FUNCTIONAL DERIVATIVES OF THIOPHENE

VI.* SYNTHESIS, AZO COUPLING, AND AMINOMETHYLATION OF α-ACYLAMINOTHIOPHENES

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

UDC 547.733.07:542.958

A method was developed for the synthesis of 5-acylamino-2,3-dimethyl- and 5-acylamino-2,3-tetramethylenethiophenes by decarboxylation of the corresponding 5-acylaminothiophene-4-carboxylic acids. The azo coupling and aminomethylation of the synthesized acylaminothiophenes were studied.

Acylaminothiophenes are usually obtained by acylation of the double tin or zinc salts of aminothiophene [2-4]. However, the method has limited application because of the difficulties involved in the synthesis of the individual starting nitrothiophenes. The simplest representative of the series – 2-acetamidothiophene – is readily formed by decarboxylation of 5-acetamidothiophene-2-carboxylic acid, obtained by a multistep synthesis [5].

In connection with the interest in stable aminothiophene derivatives, we obtained the previously unknown α-acylaminothiophenes from the accessible α-amino-β-ethoxycarbonylthiophenes (Ia, b) [6, 7]. A number of α-acylaminothiophenes (IIc-g) were obtained by acylation of Ia, b. Decarboxylation of 5-acylamino-2,3-dialkylthiophene-5-carboxylic acids (IIIa, b [7] and IIIc-g), obtained by alkaline hydrolysis of the corresponding esters, gives high yields of the previously unknown acylaminothiophenes (IVa-g). Reaction of IVb, d with benzenediazonium chloride readily leads to 4-phenylazo-5-acylamino-2,3-dialkylthiophene derivatives (Vb, d), reductive acylation of which with zinc in acetic acid in the presence of acetic anhydride gives the ortho derivative of diacylaminothiophene (VIb, d). We were able to aminomethylate the acylaminothiophene derivatives (IVb-e) by heating them with bis(dimethylamino)methane bis(dibutylamino)methane, and bis(N-methylpiperazino)methane. Mannich bases (VII-XIII) were obtained in high yields by this process. The replacement of the hydrogen in the 4 position by a dimethylaminomethyl group by the action of bis(dimethylamino)methane indicates the high reactivity of the acylaminothiophene derivatives. For comparison, it is sufficient to point out that β-substituted products are formed in low yields in the aminomethylation of other thiophene derivatives [8]. The aminomethylation of IVc, d by the action of formalin and secondary amine hydrochlorides proceeds ambiguously as a function of the basicity of the amines used for the reaction. Hydrochlorides of Mannich bases (XIV, XV) were obtained in the reaction of IVc, d with formalin and morpholine hydrochloride. The reaction of IVd with formalin and dibutylamine and N-methylpiperazine hydrochlorides leads to a dithienylmethane derivative (XVI). The latter was also obtained by the action of formalin on IVd.

An absorption maximum at 229-280 nm is observed in the UV spectra of IVa-g, while a second absorption maximum at 313-321 nm is also observed in the spectra of IVc, d, f, g. The PMR spectrum of IVa contains the distinct singlet of the proton in the 4 position of the thiophene ring at 6.38 ppm. Absorption bands appear at 1535-1540 cm^{-1} (N=N bond) in the IR spectra of Vb, d, while the 4-H singlet vanishes

---

* See [1] for communication V.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1624-1627, December, 1973. Original article submitted June 19, 1972.

