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SYNTHESIS OF SUBSTITUTED HYDROXYSPIRO([1]BENZOPYRAN-2,4'(1'H)-PYRIMIDINE)-2'(3'H)THIONES AND HYDROXYSPIRO-([1]BENZOPYRAN-2,4'(1'H)-PYRIMIDIN)-2'(3'H)ONES

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We have developed a novel regioselective method for synthesis of substituted spiro([1]benzopyran-2,4'-(1'H)pyrimidine)-2'-(3'H)thiones and spiro([1]benzopyran-2,4'-(1'H)pyrimidin)-2'-(3'H)ones having one or two hydroxyl groups on the benzene ring.

Keywords: 5-methylresorcinol, pyrogallol, resorcinol, spiro([1]-benzopyran-2,4'(1'H)pyrimidin)-2'-(3'H)one, spiro([1]-benzopyran-2,4'(1'H)pyrimidine)-2'-(3'H)thione, styryldihydropyrimidinethione, 4-chlororesorcinol.

When β-(dialkylaminoethylidene)hexahydropyrimidine-2-thiones or β-(dialkylaminoethylidene)-hexahydropyrimidin-2-ones are fused with 5 to 10-fold excess of 2,6-dimethylphenol, spiro([1]benzopyran-2,4'-(1'H)pyrimidine)-2'-(3'H)thiones or spiro([1]benzopyran-2,4'-(1'H)pyrimidin)-2'-(3'H)ones are formed in low yields [1-7]. However, there are no data in the literature on reactions between phenols and styryldihydropyrimidinethiones containing more than one hydroxyl group. At the same time, compounds in the chroman series with a hydroxyl group are of interest as potential antioxidants [8] also having other useful properties [9]. The objective of this work was to study reactions of styryl-substituted pyrimidinethiones with dihydroxybenzenes and trihydroxybenzenes.

Reaction of styryldihydropyrimidinethiones **1** with dihydroxybenzenes and trihydroxybenzenes was carried out in the presence of a catalyst: *p*-toluenesulfonic acid monohydrate [10]. In the reaction of styrylpyrimidinethiones **1** with resorcinol, the spiro compounds **2a-c** are formed. With substituted resorcinols 5-methylresorcinol and 4-chlororesorcinol, the analogous products **2d** and **2e,f** respectively are formed, and with pyrogallol the compound **2g** is formed. We found that compound **1** reacts most stereoselectively with resorcinol and pyrogallol, so we studied the structure of products **2a,g** in more detail. Furthermore, by oxidizing the thioxo group of compounds **2a,e** with hydrogen peroxide, their oxo analogs **2h,i** were obtained and characterized (Tables 1-3).

In the IR spectra of spiro compounds **2**, there are no absorption bands for the double bond in the pyrimidine ring at 1700-1630 cm^{-1}; and signals are present (although not always distinct) at 3400-3250 cm^{-1} and 1000-900 cm^{-1}, indicating the presence of a hydroxyl group in those compounds (Table 1).

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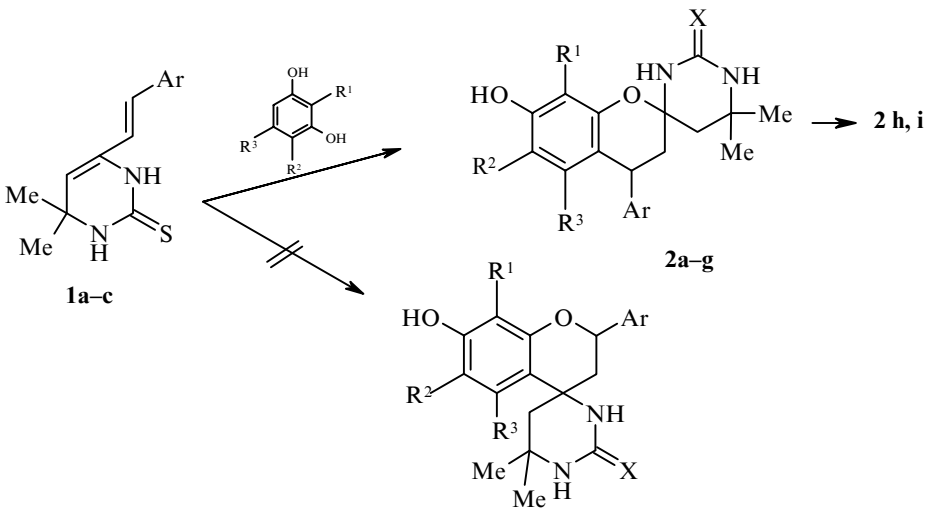

