Thienopyrimidines. VII. Reactions of the 4-Hydrazinothieno[2,3-*d*]pyrimidines

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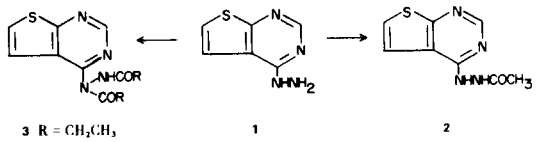
The cyclization reactions of the 4-hydrazinothieno[2,3-*d*]pyrimidines give *s*-triazolo[1,2-*c*]-thieno[3,2-*e*]pyrimidines and tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines.

The properties of the hydrazinothieno[2,3-*d*]pyrimidines (1) are mainly characterized by the possibility of fusing one five-membered nitrogen ring to the thienopyrimidine. The cyclization reactions permit the formation of tricyclic heterocycles but, under mild conditions, it is possible to obtain some acylated derivatives.

On heating in acetic acid the 4-hydrazinothienopyrimidine **1** was substituted to give **2** whose structure can be substantiated by study of the nmr spectra (non equivalency of the protons of the N^1 H and N^2 H groups).

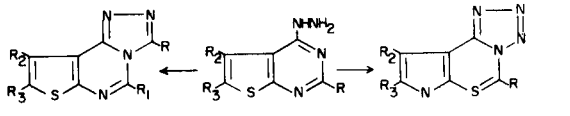
Compound **1** upon heating in pyridine with propionyl and benzoyl chloride yielded disubstituted derivatives. The structures assigned to **3** and **4** were proved by the study of the nmr spectra: the protons of the ethyl groups in **3** and the phenyl groups in **4** are not equivalent.

(SCHEME I)



3 R = CH_2CH_3
4 R = C_6H_5

1 2



8 R = R_1 = R_2 = R_3 = H
9 R = C_2H_5, R_1 = R_2 = R_3 = H
10 R = R_1 = R_3 = H, R_2 = CH_3
11 R = H, R_1 = R_2 = CH_3, R_3 = Br

1 R = R_2 = R_3 = H
5 R = R_3 = H, R_2 = CH_3
6 R = C_2H_5, R_2 = R_3 = H
7 R = H, R_2 = CH_3, R_3 = Br

12 R = R_3 = R_3 = H
13 R = R_3 = H, R_2 = CH_3
14 R = H, R_2 = CH_3, R_3 = Br

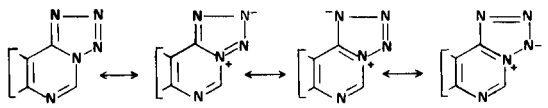
On heating in formic or acetic acids, the hydrazines **1**, **5**, **6** and **7** did not yield the expected acylated derivatives but the triazolothienopyrimidines **8**, **9**, **10** and **11**.

Comparison of the nmr spectra of the triazolothienopyrimidine **8** with that of the thieno[2,3-*d*]pyrimidine **15** led to the following considerations (Table I):

1) The assignment of the H 3 and H 5 protons which is unequivocal was permitted with the help of the long-range interproton coupling between H 5 and H 8. This long-range coupling over 6 bonds was also observed at 90 MHz on the analogous H 2 and H 6 protons of the thieno[2,3-*d*]-pyrimidines (1).

2) The joining of the triazole ring to the thienopyrimidine **15** does not change the thiophene protons chemical shifts but deshielded the pyrimidinic H 5 proton ($\Delta\delta$ = + 0.56 ppm).

Tetrazolothienopyrimidines **12**, **13** and **14** are formed by cyclization of the hydrazines **1**, **5** and **7** with nitrous acid. The assumption of the azide structures was excluded after study of the ir and nmr spectra. In the solid-state, the ir spectra do not show the azide bands which are characteristic near 2100-2200 cm^{-1}. An investigation of the nmr spectra (Table I) reveals a large deshielding effect of the H 5 proton in comparison with analogous H 2 proton of **15** ($\Delta\delta$ = + 1.02 ppm, for instance in the case of **12**). This deshielding substantiates the predominance of the tetrazole structures. This would not be the case if the azide structures made a significant contribution since they have an electron-releasing ability (2) and they would cause an upfield shift of the pyrimidine proton like the hydrazine groups.

