RESEARCHES ON NITROGEN AND SULFUR HETEROCYCLIC RINGS

IV. Pyrimido[4, 5-b]-[1, 4]Thiazines *

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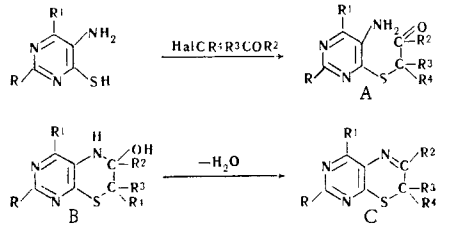
A number of 7H-pyrimido[4, 5-b]thiazines are obtained by reacting 5-amino-6-mercaptopyrimidines with α-halogeno ketones. It is established that the reaction takes place in three stages: formation of 5-amino-6-[β-ketoalkyl(aralkyl)-mercapto]pyrimidines, cyclization of these to 6-hydroxy-5, 6-dihydropyrimido[4, 5-b][1, 4]thiazines, and dehydration of the latter to 7H-pyrimido[4, 5-b][1, 4]thiazines.

We have previously published information regarding the synthesis of some pyrimido[4, 5-b][1, 4]thiazine derivatives [1]. Almost simultaneously American authors [2] published a paper describing the preparation of 4-methoxy(4-hydrazino)-6-phenylpyrimido[4, 5-b][1, 4]thiazines. Continuing work [1] on the reaction of 5-amino-6-mercaptopyrimidines with α-halogenated ketones, we have now synthesized derivatives of 7H-pyrimido-[4, 5-b][1, 4]thiazine (C, X–XXV, Table 2).

With a more detailed study of this reaction, it has been possible to isolate and prove the structures of the intermediate compounds, 5-amino-6-[β-ketoalkyl (aralkyl)]mercaptopyrimidines (A) and 6-hydroxy-5, 6-dihydropyrimido[4, 5-b][1, 4]thiazines (B). By this means it was established that thiazine ring closure involves three stages, formation of 6-S-β-keto compounds (A), their cyclization to carbinolamines (B), and dehydration of the latter to pyrimidothiazines (C):



It was also shown that, depending on the natures of the substituents at positions 2 and 4 in 5-amino-6-mercaptopyrimidines, the structures of the α-halogenated ketones, and the reaction conditions, reaction can stop at the intermediate stages A and B, or proceed to formation of the end products C.

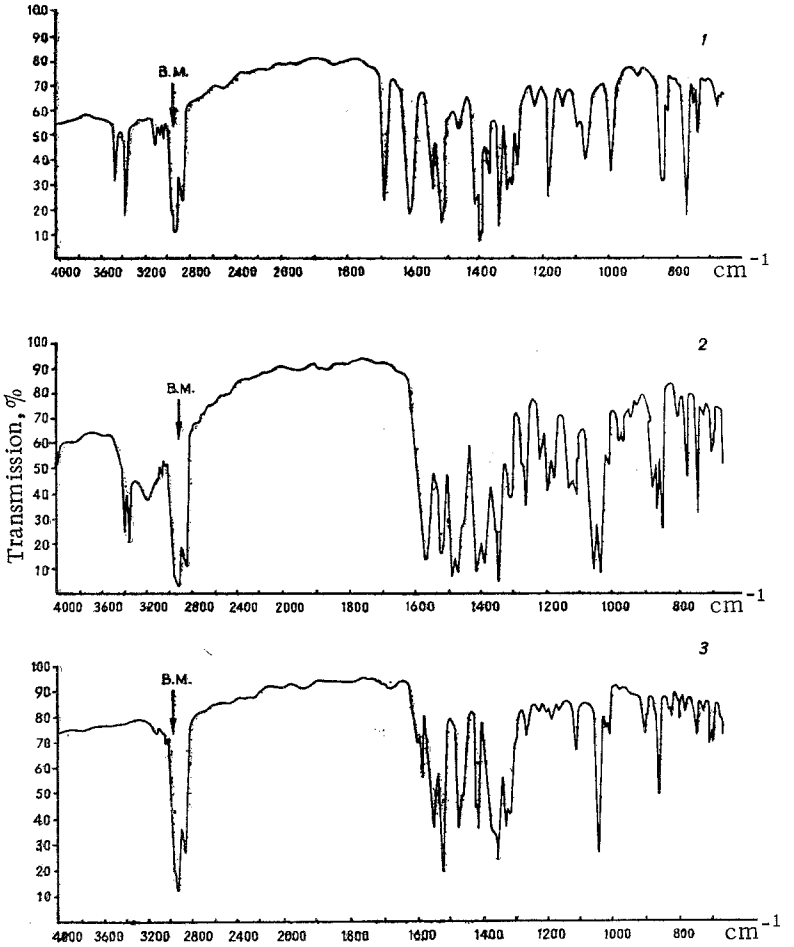
Thus reaction of 4-chloro-5-amino-6-mercaptopyrimidine (XXVII) with 4-nitrophenacyl bromide in ethanol solution, in the presence of potassium hydroxide, and at 0° C, gives an 84% yield of 4-chloro-5-amino-6-(p-nitrophenacyl)mercaptopyrimidine (XXVI). The structure of XXVI is confirmed by the IR spectrum* exhibiting an absorption band at 1690 cm^{-1}, characteristic of the CO group (see Fig. 1, plot 1). Reaction of XXVII with 2,3-dichlorophenacyl bromide under similar conditions gives 4-chloro-6-hydroxy-6-dichlorophenyl-5,6-dihydropyrimido[4,5-b][1,4]thiazine (I, Table 1). Reaction of XXVII with bromoacetophenone and 4-bromophenacyl bromide in ethanol solution, in the presence of potassium hydroxide, led to the isolation of the pyrimidothiazines **X** and **XI** (Table 2). Similarly, reaction of α-halogenated ketones (chloroacetone, α-chloroethylmethylketone, α-bromoisopropylphenylketone, 2,5-dichlorophenacyl bromide, bromoacetophenone, 4-bromophenacyl bromide, 3- and 4-nitrophenacyl bromide) gave only pyrimidothiazines XII–XIX (Table 2). It did not prove possible to isolate compounds A and B from the reaction products.

