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Synthesis of substituted 2-(4′-hydroxyphenyl) benzothiazoles

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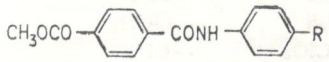
A number of new substituted benzothiazoles with the 4-hydroxyphenyl group in position 2 were prepared by oxidative cyclization of corresponding thioanilides. The influence of the substituent on the reaction of cyclization was also investigated.

Considering the wide application of the derivatives of benzothiazoles as chemotherapeutics and their technical significance in the ecomony, it was of interest to synthesize some benzothiazoles with the 4-hydroxyphenyl group in position 2. It is expected that they would show antipyretic, analgesic[1] and antitubercolostatic[2–6] actions.

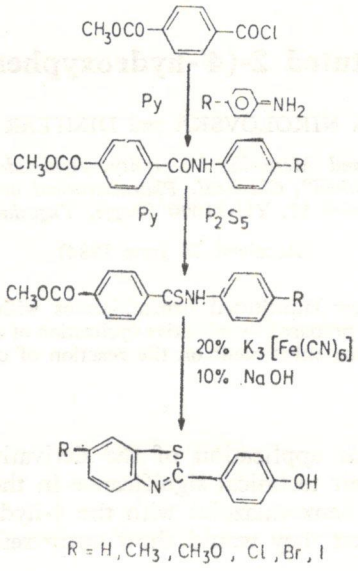
These studies illustrate the usefulness of Jacobson's reaction[7] as a general method for preparation of hydroxyphenyl-substituted benzothiazoles presented in Scheme 1. For this synthesis *p*-hydroxybenzoic acid is used as the starting substance and the conversion of its carboxyl group is done. The hydroxyl group which is rather active, is first blocked or protected from the influence of reactants used for obtaining its derivatives. For this purpose the hydroxyl group is acetylated with acetic anhydride whereby 4-acetoxybenzoic acid is obtained, which is converted by thionyl chloride into 4-acetoxybenzoyl chloride. From freshly prepared chloride in the reaction with 4-substituted primary aromatic amines in alkaline media, corresponding acetoxybenzanilides were obtained (Table I). The acetoxybenzanilides are identified by elemental microanalysis and IR spectra.

TABLE I. 4-Acetoxy-4'-substituted benzanilides.



Compd.	Formula	R	Yield, %	M.p., °C
I	$C_{16}H_{15}NO_3$	—CH_3	62	168—70
II	$C_{16}H_{15}NO_4$	—OCH_3	64	159—60
III	$C_{15}H_{12}NO_3Cl$	—Cl	84	203—5
IV	$C_{15}H_{12}NO_3Br$	—Br	75	210—12
V	$C_{15}H_{12}NO_3I$	—I	76	207—9

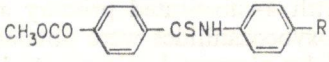
Acetoxybenzanilides were converted into corresponding acetoxythiobenzanilides by the method of Klingsberg and Papa[8], with P_4S_{10} in dry pyridine. Acet-



Sheme 1

oxythiobenzanilides (Table II) were identified by elemental microanalysis and IR spectra.

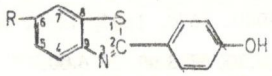
TABLE II. 4-Acetoxy-4'-substituted thiobenzanilides.



Compd.	Formula	R	Yield, %	M. p., °C
VI	$C_{16}H_{15}NO_2S$	$-CH_3$	68	148—50
VII	$C_{16}H_{15}NO_3S$	$-OCH_3$	65	164
VIII	$C_{15}H_{12}NSClO_2$	—Cl	78	162—4
IX	$C_{15}H_{12}NSBrO_2$	—Br	71	150—2
X	$C_{15}H_{12}NSIO_2$	—I	81	123—5

The acetoxy thiobenzanilides were converted by oxidative cyclization with potassium ferricyanide in alkaline medium into substituted 2-(4'-hydroxyphenyl)-benzothiazoles (Table III) indicating that during this reaction the acetyl group, used to block the hydroxyl group, is simultaneously removed.

