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D.O. Kolomieitsev [a], S.A. Varenichenko [a], V.O. Astakhina [a], V.I. Markov [a], S.I. Kovalenko [b], O.V. Kharchenko [a]

THE DIRECTION OF HETEROCYCLIZATION OF 4-HYDRAZINO-5,6,7,8-TETRAHYDRO[1]BENZOTIENO[2,3-*D*]PYRIMIDINE IN REACTION WITH DICARBOXYLIC ACID ANHYDRIDE

[a] Ukrainian State University of Chemical Technology, Dnepropetrovsk
[b] Zaporozhye State Medical University, Zaporozhye

Sulphur-containing fused pyrimidines, in particular thienopyrimidines, exhibit wide spectrum of biological activities which stimulates investigation of synthesis and reactions of these compounds. Our previous studies on new series of R^1,R^2-thieno [2,3-d] pyrimidine-4(3H)-one, thio(seleno)ne derivatives showed that some of obtained compounds have good antimicrobial activity. Another derivative of benzothieno [2,3-d] pyrimidine, 4-hydrazino-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidine 3, contains several reactive centers and the heterocyclization reactions can occur in different directions depending on the nature of cyclizing reagents. This paper reports the result of interaction of different dicarboxylic acid anhydrides (maleic, phthalic and endic anhydrides) with the multifunctional compound 4-hydrazino-5,6,7,8-tetrahydro [1] benzothieno [2,3-d] pyrimidine 3 to form novel heterocyclic compounds. The intermediate compounds of cyclization have been identified. The reaction was stated to occur either with intramolecular nucleophilic addition (for maleic anhydride) or with the formation of imid derivatives (for phthalic and m-nitrophthalic anhydrides) depending on the nature of dicarboxylic acid anhydride. The interaction of hydrazine 3 with endic anhydride occurs in one step. The new compounds were characterized by ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis.

Keywords: benzothienopyrimidines; intramolecular nucleophilic addition; dicarboxylic acid anhydrides; cyclisation; imid derivatives.

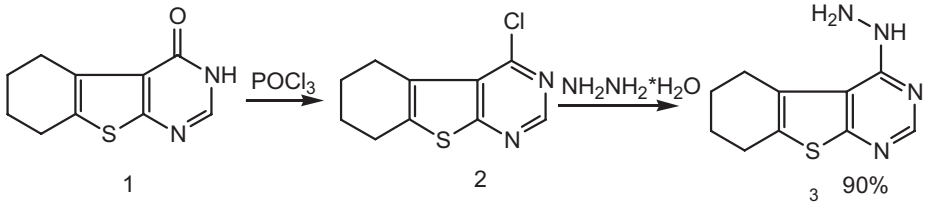
Thiophenes fused to the pyrimidine ring are of special interest among the large number of natural heterocyclic compounds − analogues of the purine [1−4].

Previously we have synthesized new series of R^1,R^2-thieno[2,3-*d*]pyrimidine-4(3*H*)-one, thio-(seleno)ne derivatives for pharmacological studies [*5*]. The in vitro antibacterial and antifungal activities of the compounds against three bacterial and two fungal pathogens have been screened using stiff plate agar diffusion method serial dilutions method. The pharmacological screening showed that some of obtained compounds have good antimicrobial activity.

Thus, the aim of our research was to study the directions of cyclization another derivative of benzothieno[2,3-*d*]pyrimidine − 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (3) with different dicarboxylic acid anhydrides.

The starting material 3 for our research was obtained in accordance with the literature in two stages: the refluxing of the corresponding 5,6,7,8-tetrahydro(1)benzothieno(2,3-d)pyrimidin-4(3H)-one (1) with excess $POCl_3$ lead to compound (2) and the following interaction of compound 2 with hydrazine hydrate in ethanol (Scheme 1) [6].

Interaction of the hydrazine 3 with maleic anhydride in refluxing acetonitrile led to the formation of the corresponding intermediate (4) (Scheme 2) at the first stage. Further cyclization of



Scheme 1

compound 4 in acetic acid resulted in 2-(3-oxo-3,4,9,10,11,12-hexahydro-2*H*-benzo[4',5']thieno-[2',3':4,5]pyrimido[6,1-*c*][1,2,4]triazin-4-yl)acetic acid (5). Proposed heterocyclization includes, probably, acylation reaction followed by intramolecular nucleophilic addition. Previously such reaction has been described for the 4-hydrazinoquinazolines [7]. The structures of all compounds were confirmed by ^{1}H NMR spectroscopy, elemental analysis and mass spectrometry. In the ^{1}H NMR spectrum of 4 and 5 a multiplet in the aliphatic region as well as two low-field broadened singlets of H-2, COOH and NH protons were observed. Synthesized compound 4 has a cis-configuration around the exocyclic C=C bond (J=12.2 Hz) [8]. While triplet signal of the proton in position 4, observed at the 5.02 ppm, was character for compound 5.

