

# Benzothiazole Compounds

## XLIII. Synthesis of Benzazoles with Heterocyclic Substituents and Their Condensation Reactions with Aldehydes

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Benzothiazole, benzoxazole, and benzimidazole derivatives substituted with a  $\gamma$ -lactone, coumarin or pyrazolone cycle have been synthesized. Condensation reactions of these derivatives with aromatic aldehydes were studied. The structure of the products was proved by IR and <sup>1</sup>H NMR spectra. The synthesized compounds are expected to have plant growth stimulating activity.

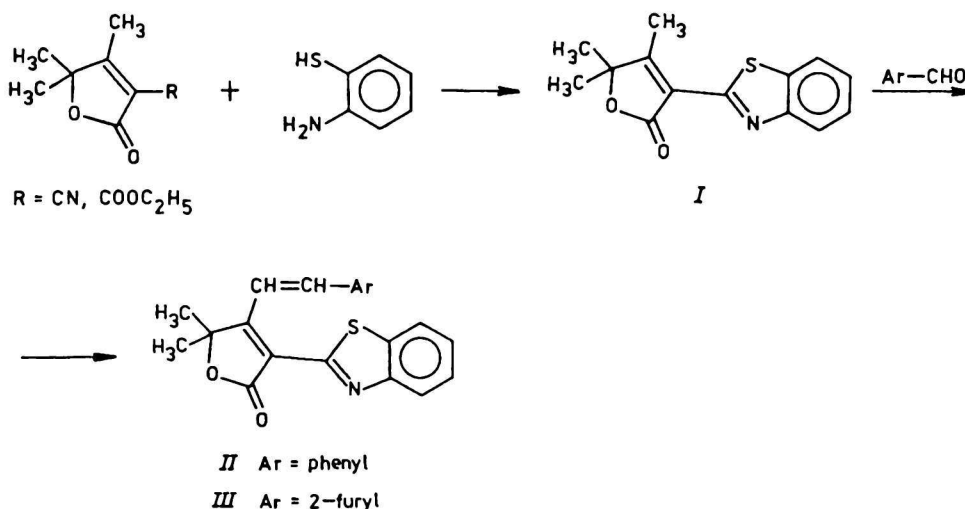
Among benzothiazole derivatives there are many with considerable biological effects [1, 2]. Compounds with an unsaturated  $\gamma$ - or  $\delta$ -lactone cycle and with another heterocycle at the same time are known for their biological activity, too [3—5]. For example, unsaturated  $\gamma$ -lactones with thiazolyl substituents have been found to stimulate germination, growth energy, mitotic activity, and chromosomal aberrations of root cells when tomato, onion, and carrot seeds were treated with the compounds before sowing [6].

Taking these facts into account we regarded as purposeful to prepare compounds with both lactone and benzothiazole system in their molecules. We used preparatively easily obtainable 3-cyano-4,5,5-trimethyl- $\Delta^3$ -butenolide [7] as starting unsaturated  $\gamma$ -lactone. The reaction was car-

ried out by heating this lactone with *o*-aminothiophenol at 200 °C for 2 h in the presence of polyphosphoric acid (Scheme 1). 3-(2-Benzothiazolyl)-4,5,5-trimethyl- $\Delta^3$ -butenolide (*I*) was obtained in high yield. The same product was formed if 3-ethoxycarbonyl-4,5,5-trimethyl- $\Delta^3$ -butenolide [8] was used as starting lactone.

In compound *I* there are conditions for relatively high acidity of hydrogen atoms of the methyl group in position 4. We carried out condensation reactions with benzaldehyde and 2-furancarbaldehyde in absolute methanol with NaOH. The condensation products were isolated with good yields (Table 1)

The structure of compounds *I—III* was confirmed by the analysis of IR (Table 2) and <sup>1</sup>H NMR spectra. The latter spectrum of 3-(2-benzothia-

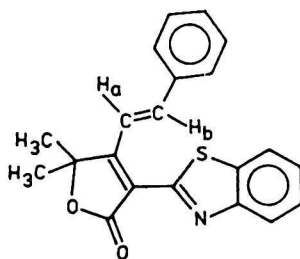


Scheme 1

**Table 1.** Characterization of the Compounds I—X

Compound	Formula	$M_r$	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$				Yield %	M.p. °C
			C	H	N	S		
I	$C_{14}H_{13}NO_2S$	259.35	64.83	5.06	5.40	12.32	87	162—163
			65.08	5.17	5.81	12.15		
II	$C_{21}H_{17}NO_2S$	347.46	72.59	4.94	4.03	9.23	79	174—175
			72.72	5.10	3.91	8.99		
III	$C_{19}H_{15}NO_3S$	337.42	67.63	4.49	4.15	9.50	76	201—202
			67.48	4.28	3.85	9.71		
IV	$C_{17}H_{11}NO_2S$	293.36	69.60	3.79	4.78	10.93	92	172—173
			69.71	4.05	4.99	11.08		
V	$C_{16}H_9NO_2S$	279.33	68.79	3.25	5.02	11.48	77	178—179
			69.12	3.43	4.88	11.20		
VI	$C_{16}H_{10}N_2O_2$	262.28	73.27	3.85	10.68	80	246—248	
			73.56	4.12	10.39			
VII	$C_{16}H_9NO_3$	263.26	72.99	3.45	5.32	71	185—186	
			73.17	3.62	5.60			
VIII	$C_{18}H_{13}N_3OS$	319.41	67.68	4.11	13.16	10.04	84	214—215
			67.44	3.84	13.25	9.92		
IX	$C_{18}H_{13}N_3O_2S$	335.41	64.45	3.91	12.53	9.56	90	186—187
			64.40	4.26	12.61	9.79		
X	$C_{19}H_{13}N_3O_3S$	363.42	62.79	3.61	11.57	8.82	88	262—264
			63.03	3.75	11.82	8.80		

