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Azines and Azoles: CXXII.[1] New Regioselective Synthesis of 1-Substituted 6-Alkyluracils

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Abstract — Readily available 5-acyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-diones with primary alkyl- and arylamines in mild conditions (boiling in propan-2-ol) to give Schiff bases. In more rigid conditions (boiling in DMF), the reaction is accompanied by COS liberation and provides 1-substituted 6-alkyluracils. This previously unknown reaction possesses a considerable synthetic potential and can be considered as a new, general, and regioselective synthetic approach to 1-substituted 6-alkyluracils.

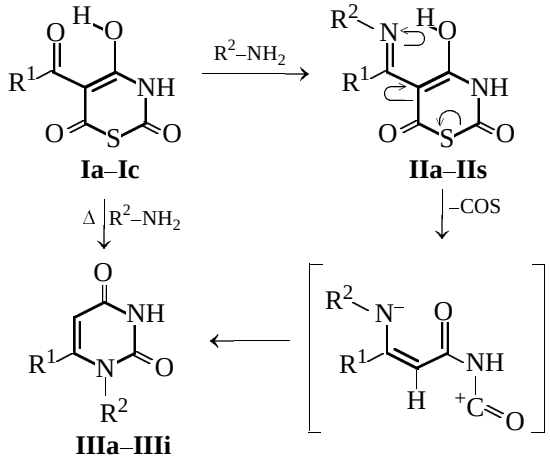
Over the past years 1,3-thiazines and their hydroxy derivatives have attracted increasing attention, which, in particular, is due to the fact that they can be converted into derivatives of malonic acid, azines, and azoles under the action of nucleophiles [2–4]. 2,4,6-Trioxo-1,3-thiazines have so far been hardly accessible, and, therefore, little has been known on their reactions with N-, O-, and S-nucleophiles, except for those involving the initial member of this series of compounds [5]. Recently we developed a facile and convenient synthesis of 5-acyl-4-hydroxy-1,3-thiazine-2,6-diones from malonic acid, potassium thiocyanate, and carboxylic acid anhydrides in a corresponding acid medium [6, 7]. Here we present data on reaction of these compounds with certain N-nucleophiles.

It was found that the reactions of thiazine **Ia** with primary alkyl- or arylamines in propan-2-ol results in exclusive formation, even in the presence of a considerable excess of the amine and under prolonged boiling, of Schiff bases **IIa**–**IIs** (Table 1). The products are stable, well-crystallized substances readily soluble in dioxane and acetone.

Thus, the reactions of 5-acylthiazines **Ia**–**Ic** with primary amines under these conditions involve no thiazine ring cleavage and give rise to ketimines **IIa**–**IIs**.

Under more rigid conditions, quite unexpected events occur: Boiling of thiazine **Ia** in excess aniline gives 6-methyl-1-phenyluracil (**IIIe**) in high yield. The same product was obtained by boiling of an equimolar mixture of thiazine **Ia** with aniline in DMF. We decided to find out if this previously unknown

Scheme 1.



I, R^1 = Me (**a**), Et (**b**), Pr (**c**). **II**, R^1 = Me; R^2 = H (**a**), $CH_2CH{=}CH_2$ (**b**), C_6H_{13} (**c**), CH_2CH_2OH (**d**), $CH_2CH(OH)CH_2OPh$ (**e**), CH_2CH_2COOH (**f**), CH_2Ph (**g**), $CH_2(C_6H_4Cl\text{-}3)$ (**h**), Ph (**i**), $2\text{-}HOC_6H_4$ (**j**), $3\text{-}AcC_6H_4$ (**k**), $3\text{-}(HOCH_2)C_6H_4$ (**l**), $4\text{-}MeC_6H_4$ (**m**), $4\text{-}MeOC_6H_4$ (**n**), 1-naphthyl (**o**), 2-naphthyl (**p**), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl (**q**), NHCOPh (**r**); R^1 = Pr, R^2 = $4\text{-}MeC_6H_4$ (**s**). **III**, R^1 = Me, R^2 = CH_2CH_2OH (**a**), $CH_2CH{=}CH_2$ (**b**), C_6H_{13} (**c**), CH_2Ph (**d**), Ph (**e**), $4\text{-}EtOOCC_6H_4$ (**f**), $2\text{-}H_2NC_6H_4$ (**g**), CH_2CH_2OAc (**h**); R^1 = Et, R^2 = Ph (**i**).

reaction works with other primary amines. It was established that 5-acylthiazines **Ia**–**Ic** react with various primary alkyl-, aryl-, or heterylamines under similar conditions convert into 1-substituted 6-alkyluracils **IIIa**–**IIIi** (Table 1). It is readily seen the first reactions product is always a Schiff base. It loses a COS molecule upon heating, and the resulting

[1] For communication CXXI, see [1].

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Table 1. Yields, melting points, TLC data, and elemental analyses of 5-imidoyl-1,3-thiazines **IIa**–**IIs** and **IV** and 1,6-disubstituted uracils **IIIa**–**IIIi, V**, and **VI**

