SYNTHESIS OF 2-SUBSTITUTED BENZOTHIAZOLES CONTAINING AMINO ACID, IMINO OR HETEROARYL MOIETIES WITH ANTICIPATED FUNGICIDAL ACTIVITY

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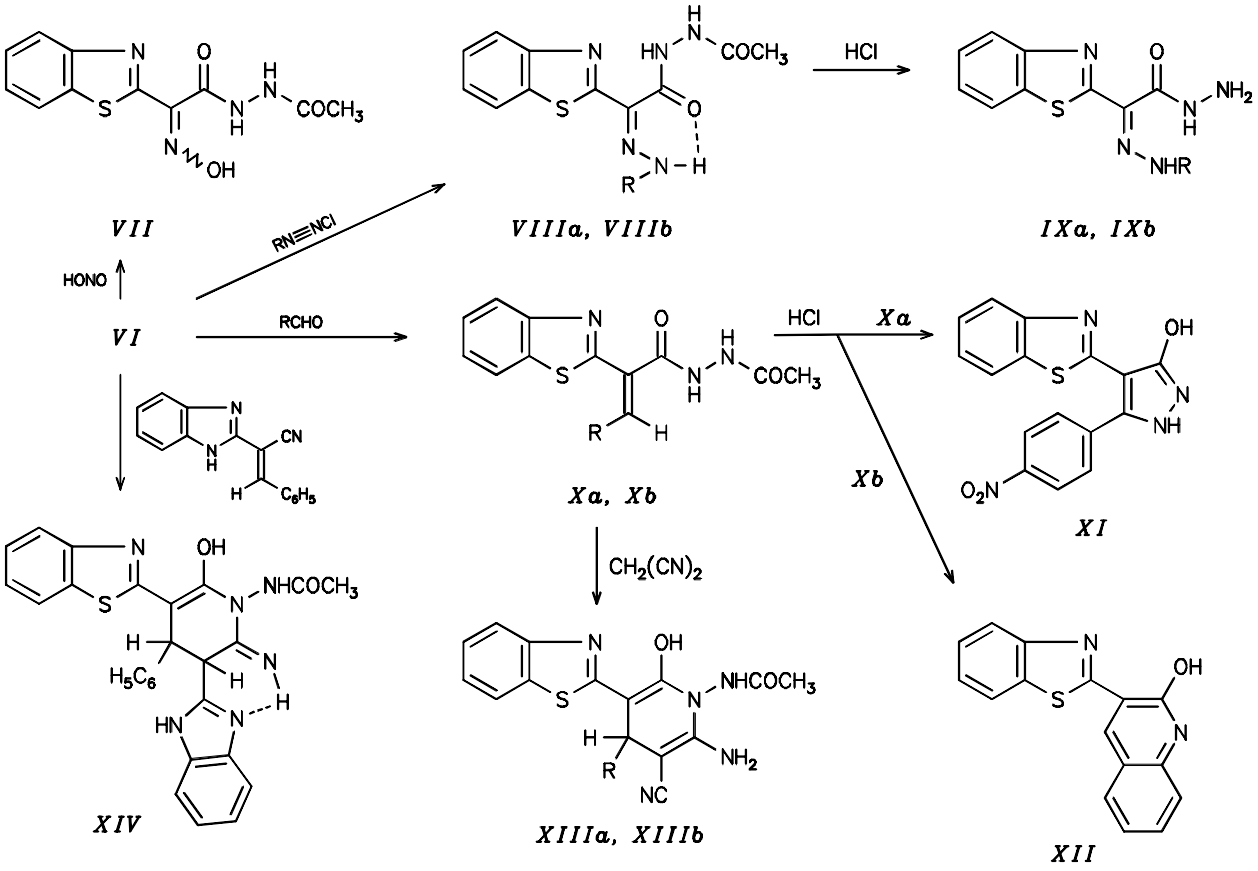
The chemistry of benzoazoles is of continuous interest for their various biological activities, the most interesting being the antifungal one[1,2]. Following our laboratory policy directed to the searching of new agrochemicals and in continuation to our previous work[3,4], the present paper deals with the synthesis of 2-substituted benzothiazoles with anticipated biological activity.