A more detailed study was made of the products of reaction of 4-methoxy-5-amino-6-mercaptopyrimidine (XXIX) with α-halogenated ketones. Reacting it with aliphatic and aliphaticaromatic α-halogenated ketones (α-chloroethylmethyl ketone, desyl chloride, 3- and 4-nitrophenacyl bromide, 4-bromophenacyl bromide, 2,5-dichlorophenacyl bromide, and α-bromoisopropylphenylketone) in solution in ethanolic potassium hydroxide gave the carbinolamines B (III–IX, Table I). Their IR spectra whether observed with a vaseline mull, or in dilute solution ($CHCl_3$, CCl_4) did not show a CO group absorption band, but had bands at 3400 and 3500 cm^{-1}, characteristic of NH and OH groups (see Fig. 1, plot 2). The carbinolamines B prepared have varying stabilities. Some (VI, VIII, Table 1) were converted to pyrimidothiazines (XX, XXI, Table 2) only when treated with dehydrating agents such as acetic anhydride, or when boiled for a long time in a high-boiling solvent (toluene, mesitylene). Other carbinolamines (V and IX, Table 1) underwent partial dehydration to XXII and XXIII (Table 2), when recrystallized from ethanol. Compounds III and VII (Table 1) darkened and resinified when kept in air.

Reaction of 4-methoxy-5-amino-6-mercaptopyrimidine (XXIX) with phenacyl(4-bromophenacyl) bromides in ethanol solution in the presence of potassium hydroxide at 50° C gave the pyrimidothiazines XXIII

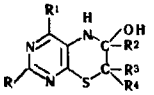
*For Part III see [5].

*The IR spectra were measured with an UR-10 spectrophotometer; I–IX as vaseline mulls, or dissolved in $CHCl_3$ or CCl_4, compounds X–XXVI as vaseline mulls.



IR spectra. 1) 4-Chloro-5-amino-6-(4-nitrophenacyl) mercaptopyrimidine (XXVI); 2) 4-methoxy-6-hydroxy-6-(4-nitrophenyl)-5,6-dihydropyrimido[4,5-b][1,4]-thiazine (VI); 3) 4-methoxy-6-(4-nitrophenyl)-7H-pyrimido[4,5-b]thiazine (XX).

