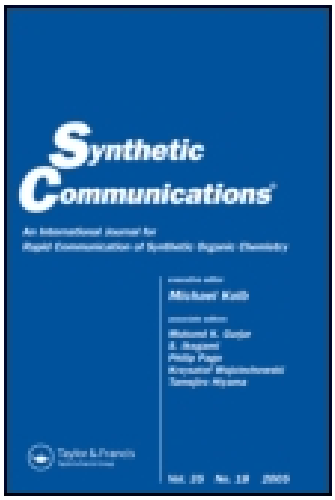

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3,7-DICHLORO-2,6-DI-(4,4′-BUTYL-AMIDINO)BENZO[2,1-b:4,5-b′]DITHIOPHENE DIHYDROCHLORIDE AS POTENTIAL ANTI-HIV AGENT

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ABSTRACT

The multistep synthesis of substituted diamidine of benzodithiophene structure as soluble salt is described. On this way was prepared the compound in title; 3,7-dichloro-2,6-di-(4,4′-*n*-butyl-amidino)benzo[2,1-b:4,5-b′]dithiophene dihydrochloride **6a**. Prepared compound could serve as new intercalator on DNA in the HIV infection.

INTRODUCTION

There is a lot of articles describing the biological activity of diamidino substituted heterocycles, specially in the recent time.[1–5] A number of aromatic diamidines have been shown to bind to the minor groove of

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DNA and to exhibit useful antimicrobial activities.[6–9] A number of hypothesis for the mode of antimicrobial action of aryl diamidines have been proposed.[10]

Recently, amidino-substituted-diphenyl-furans have been demonstrated diverse pharmacological activities. On one hand they show significant antiproliferative activities against various tumor cell lines. On the other hand, they display useful antimicrobial effects.[2]

Some carbamate analogues of 2,5-*bis*-(4-amidino-phenyl)furan are synthesized and evaluated as prodrugs against *Pneumocystis carini* pneumonia (PCP), (which is a leading cause of mortality and morbidity in patients suffering from AIDS) (acquired immune deficiency syndrome), in the immuno suppressed rat model.[4] It was shown that they were more active and less toxic than pentamidine for which was shown to inhibit DNA topoisimerases from *P. carini*.[11] Recently, 2-buten bridged diamidine analogues of pentamidine were synthesized and *in vitro* examined as novel agents to treat AIDS related infections against *P. carini*.[5]

RESULTS AND DISCUSSION

In continuation of our earlier work[12,13] we prepared in multistep synthesis the compound in title, for which we proposed its anti-HIV activity. In consideration with its structure it could serve as intercalator or groove binder of the DNA double helix.

In the first step of the reaction, it was prepared the mixture of the diacid dichlorides **2a**, **2b** and **2c** by heating overnight of *E*,*E*-1,4-phenylene-di-(2-ethenyl)-carboxylic acid with $SOCl_2$ in the presence of the catalytic amount of pyridine. Without the isolating of **2a** from **2b** and **2c**, to the mixture of diacid dichlorides was added equimolar amount of *n*-butylamine in CH_2Cl_2 and the mixture was allowed to stir at room temperature overnight. The mixture of amides **3a**, **3b**, and **3c** was separated by chromatography. The yields were as; **3a** 78%, **3b** 17% and **3c** 5%. In the next step of the reaction **3a** reacts with $SOCl_2$, and few drops of DMF in $CHCl_3$ and corresponding imidoyl chloride **4a** was isolated in the yield of the 95.2%. Without further purification **4a** was used in the next step of the reaction, saturating of **4a** in CH_2Cl_2 with dry ammonia gas at 0–5°C. The yield on the corresponding diamidine **5a** was 43.2%. In the last step of the reaction, free base of **5a** was converted into the salt by taking it up in the methanol saturated with HCl and stirring. The disalt **6a** was obtained in the yield of 8.5% and was characterized by elemental analysis, ^{1}H NMR spectra, and ^{13}C NMR spectra.

