New Polyheterocyclic Series Based on 4,5,6,7-Tetrahydrothieno[2,3-c]pyridine (1)

I. Lalezari and M. H. Jabari-Sahbari

Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran

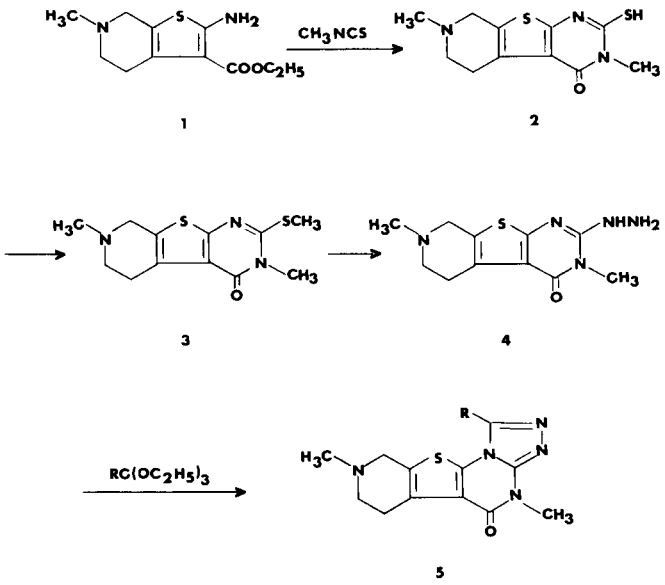
Received February 23, 1978

4,8-Dimethyl-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*e*][1,2,4]triazolo[3,4-*a*]-4*H*-pyrimidin-5-ones, 7-methyl-2,3,6,7,8,9-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrrolo[1,2-*a*]-1*H*, 10*H*-pyrimidin-10-one, 8-methyl-1,2,3,4,7,8,9,10-octahydropyrido[4',3':4,5]thieno[2,3-*d*]-11*H*-pyrimidin-11-one, and 9-methyl-2,3,4,5,8,9,10,11-octahydro[4',3':4,5]thieno[2,3-*d*]azepino-[1,2-*a*]-1*H*, 12*H*-pyrimidin-12-one which consist four new heterocyclic ring systems were synthesized from 2-amino-3-carbethoxy-5-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine.

J. Heterocyclic Chem., 15, 873 (1978)

In connection with a research program on the sythesis of polyheterocyclic compounds with possible pharmacological activities (2), a series of compounds based on 2-amino-2-carbethoxy-5-methyl-4,5,6,7-tetrahydrothieno-[2,3-*c*]pyridine (**1**) (3) were prepared. The aminoester **1** was reacted with methyl isothiocyanate in the presence of triethylamine to give 3,7-dimethyl-2-mercapto-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]-3*H*-pyrimidin-4-one (**2**). Methyl iodide, in alkali solution, coverted **2** to its 2-methyl derivative **3**. Hydrazinolysis of **3** afforded 3,7-dimethyl-2-hydrazino-5,6,7,8-tetrahydropyrido[4'3':-4,5]thieno[2,3-*d*]-3*H*-pyrimidin-4-one (**4**). Ortho esters reacted with **4** to give 4,8-dimethyl-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*e*][1,2,4]triazolo[3,4-*a*]-4*H*-pyrimidin-5-ones (**5a-c**) (See Scheme I).

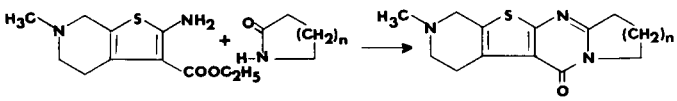
Scheme I



5a, R = H
5b, R = CH_3
5c, R = C_2H_5

Aminoester **1** was reacted with lactams in the presence of catalytic amounts of phosphorus oxychloride to give tetracyclic compounds of type **6** (See Scheme II).

Scheme II



6a, n = 1
6b, n = 2
6c, n = 3

The structure elucidation of the intermediates as well as compounds **5** and **6** which represent four new heterocyclic ring systems were based on elemental analysis, nmr and mass spectroscopy. The fragment M-43, consisted the base peak in the mass spectra of all of the compounds prepared as well as the intermediates. This was assigned to CH_2=N-CH_3 fragmentation, characteristic of *N*-methylpiperidine moiety.