1 a Ar = Ph, **b** Ar = 2-ClC_6H_4, **c** Ar = 4-$MeOC_6H_4$; **2 a** X = S, Ar = Ph, $R^1 = R^2 = R^3 = H$; **b** X = S, Ar = 2-ClC_6H_4, $R^1 = R^2 = R^3 = H$; **c** X = S, Ar = 4-$MeOC_6H_4$, $R^1 = R^2 = R^3 = H$; **d** X = S, Ar = Ph, $R^1 = R^3 = H$, $R^2 = Me$; **e** X = S, Ar = Ph, $R^1 = R^2 = H$, $R^3 = Cl$; **f** X = S, Ar = 2-ClC_6H_4, $R^1 = R^2 = H$, $R^3 = Cl$; **g** X = S, Ar = Ph, $R^1 = OH$, $R^2 = R^3 = H$; **h** X = O, Ar = Ph, $R^1 = R^2 = R^3 = H$; **i** X = O, Ar = Ph, $R^1 = R^2 = H$, $R^3 = Cl$

Based on ^1H NMR spectroscopy data, we established that compounds **2** are generally formed as a mixture of two diastereomers in the ratio 1:10 to 1:25 (for compound **2d**, the isomer ratio is 14:8); the diastereomer ratio was determined as the ratio of the integrated areas for H_e-4/H_a-4. We must note that the isomer ratio is not always preserved upon chemical conversions of compounds **2** as, for example, upon conversion of thione **2e** to the oxo compound **2i** (Table 2).

TABLE 1. Characteristics of Synthesized Compounds **2**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N	S			
2a	$C_{20}H_{22}N_2O_2S$	67.63 / 67.77	6.30 / 6.26	7.85 / 7.90	9.01 / 9.05	248-250	3340, 3280, 1612, 1597, 976, 912	86
2b	$C_{20}H_{21}ClN_2O_2S$	61.73 / 61.77	5.50 / 5.44	7.21 / 7.20	8.21 / 8.24	228-230	3400, 3216, 1616, 1592, 976, 900	82
2c	$C_{21}H_{24}N_2O_3S$	65.51 / 65.60	6.31 / 6.29	7.26 / 7.29	8.31 / 8.34	238-240	3400, 3185, 1608, 924	58
2d	$C_{21}H_{24}N_2O_2S$	68.43 / 68.45	6.57 / 6.56	7.59 / 7.60	8.69 / 8.70	246-248	3400, 3224, 1616, 1590, 980, 900	62
2e	$C_{20}H_{21}ClN_2O_2S$	61.73 / 61.77	5.50 / 5.44	7.21 / 7.20	8.21 / 8.24	228-230	3280, 3220, 1618, 993, 916	72
2f	$C_{20}H_{20}Cl_2N_2O_2S$	56.47 / 56.74	4.79 / 4.76	6.59 / 6.62	7.55 / 7.57	230-232	3400, 3220, 1616, 1583, 985, 912	76
2g	$C_{20}H_{22}N_2O_3S$	64.85 / 64.84	5.98 / 5.99	7.54 / 7.56	8.64 / 8.65	228-230	3360, 3290, 1611, 1590, 962, 942	62
2h	$C_{20}H_{22}N_2O_3$	70.87 / 70.99	6.57 / 6.55	8.26 / 8.28	—	243-246	3340, 3230, 1610, 1580, 972, 950	88
2i	$C_{20}H_{21}ClN_2O_3$	64.33 / 64.43	5.70 / 5.68	7.52 / 7.51	—	269-270	3390, 1640, 1608, 1580, 910	90