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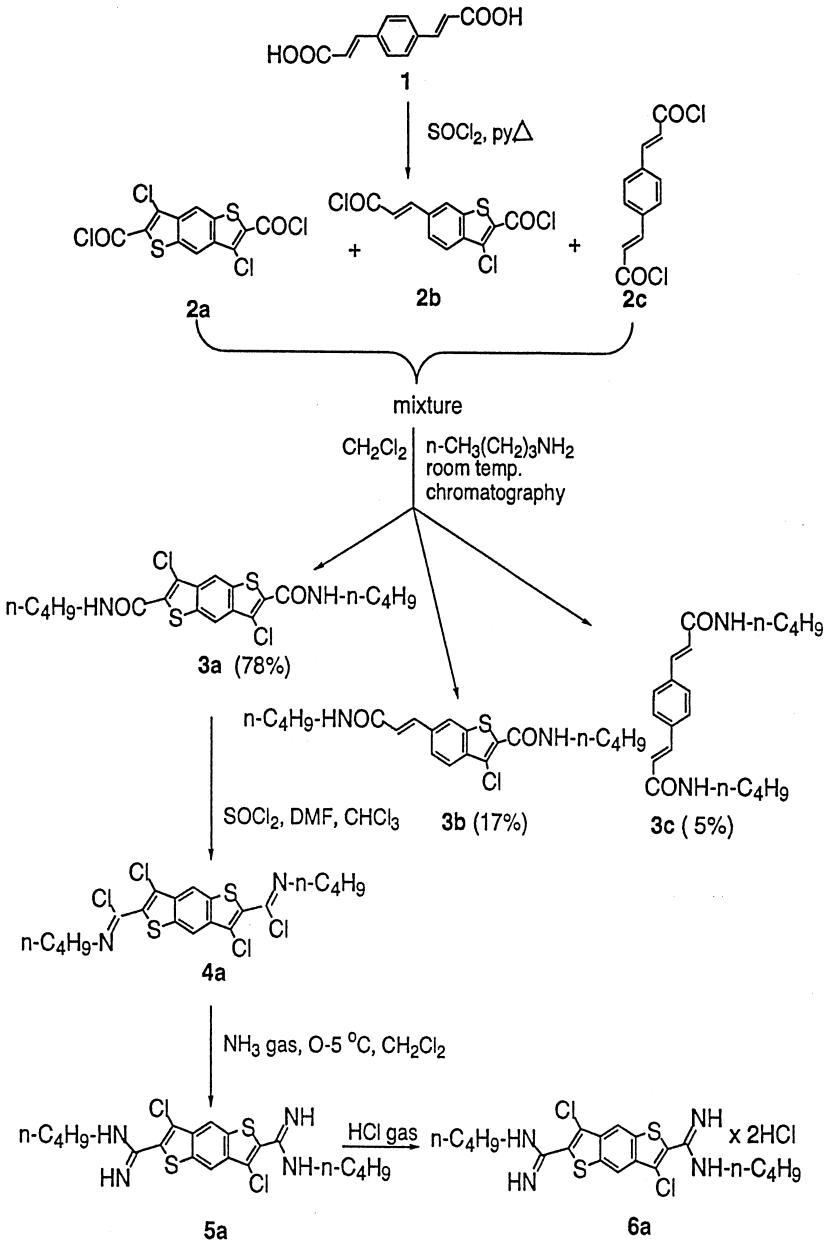

Scheme.

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EXPERIMENTAL

Mps were determined on a Kofler hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 257 spectrophotometer in KBr discs ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 (300 MHz) with TMS as internal standard in $CDCl_3$ or DMSO-d_6.

Synthesis of 3,7-Dichloro[1,2-b:4,5-b′]dithiophene-2,6-dicarbonylchloride 2a/3-Chloro-6-(2-chlorocarbonyl-ethenyl)benzo[b]thieno-2-carbonylchloride 2b and 1,4-Phenylene-di-(2-ethenyl)carboxylic Acid Dicarbonylchloride 2c

The mixture of the compounds **2a**, **2b** and **2c** was prepared by the dropwise addition of thionyl chloride (30 mL, 0.42 mol) into the stirred mixture of *E*,*E*-1,4-phenylene-di-(2-ethenyl)carboxylic acid **1** (10.06 g, 0.046 mol) and pyridine (1 mL) at room temperature. The reaction mixture was heated for 8 h at 140°C. To the reaction mixture was added 80 mL of toluene to remove successfully the excess of the thionye chloride under reduced pressure. The remaining material was extracted with chloroform (100 mL) to remove soluble by products. The obtained yellow crystals 8.47 g are the mixture of the products **2a**, **2b** and **2c**. Without further separation, the mixture was used in the next step of the reaction.

