Benzothiazole Compounds XLIV. Preparation and Growth Regulation Properties of 3-Substituted 2-Benzothiazolinones and Their 4-Chloro Derivatives

[a]V. SUTORIS, [b]A. GÁPLOVSKÝ, [c]V. SEKERKA, and [b]P. ERTL

[a]*Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, CS-842 15 Bratislava*

[b]*Institute of Chemistry, Faculty of Natural Sciences, Comenius University, CS-842 15 Bratislava*

[c]*Department of Molecular Biology and Genetics, Faculty of Natural Sciences, Comenius University, CS-842 15 Bratislava*

Received 29 January 1992

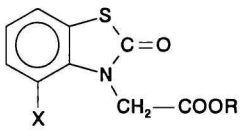
The reactions of (2-oxobenzothiazolin-3-yl)acetyl chloride and (4-chloro-2-oxobenzothiazolin-3-yl)acetyl chloride with phenol, methylphenols, dimethylphenols, and methoxyphenols in acetone in the presence of pyridine gave the corresponding 3-phenoxycarbonylmethyl-2-benzothiazolinones and their 4-chloro derivatives. The mentioned compounds have exhibited a growth stimulation effect of 6 to 60 %, at the concentration of 10^{-5} mol dm^{-3}, upon the coleoptile of *Triticum aestivum* L. The UV and IR spectra of the synthesized compounds are presented. The structures and geometry of the basic compounds have been simulated by means of the quantum chemistry semiempirical method AM1. The calculations have proved the existence of two approximately equally stable conformers differing in the dihedral angles of the phenylcarbonyl group. The differences found in the geometry of molecules may be used for explanation of the different spectroscopic behaviour.

3-Substituted 2-benzothiazolinones represent an area of compounds with promising biological activity in the field of antibacterial preparations [1—6]. For some 3-substituted 4- or 5-chloro- and 5-bromo-2-benzothiazolinones, both the herbicidal [7] and growth regulation [8—10] efficiency have been studied. We have found that 3-benzyloxycarbonylmethyl-2-benzothiazolinone and its 4-chloro derivative exhibit an applicable stimulation activity upon the plant growth (the effects of 25—35 %) and upon the difficultly rooting woody plants [11—14]. The study of the discussed problem field is based on the knowledge that relatively small alterations of the structure of the benzothiazole derivatives cause substantial changes in the biological activity. Therefore, further esters of the type of 3-phenoxycarbonylmethyl-2-benzothiazolinones and their 4-chloro derivatives, so far not described, have been prepared. The starting compounds for this synthesis have been (2-oxobenzothiazolin-3-yl)acetyl chloride [15] or (4-chloro-2-oxobenzothiazolin-3-yl)acetyl chloride and the appropriate phenol derivatives, reacting in acetone in the presence of pyridine. After 24 h standing, the reaction mixture was refluxed for 3—5 h and then diluted with twofold volume of water. The solid portion, after drying, was crystallized from the given solvents (Table 1). The reactions afforded the yields from 54 to 71 % and are not optimized.

All the synthesized compounds absorb the light in the region of λ = 215—300 nm. In the wavelength interval of 270—300 nm, they display a characteristic absorption band with low-resolved maxima of medium intensities (Table 2). A more intensive absorption band is found at λ = 215 nm. The substituents on phenyl ring have a little influence on the absorption maxima positions. However, the intensity of long-wave absorption bands changes with methyl substitution as a result of the induction effect of methyl groups. The change in absorption intensity for the discussed phenyl groups is proportional to the sum of squares of individual transition moments [16]. There is a bathochromic shift of absorption maxima in the case of 4-chloro-3-phenoxycarbonylmethyl-2-benzothiazolinones of approximately 4 nm, and an increase of the intensity ratio of short- and long-wave absorption, respectively (Fig. 1) in comparison with the corresponding nonchlorinated compounds.