TABLE 2. ^{1}H NMR Spectral Characteristics of Synthesized Compounds **2**

Compound	Chemical shift, δ, ppm (spin–spin coupling constant, *J*, Hz)	Ratio of diastereomers
1	2	3
2a	9.08 (1H, s, OH); 8.65 (1H, s, NH); 8.48 (1H, s, NH); 7.4-7.1 (5H, m, H_{Ar}); 6.4 (1H, d, *J* = 8.0, H-5); 6.2 (1H, d, *J* = 8.0, H-6); 6.15(1H, s, 8-H); 4.09 (1H, dd, J_1 = 13.0, J_2 = 6.5, H-4); 2.36 (1H, dd, J_1 =13.5, J_2 = 13.0, H_e-3); 2.19 (1H, d, *J* = 13.8, H_e-5'); 1.98 (1H, dd., J_1 = 13.0, J_2 = 6.5, H_a-3); 1.73 (1H, d, *J* = 13.8, H_a-5'); 1.34 (3H, s, CH_3); 1.25 (3H, s, CH_3)	15:1
2b	9.76 (1H, s, OH); 8.53 (1H, s, NH); 8.48 (1H, s, NH); 7.4-7.1 (5H, m, H_{Ar}); 6.48 (1H, s, H-8); 6.36 (1H, d, *J* = 8.2, H-6); 4.09 (1H, dd, J_1 = 12.8, J_2 = 6.0, H-4); 2.38 (1H, dd, J_1 = 12.8, J_2 = 13.3, H_e-3); 2.19 (1H, d, *J* = 13.3, H_e-5'); 1.98 (1H, dd, J_1 = 12.8, J_2 = 6.0, H_a-3); 1.63 (1H, d, *J* = 13.3, H_a-5'); 1.33 (3H, s, CH_3); 1.26 (3H, s, CH_3)	—*
2c	8.95 (1H, s, OH); 8.60 (1H, s, NH); 8.4 (1H, s, NH); 7.1 (2H, d, *J* = 8.5, H_{Ar}); 6.8 (2H, d, *J* = 8.5, H_{Ar}); 6.4 (1H, d, *J* = 8.5, H-5); 6.3 (2H, m, H-6, H-8); 4.0 (1H, dd, J_1 = 13.0, J_2 = 6.5, H-4); 3.75 (3H, s, OCH_3); 2.4 (1H, dd, J_1 = 13.0, J_2 = 13.5, H_e-3); 2.15 (1H, d, *J* = 14.0, H_e-5'); 1.93 (1H, dd, J_1 = 13.0, J_2 = 6.5, H_a-3); 1.65 (1H, d, *J* = 14.0, H_a-5'); 1.35 (3H, s, CH_3); 1.25 (3H, s, CH_3) **Minor diastereomer**: 8.53 (1H, s, OH); 8.05 (1H, s, NH); 7.95 (1H, s, N–H); 6.9 (2H, d, *J* = 8.5, H_{Ar}); 6.5 (2H, d, *J* = 8.5, H_{Ar}); 6.1 (3H, m, H_{Ar}); 4.5 (1H, dd, J_1 = 10.0, J_2 = 7.3, H-4); 3.75 (3H, s, OCH_3); 2.4 (1H, dd, J_1 = 10.0, J_2 = 7.3, H-3); 2.40–2.15 (3H, m, CH); 1.5 (3H, s, CH_3); 1.25 (3H, s, CH_3)	3:1
2d	9.00 (1H, s, OH); 8.45 (1H, s, NH); 8.41 (1H, s, NH); 7.3-7.0 (5H, m, H_{Ar}); 6.09 (1H, d, *J* = 1.8, H-6); 6.02 (1H, d, *J* = 1.8, H-8); 4.10 (1H, dd, J_1 = 9.6, J_2 = 9.5, H-4); 2.55 (1H, d, *J* = 14.0, H_e-5'); 2.18 (2H, m, H-3, H-5'); 1.6 (3H, s, CH_3); 1.28 (3H, s, CH_3); 1.2 (3H, s, CH_3) **Minor diastereomer**: 8.99 (1H, s, OH); 8.41 (1H, s, NH); 8.33 (1H, s, NH); 7.3-7.0 (5H, m, H_{Ar}); 6.20 (1H, d, *J* = 1.8, H-6); 6.04 (1H, d, *J* = 1.8, H-6); 4.41 (1H, dd, J_1 = 5.9, J_2 = 6.1, H-4); 2.55 (1H, d, *J* = 14.0, H_e-5'); 2.18 (2H, m, H-3); 1.79 (3H, s, CH_3); 1.38 (3H, s, CH_3); 1.05 (3H, s, CH_3)	14:8