Synthesis of 3,7-Dichloro[1,2-b:4,5-b′]dithiophene-2,6-di-(*n*-butyl)carboxamide 3a/3-Chloro-6-(2-*n*-butylcarbamoyl-ethenyl)-benzo[b]thieno-2-(*n*-butyl)carboxamide 3b and 1,4-Phenylene-di-(2-ethenyl)carboxylic Acid Di-(*n*-butyl)carboxamide 3c

To the suspension of the mixture of **2a**, **2b** and **2c** (2.00 g, 0.005 mol) in dry dichloromethane was added *n*-butylamine (2.00 mL, 0.020 mol), and stirred at room temperature 22 h. Excess of *n*-butylamine and solvent was removed under reduced pressure and water was added. The obtained solid was filtered off, washed with 10% HCl, than with 10% $NaHCO_3$. After drying the solid, which was the mixture of the products **3a**, **3b** and **3c** was chromatographed on the silica gel column with the

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dichloromethane : methanol (40:1). First was eluated **3a**. The yield of the white crystals of **3a** was 0.843 g (78.0%) mp 219–223°C. IR (cm^{-1}) (KBr): 3721–3380 (NH), 2958–2864 (CH_2), 1644 (CONH). ^{1}H NMR ($CDCl_3$), δ: 7.80 (s, 2H, NH), 7.17 (s, 2H, $H_{arom.}$), 3.55 (AB, $J_1 = 6.67$, $J_2 = 6.41$ Hz, 4H, CH_2), 1.61–1.73 (m, 4H, CH_2), 1.38–1.56 (m, 4H, CH_2), 1.00 (t, J = 7.43 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 160.25, 136.01, 133.90, 39.90, 31.26 ppm. (Found: C, 52.20; H, 4.56; N, 6.33, $C_{20}H_{22}Cl_2N_2O_2S_2$, requires C, 52.51; H, 4.85; N, 6.12%).

The yield of the white crystals of **3b** was 0.184 g (17%) mp 224–226°C. IR (cm^{-1}) (KBr): 3295 (NH), 2958–2872 (CH_2), 1652 (CONH), 1632 (C=C). ^{1}H NMR ($CDCl_3$), δ: 7.91 (s, 1H, $H_{arom.}$), 7.80 (d, J = 8.47 Hz, 1H, $H_{arom.}$), 7.71 (d, J = 15.38 Hz, $H_{ethen.}$), 7.59 (d, J = 8.46 Hz, $H_{arom.}$), 7.14 (s, 1H, NH), 6.52 (d, J = 15.38 Hz, 1H, $H_{ethen.}$), 5.87 (s, 1H, NH), 3.52 (AB $J_1 = 6.93$, $J_2 = 6.67$ Hz, 2H, CH_2), 3.42 (AB $J_1 = 6.92$, $J_2 = 6.67$ Hz, 2H, CH_2), 1.72–1.53 (m, 4H, CH_2), 1.50–1.37 (m, 4H, CH_2), 1.01–0.93 (m, 6H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 165.40, 160.72, 138.42, 137.96, 137.34, 135.24, 134.62, 125.27, 124.78, 124.00, 123.75, 39.26, 32.09, 31.84, 20.48, 20.44, 14.54 ppm. (Found: C, 60.92; H, 6.47; N, 7.00, $C_{20}H_{25}ClN_2O_2S$, requires C, 61.13; H, 6.41; N, 7.13%). The last was elueted **3c** in the yield of 0.054 g (5%) mp 285–287°C. IR (cm^{-1}) (KBr): 3290 (NH), 2959–2871 (CH_2), 1651 (CONH), 1619 (C=C). ^{1}H NMR (DMSO-d_6), δ: 8.13 (s, 2H, NH), 7.60 (s, 4H, $H_{arom.}$), 7.42 (d, J = 15.79 Hz, 2H, $H_{ethen.}$), 6.67 (d, J = 15.77 Hz, 2H, $H_{ethen.}$), 3.20 (AB, $J_1 = 6.42$, $J_2 = 6.83$ Hz, 4H, CH_2), 1.49–1.41 (m, 4H, CH_2), 1.37–1.29 (m, 4H, CH_2), 0.91 (t, J = 7.22 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 164.79, 137.74, 135.99, 128.12, 123.09, 31.35, 19.74, 3.79 ppm. (Found: C, 73.27; H, 8.32; N, 8.27, $C_{20}H_{28}N_2O_2$, requires C, 73.14; H, 8.59; N, 8.53%).

