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Saturated Heterocycles, 75**
Preparation of Tetracyclic Thiophene Derivatives with Bridgehead Nitrogen. Synthesis of Polymethylenethieno[2,3—*d*]dihydropyrrolo-, tetrahydropyrido- and tetrahydroazepino[1,2—*a*]pyrimidin-4-ones and -4-thiones

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The following tetracyclic ring systems and their derivatives have been synthesized for pharmacological investigations: Trimethylenethieno[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-one and -4-thione (**1a**, **5a**); Tetramethylenethieno[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-one and -4-thione (**1b**, **1j**, **5b**); Pentamethylenethieno[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-one and -4-thione (**1c**, **5c**); Trimethylenethieno[2,3—*d*]tetrahydropyrido[1,2—*a*]pyrimidin-4-one and -4-thione (**1d**, **5d**); Tetramethylenethieno[2,3—*d*]tetrahydropyrido[1,2—*a*]pyrimidin-4-one and -4-thione (**1e**, **5e**); Pentamethylenethieno-[2,3—*d*]tetrahydropyrido[1,2—*a*]pyrimidin-4-one and -4-thione (**1f**, **5f**); Trimethylenethieno[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-one and -4-thione (**1g**, **5g**); Tetramethylenethieno[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-on and -4-thione (**1h**, **5h**); Pentamethylenethieno[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-one and -4-thione (**1i**, **5i**); Tetramethylenethieno-[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-one (**7b**); Pentamethylenethieno-[2,3—*d*]tetrahydropyrido[1,2—*a*]pyrimidin-4-one (**7c**).

Compounds **1a–i** were synthesized from 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene **2a–c** with the corresponding lactim ethers (**3a–c**) in chlorobenzene in the presence of polyphosphoric acid (*PPA*). Compounds **7b** and **7c** were obtained in the reaction of β-amino acid esters **2b** and **2c** with 2-

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bromopyridine (**6**). The thione derivatives (**5a–i**) were prepared from compounds **1a–i** with phosphorus(V) sulphide.

(Keywords: Condensation of 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene with lactim ethers and 2-bromopyridine; Oxo-thio exchange)

Gesättigte Heterocyclen 75. Synthese von tetracyclischen Thiophenderivaten mit Brückenkopf-Stickstoff. Darstellung von Polymethylen-thieno[2,3—d]dihydropyrrolo-, tetrahydropyrido- und -tetrahydroazepino[1,2—a]pyrimidin-4-on und -4-thion

Für pharmakologische Untersuchungen synthetisierten wir die folgenden tetracyclischen Ringsysteme und deren Derivate: Trimethylen-thieno-[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-on und -4-thion (**1a**, **5a**); Tetramethylen-thieno[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-on und 4-thion (**1b**, **1j**, **5b**); Pentamethylen-thieno[2,3—*d*]dihydropyrrolo[1,2—*a*]pyrimidin-4-on und -4-thion (**1c**, **5c**); Trimethylen-thieno[2,3—*d*]tetrahydropyrido[1,2—*a*]pyrimidin-4-on und -4-thion (**1d**, **5d**); Tetramethylen-thieno[2,3—*d*]tetrahydropyrido-[1,2—*a*]pyrimidin-4-on und -4-thion (**1e**, **5e**); Pentamethylen-thieno[2,3—*d*]-tetrahydropyrido[1,2—*a*]pyrimidin-4-on und -4-thion (**1f**, **5f**); Trimethylenthieno[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-on und -4-thion (**1g**, **5g**); Tetramethylen-thieno[2,3—*d*]tetrahydroazepino[1,2—*a*]pyrimidin-4-on und -4-thion (**1h**, **5h**); Pentamethylen-thieno[2,3—*d*]tetrahydroazepino-[1,2—*a*]pyrimidin-4-on und -4-thion (**1i**, **5i**); Tetramethylen-thieno[2,3—*d*]-tetrahydropyrido[1,2—*a*]pyrimidin-4-on (**7b**); Pentamethylen-thieno[2,3—*d*]-tetrahydropyrido[1,2—*a*]pyrimidin-4-on (**7c**).

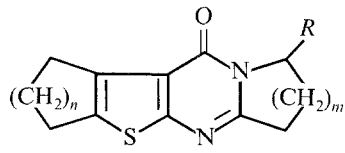
Die Verbindungen **1a—i** wurden aus 2-Amino-3-(ethoxycarbonyl)-4,5-polymethylenthiophenen (**2a—c**) mit den entsprechenden Lactimethern in Chlorbenzol mit Polyphosphorsäure-Katalysator dargestellt. Die Verbindungen **7b** und **7c** wurden aus β-Aminosäureestern **2b—c** und 2-Brompyridin (**6**) synthetisiert. Die Thionderivate (**5a—i**) erhielten wir durch die Reaktion der Verbindungen **1a—i** mit Phosphor(V)-sulfid.

