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INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 53*. REACTIONS OF 5-AMINO-6-MERCAPTO-PYRIMIDINES WITH DERIVATIVES OF *p*-CHLORONITROBENZENE. SYNTHESIS OF A NEW HETEROCYCLIC SYSTEM – PYRIMIDO[4,5-*b*]-1,4-BENZOTHIAZEPINE

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A series of pyrimidyl aryl sulfides was obtained from the reaction of 5-amino-6-mercaptopyrimidines with derivatives of p-chloronitrobenzene containing carbonyl functional groups. The properties of these sulfides and methods of their cyclization into derivatives of a new tricylic system, pyrimido[4,5-b]-1,4-benzothiazepine, were studied.

Keywords: aminomercaptopyrimidines, pyrimido[4,5-*b*]-1,4-benzothiazepines, pyrimidylarylamines, pyrimidyl aryl sulfides, Smiles rearrangement.

In a continuation of our work to discover biologically active substances among 1,4-thiazine and 1,4-thiazepine bi- and tricyclic systems [1-4] we undertook the synthesis of derivatives of the previously unknown heterocyclic system, pyrimido[4,5-*b*]-1,4-benzothiazepine. In this connection the reactions of 5-amino-6-mercaptopyrimidines **1a-e** with derivatives of *p*-chloronitrobenzene **2a-e** were studied. It was observed that the primary products of the reactions of 4-methoxy- and 4-dimethylamino-5-amino-6-mercaptopyrimidines **1a,b** with 2-chloro-1-methoxycarbonyl-5-nitrobenzene **2a** in ethanol at 60-65°C in the presence of equimolar amount of alkali were pyrimidyl aryl sulfides **3a,b**. The IR spectra of these compounds contain NH_2 group absorption bands in the 3380-3480 cm^{-1} region and ester carbonyl group absorptions at 1725 cm^{-1}, which are in agreement with their structures.

* For paper 52 see [1].

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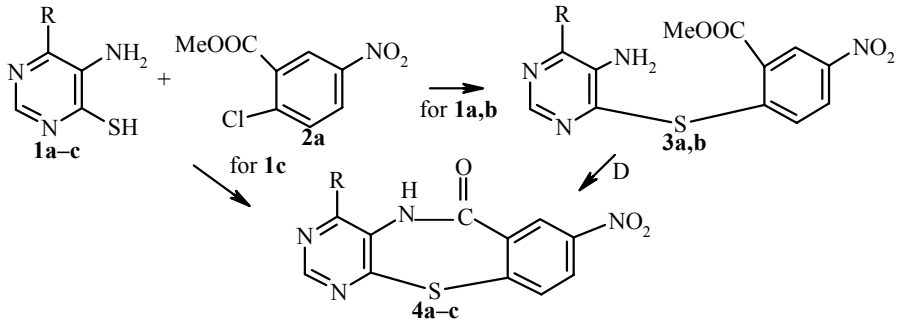
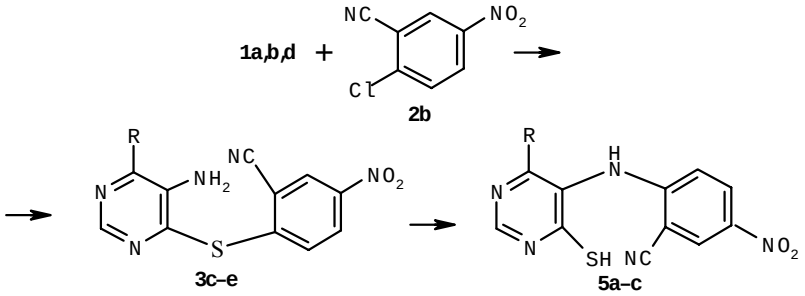


1a, 3a, 4a R = OMe; **1b, 3b, 4b** R = NMe_2; **1c, 4c** R = NHMe

Heating sulfides **3a,b** with an excess of alkali at 60-65°C led to closure of the thiazepine ring to form 4-methoxy- and 4-dimethylamino-8-nitro-6-oxo-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepines **4a,b.**