Cyanoacetic acid and 2-aminothiophenol (*I*) in one-pot reaction gave benzothiazol-2-ylacetic acid (*II*) in spite of the two step method previously reported[5] (Scheme 1).

Coupling of *II* with methyl glycinate in presence of dicyclohexylcarbodiimide afforded the compound *IIIa*, with phenylalanine methyl ester benzothiazolyl phenylalanine[6] (*IIIb*) was obtained. The method[7] of benzothiazol-2-ylacetohydrazide (*IV*) preparation from 2-aminothiophenol (*I*) and cyanoacetohydrazide was improved and methanol–acetic acid was used as the reaction medium. It is worthy to mention that preparation of the derivative *IV* in ethanol–piperidine failed and the only product was 3-amino-5-pyrazolone coming from the self-cyclization of cyanoacetohydrazide[8]. Compound *IV* was further condensed with acetylacetone to give 2-(1-amino-4,6-dimethyl-2-oxo-pyridin-3-yl)benzothiazole (*V*). Its ^{1}H NMR spectrum showed no methylene proton signals detected in the parent compound *IV* at 4.1 ppm. 2-Aminothiophenol (*I*) and *N*-acetylcyanoacetohydrazide afforded the corresponding *N*-acetylbenzothiazol-2-ylacetohydrazide (*VI*).

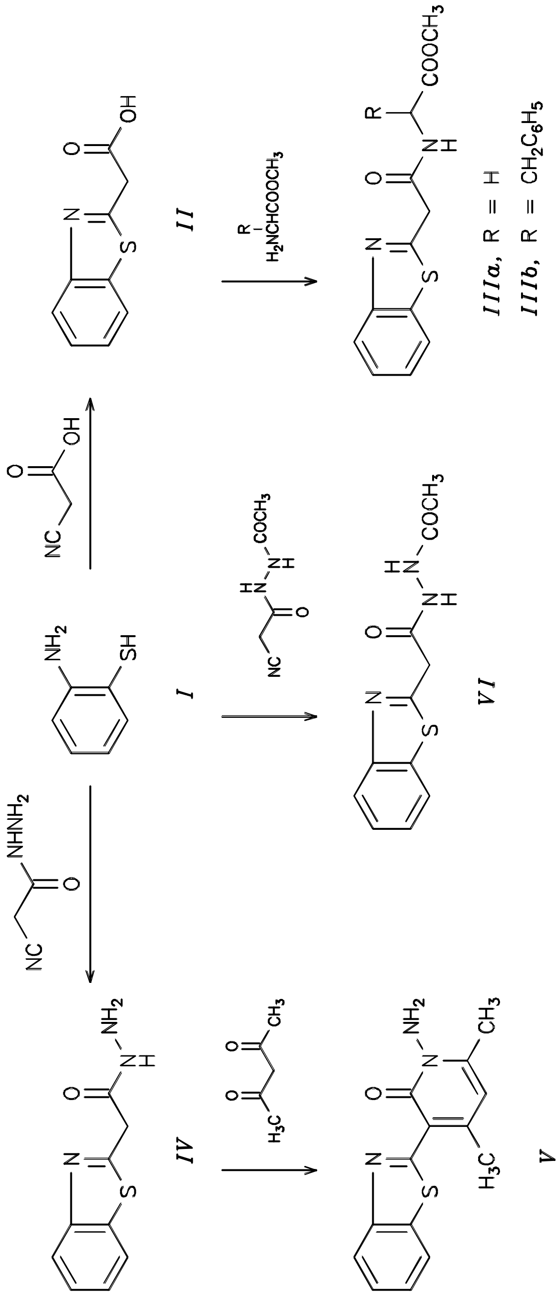
Compound *VI* condensed with nitrous acid to form the corresponding oxime derivative *VII*. Coupling of *VI* with aryl diazonium salts gave the corresponding hydrazones *VIIIa*, *VIIIb*. The marked downfield shift of the azo-NH resonance signals in the ^{1}H NMR spectra indicates the presence of *N*–H...O=C bridges[9] (Scheme 2). The hydrazones *VIII* underwent hydrolysis affording their deacetylated derivatives *IXa*, *IXb*. The latter could not be obtained directly by the diazotization reaction of the deacetylated derivative *IV*. Condensation of *VI* with aryl aldehydes afforded the corresponding arylidene derivatives *Xa*, *Xb*. When compound *Xa* was treated with 6 M hydrochloric acid, a product *XI* was formed by deacetylation and subsequent self-cyclization and oxidation. When com-