TABLE 1. α-Acylaminothiophene Derivatives*

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	S	C	H	N	S	
IIc	148—149	$C_{16}H_{17}NO_3S$	63,2	5,6	4,6	10,2	63,3	5,6	4,6	10,6	Quantitative
IId	172—173,5	$C_{18}H_{19}NO_3S$	65,8	5,9	4,1	9,7	65,6	5,9	4,2	9,7	79,5
IIe	95,5— 96	$C_{19}H_{21}NO_3S$	66,3	6,0	4,0	9,4	66,4	6,1	4,0	9,3	94,1
IIf	165—166,5	$C_{19}H_{21}NO_3S$	66,5	6,1	—	9,2	66,5	6,1	—	9,3	98,7
IIg	192,5—193,5	$C_{18}H_{18}NO_3SCl$	59,7	4,8	4,0	8,8	59,4	5,0	3,9	8,8	97,3
IIIc	216,5—217,5	$C_{14}H_{13}NO_3S$	61,2	4,5	5,0	11,5	61,0	4,8	5,0	11,6	64
IIId	211—212	$C_{16}H_{15}NO_3S$	63,8	5,0	4,6	10,6	63,8	5,0	4,6	10,6	58,5
IIIe	232—233	$C_{17}H_{17}NO_3S$	64,9	5,5	4,4	10,2	64,7	5,4	4,4	10,2	53,5
IIIf	210—211,5	$C_{17}H_{17}NO_3S$	64,6	5,5	4,1	9,9	64,7	5,4	4,4	10,2	96,5
IIIg	240—241	$C_{16}H_{14}NO_3SCl$ †	57,5	4,2	4,2	9,7	57,2	4,2	4,2	9,6	57
IVa	144—145	$C_8H_{11}NOS$	56,8	6,8	8,0	19,0	56,8	6,6	8,2	19,0	90
IVb	160—161	$C_{10}H_{13}NOS$	61,4	6,7	7,3	16,2	61,5	6,7	7,2	16,3	92,4
IVc	145—146	$C_{13}H_{13}NOS$	67,4	5,5	6,2	13,8	67,5	5,7	6,1	13,8	93
IVd	155—156	$C_{15}H_{15}NOS$	70,0	5,9	5,5	12,5	70,0	5,9	5,4	12,4	95
IVe	149,5—150,5	$C_{16}H_{17}NOS$	71,0	6,3	5,0	11,5	70,8	6,3	5,1	11,8	95
IVf	125—125,5	$C_{16}H_{17}NOS$	71,0	6,3	5,4	11,9	70,8	6,3	5,1	11,8	95,7
IVg	180—180,5	$C_{15}H_{14}NOSCl$ ‡	61,5	4,9	4,9	11,0	61,7	4,8	4,8	11,0	97
Vb	206—207	$C_{16}H_{17}N_3OS$	64,0	5,7	14,3	10,8	64,2	5,7	14,0	10,7	52,6
Vd	298,5—299,5	$C_{21}H_{19}N_3OS$	69,8	5,3	11,6	8,8	69,8	5,3	11,6	8,9	45,3
VII	100—101	$C_{16}H_{20}N_2OS$	66,6	6,9	9,9	11,1	66,6	7,0	9,7	11,1	Quantitative
VIII	119—120	$C_{13}H_{20}N_2OS$	61,8	7,8	10,9	12,7	61,7	8,0	10,9	12,7	93,5
IX	124—125	$C_{19}H_{24}N_2OS$	69,4	7,2	8,5	9,9	69,5	7,3	8,5	9,8	98
X	115,5—116,5	$C_{24}H_{34}N_2OS$	72,5	8,3	7,3	8,0	72,3	8,6	7,0	8,0	92,5
XII	123—124	$C_{19}H_{25}N_3OS$	66,7	7,2	12,3	9,4	66,5	7,3	12,2	9,3	87,3
XIII	176,5—177,5	$C_{21}H_{27}N_3OS$	68,0	7,5	11,3	8,5	68,2	7,4	11,4	8,7	95
XIV	213—214	$C_{18}H_{22}N_2O_2S \cdot HCl$	58,8	6,4	7,6	8,6	58,9	6,3	7,6	8,8	84,3
XV	162,5—163,5	$C_{20}H_{24}N_2O_2S \cdot HCl$	60,9	6,6	6,9	8,3	60,9	6,4	7,1	8,2	88