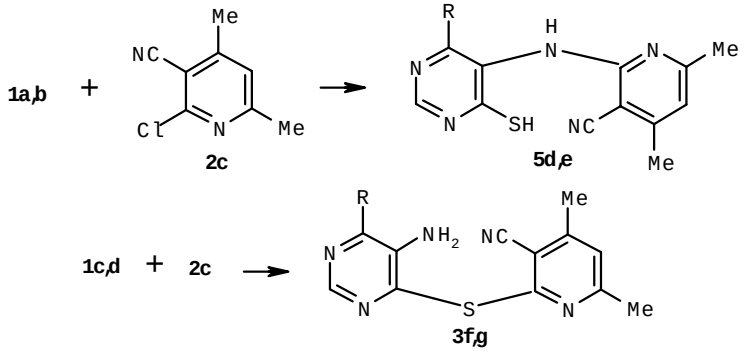
When 5-amino-4-methylamino-6-mercaptopyrimidine (**1c**) reacted with compound **2a** by boiling in ethanol in the presence of alkali for 5 h the final reaction product – pyrimidobenzothiazepine **4a** – was formed without isolation of the intermediate pyrimidyl aryl sulfide and this is more suitable for synthetic purposes. The structures of pyrimidobenzothiazepines **4a-c** were confirmed by the presence of amide NH and CO group absorption bands in their IR spectra at 3200-3190 and 1650-1665 cm^{-1} respectively.

Reactions of 5-amino-6-mercaptopyrimidines **1a,b,d** with 2-chloro-1-cyano-5-nitrobenzene (**2b**) in ethanol in the presence of alkali at 60-65°C gave sulfides **3c-e**. These when boiled with sodium methoxide in methanol underwent the Smiles rearrangement to give pyrimidylarylamines **5a-c**. These compounds, unlike the sulfides **3c-e**, dissolve in aqueous alkali solutions and their IR spectra contain secondary amino group absorption bands in the 3310-3320 cm^{-1} region.



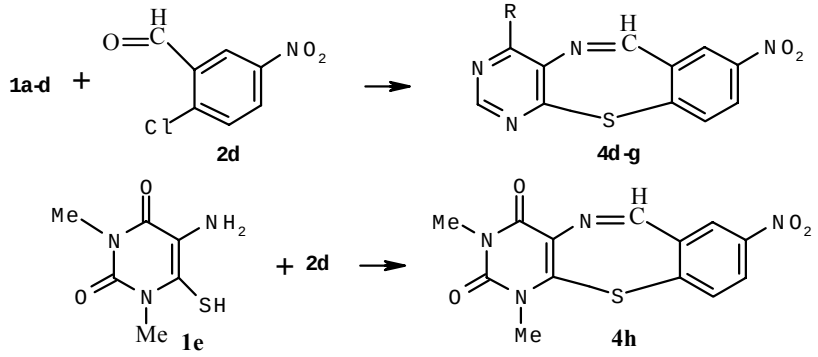
1a,3c,5a R = OMe; **1b,3d,5b** R = NMe_2; **1d,3e,5c** R = NH_2

The analogous reaction of compounds **1a-d** with 6-chloro-5-cyano-2,4-dimethylpyridine (**2c**) gave either pyrimidylpyridylamines **5d,e** or sulfides **3f,g** depending on the nature of substituent at $C_{(4)}$ in the pyrimidine ring.



1a, 5d R = OMe; **1b, 5e** R = NMe_2; **1c, 3f** R = NHMe; **1d, 3g** R = NH_2

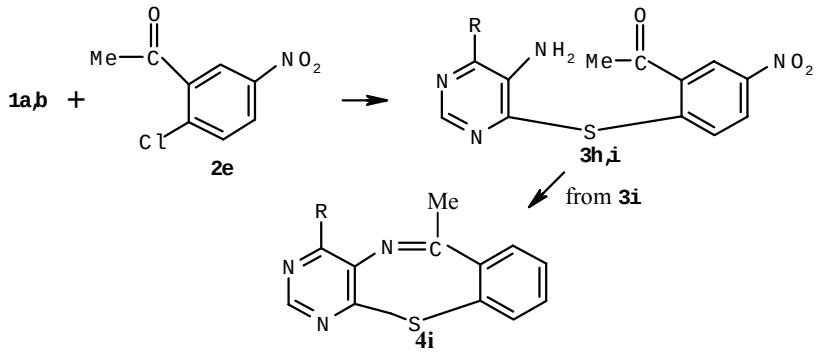
Pyrimidobenzothiazepines **4d-h** are readily formed by the reaction 5-amino-6-mercaptopyrimidines **1a-d** and 5-amino-6-mercapto-1,3-dimethyluracil (**1e**) with 2-chloro-1-formyl-5-nitrobenzene (**2d**) in ethanolic alkali solution. Their structures were confirmed by the presence of molecular ion peaks in their mass spectra and signals for the azomethine proton at 8.64-9.67 ppm in their ^{1}H NMR spectra.