2e	8.71 (1H, s, OH); 8.67 (1H, s, OH); 8.48 (1H, s, NH); 7.94 (1H, s, NH); 7.32 (2H, m, H_{Ar}); 7.23 (1H, m, H_{Ar}); 7.14 (2H, d, *J* = 8.0, H_{Ar}); 6.23 (1H, d, *J* = 8.5, H-5); 5.87 (1H, d, *J* = 8.5, H-6); 4.12 (1H, dd, J_1 = 12.5, J_2 = 5.9, H-4); 2.34 (1H, dd, J_1 = 12.5, J_2 = 13.2, H_e-3); 2.16 (1H, d, *J* = 14.0, H-3'); 1.96 (1H, dd, J_1 = 13.2, J_2 = 5.9, H-3); 1.72 (1H, d, *J* = 14.0, H-3'); 1.33 (3H, s, CH_3); 1.19 (3H, s, CH_3)	—*
2f	9.82 (1H, s, OH); 8.68 (1H, s, NH); 8.50 (1H, s, NH); 7.44 (1H, m, H_{Ar}); 7.3 (2H, m, H_{Ar}); 7.1 (1H, m, H_{Ar}); 6.49 (1H, s, H-5); 6.38 (1H, s, H-8); 4.65 (1H, dd, J_1 = 13.0, J_2 = 6.2, H-4); 2.30 (1H, dd, J_1 = 13.0, J_2 = 13.3, H_e-3'); 2.22 (1H, d, *J* = 13.3, H_e-5'); 2.03 (1H, dd, J_1 = 13.0, J_2 = 6.2, H_a-3); 1.73 (1H, d, *J* = 13.3, H_a-5'); 1.38 (3H, s, CH_3); 1.27 (3H, s, CH_3)	15:1
2g	9.76 (1H, s, OH); 8.53 (1H, s, NH); 8.48 (1H, s, NH); 7.4-7.1 (5H, m, H_{Ar}); 6.48 (1H, s, H-5); 6.36 (1H, s, H-8); 4.09 (1H, dd, J_1 = 13.0, J_2 = 6.0, H-4); 2.38 (1H, dd, J_1 = 13.0, J_2 = 13.2, H-3); 2.19 (1H, d, *J* = 14.4, H_e-5'); 1.98 (1H, dd, J_1 = 13.0, J_2 = 6.0, H_a-3); 1.63 (1H, d, *J* = 14.4, H_a-5'); 1.33 (3H, s, CH_3); 1.26 (3H, s, CH_3)	20:1
2h	9.00 (1H, s, OH); 7.4–7.1 (6H, m, H_{Ar}, NH); 6.55 (1H, s, NH); 6.42 (1H, d, *J* = 8.3, H-5); 6.18 (1H, dd, J_1 = 8.3, J_2 = 1.7, H-6); 6.12 (1H, d, *J* = 1.7, H-8); 4.09 (1H, dd, J_1 = 13.2, J_2 = 6.6, H-4); 2.12 (1H, t, J_1 = 13.2, J_2 = 13.2, H-3); 2.10 (1H, d, *J* = 13.8, H_e-5'); 1.98 (1H, dd, J_1 = 13.2, J_2 = 6.6, H_a-3); 1.64 (1H, d, *J* = 13.8, H_a-5'); 1.34 (3H, s, CH_3); 1.18 (3H, s, CH_3) **Minor diastereomer**: 8.95 (1H, s, OH); 7.4-7.1 (6H, m, H_{Ar}, NH); 6.90 (1H, s, NH); 6.45 (1H, d, *J* =8.5, 5-H); 6.20 (1H, dd, J_1 = 8.5, J_2 = 1.5, H-6); 6.12 (1H, d, *J* = 1.5, H-8); 4.45 (1H, dd, J_1 = 10.5, J_2 = 7.15, H-4); 2.12 (1H, t, J_1 = 13.2, J_2 = 13.2, H-3); 2.10 (1H, d, *J* = 13.8, H_e-5'), 1,98 (1H, dd, J_1 = 13.2, J_2 = 6.6, H_a-3); 1.68 (1H, d, *J* = 13.8, H_a-5'); 1.52 (3H, s, CH_3); 1.20 (3H, s, CH_3)	13:1