The mentioned difference is probably caused either by the auxochromic effect of chlorine or by an intramolecular interaction connected with the stability of the conformers. The optimal space conformations of the nonchlorinated compound *I* and chlorinated *II* have been calculated using quantum chemistry methods. The geometry of both derivatives has been optimized employing the semiempirical AM1

Table 1. Characterization of the Synthesized Compounds



Compound	R	X	Formula	M_r	w_i(calc.)/% / w_i(found)/% C	H	N	S	Yield %	M.p./°C Solvent (φ_r)
I	C_6H_5	H	$C_{15}H_{11}NO_3S$	285.32	63.15 63.08	3.89 3.96	4.91 4.78	11.24 11.14	68	111—113 Ether—acetone (1 : 1)
II	C_6H_5	Cl	$C_{15}H_{10}ClNO_3S$	319.76	56.34 56.50	3.15 3.01	4.38 4.46	10.03 10.26	71	104—106 Acetone—ether (2 : 1)
III	2-$CH_3C_6H_4$	H	$C_{16}H_{13}NO_3S$	299.35	64.20 64.40	4.38 4.19	4.68 4.51	10.71 10.59	65	135—136 Ether—acetone (3 : 1)
IV	2-$CH_3C_6H_4$	Cl	$C_{16}H_{12}ClNO_3S$	333.80	57.57 57.72	3.62 3.50	4.20 4.31	9.61 9.46	69	149—151 Acetone—ether (1 : 1)
V	3-$CH_3C_6H_4$	H	$C_{16}H_{13}NO_3S$	299.35	64.20 63.99	4.38 4.23	4.68 4.62	10.71 10.42	58	150—153 Ether
VI	3-$CH_3C_6H_4$	Cl	$C_{16}H_{12}ClNO_3S$	333.80	57.57 57.36	3.62 3.74	4.20 4.05	9.61 9.55	63	160—162 Acetone
VII	4-$CH_3C_6H_4$	H	$C_{16}H_{13}NO_3S$	299.35	64.20 64.11	4.38 4.27	4.68 4.49	10.71 10.61	60	132—135 Acetone—ether (1 : 2)
VIII	4-$CH_3C_6H_4$	Cl	$C_{16}H_{12}ClNO_3S$	333.80	57.57 57.39	3.62 3.80	4.20 4.03	9.61 9.49	62	148—151 Acetone—ether (1 : 1)
IX	2,3-$(CH_3)_2C_6H_3$	H	$C_{17}H_{15}NO_3S$	313.75	65.23 65.06	4.83 4.69	4.47 4.32	10.24 10.18	55	166—167 Acetone—ether (1 : 1)
X	2,3-$(CH_3)_2C_6H_3$	Cl	$C_{17}H_{14}ClNO_3S$	347.82	58.67 58.53	4.05 4.11	4.02 3.91	9.21 9.24	57	153—154 Acetone
XI	2,5-$(CH_3)_2C_6H_3$	H	$C_{17}H_{15}NO_3S$	313.75	65.23 65.40	4.83 4.98	4.47 4.31	10.24 10.30	60	163 Acetone
XII	2,5-$(CH_3)_2C_6H_3$	Cl	$C_{17}H_{14}ClNO_3S$	347.82	58.67 58.82	4.05 4.12	4.02 3.93	9.21 9.29	64	158—160 Acetone
XIII	3,4-$(CH_3)_2C_6H_3$	H	$C_{17}H_{15}NO_3S$	313.75	65.23 65.11	4.83 4.70	4.47 4.63	10.24 10.32	60	149—152 Acetone—ether (1 : 2)
XIV	3,4-$(CH_3)_2C_6H_3$	Cl	$C_{17}H_{14}ClNO_3S$	347.82	58.67 58.49	4.05 3.87	4.02 4.08	9.21 9.28	58	124—127 Acetone—ether (3 : 1)
XV	3,5-$(CH_3)_2C_6H_3$	H	$C_{17}H_{15}NO_3S$	313.75	65.23 65.31	4.83 4.72	4.47 4.42	10.24 10.43	63	122—126 Acetone—petroleum ether (2 : 1)
XVI	3,5-$(CH_3)_2C_6H_3$	Cl	$C_{17}H_{14}ClNO_3S$	347.82	58.67 58.60	4.05 3.90	4.02 4.13	9.21 9.31	62	157—159 Acetone
XVII	2-$OCH_3C_6H_4$	H	$C_{16}H_{13}NO_3S$	315.35	61.00 61.12	4.15 4.03	4.44 4.47	10.17 10.37	54	129—131 Acetone—ether (1 : 1)
XVIII	2-$OCH_3C_6H_4$	Cl	$C_{16}H_{12}ClNO_3S$	349.79	54.90 54.78	3.74 3.65	4.00 4.09	9.16 9.04	57	146—148 Acetone—ether (2 : 1)
XIX	cyclo-C_6H_{11}	H	$C_{15}H_{17}NO_3S$	291.28	61.91 62.12	5.88 5.70	4.81 4.87	11.01 10.85	56	103—104 Acetone—ether (1 : 2)
XX	cyclo-C_6H_{11}	Cl	$C_{15}H_{16}ClNO_3S$	325.81	55.26 55.41	4.94 4.92	4.29 4.16	9.83 10.08	54	70—71 Acetone—ether (1 : 2)

