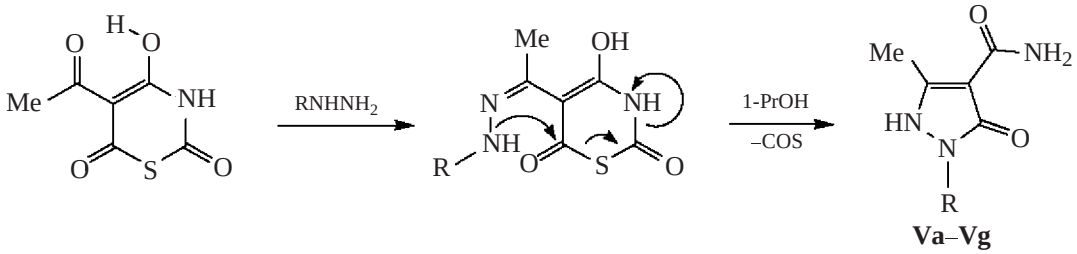
Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)				
			N^3H	C^5H	Me	R	R^1
IIIq	207 (1.87), 258 (0.89)	412, 427, 446, 490, 517, 547, 558, 627, 645, 656, 675, 712, 743, 761, 811, 829, 884, 929, 1041, 1051, 1067, 1081, 1157, 1202, 1219, 1241, 1275, 1304, 1371, 1386, 1406, 1426, 1435, 1450, 1547, 1631, 1680, 1732, 2844, 2976, 3040, 3187, 3433	11.34 s	5.51 s	2.11 s	11.21 s (1H)	8.12 d (1H, *J* 1.6), 7.94 d (1H, *J* 7.7), 7.74 d (1H, *J* 7.7), 7.46 t (1H, *J* 7.7)
IIIr	205 (1.95), 227 (1.70), 274 (0.65)	429, 477, 513, 532, 555, 577, 589, 661, 730, 750, 765, 797, 879, 933, 979, 1012, 1047, 1067, 1093, 1157, 1227, 1288, 1376, 1391, 1459, 1466, 1500, 1588, 1648, 1655, 1701, 1730, 1734, 1970, 2191, 2414, 2784, 2923, 2973, 3159, 3296, 3420	11.50 s	5.62 s	2.05 s	11.12 s (1H)	7.99 s (1H), 7.35 d (1H, *J* 3.3), 6.73 d.d (1H, *J* 3.3, 1.5)
IIIs	204 (1.59), 226 (1.43), 259 (1.17)	428, 442, 503, 519, 534, 632, 653, 665, 704, 757, 799, 824, 841, 874, 893, 956, 983, 1006, 1072, 1092, 1102, 1169, 1242, 1280, 1410, 1437, 1465, 1489, 1509, 1585, 1596, 1622, 1699, 1717, 1739, 2830, 2853, 2901, 2923, 3011, 3086, 3126, 3335	11.29 s	5.45 s	2.03 s	10.81 s (1H)	7.26 d (1H, *J* 8.9), 7.01 d (1H, *J* 8.9), 4.73 d (1H, *J* 15.2), 4.68 d (1H, *J* 15.2)
IIIt	205 (1.50), 270 (0.91), 297 (1.12)	419, 435, 488, 499, 511, 542, 600, 620, 638, 654, 720, 745, 775, 817, 890, 916, 937, 1229, 1258, 1287, 1312, 1410, 1431, 1464, 1489, 1518, 1557, 1594, 1620, 1684, 1707, 1746, 2805, 2835, 2850, 2899, 2923, 2939, 3013, 3135, 3300, 3450	11.51 br.s	5.65 s	2.81 s	11.37 br.s (2H)	8.03 d (2H, *J* 7.8), 7.60 d (2H, *J* 7.8), 5.69 s (1H), 2.10 s (3H)

7.93–8.67 ppm (R = Ar, Alk). In the ^{13}C NMR spectra of 1-amino-6-methyluracils **IIIa**–**IIIt** (Table 4), carbon nuclei characteristically resonated at δ_C 99.4–100.4 (C^5), 161.8–162.3 (C^2), 153.0–156.9 (C^4), 149.3–150.6 (C^6), and 17.5–18.7 ppm (6-CH_3). The observed chemical shifts are consistent with limited published data for structurally related compounds synthesized previously by other methods [2–5].