* The mixture contains less than 3-4% of the minor diastereomer.

TABLE 2 (continued)

1	2	3
2i	9.78 (1H, s, OH); 7.4–7.1 (6H, m, H_{Ar}, NH); 7.0 (1H, s, NH); 6.48 (1H, s, H-5); 6.32 (1H, s, H-8); 4.55 (1H, dd, J_1 = 12.6, J_2 = 6.0, H-4); 2.12 (3H, m, H-3, H-5'); 1.68 (1H, d, J = 13.8, H_a-5'); 1.50 (3H, s, CH_3); 1.21 (3H, s, CH_3) **Minor diastereomer**: 9.78 (1H, s, OH); 7.4-7.1 (6H, m, H_{Ar}, NH); 7.0 (1H, s, NH); 6.48 (1H, s, H-5); 6.32 (1H, s, H-8); 4.55 (1H, dd, J_1 = 9.6, J_2 = 7.0, H-4); 2.12 (3H, m, H-3, H-5'); 1.68 (1H, d, J = 13.8, H_a-5'); 1.50 (3H, s, CH_3); 1.21 (3H, s, CH_3)	3:1

TABLE 3. ^{13}C NMR Spectral Characteristics of Compounds **2a,g**

Com-pound	Chemical shifts, δ, ppm.
2a	175.12 (C_q, $C_{(2')}$=S); 157.07 (C_q, $C_{(8)}$); 153.57 (C_q, $C_{(7)}$–O); 144.37 ($C_{(8)}$); 129.78, 128,53, 128.45, 128.31, 127.64, 126.57 ($6C_{Ph}$); 114.67 ($C_{(5)}$); 108.70 ($C_{(6)}$); 102.73 (C_q, $C_{(4)}$); 82.84 (C_q, $C_{(2)}$–O); 50.25 (2C, $C_{(4')}$, $C_{(4)}$); 41.07 (CH_2, $C_{(5')}$); 38.26 (CH_2, $C_{(3)}$); 30.40, 27.82 (CH_3)
2g	175.11 (C_q, $C_{(2')}$=S); 152.53 (C_q, $C_{(7)}$–O); 152.32 (C_q, $C_{(8)}$–O); 143.74 (C_q); 129.46 (C–H); 128.79 (2C–H); 128.36 (2C–H); 126.92 (C–H); 116.48 (C_q); 111.96 (C_q, $C_{(8)}$); 104.14 (C–H); 83.27 (C_q, $C_{(2)}$–O); 50.24 (C_q, $C_{(6')}$); 40.38 (CH_2, $C_{(5')}$); 38.84 (CH_2, $C_{(3)}$); 38.04 (CH, $C_{(4)}$); 30.33, 27.78 (CH_3)