method [17] whereby the parameter PRECISE has been applied, securing an increased precision of the calculation. The studied molecules are composed of two aromatic systems linked by a chain of four single bonds, and we can assume a considerable conformation flexibility and hence the occurrence of more local energetic minima. The calculations suggested the existence of two approximately equally stable conformers differing in the dihedral angle of phenylcarbonyl group. In both cases, the aromatic systems of the molecule are almost perpendicular. The conformation of *I* with lower energy is depicted in Fig. 2. The energy of the other conformer with twisted phenylcarbonyl moiety is higher by only 0.80 kJ mol^{-1}. The opposite applies to the 4-chloro-substituted *II* where the conformation depicted in Fig. 3 is more advantageous by 2.00 kJ mol^{-1}.

The conformers of the molecule *I* are separated by a barrier of 5.00 kJ mol^{-1} whereas the barrier in the case of derivative *II* is higher, having the value of 16.00 kJ mol^{-1}. The found differences of the geometry of molecules *I* and *II* might explain their different spectroscopic behaviour. Although the π systems of the main skeleton and phenylcarbonyl group are not in a direct conjugation, they may influence each other through space. This influence is, with respect to the opposite phenylcarbonyl moiety twisting, different.

Table 2. IR and UV Spectral Data of the Synthesized Compounds

Compound	$\tilde{\nu}$(ν(C=O))/cm^{-1}	λ_{max} /nm (log (ε/(m^2 mol^{-1})))		
I	1692	214 (3.53)	282 (2.45)	308 (1.98)
II	1692	220 (3.59)	286 (2.29)	294 (2.32)
III	1700	216 (3.54)	282 (2.40)	288 (2.40)
IV	1694	220 (3.60)	272 (1.94)	284 (2.22)
V	1748	214 (3.54)	282 (2.42)	288 (2.41)
VI	1692	218 (2.92)	286 (1.31)	294 (1.33)
VII	1692	216 (3.46)	282 (2.36)	288 (2.36)
VIII	1692	220 (3.54)	286 (2.15)	292 (2.19)
IX	1692	216 (3.49)	282 (2.42)	288 (2.42)
X	1694	218 (2.69)	286 (1.24)	294 (1.33)
XI	1692	216 (3.56)	282 (2.44)	288 (2.42)
XII	1692	220 (3.61)	284 (2.27)	292 (2.30)
XIII	1692	216 (3.35)	282 (2.24)	288 (2.23)
XIV	1692	220 (3.48)	284 (2.12)	292 (2.16)
XV	1692	214 (3.29)	282 (2.06)	288 (2.06)
XVI	1692	218 (3.60)	284 (2.24)	292 (2.27)
XVII	1692	216 (3.37)	280 (2.40)	286 (2.26)
XVIII	1694	220 (3.32)	284 (2.26)	292 (2.20)
XIX	1692	214 (3.55)	282 (2.53)	288 (2.52)
XX	1692	220 (3.64)	286 (2.47)	294 (2.49)

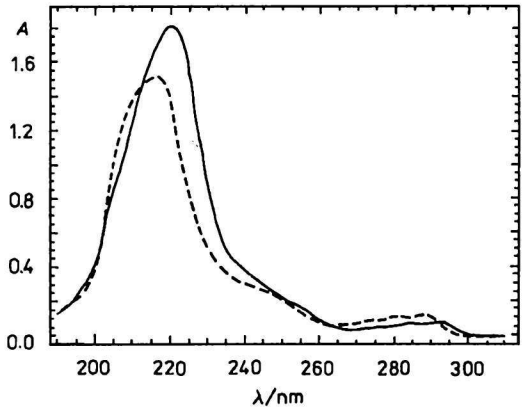


Fig. 1. UV spectra of compounds *VII* (– – – –) and *VIII* (———) in methanol (c = 10^{-4} mol dm^{-3}).

