UDC 547.853 + 547.869 + 543.422

NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

I. Pyrimido [4, 5-b] [1, 4]-6-thiazinones

T. S. Safonova and M. P. Nemeryuk

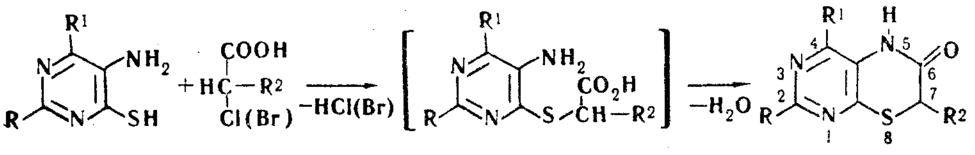
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 5, pp. 714-716, 1966

A number of derivatives of pyrimido [4, 5-b]- [1, 4]-6-thiazinone have been obtained by the reaction of 2, 5-diamino-4-methyl-6-mercapto- and 4-methoxy-5-amino-6-mercaptopyrimidines with α-halo acids.

A few derivatives of pyrimido [4, 5-b] [1, 4]-6-thiazinone have been described in the literature; they were obtained by the reaction of 5-amino-6-mercaptopyrimidines with chloroacetic acid [1, 2] or by the reduction of 4-methoxy-5-nitro-6-carboxymethylmercaptopyrimidine with simultaneous closure of the thiazine ring [3].

In a search for biologically active substances, we have achieved the synthesis of a number of derivatives of pyrimido [4, 5-b] [1, 4]-6-thiazinone. 2, 5-Diamino-4-methyl-6-mercaptopyrimidine [1] and 4-methoxy-5-amino-6-mercaptopyrimidine [4] were used as starting substances. By heating 2, 5-diamino-4-methyl-6-mercaptopyrimidine with an excess of chloroacetic, α-chloropropionic, α-bromobutyric, and α-bromoisovaleric acid at 130°-140°, there were synthesized the corresponding pyrimido-6-thiazinones I-IV, with a yield of 50-70%. This method proved unacceptable for obtaining 4-alkoxy-substituted pyrimido-6-thiazinones, since under the reaction conditions hydrolysis of the alkoxy group to the hydroxy group takes place. Thus the 4-hydroxypyrimido-6-thiazinones V, VII, and VIII, and not the corresponding 4-methoxy derivatives, were obtained (60-80% yield) on heating 4-methoxy-5-amino-6-mercaptopyrimidine with chloroacetic, α-bromobutyric, and α-bromoisovaleric acids. The structure of these substances was confirmed by hydrolysis of the 4-methoxypyrimido-6-thiazinones IX-XI in hydrochloric acid to the corresponding 4-hydroxy derivatives V-VII.

A more convenient general method of obtaining pyrimido-6-thiazinones is to heat 5-amino-6-mercaptopyrimidines with α-haloacids in aqueous alkaline solution at 90°-95° with subsequent acidification of the reaction mixture with hydrochloric acid. In this case the pyrimido-6-thiazones are formed with a yield of 60-80% in a state of higher purity. The compounds I-IV and IX-XI were synthesized by heating 2, 5-diamino-4-methyl-5-amino-6-mercapto- and 4-methoxy-5-amino-6-mercaptopyrimidines with α-haloacids.



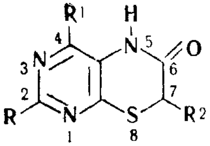
Compounds I-XI may exist in two tautomeric forms, as 6-oxo- or 6-hydroxy derivatives of pyrimidothiazine. Investigation of the IR spectra shows that, in the crystalline state, these compounds are derivatives of pyrimido [4, 5-b]-[1, 4]-6-thiazinone. In the IR spectra of substances IX-XI, there are absorption bands characteristic of the NH group (about 3200 cm^{-1}) and the CO group of amides (about 1680-1690 cm^{-1}). Carbonyl group absorption bands (1670-1680 cm^{-1}) are also found in the spectra of compounds I-IV. Substances V-VIII have the absorption bands of the NH group (3200-3210 cm^{-1}) and a broad carbonyl group band (1640-1690 cm^{-1}) which is probably explained by the presence of two carbonyl groups (in positions 4 and 6 of the bicyclic structure).

Compounds I-XI are colorless crystalline substances. The 2-amino derivatives I-IV possess pronounced basic properties, being soluble in mineral acid solutions but insoluble in water and in solutions of bases. Compounds VII-XI are soluble in alcohols and insoluble in water, while V and VI are soluble in hot water (see table).

Experimental

2-Amino-4, 7-dimethylpyrimido [4, 5-b] [1, 4]-6-thiazinone (II). A mixture of 1 g 2, 5-diamino-4-methyl-6-mercaptopyrimidine [1] and 2 ml α-chloropropionic acid was heated 5 min at 135° - 140° and cooled to 18° -20°; 20 ml water was added and the resulting precipitate was filtered and washed with water. Yield 0.7 g. Compounds I, III, and IV were obtained analogously.

