FUNCTIONAL DERIVATIVES OF THIOPHENE

VIII.* SYNTHESIS OF FORMYL DERIVATIVES OF ACYLAMINOTHIOPHENES, THIENO[2,3-b]PYRIDINES, THIENO[2,3-d]PYRIMIDINES, AND THIENO[3',2':5,6]PYRIDO[2,3-d]PYRIMIDINES

V. I. Shvedov, I. A. Kharizomenova,
and A. N. Grinev

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A method is proposed for the synthesis of 5-acylamino-2,3-dimethylthiophene-4-carbaldehydes and 5-acylamino-2,3-tetramethylenethiophene-4-carbaldehydes by the formylation of the corresponding thiophenes using the Vilsmeier reaction. From the formyl derivatives obtained, previously unaccessible derivatives of thieno[2,3-b]pyridine, thieno[2,3-d]pyrimidine, and thieno[3',2':5,6]pyrido[2,3-d]-pyrimidine have been synthesized.

The formylation by the Vilsmeier method of the 5-acylamino-2,3-dimethyl- and 5-acylamino-2,3-tetramethylenethiophenes (Ia-e) that have now become widely available [2] has enabled a series of previously unknown formyl derivatives (IIa-e) to be obtained in high yield. The IR spectra of (IIa-e), as compared with those of (Ia-e), have an additional absorption band in the region of the frequencies of the vibrations of the carbonyl group at 1600-1690 cm^{-1}. In the PMR spectrum, a singlet in the region of aromatic protons that is observed for 4-H in compounds (Ia-e) has disappeared.

To characterize the compounds obtained, derivatives of them were synthesized: the phenylhydrazone (III), the isonicotinoylhydrazone (IV), the thiosemicarbazone (V), and the anil (VI). The reduction of (VI) with sodium tetrahydroborate gave 4-anilinomethyl-5-benzoylamino-2,3-tetramethylenethiophene (VII).

In the acylaminothiophenecarbaldehydes (IIa-e), the functional groups are located in the ortho position with respect to one another, and therefore they are of interest as the starting compounds for the synthesis of various condensed heterocycles.

The action of cyanoacetic ester in the presence of piperidine on (IIa, b, d) gave high yields of 6-amino-5-ethoxycarbonylthieno[2,3-b]pyridines (VIII, IX). The reaction of (IIa, d) with malononitrile and benzonitrile took place similarly and also led to derivatives of 6-aminothieno[2,3-b]pyridine (X, XI, XII). The acyl residue substituted in the amino group of (IIa, b, or d) was eliminated by the piperidine in the reaction process. On reaction with cyanoacetic ester, (IIb) and (IId), differing by their acyl substituents, both gave (IX). The IR spectra of (VIII) and (IX) each had a band at 1690 cm^{-1} which is characteristic for the C=O of an ethoxycarbonyl group, and the spectra of (X) and (XI) each had a band at 2230 cm^{-1} characterizing a CN group. In all the derivatives (VIII-XII) obtained, the absorption bands of the NH_2 group were found in the 3400-3490 cm^{-1} region.

The reaction of (IX) and (X) with an excess of formamide gave the thienopyridopyrimidines (XIII) and (XIV). In the IR spectrum of (XIII), the carbonyl group is characterized by a band at 1670 cm^{-1}, which shows the presence of a lactam structure in (XIII).

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* For Communication VII, see [1].

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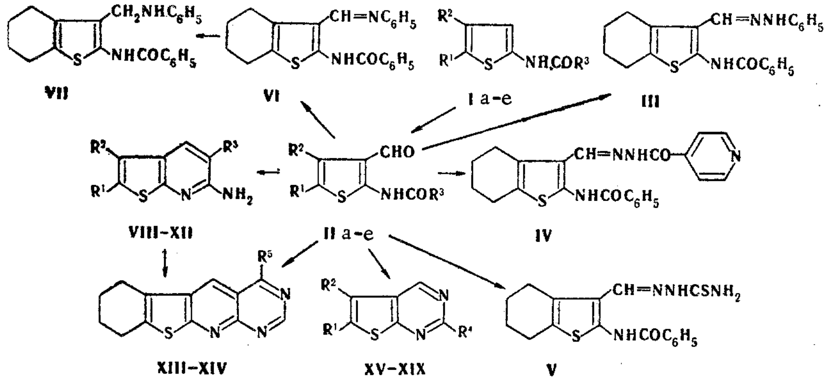

Ia, IIa, XV $R^1 = R^2 = R^4 = CH_3$; Ib, IIb, XVI $R^1 + R^2 = (CH_2)_4$, $R^4 = CH_3$; Ic, IIc, XVII $R^1 = R^2 = CH_3$, $R^4 = C_6H_5$; Id, IId, XVIII $R^1 + R^2 = (CH_2)_4$, $R^4 = C_6H_5$; Ie, IIe XIX $R^1 + R^2 = (CH_2)_4$, $R^4 = CH_2C_6H_5$; VIII $R^1 = R^2 = CH_3$, $R^3 = COOC_2H_5$; IX $R^1 + R^2 = (CH_3)_4$, $R^3 = COOC_2H_5$; X $R^1 = R^2 = CH_3$, $R^3 = CN$; XI $R^1 + R^2 = (CH_2)_4$, $R^3 = CN$; XII $R^1 + R^2 = (CH_2)_4$, $R^3 = COC_6H_5$; XIII $R^5 = OH$, XIV $R^5 = NH_2$.