Comp. no	R^1	R^2	Yield, %	mp, °C	R_f (acetone–hexane, 1:1)	Found, %			Formula	Calculated, %		
						C	H	N		C	H	N
IIa	Me	H	76	>300	0.68	38.63	3.24	15.08	$C_6H_6N_2O_3S$	38.71	3.25	15.05
IIb	Me	$CH_2CH=CH_2$	82	156–157	0.56	47.73	4.46	12.35	$C_9H_{10}N_2O_3S$	47.78	4.45	12.38
IIc	Me	C_6H_{13}	88	114–115	0.62	53.41	6.69	10.37	$C_{12}H_{18}N_2O_3S$	53.31	6.71	10.36
IId	Me	CH_2CH_2OH	80	196–179	0.20	41.77	4.37	12.19	$C_8H_{10}N_2O_4S$	41.73	4.38	12.17
IIe	Me	$CH_2CH(OH)CH_2OPh$	82	180–181	0.58	53.59	4.80	8.31	$C_{15}H_{16}N_2O_5S$	53.56	4.79	8.33
IIf	Me	CH_2CH_2COOH	74	191–192	0.72[a]	41.78	3.91	10.84	$C_9H_{10}N_2O_5S$	41.86	3.90	10.85
IIg	Me	CH_2Ph	83	187–188	0.60	56.57	4.37	10.16	$C_{13}H_{12}N_2O_3S$	56.51	4.38	10.14
IIh	Me	$CH_2(3\text{-}ClC_6H_4)$	79	157–158	0.53	50.34	3.58	8.99	$C_{13}H_{11}ClN_2O_3S$	50.25	3.57	9.01
IIi	Me	Ph	85	244–245	0.58	54.89	3.83	10.83	$C_{12}H_{10}N_2O_3S$	54.95	3.84	10.86
IIj	Me	$2\text{-}OHC_6H_4$	76	228–230	0.49	51.89	3.63	10.04	$C_{12}H_{10}N_2O_4S$	51.79	3.62	10.07
IIk	Me	$3\text{-}(MeCO)C_6H_4$	80	202–203	0.46	55.15	3.98	9.23	$C_{14}H_{12}N_2O_4S$	55.26	3.97	9.21
IIl	Me	$3\text{-}(HOCH_2)C_6H_4$	87	197–198	0.37	53.51	4.14	9.56	$C_{13}H_{12}N_2O_4S$	53.42	4.14	9.58
IIm	Me	$4\text{-}Me\text{-}C_6H_4$	86	232–233	0.69	56.39	4.39	10.17	$C_{13}H_{12}N_2O_3S$	56.51	4.38	10.14
IIn	Me	$4\text{-}OC_6H_4$	89	206–207	0.50	53.32	4.15	9.56	$C_{13}H_{12}N_2O_4S$	53.42	4.14	9.58
IIo	Me	1-Naphthyl	77	208–209	0.55	61.47	3.86	8.99	$C_{16}H_{12}N_2O_3S$	61.53	3.87	8.97
IIp	Me	2-Naphthyl	82	229–230	0.56	61.59	3.88	8.95	$C_{16}H_{12}N_2O_3S$	61.53	3.87	8.97
IIq	Me	4-Antipyryl	81	226–227	0.19	54.94	4.32	15.06	$C_{17}H_{16}N_4O_4S$	54.83	4.33	15.04
IIr	Me	$NHCOC_6H_5$	67	244–245	0.94[a]	51.04	3.63	13.72	$C_{15}H_{16}N_2O_3S$	51.14	3.63	13.76
IIs	Pr	$4\text{-}Me\text{-}C_6H_4$	87	217–218	0.61	59.05	5.31	9.18	$C_{13}H_{11}N_3O_4S$	59.19	5.30	9.20
IIIa	Me	CH_2CH_2OH	55	234–235	0.07	49.42	5.93	16.43	$C_7H_{10}N_2O_3$	49.41	5.92	16.46
IIIb	Me	$CH_2CH=CH_2$	61	174–175[b]	0.27	57.71	6.08	16.81	$C_8H_{10}N_2O_2$	57.82	6.07	16.86
IIIc	Me	C_6H_{13}	63	109–110[c]	0.33	62.74	8.65	13.29	$C_{11}H_{18}N_2O_2$	62.83	8.63	13.32
IIId	Me	CH_2Ph	72	231–232[d]	0.30	66.61	5.58	12.97	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95
IIIe	Me	Ph	75	284–285[e]	0.23	65.40	4.90	13.82	$C_{11}H_{10}N_2O_2$	65.34	4.89	13.85
IIIf	Me	$4\text{-}EtOOCC_6H_4$	73	238–240	0.26	61.24	5.15	10.23	$C_{14}H_{14}N_2O_4$	61.31	5.14	10.21
IIIg	Me	$2\text{-}NH_2C_6H_4$	67	275–276	0.11	60.93	5.11	19.35	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.34
IIIh	Me	CH_2CH_2OAc	64	189–190	0.15	50.96	5.69	13.18	$C_9H_{12}N_2O_4$	50.94	5.70	13.20
IIIi	Et	Ph	73	274–275	0.27	66.71	5.58	12.94	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95
IV	Me		68	268 (decomp.)	0.67[a]	42.25	3.53	14.04	$C_{14}H_{14}N_4O_6S_2$	42.20	3.54	14.06
V	Me		45	>350	0.60[a]	51.75	5.06	20.15	$C_{12}H_{14}N_4O_4$	51.80	5.07	20.13
VI	Me		52	243–244	0.80[a]	52.31	4.72	13.11	$C_{14}H_{15}N_3O_6$	52.34	4.71	13.08

[a] Eluent toluene–dioxane–EtOH–AcOH, 2:2:1:1. Published data: [b] mp 168°C [8]; [c] mp 108–109°C [9]; [d] mp 230–231°C [10]; [e] mp 280°C [11].

linear intermediate undergoes recylization to form a 1-substituted 6-alkyluracil. Actually, by heating Schiff bases **II** in DMF was obtained the same 1-substituted 6-alkyluracils **III**.

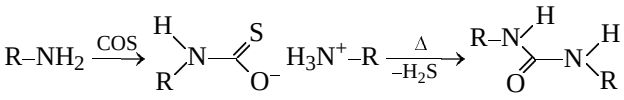
It is interesting that in nonpolar high-boiling solvents, such as *o*-xylene, under reflux, Schiff bases do not change within 30 min, but if 5–10% of DMF is added to the reaction mixture, 1-substituted uracils appear already within a few minutes.

Electron-donor substituents in substituted anilines favor the reaction. Electron-acceptor substituents decrease the electron density on the aniline nitrogen, thus adversely affecting its reactivity and prolonging time required for comparable product yields.

The fact that 5-acylthiazines **Ia**–**Ic** evolve COS when heated with an excess of highly basic amines, such as benzyl- and hexylamines, is confirmed by the formation, along with 1-substituted uracils **III**, of

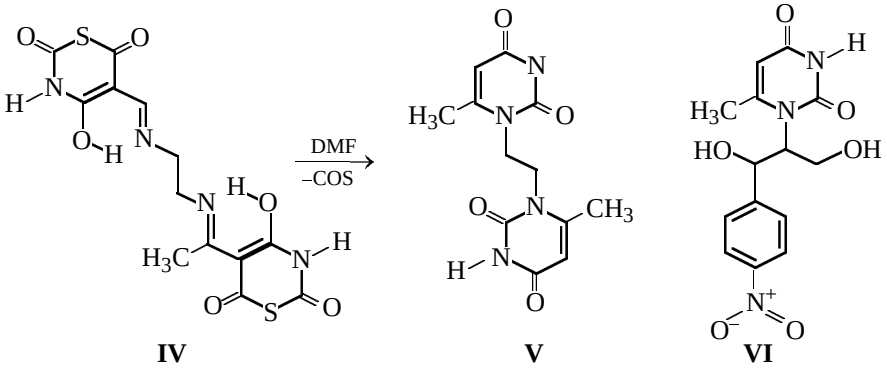
symmetrical *N*,*N*'-disubstituted ureas. The products are easy to separate, since uracils **III** are soluble in aqueous alkalis, while ureas not. It should be noted that the formation of symmetrical disubstituted ureas (Scheme 2) on reactions of amines with COS is well known [12].

Scheme 2.



Our method has proved feasible for synthesis of 6-methyluracil derivatives containing complex polyfunctional substituents on N^1. For example, heating in DMF of Schiff base **IV** (Scheme 3) prepared from ethylenediamine and 2 mol of thiazine **Ia** gives ethylenebis(6-methyluracil) **V**.

Scheme 3.



IV **V** **VI**

The utility of this method for preparing at least acyclic N^1-nucleosides derived from 6-alkyluracils was demonstrated by the reactions with certain alkanolamines. In particular, even with a primary dialkanolamine, 2-amino-1-(*p*-itrophenyl)propane-1,3-diol, the product of Levomycetin hydrolysis [13], we obtained 6-methyluracil **VI** (yield 52%).