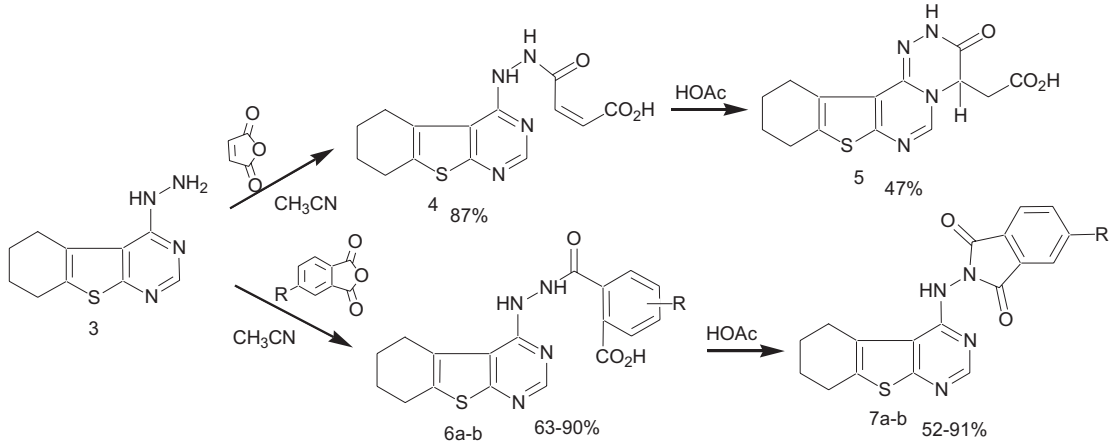
The reaction with phthalic and nitrophthalic anhydrides proceeded similarly at the first stage. Intermediates (6a–b) were isolated. But their further heating in acetic acid led to the formation of imides (7a–b). In contrast cyclization of such in the case of phthalic anhydride is due to the lack of butene fragment in intermediates 6a–b and inability to further cyclization at carbon atom, so the reaction proceeds with the formation of stable cyclic imids 7a–b.

Acylation of hydrazine 3 with endic anhydride in acetonitrile proceeded in good yield (71%) forming the cyclised product – imide (8) (Scheme 3). The cyclisation occurred in one step, the intermediate acylated product was not isolated.

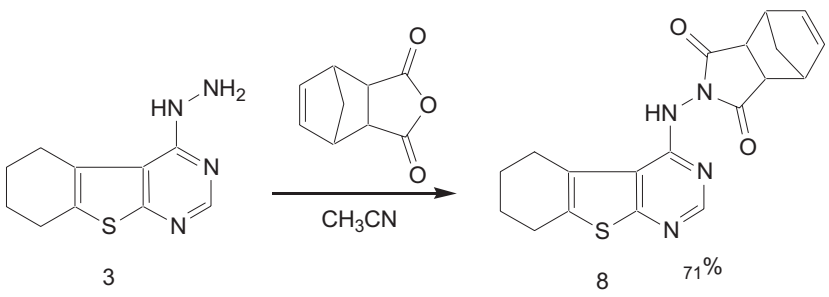
In the ^{1}H NMR spectra resonance of the imids 7a–b, 8 protons are diagnostic since they appear in the areas typical for this heterocycle. Of particular in the ^{1}H NMR spectrum use is the singlet of H-2, which occur in the narrow range of 8.24–8.32 ppm respectively. Other signals related to the isoindole-1,3-dioneprotons in the aromatic region and NH-protons at 9.3 ppm. In the ^{1}H NMR spectrum of compound 8 the two protons of the endocyclic methylene group appeared as a broad singlet at 6.15 ppm. The mass spectrum of compounds 7a and 8 an intense peak was found of quazimolecular ion [MH^+] (351 or 367 correspondingly). Further destruction was related to the NH and N(2)isoindole-1,3-dione bond breaking with formation of ion (*m/z* 204).