1a,4d R = OMe; **1b,4e** R = NMe$_2$; **1c,4f** R = NHMe; **1d,4g** R = NH$_2$

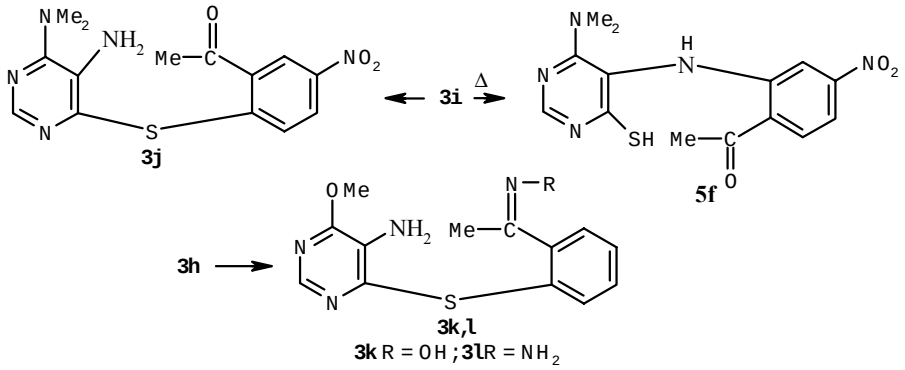
Reactions of 5-amino-6-mercaptopyrimidines **1a,b** with 1-acetyl-2-chloro-5-nitrobenzene (**2e**) gave sulfides **3h,i**. Attempts to cyclize sulfide **3h** with either basic or acidic reagents were unsuccessful, whereas sulfide **3i** readily formed the pyrimidobenzothiazepine **4i** on heating with ethanolic solution of hydrogen chloride or phosphorus oxychloride.

The structures of sulfides **3h,i** and the tricycle **4i** were confirmed by the presence of peaks of the corresponding molecular ions in their mass spectra. The IR spectra of compounds **3h,i** contain absorption bands for the NH_2 and CO groups at 3340, 3430, and 1680 cm^{-1} respectively, while the IR spectrum of the tricycle **4i** contains C=C and C=N absorption bands at 1600 and 1620 cm^{-1}.



3h R = OMe; **3i,4i** R = NMe$_2$

Sulfide **3i** underwent the Smiles rearrangement on boiling in ethanol to give pyrimidylarylamine **5f**. Sulfide **3h** did not undergo a similar rearrangement.



Compounds **3h** and **3i** gave characteristic derivatives at the carbonyl group (e.g., oximes **3j,k** and hydrazone **3l**). Their structures were confirmed by the presence of the corresponding molecular ions in their mass spectra.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (crystallization solvent)	IR spectra, ν, см$^{-1}$	Yield, %
		C	H	N	S			
1	2	3	4	5	6	7	8	9
3a	$C_{13}H_{12}N_4O_5S$	46.60 / 46.50	3.66 / 3.58	16.54 / 16.65	9.80 / 9.53	189-192 (methanol)	1725, 3380, 3480	54
3b	$C_{14}H_{15}N_5O_4S$	48.08 / 48.14	4.37 / 4.29	20.16 / 20.05	9.29 / 9.17	144-146 (methanol)	1725, 3280, 3370	47
3c	$C_{12}H_9N_5O_3S$	47.33 / 47.52	2.80 / 2.97	23.36 / 23.10	10.49 / 10.56	147-150 (methanol)	2200, 3260, 3360	69
3d	$C_{13}H_{12}N_6O_2S$	49.15 / 49.36	3.67 / 3.76	26.87 / 26.58	10.19 / 10.12	185-187 (methanol)	2217, 3270, 3380	76
3e	$C_{11}H_8N_6O_2S$	45.89 / 45.83	2.74 / 2.77	29.34 / 29.16	10.94 / 11.11	228-229 (H_2O–DMF, 1 : 3)	2219, 3285, 3375	82
3f	$C_{13}H_{14}N_6S$	54.30 / 54.54	4.84 / 4.89	29.42 / 29.37	—	305-307 (dec.) (DMF)	2216, 3270, 3390	78
3g	$C_{12}H_{12}N_6S$	52.81 / 52.94	4.33 / 4.41	31.14 / 30.88	11.63 / 11.76	300 (H_2O–DMF, 1 : 3)	2218, 3275, 3385	96
3h	$C_{13}H_{12}N_4O_4S$	48.34 / 48.75	3.71 / 3.75	17.83 / 17.50	9.99 / 10.00	184-186 (ethanol)	1680, 3370, 3470	54
3i	$C_{14}H_{15}N_5O_3S$	50.41 / 50.45	4.43 / 4.50	21.21 / 21.02	9.68 / 9.61	148-149	1680, 3340, 3430	40
3j	$C_{14}H_{16}N_6O_3S$	47.98 / 48.26	4.63 / 4.63	24.25 / 24.13	—	183-185 (ethanol)	3170, 3340, 3500	95
3k	$C_{13}H_{13}N_5O_4S$	46.37 / 46.56	3.85 / 3.91	20.90 / 20.89	—	186-188 (ethanol)	3200, 3320, 3455	95
3l	$C_{13}H_{14}N_6O_3S$	46.45 / 46.70	4.06 / 4.19	25.26 / 25.14	—	185-187 (ethyl acetate)	1625, 3190, 3410	46
4a	$C_{12}H_8N_4O_4S$	47.30 / 47.37	2.65 / 2.63	18.44 / 18.42	—	265-267 (H_2O–DMF, 1 : 1)	1665, 3200	62