In formulae *VIII*, *IX* : *a*, R = C_6H_5; *b*, R = 2-OH-C_6H_4

In formulae *X*, *XIII* : *a*, R = 4-NO_2-C_6H_4; *b*, R = 2-Cl-C_6H_4

SCHEME 2



SCHEME 1

pound *Xb* was treated with 6 M hydrochloric acid, a different product was obtained, which was identified as 2-hydroxy-3-(benzothiazol-2-yl)quinoline (*XII*). Similar nucleophilic displacement by the hydrazino nitrogen in acetohydrazide derivatives has been previously reported[10].

Compounds *Xa*, *Xb* reacted with malononitrile in dioxane–piperidine in a Michael type reaction to afford 3-(benzothiazol-2-yl)dihydropyridines *XIII*. Their IR spectra showed NH_2, NH, OH and CN group absorption at 3 450–3 200 and 2 200 cm^{-1}, respectively, their ^1H NMR spectra showed the dihydropyridine H-4 as doublet at 4.6 ppm and the mass spectrum of *XIIIb* contained the ion base peak at *m/z* = 380 corresponding to the 2-hydroxy-3-(benzothiazol-2-yl)-4-(2-chlorophenyl)-5-cyano-6-amino-1,4-dihydropyridine fragment. Reaction of the compound *VI* with 2-(benzimidazol-2-yl)cinnamonitrile[11] under similar reaction conditions afforded a new product lacking the CN absorption and showing a dihydropyridine H-4 as doublet at 4.0 ppm and dihydropyridine H-5 as doublet at 5.8 ppm. Based on these data and our previous report[12], the 3-(benzothiazol-2-yl)-5-(benzimidazol-2-yl)dihydropyridine structure *XIV* was assigned to this product.

Preliminary fungicidal tests showed that compounds *VI*, *XIIIb* and *Xa*, as representative examples, exhibit remarkable activity against *Fusarium manilifarum*, *Penicillium oxalicum* and *Aspergillus niger*. Further work is in progress and will be published elsewhere[13].

EXPERIMENTAL

Melting points were uncorrected. The IR spectra were recorded in KBr with a Pye–Unicam Sp-1000 spectrometer. The ^1H NMR spectra were run on a Jeol GLM. EX (270 MHz) or Gemini-200 (200 MHz) spectrometer using TMS as an internal standard. The mass spectra were recorded at 70 eV with a Schimadzu GC/MS QP 1000 EX spectrometer. Elemental analyses were performed by the Central Service Unit at Cairo University and National Research Center. The characteristic data of the prepared compounds are given in Table I, their IR and ^1H NMR spectra in Table II.

2-(Benzothiazol-2-yl)acetic Acid (*II*) and 2-(Benzothiazol-2-yl)acetohydrazide (*IV*)

A mixture of 2-aminothiophenol (*I*, 1.25 g, 0.01 mol) and cyanoacetohydrazide or cyanoacetic acid (0.01 mol) was heated to 60 °C in a mixture of methanol–glacial acetic acid (10 ml each) for one hour, then refluxed for 15 min. After cooling, ether was added to the solution, the precipitate formed was collected by filtration and crystallized.

Methyl 2-[2-(Benzothiazol-2-yl)acetamido]acetate (*IIIa*) and -3-phenylpropionate (*IIIb*)

A mixture of the amino acid (glycine or phenylalanine) methyl ester hydrochloride (0.01 mol) and triethylamine (2.0 g, 0.02 mol) in dry tetrahydrofuran (30 ml) was stirred at room temperature for 15 min. The solution of the amino acid ester was decanted and an equimolar amount of the acid *II* (1.93 g) was added to this reaction mixture, a solution of dicyclohexylcarbodiimide (2.1 g, 0.01 mol in 20 ml dry tetrahydrofuran) was dropped during a period of 2 h at 0–5 °C and the stirring was maintained for further 6 h. Working up of the reaction mixture was carried out as previously reported[6].