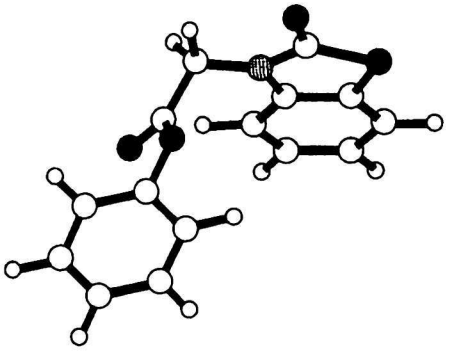


Fig. 2. AM1 optimized geometry of compound *I*.

All the synthesized compounds have been tested on *Triticum aestivum* L., in the concentration of 10^{-5} mol dm^{-3}, at which the standards 3-indolylacetic acid (IAA) and (2,4-dichlorophenoxy)acetic acid (2,4-D) exhibit the highest activity and we found that the compounds are very efficient growth stimulators. For the compounds with the highest activities (*I—III, V, VIII, X, XVII*), tests have been performed in the concentration scale of 10^{-3} to 10^{-13} mol dm^{-3}. In all cases, the highest activity has been found for the concentration of 10^{-5} mol dm^{-3}. From 20 synthesized compounds, 16 have shown highly significant efficiency (Table 3). The listed values are averaged from 10 experiments.

In the previous works [11—14], 3-benzyloxycarbonylmethyl-2-benzothiazolinone and its 4-chloro derivative were described as the most active materials, fulfilling all the criteria for practical application. Their stimulation efficiency varies from 25 to 35 % at the concentration of 10^{-5} mol dm^{-3}, depending on the tested object. Starting from this information, two structural changes have been accomplished in these derivatives. In the benzyloxy group, the methylene has been omitted resulting in a substantial increase of stimulation effect, and in the phenyl group, the hydrogens in various positions have been substituted for one or two methyl or methoxy groups. To assess its influence on activity, the phenoxy group has been replaced with cyclohexyloxy one. The effect of these changes has been thoroughly studied regarding the growth regulation activity. For 4-chloro-3-phenoxycarbonylmethyl-2-benzothiazolinone (*II*), the highest stimulation efficiency (60.18 %), from all up-to-date synthesized benzothiazole derivatives, has been achieved which is comparable to that of 2,4-D (51.09 %). The second highest activity has

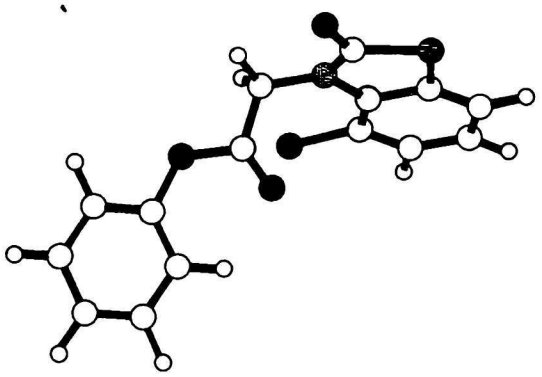


Fig. 3. AM1 optimized geometry of compound *II*.

been recorded for 3-(2-methoxyphenoxycarbonylmethyl)-2-benzothiazolinone (*XVII*; 53.76 %). The substitution of phenoxy group for cyclohexyloxy group (*XIX, XX*) meant a substantial decrease of the stimulation activity. The exchange of a phenyl hydrogen for methyl or methoxy group in the position 2 (*I, III, XVII*) resulted in improved stimulation efficiency from 32.71 % to 41.09 and 53.76 %, respectively. The substitution of hydrogen for methyl group in the position 3 (*V*) increased the activity (43.03 %) but the presence of methyl in the position 4 (*VII*) caused a considerable decrease of the stimulation effect (16.48 %). In the case of compounds *IV*, *VI*, and *VIII* in comparison with *II*, the activity is lower, being approximately equal for all three derivatives. An interesting fact is the effect of *XI* and *XII* with two methyl groups in positions 2 and 5, where an extreme reduction of activity has been observed (7.52 %, 6.27 %). The other derivatives with methyl groups in positions 3,4 (*XIII, XIV*) and 3,5 (*XV, XVI*) have not exhibited significant changes.