Derivatives of Pyrimido [4, 5-b] [1, 4]-6-thiazinone



Compound No.	R	R¹	R²	Mp, °C (decomp.)	Formula	Found, %				Calculated, %			
						C	H	N	S	C	H	N	S
I*	NH_2	CH_3	H	>300**	$C_7H_8N_4SO$***	42.49	4.09	28.75	16.60	42.85	4.08	28.56	16.32
II	NH_2	CH_3	CH_3	267—268	$C_8H_{10}N_4SO$	45.61	4.87	26.30	15.30	45.70	4.80	26.65	15.25
III	NH_2	CH_3	C_2H_5	226—227	$C_9H_{12}N_4SO$	48.25	5.40	24.90	14.33	48.19	5.40	24.98	14.29
IV	NH_2	CH_3	i-C_3H_7	224—225	$C_{10}H_{14}N_4SO$	50.64	5.68	23.43	13.30	50.40	5.92	23.51	13.45
V	H	OH	H	263—265	$C_6H_5N_3SO_2$	39.02	2.83	22.85	17.62	39.33	2.75	22.94	17.50
VI	H	OH	CH_3	237—239.5	$C_7H_7N_3SO_2$	42.87	3.71	21.66	16.10	42.63	3.58	21.31	16.26
VII	H	OH	C_2H_5	230—232	$C_8H_9N_3SO_2$	45.19	4.02	20.05	15.11	45.48	4.30	19.89	15.14
VIII	H	OH	i-C_3H_7	274—276	$C_9H_{11}N_3SO_2$	48.28	4.97	18.90	14.40	47.98	4.92	18.65	14.23
IX	H	OCH_3	H	191—193****	$C_7H_7N_3SO_2$	—	—	—	—	—	—	—	—
X	H	OCH_3	CH_3	175—176.5	$C_8H_9N_3SO_2$	45.29	4.02	19.82	15.08	45.48	4.29	19.89	15.18
XI	H	OCH_3	C_2H_5	138—140	$C_9H_{11}N_3SO_2$	48.23	4.86	18.55	14.03	47.98	4.92	18.65	14.23

---

* IR spectra (taken in paraffin oil on a UR-10 instrument), cm^{-1}; I–1675, 3200, 3480; II–1670, 3200, 3310, 3480; III–1670, 3200, 3310, 3485; IV–1680, 3200, 3310, 3480; V–1640–1680, 3200; VI–1660–1690, 3280; VII–1660–1690, 3200; VIII–1660–1680, 3290; IX–1670, 3220; X–1670, 3210; XI–1680, 3200.

** For analysis, the compounds were purified by crystallization: II and VII–XI from ethanol, V and VI from water, I, III, and IV by precipitation from 2 N hydrochloric acid with aqueous ammonia.

*** Hydrochloride of compound I: mp 332°–335° decomp. Found: Cl 14.20%. Calculated for $C_7H_8N_4SO \cdot HCl$: Cl 14.15%.

**** According to [3], mp 190°–191°.

4-Methoxy-7-ethylpyrimido [4, 5-b] [1, 4]-6-thiazinone (XI). A mixture of 1 g 4-methoxy-5-amino-6-mercaptopyrimidine and 1.1 g α-bromobutyric acid in 10 ml 2 N sodium hydroxide was heated 1 hr at 90°–95° and cooled to room temperature; 2 N hydrochloric acid was added until the mixture was acid to litmus, and the precipitate was filtered off. Yield 0.95 g, mp 132°–135°. Compounds I–IV, IX, and X were synthesized analogously. In obtaining I–IV, after acidification with hydrochloric acid, an aqueous solution of ammonia was added to the reaction mixture until it became basic to litmus.

4-Oxo-7-ethylpyrimido [4, 5-b] [1, 4]-6-thiazinone (VII). A mixture of 1 g 4-methoxy-5-amino-6-mercaptopyridine [4] and 2.5 ml α-bromobutyric acid was heated 10 min at 135°–140° and cooled to room temperature; 10 ml of ethanol was added and the precipitate filtered off. Yield 0.81 g. Compounds V and VIII were obtained analogously.

4-Oxo-7-methylpyrimido [4, 5-b] [1, 4]-6-thiazinone (VI). A mixture of 0.65 g X and 7 ml 2 N hydrochloric acid was boiled 1 hr, the solution was cooled to 0°, and the precipitate was filtered and washed with water. Yield 0.35 g, mp 236°–238°. Substances V and VII were obtained analogously.

REFERENCES

1. F. Rose, J. Chem. Soc., 3448, 1952.
2. M. Ishidate and H. Yuki, Chem. Pharm. Bull., 8, 131, 1960.
3. E. Taylor and E. Garcia, J. Org. Chem., 29, 2121, 1964.
4. E. Taylor, J. Barton, and W. Paudler, J. Org. Chem., 26, 4961, 1961.

12 April 1965

Ordzhonikidze All-Union Chemical-Pharmaceutical
Scientific Research Institute, Moscow