SYNTHESIS OF NITRO-SUBSTITUTED 4-OXO-4*H*-PYRIMIDO[2,1-*b*]BENZOTHIAZOLE-3-CARBOXYLIC ACIDS AND THEIR SPECTRAL CHARACTERISTICS

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The Gould–Jacobs reaction of all position isomeric 2-aminonitrobenzothiazoles *II* with diethyl ethoxymethylenemalonate has been studied. The structure of substitution (*IV*) and cyclization (*VI*) products and of the corresponding acids (*VIII*) was confirmed by elemental analysis, IR, UV, ^{1}H and ^{13}C NMR spectra. Analogous derivatives *III*, *V* and *VII*, derived from the unsubstituted 2-aminobenzothiazole *I*, were used as standards in interpretation of the spectra. The synthesized derivatives *I* – *VIII* were tested for antimicrobial activity.

Substituted aminobenzothiazoles have often received attention in connection with the synthesis of pyrimidobenzothiazoles[1–6] as well as with their antimicrobial properties[3,6,7]. Alaimo[3] used 2-aminobenzothiazole and 2-amino-6-nitrobenzothiazole as starting compounds in the Gould–Jacobs reaction. Substitution and cyclization products of 2-amino-5- and 2-amino-6-nitrobenzothiazole are described in a patent[6]. Unsubstituted 2-aminobenzothiazole (*I*) reacts with diethyl ethoxymethylenemalonate (EMME) to give a cyclization product exhibiting anxiolytic activity[7].

In our present communication we have studied the chemical behaviour of all the four position isomeric nitro-2-aminobenzothiazoles *II* under conditions of the Gould–Jacobs reaction and isolated the individual substitution products (*IV*). Their subsequent cyclization in an aprotic solvent (Dowtherm) required a substantially higher temperature than the preparation of the substitution products. Since the individual starting amines *II* differed in solubility, the reaction with EMME had to be performed in different solvents. The reaction conditions for the substitution reactions are given in Table I. The thermal cyclizations, leading to esters *VI*, were carried out at 240 – 250 °C. The corresponding acids *VIII* were obtained by acid hydrolysis of the esters *VI*. However, the

derivative *VIa* resisted acid hydrolysis and therefore it was saponified with sodium hydroxide. The physicochemical properties of the obtained derivatives are given in Table II. For comparison, also the physicochemical properties of compounds *III*, *V* and *VII* derived from 2-aminobenzothiazole (*I*; Scheme 1) are given.

Infrared spectra of compounds *II* exhibit characteristic vibrations of aromatic C–H bonds, ν(C–H), in the region 700 – 900 cm^{-1}. Bands due to symmetric and antisymmetric vibrations of the NO_2 group appear in the region 1 340 – 1 530 cm^{-1}. Introduction of the ethylenediester fragment results in a marked split band of ν(C=O) above 1 684 cm^{-1}. Antisymmetric stretching vibrations of the ester or carboxyl groups, ν(C–O), are located at about 1 216 – 1 272 cm^{-1}; derivatives *IV* exhibit two strong bands close to each other (see Table III). Weaker bands at 1 084 – 1 144 cm^{-1} correspond to symmetric stretching vibrations. The spectra of derivatives *VI*, arising by cyclocondensation of compounds *IV*, exhibit two types of carbonyl bands: the ester carbonyl band above 1 700 cm^{-1} and the pyrimidone carbonyl band below 1 700 cm^{-1}. In the spectra of derivatives *VIII* these bands are shifted towards lower wavenumbers, the largest shifts being observed for compound *VIIIc* (Table III).

The ultraviolet spectra are given in Table IV. Introduction of the NO_2 group into various positions of the benzene ring in benzothiazole results in appearence of a new weak band above 330 nm, introduction of the ethylenediester moiety brings about a marked bathochromic shift of 71 nm (see spectra of the unsubstituted compounds *I* and *III*). In the UV spectra of nitro derivatives *IV* the absorption bands are stronger due to mutual interaction of the two chromophores; however, according to their position, this interaction is only weak. The most complicated UV spectra were found for compounds *V* and *VI*. The influence of the position of the nitro group on the UV spectrum is reduced by the presence of pyrimidone ring, on the other hand, the band intensity increases.