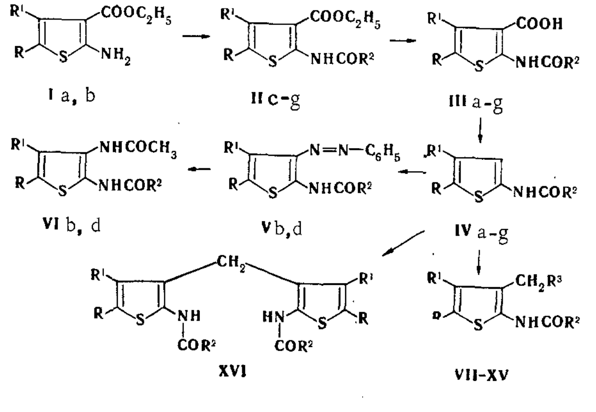
---

* The substances were purified for analysis by recrystallization; IIe, g, IIIc, d, g, IVg, VII, IX, X, XIV, and XV from methanol; IIc, d, IVa-e, and Vb from acetone; IIf, IIIf, and Vd from dioxane; IIIe from methanol–dioxane (1 : 1); IVf from ether–petroleum ether (3 : 1), VIII from ether; XII from 50% aqueous alcohol; and XIII from alcohol.

† Found: Cl 10.7%. Calculated: Cl 10.6%.

‡ Found: Cl 12.1%. Calculated: Cl 12.1%.

in the PMR spectra of these compounds. The structure of the dialkylaminomethyl derivatives (VII-XV) was proved by means of the IR and PMR spectra. The IR spectra of XI, XIV, and XV indicate the presence in the molecule of a group of basic character – at 2400-2700 cm^{-1} there is a series of absorption bands due to NH^+ stretching vibrations, while the absorption band of CN^+ stretching vibrations is observed at 950 cm^{-1}. It was demonstrated by means of the PMR spectra that the dialkylaminomethyl substituent enters the 4 position of IVb-e rather than adding to the amide nitrogen.*



a $R=R^1=R^2=CH_3$; b $R+R^1=(CH_2)_4$, $R^2=CH_3$; c $R=R^1=CH_3$, $R^2=C_6H_5$; d $R+R^1=(CH_2)_4$, $R^2=C_6H_5$; e $R+R^1=(CH_2)_4$, $R^2=CH_2C_6H_5$; f $R+R^1=(CH_2)_4$, $R^2=p\text{-}CH_3C_6H_4$; g $R+R^1=(CH_2)_4$, $R^2=p\text{-}ClC_6H_4$; VII $R=R^1=CH_3$, $R^2=C_6H_5$, $R^3=N(CH_3)_2$; VIII $R+R^1=(CH_2)_4$, $R^2=CH_3$, $R^3=N(CH_3)_2$; IX $R+R^1=(CH_2)_4$, $R^2=CH_2C_6H_5$, $R^3=N(CH_3)_2$; X $R=R^1=(CH_2)_4$, $R^2=C_6H_5$, $R^3=N(C_4H_9)_2$; XI $R+R^1=(CH_2)_4$, $R^2=C_6H_5$, $R^3=N(CH_3)_2HCl$; XII $R=R^1=CH_3$, $R^2=C_6H_5$, R^3=piperazino-CH_3 XIII $R+R^1=(CH_2)_4$, $R^2=C_6H_5$, R^3=piperazino-CH_3 XIV $R=R^1=CH_3$, $R^2=C_6H_5$, R^3=morpholino · HCl, XV $R+R^1=(CH_2)_4$, $R^2=C_6H_5$, R^3=morpholino · HCl; XVI $R+R^1=(CH_2)_4$, $R^2=C_6H_5$.

---

* The Mannich reaction with replacement of the hydrogen attached to the amide nitrogen was previously observed for formanilide [9].

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrometer, the UV spectra were recorded with an EPS-3 spectrophotometer, and the PMR spectra were recorded with a JEOL-4H spectrometer at 100 MHz.

5-Benzamido-4-ethoxycarbonyl-2,3-dimethylthiophene (IIc) and 5-Acylamino-4-ethoxycarbonyl-2,3-tetramethylenethiophene (IId-g). A 1.4-mole sample of the acid chloride was added by drops with stirring and heating (on a water bath) to a solution of 0.5 mole of Ia, b in 140 ml of dioxane, after which the mixture was heated on a boiling-water bath for 30 min and cooled. The precipitate was removed by filtration. Compound IIe was similarly obtained, but the reaction mixture was poured into water, and the precipitate was removed by filtration and boiled with petroleum ether to dissolve the phenylacetic acid. Data on IIc-g are presented in Table 1.