The composition of the resulting compounds was proved by elemental analysis and their structure, by ^{1}H and ^{13}C NMR, UV, and IR spectroscopy and mass spectrometry.

The mass spectra of compounds **IIa**–**IIs** (Table 2) contain a series of characteristic molecular and daughter ions: $M^{+\cdot}$, $[M - CO]^{+\cdot}$, $[M - COS(COSH)]^{+\cdot}$, $[M - CO - HNCO]^{+\cdot}$, $[M - R^2]^+$, $[M - CO - COS(COSH)]^+$, $[M - 2CO - HNCO]^{+\cdot}$, $[M - CO - COS(COSH) - R^1]^+$, $[M - R^2N{=}CR^1]^+$, $[R^2N{=}CR^1]^+$, $[M - CO - HNCO - COS(COSH)]^+$, and $[M - COS(COSH) - R^1NCO]^+$. The proposed fragmentation pathways of these compounds under electron impact are presented in Scheme 4. In most cases, pathways *a*–*c* are preferable. The latter pathway is especially characteristic of aromatic substituents R^2.

The ^{1}H NMR spectra of 5-alkyl(aryl)iminothiazines **IIa**–**IIc** in DMSO-d_6 (Table 3) contain singlets of the OH (12.58–14.67 ppm) and NH groups (11.32–11.87 ppm), as well as signals alkyl groups attached to C^5 (0.75–2.77 ppm) and alkyl and aryl groups at the imino nitrogen atom. In the ^{13}C NMR spectra (Table 4), there are signals of the $C^5C{=}N$ carbon atom (~180 ppm), carbon atoms of the *N*-alkyl and *N*-aryl substituents, that are lacking in the spectra of the starting 5-acylthiazines, and the C^5 and C^2–C^6 atoms of the thiazine ring (96–98 and 171–175 ppm, respectively). Therewith, the spectra of iminothiazines **IIa**–**IIs** lack signals quite characteristic of the starting 5-acylthiazines, i.e. those of the hydrogen-bonded hydroxyl proton at 17–18 and of the acyl carbons near 200 ppm. The IR spectra of compounds **IIa**–**IIs** in KBr (Table 3) show stretching and deformation vibration bands of hydrogen-bonded NH and OH groups (3100–3500 cm^{-1}) and stretching vibration bands of the C=O and C=N groups (1570–1700 cm^{-1}).

Table 2. Mass spectra of thiazines **IIa**–**IIs**, *m/z* (I_{rel}, %)[a]

Comp. no	$M^{+\cdot}$	$[M - CO]^{+\cdot}$	$[M - COS(COSH)]^{+}$	$[M - CO - HNCO]^{+\cdot}$	$[M - R^2]^{+}$	$[M - CO - COS(COSH)]^{+\cdot}$	$[M - 2CO - HNCO]^{+\cdot}$	$[M - CO - COS(COSH) - R^1]^{+}$
IIa	186 (83)	158	126 (90)	115	–	98	87	83 (100)
IIb	226 (76)	198 (10)	166 (20)	155 (15)	185	138, 137	127	123
IIc	270 (83)	242 (26)	210	199 (22)	185	182, 181	171 (33)	167
IId	230 (33)	202	170	159		142	131	127
IIe	336 (8)	308 (4)	276	265	185	–	237	–
IIf	258 (19)	230 (6)	198 (45)	187	185	170	159	154, 153
IIg	276 (45)	248	216	205	185	188, 187 (25)	177	173
IIh	310 (63)	282	250	239	185	221 (25)	211	207 (20)
IIi	262 (100)	234 (15)	202, 201 (23)	191	185	173, 174	163 (27)	158 (65)
IIj	278 (40)	250	219, 218	207	186	190	179 (11)	175, 174
IIk	304 (19)	276	244, 243	233	186	216, 215	205	201, 200
IIl	292 (100)	264	232 (86), 231	221	185	204, 203	–	188, 187 (49)
IIm	276 (100)	248	216, 215	205	–	188, 187	177 (27)	201
IIn	292	264	232, 231	–	–	204, 203	193	189, 188
IIo	312 (100)	284	252, 251	241	–	224	213	209, 208 (25), 207 (25)
IIp	312 (100)	284	252, 251	241	–	224	213	208, 207
IIq	372	344	312 (100)	–	–	–	–	269
IIr	–	–	–	–	–	–	–	–
IIs	304 (100)	276	244, 243	–	–	216	205	201, 200

Table 2. (Contd.)

Comp. no	$[R^2N{=}CR^1]^{+}$	$[M - R^2N{=}CR^1]^{+}$	$[M - CO - HNCO - COS(COSH)]^{+}$	$[M^{+} - COS(COSH) - R^1NCO]^{+}$	$[R^2]^{+}$	Other ions
IIa	42 (67)	144	55	–	–	68 (75), 55 (60)
IIb	82	–	94 (100), 95	83	41	149 (17), 123 (15), 80 (30), 67 (22), 54 (15), 42 (44), 41 (63)
IIc	126	–	138, 139	83	85	136 (33), 123 (57), 110 (80), 79 (85), 84 (33), 67 (72), 55 (33), 43 (59), 42 (100)
IId	86	–	98 (28)	83 (38)	45	215, 139 (38), 84 (63), 67 (70), 42 (100)
IIe	192	144	–	–	–	258 (10), 183 (100), 169 (20), 165 (16), 139 (20), 133 (34), 107 (16), 96 (50), 77 (34), 67 (22), 60 (36), 55 (20)
IIf	114		127, 126	83 (26)	73 (39)	180 (45), 152 (23), 126 (22), 110 (65), 96 (100), 68 (29), 67 (29), 60 (55), 55 (68)
IIg	132	144 (35)	143, 144	83	91	65 (27), 39 (15)
IIh	166	144	178 (40)	–	125	187 (20)
IIi	118 (42)	144	130 (69), 131	83	77	67 (38), 51 (54)
IIj	134 (100)	144	147, 146	83	93	263 (11), 201 (9), 109 (11), 67 (19), 65 (15), 42 (15), 39 (23)
IIk	160	144	173, 172	83	–	199 (91), 158 (44), 130 (19), 91 (25), 77 (22), 67 (38), 43 (100)

Table 2. (Contd.)