zoyl)-4-styryl-5,5-dimethyl- $\Delta^3$ -butenolide (II) showed two doublets corresponding with the two hydrogen atoms  $H_a$  and  $H_b$  of ethylene group with chemical shifts  $\delta = 7.325$  (d, 1H),  $J = 15$  Hz for  $H_a$  and  $\delta = 8.864$  (d, 1H),  $J = 15$  Hz for  $H_b$ . The value of the coupling constant as well as the fact that only one signal ( $\delta = 1.848$ ) appeared in the



II  
Formula 1

**Table 2.** IR Spectral Data of the Compounds I—X

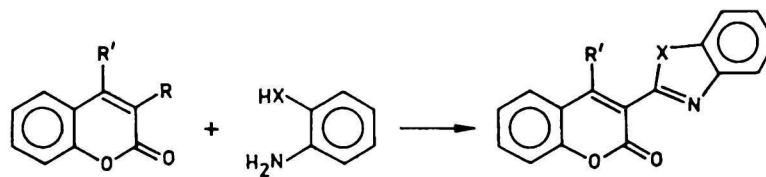
Compound	$\tilde{\nu}/\text{cm}^{-1}$			
	$\nu(\text{C}=\text{N})$	$\nu(\text{C}\cdots\text{C})_{\text{arom}}$	$\nu(\text{C}=\text{C})$	$\nu(\text{C}=\text{O})$
I	1595		1640	1740 <sup>a</sup>
II	1590	1595	1610	1735 <sup>a</sup>
III	1580	1590	1605	1730 <sup>a</sup>
IV	1590	1603	1640	1715 <sup>a</sup>
V	1590	1605	1650	1720 <sup>a</sup>
VI	1570		1610	1710 <sup>a</sup>
VII	1560		1610	1735 <sup>a</sup>
VIII	1585	1610	1690	1675 <sup>b</sup>
IX	1595		1630	1650 <sup>b</sup>
X	1570	1600	1645	1675 <sup>b</sup>

a)  $\nu(\text{C}=\text{O})_{\text{lactone}}$ ; b)  $\nu(\text{C}=\text{O})_{\text{amide}}$ .

region of methyl group protons indicate *trans* configuration at the styryl C=C bond (Formula 1). Also in IR spectrum of II a strong absorption band at  $\tilde{\nu} = 975$   $\text{cm}^{-1}$  occurs which is typical for out-of-plane bending =C—H vibrations in *trans* derivatives. No *cis* isomer was detected after keeping II in chloroform solution for two weeks. That makes a difference from *trans*-3-cyano-4-styryl-5,5-dimethyl- $\Delta^3$ -butenolide, which afforded 40 % of *cis* isomer after six-day standing in chloroform solution at room temperature [9]. This different behaviour can be explained by the assumption that *trans*-*cis* isomerization is hindered by the bulky benzothiazolyl substituent in II.

Coumarin derivatives are widespread in nature and some of them are efficacious growth stimulators [5]. We used 3-cyano-4-methylcoumarin [10] and 3-carboxycoumarin [11] as starting compounds for the synthesis of benzazoyl-substituted coumarins (Scheme 2). The cyclization reactions of the coumarin derivatives with *o*-aminothiophenol, *o*-aminophenol, or *o*-phenylenediamine were accomplished under the same conditions as the synthesis of I. Products were isolated with yields 71—94 %.

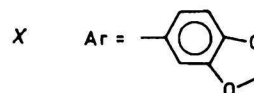
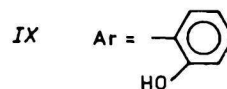
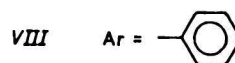
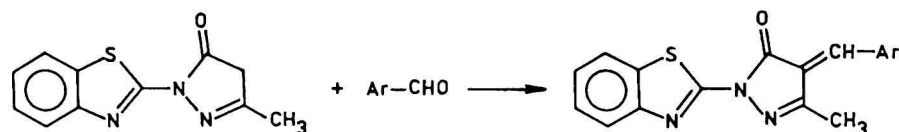
2-(2-Benzothiazolyl)-5-methylpyrazolone [12] was the third type of a compound with both benzothiazole and another heterocyclic moiety. The derivatives obtained by its condensation with aromatic aldehydes (Scheme 3) may be useful in emulsions for colour photography and as bioactive dyes [13]. The reactions were carried out in glacial acetic acid at room temperature for 10 h. The reaction products are insoluble in the reaction medium



For *IV* R = CN  
 For *V-VII* R = COOH

	R'	X
<i>IV</i>	CH <sub>3</sub>	S
<i>V</i>	H	S
<i>VI</i>	H	NH
<i>VII</i>	H	O

Scheme 2



Scheme 3

and precipitate in the course of reaction. Compounds *VIII* and *X* are soluble in acetone and *IX* in ethanol. They are powdery, intensively coloured substances.