Synthesis of 3,7-Dichloro[1,2-b:4,5-b′]dithiophene-2,6-di-(*n*-butyl)-imidoylchloride 4a

To a suspension of **3a** (1.12 g, 0.0024 mol) in dry $CHCl_3$ (40 mL) and thionylchloride (1 mL, 0.014 mol) was added a few drops of *N*,*N*-dimethylformamide and the mixture was allowed to reflux for 30 h. The solution was filtered hot and the filtrate was distilled under reduced pressure and the solid trituated with dry hexane (40 mL) on the reflux 30 min. The solution was left on ice 24 h, and the crystals filtered off and dried under vacuum at 40°C to yield 1.13 g (95.2%) yellow crystals of di-imidoyl chloride which was used directly in the next step without further characterization.

Synthesis of 3,7-Dichloro[1,2-b:4,5-b′]dithiophene-2,6-di-(*n*-butyl)amidine 5a

The solution of di-imidoyl chloride **4a** (1.5 g, 0.003 mol) in dry CH_2Cl_2 (45 mL) was saturated with dry ammonia at 0–5°C. The mixture was stirred at room temperature for 24 h and the solvent was removed under reduced pressure. The residue was treated with ice water and the pH of the slurry was adjusted to a value of 10 by adding 2 M NaOH. The resulting solid was filtered, washed with water and dried under vacuum. The obtained orange crystals of the base were recrystallized from CH_2Cl_2 : dioxane (1:1). The yield was 0.5 g (43.2%) mp 199–202°C. IR (cm^{-1}) (KBr): 3417 (NH), 2959–2872 (CH), 1668 (C=N). ^{1}H NMR (DMSO-d_6), δ: 7.84 (s, 2H, $H_{arom.}$), 7.00–6.25 (m, 4H, NH), 3.15 (AB, $J_1 = 6.89$, $J_2 = 6.67$ Hz, 4H, CH_2), 1.61–1.54 (m, 4H, CH_2), 1.47–1.37 (m, 4H, CH_2), 0.95 (t, J = 7.27 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 150.07, 135.52, 135.04, 130.18, 119.80, 117.13, 32.30, 20.31, 14.03 ppm. (Found: C, 52.29; H, 5.03; N, 12.05, $C_{20}H_{24}Cl_2N_4S_2$, requires, C, 52.74; H, 5.31; N, 12.30%).

Synthesis of 3,7-Dichloro[1,2-b:4,5-b′]dithiophene-2,6-di-(*n*-butyl)amidine Dihydrochloride 6a

The free base **5a** was converted into the salt by dissolving 0.67 g (0.0015 mol) in absolute methanol (60 mL). Dry HCl gas was bubbled through the solution at 0–5°C for 1 h. The solution was stirred at room temperature for 24 h. After reducing the solvent volume (1/3) under reduced pressure, addition of dry ether (200 mL) caused precipitation of the pale yellow salt, which was filtered, washed with ether, dissolved once more in methanol and precipitated with ether, crystals filtered off and dried under vacuum to yield 0.46 g (58.5%) dihydrochloride **6a** mp 223–228°C. IR (cm^{-1}) (KBr): 3417 (NH), 2959–2872 (CH), 1668 (C=N). ^{1}H NMR (DMSO-d_6), δ: 10.60–9.94 (m, 4H, NH), 8.20 (s, 2H, $H_{arom.}$), 1.72–1.62 (m, 4H, CH_2), 1.53–1.38 (m, 4H, CH_2), 0.95 (t, J = 7.29 Hz, 6H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 155.26, 135.10, 131.61, 124.45, 121.81, 43.34, 29.36, 19.59, 13.70 (Found: C, 45.013; H, 4.59; N, 10.37, $C_{20}H_{26}Cl_4N_4S_2$, requires C, 45.46; H, 4.96, N, 10.60%).

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