Introduction

Previously we have synthesized numerous bi and tricyclic pyridoquinazoline derivatives for stereochemical and pharmacological studies [1–4]. Some of the prepared compounds exhibited marked analgesic activity. Since the tetracyclic thienopyrimidines **1** having a bridgehead nitrogen can be regarded as polycyclic isosteres of these pyridoquinazoline, it seemed to be of interest to extend our studies to the synthesis of the title compounds **1** (Scheme 1).

The timeliness of the syntheses of the compounds is stressed by the fact that a great number of 2-aminothiophene carboxylate derivatives fused with pyrimidine [5–13, 16–19, 21–23], thiazine, oxazine [14], pyrrole [24], piperidine [16], imidazole [25] and triazole rings [28], with various ester and amide [20, 32–35, 37], carboxamide [19, 20, 35–37] and *Schiff*-base [34] substitutents, and with side-chains bearing substituted amino groups [35, 37] have been synthesized.

Scheme 1



1

	n	*m*	*R*		*n*	*m*	*R*
a	1	1	H	**f**	3	2	H
b	2	1	H	**g**	1	3	H
c	3	1	H	**h**	1	3	H
d	1	2	H	**i**	3	3	H
e	2	2	H	**j**	2	1	CH_3

Results and Discussion

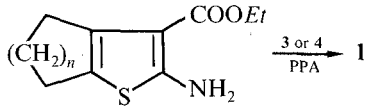
In the design of the syntheses we took into account that the potential pharmacons obtainable from the easily accessible 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene (**2**) display numerous valuable pharmacological activities. Related derivatives have been described with antiallergic [15, 18, 19, 21, 23], analgesic [31, 35], CNS-depressant [36, 37], anti-inflammatory [16], chemotherapeutic [29], folic acid antagonist [8, 10], antimalarial [8–10], antirhinitic [20], thrombocyte aggregation blocking [11, 51] or anticoncipient [22] activity.

The starting material **2** is obtained, in accordance with the literature, from the reaction of the corresponding cyclic ketone, ethyl cyanoacetate and sulphur in absolute ethanol in the presence of a base such as piperidine [32], diethylamine, morpholine [33, 34, 36] or triethylamine [35].

Our earlier investigations [3] and the literature sources [16, 38, 39] showed that tricyclic pyridopyrimidinone derivatives can be obtained from lactams [16] or lactim ethers [3, 38, 39] with β-amino acid esters. The lactim ether reaction, which supposedly leads to compounds valuable from the point of view of pharmacology, was therefore also carried out with compounds **2**. Compounds **2** reacted with lactim ethers in chlorobenzene in the presence of *PPA* to afford the tetracyclic thienopyridopyrimidinones as follows (Scheme 2).

Synthesis of the tetracyclic compounds **1** starting from the lactams **4** instead of the lactim ethers **3** was also attempted [16]. The method utilizing lactim ethers gave higher yields. Through the reaction of thiophene derivatives **2** and lactim ethers **3**, the homologues listed in Table 2 were synthesized.

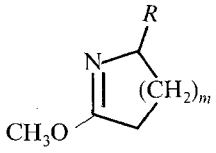
Scheme 2



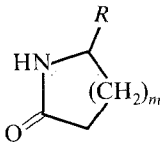
2

$m = n = 1, 2, 3$

$R = H, CH_3$



3

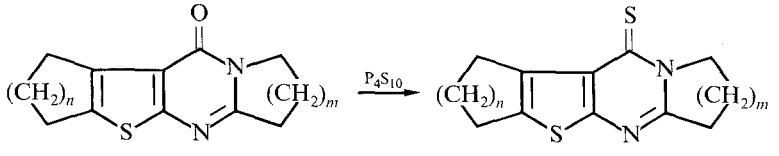


4

Certain of the synthesized compounds (e.g. **1 d**) were effective in 5 μg/ml concentration against dermatomycosis and other mycotic diseases (*Stemphylium, Colletotrichum, Cercospora*), and against *Phytophthora infestans* (**1 d**) and *Taphrina deformans* (**7 b**). The introduction of an additional sulphur atom generally enhances the fungicidal activity of the compounds, and therefore, in order to attain a more advantageous effect, the thiocarbonyl derivatives too were prepared by oxo-thio exchange.

Unsuccessful attempts at oxo-thio exchange have been made with phosphorus(V) sulphide in pyridine [40], xylene [40, 41], toluene [42] and acetonitrile-triethylamine [43]. When heated with phosphorus(V) sulphide [44], the oxo derivatives gave the thio derivatives **5** in acceptable yield (Scheme 3).

