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SYNTHESIS OF 6-PHENYLTHIOBENZO[b]THIOPHENES

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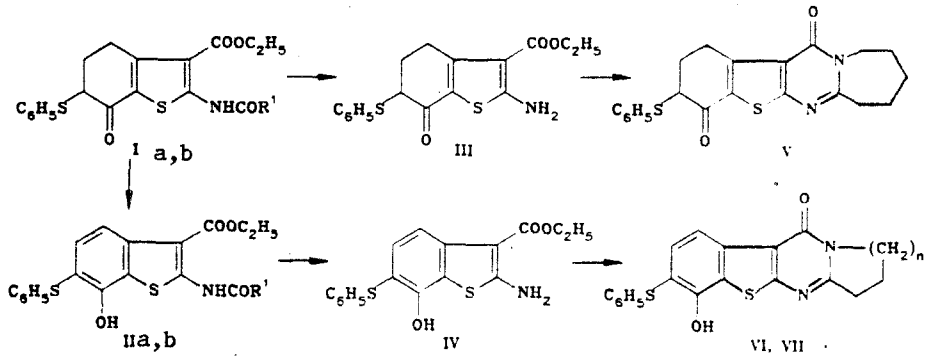
A method of synthesizing 2-acetylamino-7-hydroxy-6-phenylthio-3-carbethoxybenzo[b]thiophenes from 6-phenylthio-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes has been developed. A method is also proposed for synthesis of 7-phenylthiobenzothieno[2,3-d]pyrimidines.

In a number of examples the introduction of an alkylthio or arylthio group into bioactive substances can lead to an important change in their biological activity [1-4].

In continuation of our development of methods for synthesis of polyfunctional thiophenes and benzothiophenes having biological (in particular antiviral) activity [5], we have prepared 6-phenylthiobenzothiophenes. In [6] there was reported a synthesis of 6-bromo-7-hydroxybenzo[b]thiophenes by dehydrobromination of 6,6-dibromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes and the possibility of using the method for making substituted 6-phenylthiobenzo[b]thiophenes was also examined. Isolation of the intermediate 6-bromo-6-phenylthio-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes was not achieved due to spontaneous dehydrobromination to the 7-hydroxy-6-phenylthiobenzothiophenes IIa, b. The structures of the prepared compounds were proved by PMR and IR spectroscopy. For IIa the signals of the two 4-H and 5-H aromatic protons appeared at 7.42 and 7.80 ppm as doublets and the IR spectrum showed a phenolic hydroxyl group absorption band at 3400 cm^{-1}.



I, IIa $R^1=CH_3$, b $R^1=C_2H_5$; VI $n=1$, VII $n=3$

Thienopyrimidines as thiophene isosteres of quinazolines have been widely used as key compounds for synthesizing polyfunctional compounds with a broad spectrum of biological activity [8, 9]. In this connection, some previously unknown benzothienopyrimidines have been synthesized.

The acetyl groups of Ia and IIa were hydrolyzed using aqueous alcoholic base to prepare bifunctional 2-amino-3-carbethoxybenzo[b]thiophenes III and IV, which can be used for construction of the pyrimidine ring. The IR spectra of III and IV showed absorptions for the NH_2 group at 3240-3390 cm^{-1}.

Using a known method [9], the reaction of III and IV with lactams (pyrrolidone and caprolactam) in the presence of phosphorus oxychloride gave the 4,8-dioxo-7-phenylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine V and the 8-hydroxy-4-oxo-7-phenylthiobenzothieno[2,3-d]pyrimidines VI and VII (Table 1).

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TABLE 1. Parameters for Compounds I-VII

Compound	Empirical formula	mp, °C (solvent)	IR spectrum, cm^{-1}	M^+ found	M calc.	Yield, %
I b	$C_{20}H_{21}NO_4S_2$	98...99(alcohol)				95
IIa*	$C_{19}H_{17}NO_4S_2$	183...184 (alcohol-dioxane, 3:1)	1655, 1680 (CO); 3180 (NH); 3400 (OH)	387	387	71,4
IIb	$C_{20}H_{19}NO_4S_2$	155...156 (alcohol-dioxane)				50,3
III	$C_{17}H_{17}NO_3S_2$	142...143,5(alcohol)	1630, 1660 (CO); 3240, 3360 (NH_2)	347	347	82,7
IV	$C_{17}H_{15}NO_3S_2$	158...159 (benzene-hexane 1:1)	1670 (CO); 3280, 3990 (NH_2)	345	345	53,9
V	$C_{21}H_{20}N_2O_2S_2$	162...163 (alcohol-dioxane, 10:1)	1660, 1680 (CO)	396	396	62,6
VI	$C_{19}H_{14}N_2O_2S_2$	249...250,5 (alcohol)	1700 (CO); 3440 (OH)	366	366	54,7
VII	$C_{21}H_{18}N_2O_2S_2$	213...214 (alcohol)	1660 (CO); 3440 (OH)	394	394	50,8

*PMR spectrum (DMSO): 7.80, 7.42 (dd, 4-H, 5-H); 1.41, 4.43 (tq, $COOCH_2CH_3$); 2.34 (s, $NHCOCH_3$); 7.1 ppm (m, C_6H_5).

The structures of V-VII were confirmed by IR spectroscopy. Absorption bands for starting material (III, IV) amino groups were absent in the benzothieno[2,3-d]pyrimidines V-VII. Bands for CO groups appear at 1660, 1680 (V), 1700 (VI), and 1660 cm^{-1} (VII). The IR spectra of VI and VII showed OH group absorption at 3440 cm^{-1}.