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
4b	$C_{13}H_{11}N_5O_3S$	49.32 49.21	3.53 3.47	21.95 22.08	10.18 10.09	280-282 (H_2O–DMF, 1 : 1)	1660, 3200	71
4c	$C_{12}H_9N_5O_3S$	47.48 47.52	2.99 2.97	23.34 23.40	10.86 10.56	300 (ethanol)	1650, 3190, 3420	87
4d	$C_{12}H_8N_4O_3S$	50.00 49.99	2.74 2.79	19.25 19.43	11.31 11.12	270-271 (DMF)	—	76
4e	$C_{13}H_{11}N_5O_2S$	51.65 51.81	4.02 3.68	23.17 23.24	10.57 10.64	229-231 (ethanol)	—	79
4f	$C_{12}H_9N_5O_2S$	50.11 50.17	3.31 3.13	24.43 24.39	11.44 11.14	235-237 (ethanol)	—	94
4g	$C_{11}H_7N_5O_2S$	48.55 48.34	2.57 2.58	25.89 25.63	11.70 11.73	257-259 (DMF)	—	93
4h	$C_{13}H_{10}N_4O_4S$	49.15 49.05	3.16 3.16	17.45 17.60	10.22 10.07	242-243 (H_2O–DMF, 1 : 1)	—	70
4i	$C_{14}H_{13}N_5O_2S$	53.19 53.33	4.18 4.13	22.43 22.22	—	198-199 (ethanol)	1600, 1620	84
5a	$C_{12}H_9N_5O_3S$	47.33 47.57	3.00 2.97	23.10 23.10	10.46 10.56	232-234 (H_2O)	2210, 3310	90
5b	$C_{13}H_{12}N_6O_2S$	49.53 49.36	4.01 3.76	26.78 26.58	10.34 10.12	214-216 (methanol)	2205, 3320	89
5c	$C_{11}H_8N_6O_2S$	45.88 45.83	3.00 2.77	29.08 29.16	11.09 11.11	252-254 (ethanol)	2218, 3210, 3320	80
5d	$C_{13}H_{13}N_5OS$	54.34 54.35	4.27 4.52	24.61 24.39	10.82 11.18	228-230 (ethanol)	2220, 3340	77
5e	$C_{14}H_{16}N_6S$	56.11 56.00	5.23 5.37	28.24 28.00	10.84 10.66	212-213 (ethanol)	2225, 3380	71
5f	$C_{14}H_{15}N_5O_3S$	50.59 50.50	4.62 4.50	20.95 21.02	—	228-230 (ethanol)	1660, 3200	80

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a Perkin Elmer 457 spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Varian XL-200 apparatus. Mass spectra were recorded with MX-1303 mass spectrometer. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates with 5:5:1.5 benzene–ethyl acetate–ethanol as eluent. Spots were visualized in UV light.

Elemental analyses and physicochemical characteristics of the compounds obtained are given in Table 1.

5-Amino-4-methoxy-6-(2-methoxycarbonyl-4-nitrophenyl)thiopyrimidine (3a). Solution of 2-chloro-1-methoxycarbonyl-5-nitrobenzene **2a** (1.08 g, 5 mmol) in methanol (25 ml) was added to solution of 5-amino-6-mercapto-4-methoxypyrimidine **1a** (0.79 g, 5 mmol) and sodium hydroxide (0.2 g, 5 mmol) in methanol (30 ml). The mixture was boiled for 3 h with stirring, cooled, the precipitate filtered off and dried to give compound **3a** (1.8 g). Compounds **3b-i** were prepared analogously with the following boiling times: for **3c-e** 1 h, for **3f** 8 h, for **3g** 20 h, and for **3h,i** 2 h.