2-(1-Amino-4,6-dimethyl-2-oxopyridin-3-yl)benzothiazole (*V*)

Compound *IV* (2.07 g, 0.01 mol) was refluxed with acetyl acetone (0.01 mol, 1 ml) in methanolic potassium hydroxide (30 ml) for 3 h. The reaction mixture was then neutralized with diluted hydrochloric acid, the precipitate obtained was filtered off, washed with water and crystallized from proper solvent (Table I). Mass spectrum (*m/z*): 271.

2-(Benzothiazol-2-yl)-*N*-acetylacetohydrazide (*VI*)

A mixture of 2-aminothiophenol (*I*, 1.25 g, 0.01 mol) and *N*-acetylcyanoacetohydrazide (0.01 mol, 2.49 g) was boiled under reflux in methanol (25 ml) for 3 h in the presence of piperidine (3 drops). The solution was concentrated and left to cool. The solid formed was filtered off and crystallized from the appropriate solvent (Table I). Mass spectrum (*m/z*): 249.

2-(Benzothiazole-2-yl)-2-hydroxyimino-*N*-acetylacetohydrazide (*VII*)

To a stirred solution of compound *VI* (2.49 g, 0.01 mol) in acetic acid (20 ml) and methanol (10 ml) in an ice bath, an equimolecular amount of sodium nitrite was added during a period of 30 min and stirring was continued for further 9 h. The formed precipitate was filtered off and crystallized. Mass spectrum (*m/z*): 278.

2-(Benzothiazol-2-yl)-2-arylhydrazo-*N*-acetylacetohydrazides *VIIIa*, *VIIIb*

The diazonium salts of aniline and 2-hydroxyaniline were prepared according to the literature[14]. To a stirred solution of compound *VI* (2.49 g, 0.01 mol) in methanol (30 ml) in an ice bath, the prepared diazonium salt was added. After removing the ice bath, the stirring was maintained for 30 min, water was added to the solution till precipitation occurred. The formed solid product was washed with water and crystallized (Table I).

2-(Benzothiazol-2-yl)-2-arylhydrazonoacetohydrazides *IXa*, *IXb*, 3-Hydroxy-4-(benzothiazol-2-yl)-5-(4-nitrophenyl)pyrazole (*XI*) and 2-Hydroxy-3-(benzothiazol-2-yl)quinoline (*XII*)

A solution of each of compounds *VIIIa*, *VIIIb* and *Xa*, *Xb* in methanol (30 ml) in presence of 6 M HCl (10 ml) was refluxed for 3 h. The precipitate formed was filtered off, washed with water and crystallized (Table I). Mass spectra (*m/z*): 311 (*IXa*), 338 (*XI*), 278 (*XII*).

N-Acetyl-2-(benzothiazole-2-yl)cinnamohydrazides *Xa*, *Xb*

A mixture of compound *VI* (2.49 g, 0.01 mol) with the corresponding aldehyde (0.01 mol) in methanol (30 ml) in presence of piperidine (4 drops) was refluxed for 4–5 h. A precipitate was formed immediately, filtered and crystallized (Table I).

1-Acetamido-6-amino-4-aryl-3-(benzothiazol-2-yl)-5-cyano-2-hydroxy-1,4-dihydropyridines *XIIIa*, *XIIIb*

A solution of *Xa* or *Xb* (0.01 mol) in dioxane (25 ml) was refluxed with malononitrile (0.66 g, 0.01 mol) in presence of piperidine (4 drops) for 4 h. The reaction mixture was then evaporated to dryness, leaving an oily residue which was triturated with methanol and the solid obtained was crystallized from the proper solvent (Table I).