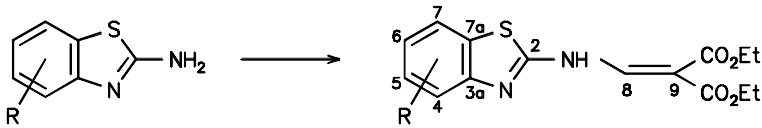
In the interpretation of the ^1H and ^{13}C NMR spectra we made use of a model series based on 2-aminobenzothiazole (*I*), diethyl *N*-(2-benzothiazolyl)aminomethylene-

TABLE I
Reaction conditions for the preparation of compound *IV*

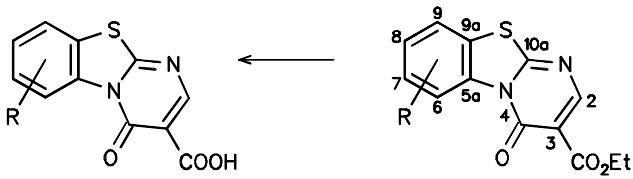
Compound	Solvent	Solvent amount ml	Reaction time h	Crystallization solvent
IVa	ethanol	20	20	ether
IVb	dioxane	25	20	ethanol
IVc	ethanol	50	6	ethanol
IVd	butanol	100	10	hexane

malonate (*III*), ethyl 4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylate (*V*) and its hydrolysis product, 4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylic acid (*VII*) (refs[3,8,9]). For the nitro derivatives, the proton and carbon NMR spectra have been hitherto described only for the 6-nitro compound *IIc* (refs[3,8]). The ^{13}C NMR signals were assigned using data for a series of 2-unsubstituted nitrobenzothiazoles[9].

The proton chemical shifts for 2-aminobenzothiazole (*I*), the nitro compounds *II* and their derivatives *III* and *IV* are given in Table V. Attachement of the ethylenediester fragment to the 2-amino group results in a downfield shift of all the aromatic protons (about 0.4 ppm). The olefinic proton signal appears in the region 8.60 – 8.72 ppm. The



I, II *III, IV*



VII, VIII *V, VI*

	R
I, III	H
IIa, IVa	4-NO_2
IIb, IVb	5-NO_2
IIc, IVc	6-NO_2
IId, IVd	7-NO_2

	R
V, VII	H
VIa, VIIIa	6-NO_2
VIb, VIIIb	7-NO_2
VIc, VIIIc	8-NO_2
VId, VIIId	9-NO_2

SCHEME 1

TABLE II
Physicochemical properties of compounds *IV*, *VI* and *VIII*

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
IVa	$C_{15}H_{15}N_3O_6S$	128 – 129	49.27	4.14	11.50	8.77
	(365.4)	61	49.01	4.31	11.26	8.50
IVb	$C_{15}H_{15}N_3O_6S$	180 – 182	49.27	4.14	11.50	8.77
	(365.4)	52	49.19	4.12	11.36	8.69
IVc	$C_{15}H_{15}N_3O_6S$	198 – 201	49.27	4.14	11.50	8.77
	(365.4)	59	49.05	4.20	11.32	8.96
IVd	$C_{15}H_{15}N_3O_6S$	138 – 140	49.27	4.14	11.50	8.77
	(365.4)	43	49.53	4.41	11.67	8.70
VIa	$C_{13}H_9N_3O_5S$	216 – 217	48.90	2.82	13.15	10.04
	(319.3)	72	49.09	2.74	13.28	10.26
VIb	$C_{13}H_9N_3O_5S$	255 – 258	48.90	2.82	13.15	10.04
	(319.3)	68	49.10	2.63	13.36	9.78
VIc	$C_{13}H_9N_3O_5S$	251 – 254	48.90	2.82	13.15	10.04
	(319.3)	68	49.02	2.96	13.28	10.08
VId	$C_{13}H_9N_3O_5S$	225 – 230	48.90	2.82	13.15	10.04
	(319.3)	80	48.81	2.92	13.17	10.22
VIIIa	$C_{11}H_5N_3O_5S$	140 – 142	45.36	1.72	14.43	11.01
	(291.3)	93	45.12	1.97	14.17	10.84
VIIIb	$C_{11}H_5N_3O_5S$	263 – 265	45.36	1.72	14.43	11.01
	(291.3)	70	45.59	1.96	14.12	10.82
VIIIc	$C_{11}H_5N_3O_5S$	254 – 258	45.36	1.72	14.43	11.01
	(291.3)	75	45.21	1.97	14.16	11.28
VIIId	$C_{11}H_5N_3O_5S$	260 – 262	45.36	1.72	14.43	11.01
	(291.3)	86	45.18	1.83	14.11	10.79