Comp. no	$[R^2N{=}CR^1]^+$	$[M - R^2N{=}CR^1]^+$	$[M - CO - HNCO - COS (COSH)]^+$	$[M^+ - COS (COSH) - R^1NCO]^+$	$[R^2]^+$	Other ions
IIl	148 (46)	144	161, 160	83	107	174 (38), 158 (51), 132 (30), 89 (75), 77 (76), 67 (46), 60 (89), 51 (32)
IIm	132 (35)	144 (46)	144, 145	83	91 (62)	170 (38), 171 (30), 158 (35), 77 (19), 67 (27), 65 (42), 51 (15)
IIn	148 (23)	–	161, 160	83	107	292 (100), 193 (16), 188 (18), 161 (14), 146 (20), 92 (11), 77 (16), 67 (16)
IIo	168 (26)	144	181 (56), 180 (40)	83	127 (60)	213 (21), 115 (21), 90 (14), 77 (19), 67 (16)
IIp	168 (19)	143	181, 180	83	127	235 (15), 213 (29), 207 (31), 181 (48), 180 (42), 143 (13), 127 (57), 115 (19), 77 (15), 67 (17)
IIq	228	–	241, 240	83 (18)	–	295 (18), 212 (43), 150 (16), 149 (16), 123 (20), 91 (12), 77 (40), 60 (83), 56 (80)
IIr	–	–	–	–	–	217 (24), 200 (100), 132 (20), 91 (90), 77 (18), 67 (14), 51 (10)
IIs	160	144	173	83	91	276 (8), 227 (26), 205 (16), 200 (16), 184 (15), 158 (21), 144 (29), 107 (47), 91 (52), 65 (47)

[a] Peaks with $I_{rel} \geq 10\%$ are shown.

Scheme 4.

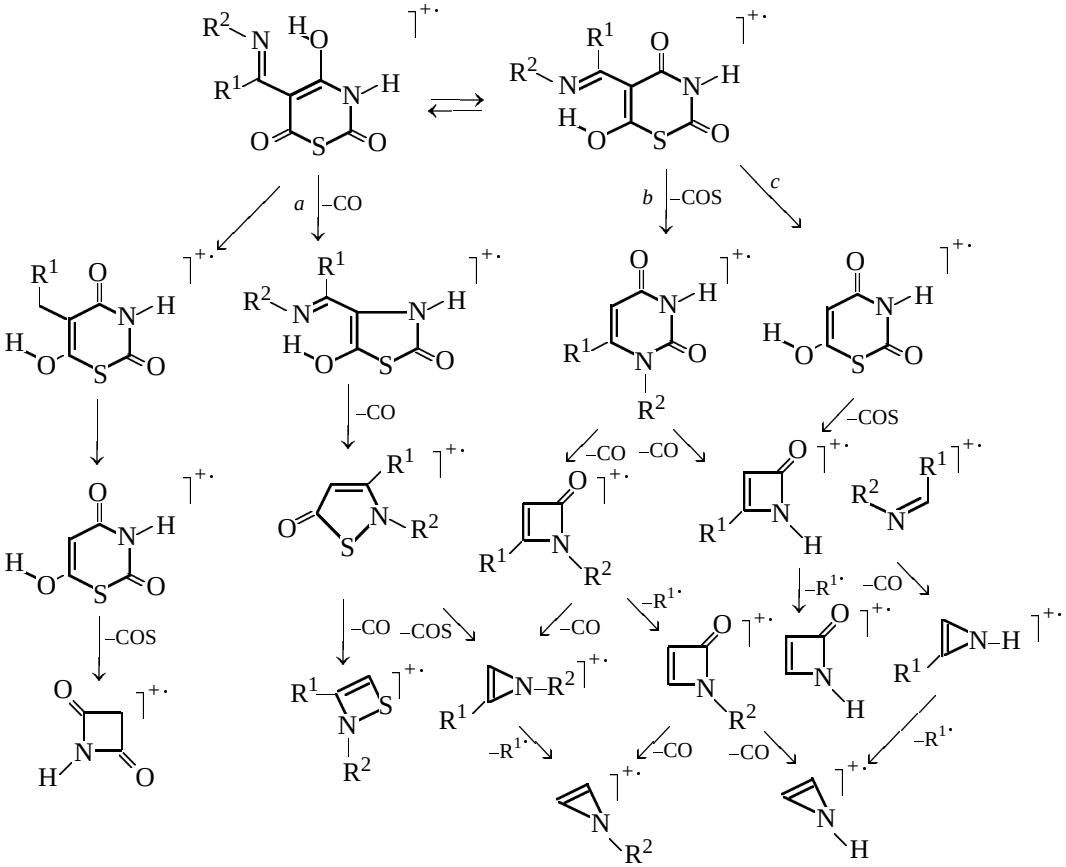


Table 3. UV, IR, and ^{1}H NMR spectra of 1,3-thiazines **IIa**–**IIs** and **IV**