Our further studies showed that the reaction of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**) with monosubstituted alkyl- and arylhydrazines takes different pathways, depending on the conditions. By heating equimolar mixtures of the reactants in ethanol or propan-1-ol we obtained the corresponding 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg** rather than 1-amino-6-methyluracil derivatives **III**. A probable mechanism is given in Scheme 2. The process is also accompanied by evolution of carbonyl sulfide, but in this case the C^2OS rather than C^6OS fragment is likely to be lost (in contrast to the reaction in boiling DMF). However, detailed study on the mechanism of this reaction was not performed in the present work.

The reaction is quite sensitive to steric and electronic factore. For example, no pyrazolone derivatives were formed in the reactions with 2-tolylhydrazine

Scheme 2.



Va–**Vg**

R = H (**a**), Me (**b**), CH_2COOEt (**c**), CH_2Ph (**d**), Ph (**e**), 4-$MeOC_6H_4$ (**f**), 2-pyridyl (**g**).

and 2,4,6-trichlorophenylhydrazine: the process stopped at the stage of formation of the corresponding hydrazone, while under more severe conditions (boiling DMF) 1-amino-6-methyluracils were obtained.

The presence of a nitro group in the *para* position of phenylhydrazine reduces nucleophilicity of the NH nitrogen atom so that pyrazole ring closure does not occur, and the product is the corresponding hydrazone which is converted into 1-amino-6-methyluracil under drastic conditions. By contrast, nucleophilicity of the NH nitrogen atom in 4-methoxyphenylhydrazine is so high that the formation of pyrazolone **Vf** becomes the only reaction direction (no 1-aminouracil is formed even on heating in boiling DMF). Likewise, pyrazolone derivative **Vg** was formed in the reaction of **Ia** with 2-pyridylhydrazine.

The structure of compounds **Va**–**Vg** was confirmed by the data of elemental analysis (Table 5), ^1H and ^{13}C NMR, UV, and IR spectroscopy, and mass spectrometry. The mass spectra of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg** (Table 6) contained the molecular ion peaks and peaks from the $[M - 17]^+$ ions resulting from elimination of hydroxyl. In the ^1H NMR spectra of **Va**–**Vg** in $CDCl_3$–DMSO-d_6 (10 : 1) (Table 7), the NH proton in the pyrazole ring resonated at δ 11.46–12.43 ppm as a broadened singlet, and two slightly

Table 4. ^{13}C NMR spectra of 1-amino-6-methyluracils **IIIa**–**IIIt** in DMSO-d_6, δ_C, ppm

Comp. no.	C^2	C^4	C^5	C^6	Me	R
IIIa	162.2	156.0	99.2	150.9	18.1	36.7
IIIb	162.3	156.8	99.4	150.1	18.7	42.8
IIIc	162.15	156.5	99.1	151.1	18.4	136.9, 129.2, 128.3, 127.5, 53.2
IIId	162.2	156.9	99.9	150.6	17.9	147.3, 129.1, 120.0, 111.9
IIIe	162.2	156.9	99.96	150.5	17.8	144.7, 130.4, 126.8, 122.0, 119.9, 109.8, 17.0
IIIf	162.1	155.9	100.7	150.2	17.6	153.1, 139.8, 125.8, 111.3
IIIg	162.1	156.8	100.1	150.2	19.2	138.3, 129.0, 128.8, 124.9
IIIh	162.0	156.1	101.5	150.0	17.8	143.5, 129.4, 123.1, 118.0
IIIi	162.0	156.7	100.1	149.9	18.1	147.9, 135.65, 129.3, 129.0, 128.5, 127.8, 120.3, 112.7, 55.1
IIIj	161.9	153.0	99.1	146.3	18.5	178.3, 135.4, 133.9, 132.2, 129.8, 128.8, 128.6, 128.1, 127.4
IIIk	162.1	155.4	99.6	149.7	17.5	169.4, 20.0
IIIl	161.8	153.7	101.8	149.5	17.1	170.5, 24.2
IIIm	162.2	153.3	99.8	149.7	17.5	172.3, 34.7, 18.1, 13.3
IIIn	162.2	155.45	100.15	149.8	17.5	166.2, 132.65, 131.0, 128.7, 127.6
IIIo	162.2	155.6	99.8	149.6	17.7	164.9, 157.5, 133.7, 130.7, 120.6, 119.8, 112.2, 56.0
IIIp	162.15	155.4	100.2	149.8	17.5	165.9, 159.3, 132.2, 129.9, 119.8, 118.5, 112.7, 55.3
IIIq	162.1	155.3	100.2	149.7	17.5	164.8, 135.4, 133.1, 131.0, 130.2, 126.8, 121.9
IIIr	162.1	155.4	100.16	149.7	17.55	157.2, 146.6, 144.8, 116.4, 112.2
IIIs	162.1	155.1	100.1	149.4	17.5	167.8, 156.2, 129.2, 125.2, 116.6, 66.1
IIIt	162.1	155.3	100.2	149.7	17.5	165.5, 162.7, 153.1, 151.15, 140.35, 131.4, 129.68, 129.63, 128.8, 128.62, 101.1, 20.25