The major spectral difference between the diastereomers involves the 0.4-0.6 ppm difference in the chemical shifts of the H-4 proton on the benzopyran ring, with a change in the spin–spin coupling constant. Thus for the dominant diastereomer, the signal from the H-4 proton at 4.0-4.1 ppm has the form of a doublet of doublets with spin–spin coupling constants J_1 within the range of 13.5-11.5 Hz and J_2 within the range of 6.0-6.5 Hz, while for the minor diastereomer the H-4 signal is shifted downfield (4.5-4.7 ppm) and degenerates into a triplet with spin–spin coupling constants J_1 = 9.0-10.5 Hz and J_2 = 7.0-7.5 Hz. Based on these data, we can hypothesize that the diastereomers differ in the orientation of the phenyl substituent: in the dominant diastereomer, the H-4 proton is located in the axial position, while the phenyl substituent is located in the equatorial position, which changes the conformation of the benzopyran moiety and affects the signals from the pyrimidine ring (0.1-0.3 ppm upfield shift relative to the minor diastereomer). An increase in the content of the diastereomer with the phenyl substituent in the axial position in compound **2d** is probably connected with the presence of a methyl group in the α-position relative to it.

In analogy with the previously studied reaction of pyrimidinethiones with resorcinol [10], we could hypothesize formation of 4,4'-spirochromans, but the spectral data show that 2,4'-spirochromans are formed exclusively. The structure of compounds **2a,g** was studied in detail by ^{13}C NMR spectroscopy using the DEPT method (Table 3). Analysis of the spectra showed that the carbon atom with chemical shift of 83 ppm is a quaternary carbon and can be assigned only to the C-2 atom of the chroman ring, and consequently compound **2a,g** has the 2,4'-spirochroman structure. Probably regioselective acid-catalyzed Michael addition of dihydroxybenzenes and trihydroxybenzenes occurs through a 1,3-diene system of styrylpyrimidinethiones, followed by cyclization to 2,4'-spirochroman, but the intermediates (noncyclic) were not isolated.

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS-88 spectrometer in the form of a suspension in vaseline oil in the range of 700 cm^{-1} to 4000 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in DMSO-d_6, internal standard HMDS (0.055 ppm).

The starting compounds **1** were synthesized by the familiar procedures in [3].

General Procedure for Synthesis of Substituted 7-Hydroxy-6',6'-dimethyl-3,4,5',6'-tetrahydrospiro([1]benzopyran-2,4'-(1'H)pyrimidine)-2'-(3'H)thiones (2a-g). Solution of styrylpyrimidinethione **1** (10 mmol), dihydroxybenzene or trihydroxybenzene (15 mmol), and *p*-toluenesulfonic acid monohydrate (1 mmol) in chloroform (20-30 ml) was boiled for 0.5-1 h until a precipitate formed, which was filtered off and washed with isopropanol and water. If the precipitate did not separate out, the reaction mass was evaporated down and the remaining oil was dissolved in hot isopropanol and cooled, and the precipitate was filtered off.

General Procedure for Synthesis of Substituted 7-Hydroxy-6',6'-dimethyl-3,4,5',6'-tetrahydrospiro([1]benzopyran-2,4'-(1'H)pyrimidine)-2'-(3'H)ones (2h-i). Compound **2a,e** (10 mmol) was added to a solution of potassium hydroxide (25 mmol) in ethanol (30 ml) with vigorous stirring, and then 30% hydrogen peroxide (50 mmol) was carefully added dropwise, making sure that the temperature of the mixture did not go above 40°C to 50°C. The reaction mixture was stirred at 40°C to 50°C for 1 h, cooled, and carefully acidified with 5% hydrochloric acid to pH 2-3. The residue was filtered off.

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