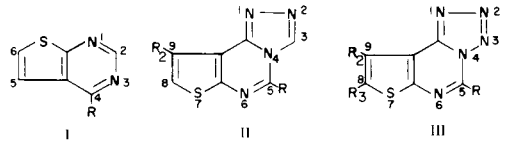


12 12a 12b 12c

By comparing the deshielding of H 5 protons of the triazole **8** ($\Delta\delta$ = + 0.56 ppm) and the tetrazole **12** ($\Delta\delta$ = + 1.02 ppm) with reference to the H 2 proton of thienopyrimidine **15**, a more pronounced effect can be observed in the latter. The ring-current effect is probably not the only factor involved. The existence of zwitterionic structures such as **12a-12c** would also cause deshielding due to

Table I

60 MHz Nmr Spectra of Hydrazinothienopyrimidines, Triazolo- and Tetrazolothienopyrimidines.



I II III

Structure	N°	R	R_2	R_3	δ H_2	δ H_3	δ H_5	δ H_6	δ H_8	δ H_9	δ other protons	Coupling constants	Solvent
I	15	H			9.12 (s)		7.61 (d)	8.02 (d)			H_4, 9.36 (s)	JH5H6, 6.0	(a)
I	1	$NHNH_2$			8.41 (s)		7.51 (d)	7.69 (d)			NH_2, 5.16 NH, 3.60	JH5H6, 5.95	(a)
I	2	$NHNHCOCH_3$			8.40 (s)		7.61 (s)	7.61 (s)			CH_3, 2.0 NH, 9.70 and 9.98		(a)
I	3	$NNHCOC_2H_5$ | COC_2H_5			8.95 (s)		7.28 (d)	7.90 (d)			CH_3, 1.08 and 1.13 CH_2, 2.24 and 2.60 NH, 11.90	JH5H6, 5.9	(a)
I	4	$NNHCOC_6H_5$ | COC_6H_5			8.83 (s)		7.39 (d)	7.96 (d)			C_6H_5, 7.46 and 7.79 NH, 11.63	JH5H6, 6.0	(a)
II	8	H	H			8.66 (s)	9.68 (d)		8.06 (dd)	7.81 (d)		JH8H9, 6.0 JH5H8, 0.5	(a)
II	9	C_2H_5	H			8.85 (s)			7.78 (d)	7.52 (d)	CH_3, 1.56 CH_2, 3.23	JH8H9, 6.0	(b)
II	10	H	CH_3			8.48 (s)	9.28 (s)		7.33 (d)		CH_3, 2.80 (d)	JH8CH_3, 1.20	(b)
III	12	H	H	H			10.14 (s)		8.29 (d)	8.04 (d)		JH8H9, 5.9	(a)
III	13	H	CH_3	H			9.58 (s)		7.55 (d)		CH_3, 2.90 (d)	JH8CH_3, 1.20	(b)
III	14	H	CH_3	Br			10.13 (s)				CH_3, 2.65 (s)		(a)

Chemical shifts are given in ppm relative to tetramethylsilane as internal standard. Coupling constants are given in Hertz. Lines shapes: s, singlet; d, doublet. Solvent: (a) DMSO-d6; (b) Deuteriochloroform.

the electron-withdrawing effect of the positively charged nitrogen at position 4.

EXPERIMENTAL

All melting points were taken on a Kofler block. Infrared spectra were obtained with a Perkin-Elmer 337 or 225 spectrophotometer. Nmr spectra were determined on a Varian A-60 using tetramethylsilane as an internal standard.

4-N^2-Acetylhydrazinothieno[2,3-*d*]pyrimidine (**2**).

A solution of 1 g. of 4-hydrazinothieno[2,3-*d*]pyrimidine in 10 ml. of acetic acid was refluxed for 30 minutes. After removal of solvent under reduced pressure, the residue was washed with water, filtered and recrystallized from ethanol, m.p. 142°, yield, 0.68 g. (50%) of the monohydrate of **2**.

Anal. Calcd. for $C_6H_8N_4OS.H_2O$: C, 42.48; H, 4.46; N, 24.77; S, 14.14. Found: C, 42.42; H, 4.41; N, 24.71; S, 14.26.

4-N^1,N^2-Dipropionylhydrazinothieno[2,3-*d*]pyrimidine (**3**).

A solution of 2 g. of 4-hydrazinothieno[2,3-*d*]pyrimidine and 3.5 ml. of propionyl chloride in 30 ml. of dry pyridine was refluxed for 40 minutes. After removal of the solvent under reduced pressure, the residue was dissolved in 20 ml. of aqueous sodium hydroxide and extracted with chloroform. The dried (sodium sulfate) chloroform extract was evaporated *in vacuo* to give a solid which was crystallized from a 1:1 mixture of ether-acetone, m.p. 191° yield, 1.66 g. (50%), ir (nujol): cm^{-1}, ν 3285 (NH), 1675, 1700 (broad, CO).

Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.79; H, 5.07; N, 20.14; S, 11.50. Found: C, 51.84; H, 5.45; N, 19.94; S, 11.58.