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			
		NH, OH	C=N, C=O	OH	NH	R^1	R^2
IIa	203 (1.29), 227 (1.03), 287 (1.79)	3360, 3170, 3020	1660, 1580, 1440	11.51 s (1H)	9.38 br.s (1H)	2.48 s (3H)	11.10 br.s (1H)
IIb[a]	233 (3.71), (1.48), 298 (1.56)	3135, 2995	1685, 1600,	12.67 br.s (1H)	8.96 s (1H)	2.59 s (3H)	5.86–5.91 m (1H), 5.27–5.34 m (2H), 4.11 d (2H, *J* 5 Hz)
IIb	233 (3.71), 284 (1.48), 298 (1.56)	3135, 2995	1685, 1600,	12.51 br.s (1H)	11.57 br.s (1H)	2.50 s (3H)	5.92–5.98 m (1H), 5.21–5.27 m (2H), 4.23 s (2H)
IIc	200 (1.33), 263 (0.87), 298 (1.97)	3135, 2925	1685, 1610	12.58 br.s (1H)	8.87 s (1H)	2.60 s (3H)	3.46 t (2H), 1.67–1.72 m (2H), 1.31–1.41 m (6H), 0.88 t (3H, *J* 7 Hz)
IId	201 (1.33), 263 (0.86), 297 (1.94)	3505, 2940	1655, 1630, 1605	12.67 s (1H)	11.32 s (1H)	2.56 s (3H)	5.00 s (1H), 3.65 t (2H), 3.59 t (2H)
IIe	199 (2.05), 264 (0.97), 299 (2.04)	3470, 3160, 3035	1650, 1615, 1595	12.80 s (1H)	11.36 s (1H)	2.57 s (3H)	7.24–7.27 m (2H), 6.92 d (3H, *J* 9 Hz), 5.63 d (1H, *J* 4 Hz), 3.63–4.09 m (5H)
IIf	200 (1.64), 262 (0.98), 299 (2.24)	3435, 3205, 3180	1735, 1615	12.69 s (1H)	11.35 br.s (1H)	2.57 s (3H)	3.73 t (2H, *J* 5 Hz), 3.20 br.s, 2.63 t (2H, *J* 6 Hz)
IIg	205 (2.18), 261 (0.96), 300 (2.49)	3125, 3025	1685, 1605	12.88 br.s (1H)	11.40 s (1H)	2.58 s (3H)	7.32–7.40 m (5H), 4.69 d (2H, *J* 5 Hz)
IIg[a]	205 (2.18), 261 (0.96), 300 (2.49)	3125, 3025	1685, 1605	12.93 br.s (1H)	8.62 s (1H)	2.64 s (3H)	7.26–7.41 m (5H), 4.67 d (2H, *J* 5 Hz)
IIh	203 (2.29), 261 (0.81), 301 (2.26)	3135, 3000	1690, 1610	12.87 br.s (1H)	11.43 s (1H)	2.56 s (3H)	7.27–7.39 m (4H), 4.81 d (2H, *J* 6 Hz)
IIi	209 (1.45), 260 (0.76), 307 (1.85)	3205, 3054	1680, 1570	14.14 s (1H)	11.87 s (1H)	2.47 s (3H)	7.38–7.54 m (5H)
IIj	203 (2.51), 262 (0.96), 308 (2.01)	3170	1700, 1615, 1555	13.97 s (1H)	11.58 s (1H)	2.48 s (3H)	10.15 s (1H), 6.85–7.21 m (4H)
IIk	201 (2.25), 228 (2.44), 306 (1.19), 282 (1.16)	3150, 3015	1685, 1615, 1575	14.33 s (1H)	11.73 s (1H)	2.52 s (3H)	7.89–7.99 m (2H), 7.57–7.65 m (2H), 2.61 s (3H)
IIl	203 (2.55), 263 (0.78), 307 (1.70)	3420, 3140, 3025	1660, 1585, 1560	14.29 s (1H)	11.67 s (1H)	2.52 s (3H)	7.14–7.45 m (4H), 5.16 s (1H), 4.55 s (2H)
IIm	201 (2.39), 262 (0.79), 307 (1.88)	3130, 3000	1685, 1605	14.12 s (1H)	11.63 s (1H)	2.49 s (3H)	7.22 d (2H, *J* 9 Hz), 7.00 d (2H, *J* 9 Hz), 3.82 s (3H)
IIn	201 (1.92), 260 (0.79), 310 (2.03)	3140, 3075	1700, 1610, 1575	14.07 s (1H)	11.83 s (1H)	2.46 s (3H)	7.25–7.33 d.d (4H), 2.35 s (3H)
IIo	220 (5.77), 262 (1.01), 306 (1.92)	3440, 3140, 2990	1680, 1610, 1360	14.57 s (1H)	11.76 s (1H)	2.45 s (3H)	7.51–8.01 m (7H)
IIp	220 (3.79), 292 (1.35), 311 (1.5)	3445, 3135, 2995	1685, 1605, 1355	14.46 s (1H)	11.73 s (1H)	2.59 s (3H)	7.87–8.01 m (4H), 7.41–7.57 m (3H)
IIq[a]	203 (3.28), 261 (1.59), 315 (1.66)	3460, 2970, 2810	1675, 1615, 1550	13.47 s (1H)	11.65 s (1H)	2.54 s (3H)	7.35–7.52 m (5H), 3.23 s (3H), 2.30 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			
		NH, OH	C=N, C=O	OH	NH	R^1	R^2
IIq	203 (3.28), 261 (1.59), 315 (1.66)	3460, 2970, 2810	1675, 1615, 1550	13.50 br.s (1H)	8.85 br.s (1H)	2.64 s (3H)	7.35–7.50 m (5H), 3.20 s (3H), 2.28 s (3H)
IIr	201 (2.42), 228 (1.82), 306 (1.64)	3160, 3030	1670, 1640, 1615	14.06 br.s (1H)	11.82 s (1H)	2.62 s (3H)	11.70 br.s (1H), 7.56–7.94 m (5H)
IIs	199 (2.28), 261 (0.78), 304 (2.40)	3440, 3305, 3165	1680, 1640	14.05 s (1H)	11.85 s (1H)	2.77 t (2H), 1.43–1.45 m (2H), 0.75 t (3H)	7.29 d. d (4H), 2.36 s (3H)
IV	200 (1.68), 229 (1.15), 262 (0.97), 308 (1.88)	3150, 2935	1675, 1630	12.50 s (2H)	11.59 s (2H)	2.55 s (6H)	3.88 s (4H)

[a] The spectrum was recorded in $CDCl_3$.

Table 4. ^{13}C NMR spectra of 1,3-thiazines **IIa**–**IIs** and **IV** in DMSO-d_6, δ_C, ppm

Comp. no	C^2	C^4	C^5	C^6	R^1	R^2
IIa	174.8	167.2	96.3	163.1	180.2, 24.7	–
IIb	174.4	167.9	96.9	163.1	180.1, 18.6	132.3, 117.2, 45.8
IIc[a]	174.3	168.5	97.3	164.0	180.6, 18.8	44.6, 31.1, 28.7, 22.3, 26.3, 13.9
IId	173.9	167.7	96.7	163.2	179.9, 18.7	58.7, 46.3
IIe	174.0	167.8	96.7	163.2	180.0, 18.7	158.2, 129.4, 120.7, 114.4, 69.5, 66.6, 46.9
IIf	173.8	167.8	96.7	163.1	179.9, 18.3	172.2, 39.1, 32.9
IIg	174.1	167.7	96.9	163.1	180.1, 18.8	135.8, 128.9, 127.9, 127.5, 47.3
IIh	174.3	167.9	97.1	163.1	180.2, 18.2	138.4, 133.4, 130.7, 127.8, 127.4, 126.1, 46.6
IIi	173.4	168.4	97.6	163.0	180.6, 20.7	135.7, 129.5, 128.3, 125.9
IIj	173.6	168.3	97.6	163.1	180.5, 20.5	151.5, 129.6, 126.9, 122.9, 119.3, 116.4
IIk	173.6	168.3	97.7	163.0	180.6, 20.8	197.1, 137.9, 136.2, 130.6, 129.9, 127.7, 125.8, 26.8
IIl	173.3	168.4	97.6	163.0	180.5, 20.7	144.5, 135.5, 129.2, 126.1, 124.0, 123.4, 62.2
IIm	173.5	168.3	97.4	163.0	180.4, 20.6	158.9, 128.3, 127.1, 114.7, 55.4
IIn	173.9	168.9	98.1	163.6	181.0, 21.1	138.5, 133.6, 130.5, 126.1, 21.15
IIo	174.5	168.6	98.0	163.1	180.7, 20.8	133.6, 131.8, 128.8, 128.5, 128.2, 127.7, 127.0, 125.5, 124.4, 121.7
IIp	173.4	168.4	97.8	163.0	180.6, 20.9	133.1, 132.7, 131.96, 129.3, 127.9, 127.7, 12.1, 126.9, 124.2, 123.9
IIq	175.3	168.2	98.1	163.0	180.6, 20.2	159.5, 150.7, 134.2, 129.2, 127.3, 124.9, 104.9, 35.1, 10.4
IIr	171.0	167.7	95.8	163.1	180.2, 17.8	165.0, 132.6, 131.1, 128.6, 127.8
IIs	176.8	168.7	96.4	162.9	180.2, 20.5	138.2, 132.9, 129.9, 125.9, 32.6, 21.3,14.0
IV	174.8	167.7	97.2	163.0	180.1, 18.6	42.6

[a] The spectrum was recorded in $CDCl_3$.