Table 5. Yields, melting points, R_f values, and elemental analyses of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg**

Comp. no.	Yield, %	mp, °C	R_f (acetone–hexane, 2 : 1)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
Va	68	261–263	0.26 [a]	42.47	4.99	29.79	$C_5H_7N_3O_2$	42.55	5.00	29.77
Vb	65	278–279	0.37	46.41	5.86	27.13	$C_6H_9N_3O_2$	46.45	5.85	27.08
Vc	72	96–98	0.44	47.65	5.77	18.52	$C_9H_{13}N_3O_4$	47.57	5.77	18.49
Vd	83	217–218	0.33	62.25	5.68	18.13	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17
Ve	74	227–228	0.29	60.87	5.09	19.31	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.34
Vf	82	207–209	0.31	58.47	5.29	16.97	$C_{12}H_{13}N_3O_3$	58.29	5.30	16.99
Vg	73	256–257	0.17 [a]	55.16	4.63	25.65	$C_{10}H_{10}N_4O_2$	55.04	4.62	25.68

[a] Benzene–acetic acid, 10 : 1.

Table 6. Mass spectra of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg**

Comp. no.	*m/z* (I_{rel}, %)
Va	141 M^+ (53), 124 (100), 67 (30), 56 (44), 44 (12), 39 (12)
Vb	155 M^+ (78), 138 (100), 96 (42), 67 (47), 56 (6), 44 (15), 39 (12)
Vc	227 M^+ (10), 210 (34), 154 (5), 137 (100), 124 (4), 69 (45), 67 (14), 42 (27)
Vd	231 M^+ (32), 214 (26), 186 (20), 172 (7), 158 (12), 145 (4), 137 (5), 117 (6), 105 (6), 104 (8), 91 (100), 89 (3), 84 (5), 77 (6), 67 (16), 65 (20), 55 (7), 44 (10)
Ve	217 M^+ (24), 200 (100), 132 (27), 103 (5), 91 (98), 77 (25), 67 (20), 51 (18), 44 (15)
Vf	247 M^+ (4), 232 (100), 217 (31), 215 (10), 204 (9), 189 (11), 147 (6), 134 (7), 122 (10), 107 (8), 92 (7), 80 (9)
Vg	218 M^+ (7), 175 (100), 160 (20), 134 (24), 118 (4), 119 (4), 93 (6), 79 (27), 52 (9), 52 (9), 44 (9)

Table 7. UV, IR, and ^{1}H NMR spectra of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg**

Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)			
			NH	$CONH_2$	Me	R
Va	207 (1.11), 262 (0.70)	412, 467, 592, 635, 670, 718, 783, 988, 1052, 1125, 1175, 1265, 1369, 1385, 1406, 1430, 1543, 1578, 1630, 1648, 2520, 2924, 2963, 3252, 3305, 3405	11.50 br.s	6.94 br.s (2H)	2.32 s	
Vb	205 (1.10), 225 (0.84), 241 (0.82)	445, 544, 603, 642, 721, 736, 787, 870, 1038, 1124, 1193, 1280, 1347, 1372, 1407, 1455, 1506, 1576, 1630, 1651, 2516, 2577, 2754, 2814, 2944, 3192, 3311, 3447	11.46 br.s	6.85 br.s, 6.78 br.s (2H)	2.39 s	3.51 s (3H)
Vc	209 (1.44), 262 (0.91)	420, 520, 594, 643, 679, 755, 794, 881, 925, 957, 1023, 1051, 1090, 1111, 1220, 1237, 1308, 1342, 1392, 1426, 1542, 1581, 1626, 1746, 2595, 2734, 2921, 2973, 3300, 3322, 3405, 3548	12.43 br.s	7.74 br.s (1H), 6.85 br.s (1H)	2.37 s	4.56 s (2H), 4.15 q (2H, J 7.1), 1.20 t (3H, J 7.1)

Table 7. (Contd.)