The reaction of (IIa-d) with ammonium acetate was performed with heating in acetic acid, i.e., under conditions differing from those for the synthesis of the quinazolinones [3]. As a result, we obtained high yields of the thienopyrimidine derivatives (XV-XIX) with position 4 free from substituents. In the PMR spectrum for (XV), singlets of the protons of the CH_3 groups are observed at 2.78, 2.28, and 2.45 ppm, and the singlet of a proton at 8.77 ppm, corresponding to the 4-H atom.

EXPERIMENTAL

The PMR spectra were taken on a JEOL-4H-100 instrument using HMDS as internal standard. The IR spectra were taken on a UR-10 instrument with the liquid substances in the form of thin films and the solids in paraffin oil.

5-Acetylaminothiophene-4-carbaldehydes (IIa-e). In drops, 0.3 mole of freshly-distilled phosphorus oxychloride was added to 0.3 mole of dimethylformamide cooled to ~0°C. The mixture was kept at room temperature for 15 min and was then cooled again, and 30 ml of dry dichloroethane and a solution of 0.195 mole of a compound (Ia-e) in 900 ml of dry dichloroethane was added. The mixture was boiled for 15 min and was then cooled, 0.9 mole of sodium acetate in 600 ml of water was added to it, and the new mixture was boiled for 20 min. After cooling, the organic layer was separated off, and the aqueous layer was extracted several times with dichloroethane. The combined extracts were washed with potassium carbonate solution and then with water until the wash-waters were neutral. The dichloroethane was distilled off to dryness and the residue was recrystallized from ethanol. Information on compounds (IIa-e) is given in Table 1.

The phenylhydrazone of 5-benzoylamino-2,3-tetramethylenethiophene-4-carbaldehyde (III), the isonicotinoylhydrazone of 5-benzoylamino-2,3-tetramethylenethiophene-4-carbaldehyde (IV), and the thiosemicarbazone of 5-benzoylamino-2,3-tetramethylenethiophenyl-4-carbaldehyde (V) were obtained by the usual methods. Information on compounds (III-V) is given in Table 1.

5-Benzoylamino-2,3-tetramethylene-4-thenylidenaniline (VI). To a solution of 2.85 g (0.01 mole) of (IId) in 100 ml of absolute ethanol was added 1 ml (0.01 mole) of aniline. The reaction mixture was boiled for 3 h 30 min and was then cooled, and the precipitate that deposited was filtered off and was recrystallized from dioxane. Yield 1.4 g (39%) of (VI) with mp 196-197°C (from dioxane). Found %: C 73.3; H 5.6; N 7.8; S 9.0. $C_{22}H_{20}N_2OS$. Calculated %: C 73.3; H 5.6; N 7.7; S 8.9.

4-Anilinomethyl-5-benzoylamino-2,3-tetramethylenethiophene (VII). With stirring, 0.6 g (160 mmoles) of sodium tetrahydroborate was added in small portions to a solution of 1.1 g (2.8 mmoles) of (VI) in a mixture of 40 ml of dioxane and 20 ml of methanol. After the addition of the whole of the sodium tetrahydroborate, the mixture was stirred for 30 min and was then poured onto ice. The precipitate that deposited was filtered off and was recrystallized from methanol. Yield 0.8 g (75%) of (VII) with mp 134-135°C (from methanol). Found %: C 73.0; H 6.1; N 7.8; S 9.0. $C_{22}H_{22}N_2OS$. Calculated %: C 72.9; H 6.1; N 7.7; S 8.8.

6-Amino-5-ethoxycarbonyl-2,3-dimethylthieno[2,3-b]pyridine (VIII) and 6-Amino-5-ethoxycarbonyl-2,3-tetramethylenethieno[2,3-b]pyridine (IX). The reaction mixture obtained from 0.02 mole of (IIa, b, or d), 0.037 mole of cyanoacetic ester, 40 ml of ethanol, and 0.5 ml of piperidine was boiled for 1 h 30 min