5-Benzamido-2,3-dimethylthiophene-4-carboxylic Acid (IIIc) and 5-Acylamino-2,3-tetramethylenethiophene-4-carboxylic Acids (IIId-g). A solution of 0.3 mole of sodium hydroxide in 150 ml of 50% aqueous methanol was added to a solution of 0.165 mole of IIc-g in 100 ml of dioxane and 50 ml of methanol, after which the solution was refluxed for 2.5 h and poured into 1 liter of water. The aqueous mixture was acidified with 50 ml of concentrated hydrochloric acid, and the precipitate was removed by filtration, washed with water until the wash waters were neutral, recrystallized, and dried. Data on IIIc-g are presented in Table 1.

5-Acylamino-2,3-dimethylthiophenes (IVa, c) and 5-Acylamino-2,3-tetramethylenethiophenes (IVb, d-g). Compounds IIIa-g were heated at 240-250° (bath temperature) until bubbles of carbon dioxide were no longer evolved. The melt was then cooled. Data on IVa-g are presented in Table 1.

4-Phenylazo-5-acylamino-2,3-tetramethylenethiophene (Vb, d). A solution of 0.075 mole of IVb, d in 300 ml of acetic acid was added to a diazonium salt solution prepared from 7 ml (0.075 mole) of aniline, 25 ml of concentrated hydrochloric acid, and 5.25 g (0.075 mole) of sodium nitrite, the whole neutralized with sodium acetate at 0-5°. Concentrated sodium hydroxide solution was then added rapidly with cooling and stirring until the mixture was alkaline, during which the temperature of the mixture rose to 60°. After 10 min, the precipitate was removed by filtration, washed to neutrality with water, and suspended in 50 ml of methanol. The suspension was refluxed for a few minutes and cooled, and the precipitate was removed by filtration. Data on Vb, d are presented in Table 1.

4,5-Diacetamido-2,3-tetramethylenethiophene (VIb). A 6.5-g (0.01 mole) sample of zinc dust was added in portions to a heated (to 60°) mixture of 5.98 g (0.02 mole) of Vb, 70 ml of glacial acetic acid, 4 ml of acetic anhydride, and 2 g of fused sodium acetate. The mixture was then stirred and refluxed for 2 h and poured into water. The sediment was removed by filtration, and 10-15% ammonium hydroxide was added gradually to the mother liquor until it was alkaline. The alkaline mixture was filtered, and the filtrate was extracted with chloroform. The chloroform was partially removed by distillation, and the resulting precipitate was removed by filtration and washed with ether to give 2.6 g (51.5%) of VIb with mp 216-217.5° (from methanol). Found: C 57.3; H 6.3; N 10.9; S 12.8%. $C_{12}H_{16}N_2O_2S$. Calculated: C 57.1; H 6.4; N 11.1; S 12.7%.

4-Acetamido-5-benzamido-2,3-tetramethylenethiophene (VId). This compound was similarly obtained from 2.7 g (0.075 mole) of Vd. The precipitate that formed from the aqueous solution was removed by filtration and recrystallized from methanol to give 0.9 g (39.3%) of VId with mp 192-193° (from methanol). Found: C 65.0; H 5.8; N 8.9; S 10.2%. $C_{17}H_{18}N_2SO_2$. Calculated: C 65.0; H 5.8; N 8.9; S 10.2%.

5-Benzamido-2,3-dimethyl-4-dimethylaminomethylthiophene (VII) and 5-Acylamino-2,3-tetramethylene-4-dialkylaminomethylthiophenes (VII, IX, and X). A mixture of 0.01 mole of IVb, c, d, e, 0.0176 mole of bis(dialkylamino)methane, and 15 ml of dry dioxane was refluxed for 2.5 h. The solvents were removed by vacuum distillation. Data on VII-X are presented in Table 1.

5-Benzamido-2,3-tetramethylene-4-dimethylaminomethylthiophene Hydrochloride (XI). This was obtained as in the preceding experiment from 2.57 g (0.01 mole) of IVd, 1.8 g (0.0176 mole) of bis(dimethylamino)methane, and 15 ml of dry dioxane. The solvents were removed by vacuum distillation, and the solid residue was dissolved in absolute ether. A solution of hydrogen chloride in absolute ether was added to the ether solution, and the precipitate was removed by filtration and washed with ether to give 3.5 g (100%) of XI with mp 212-213° (from alcohol). Found: C 61.8; H 6.6; N 7.7; S 9.0; Cl 9.9%. $C_{18}H_{22}N_2OS \cdot HCl$. Calculated: C 61.6; H 6.6; N 8.0; S 9.1; Cl 10.0%.