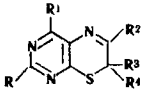
Table 1



Compound	R	R¹	R²	R³	R⁴	Mp, ° C	Formula	Found, %					Calculated, %					Yield, %
								C	H	N	Hal	S	C	H	N	Hal	S	
I	H	Cl	2,5-$C_6H_3Cl_2$	H	H	138—139	$C_{12}H_8Cl_3N_3OS$	41.36	2.36	11.97	—	9.30	41.34	2.31	12.05	—	9.20	55
II	H	Cl	CH_3	H	H	104—106	$C_7H_8ClN_3OS$	38.78	3.99	19.28	16.02	15.04	38.62	3.70	19.30	16.29	14.73	46
III	H	OCH_3	CH_3	CH_3	H	97—99	$C_9H_{13}N_3O_2S$	47.30	5.89	18.63	—	14.35	47.56	5.76	18.49	—	14.12	46
IV	H	OCH_3	C_6H_5	C_6H_5	H	155—157	$C_{19}H_{17}N_3O_2S$	64.58	4.87	11.87	—	8.82	64.93	4.87	11.95	—	9.12	53
V	H	OCH_3	3-$C_6H_4NO_2$	H	H	161—163	$C_{13}H_{12}N_4O_4S$	48.59	3.77	17.65	—	9.93	48.74	3.77	17.49	—	10.01	73
VI	H	OCH_3	4-$C_6H_4NO_2$	H	H	>300	$C_{13}H_{12}N_4O_4S$	48.64	3.85	17.60	—	10.26	48.74	3.77	17.49	—	10.01	45
VII	H	OCH_3	4-C_6H_4Br	H	H	145—147	$C_{13}H_{12}BrN_3O_2S$	44.31	3.46	11.91	22.52	8.55	44.08	3.41	11.86	22.56	9.05	84
VIII	H	OCH_3	2,5-$C_6H_3Cl_2$	H	H	148—150	$C_{13}H_{11}Cl_2N_3O_2S$	45.38	3.13	12.5	20.67	9.42	45.36	3.22	12.2	20.6	9.31	84
IX	H	OCH_3	C_6H_5	CH_3	CH_3	148—150	$C_{15}H_{17}N_3O_2S$	59.59	5.40	14.05	—	10.56	59.36	5.68	13.85	—	10.56	69

*For analysis compound I was purified by percipitation from MeOH solution with water, compound II was recrystallized from MeOH, III from MeOH-ether (1:10), IV-VIII ex EtOH, and IX from heptane.

Table 2



Compound	R	R¹	R²	R³	R⁴	Mp, ° C	Formula	Found, %					Calculated, %					Yield, %
								C	H	N	Hal	S	C	H	N	Hal	S	
X	H	Cl	4-C_6H_4Br	H	H	149—151	$C_{12}H_7BrClN_3S$	42.49	2.23	12.13	—	9.53	42.31	2.07	12.34	—	9.41	42
XI	H	Cl	C_6H_5	H	H	138—139	$C_{12}H_8ClN_3S$	55.18	3.25	16.08	13.37	12.01	55.06	3.08	16.05	13.55	12.55	61
XII	NH_2	CH_3	CH_3	H	H	223—224	$C_8H_{10}N_4S$	49.49	5.04	29.04	—	16.42	49.45	5.20	28.83	—	16.50	80
XIII	NH_2	CH_3	CH_3	CH_3	H	200—222,5	$C_9H_{12}N_4S$	52.15	5.97	26.91	—	15.24	51.89	5.80	26.90	—	15.39	47
XIV	NH_2	CH_3	2,5-$C_6H_3Cl_2$	H	H	204—205,5	$C_{13}H_{10}Cl_2N_4S$	48.03	3.07	17.21	21.81	10.00	48.00	3.10	17.23	21.80	9.86	62
XV	NH_2	CH_3	C_6H_5	H	H	281—283	$C_{13}H_{12}N_4S$	60.60	4.55	22.15	—	12.41	60.91	4.72	21.86	—	12.57	67
XVI	NH_2	CH_3	4-C_6H_4Br	H	H	240—242	$C_{13}H_{11}BrN_4S$	46.29	3.20	16.91	23.62	9.67	46.57	3.08	16.71	23.84	9.56	50
XVII	NH_2	CH_3	4-$C_6H_4NO_2$	H	H	>300	$C_{13}H_{11}N_5O_2S$	51.52	3.66	22.91	—	10.65	51.81	3.68	23.37	—	10.64	64
XVIII	NH_2	CH_3	3-$C_6H_4NO_2$	H	H	>300	$C_{13}H_{11}N_5O_2S$	51.77	3.56	22.40	—	10.47	51.81	3.68	23.37	—	10.64	73
XIX	NH_2	CH_3	C_6H_5	CH_3	CH_3	179—181	$C_{15}H_{16}N_4S$	63.28	5.84	19.47	—	10.99	63.35	5.67	19.70	—	11.27	44
XX	H	OCH_3	4-$C_6H_4NO_2$	H	H	>300	$C_{13}H_{10}N_4O_3S$	51.53	3.37	17.93	—	10.67	51.65	3.33	18.53	—	10.61	53
XXI	H	OCH_3	2,5-$C_6H_3Cl_2$	H	H	219—220	$C_{13}H_9Cl_2N_3O_2S$	48.18	2.59	13.02	21.47	9.71	47.86	2.78	12.88	21.74	9.83	55
XXII	H	OCH_3	3-$C_6H_4NO_2$	H	H	>300	$C_{13}H_{10}N_4O_3S$	51.65	3.33	18.53	—	10.61	51.45	3.07	18.90	—	10.56	71
XXIII	H	OCH_3	4-C_6H_4Br	H	H	175—177	$C_{13}H_{10}BrN_3OS$	46.50	2.98	12.55	23.80	9.66	46.44	2.99	12.50	23.77	9.54	65
XXIV	H	OCH_3	C_6H_5	CH_3	CH_3	141—142	$C_{16}H_{15}N_3OS$	63.16	5.19	15.01	—	11.03	63.10	5.33	14.72	—	11.23	68
XXV	H	OCH_3	C_6H_5	H	H	171—173	$C_{13}H_{11}N_3OS$	60.84	4.51	16.23	—	12.43	60.68	4.32	16.33	—	12.46	55