TABLE III
Infrared spectra of compounds *II*, *IV*, *VI* and *VIII*

Compound	ν(C–H)	ν(C=C), ν(C=N)	ν(C=O)	ν_{as}(C–O)	$\nu_s(NO_2)$ $\nu_{as}(NO_2)$
IIa	728 880	1 448, 1 528, 1 656	–	–	1 344 1 528
IIb	734 881	1 424, 1 505, 1 652	–	–	1 339 1 537
IIc	750 887	1 424, 1 505, 1 653	–	–	1 329 1 531
IId	729 883	1 448, 1 493, 1 655	–	–	1 341 1 500
IVa	758 792	1 416, 1 612, 1 664	1 720 1 708	1 225 1 216	1 334 1 524
IVb	736 796	1 429, 1 600, 1 664	1 704 1 684	1 256 1 232	1 344 1 516
IVc	736 800	1 440, 1 596, 1 656	1 696 1 688	1 264 1 232	1 336 1 504
IVd	736 812	1 416, 1 608, 1 664	1 728 1 702	1 256 1 228	1 336 1 520
VIa	768 792	1 292, 1 504, 1 536	1 740 1 688	1 264	1 360 1 524
VIb	742 796	1 296, 1 493, 1 529	1 732 1 668	1 263	1 344 1 529
VIc	740 792	1 300, 1 492, 1 584	1 740 1 696	1 272	1 348 1 525
VId	740 792	1 292, 1 504, 1 560	1 740 1 672	1 268	1 344 1 552
VIIIa	760 800	1 412, 1 476, 1 576	1 728 1 620	1 256	1 344 1 532
VIIIb	736 800	1 420, 1 472, 1 560	1 728 1 624	1 248	1 348 1 520
VIIIc	744 784	1 448, 1 472, 1 560	1 680 1 616	1 260	1 344 1 548
VIIId	736 812	1 384, 1 504, 1 576	1 708 1 650	1 252	1 328 1 548

position of this signal is only little affected by the position of the nitro group; this indicates only a weak conjugation of the aminoethylene moiety with the benzothiazole nucleus. The ester groups appear as two triplets and two quartets, which shows that the ethoxycarbonyl groups are not equivalent.

The proton spectra of the cyclized products *V*, *VI*, *VII* and *VIII* are given in Table VI. The cyclization results in a marked downfield shift of the 6-proton signal (more than 1 ppm) caused by interaction of the mentioned proton with the carbonyl oxygen atom in position 4 of the obtained pyrimido[2,1-*b*]benzothiazole derivative[10].

Signals in ^{13}C NMR spectra of the nitro-substituted 2-aminobenzothiazoles are in accord with the corresponding signals of the 2-unsubstituted analogues[9]. Signals of the benzene carbon atoms bearing the nitro groups are markedly shifted downfield into the

TABLE IV
Ultraviolet spectrum of compounds *I* – *VIII*

Compound	λ_{max}, nm (log ε)
I	223 (3.27), 262 (3.13)
IIa[a]	217 260 367
IIb	216 (3.01), 263 (3.49), 307 (2.80), 333 (2.54)
IIc	224 (3.52), 258 (2.88), 355 (3.42)
IId[a]	213 267 333
III	214 (3.50), 333 (3.54)
IVa	208 (3.50), 304 (3.37), 349 (3.37)
IVb	203 (3.52), 246 (3.17), 321 (3.57)
IVc[a]	217 351
IVd	208 (3.52), 316 (3.35)
V	204 (3.14), 291 (2.10), 343 (3.30)
VIa[a]	214 284 368
VIb[a]	226 356
VIc[a]	223 250 308 367
VId[a]	206 267 289 370
VII	205 (3.38), 292 (2.71), 355 (2.97)
VIIIa	216 (3.41), 243 (3.27), 276 (3.20), 335 (2.18)
VIIIb[a]	203 279 333
VIIIc[a]	210 258 370
VIIId[a]	207 289 369

[a] Saturated solution.

