HERBICIDAL ACTIVITY OF 5-HALOIMIDAZO[2,1-*b*]THIAZOLES

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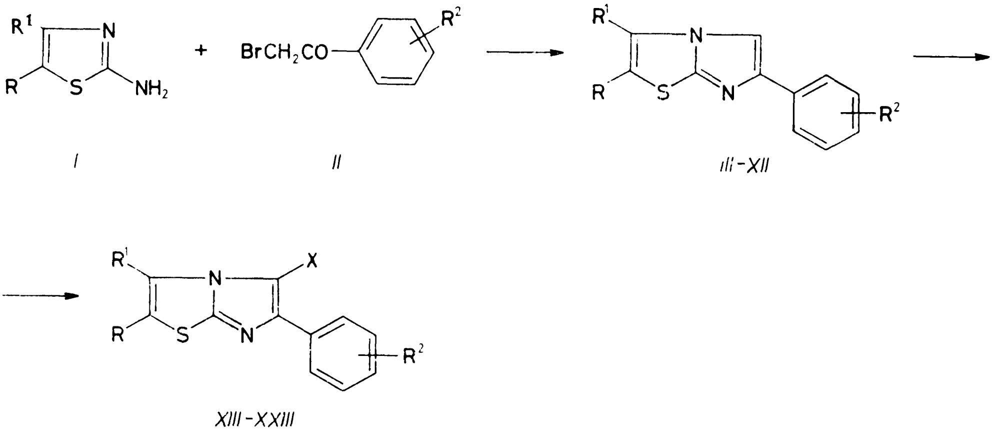
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

A series of 5-haloimidazo[2,1-*b*]thiazoles, related to 5-bromo-6-phenylimidazo[2,1-*b*]thiazole *XIII*, was prepared and tested for their herbicidal activity against seven species of plants.

A few years ago we had the opportunity of preparing 5-bromo-6-phenylimidazo[2,1-*b*]thiazole *XIII* (Scheme 1) as an intermediate for the synthesis of imidazo[2,1-*b*]thiazoles with potential antitumor activity. The synthetic procedure was reported in the literature[1] but to our knowledge reports on the biological activity had not been published, so we sent a sample to FMC, agricultural chemical group (Princeton, NJ), for screening. The significant herbicidal activity shown by this



R, R^1, R^2, X see Table I

SCHEME 1

TABLE I

Physico-chemical data of 5-haloimidazo[2,1-*b*]thiazoles *XIII*—*XXIII*

Compound	R	R¹	R²	X	Starting material	Reference	Formula (M.w.)	M.p., °C	Calculated/Found		
									%C	%H	%N
XIII	H	H	H	Br	*III*	2	$C_{11}H_7BrN_2S$ (279·2)			ref.[1]	
XIV	H	H	H	Cl	*III*	2	$C_{11}H_7ClN_2S$ (234·7)	96—100[b]	56·28 56·56	3·01 3·03	11·94 12·03
XV	Cl	H	H	Br	*IV*	3	$C_{11}H_6BrClN_2S$ (313·6)	124—125	42·12 41·80	1·93 1·85	8·93 8·72
XVI	CH_3	H	H	Br	*V*	1	$C_{12}H_9BrN_2S$ (293·2)			ref.[1]	
XVII	H	CH_3	H	Br	*VI*	4	$C_{12}H_9BrN_2S$ (293·2)			ref.[1]	
XVIII	CH_3	CH_3	H	Br	*VII*	5	$C_{13}H_{11}BrN_2S$ (307·2)	184—186 dec.	50·82 50·86	3·61 3·56	9·12 8·84
XIX	H	H	2-Cl	Br	*VIII*	[a]	$C_{11}H_6BrClN_2S$ (313·6)	123—124	42·12 42·21	1·93 1·99	8·93 9·15
XX	H	H	4-Br	Br	*IX*	1	$C_{11}H_6Br_2N_2S$ (358·1)	157—160	36·89 37·12	1·69 1·69	7·82 7·64
XXI	H	H	2,4-Cl_2	Br	*X*	6	$C_{11}H_5BrCl_2N_2S$ (348·1)	172—175	37·96 38·26	1·45 1·53	8·05 8·25
XXII	H	H	4-OCH_3	Br	*XI*	7	$C_{12}H_9BrN_2OS$ (309·2)	77—80	46·61 46·38	2·93 2·98	9·06 9·10
XXIII	H	H	4-NO_2	Br	*XII*	8	$C_{11}H_6BrN_3O_2S$ (324·2)			ref.[9]	

[a] See Experimental; [b] crystallized from petroleum ether.

compound, prompted us to prepare a number of analogs in order to evaluate the effect of different substituents at the positions 2, 3, 5, 6. In compound *XIV* chlorine is present in place of bromine; compounds *XV*–*XVIII* have substituents at position 2, 3 and finally compounds *XIX*–*XXIII* bear a substituted phenyl ring at position 6 (see Table I).