Comp. no.	UV spectrum (EtOH), λ_{max}, nm ($\varepsilon \times 10^4$)	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)			
			NH	$CONH_2$	Me	R
Vd	210 (1.75), 262 (0.57), 300 (1.15)	444, 521, 557, 698, 741, 751, 822, 838, 852, 894, 1072, 1101, 1156, 1219, 1331, 1358, 1371, 1407, 1415, 1429, 1440, 1457, 1466, 1496, 1567, 1607, 1631, 1675, 2839, 3007, 3037, 3064, 3170, 3450	12.07 br.s	8.20 br.s (1H), 5.64 br.s (1H)	2.36 s	7.19–7.28 m (5H), 4.91 s (2H)
Ve	208 (1.49), 248 (1.77)	407, 423, 461, 499, 579, 615, 652, 694, 750, 768, 789, 839, 909, 999, 1040, 1092, 1119, 1211, 1240, 1304, 1350, 1369, 1412, 1502, 1542, 1574, 1630, 1650, 1797, 1874, 1954, 2924, 3078, 3241, 3286, 3367	12.33 br.s	8.14 br.s (1H), 5.85 br.s (1H)	2.48 s	7.55–7.62 m (2H), 7.34–7.39 m (2H), 7.17–7.21 m (1H)
Vf	206 (1.88), 229 (1.15), 252 (1.35)	519, 588, 595, 682, 690, 754, 788, 829, 853, 910, 1023, 1100, 1174, 1215, 1255, 1301, 1370, 1410, 1426, 1455, 1509, 1536, 1583, 1593, 1616, 1645, 1672, 2037, 2765, 2934, 3013, 3291, 3400	12.75 br.s	7.88 br.s (1H), 6.95 br.s (1H)	2.44 s	7.53 d (2H, J 9.0), 7.05 d (2H, J 9.0), 3.78 s (3H)
Vg	204 (1.80), 245 (2.04), 289 (1.30)	443, 478, 513, 562, 607, 672, 707, 760, 845, 904, 1007, 1065, 1086, 1131, 1162, 1212, 1304, 1342, 1400, 1502, 1424, 1462, 1481, 1514, 1586, 1641, 3101, 3128, 3298, 3403	13.35 br.s	7.74 br.s (1H), 7.00 br.s (1H)	2.49 s	8.45 d (1H, J 4.7), 8.37 d (1H, J 8.4), 7.96 d.t (1H, J 1.7, 6.9), 7.26–7.30 m (1H)

Table 8. ^{13}C NMR spectra of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg** in DMSO-d_6, δ_C, ppm

Comp. no.	C^5	C^4	C^3	$CONH_2$	Me	R
Va	165.2	97.3	144.1	160.8	11.6	–
Vb	164.7	97.6	142.6	158.5	10.3	34.8
Vc	167.5	96.7	148.3	162.1	12.1	164.8, 61.1, 44.1, 13.9
Vd	165.0	97.0	147.6	161.8	12.0	136.4, 128.5, 128.4, 127.9, 45.96
Ve	164.9	97.2	150.0	161.3	12.5	136.1, 128.9, 125.5, 119.9
Vf	164.9	97.3	148.9	160.8	12.3	157.4, 128.7, 122.7, 114.2, 55.3
Vg	164.4	97.5	150.5	160.9	12.1	147.4, 147.2, 139.3, 120.7, 111.6

broadened singlets (overlapped in some cases) were present at δ 5.64–8.20 ppm due to protons in the amide group. Also, a singlet at δ 2.32–2.48 ppm (5-CH_3) and signals belonging to protons in the substituent on N^1 were observed. The spectra were recorded from solutions in a 10 : 1 $CDCl_3$–DMSO-d_6 mixture, taking into account that pyrazolones **V** are insoluble in $CDCl_3$, while the spectral patterns obtained from solutions in pure DMSO-d_6 were considerably impaired: the NH signal was broadened so strongly that it merged into the baseline, signals from the amide protons were also strongly broadened and partially or completely overlapped by signals from protons in the aromatic substituent on the nitrogen

atom, and the 5-Me singlet was generally obscured by the quintet from residual protons in the solvent.