Scheme 3

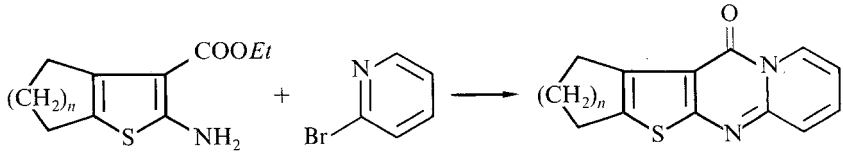


1 **5**

	n	*m*		*n*	*m*
a	1	1	**f**	3	2
b	2	1	**g**	1	3
c	3	1	**h**	2	3
d	1	2	**i**	3	3
e	2	2			

Through the reaction of β-amino acid esters **2** and 2-bromopyridine [45], analogues with unsaturated D ring were synthesized (Scheme 4, Table 4).

Scheme 4



2 **6** **7**

Despite numerous attempts, the synthesis of analogue **7 a** failed. For as yet unknown reasons, the reaction proceeded in an unexpected way, and no defined end-product could be isolated from the resinous reaction mixture.

Experimental

The melting points, measured on a *Boetius* micro-apparatus (Franz Küstner, Dresden), are uncorrected. The compounds obtained were found to be pure on thin layer chromatography (silica gel G, benzene : ethanol 4 : 1 developing solvent, iodine vapour detection) and satisfactory elemental analytical results (C, H, N, S) were obtained in each case. The IR and NMR spectra (recorded on a Spektromom 2000 and a JEOL-60 instrument, respectively) corresponded with the given structures.

2-Amino-3-ethoxycarbonyl-4,5-polymethylenethiophene

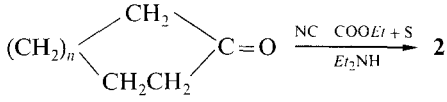
To a suspension of 0.1 mol cyclic ketone, 0.1 mol ethyl cyanoacetate and 0.1–0.11 g atom sulphur powder in 20–30 ml ethanol, 10 ml diethylamine was added dropwise. The sulphur continuously dissolved during the addition of diethylamine, while the temperature of the reaction mixture was kept at 40–60 °C. This temperature was maintained for 3 h after the completion of the addition, and the mixture was then allowed to stand overnight at + 4 °C. The crystals that formed were filtered off and washed with dry ethanol. If the product failed to crystallize, 2–3-fold water was added to the reaction mixture, which was subsequently allowed to stand at + 4 °C for several days. The product was purified by recrystallization from ethanol.

Data on the prepared compounds are given in Table 1.

Polymethylenethieno[2,3—d]dihydropyrrolo-, tetrahydropyrido- and tetrahydroazepino[1,2—a]pyrimidin-4-ones (**4**)

(a) To a solution of 0.01 mol 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene (**2**) in 20 ml chlorobenzene, 0.015 mole lactim ether (**3**) and 1–2 drops *PPA* were added and the reaction mixture was heated on an oil-bath at 140–150 °C for 12–24 h. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the mixture was evaporated, and the product was

Table 1. *2-Amino-3-ethoxycarbonyl-4,5-polymethylenethiophene* (**2 a–c**)



Compound	*n*	M. p. (°C)	Yield %	Literature		Ref.
				M. p. °C	yield %	
2 a	1	94–96	45–50	91	45–52	[34]
2 b	2	116–118	80–90	115	82–91	[34]
2 c[a]	3	84–85	45–50	—[b]	—[b]	[36][b]

[a] Analysis of **2 c**, calculated for $C_{12}H_{17}NO_5$. Calc.: C 60.22 H 7.16 N 5.85. Found: C 59.95 H 7.35 N 5.60.
[b] No experimental data are given in the cited Ref. [36].

Table 2. *Polymethylenethieno[2,3—d]dihydropyrrolo-, tetrahydropyrido- and tetrahydroazepino[1,2—a]pyrimidin-4-ones* (**1 a–j**)

Compound	*n*	*m*	*R*	Formula[a] (Mol. wt.)	M. p. (°C)[b]	Yield %	IR (cm^{-1})
1 a	1	1	H	$C_{12}H_{12}N_2OS$ (232.31)	200–201	54	2930, 1659 1545
1 b	2	1	H	$C_{13}H_{14}N_2OS$ (264.28)	212–214	60	2950, 1650 1580
1 c	3	1	H	$C_{14}H_{16}N_2OS$ (260.36)	156–158	62	2910, 1650 1575
1 d	1	2	H	$C_{13}H_{14}N_2OS$ (246.34)	180–183	80	2930, 1651 1530
1 e	2	2	H	$C_{14}H_{16}N_2OS$ (260.36)	215–216	85	2950, 1660 1540
1 f	3	2	H	$C_{15}H_{16}N_2OS$ (274.39)	155–157	78	2940, 1660 1545
1 g	1	3	H	$C_{14}H_{16}N_2OS$ (260.36)	196–198	75	2940, 1665 1550
1 h	2	3	H	$C_{15}H_{18}N_2OS$ (274.39)	150–152	67	2950, 1659 1550
1 i	3	3	H	$C_{16}H_{20}N_2OS$ (288.42)	159–160	65	2950, 1659 1550
1 j	2	1	CH_3	$C_{14}H_{17}N_2OS$ (261.32)	128–130	57	2940, 1650 1570