Compounds **5** are reported in Table I and the spectroscopical parameters of compounds **5** and **6** are summarized in Table II.

EXPERIMENTAL

Melting points were taken using a hot stage microscope and are uncorrected. The nmr spectra were recorded using a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Matt 311 spectrometer at 70 eV.

3,7-Dimethyl-2-mercapto-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-*d*]-3*H*-pyrimidin-4-one (**2**).

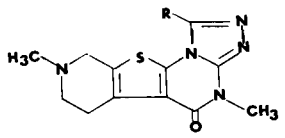
A mixture of 4.8 g. (0.02 mole) 2-amino-3-carbethoxy-5-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**1**) (3), 1.46 g. (0.02 mole) methylisothiocyanate and 0.2 ml. triethylamine was heated on a steam bath for 6 hours. The solid was recrystallized from ethanol to give 3 g. (54%) of **2**, m.p. 262°; m/e: 267 (59%) (molecular ion), 224 (100%).

Anal. Calcd. for $C_{11}H_{13}N_3OS_2$: C, 49.43; H, 4.86; N, 15.73. Found: C, 49.67; H, 4.78; N, 15.81.

3,7-Dimethyl-2-methylthio-5,6,7,8-tetrahydropyrido[4',3':4,5]-[2,3-*d*]-3*H*-pyrimidin-4-one (**3**).

The mercapto derivative **2**, 5.7 g. (0.02 mole) was dissolved in a solution of 1.2 g. of potassium hydroxide in 35 ml. 90% ethanol. To the solution obtained was added 2.84 g. (0.02 mole) of methyl iodide. The mixture was stirred for one hour and

Table I



Compound	R	M.P. °C	Yield %	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	H% Calcd.	H% Found
5a	H	185	74	$C_{12}H_{13}N_5OS$	52.36	52.47	4.72	4.66	25.45	25.38
5b	CH_3	215	69	$C_{13}H_{15}N_5OS$	53.97	54.04	5.19	5.14	24.22	24.54
5c	C_2H_5	217	65	$C_{14}H_{17}N_5OS$	55.44	55.47	5.61	5.51	23.10	23.08

Table II

Spectroscopical Parameters

Compound	δ, Deuteriochloroform	Molecular ion	Base Peak	Other important fragment
5a	2.5 (s, 3H, N_8CH_3), 2.8 (t, 2H, C_6H), 2.03 (t, 2H, C_7H), 3.1 (s, 2H, C_9H), 3.75 (s, 3H, N_4CH_3), and 8.48 (s, 1H, C_1H).	275 (88)	232 and 42	274 (59), 43 (45)
5b	2.5 (s, 3H, N_8CH_3), 2.66 (s, 3H, C_1CH_3), 2.75 (t, 2H, C_6H), 3.06 (t, 2H, C_7H), 3.58 (s, 2H, C_9H) and 3.64 (s, 3H, N_4CH_3).	289 (78)	246	288 (42)
5c	1.5 (t, 3H, ethyl CH_3), 2.5 (s, 3H, N_8CH_3), 2.88 (t, 2H, C_6H), 2.84-3.19 (m, 4H, C_7H and ethyl CH_2), 3.62 (s, 2H, C_9H), and 3.7 (s, 3H, N_4CH_3).	303 (56)	260	302 (38)
6a	2.25 (t, 2H, C_9H), 2.50 (s, 3H, NCH_3), 2.74 (m, 2H, C_2H), 3.15 (m, 4H, C_3H and C_8H), 3.62 (s, 2H, C_6H) and 4.2 (t, 2H, C_1H).	261 (53)	218	260 (44)
6b	2.0 (m, 4H, C_3H and $C_{10}H$), 2.5 (s, 3H, NCH_3), 2.95 (m, 2H, C_2H), 3.03 (t, 2H, C_4H, 3.16 (t, 2H, C_9H), 3.66 (s, 2H, C_7H) and 4.1 (t, 2H, C_1H).	275 (48)	232	274 (41)
6c	1.96 (s, broad, 6H, C_2H, C_3H, C_4H), 2.51 (s, 3H, NCH_3), 2.88 (t, 2H, $C_{11}H$), 3.15 (m, 4H, C_5H and $C_{10}H$), 3.68 (s, 2H, C_8H) and 4.24 (t, 2H, C_1H).	289 (59)	246	288 (49)

refrigerated overnight. The solid was filtered and recrystallized from alcohol to give 2.3 g. (42%) of **3**, m.p. 171°; m/e 281.