TABLE 1. Characteristics of the Compounds Obtained

Compound	Mp, °C*	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	N	S	C	H	N	S	
IIa	134,5—135,5	$C_{19}H_{11}NO_2S$	54,8	5,7	7,0	16,4	54,8	5,6	7,1	16,2	73
IIb	123—124	$C_{11}H_{13}NO_2S$	59,5	5,9	6,3	14,6	59,2	5,9	6,3	14,4	78
IIc	156—157	$C_{14}H_{13}NO_2S$	65,0	5,0	5,3	12,4	64,8	5,0	5,4	12,4	80
IId	134—135	$C_{16}H_{15}NO_2S$	67,2	5,2	4,9	11,2	67,3	5,3	4,9	11,2	80
IIe	105,5—106,5	$C_{17}H_{17}NO_2S$	68,0	5,6	4,8	10,7	68,2	5,7	4,7	10,7	84
III	214—215	$C_{22}H_{21}N_3OS$	—	—	11,1	8,7	—	—	11,2	8,6	88
IV	280.5—281.5	$C_{22}H_{20}N_4O_2S$	65,1	5,0	13,8	8,0	65,4	5,0	13,9	7,9	99
V	245—248(decomp.)	$C_{17}H_{18}N_4O_2S$	57,3	5,2	15,5	17.8	57,0	5,1	15,6	17,9	89
VIII	193,5—194,5	$C_{12}H_{14}N_2O_2S$	57,6	5,6	10,9	—	57,6	5,6	11,2	—	90
IX	199,5—200,5	$C_{14}H_{16}N_2O_2S$	61,0	5,7	10,1	11,6	60,8	5,8	10,1	11,6	88
X	249,5—250,5	$C_{10}H_9N_3S$	59,0	4,4	20,7	15,7	59,1	4,5	20,7	15,8	93
XI	218,5—219,5	$C_{12}H_{11}N_3S$	62,7	4,8	18,0	13,9	62,8	4,8	18,3	14,0	97
XIII	>330 (decomp.)	$C_{13}H_{11}N_3OS$	60,6	4,6	16,3	—	60.7	4,3	16,3	—	86
XIV	>350	$C_{13}H_{12}N_4S$	61,3	4,6	21,8	—	60.9	4,7	21,8	—	70
XV	163—164/9† mm 88—89	$C_9H_{10}N_2S$	60,4	5,4	18,0	—	60.6	5,6	18.0	—	94
XVI	184—186/7† mm 57—58	$C_{11}H_{12}N_2S$	64,9	5,9	—	15.5	64,7	5,9	—	15,6	95
XVII	164—165	$C_{14}H_{12}N_2S$	70,0	5,0	11,8	13.3	70,0	5,0	11,6	13,3	98
XVIII	120,5—121,5	$C_{16}H_{14}N_2S$	72,2	5,3	10,3	12,0	72,1	5,3	10,5	12,0	98
XIX	87—88	$C_{17}H_{16}N_2S$	72,9	5,7	9,7	11,2	72,8	5,8	10,0	11,4	95

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*The substances were purified by recrystallization: (IIa-e) from ethanol; (V, VII, VIII, X, XIV) from dioxane; (VI) from dioxane–dimethylformamide (4:1); (IX, XVII, and XVIII) from acetone; (XI) from methanol; (XIII) from dimethylformamide; (XIX) from aqueous methanol.

†Bp.

and was then cooled, and the precipitate that deposited was filtered off. Information on compounds (VIII) and (IX) is given in Table 1.

6-Amino-5-cyano-2,3-dimethylthieno[2,3-b]pyridine (X) and 6-Amino-5-cyano-2,3-tetramethylenethieno[2,3-b]pyridine (XI). The experiment was performed with 12.7 mmoles of (IIa or d), 21 mmoles of malonodinitrile, 40 ml of ethanol, and 0.5 ml of piperidine. The reaction and the isolation of the substances were performed under the conditions of the synthesis of (VIII) and (IX). Information on compounds (X) and (XI) is given in Table 1.

6-Amino-5-benzoyl-2,3-tetramethylenethieno[2,3-b]pyridine (XII). The experiment was performed with 5.6 g (19.5 mmoles) of (IId), 2.91 g (20 mmoles) of benzoylacetonitrile, 100 ml of ethanol, and 3 ml of piperidine. The reaction and the isolation of the substance were performed under the conditions for the synthesis of (VIII) and (IX). Yield 5.6 g (98.2%) of (XII) with mp 199-200°C (from acetone). Found %: C 70.1; H 5.3; N 9.0; S 10.5. $C_{18}H_{15}N_2OS$. Calculated %: C 70.1; H 5.2; N 9.1; S 10.4.

3,4-Dihydro-6,7-tetramethylenethieno[2,3-b]pyrido[2,3-d]pyrimidin-4-one (XIII) and 4-Amino-6,7-tetramethylenethieno[2,3-b]pyrido[2,3-d]pyrimidine (XIV). A solution of 0.01 mole of (IX) or (XI) in 5 ml of formamide was boiled for 1 h 30 min. The reaction mixture was cooled, and the precipitate was filtered off and washed with methanol. Information on compounds (XIII) and (XIV) is given in Table 1.

The Thienopyrimidine Derivatives (XV-XIX). A mixture of 21 mmoles of a compound (IIa-e), 5.6 g of ammonium acetate, and 35 ml of acetic acid was boiled for 1 h. Part of the acetic acid was distilled off under reduced pressure, and the residue was poured into 200 ml of water and extracted with ether (or, if the desired product separated out in the form of crystals, these were filtered off). The combined extracts were washed with sodium carbonate solution and with water, and were dried with magnesium sulfate, and the ether was distilled off. Information on compounds (XV-XIX) is given in Table 1.

LITERATURE CITED

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