Conclusion

The objective of the present study was to investigate the possibility of benzothienopyrimidines modification under mild conditions with the formation of new heterocyclic systems. The interaction of 4-hydrazino-5,6,7,8-tetrahydro[1]-benzotieno[2,3-d]pyrimidine (3) with anhydrides of dicarboxylic acids has been studied. The first step is common for all reactions except the reaction with endic anhydride. Cyclisation of intermediate compounds 4 and 6a–b in acetic acid leads to the



Scheme 2 (a – R=H; b – R=NO_2)



Scheme 3

formation of 1,2,4-triazine (for maleic anhydride) or imid derivatives (for phthalic and nitrophthalic anhydrides). The interaction of hydrazine 3 with endic anhydride occurred in one step, as a result only imid was formed.

Experimental section

The ^{1}H NMR spectra of compounds were recorded in DMSO-d_6 on a Varian VXR 200 instrument (200 MHz). The internal standard for all the NMR spectra was TMS. The mass spectra were recorded on an MX1321 instrument with direct injection of the sample at an ionization chamber temperature of 200^{0}C and with 70 eV ionizing electrons. The FAB spectra were recorded on a VG7070 spectrometer. Desorption of the ions from the solution of the samples in *meta*-nitrobenzyl alcohol was realized with a beam of argon atoms with energy 8 keV. Elemental analysis was performed on an LECO CHNS-900 instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–2-PrOH as eluent.

General procedure of 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine 3 acylation: 1 g (0.005 mol) hydrazine 3 was dissolved in 15 ml CH_3CN. Then 0.01 mol corresponding anhydride was added. The reaction mixture was refluxed for 1.5 h at 70^{0}C. The precipitate formed was filtered, dried and crystallized from EtOH. The analytical data of the synthesized compounds are shown in Table.

(2E)-4-oxo-4-[2-(6,7,8,9-tetrahydro[1]-benzothieno[3,2-d]pyrimidin-4-yl)hydrazino]but-2-enoic acid (4): orange crystals, mp 240^{0}C, yield 1.3 g (89.6%); ^{1}H NMR, δ, ppm (*J*, Hz): 10.1 (1H, s, CO_2H), 8.72 (1H, s, CH), 8.36 (2H, s, 2NH), 6.42, 6.63 (2H, dd, *J*=12.2, CH=CH), 2.96 (2H, m, CH_2), 2.79 (2H, m, CH_2), 1.82 (4H, m, $2CH_2$).

2-{[2-(6,7,8,9-tetrahydro[1]benzothieno[3,2-d]pyrimidin-4-yl)hydrazino]carbonyl}benzoic acid (6a): yellow crystals, mp 253^{0}C, yield 1.5 g (90%); ^{1}H NMR, δ, ppm (*J*, Hz): 10.46 (1H, s, CO_2H), 8.59 (1H, s, CH), 8.39 (2H, s, 2NH), 7.86 (1H, dd, *J*=6.84, CH_{ap}), 7.79 (1H, dd, *J*=7.32, CH_{ap}), 7.67 (1H, dd, *J*=7.31, CH_{ap}), 7.59 (1H, dd, *J*=7.31, CH_{ap}), 3.03 (2H, m, CH_2), 2.80 (2H, m, CH_2), 1.83 (4H, m, $2CH_2$). MS (FAB), *m/z* ($I_{отн}$, %): 369[M]$^+$ (13).

5-Nitro-2-{[2-(6,7,8,9-tetrahydro[1]-benzotieno[3,2-d]pyrimidine-4-yl)hydrazine]carbonyl}-benzoic acid (6b): yellow crystals, mp 277^{0}C, yield 1.2 g (63%).

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.76 (1H, s, CO_2H), 8.43 (1H, s, NH), 8.23 (2H, s, 2NH), 7.74 (2H, dd, *J*=6.81, CH_{ap}), 7.67 (1H, dd, *J*=7.30, CH_{ap}), 7.63 (2H, dd, *J*=7.30, CH_{ap}), 7.58 (1H, dd, *J*=7.31, CH_{ap}), 3.01 (2H, m, CH_2), 2.95 (2H, m, CH_2), 1.88 (4H, m, $2CH_2$).