The UV spectra (Table 3) of compounds **IIa**–**IIs** in 96.5% ethanol contain three strong absorption bands at 297–310, 260–263, and 199–205 cm^{-1} (starting thiazines **Ia**–**Ic** absorb at 276–279, 216–218, and 199 nm).

The ^1H NMR spectra of uracils **IIIa**–**IIIi** in DMSO-d_6 (Table 5) display signals characteristic of 6-methyluracil: three singlets from the NH (11.2–11.35 ppm), C^5H (5.44–5.65 ppm), and C^6CH_3 pro-

Table 5. UV, IR, and ^{1}H NMR spectra of uracils **IIIa**–**IIIi, V**, and **VI**

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			
		NH, OH	C=N, C=O	NH	C^{5}H	R^1	R^2
IIIa	208 (0.40), 263 (0.55)	3260, 3150	1710, 1670	10.99 s (1H)	5.44 s (1H)	2.26 s (3H)	4.94 br.s (1H), 3.77 t (2H), 3.56 t (2H)
IIIb	208 (0.40), 263 (0.55)	3140, 2990	1710, 1670	11.21 s (1H)	5.51 s (1H)	2.19 s (3H)	5.88 m (1H), 5.15 d (1H), 5.02 d (1H), 4.39 s (1H)
IIIc	208 (0.89), 267 (1.11)	3130, 2965	1710, 1655	11.11 s (1H)	5.46 s (1H)	2.22 s (3H)	3.68 t (2H), 1.47–1.55 m (2H), 1.23–1.35 m (6H), 0.86 t (3H, *J* 7 Hz)
IIId	206 (1.23), 265 (0.89)	3030, 2780	1710, 1660	11.36 s (1H)	5.56 s (1H)	2.11 s (3H)	7.27 m (5H), 5.04 s (2H)
IIIe	199 (1.38), 264 (1.01)	3165, 3095	1715, 1675	11.31 s (1H)	5.56 s (1H)	1.76 s (3H)	7.43 m (5H)
IIIf	199 (1.86), 266 (1.42)	3180, 3060	1715, 1680	11.34 s (1H)	5.69 s (1H)	1.78 s (3H)	8.06 d (2H), 7.55 d (2H), 4.35 q (2H), 1.33 t (3H)
IIIg	202 (2.78), 240 (1.60), 260 (1.34)	3350, 3105, 3025	1705, 1665, 1610	11.11 s (1H)	6.60 s (1H)	1.76 s (3H)	7.09 t (1H), 6.94 d (1H), 6.75 d (1H), 6.57 t (1H), 5.32 s (1H)
IIIh	206 (0.96), 264 (1.21)	3445, 3010	1735, 1660	11.13 s (1H)	5.45 s (1H)	2.25 s (3H)	4.21 t (2H), 3.95 t (2H), 2.02 s (3H)
IIIi	205 (1.34), 263 (1.07)	3170, 3050	1690, 1615	11.34 s (1H)	5.56 s (1H)	2.01 q (2H), 0.93 t (3H)	7.44 m (5H)
V	267 (0.88), 205 (1.12)	3150, 2980	1730, 1665	11.19 br.s (2H)	5.49 s (2H)	2.23 s (6H)	3.95 s (4H)
VI	201 (1.26), 270 (2.35)	3550, 3470, 3180	1680, 1520, 1402	11.09 br.s (1H)	5.50 s (1H)	2.29 s (3H)	8.23 d (2H), 7.68 d, (2H) 6.03 d (1H), 5.32 q (1H), 4.76 br.t (1H), 4.07 m (2H), 3.01 br.t (1H)

tons (1.75–2.25 ppm). The ^{13}C NMR spectra of these compounds (Table 6) contain characteristic signals of the C^5 (100.6–101.2 ppm), C^2 (162.4–163.3 ppm), C^4 (153.6–155 ppm), and C^6 atoms (151.1–151.9 ppm) and the C^{6}CH$_3$ group (19.1–20.3 ppm). The chemical shifts are fully consistent with published data for previously obtained compounds [8–11].

In the IR spectra of 1-substituted 6-methyluracils **IIIa**–**IIIi** in KBr (Table 5), there are stretching and deformation vibration bands of the NH (3025–3260 cm^{-1}) and C=O groups (1655–1670 and 1705–1715 cm^{-1}) [14].

The UV spectra (Table 5) of compounds **IIIa**–**IIIi** in 96.5% ethanol show two absorption maxima at 260–267 and 199–208 nm.

The mass spectra of uracils **III** are given in Table 7.

The reaction mechanism can be exemplified by the transformation of model 5-(1-methylamino)ethylidenethiazine **IIt** (R = R^2 = CH$_3$) to 1,6-dimethyluracil **IIIj** (R = R^1 = CH$_3$) (Scheme 5). To gain a deeper insight into the reaction mechanism, we made use of the semiempirical PM3 method to calculate the enthalpies of formation of the starting, probable intermediate, and final products in the gas phase at 0 K, as well as the heat effect of the reaction in terms of the Hess law.

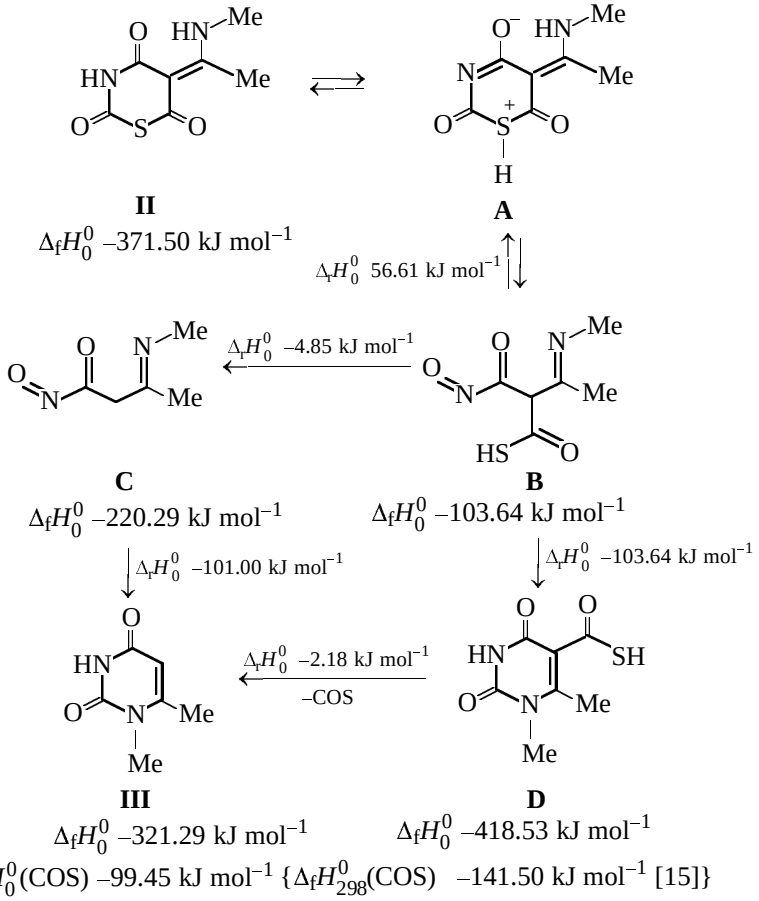
It should be noted that the starting compound can have a great number of tautomers, and, in addition, certain tautomers can exist as geometric isomers. Moreover, ring–chain tautomerism is possible. Obviously, the reaction involves tautomeric transitions

