FUNCTIONAL DERIVATIVES OF THIOPHENES. X.* SYNTHESIS OF DERIVATIVES OF THIENO[2,3-d]PYRIMIDINE AND 2,3-POLYMETHYLENE-4-OXOPYRIMIDINE

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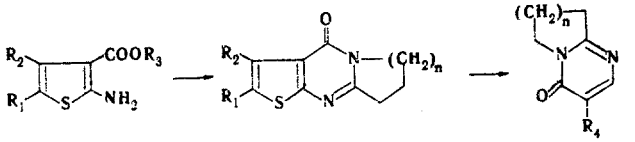
2,3-Polymethylene-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine derivatives were obtained by reaction of esters of α-aminothiophene-β-carboxylic acids with lactame or α-aminothiophene-β-carboxylic acids with lactims. Desulfuration of the thienopyrimidines obtained in this manner is a convenient method for the synthesis of pyrrolo-, pyrido-, and azepino[1,2-a]pyrimidine derivatives.

Aminothiophene derivatives containing carbethoxy, formyl, and other functional groupings in the ortho position relative to the amino group are convenient starting compounds for the annelation of a second heterocycle, for example, pyrimidine [2, 3], to the thiophene ring. We have found that esters of α-aminothiophene-β-carboxylic acids (I-III) undergo reaction with lactams, for example, with butyrolactam, valerolactam, and caprolactam, by refluxing in absolute dichloroethane in the presence of phosphorus oxychloride. Thienopyrimidines V-XI are obtained in 40-90% yields. Thienopyrimidine derivatives are also formed in the reaction of α-aminothiophene-β-carboxylic acids with O-lactim ethers. For example, thienopyrimidine XI was obtained in 30.5% yield by reaction of thiophenecarboxylic acid IV with O-methylcaprolactims. The absorption bands of the NH_2 group observed in the spectra of starting thiophenes I-III are absent in the IR spectra of V-XI. The absorption band of the carbonyl group of the pyrimidine ring appears at 1650-1670 cm^{-1}. Reaction with butyrolactam gave thieno[2,3-d]pyrrolo[1,2-a]pyrimidines V-VII, which are structurally analogous to the alkaloid peganol [4]. Thieno[2,3-d]pyrido[1,2-a]pyrimidine derivatives VIII and IX were obtained by condensation of II and III with valerolactam. Thieno[2,3-d]-azepino[1,2-a]pyrimidines (X, XI) were obtained by reaction of II and III with caprolactam or IV with O-methylcaprolactim.

When V, VI, VIII, and X are heated in alcohol in the presence of Raney nickel, the thiophene fragment undergoes hydrodesulfuration, and derivatives of pyrrolo[1,2-a]pyrimidine (XII, XIII), pyrido[1,2-a]pyrimidine (XIV), and azepino[1,2-a]pyrimidine (XV) are obtained in 48-65% yields.



I-IV V-XI XII-XV

I $R_1=R_2=CH_3$, $R_3=C_2H_5$; II $R_1=H$, $R_2=C_6H_5$, $R_3=C_2H_5$; III $R_1R_2=(CH_2)_4$, $R_3=C_2H_5$; IV $R_1R_2=(CH_2)_4$, $R_3=H$; V $R_1=R_2=CH_3$, $n=1$; VI $R_1=H$, $R_2=C_6H_5$, $n=1$; VII $R_1R_2=(CH_2)_4$, $n=1$; VIII $R_1=H$, $R_2=C_6H_5$, $n=2$; IX $R_1R_2=(CH_2)_4$, $n=2$; X $R_1=H$, $R_2=C_6H_5$, $n=3$; XI $R_1R_2=(CH_2)_4$, $n=3$; XII $R_4=CH(CH_3)CH_2CH_3$, $n=1$; XIII $R_4=CH(CH_3)C_6H_5$, $n=1$; XIV $R_4=CH(CH_3)C_6H_5$; $n=2$; XV $R_4=CH(CH_3)C_6H_5$, $n=3$.