In connection with the testing, stability of some derivatives in 90 % ethylene glycol has been examined. A time-dependent change in UV spectra has been recorded. Hydrolysis of esters occurs, proved by means of IR spectra of the corresponding acid and the reaction mixture after preceding gas-chromatographic separation. The rate of the reaction depends on the structure of the reagent. The substitution of benzothiazolinone skeleton with chlorine in the position 4 increases the reaction rate 2.50 times in comparison to the nonchlorinated derivatives. For example, for *I* $k_r = 2.75 \times 10^{-3}$ mol dm^{-3} s^{-1} and for *II* $k_r = 6.78 \times 10^{-3}$ mol dm^{-3} s^{-1}. A similar effect on the rate of the hydrolysis has been observed for methyl group on phenyl in the position 2 (*IV*, $k_r = 14.10 \times 10^{-3}$ mol dm^{-3} s^{-1}) and in the position 3 (*VI*, $k_r = 16.45 \times 10^{-3}$ mol dm^{-3} s^{-1}). Methyl group in the position 4 has no influence (*VIII*, $k_r = 6.68 \times 10^{-3}$ mol dm^{-3} s^{-1}) and the hydrolysis rate remains on the level of compound *II*. This information is important from the point of view of the biological tests results. As it has been mentioned earlier, the studied derivatives exhibit the highest stimulation activity observed for benzothiazolinone derivatives so far. It can be assumed, however, that the investigated compounds undergo hydrolysis during the biological tests. This leads to the question whether the biologically active compound is the ester or the corresponding acid formed by the hydrolysis, eventually the reaction mixture, the equilibrium of which may be shifted depending on the consumption of a particular component by the plant material. This is one of the important factors, beside the differences in the geometry of molecules, which hinders the generalization of the dependence of the biological activity on the structure. The starting acids (2-oxobenzothiazolin-3-yl)acetic acid (A-1) and (4-chloro-2-oxobenzothiazolin-3-yl)acetic acid (A-2) have been synthesized and tested as well. Also phenol (P) has been included in the comparison. The stimulation effects are presented in Table 3 and they are evidently lower than those of some synthesized compounds (*II, V, VI, XVII*).

Table 3. Growth Regulation Activity of the Synthesized Compounds Tested on *Triticum aestivum* L.

Compound	Stimulation ($c = 10^{-5}$ mol dm^{-3})		Compound	Stimulation ($c = 10^{-5}$ mol dm^{-3})	
	Δ*l*/mm	Δ*l*/%		Δ*l*/mm	Δ*l*/%
I	1.75	32.71*	*XIV*	1.29	23.62*
II	3.22	60.18*	*XV*	1.21	21.68*
III	1.87	41.09*	*XVI*	1.21	22.16*
IV	1.43	31.42	*XVII*	3.00	53.76*
V	2.41	43.03*	*XVIII*	1.92	34.40*
VI	2.15	33.75*	*XIX*	1.27	23.73*
VII	1.05	16.48*	*XX*	0.66	12.33
VIII	1.69	22.52*	IAA	5.93	100.33
IX	0.57	10.21	2,4-D	2.56	51.09
X	1.80	32.14*	A-1	0.72	14.84
XI	0.42	7.52	A-2	1.29	26.59
XII	0.40	6.27	P	0.20	4.12
XIII	1.29	23.11*			

* Highly significant activity.

EXPERIMENTAL

The microanalysis of the synthesized compounds is summarized in Table 1. The UV spectra were measured using methanolic solutions ($c = 10^{-4}$ mol dm^{-3}) in 1 cm thick cuvette on HP 8452 A spectrophotometer. The IR spectra were measured on PE 180 apparatus in NaCl cuvettes of 0.1 mm thickness, the compounds being dissolved in $CHCl_3$. The time dependence of the hydrolysis was monitored by means of HP 8452 A spectrophotometer at 25 °C and the concentration of 10^{-4} mol dm^{-3} in 90 % ethylene glycol. The reaction rate was calculated employing the standard program of HP company which uses fitting of the experimental data by the second-order equation. The growth regulation tests were aimed at the prolongation growth of primary roots of wheat (*Triticum aestivum* L.) according to the established methodology [18] and they were compared to the growth regulation activity of the best known phytohormones — 3-indolylacetic acid (IAA) and (2,4-dichlorophenoxy)acetic acid (2,4-D).