Table 6. ^{13}C NMR spectra of uracils **IIIa**–**IIIi, V**, and **VI** in DMSO-d_6, δ_C, ppm

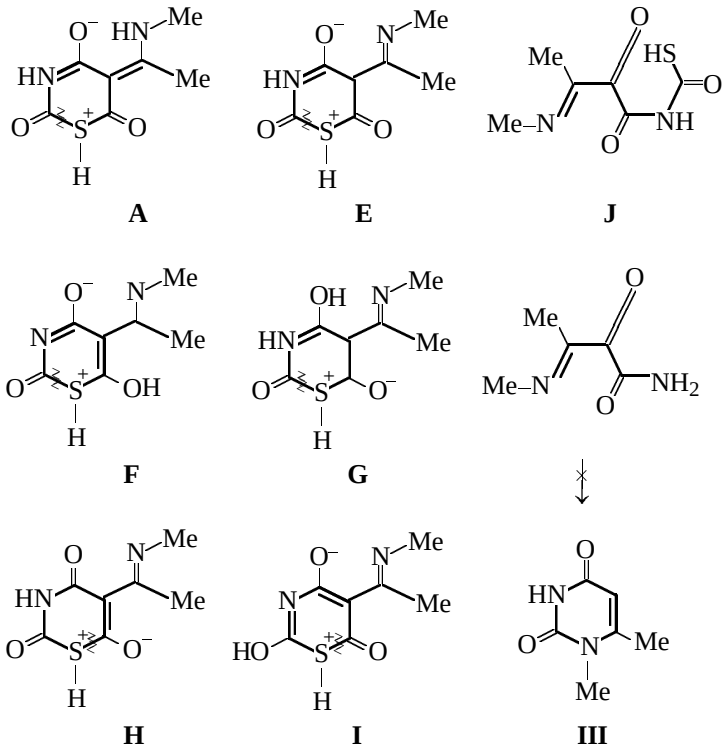
Comp. no	C^2	C^4	C^5	C^6	R^1	R^2
IIIa	162.5	155.0	100.6	151.5	19.8	58.4, 45.8
IIIb	162.4	154.2	100.97	151.3	18.75	133.2, 115.6, 44.9
IIIc	162.4	154.0	100.9	151.4	19.0	43.3, 30.7, 28.1, 25.7, 21.9, 13.7
IIId	162.4	154.3	101.3	151.9	19.1	136.9, 128.7, 127.2, 125.8, 45.9
IIIe	162.8	153.6	100.8	151.3	20.3	136.6, 129.3, 128.9, 128.8
IIIf	162.7	153.0	101.1	151.1	20.2	164.9, 140.8, 130.3, 103.0, 129.6, 60.9, 14.0
IIIg	163.2	154.1	101.2	151.1	19.2	145.5, 129.5, 129.4, 120.9, 115.9, 115.5
IIIh	162.4	154.1	101.1	151.5	20.4	170.1, 61.1, 42.4, 19.3
IIIi	163.0	158.4	98.7	151.4	25.7, 10.96	136.3, 129.24, 129.19, 128.8
V	162.3	153.7	101.3	151.7	18.8	41.6
VI	162.9	156.2	101.2	151.5	20.9	150.6, 146.96, 128.1, 123.5, 69.2, 66.5, 57.7

and conversions of cyclic tautomers (or tautomer) into acyclic intermediates, and recyclization of the latter. It is acyclic tautomers that should act as reaction intermediates. The calculations show that the heats of formation $\Delta_f H_0^0$ of most of such tautomers vary from –371 to –262 kJ mol^{-1}. The most preferred tautomer of the starting model compound in the gas phase is (5*E*)-5-[1-(methylamino)ethylidene]-1,3-thiazinane-

Scheme 5.



Scheme 6.



2,4,6-trione (**IIt**) ($\Delta_f H_0^0$ –371.50 kJ mol^{-1}). At the same time, zwitter-ionic tautomers **A** and **E**–**I** (Scheme 6) are quite unstable, since their thiazine ring spontaneously and activationless opens. Probably, these tautomers are key reaction intermediates. If there is a proton at the thiazine N^3 atom or at the oxygen atom of the C^2–OH fragment in zwitter-ionic intermediates **H** and **I**, cleavage of the S^1–C^6 bond takes place to form 2-(*N*-methylethanimidoyl)-3-oxoacryloylcarbamothioic S-acid (**J**) ($\Delta_f H_0^0$ –281.46 kJ mol^{-1}). The heat effects of the tautomeric transitions of the starting cyclic compound **IIt** into linear (**B** and **J**) are $\Delta_r H_0^0$ 56.6 and 90.1 kJ mol^{-1}, respectively. Consequently, the conversion of compound **IIt** into tautomer **J** is less probable, and this transition is unlikely. Moreover, it is difficult to imagine that compound **J** converts into 1,6-disubstituted uracil **III**.

On the other hand, zwitter-ionic intermediates with a pyridine N^3 atom (**A**, **E**–**G**) undergo S^1–C^2 bond cleavage to give 2-(isocyanatocarbonyl)-3-methyliminobutanethioic acid *S*-acid (**B**) ($\Delta_f H_0^0$ –314.89 kJ mol^{-1}). This process is less endothermic ($\Delta_r H_0^0$ 56.61 kJ mol^{-1}) than the above-described one. Conversion of compound **B** into final reaction products can occur in two ways differing from each other by the order of the COS cleavage and pyrimidine ring closure stages.

Conversion of cyclic tautomers into the more flexible acyclic tautomers should increase the entropy of the system, i.e. for the tautomeric transition **II** → **B** the expression $\Delta_r S^0 > 0$ should be valid. At a certain fairly high temperature, the Gibbs energy term in the Gibbs–Helmholtz equation $\Delta_r G_T^0 = \Delta_r H_T - T\Delta_r S_T$ for this tautomeric transition may prove negative and thus render this transition spontaneous.

Further reaction stages, like the reaction in whole ($\Delta_r H_0^0$ –49.25 kJ mol^{-1}), are exothermic. Therewith, the heat effect of COS cleavage either from acid **B** ($\Delta_r H_0^0$ –4.85 kJ mol^{-1}) or from acid **D** ($\Delta_r H_0^0$ –2.18 kJ mol^{-1}) is close to 0. The highly exothermic process is pyrimidine ring closure: The $\Delta_r H_0^0$ for the **B** → **D** and **C** → **III** transitions are –103.64 and –101.00 kJ mol^{-1}, respectively.