*For analysis compound X was purified by precipitation from EtOH with water; compounds XI, XIII-XV, XXIII, and XXV were recrystallized from EtOH, XII, XVII, XVIII, and XXI from dimethylformamide, XVI, XIX from EtOH-dimethylformamide (2:1), XX and XXII were purified by washing with hot dimethylformamide, XXIV were purified by recrystallizing from heptane.

and XXV (Table 2). When the reaction was run at 5°, bromoacetopheone gave the pyrimidine XXV, and 4-bromophenacyl bromide gave carbinolamine VII (Table 1). That the pyrimidothiazines had a 7H-pyrimido[4,5-b][1,4]thiazine one, was confirmed by their IR spectra, which did not exhibit a NH group absorption band (see Fig. 1, plot 3). This structure was supported by the method of synthesis and properties of 4-methoxy-6-phenyl-7,7-dimethylpyrimido[4,5-b][1,4]thiazine (XXIV, Table 2), prepared in one stage by reacting 4-methoxy-5-amino-6-mercaptopyrimidine with α-bromoisopropylphenylketone, or by dehydrating the intermediate carbinolamine IX (Table 1) itself. There is no doubt about the structure of the compound 7H-pyrimido[4,5-b][1,4]-thiazine.

EXPERIMENTAL

The starting 4-chloro-5-amino-6-mercaptopyrimidine (XXVII), 2,5-diamino-4-methyl-6-mercaptopyrimidine (XXVII), and 4-methoxy-5-amino-6-mercaptopyrimidine (XXIX), were prepared as described in [3,4].

2-Amino-4,6-dimethyl-7H-pyrimido[4,5-b][1,4]thiazine (XII). a) 0.6 g (0.006 mole) chloroacetone was added to a solution of 1 g (0.006 mole) XXVIII in 24 ml 1.5% aqueous NaOH at 50° C, the whole stirred for 30 min at that temperature, cooled, to 18°–20° C, and the precipitate filtered off, yield 1 g (80%), mp 215°–217° C. After recrystallizing from dimethylformamide it had mp 225°–226° C. XIII was prepared similarly. b) Compound XII was prepared by carrying out the reaction at 0° C, yield 80%.

2-Amino-4-methyl-6-(4'-bromophenyl)-7H-pyrimido[4,5-b][1,4]thiazine (XVI). 1.78 g (0.006 mole) 4-bromophenacyl bromide in 20 ml toluene was added to a solution of 1 g (0.006 mole) XXVIII in 24 ml aqueous 1.5% NaOH at 50° C. The mixture was stirred for 3 hr, cooled to 18–°20° C, the solid filtered off, washed with water, and then with toluene. Yield 1.07 g (50%), mp 236°–238° C. After recrystallizing from EtOH-dimethylformamide (2:1) it had mp 240°–242° C. Compounds XV, XVII, XXIII, and XXV were prepared similarly.

2-Amino-4-methyl-6-(3'-nitrophenyl)-7H-pyrimido[4,5-b][1,4]thiazine (XVIII). 0.7 g (0.003 mole) 3-nitrophenacyl bromide in 20 ml EtOH was added to a solution of 0.5 g (0.003 mole) XXVIII and 0.2 g (0.0035 mole) KOH in 15 ml EtOH at 18°–20° C. The whole was stirred for 2 hr, then evaporated to dryness under vacuum, 10 ml water added to the residue, and the solid filtered off, and washed with water, yield 0.7 g (73%), mp > 300° C. After recrystallizing from dimethylformamide it had mp > 300° C.