The ^{13}C NMR spectra of 2-substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides **Va**–**Vg** in DMSO-d_6 (Table 8) contained signals from the methyl carbon atom (δ_C 10.3–12.5 ppm), amide carbonyl group (δ_C 158.5–162.1 ppm) and C^3, C^4, and C^5 in the pyrazole ring (δ_C 142.6–150.0, 96.7–97.6, 164.7–167.5 ppm, respectively). Compound **Va**–**Vg** showed in the IR spectra (KBr) absorption bands corresponding to stretching vibrations of the NH (3025–3260 cm^{-1}) and C=O groups (1655–1670 and 1705–1715 cm^{-1}) (Table 7). Their UV spectra recorded from solutions in 96.5% ethanol (Table 7) were characterized by the presence of two absorption maxima at λ 260–262 and 207–208 nm.

EXPERIMENTAL

The mass spectra (electron impact, 70 eV) were recorded on an MKh-1321 mass spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-500 instrument at 500 and 125 MHz, respectively, from solutions in DMSO-d_6 or $CDCl_3$. The IR spectra were recorded in KBr on an FSM 1201 spectrometer with Fourier transform. The UV spectra of solutions in 96.5% ethanol were obtained on an SF-2000 spectrophotometer (cell path length 1 cm). The progress of reactions and the purity of products were monitored by TLC using Sorbfil® plates. The melting points were determined in capillaries and were not corrected. The yields, melting points, and elemental analyses of compounds **IIIa**–**IIIt** and **Va**–**Vg** are given in Tables 1 and 5.

5-Acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (Ia). The synthesis was carried out in a 2000-ml beaker. Dry malonic acid, 80 g, was mixed with 180 ml of acetic anhydride, and ~400 ml of glacial acetic acid was added under vigorous stirring. The mixture was stirring until it became homogeneous (the solution appreciable cooled down), and 85 g of dry finely powdered potassium isothiocyanate was added in one portion under stirring, maintaining the temperature at 25–30°C (a slight heat evolution was observed) by cooling with water. Immediately after addition of KSCN, the solution turned violet, and it then changed to goldish yellow (in 15–20 min) and gradually turned red. The mixture was stirred for 4–5 h at room temperature, and the product began to abundantly crystallize from the solution. The mixture was stirred for 2–3 h more and was left to stand for 72 h at ~20°C. The mixture was diluted with a mixture of 1000 ml of water and 200 ml of 35% hydrochloric acid and stirred for 30 min, and the precipitate was filtered off, washed with 200 ml of water, dried in air, and recrystallized from benzene. It is advisable to use a Soxhlet apparatus for crystallization. Yield ~100 g (69%), mp 198–200°C. The product sublimed appreciably at the melting point.

N-Substituted 1-amino-6-methyluracils IIIa–IIIj *(general procedure)* (Table 1). A mixture of 1 g of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**) and 5.5 mmol of mono- or N,N-disubstituted hydrazine in 10 ml of dimethylformamide was kept for 15 min at 18–25°C and was then heated as quickly as possible to the boiling point and maintained boiling until the reaction was complete (0.5–1 h, TLC). Vigorous evolution of carbonyl sulfide with a characteristic odor was observed during the process, and the DMF condensate usually had greenish-blue color. The solvent was distilled off on a rotary evaporator, and the residue was recrystallized from propan-2-ol.

1-Acylamino-6-methyluracils IIIk–IIIt *(general procedure)* (Table 1). A mixture of 1 g of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**) and 5.5 mmol of the corresponding carboxylic acid hydrazide in 15 ml of dimethylformamide was heated under reflux until the reaction was complete (0.5–1 h, TLC). Vigorous evolution of carbonyl sulfide was observed during the process. The solvent was distilled off on a rotary evaporator, and the residue was recrystallized from ethanol or propan-2-ol.

2-Substituted 5-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxamides Va–Vg *(general procedure)* (Table 5). A mixture of 1 g of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6-dione (**Ia**), 5.34 mmol of monosubstituted hydrazine, and 15 ml of propan-1-ol was heated under reflux until the reaction was complete (1–2 h, TLC). Vigorous evolution of carbonyl sulfide was observed during the process. The solvent was distilled off on a rotary evaporator, and the residue was recrystallized from chloroform–ethanol.

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