EXPERIMENTAL

PMR spectra were recorded on a Varian XL-200 spectrophotometer with TMS as internal standard and IR spectra on a Perkin—Elmer 599 instrument as Vaseline mulls. Molecular weights for the synthesized compounds were determined mass spectrometrically on a Varian MAT-112 with direct sample introduction into the ion source and an electron ionization energy of 70 eV.

Elemental analytical data for C, H, N, and S agreed with those calculated.

2-Propionylamino-3-carbethoxy-6-phenylthio-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (Ib) was obtained similarly to Ia [10] in 95% yield.

2-Acetylamino-7-hydroxy-6-phenylthio-3-carbethoxybenzo[b]thiophene (IIa, $C_{19}H_{17}NO_4S_2$). A solution of bromine (9.9 g, 55 mmole) in chloroform (50 ml) was added dropwise to a refluxing solution of Ia (19.5 g, 50 mmole) in chloroform (200 ml). The reaction mixture was refluxed for 1 h, cooled, washed with water, and the chloroform distilled off. The residue was recrystallized from alcohol—dioxane (3:1) to give thiophene IIa (13.85 g). Found: M^+ 387. Calculated: M 387.

2-Propionylamino-7-hydroxy-6-phenylthio-3-carbethoxybenzo[b]thiophene (IIb) was obtained similarly to IIa.

2-Amino-6-phenylthio-3-carbethoxy-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (III). A solution of sodium hydroxide (2.2 g, 55 mmole) in water (10 ml) was added to a suspension of Ia (16 g, 40 mmole) in alcohol (60 ml) and allowed to stand for 45 min at 20°C. The product was cooled and the precipitate filtered off, washed with alcohol, and dried to give III (11.8 g). Found: M^+ 347. Calculated: M 347.

2-Amino-7-hydroxy-6-phenylthio-3-carbethoxybenzo[b]thiophene (IV). A solution of sodium hydroxide (2.2 g, 55 mmole) in water (25 ml) was added to a suspension of IIa (5 g, 13 mmole) in alcohol (25 ml) at 40°C. The reaction mixture was heated to 55-60°C and held at 20°C for 1.5 h, and then diluted with water and acidified with acetic acid. The precipitate was filtered off and recrystallized from aqueous alcohol to give IV (2.4 g). Found: M^+ 345. Calculated: M 345.

7-Phenylthio-2,3-pentamethylene-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (V). Phosphorous oxychloride (2 ml, 220 mmole) was added to a mixture of III (7 g, 20 mmole), caprolactam (2.5 g, 22 mmole), and dry dioxane (50 ml). The mixture was refluxed for 1 h, poured into water, and saturated aqueous sodium acetate (50 ml) added. The product was stirred for 4 h to give an oily precipitate and the aqueous layer decanted off. The residue was treated with alcohol, heated for 5 min, and the precipitate filtered off to give V (5 g). Found: M^+ 396. Calculated: M 396.

8-Hydroxy-7-phenylthio-2,3-trimethylene-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (VI). Pyrrolidone (0.94 g, 11 mmole) and phosphorus oxychloride (1 ml, 11 mmole) were added to a solution of IV (3.45 g, 10 mmole) in dry dichloroethane (30 ml) and the reaction mixture was heated for 1.5 h. It was cooled, saturated aqueous sodium acetate solution (30 ml) added, and refluxed for 20 min. After cooling, the organic layer was separated, washed with water, and the dichloroethane distilled off. The residue was treated with alcohol, heated to reflux, cooled, and the precipitate filtered off to give VI (2 g). Found: M^+ 366. Calculated: M 366.

8-Hydroxy-7-phenylthio-2,3-pentamethylene-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (VII) was prepared similarly to VI. Found: M^+ 394. Calculated: M 394.

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SYNTHESIS AND SOME REACTIONS OF 4-CARBOXY-2-THIAZOLYLHYDRAZONES

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The condensation of thiosemicarbazones with bromopyruvic acid gives thiazolylhydrazone hydrobromides, which were converted to the free bases. The question of the site of protonation was studied by PMR spectroscopy. The possibility of self-protonation in 4-carboxythiazolylhydrazone crystals is not excluded. The thiazolylhydrazones are brominated in the 5 position. Both cyclization to thiazolyltriazoles and the Chetteueya—Walker reaction are realized in the case of oxidation with lead tetraacetate.

The most thoroughly studied method for obtaining 2-thiazolylhydrazones is the Hantzsch reaction — the reaction of α-halo carbonyl compounds with thiosemicarbazones (TSC) [1, Part 1, pp. 66-80, 249-257; Part 2, pp. 17-20]. Changes in the structure of the α-halo carbonyl compound and the TSC, as well as in the pH of the medium, may lead not only to thiazole derivatives but also to other heterocycles such as thiadiazines [2].

In the present research we used bromopyruvic acid as the halo carbonyl compound for the first time. One might have assumed that the carboxy group of the halo carbonyl compound would first protonate the TSC and thereby change the centers of attack in its molecule. However, this assumption was not confirmed, and the reaction of acid Ia with acetone TSC and the TSC of a series (IIa-f) of aldehydes gave 4-carboxythiazolylhydrazone hydrobromides IIIa-f, which were converted to the corresponding thiazolylhydrazones IVa-e (Table 1). An analytically pure sample of salt IIIe was not isolated but was converted immediately to hydrazone IVe.

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