Oxime of 6-(2-Acetyl-4-nitrophenyl)-5-amino-4-methoxythiopyrimidine (3l). Solution of hydroxylamine hydrochloride (0.2 g, 2.9 mmol) in water (15 ml) and sodium acetate (0.24 g) were added to solution of sulfide **3i** (0.5 g, 1.56 mmol) in ethanol (30 ml). The mixture was boiled for 5 h, the solution was evaporated to dryness in vacuum, water (1 ml) was added to the residue which was then filtered, washed with water, and dried to give compound **3l** (0.5 g). Oxime **3k** was prepared analogously.

Hydrazone of 6-(2-Acetyl-4-nitrophenyl)-5-amino-4-methoxythiopyrimidine (3m). Solution of sulfide **3h** (0.5 g, 1.55 mmol) and hydrazine hydrate (2 ml) in ethanol (10 ml) was boiled for 1.5 h, cooled, and the precipitate was filtered off to give compound **3m** (0.24 g).

4-Methoxy-8-nitro-6-oxo-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (4a). Mixture of sodium hydroxide (0.1 g, 2.5 mmol) and thioether **3a** (0.64 g, 1.9 mmol) in methanol (20 ml) was boiled for 4 h and then evaporated to dryness in vacuum. Water (10 ml) was added to the residue, the solution was acidified to pH 5-6 with 10% HCl, the precipitate was filtered off, washed with water and dried to give compound **4a** (0.36 g). Benzothiazepine **4b** was prepared analogously.

4-Methylamino-6-oxo-5,6-dihydropyrimido[4,5-*b*]-1,4-benzothiazepine (4c). Solution of 2-chloro-1-methoxycarbonyl-5-nitrobenzene **2a** (1.08 g, 5 mmol) in methanol (20 ml) was added to solution of 5-amino-6-mercapto-4-methylaminopyrimidine **1c** (0.78 g, 5 mmol) and sodium hydroxide (0.4 g, 10 mmol) in methanol (30 ml). The mixture was heated at 60-63°C for 5 h, then methanol was evaporated in vacuum, water (10 ml) was added to the residue, the solution was acidified to pH 5-6 with 10% HCl, the precipitate was filtered off, washed with water, and dried to give compound **4c** (1.30 g).

4-Methoxy-8-nitropyrimido[4,5-*b*]-1,4-benzothiazine (4d). 2-Chloro-1-formyl-5-nitrobenzene **2b** (0.56 g, 3 mmol) was added to solution of 5-amino-6-mercapto-4-methoxypyrimidine **1a** (0.47 g, 3 mmol) in methanol (30 ml) containing sodium hydroxide (0.2 g, 5 mmol) at 60-65°C. The mixture was boiled for 2 h with stirring, cooled, the precipitate filtered off and dried to give compound **4d** (0.6 g). Pyrimidobenzothiazepines **4e-h** were prepared analogously.

4-Dimethylamino-6-methyl-8-nitropyrimido[4,5-*b*]-1,4-benzothiazine (4i). Phosphorus oxychloride (15 ml) was added to sulfide **3i** (1 g, 3 mmol) and the mixture was kept at 20°C for 4 h. The reaction mixture was poured onto ice and neutralized with aqueous ammonia. The precipitate was filtered off, washed with water, and dried to give compound **4i** (0.8 g). M^+ 315.

6-Mercapto-4-methoxy-5-(2-cyano-4-nitrophenyl)aminopyrimidine (5a). Solution of sodium methoxide in methanol (2.3 ml, 4%) was added at 60-65°C to solution of sulfide **3a** (0.3 g, 10 mmol) in methanol (16 ml). The reaction mixture was boiled for 1 h, evaporated to dryness in vacuum, and the residue acidified to pH 6-7 with 10% HCl. The precipitate was filtered off, washed with ether, then water, and dried to give compound **5a** (0.24 g). Pyrimidylarylamines **5b** and **5c** were prepared analogously.

5-(3-Cyano-4,6-dimethylpyridyl-2)amino-6-mercapto-4-methoxypyrimidine (5d). Mixture of compound **1a** (0.78 g, 0.05 mol) and 2-chloro-3-cyano-4,5-dimethylpyridine **2c** (0.83 g, 0.05 mol) in ethanol (35 ml) was boiled for 8 h. The reaction mixture was cooled, the precipitate was filtered off, and dried to give compound **5d** (1.1 g). Compound **5e** was made analogously.

4-Dimethylamino-6-mercapto-5-(2-acetyl-4-nitrophenyl)aminopyrimidine (5f). Suspension of sulfide **3i** (0.92 g, 25 mmol) in ethanol (30 ml) was boiled for 40 h, cooled, the precipitate filtered off, and dried to give compound **5f** (0.64 g).

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