FUNCTIONAL DERIVATIVES OF THIOPHENE

XIV.* ALKYLAMINOMETHYLATION OF α-ACYLAMINOTHIOPHENES AND SYNTHESIS OF 1,2,3,4-TETRAHYDROTHIENO[2,3-d]PYRIMIDINE DERIVATIVES

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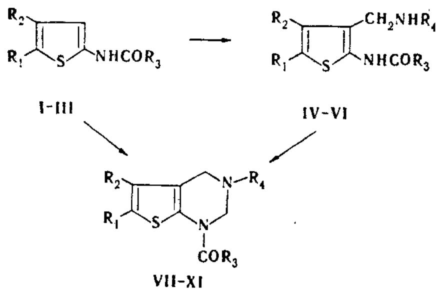
The Mannich reaction with primary amines is a convenient method for the synthesis of β-acylaminomethyl derivatives of α-acylaminothiophenes, which are readily cyclized to substituted 1,2,3,4-tetrahydrothieno[2,3-d]pyrimidenes by the action of formaldehyde.

α-Acylaminothiophene derivatives readily undergo various electrophilic substitution reactions. For example, Mannich bases are obtained in high yields by the action of bis(dialkylamino)methanes on acylaminothiophenes I-III [2]. As a result of the reaction of thiophene I with aminals we isolated alkylaminomethylthiophene derivatives IV-VI. Aminals obtained by heating primary amines with formalin were subjected to the reaction without additional purification. The reaction is carried out by refluxing I with the aminals in dioxane for 2.5 h.



I $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$; II $R_1=R_2=CH_3$, $R_3=C_6H_5$; III $R_1R_2=(CH_2)_4$, $R_3=CH_3$; IV $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH(CH_3)_2$; V $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH_2C_6H_5$; VI $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH_2(CH_2)_2CH_3$; VII $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH(CH_3)_2$; VIII $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH_2C_6H_5$; IX $R_1R_2=(CH_2)_4$, $R_3=C_6H_5$, $R_4=CH(CH_2)_2CH_3$; X $R_1=R_2=CH_3$, $R_3=C_6H_5$, $R_4=CH(CH_2)_2CH_3$; XI $R_1R_2=(CH_2)_4$, $R_3=CH_3$, $R_4=CH_2C_6H_5$

It is known that formanilide is aminomethylated under the conditions of the Mannich reaction with replacement of the hydrogen of the amide group [3]. Considering the analogy between acylaminothiophenes and formanilide, we studied the reaction of IV and V with formalin. In this case we observed the formation of a pyrimidine ring to give thieno[2,3-d]pyrimidines VII and VIII. It is not absolutely necessary to isolate the alkylaminomethylthiophenes. Thieno[2,3-d]pyrimidine derivatives VII and IX-XI are also formed in high yields by treatment of the reaction mixture contianing the alkylaminomethylthiophene with formalin. The structure of VII-XI was confirmed by spectral data. The thieno[2,3-d]pyrimidines obtained (VII-XI) are thiophene analogs of the little-studied 1,2,3,4-tetrahydroquinazolines [4].

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*See [1] for communication XIII.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	S	C	H	N	S	
IV	133—134 (methanol)	$C_{19}H_{24}N_2OS$	69,4	7,3	8,5	9,7	69,5	7,4	8,5	9,8	91,5
V	143—144 (methanol)	$C_{23}H_{24}N_2OS$	73,5	6,4	7,2	8,5	73,4	6,4	7,4	8,5	70,5
VI (oxalate)	183—184 (50% aqueous methanol)	$C_{20}H_{26}N_2OS \cdot C_2H_2O_4$	61,2	6,5	6,5	7,2	61,1	6,5	6,5	7,4	55.5
VII	100—101 (70% aqueous alcohol)	$C_{20}H_{24}N_2OS$	70,2	7,1	8,3	9,4	70,5	7,1	8,2	9,4	88,2*
VIII	155—156 (dioxane – methanol)	$C_{24}H_{24}N_2OS$	74,1	6,3	7,2	8,0	74,2	6,4	7,2	8,2	97
IX	99—100 (70% aqueous alcohol	$C_{21}H_{26}N_2OS$	71,0	7,2	7,7	9,0	71,1	7,4	7,9	9,0	91
X	95,5—96,5 (70% aqueous methanol)	$C_{19}H_{24}N_2OS$	69,5	7,4	—	9,7	69,6	7,4	—	9,8	96
XI	143—144 (70% aqueous methanol)	$C_{19}H_{22}N_2OS$	69,8	6,8	—	9,8	69,9	6,8	—	9,8	62,7

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*The yield was 79.5% in the case of method B.

EXPERIMENTAL

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

5-Benzamido-2,3-tetramethylene-4-alkyl(or benzyl)aminomethylthiophenes (IV-VI). A solution of 0.08 mole of the primary amine and 0.04 mole of formalin in 25 ml of dioxane was refluxed for 20 min, after which a solution of 0.02 mole of I in 25 ml of dioxane was added. The mixture was then refluxed for 2.5 h, after which the solvents were removed by vacuum distillation. The residual IV and V were recrystallized. The oxalate was obtained from VI (obtained as an oil after removal of the solvents by distillation). Data on IV and V and the oxalate of VI are presented in Table 1. IR spectrum of IV and V: 1640 (CO) and 3260-3270 (NH) cm^{-1}. PMR spectrum of IV, δ, ppm: 1.10; 1.17 [$CH(CH_3)_2$]; 1.75, 2.34, and 2.64 ($CH_2CH_2CH_2CH_2$); 2.87 [$CH(CH_3)_2$]; 3.79 (CH_2NH); 7.40-7.80 (C_6H_5).

A. 1-Benzoyl-3-isopropyl-5,6-tetramethylene-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine (VII) and 1-Benzoyl-3-benzyl-5,6-tetramethylene-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine (VIII). A solution of 5 mmole of IV or V and 0.02 mole of formalin in 10 ml of dioxane was refluxed for 2 h, after which the solvents were removed by distillation, and the residue was recrystallized. Data on VII and VIII are presented in Table 1. IR spectrum of VII and VIII: 1640 cm^{-1} (CO). PMR spectrum of VII, δ, ppm: 0.93, 1.01 [$CH(CH_3)_2$]; 1.80-2.90 ($CH_2CH_2CH_2CH_2$); 3.76 (4-CH_2); 4.57 (2-CH_2); 7.40-7.80 (C_6H_5).

B. 1-Acyl-3-alkyl(benzyl)-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidines (VII, IX-XI). A solution of 0.08 mole of primary amine and 0.04 mole of formalin in 25 ml of dioxane was refluxed for 20 min, after which a solution of 0.02 mole of I-III in 25 ml of dioxane was added to it, and the resulting mixture was refluxed for 2.5 h. The solvents were then removed by vacuum distillation, 25 ml of dioxane and 0.08 mole of formalin were added to the residue, and the mixture was refluxed for 2 h. The solvents were then removed by vacuum distillation, and the residue was recrystallized. No melting-point depression was observed for a mixture of samples of VII obtained by method A and B. Data on VII and IX-XI are presented in Table 1.

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