Physicochemical properties of compounds 4–8

Compd No	Found, %			Mol. formula	Calc, %		
	C	H	N		C	H	N
4	52.78	4.46	17.60	$C_{14}H_{14}N_4O_3S$	52.82	4.43	17.60
6a	58.68	4.39	15.21	$C_{18}H_{16}N_4O_3S$	58.68	4.38	15.21
6b	52.35	3.64	16.97	$C_{18}H_{15}N_5O_5S$	52.30	3.66	16.94
5	53.17	3.80	17.68	$C_{14}H_{12}N_4O_3S$	53.16	3.82	17.71
7a	61.71	4.09	15.98	$C_{18}H_{14}N_4O_2S$	61.70	4.03	15.99
7b	54.70	3.34	17.75	$C_{18}H_{13}N_5O_4S$	54.68	3.31	17.71
8	55.68	5.19	14.43	$C_{19}H_{18}N_4O_2S$	62.28	4.95	15.29

General procedure of cyclisation of compounds 4 and 6a–b: 1 g compounds 4 or 6a–b was dissolved in 15 ml acetic acid and then refluxed for 4 h. After the mixture was cooled, the precipitate formed was filtered and crystallized from MeOH. The analytical data of the synthesized compounds are shown in Table.

2-(3-oxo-3,4,9,10,11,12-hexahydro-2H-benzo-[4',5']thieno[2',3':4,5]pyrimido[6,1-c][1,2,4]triazin-4-yl)acetic acid (5): colorless crystals, mp 210^{0}C, yield 0.6 g (47%); ^{1}H NMR, δ, ppm (*J*, Hz): 12.57 (1H, s, CO_2H), 10.79 (1H, s, NH), 7.72 (1H, s, CH), 5.02 (1H, t, –CH), 2.68 (10H, m, $-CH_2COOH$, $4CH_2$).

2-(5,6,7,8-Tetrahydro[1]benzothieno[3,2-d]-pyrimidin-4-ylamino)-1H-isoindole-1,3(2H)-dione (7a): colorless crystals, mp 253^{0}C, yield 1.3 g (91%); ^{1}H NMR, δ, ppm (*J*, Hz): 9.31 (1H, s, NH), 8.24 (1H, s, CH), 7.95–7.98 (4H, m, CH_{ap}), 3.05 (2H, m, CH_2), 2.83 (2H, m, CH_2), 1.86–1.90 (4H, m, $2CH_2$). MS (FAB), *m/z* ($I_{отн}$, %): 351[M]$^+$ (83).

5-Nitro-2-(6,7,8,9-tetrahydro[1]benzothieno-[3,2-d]pyrimidin-4-ylamino)-1H-isoindole-1,3(2H)-dione (7b): colorless crystals, mp 220 ^{0}C, yield 0.65 g (52%); ^{1}H NMR, δ, ppm (*J*, Hz): 9.31–9.43 (1H, s, NH), 8.24 (1H, s, CH), 7.95–7.98 (4H, m, CHap.), 1.86–1.90 (8H, m, $4CH_2$)

2-(6,7,8,9-tetrahydro[1]benzothieno[3,2-d]pyrimidin-4-ylamino)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3-dione (8): 1 g (0.005 mol) hydrazine 3 was dissolved in 15 ml CH_3CN. Then 1 g (0.01 mol) endic anhydride was added. The reaction mixture was refluxed for 1.5 h at 70^{0}C. The precipitate formed was filtered, dried and recrystallized from DMF. Dark-green crystals, mp 298^{0}C, yield 1.2 g (71%). The analytical data of compounds 8 is shown in Table.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.16 (1H, s, NH), 8.32 (1H, s, CH), 6.15 (2H, br.s, CH=CH), 3.50 (1H, m, CH_2), 2.80–2.93 (4H, m, $2CH_2$), 1.59–1.82 (4H, m, $2CH_2$). MS (FAB), *m/z* ($I_{отн}$, %): 367[M]$^+$ (97).

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REFERENCES

1. *Discovery* of novel thieno[2,3-*б*]pyrimidin-4-yl hydrazine-based inhibitors of Cyclin D1-CDK4: Synthesis, biological evaluation, and structure-activity relationships / T. Horiuchi, J. Chiba, K. Uoto, T. Soga // Bioorganic and Medicinal Chemistry Letters. – 2009. – Vol.19. – № 2. – P.305-308.

2. *Synthesis* and biological evaluation of substituted (thieno[2,3-d]pyrimidin-4-ylthio)carboxylic acids as inhibitors of human protein kinase CK2 / A.G. Golub, V.G. Bdzhola, N.V. Briukhovetska, A.O. Balanda // European J. of Medicinal Chemistry. – 2011. – Vol.46. – № 3. – P.870-876.