TABLE V
^{1}H NMR chemical shifts[a] (ppm) for compounds *I – IV*

Compound	H-4	H-5	H-6	H-7	NH_2	NH	CH	CH_2	CH_3
I	7.63 d	7.20 t	7.00 t	7.33 d	7.46	–	–	–	–
IIa	–	8.03 d	7.14 t	7.91 d	8.29	–	–	–	–
IIb	8.03 d	–	7.91 dd	7.85 d	7.95	–	–	–	–
IIc	7.40 d	8.08 dd	–	8.66 d	8.23	–	–	–	–
IId	7.72 d	7.47 t	7.97 d	–	7.91	–	–	–	–
III	7.91 d	7.42 t	7.28 t	7.75 d	–	11.22 s	8.67 s	4.21, 4.27	1.27, 1.29
IVa	–	8.34 d	7.44 t	8.11 d	–	11.60 s	8.72 s	4.19, 4.26	1.26, 1.28
IVb	8.50 d	–	8.12 dd	8.22 d	–	11.51 s	8.67 s	4.19, 4.26	1.27, 1.29
IVc	7.90 d	8.26 dd	–	9.00 d	–	11.61 s	8.67 s	4.20, 4.27	1.26, 1.28
IVd	8.13 d	7.67 t	8.21 d	–	–	11.37 s	8.62 s	4.21, 4.28	1.28, 1.30

[a] *J* (Hz) for *I*: *J*(4,5) = *J*(6,7) = 8.1, *J*(4,6) = *J*(5,7) = 1.2; *IIa*: *J*(5,6) = *J*(6,7) = 8.0; *IIb*: *J*(6,7) = 8.5, *J*(4,6) = 1.9; *IIc*: *J*(4,5) = 8.8, *J*(4,5) = 2.5; *IId*: *J*(4,5) = *J*(5,6) = 8.1; *III*: *J*(4,5) = *J*(6,7) = 8.1, *J*(5,6) = 7.6; *IVa*: *J*(5,6) = *J*(6,7) = 8.5; *IVb*: *J*(6,7) = 8.7, *J*(4,6) = 2.0; *IVc*: *J*(4,5) = 8.9, *J*(5,7) = 2.4; *IVd*: *J*(4,5) = *J*(5,6) = 8.1.

TABLE VI
^{1}H NMR chemical shifts[a] (ppm) for compounds *V – VIII*

Compound	H-6	H-7	H-8	H-9	H-2	CH_2	CH_3
V	8.92 d	7.55 m	7.55 m	8.04 d	8.51 s	4.22	1.26
VIa	–	8.44 dd	7.80 t	8.06 dd	8.59 s	4.26	1.29
VIb	9.71 d	–	8.49 dd	8.43 d	8.67 s	4.31	1.33
VIc	9.15 d	8.49 dd	–	9.15 d	8.65 s	4.29	1.32
VId	9.42 d	7.97 t	8.58 d	–	8.68 s	4.33	1.34
VII	8.97 dd	7.68 m[b]	7.65 m[b]	8.15 dd	8.69 s	–	–
VIIIa	–	8.20 d	7.76 t	8.00 d	8.46 s	–	–
VIIIb	8.45 d	–	8.28 dd	7.86 d	8.40 s	–	–
VIIIc	9.11 d	8.42 dd	–	9.14 d	8.84 s	–	–
VIIId	9.40 d	7.98 t	8.59 d	–	8.71 s	–	–

[a] *J* (Hz) for *V*: *J*(6,7) = *J*(8,9) = 7.5; *VIa*: *J*(7,8) = *J*(8,9) = 8.1, *J*(7,9) = 0.9; *VIb*: *J*(8,9) = 9.0, *J*(6,8) = 2.1; *VIc*: *J*(6,7) = 9.3, *J*(7,9) = 2.7; *VId*: *J*(6,7) = *J*(7,8) = 8.6; *VII*: *J*(6,7) = *J*(8,9) = 7.2; *VIIIa*: *J*(6,7) = *J*(7,8) = 8.1; *VIIIb*: *J*(8,9) = 8.7, *J*(6,8) = 2.4; *VIIIc*: *J*(6,7) = 9.5, *J*(7,9) = 1.8; *VIIId*: *J* (6,7) = *J*(7,8) = 8.4.
[b] Signals may be interchanged.