4-N^1,N^2-Dibenzoylhydrazinothieno[2,3-*d*]pyrimidine (**4**).

This compound was obtained as for **3** on refluxing for 1 hour the hydrazine **1** and benzoyl chloride in pyridine, m.p. 230° (acetone), yield, 40%; ir (nujol): cm^{-1}, ν 3250 (NH), 1705, 1655 (CO).

Anal. Calcd. for $C_{20}H_{14}N_4O_2S$: C, 64.17; H, 3.77; N, 14.97; S, 8.55. Found: C, 64.45; H, 3.68; N, 14.82; S, 8.69.

s-Triazolo[1,2-*c*]thieno[3,2-*e*]pyrimidine (**8**).

A solution of 2 g. of hydrazine **1** in 30 ml. of formic acid was refluxed for 50 minutes. The mixture was concentrated *in vacuo* and 20 ml. of water was added to the residue. The product was filtered off and crystallized from methanol, m.p. 130°, yield, 1.06 g. (50%); ir (nujol): cm^{-1}, ν 3110, 3040, (CH), 1635, 1510, 1430, 1340, 1250, 1170, 1060, 975, 855, 780, 720.

Anal. Calcd. for $C_7H_4N_4S$: C, 47.73; H, 2.29; N, 31.81; S, 18.17. Found: C, 47.66; H, 2.54; N, 31.51; S, 17.93.

5-Ethyl-*s*-triazolo[1,2-*c*]thieno[3,2-*e*]pyrimidine (**9**).

This compound was obtained as for **8** on refluxing for 40 minutes the hydrazine **6** in formic acid, m.p. 204° (acetone), yield, 50%.

Anal. Calcd. for $C_9H_8N_4S$: C, 52.94; H, 3.95; N, 27.44; S, 15.67. Found: C, 53.12; H, 3.99; N, 27.16; S, 15.92.

9-Methyl-*s*-triazolo[1,2-*c*]thieno[3,2-*e*]pyrimidine (**10**).

This compound was obtained as for **8** on refluxing for 1 hour the hydrazine **5** in formic acid, m.p. 122° (methanol), yield, 60%.

Anal. Calcd. for $C_8H_6N_4S$: C, 50.53; H, 3.18; N, 29.47; S, 16.83. Found: C, 50.36; H, 3.46; N, 29.21; S, 16.61.

8-Bromo-3,9-dimethyl-*s*-triazolo[1,2-*c*]thieno[3,2-*e*]pyrimidine (**11**).

A solution of 2 g. of hydrazine **7** in 20 ml. of acetic acid was refluxed for 10 minutes. After removal of the solvent *in vacuo*, 30 ml. of water was added to the residue and the product was filtered off and crystallized from cyclohexane, m.p. 184°, yield, 1.60 g. (50%).

Anal. Calcd. for $C_9H_7BrN_4S$: C, 38.15; H, 2.50; Br, 28.16; N, 19.78. Found: C, 38.16; H, 2.29; Br, 28.31; N, 19.86.

Tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine (**12**).

A mixture of 2 g. of hydrazine **1**, 1 g. of sodium nitrite, 5 ml. of water and 20 ml. of acetic acid was stirred for 1 hour at 40°. The yellow solid obtained was filtered off and crystallized from methanol and acetone, m.p. 178°, yield, 1.91 g. (90%); ir (nujol): cm^{-1}, ν 3085, 3045 (CH), 1615, 1345, 1285, 1085, 1060, 980, 955, 860, 780, 740.

Anal. Calcd. for $C_6H_3N_5S$: C, 40.69; H, 1.71; N, 39.54; S, 18.07. Found: C, 40.82; H, 1.53; N, 39.66; S, 18.01.

9-Methyltetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine (**13**).

This compound was obtained as for **12** from the hydrazine **5** on stirring for 1 hour at 40° and 7 hours at 20°, m.p. 164° (diethyl ether = 10, ethanol = 1), yield 80%.

Anal. Calcd. for $C_7H_5N_5S$: C, 43.98; H, 2.64; N, 36.64; S, 16.74. Found: C, 43.86; H, 2.50; N, 36.84; S, 16.89.

8-Bromo-9-methyltetrazolo[1,5-*c*]thieno[3,2-*d*]pyrimidine (**14**).

This compound was obtained as for **13** from the hydrazine **7**. m.p. 165° (cyclohexane), yield, 80%.

Anal. Calcd. for $C_7H_4BrN_5S$: C, 31.12; H, 1.49; Br, 29.58; N, 25.92. Found: C, 31.02; H, 1.43; Br, 29.78; N, 26.03.

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