(4-Chloro-2-oxobenzothiazolin-3-yl)acetyl Chloride

The solution of 4-chloro-3-carboxymethyl-2-benzothiazolinone (4.8 g; 0.02 mol) and thionyl chloride (5.95 g; 0.05 mol) in 50 cm^3 of dry benzene was heated to reflux for 5 h. After cooling of the reaction mixture to 5—10 °C, the precipitated chloride was filtered off and washed with dry benzene, affording 4.1 g (78 %) of the product with m.p. = 90—92 °C. For $C_9H_5Cl_2NO_2S$ (M_r = 262.11) w_i(calc.): 41.25 % C, 1.92 % H, 5.34 % N, 12.23 % S; w_i(found): 41.42 % C, 1.79 % H, 5.27 % N, 12.40 % S.

3-Phenoxycarbonylmethyl-2-benzothiazolinones

To the solution of (2-oxobenzothiazolin-3-yl)acetyl chloride (2.27 g; 0.01 mol) in 10 cm^3 of dry acetone, dry pyridine (0.79 g; 0.01 mol) and corresponding phenol derivative, resp. cyclohexanol (0.01 mol) were added. After 24 h of standing at room temperature, the reaction mixture was refluxed for 5 h. Acetone was then distilled off and 40—50 cm^3 of cold water were added. The precipitated crystalline portion was dried and crystallized from the acetone—ether (φ_r = 1 : 1) mixture.

4-Chloro-3-phenoxycarbonylmethyl-2-benzothiazolinones

To 15 cm^3 of dry acetone or dimethylformamide, (4-chloro-2-oxobenzothiazolin-3-yl)acetyl chloride (2.62 g; 0.01 mol) was added. After the chloride had dissolved, dry pyridine (1.18 g; 0.015 mol) and corresponding phenol derivative, resp. cyclohexanol (0.015 mol) were added. The reaction mixture was heated to 50—60 °C for 6 h and then poured into 50—70 cm^3 of cold water. The solid portion was dried and crystallized from the solvent mixture.

REFERENCES

1. Elvood, J. K. and Gates, J. W., *J. Org. Chem. 32*, 2956 (1967).
2. Nimmich, W., *J. Prakt. Chem. 27*, 220 (1965).
3. Hunter, R. F., *J. Chem. Soc. 1930*, 125.
4. Hunter, R. F., *J. Chem. Soc. 1935*, 1755.
5. Zinner, H. and Nimmich, W., *J. Prakt. Chem. 14*, 139 (1961).
6. Pilgram, K. and Skiles, R. D., *J. Org. Chem. 39*, 3277 (1974).
7. Godson, D. H., Leafe, E. L., Lush, G. B., and Stevenson, H. A., *Brit.* 862 225 (1961).
8. Sutoris, V., Sekerka, V., and Gáplovský, A., *Chem. Papers*, submitted for publication.
9. Godson, D. H., Leafe, E. L., Lush, G. B., and Stevenson, H. A., *Ger.* 1 417 402 (1973).
10. D'Amico, J. J., *U.S.* 3 993 468 (1976); *Chem. Abstr. 86*, 66 853 (1977).
11. Sutoris, V., Mikulášek, S., Sekerka, V., and Konečný, V., *Czech.* 252 502 (1988).
12. Varkonda, Š., Hýblová, O., Sutoris, V., Konečný, V., and Mikulášek, S., *Czech.* 252 503 (1988).
13. Beška, E., Konečný, V., Sutoris, V., Varkonda, Š., Mikulášek, S., and Sekerka, V., *Czech.* 245 866 (1987).
14. Sutoris, V., *Agrochemia* (Bratislava) *30*, 15 (1990).
15. D'Amico, J. J. and Bollinger, F. G., *J. Heterocycl. Chem. 25*, 1183 (1988).
16. Platt, J. R., *J. Chem. Phys. 19*, 263 (1951).
17. Dewar, M. I. S., Zoebisch, E. G., Healy, E. F., and Stewart, J. J. P., *J. Am. Chem. Soc. 107*, 3902 (1985).
18. Šebánek, J., Sladký, Z., and Procházka, S., *Experimentální morfologie rostlin.* (Experimental Morphology of Plants.) P. 31. Academia, Prague, 1983.

Translated by M. Hudeček