TABLE VII
^{13}C NMR spectra of compounds *I* and *II*

Carbon	*I*	*IIa*	*IIb*	*IIc*	*IId*
C-2	166.4	170.1	169.0	171.7	169.2
C-3a	152.8	146.3	153.2	155.6	155.4
C-4	117.3	137.9	111.4	117.6	126.2
C-5	125.4	126.3	146.0	122.0	123.6
C-6	120.8	119.7	115.3	140.7	116.5
C-7	120.8	121.4	121.5	116.8	141.6
C-7a	130.9	134.5	139.1	131.6	127.0

TABLE VIII
^{13}C NMR spectra of compounds *III* and *IV*

Carbon	*III*	*IVa*	*IVb*	*IVc*	*IVd*
C-2	160.5	164.8	164.9	166.4	164.0
C-3a	149.8	142.6	150.0	154.7	151.9
C-4	120.4	140.1	115.0	121.9	125.8
C-5	126.0	122.2	146.5	120.4	126.6
C-6	121.4	123.1	118.0	143.0	119.3
C-7	123.5	127.8	123.0	118.9	141.6
C-7a	131.8	135.6	139.7	132.9	127.5
C-8	145.2	144.3	144.3	143.0	144.0
C-9	100.0	101.6	101.6	102.0	101.5
C=O	164.2	164.3	164.3	164.3	164.1
	165.1	164.8	164.4	164.7	164.6
CH_2	59.8	60.3	60.4	60.4	59.9
	60.0	60.5	60.5	60.5	60.1
CH_3	13.7	13.9	14.0	14.0	13.7
	13.8	14.0	14.1	14.1	13.8

region 137.9 – 146.0 ppm, whereas those of the unsubstituted carbon atoms appear in the region 111.4 – 126.3 ppm. Spectra of the substitution products *III* and *IV* show no significant changes in the aromatic carbon shifts. Two nonequivalent ethoxycarbonyl groups can be distinguished (Tables VII and VIII).

Thermal cyclization of the substitution products *III* and *IV*, leading to tricyclic derivatives, is accompanied by a significant change in chemical shifts of quaternary carbon atoms 5a and 9a, common for the benzene and the thiazole rings. The ^{13}C NMR data for compounds *V – VIII* are given in Table IX.

The results of antimicrobial activity assays for compounds *I – IV* are summarized in Table X. None of them showed any significant in vitro antimicrobial activity against Gram-positive or Gram-negative bacteria tested or against yeast fungus *Saccharomyces cerevisiae*. Compounds *V – VIII* did not inhibit the microorganism growth even at the highest concentration used (500 μg ml^{-1}).

TABLE IX
^{13}C NMR spectra of compounds *V – VIII*

Carbon	*V*	*VIa*	*VIb*	*VIc*	*VId*	*VII*	*VIIIa*	*VIIIb*	*VIIIc*	*VIIId*
C-2	156.0	156.9	156.8	156.8	156.1	156.6	150.2	149.4	161.0	156.5
C-3	110.3	109.8	111.1	111.0	111.5	109.7	103.1	102.7	103.9	111.5
C-4	163.1	162.7	163.2	163.2	162.8	164.1	159.2	160.6	164.2	162.0
C-5a	135.7	128.5	132.6	145.4	137.7	135.6	146.5	142.9	145.5	137.6
C–NO_2	–	141.1	146.0	140.3	141.0	–	138.2	147.1	140.9	141.3
C-6 to C-9	119.1	–	–	–	–	119.3	–	–	–	–
	126.9	122.8	114.1	122.7	128.3	123.1	125.5	124.5	118.7	123.1
	122.8	127.7	122.0	119.8	124.7	127.2	131.5	125.3	119.0	124.9
	127.1	128.0	124.4	119.4	122.8	127.4	133.9	128.6	122.5	128.5
C-9a	124.2	127.7	132.2	126.4	122.0	124.5	126.5	133.5	129.5	122.1
C-10a	156.5	156.1	156.9	156.9	156.4	159.2	149.5	149.5	152.7	157.9
C=O	166.2	167.4	167.0	167.7	166.5	–	–	–	–	–
CH_2	60.1	60.6	60.7	60.6	60.4	–	–	–	–	–
CH_3	13.8	14.1	14.1	14.1	13.8	–	–	–	–	–
COOH	–	–	–	–	–	166.3	163.2	163.0	164.6	163.8

EXPERIMENTAL

Infrared spectra were recorded on a double-beam UR 20 Zeiss spectrophotometer using the KBr technique (0.5 mg/300 mg KBr), UV spectra were taken on a Specord UV-VIS Zeiss spectrometer at room temperature; concentration 1 . 10^{-4} mol l^{-1} or saturated solution in ethanol. Proton and ^{13}C NMR spectra (δ, ppm) were measured on a Varian VXR-300 instrument in hexadeuteriodimethyl sulfoxide at 298 – 353 K. Elemental analyses were performed on a CHNS+O Mod 1108 Carlo Erba analyzer.