TABLE III. Substituted 2-(4'-hydroxyphenyl)benzothiazoles.



Compd.	Formula	R	Yield, %	M. p., °C
XI	$C_{13}H_1NOS$	—H	64	214—16
XII	$C_{14}H_{11}NOS$	—CH_3	78	191
XIII	$C_{14}H_{11}NO_2S$	—OCH_3	76	200—2
XIV	$C_{13}H_8NSClO$	—Cl	63	193—5
XV	$C_{13}H_8NSBrO$	—Br	61	171
XVI	$C_{13}H_8NSIO$	—I	62	181—4

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer Model 398 using potassium bromide pellets.

4-Acetoxy-4'-substituted benzanilides (Table I) I, III, IV and V are known in the literature[9–12].

4-Acetoxy-4'-methoxybenzanilide (*II*): Freshly prepared 4-acetoxybenzoyl chloride[13] (8.8 g; 0.044 mol) was added dropwise to the cooled, stirred solution of 4-methoxyaniline (5.5 g; 0.044 mol) dissolved in pyridine (12 ml). After being lift for 0.5 h the reaction mixture was poured into ice water (300 ml) and the separated crystalline product was filtered off, washed and dried. The yield of the crude anilide was 7.1 g (64%). Recrystallization from ethanol yielded colourless crystals melting at 159—60°.

IR spectra (ν_{max}): 3330, 2960, 1750, 1640, 1500, 1380 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91.
Found: C 66.96, H 5.20, N 5.40 %.

4-Acetoxy-4'-substituted thiobenzanilides (Table II): VI, VIII, IX, and X are known in the literature[9–12].

4-Acetoxy-4'-methoxythiobenzanilide (*VII*): Phosphorus pentasulphide (2.00 g; 0.007 mol) was added to the hot solution of compound II (2.00 g; 0.007 mol) in dry pyridine (8 ml). The reaction mixture was heated to boiling for 45 min. In the course of heating the colour of the reaction mixture changed from yellow to red and then dark red, showing that the reaction was going in the desired direction. The warm reaction mixture was then poured into ice water (300 ml) and the separated dark yellow oil soon crystallized. After being left overnight at room temperature the yellow crystalline thiobenzanilide was filtered off, washed with water and dried. The yield was 1.3 g (65%). Recrystallization from ethanol gave yellow crystals melting at 164°.

IR spectra (ν_{max}): 3400, 2910, 1420, 1170, 880 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO_3S$: C 63.77, H 5.02, N 4.65.
Found: C 63.67, H 5.32, N 4.80%.

General procedure for preparation of substituted 2-(4'-hydroxyphenyl)benzothiazoles. To the warm solution (50°) of appropriate thioanilide in 10% aqueous sodium hydroxide, a warm 20% aqueous solution of potassium ferricyanide was added dropwise with concomitant stirring. The reaction mixture was heated at 50° for 30 min and left at room temperature for 16—20 h. The precipitate was filtered, rinsed with water and dried, and then was purified by dissolving in warm conc. hydrochloric acid, diluted with water and left overnight. The separated precipitate was filtered off, washed with water and dried. Finally the product was recrystallized from an appropriate solvent.

2-(4'-Hydroxyphenyl)benzothiazole (*XI*): From 0.3 g (0.013 mol) of 4-acetoxy-4'-thiobenzanilide[14] in 12 ml of 10% sodium hydroxide and 12 ml of 20% potassium ferricyanide at 50°. The

yield of the crude benzothiazole was 0.20 g (64%), m.p. 206—8°. After recrystallization from ethanol yellow crystals melting at 214—16° were obtained.

IR spectra (ν_{max}): 3450, 3000, 1670, 1605, 1450, 1010 cm^{-1}.

Anal. Calcd. for $C_{13}H_9NOS$: C 68.70, H 3.99, N 6.00.
Found: C 68.32, H 3.83, N 5.71%.