The possibility of the whole reaction can also be substantiated by the following reasoning. The conversion of thiazine **II** into 1,6-dimethyluracil **III** is accompanied by heat release, i.e. $\Delta_r H_T^0 < 0$. Therewith, the number of molecules increases (one of the reaction products, COS, is gaseous), which implies increase in the entropy of the reaction system, i.e. $\Delta_r S_T^0 > 0$. Thus, the reaction is possible at any conditions, since $\Delta_r G_T^0 < 0$. In practice, however, the reaction occurs only at a fairly high temperature or in the basic solvent DMF, probably because these conditions favor the endothermic reaction stage, i.e. the opening of the thiazine ring to form an acyclic intermediate.

Table 7. Mass spectra of 1,6-disubstituted uracils **IIIa**–**IIIi, V**, and **VI**, *m/z* (I_{rel}, %)[a]

Comp. no	$M^{+\cdot}$	$[M - R^1]^+$	$[M - HNCO]^{+\cdot}$	$[M - HNCO - CO]^{+\cdot}$	$[M - HNCO - CO - H]^+$	$[M - HNCO - CH_3]^+$	$[M - R^1NCO]^{+\cdot}$	$[M - R^1NCO - CO]^{+\cdot}$	$[R^1 - NCO]^+$	$[R^2]^+$	Other ions
IIIa	170 (20)	–	127 (29)	–	98	112	83 (10)	55 (32)	–	45	140 (15), 139 (12), 126 (41), 96 (100), 67 (10)
IIIb	166 (95)	151 (34)	123 (100)	95	94 (71)	108	125	–	–	–	80 (24), 68 (42), 54 (52)
IIIc	210 (31)	195 (46)	–	139 (13)	–	–	83 (38)	55 (25)	127 (33)	–	140 (21), 126 (100), 96 (92), 43 (25), 41 (46)
IIId	216 (21)	–	–	–	–	–	–	–	–	91 (100)	77 (4), 65 (11), 51 (4)
IIIe	202 (100)	–	159 (51)	131 (25)	130 (30)	144 (57)	119	91	–	77 (79)	118 (42), 51 (38)
IIIf	274 (100)	–	231 (49)	203	202	216 (20)	–	–	–	–	186 (20), 159 (13), 158 (15), 130 (12), 103 (12), 93 (10), 65 (15), 58 (10)
IIIg	217 (100)	202	174	146	145	159 (52)	–	–	134	–	133 (88), 92 (20), 65 (28)
IIIh	212 (19)	–	169	140 (23)	139	–	83	55	–	87	152 (100), 128 (14), 127 (12), 109 (40), 96 (86), 43 (95)
IIIi	216 (100)	–	173 (47)	145	144 (97)	–	–	69	–	77 (84)	172 (29), 130 (16), 51 (39)
V	278 (27)	–	–	–	–	–	–	–	–	153 (41)	152 (76), 140 (18), 139 (17), 126 (14), 110 (18), 109 (33), 96 (100), 55 (29)
VI	321	306	–	–	–	–	–	–	–	–	290 (15), 276 (5) 205 (11), 169 (65), 152 (100), 135 (16), 125 (40), 126 (65), 109 (45), 84 (45)

[a] Peaks with I_{rel} – 10% are shown.

Thus, we have developed a new efficient synthetic approach to 1-substituted 6-alkyluracils from readily available precursors. Moreover, the advantage of the proposed synthesis of 1-substituted 6-alkyluracils over existing ones is that it provides high yields of uracils free of admixtures of 3-substituted isomers [9].

EXPERIMENTAL

The UV spectra in 96.5% ethanol were obtained on a Shimadzu UV-mini spectrophotometer. The 1H and ^{13}C NMR spectra in DMSO-d_6 were recorded on a Bruker AM-500 spectrometer (500 and 125 MHz, respectively). The IR spectra in KBr were taken on an FSM-1201 Fourier spectrometer. The reaction progress and the purity of products were controlled by TLC on Sorbfil plates. Quantum-chemical calculations were performed by the semiempirical PM3 method with the GAMESS program package [16].

5-Acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione (Ia) was prepared as described in [7]. Acetic anhydride, 45 ml, was added to a solution of 21 g of malonic acid in 100 ml of acetic acid. The solution was stirred for 15 min at 20–25°C, after which 19 g of KSCN was added in one portion, and stirring was continued for 1 h at 18–25°C. The transparent yellow solution was left to stand for 48 h at ~20°C. The reaction mixture crystallized and was diluted with 300 ml of water, filtered off, dried in air, and recrystallized from benzene (Soxhlet apparatus is very convenient here) to obtain 25 g (46%) of thiazine **Ia**, mp 198–200°C.

4-Hydroxy-5-[1-alkyl(aryl)iminoethyl]-3,6-dihydro-2*H*-1,3-thiazine-2,6-diones IIa–IIs (Tables 1–4). A mixture of 1 g of 5-acyl-4-hydroxy-1,3-thiazine-2,6-dione **Ia–Ic** and 5.5 mmol of primary amine was refluxed for 30 min in 20 ml of propan-2-ol. Most commonly, the reaction product began to crystallize already within 10 min. After cooling, the crystals were filtered off, washed with propan-3-ol, and dried in air. Pure compounds not requiring recrystallization were obtained almost always. When required, the products may be recrystallized from ethanol, propan-2-ol, or butan-1-ol.

1-Substituted 6-methyluracils IIIa–IIIi (Tables 1 and 5–7). *a*. A mixture of 1 g of 5-acylthiazine **Ia–Ic** and 10–15 ml of primary amine was refluxed until reaction completion (15–60 min, TLC control). Excess amine was removed in a vacuum (~10–20 mm Hg). The residue was recrystallized from ethanol or butan-1-ol.

With aliphatic primary amines, the residue was poured with 20 ml of 0.5 N aqueous NaOH, the mixture was stirred for 15 min at 18–25°C, and undissilved 1,3-disubstituted urea was filtered off. The filtrate was neutralized with HCl, the uracil that precipitated was filtered off, washed with water, and recrystallized from ethanol or butan-1-ol.

b. A mixture of 1 g of thiazine **Ia–Ic**, 5.5 mmol of primary amine, and 15 ml of DMF was refluxed until reaction completion (1–2 h, TLC control). Excess DMF was removed in a vacuum (~10–20 mm Hg). The residue was recrystallized from ethanol or butan-1-ol.

c. A solution of 1 g of 4-hydroxy-5-[1-alkyl(aryl)-iminoethyl]-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione **IIa–IIc** in 15 ml of DMF was refluxed until reaction completion (TLC control). The solvent was removed in a vacuum (~10–20 mm Hg). The residue was recrystallized from ethanol or butan-1-ol.

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