Compounds XI and XIV were prepared similarly. When the reaction was run at 50° C, compound XIX was the product, while when it was run at 0° C, the product was XXV (yield 64%).

In the preparation of compound X the difference was that the residue obtained by vacuum-evaporation of the reaction products was triturated with 10 ml 2 N NaOH, the solution filtered, the solid washed with water, dried, triturated with EtOAc, run onto an alumina column, then eluted with ether, and the ether eluates bulked and evaporated under vacuum, yield 42%, mp 136°–140° C. Dissolved in EtOH, and precipitated with water, to give X, mp 149°–151° C.

4-Methoxy-6-(2',5'-dichlorophenyl)-6-hydroxy-5,6-dihydropyrimido[4,5-b]-[1,4]thiazine (VI). 0.5 g (0.002 mole) 2,5-dichlorophenacyl bromide was added to a solution of 0.32 g (0.002 mole) XXIX and 0.15 g (0.0027 mole) KOH in 20 ml EtOH, at 18°–20° C. The subsequent reaction conditions, and the working up, were as described in the preparation of XVIII. Yield 0.55 g (84%), mp 144°–146° C. After recrystallizing from EtOH it had mp 148°–150° C.

Compounds II, IV, V were prepared similarly. Compounds I, III, and VII were obtained by running the reaction at 0° C, and IX by running it at 50° C.

4-Methoxy-6-(4'-nitrophenyl)-6-hydroxy-5,6-dihydropyrimido[4,5-b][1,4]-thiazine (VI). 0.7 g (0.003 mole) 4-nitrophenacyl bromide in 7 ml $CHCl_3$ was added to a solution of 0.5 g (0.003 mole) XXIX in 3 ml 10% NaOH at 50° C. The whole was stirred for 1 hr, cooled to 18°–20° C, and the precipitate filtered off, yield 0.47 g (45%), mp > 300° C. After recrystallizing from EtOH mp > 300° C.

4-Methoxy-6-phenyl-7,7-dimethylpyrimido[4,5-b]thiazine (XXIV). A mixture of 0.2 g (0.6 mmole) IX and 10 ml toluene was refluxed for 2 hr, the solution vacuum-evaporated to dryness, and the resiude recrystallized from heptane, yield 0.13 g (68%), mp 141°–142° C.

Compound XXII was obtained by boiling V in mesitylene. Similarly VIII gave XXI.

4-Methoxy-6-(4'-nitrophenyl)-7H-pyramido[4,5-b][1,4]thiazine (XX). a) A mixture of 0.04 g VI and 10 ml Ac_2O was heated at 95° C for 2 hr, vacuum-evaporated to dryness, 5 ml MeOH added to the residue, and the solid filtered off, yield 0.03 g (78%), mp > > 300° C.

b) Compound XX was also prepared by boiling VI in mesitylene, yield 53%.

4-Chloro-5-amino-6-(4'-nitrophenacyl)mercaptopyrimidine (XXVI). A solution of 0.5 g (0.003 mole) XXVII and 0.2 g (0.0035 mole) KOH in 20 ml EtOH was cooled to 0° C, and 0.65 g (0.0027 mole) 4-nitrophenacyl bromide in 30 ml EtOH added, the whole then stirred for 2 hr, and the precipitate which formed filtered off, yield 0.85 g (84%), mp 144°–145° C (frothed vigorously). Pale yellow crystals, soluble in EtOAc and Me_2CO, insoluble in EtOH. Found: C 44.48; H 2.85; Cl 10.78; N 17.11; S 10.02%. Calculated for $C_{12}H_9ClN_4O_3S$: C 44.38; H 2.80; Cl 10.92; N 17.25; S 9.87%.

Properties of 6 hydroxy-5,6-dihydropyrimido[4,5-b][1,4]thiazines (I–IX, Table 1): Compounds I–V, VII–IX colorless crystals, compound VI pale yellow crystalline substance, soluble in alcohols, Me_2CO, EtOAc, insoluble in water, ether, and petrol ether.

Properties of 7H-pyrimido[4,5-b][1,4]thiazines (X–XXV, Table 2): Compound XIV colorless, XII, XIII, XV, XX, and XXIV pale-yellow, XI, XIV, XXII,

X and XXV yellow, XVIII dark yellow, XVII orange, XVI and XXIII yellowish-green and crystalline, XVIII dark yellow, XVII orange, XVI and XXIII yellowish-green and crystalline, XXII, pale yellow and amorphous. Soluble in various organic solvents, insoluble in water; compounds XVIII, XX, XXIV were insoluble in most organic solvents, and in water.

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