6-*Methyl*-2-(4'-*hydroxyphenyl*)*benzothiazole* (*XII*): From 0.6 g (0.0024 mol) of 4-acetoxy-4'--methylthiobenzanilide in 23 ml of 10% sodium hydroxide and 23 ml of 20% potassium ferricyanide at 50°. The yield of the crude benzothiazole was 0.42 g (78%), m.p. 181—6°. After recrystallization from ethanol yellow crystals were obtained melting at 191°.

IR spectra (ν_{max}): 3460, 3000—3100, 1670, 1600—1450, 1010 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NOS$: C 69.68, H 4.59, N 5.80%.
Found: C 69.31, H 4.42, N 5.32%.

6-*Methoxy*-2-(4'-*hydroxyphenyl*)*benzothiazole* (*XIII*): From 1 g (0.0048 mol) of 4-acetoxy-4'--methoxythiobenzanilide in 38 ml of 10% sodium hydroxide and 38 ml of 20% potassium ferricyanide at 50°. The yield of the crude benzothiazole was 0.76 g (76%), m.p. 191—196°. After recrystallization from ethanol yellow crystals melting at 200—2° were obtained.

IR spectra (ν_{max}) 3450, 3000, 1670, 1605—1430, 1015 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C 65.35, H 4.31, N 5.44%.
Found: C 65.04, H 4.31, N 5.32%.

2-(4'-*Hydroxyphenyl*)-6-*chlorobenzothiazole* (*XIV*): From 0.8 g (0.0026 mol) of 4-acetoxy-4'--chlorothiobenzanilide in 30 ml of 10% sodium hydroxide and 30 ml of 20% potassium ferricyanide at 50°. The yield of the crude benzothiazole was 0.504 g (63%), m.p. 184—8°. After recrystallization from ethanol yellow crystals melting at 193—5° were obtained.

IR spectra (ν_{max}) 3450, 2980, 1660, 1510—1450, 1010 cm^{-1}.

Anal. Calcd. for $C_{13}H_8ClNOS$: C 60.31, H 3.18, N 5.31%.
Found: C 60.74, H 3.58, N 4.83%.

6-*Bromo*-2-(4'-*hydroxyphenyl*)*benzothiazole* (*XV*): From 0.6 g (0.002 mol) of 4-acetoxy-4'-bromothiobenzanilide in 23 ml of 10% sodium hydroxyde and 23 ml of 20% potassium ferricyanide at 50°. The yield of the crude benzothiazole was 0.372 g (61%), m.p. 163—7°. After recrystallization from ethanol yellow crystals melting at 171° were obtained.

IR spectra (ν_{max}) 3450, 2980, 1660, 1550—1390, 1015 cm^{-1}.

Anal. Calcd. for $C_{13}H_8BrNOS$: C 50.69, H 2.83, N 4.49%.
Found: C 50.23, H 3.14, N 4.03%.

6-*Iodo*-2-(4'-*hydroxyphenyl*)*benzothiazole* (*XVI*): From 0.8 g (0.001 mol) of 4-acetoxy-4'-iodothiobenzanilide in 30 ml of 10% sodium hydroxide and 30 ml of 20% potassium ferricyanide at 50°. The yield of the crude benzothiazole was 0.50 g (62%), m.p. 173—7°. After recrystallization from ethanol yellow crystals melting at 182—4° were obtained.

IR spectra (ν_{max}) 3450, 2980, 1620, 1550—1450, 1010 cm^{-1}.

Anal. Calcd. for $C_{13}H_8INOS$: C 44.23, H 2.42, N 3.51%.
Found: C 43.88, H 2.87, N 3.37%.

ИЗВОД

СИНТЕЗА НА СУПСТИТУИРАНИ 2-(4'-ХИДРОКСИФЕНИЛ) БЕНЗОТИАЗОЛИ

МИРОСЛАВА НИКОЛОВСКА и ДИМИТАР ХРИСТОВ*

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Повеќе нови супституирани бензотиазоли со 4-хидроксифенил група во положба 2 со оксидативна циклизација на соодветни тиоанилиди се добиени во добар принос. Исто така испитувано е влијанието на супституентите врз реакција на циклизација.

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