The antibacterial activity of the twenty derivatives was tested in vitro using a selected spectrum of standard strains of Gram-positive and Gram-negative bacteria (Table X). Strains No. 1, 3 and 6 were from Czechoslovak national collection of type cultures in Prague, strains No. 2, 4 and 5 from Czechoslovak collection of microorganisms in Brno and strain No. 7 from collection of microorganisms of the Department of Microbiology and Virology, Faculty of Natural Sciences, Comenius University, Bratislava. The tested derivatives were dissolved in dimethyl sulfoxide. Starting from concentration 500 μg ml^{-1}, ten concentrations in the range 500 – 1.25 μg ml^{-1} were obtained by dilution. The antibacterial activity was characterized as the minimum inhibitory concentration (MIC) in μg ml^{-1} and was determined using the test-tube dilution method. The cultivation medium (2 ml of Muller–Hinton medium for strains No. 1 – 6 and 2 ml of Sabourad medium for strain No. 7) contained defined concentration of the compound tested together with starting inoculum of the given strain (10^5 cells per ml). The MIC data were evaluated after cultivation at 37 °C for 24 h.

The starting 2-aminonitrobenzothiazoles were prepared by described methods: 2-amino-4-nitrobenzothiazole[11], 2-amino-5-nitrobenzothiazole[12], 2-amino-6-nitrobenzothiazole[13] and 2-amino-7-nitrobenzothiazole[14].

TABLE X
Antimicrobial activity of compounds[a] *I – IV*, MIC (μg ml^{-1})

Compound	1	2	3	4	5	6	7
I	500	500	>500	250	500	500	500
IIa	>500	>500	>500	>500	500	500	125
IIb	>500	500	>500	500	125	500	250
IIc	500	500	500	500	125	250	125
IId	>500	>500	>500	>500	500	500	50
III	>500	500	>500	250	250	>500	125
IVa	>500	>500	>500	500	500	500	125
IVb	>500	>500	>500	>500	>500	>500	>500
IVc	>500	>500	>500	>500	>500	>500	>500
IVd	>500	>500	>500	250	250	500	>500

[a] Strain: 1 *Escherichia coli* Ec 326/71, 2 *Serratia marcescens* CCM 303, 3 *Pseudomonas aeruginosa* Ps 133/71, 4 *Bacillus subtilis* CCM 2216, 5 *Enterococcus faecalis* CCM 1875, 6 *Staphylococcus aureus* Mau 78/71, 7 *Saccharomyces cerevisiae* DT XII.

Diethyl 2-[5(6,7 or 8)-Nitrobenzothiazolyl]aminomethylenemalonates (*IVa – IVd*)

A solution of nitro-substituted 2-aminobenzothiazole *IIa – IId* (1.95 g, 0.01 mol) in an appropriate solvent was refluxed for 6 – 20 h. The reaction mixture was concentrated to a half, cooled, the deposited product was collected, washed with the solvent and recrystallized. The reaction conditions for the individual compounds are given in Table I.

Ethyl Nitro-Substituted 4-Oxo-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxylates (*VIa – VId*)

Diethyl ester *IVa – IVd* (2.0 g, 0.0055 mol) was dissolved in warm Dowtherm (50 ml) and the temperature was gradually increased to 240 – 250 °C. This temperature was maintained for 1 h under simultaneous removal of the arising ethanol by distillation. Then Dowtherm was distilled off in vacuo (30 ml) and the reaction mixture was cooled. The deposited product was collected, washed with hexane and ether and crystallized from dioxane or butanol. The yields of the cyclizations were 68 – 80%.

Nitro-Substituted 4-Oxo-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxylic Acids (*VIIIa – VIIId*)

Ester *VIb – VId* (1.0 g, 0.003 mol) was heated at 85 – 95 °C with a mixture of concentrated hydrochloric acid and concentrated acetic acid (1 : 10, 30 ml). After cooling and dilution with water (20 ml), the deposited acid was collected and washed with a small amount of cold water. Yield 70 – 86%.

A mixture of ester *VIa* (1.0 g, 0.003 mol) and 1 M NaOH (20 ml) was heated at 85 – 95 °C for 45 min. The brown-red solution was filtered and adjusted to pH 5 with 4% hydrochloric acid. The beige precipitate was collected, washed with water and dried in vacuo at 70 °C. Yield 93%.

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