TABLE I
Characteristic data of the compounds prepared

Compound	Yiekd, %	M.p., °C Solvent	Formula M.w.	Calculated/Found			
				% C	% H	% N	% S
IIIa	65	176–178	$C_{12}H_{12}N_2O_3S$	54.53	4.58	10.65	12.13
		ethyl acetate	264.3	54.41	4.50	10.40	11.93
V	40	>300	$C_{14}H_{13}N_3OS$	61.97	4.82	15.48	11.81
		dioxane	271.3	61.83	4.62	15.14	11.73
VI	80	170–172	$C_{11}H_{11}N_3O_2S$	53.00	4.45	16.86	12.86
		methanol	249.3	52.92	4.24	16.53	12.51
VII	80	185–186	$C_{11}H_{10}N_4O_3S$	47.47	3.62	20.13	11.52
		dioxane	278.3	47.23	3.34	20.00	11.23
VIIIa	70	252–254	$C_{17}H_{15}N_5O_2S$	57.77	4.28	19.82	9.07
		dioxane	353.4	57.52	4.04	19.73	8.93
VIIIb	65	256–257	$C_{17}H_{15}N_5O_3S$	55.27	4.09	18.96	8.68
		dioxane	369.4	55.04	4.03	18.72	8.44
IXa	60	237–239	$C_{15}H_{13}N_5OS$	57.86	4.20	22.50	10.30
		dioxane	311.4	57.64	4.10	22.30	10.13
IXb	60	242–243	$C_{15}H_{13}N_5O_2S$	55.03	4.00	21.40	9.78
		dioxane	327.4	55.01	3.94	21.32	9.63
Xa	80	228–229	$C_{18}H_{14}N_4O_4S$	56.54	3.69	14.65	8.38
		methanol	382.4	56.50	3.52	14.44	8.23
Xb[a]	80	224–226	$C_{18}H_{14}ClN_3O_2S$	58.14	3.80	11.30	8.62
		dioxane	371.8	58.04	3.82	11.14	8.40
XI	55	273–274	$C_{16}H_{10}N_4O_3S$	56.79	2.98	16.56	9.48
		methanol	338.3	56.62	2.74	16.33	9.24
XII	50	147–149	$C_{16}H_{10}N_2OS$	69.04	3.62	10.07	11.50
		dioxane	278.3	68.93	3.44	9.84	11.41
XIIIa	65	225–226	$C_{21}H_{16}N_6O_4S$	56.24	3.60	18.74	7.15
		dioxane	448.5	56.13	3.80	18.44	6.91
XIIIb[b]	45	208–210	$C_{21}H_{16}ClN_5O_2S$	57.60	3.68	16.00	7.31
		DMF–water	437.9	57.52	3.54	15.90	7.14
XIV	70	283–285	$C_{27}H_{22}N_6O_2S$	65.57	4.48	17.00	6.48
		dioxane	494.6	65.34	4.42	16.93	6.24

% Cl: [a] Calculated 9.53, found 9.24. [b] Calculated 8.10, found 7.93.