3. *Maddila Suresh, Kumar Avula S. Gorle Sridevi*. Synthesis and Antioxidant Activity of 1,2,4-Triazole linked Thieno[2,3-*d*]pyrimidine Derivatives// Letters in Drug Design and Discovery – 2013. – Vol. 10. – № 2. – P.186-193.

4. *Хрипак С.М., Сливка М.В., Лендєл В.Г.* Синтез та властивості тієно[2,3-*d*]піримідинів. – Ужгород: ВАТ «Патент», 2009. – 134 с.

5. *The synthesis,* reactivity and the antimicrobial activity of substituted thieno[2,3-*d*]pyrimidine-4(3H)-thio(seleno)nes / D.O. Kolomieitsev, V.I. Markov, V.O. Astakhina, S.I. Kovalenko, S.A. Varenichenko, O.V. Kharchenko // J. of Organic and Pharmaceutical Chemistry. – 2015. – Vol.13. – № 52. – P.32-38.

6. *Vishnu Ji Ram*. Thieno[2,3-*d*]pyrimidines as potential chemotherapeutic agents // Archiv der Pharmazie. – 1979. – Vol.312. – № 1. – P.19-25.

7. *Novel* methods for the synthesis of [1,2,4]triazino-[4,3-*c*]quinazoline system / S.I. Kovalenko, O.V. Karpenko, O.V. Krivoshey, S.V. Shishkina, O.V. Shishkin // Synthetic Communications. – 2007. – Vol.37. – P.3719-3727.

8. *Преч Є. Бюльманн Ф., Аффольтер К.* Определение строения органических соединений. Таблицы спектральных данных: пер. с англ. Б.Н. Тарасевича. – М.: Мир, 2006. – С.438.

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[a] Ukrainian State University of Chemical Technology, Dnepropetrovsk, Ukraine

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Keywords: benzothienopyrimidines; intramolecular nucleophilic addition; dicarboxylic acid anhydrides; cyclisation; imid derivatives.

REFERENCES

1. Horiuchi T., Chiba J., Uoto K., Soga T. Discovery of novel thieno [2,3-±] pyrimidin-4-yl hydrazine-based inhibitors of Cyclin D1-CDK4: synthesis, biological evaluation, and structure-activity relationships. *Bioorganic and Medicinal Chemistry Letters*, 2009, vol. 19, no. 2, pp. 305-308.

2. Golub A.G., Bdzhola V.G., Briukhovetska N.V., Balanda A.O. Synthesis and biological evaluation of substituted (thieno [2,3-d] pyrimidin-4-ylthio) carboxylic acids as inhibitors of human protein kinase CK2. *European Journal of Medicinal Chemistry*, 2011, vol. 46, no. 3, pp. 870-876.

3. Maddila S., Kumar S.A., Gorle S., Singh M., Lavanya P., Jonnalagadda S.B. Synthesis and antioxidant activity of 1,2,4-triazole linked thieno [2,3-d] pyrimidine derivatives. *Letters in Drug Design and Discovery*, 2013, vol. 10, no. 2, pp. 186-193.

4. Hripak S.M., Slivka M.V., Lendel V.G., *Sintez ta vlastyvosti tiyeno[2,3-d] pirymidyniv* [Synthesis and properties of thieno [2,3-d] pyrimidines]. VAT Patent Publishers, Uzhgorod, 2009. 134 p. (*in Ukrainian*).

5. Kolomietsev D.O., Markov V.I., Astakhina V.O., Kovalenko S.I., Varenichenko S.A., Kharchenko O.V. The synthesis, reactivity and the antimicrobial activity of substituted thieno [2,3-d] pyrimidine-4(3H)-thio(seleno)nes. *Journal of Organic and Pharmaceutical Chemistry*, 2015, vol. 13, no. 52, pp. 32-38.

6. Vishnu J.R. Thieno [2,3-d] pyrimidines as potential chemotherapeutic agents. *Archiv der Pharmazie*, 1979, vol. 312, no. 1, pp. 19-25.

7. Kovalenko S.I., Karpenko A.V., Krivoshey O.V., Shishkina S.V., Shishkin O.V. Novel method for the synthesis of [1,2,4] triazino [4,3-*c*] quinazoline system. *Synthetic Communications*, 2007, vol. 37, pp. 3719-3727.

8. Prech E., Byul'mann F., Affol'ter K., *Opredelenie stroeniya organicheskikh soedinenii. Tablitsy spektral'nykh dannykh* [Determining the structure of organic compounds. Tables of spectral data]. Mir, Moscow, 2006. 438 p. (*in Russian*).