[a] All compounds gave satisfactory elemental analyses (C, H, N).
[b] Recrystallization from ethanol.

Table 3. *Polymethylenethieno[2,3—d]dihydropyrrolo-, tetrahydropyrido- and tetrahydroazepino[1,2—a]pyrimidine-4-thiones* (**5a–i**)

Compound	*n*	*m*	Formula[a] (Mol. wt.)	Mp. (°C)[b]	Yield %
5a	1	1	$C_{12}H_{12}N_2S_2$ (248.39)	263–265	
5b	2	1	$C_{13}H_{14}N_2S_2$ (251.39)	268–270	30
5c	3	1	$C_{14}H_{16}N_2S_2$ (276.42)	194–196	42
5d	1	2	$C_{13}H_{14}N_2S_2$ (262.396)	218–220	65
5e	2	2	$C_{14}H_{16}N_2S_2$ (276.43)	233–235	62
5f	3	2	$C_{15}H_{18}N_2S_2$ (290.16)	220–222	70
5g	1	3	$C_{14}H_{16}N_2S_2$ (276.43)	160–162	75
5h	2	3	$C_{15}H_{18}N_2S_2$ (290.16)	180–185	76
5i	3	3	$C_{16}H_{20}N_2S_2$ (304.484)	174–176	85

[a] All compounds gave satisfactory elemental analyses (C, H, N, S).
[b] Recrystallized from ethanol-benzene.

collected by filtration after trituration with ether. It was washed with ether and recrystallized several times from ethanol.

Data on the synthesized compounds are given in Table 2.

(b) To a solution of 0.01 mol 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene (**2**) in 100 ml 1,2-dichloroethane, 0.011 mol lactam (**4**) and 50 drops phosphorusoxychloride were added. The solution was kept boiling for 1 h and the solvent was then distilled off. The residue was taken up in water, and the solution was made alkaline with 20% potassium hydroxide solution and extracted with 3 × 50 ml chloroform. The chloroformic layer was dried over anhydrous sodium sulphate. After evaporation of the solvent, the residue was crystallized from ethanol.

Note: The lactam (**4**) condensation of type (b) was performed only in the case of compound **1b**. This method gave a yield of 44%, which is inferior to the 67% of the lactim ether (**3**) method (a), and accordingly it was not adopted.

Polymethylenethieno[2,3—d]dihydropyrrolo-, tetrahydropyrido- and tetrahydroazepino[1,2—a]pyrimidine-4-thiones (**5**)

1 g compound **1a–i**, mixed with 2.25 g phosphorus(V) sulphide, was heated in a round-bottomed flask in an oil-bath at 125 °C for 2 h. After standing overnight, the hardened material was powdered and suspended in 40 ml 10% sodium hydroxide. The aqueous, alkaline suspension was transferred to a separation

Table 4. *Polymethylenethieno[2,3—d]tetrahydropyrido[1,2—a]pyrimidin-4-ones* (7)

Compound	*n*	Formula Mol. wt.	M. p. (°C)[a]	Yield %	Analysis: Calc. Found %		
					C	H	N
7b	2	$C_{14}H_{12}N_2OS$ (256.31)	207–209	85	65.60 65.67	4.72 4.95	10.92 11.16
7c	3	$C_{15}H_{14}N_2OS$ (270.36)	148–150	84	66.64 66.14	5.22 5.84	

[a] Recrystallization from ethanol-*DMF*.

funnel and extracted with 4 × 50 ml ether-benzene (1 : 1). The combined organic phases were dried over anhydrous sodium sulphate. After evaporation of the solvent, the crystalline residue was recrystallized from benzene-ethanol.

The compounds synthesized are listed in Table 3.

Polymethylenethieno[2,3—d]pyrido[1,2—a]pyrimidin-4-ones (7)

0.02 mol 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophene (**2**) and 0.04 mol 2-bromopyridine were fused together and kept at 160 °C in an oil-bath for 2 h. After cooling and standing overnight, the mixture was filtered, and the crystalline product was purified by washing with acecetone, and then recrystallized from ethanol-*DMF*.

The compounds synthesized are listed in Table 4.

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