*See [1] for communication IX.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	S	C	H	N	S	
V	144—145	$C_{11}H_{12}N_2OS$	60,0	5,5	12,8	14,6	60,0	5,5	12,7	14,6	76
VI	226—227	$C_{15}H_{12}N_2OS$	67,0	4,4	10,3	12,0	67,1	4,5	10,4	12,0	91,2
VII	206—207	$C_{13}H_{14}N_2OS$	63,2	5,7	11,5	13,0	63,4	5,7	11,4	13,0	40,6
VIII	202—203	$C_{16}H_{14}N_2OS$	68,3	5,0	9,9	11,5	68,2	5,0	9,9	11,4	75,5
IX	217—218	$C_{14}H_{16}N_2OS$	64,6	6,1	10,7	12,3	64,6	6,2	10,8	12,3	60,0
X	139—140	$C_{17}H_{16}N_2OS$	68,5	5,5	9,6	11,0	68,9	5,4	9,5	10,9	55,5
XI	153—154	$C_{15}H_{18}N_2OS$	65,4	6,7	10,0	11,7	65,7	6,6	10,2	11,7	50
XII	216—217	$C_{11}H_{16}N_2O \times C_6H_3N_3O_7$	48.6	4,6	16,6	—	48,5	4,6	17,1	—	48
XIII	172—173	$C_{15}H_{16}N_2O \times HCl \times \times H_2O$†	—	—	9,6	—	—	—	9,5	—	65,4
XIV	78—79	$C_{16}H_{18}N_2O$	75,6	7,2	11,0	—	75,6	7,2	11,0	—	48,3
XV	177—177,5	$C_{17}H_{20}N_2O \times HCl$‡	67,1	6,8	9,3	—	67,2	6,6	9,2	—	59

*The compounds were recrystallized: IV-XI from methanol, XII from methanol—acetone (9:1), XIII from petroleum ether (40-70°), and XIV from acetone.
†Found: Cl 12.0%. Calculated: Cl 12.0%.
††Found: Cl 11.3%. Calculated: Cl 11.7%.

EXPERIMENTAL METHOD

The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JEOL-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard.

2,3-Trimethylene-4-oxothieno[2,3-d]pyrimidines (V-VII), 2,3-Tetramethylene-4-oxothieno-[2,3-d]pyrimidines (VIII, IX), and 2,3-Pentamethylene-4-oxothieno[2,3-d]pyrimidines (X, XI). A 4-ml sample of phosphorus oxychloride was added to a cooled solution of 0.04 mole of I-III and 0.044 mole of lactam in 30 ml of absolute dichloroethane, after which the mixture was refluxed for 20 min. It was then cooled, a solution of 5 g of sodium acetate in 30 ml of water was added, and the mixture was refluxed for 20 min. It was then cooled, the organic layer was separated, and the aqueous layer was extracted with dichloroethane. The combined extracts were washed with water, the dichloroethane was removed by distillation, and the residue was washed with methanol. Data on V-XI are presented in Table 1.

Pentamethylene-4-oxo-3,4-dihydro-5,6-tetramethylenethieno[2,3-d]pyrimidine (XI). A solution of 2.7 g (14 mmole) of 5-amino-2,3-tetramethylenethiophene-4-carboxylic acid (IV) and 2.6 g (19 mmole) of O-methylcaprolactim in 100 ml of benzene was refluxed for 1 h, after which 90 ml of benzene was removed by distillation. The residue was cooled, and the resulting solid was removed by filtration and washed on the filter with alcohol to give 1.14 g (30.5%) of product. No melting-point depression was observed for a mixture of this product with a sample of XI obtained as described above.

2,3-Polymethylene-4-oxopyrimidines (XII-XV). Raney nickel (30-40 g) was added to a solution of 0.07 mole of V, VI, VIII, or X in 70 ml of alcohol, and the mixture was refluxed for 25 h. The catalyst was then removed by filtration, the alcohol was removed by distillation, and the residue was fractionated. Compounds XIII and XV were isolated as the hydrochlorides, and XII was isolated in the form of the picrate. Data on XII-XV are presented in Table 1. PMR spectrum of XIV, δ, ppm: 1.53 (CH_3), 1.87, 2.84, 3.88 ($CH_2CH_2CH_2CH_2$), 4.25 [$CH(C_6H_5)CH_3$], 7.2-7.3 (C_6H_5), and 7.77 (6-H).

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