TABLE II
IR and ^{1}H NMR spectra of the compounds prepared

Compound	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm)	
		benzothiazole and aryl protons	other protons
IIIa	3 300 (NH), 1 700 (CO ester), 1 650 (CONH)	7.4 m, 2 H (H-5,H-6); 7.9–8.1 m, 2 H (H-4,H-7)	3.65 s, 3 H (CH_3); 3.95 s (NHC**H**$_2$); 4.15 s, 2 H (CH_2); 8.8 brs, 1 H (NH)
V	3 300–2 800 (NH_2), 1 650 (CO)	7.4–7.5 m, 2 H (H-5,H-6); 8.0–8.1 m, 2 H (H-4,H-7)	2.6 s, 3 H (CH_3); 2.65 s, 3 H (CH_3); 4.75 s, 1 H (H-5); 5.8 s, 2 H (NH_2)
VI	3 185 (NH–NH), 1 606 (CONH)	7.4–7.5 m, 2 H (H-5,H-6); 7.9–8.1 m, 2 H (H-4,H-7)	1.9 s, 3 H (CH_3); 4.1 s, 2 H (CH_2); 9.95 s, 1 H (NH); 10.3 s, 1 H (NH)
VII	3 200–2 700 (NH–NH and oximino OH), 1 680, 1 640 (CONH)	7.5–7.6 m, 2 H (H-5,H-6); 8.0–8.2 m, 2 H (H-4,H-7)	1.95 s, 3 H (CH_3); 10.2 s, 1 H (NH); 10.7 s, 1 H (NH)
VIIIa	3 400–3 200 (NH–NH and NH), 1 680, 1 640 (CONH)	7.0–7.5 m, 5 H (C_6H_5); 7.8 m, 2 H (H-5,H-6); 8.1–8.3 m, 2 H (H-4,H-7)	1.95 s, 3 H (CH_3); 9.85 s, 1 H (NH); 10.1 s, 1 H (NH); 14.9 s, 1 H (NH)
VIIIb	3 400 (OH), 3 200–2 850 (NH–NH and NH), 1 670, 1 640 (CONH)	7.0 m, 4 H (C_6H_4); 7.5 m, 2 H (H-5,H-6); 7.9–8.2 m, 2 H (H-4,H-7)	2.0 s, 3 H (CH_3); 9.9–10.2 brs, 1 H (NH); 10.15 s, 1 H (NH); 10.5 brs, 1 H (OH); 15.0 s, 1 H (NH)
IXa	3 400 (NH), 2 900, 2 600 (NH–NH), 1 645 (CO)	7.2–7.6 m, 5 H (C_6H_5); 7.8 m, 2 H (H-5,H-6); 8.2–8.4 m, 2 H (H-4,H-7)	11.0 s, 1 H (NH); 15.0 s, 1 H (NH)
IXb	3 450–3 400 (OH,NH), 2 900–2 600 (NH–NH), 1 650 (CO)	6.95–8.2 m, 8 H	10.3 s, 1 H (NH); 10.5 brs, 1 H (OH); 15.0 s, 1 H (NH)
Xa	3 000–3 100 (NH), 1 600 (CONH)	7.4–7.6 m, 2 H (H-5,H-6); 7.9–8.2 m, 6 H (H-4,H-7,C_6H_4)	2.0 s, 3 H (CH_3); 7.8 s, 1 H (CH); 10.1 s, 1 H (NH); 10.3 s, 1 H (NH)
Xb	3 200–3 100 (NH), 1 605–1 600 (CONH)	7.3–7.6 m, 4 H (C_6H_4); 8.0–8.2 m, 4 H (H-4,H-5,H-6,H-7)	2.1 s, 3 H (CH_3); 7.9 s, 1 H (CH); 10.1 s, 1 H (NH); 10.85 s, 1 H (NH)
XI	3 400–3 200 (OH,NH)	7.5 m, 2 H (H-5,H-6); 7.8–8.4 m, 6 H (H-4,H-7,C_6H_4)	8.8 s, 1 H (NH)
XII	3 400 (OH)	7.4–7.6 m, 6 H (H-5,H-6,C_6H_4); 8.1–8.2 m, 2 H (H-4,H-7)	9.0 s, 1 H (H-4)

TABLE II
(*Continued*)

Compound	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm)	
		benzothiazole and aryl protons	other protons
XIIIa	3 400–3 200 (NH_2,NH and OH), 2 200 (CN), 1 650 (CO)	7.0–8.1 m, 8 H	2.0 s, 3 H (CH_3); 4.5 d, 1 H (H-4); 6.4 s, 2 H (NH_2); 10.1 s, 1 H (NH); 12.4 s, 1 H (OH)
XIIIb	3 450–3 200 (NH_2,NH and OH), 2 200 (CN), 1 650 (CO)	7.0–8.0 m, 8 H	2.0 s, 3 H (CH_3); 4.6 d, 1 H (H-4); 6.4 s, 2 H (NH_2); 10.0 s, 1 H (NH); 12.4 s, 1 H (OH)
XIV	3 240–2 923 (OH,NH,NHCO and ring NH), 1 630 (NHCO)	7.4–7.5 m, 5 H (C_6H_5); 7.7–8.2 m, 4 H (H-4,H-5,H-6,H-7)	2.2 s, 3 H (CH_3); 4.05 d, 1 H, J = 10 Hz (H-4); 5.8 d, 1 H, J = 10 Hz (H-5); 6.8–7.1 m, 4 H (benzimidazole protons); 11.2 s, 1 H (NH); 11.8 s, 1 H (NH)

1-(Acetamido-5-(benzimidazol-2-yl)-3-(benzothiazol-2-yl)-2-hydroxy-6-imino-4-phenyl-4,5-dihydropyridine (*XIV*)

A solution of the compound *VI* (2.49 g, 0.01 mol) in dioxane (25 ml) was boiled under reflux with 2-(benzimidazol-2-yl)cinnamonitrile (2.45 g, 0.01 mol) in presence of triethylamine (3 drops) for 6 h. The solution was concentrated and left to cool. The solid formed was filtered off, and crystallized from the appropriate solvent (Table I). Mass spectrum (*m/z*): 494.

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