Anal. Calcd. for $C_{12}H_{15}N_3OS_2$: C, 51.24; H, 5.33; N, 14.94. Found: C, 51.33; H, 5.50; N, 15.07.

3,7-Dimethyl-2-hydrazino-5,6,7,8-tetrahydropyrido[4′,3′:4,5]-thieno[2,3-*d*]-3*H*-pyrimidin-4-one (**4**).

A solution of 2.81 g. (0.01 mole) of **3** in 25 ml. of ethanol and 3 ml. of 98 per cent hydrazine hydrate was refluxed for 12 hours. The solution was diluted with water and cooled. The precipitate was filtered and recrystallized from aqueous ethanol to give 1.66 g. (63%) of white crystals m.p. 232-233°.

Anal. Calcd. for $C_{11}H_{15}N_5OS$: C, 49.81; H, 5.66; N, 26.41. Found: C, 49.70; H, 5.80; N, 26.33.

4,8-Dimethyl-6,7,8,9-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*e*]-[1,2,4]triazolo[3,4-*a*]-4*H*-pyrimidin-5-one (**5a**).

A solution of 265 mg. (1 mmole) of hydrazine **4** and 222 mg. (1.5 mmoles) of triethylorthoformate in 10 ml. absolute ethanol was refluxed for 8 hours. The solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol to give 203 mg. (74%) of **5a**, m.p. 185°.

Compounds **5b** and **5c** were prepared similarly by using triethyl orthoacetate and triethyl orthopropionate, instead of triethyl orthoformate, respectively.

Compounds **5** are listed in Table I and their spectral parameters are reported in Table II.

7-Methyl-2,3,6,7,8,9-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrrolo[1,2-*a*]-1*H*, 10*H*-pyrimidin-10-one (**6a**).

To a mixture of 240 mg. (1 mmole) of aminoester **1** and 85 mg. (1 mmole) of pyrrolidone in 10 ml. of 1,2-dichloroethane was added 5 drops of phosphorous oxychloride and refluxed for

one hour. After evaporation of the solvent under reduced pressure, the residue was dissolved in water, alkalinized with dilute potassium hydroxide solution and extracted with chloroform. The extract was evaporated and the residue was recrystallized from ethanol to give 117 mg. (45%) of **6a** m.p. 205°.

Anal. Calcd. for $C_{13}H_{15}N_3OS$: C, 56.77; H, 5.74; N, 16.09. Found: C, 56.63; H, 5.70; N, 15.95.

8-Methyl-1,2,3,4,7,8,9,10-octahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrido[1,2-*a*]-11*H*-pyrimidin-11-one (**6b**).

Molar portions of aminoester **1** and valerolactame were treated as described for the preparation of **6a**. The yield of the recrystallized compound was 40%, m.p. 162°.

Anal. Calcd. for $C_{14}H_{17}N_3OS$: C, 61.09; H, 6.18; N, 15.27. Found: C, 60.88; H, 6.20; N, 15.40.

9-Methyl-2,3,4,5,8,9,10,11-octahydro[4′,3′: 4,5]thieno[2,3-*d*]-azepino[1,2-*a*]-1*H*-12*H*-pyrimidin-12-one (**6c**).

Upon treatment of aminoester **1** with caprolactame as described for the preparation of **6a** a 55% yield of recrystallized **6c** was obtained, m.p. 145°.

Anal. Calcd. for $C_{15}H_{19}N_3OS$: C, 62.28; H, 6.57; N, 14.53. Found: C, 62.20; H, 6.51; N, 14.49.

Acknowledgment.

This work was supported by a grant of Tehran University Research Council.

REFERENCES AND NOTES

(1) This work was partly presented at the 6th International Congress of Heterocyclic Chemistry, July 9-13, 1977, Tehran, Iran.

(2) I. Lalezari, *J. Heterocyclic Chem.*, **13**, 1249 (1977).

(3) A. Rosowsky, M. Chaykovsky, K. K. N. Chen, M. Lin and E. J. Modest, *J. Med. Chem.*, **16**, 185 (1973).