Preliminary biological tests show that compounds *I* and *III* cause growth and morphological effects analogical to those of phytohormonal compounds 3-indolylacetic acid and 2,4-dichlorophenoxyacetic acid both *in vitro* and *in vivo*. The data in detail will be published in a separate paper.

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are, together with the elemental analysis data, presented in Table 1. IR spectra of the studied compounds (Table 2) were taken in chloroform using a Specord IR 75 instrument and <sup>1</sup>H NMR spectra were measured with a Varian 300 apparatus.

### 3-(2-Benzothiazolyl)-4,5,5-trimethyl- $\Delta^3$ -butenolide (*I*) and Coumarin Derivatives *IV-VII*

The mixture of 3-cyano-4,5,5-trimethyl- $\Delta^3$ -butenolide (3.0 g; 0.02 mol), *o*-aminothiophenol (2.75 g; 0.022 mol), and polyphosphoric acid (10 g) (resp. starting compounds according to Scheme 2) was heated at 200 °C for 2 h. After cooling, the mixture was washed with 0.25 M-NaHCO<sub>3</sub> solution, then with water and filtered off. The product was crystallized from ethanol.

### 3-(2-Benzothiazolyl)-4-styryl-5,5-dimethyl- $\Delta^3$ -butenolide (*II*) and Furyl Derivative *III*

Compound *I* (1.3 g; 5 mmol) and benzaldehyde (0.64 g; 6 mmol) (resp. 2-furancarbaldehyde) were added to the solution of NaOH (0.5 g; 12 mmol) in absolute methanol (10 cm<sup>3</sup>). The mixture was refluxed for 2 h and, after cooling, neutralized with diluted hydrochloric acid. Solid product was filtered off and crystallized from ethanol.

### 2-(2-Benzothiazolyl)-4-benzylidene-5-methyl-3-pyrazolone (*VIII*) and Substituted Derivatives *IX* and *X*

The mixture of 2-(2-benzothiazolyl)-5-methyl-3-pyrazolone (1.15 g; 5 mmol), benzaldehyde (0.64 g; 6 mmol) (resp. substituted benzaldehydes), and glacial acetic acid (10 cm<sup>3</sup>) was stirred at room temperature for 10 h. Precipitate was filtered off and crystallized from methanol.

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## 3-Substituted 6-Bromo-2-benzothiazolinones and Their Antialgal and Plant Growth Regulating Activity

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6-Bromo-2-benzothiazolinone and its 3-substituted derivatives were synthesized. The compounds were tested for plant growth regulating and antialgal activity.

6-Acetamido-3-alkyl-2-benzothiazolinones and especially 3-alkyl-6-nitro-2-benzothiazolinones [1] were found to be active as stimulators of fresh green mass and chlorophyll production in *Zea mays* L. Stimulation of green algae *Chlorella vulgaris* by the above-mentioned compounds was not significant. 3-(2-Alkylthio-6-benzothiazolylamino-methyl)-6-bromo-2-benzothiazolinones with alkyls C<sub>3</sub> to C<sub>6</sub> proved good antialgal activity [2]. These facts pointed to the necessity of testing the related 6-bromo-2-benzothiazolinones with different substituents at position 3. Of the synthesized group of compounds, III—V, VIII and IX (Table 1) are new.

The starting compound, 6-bromo-2-benzothiazolinone (I) was synthesized using a convenient newly developed method. According to it, 2-benzothiazolinone was brominated with *N*-bromo-succinimide in chloroform [2, 3].

Alkylation of 6-bromo-2-benzothiazolinone with alkyl halides was carried out in aqueous ethanol

in the presence of equivalent amount of potassium hydroxide at reflux temperature.

Compound VIII (Table 1) is the product of amidomethylation of 6-bromo-2-benzothiazolinone with two equivalents of *N*-hydroxymethylbenzamide in 85 % formic acid at reflux temperature. Originally the compound was gained by chance in the course of a reaction using 1 : 1 mole ratio. Later on in order to get a better yield the reaction was repeated using the due mole ratio according to the structure verified by IR spectra. The benzoyl derivative IX was prepared by benzoylation of 6-bromo-2-benzothiazolinone with benzoyl chloride in pyridine at reflux temperature. IR spectra are in accordance with the expected structures (Table 1).

The synthesized compounds were tested for growth-regulating activity and for synthesized chlorophyll content of green algae *Chlorella vulgaris* and of wheat plants. Further their influence on the prolongation of roots and stems of maize germinating in dark was investigated.