5-Benzamido-2,3-dimethyl-4-(N-methylpiperazino)methylthiophene (XII) and 5-Benzamido-2,3-dimethyl-4-(N-methylpiperazino)methylthiophene (XIII). A 0.1-mole sample of N-methylpiperazine was added to 0.047 mole of formalin at room temperature, and the mixture was refluxed for 10 min. It was then treated with a solution of 0.025 mole of IVc, d in 10 ml of dioxane, and the resulting solution was refluxed for 2.5 h. The solvents were removed by distillation, and the residue was cooled. The resulting crystals were washed on the filter with petroleum ether and dried. Data on XII and XIII are presented in Table 1.

5-Benzamido-2,3-dimethyl-4-morpholinomethylthiophene Hydrochloride (XIV) and 5-Benzamido-2,3-tetramethylene-4-morpholinomethylthiophene Hydrochloride (XV). A solution of 0.031 mole of morpholine hydrochloride and 0.031 mole of formalin was added to a solution of 0.0155 mole of IVc, d in 20 ml of dioxane, and the mixture was heated at 40-50° for 4 h. The solvents were removed by distillation, and 10 ml of water was added to the residue. The aqueous mixture was heated for 15 min on a water bath and cooled. The resulting precipitate was removed by filtration and dried. Data on XIV and XV are presented in Table 1.

Bis(5-benzamido-2,3-tetramethylene-4-thienyl)methane (XVI). 1) A 2.5-ml (0.031 mole) sample of formalin was added to a solution of 4 g (0.0155 mole) of IVd in 20 ml of dioxane, and the mixture was heated at 45-50° for 4 h. The solvents were then removed by distillation, and the residue was triturated with 5 ml of absolute alcohol and removed by filtration to give 2.95 g (72%) of XVI with mp 253-254.8° (from dioxane) and R_f 0.55 on Silufol with a benzene–methanol (10 : 1) system. Found: C 70.5; H 6.1; N 12.1%. $C_{31}H_{32}N_2O_2S_2$. Calculated: C 70.4; H 6.1; N 12.1%.

2) The compound was also prepared from 2.57 g (0.01 mole) of IVd, 3.3 g (0.02 mole) of dibutylamine hydrochloride, and 1.6 ml (0.02 mole) of formalin. The reaction was carried out and the products were isolated under the conditions used for the synthesis of XIV-XV. The yield was 1.4 g (53%). No melting-point depression was observed for a mixture of this product with a sample of XVI obtained by method 1. The product had R_f 0.55 on Silufol with a benzene–methanol (10 : 1) system.

LITERATURE CITED

1. V. I. Shvedov, O. B. Romanova, V. K. Vasil'eva, and A. N. Grinev, Khim. Geterotsikl. Soedin., 1024 (1973).
2. W. Steinkopf, Ann., 403, 17 (1914).
3. H. D. Hartough, Thiophene and Its Derivatives, New York (1952), p. 230.
4. V. G. Zhiryakov and I. I. Levkoev, Dokl. Akad. Nauk SSSR, 120, 1035 (1958).
5. Ya. L. Gol'dfarb, M. M. Polonskaya, B. P. Fabrichnyi, and I. F. Shalavina, Dokl. Akad. Nauk SSSR, 126, 86 (1959).
6. V. I. Shvedov and A. N. Grinev, Zh. Organ. Khim., 1, 2228 (1965).
7. V. I. Shvedov and A. N. Grinev, Khim. Geterotsikl. Soedin., 515 (1966).
8. Ya. L. Gol'dfarb, A. P. Yakubov, and L. I. Belen'kii, Izv. Akad. Nauk SSSR, Ser. Khim., 2509 (1967).
9. H. Möhrle and P. Spillmann, Tetrahedron, 25, 5595 (1969).