The imidazo[2,1-*b*]thiazoles *III*–*XII* were prepared by reacting 2-aminothiazole *I* with the appropriate 2-bromo-acetophenone *II* according to previously reported methods[1–8]. The imidazo[2,1-*b*]thiazole thus obtained was treated with N-bromosuccinimide (NBS) or with bromine in order to prepare the 5-bromo derivative;

TABLE II
IR and ^{1}H NMR data of compounds *XIII*–*XXIII*

Compound	$\tilde{\nu}_{max}$, cm^{-1}	δ^a, ppm
XIII	1 540, 845, 757, 635	7·50 d, 1 H (th, *J* = 4·4); 7·50 m, 3 H (ar); 7·95 d, 1 H (th, *J* = 4·4); 8·0 m, 2 H (ar)
XIV	1 545, 1 150, 760, 650	7·50 d, 1 H (th, *J* = 4·4); 7·50 m, 3 H (ar); 7·95 d, 1 H (th, *J* = 4·4); 8·0 m, 2 H (ar)
XV	1 117, 1 012, 758, 687	7·45 m, 3 H (ar); 7·98 m, 2 H (ar); 8·32 s, 1 H (th)
XVI	1 605, 1 115, 760, 682	2·43 d, 3 H (CH_3, *J* = 1·4); 7·45 m, 3 H (ar); 7·68 q, 1 H (th, *J* = 1·4); 8·0 m, 2 H (ar)
XVII	1 050, 763, 721, 679	2·63 d, 3 H (CH_3, *J* = 1·4); 7·0 q, 1 H (th, *J* = 1·4); 7·45 m, 3 H (ar); 7·95 m, 2 H (ar)
XVIII	1 600, 1 121, 760, 685	2·30 s, 3 H (CH_3); 2·56 s, 3 H (CH_3); 7·45 m, 3 H (ar); 7·95 m, 2 H (ar)
XIX	1 320, 970, 760, 642	7·49 d, 1 H (th, *J* = 4·4); 7·52 m, 4 H (ar); 7·90 d, 1 H (th, *J* = 4·4)
XX	1 325, 823, 705, 662	7·48 d, 1 H (th, *J* = 4·4); 7·70 d, 2 H (ar, *J* = 9); 7·90 d, 1 H (th, *J* = 4·4); 7·95 d, 2 H (ar, *J* = 9)
XXI	1 325, 1 119, 972, 642	7·54 d, 1 H (th, *J* = 4·4); 7·60 m, 2 H (ar); 7·80 m, 1 H (ar); 8·0 d, 1 H (th, *J* = 4·4)
XXII	1 300, 1 130 1 100, 1 020	3·80 s, 3 H (OCH_3); 7·04 d, 2 H (ar, *J* = 9); 7·45 d, 1 H (th, *J* = 4·4); 7·88 d, 1 H (th, *J* = 4·4); 7·90 d, 2 H (ar, *J* = 9)
XXIII	1 595, 1 505, 1 340, 1 160	7·80 d, 1 H (th, *J* = 4·4); 8·06 d, 1 H (th, *J* = 4·4); 8·13 d, 2 H (ar, *J* = 9); 8·60 d, 2 H (ar, *J* = 9)

[a] *J* given in Hz; th thiazole, ar aromatics.

in one trial experiment the yield was better with bromine than with NBS, so we chose to use bromine to synthesize compounds *XV–XXIII*. On the other hand we found the 5-chloro derivative *XIV* easier to prepare with N-chlorosuccinimide (NCS) instead of chlorine. The spectroscopic data of compounds *XIII–XXIII* agree with the assigned structures (see Table II).

The herbicidal activity of the compounds *XIII–XXIII* against seven different species of plants is reported in Table III. The substitution of bromine in position 5 by chlorine (*XIV*) as well as the introduction of a second halogen at the 2-position (*XV*) brings no significant differences in comparison to the activity of the parent compound *XIII*. On the contrary, the introduction of a methyl group in position 2 or 3 gives rise to a complete loss of activity. As far as the substituent in the phenyl ring is concerned, the only *o*-substituted compound (*XIX*) is quite inactive.

EXPERIMENTAL

Chemistry

The melting points are uncorrected; unless stated otherwise the compounds were crystallized from ethanol. Bakerflex plates (Silica gel IB2-F) were used for TLC, the eluent was a mixture

TABLE III

Herbicidal activity of compounds *XIII–XXIII* expressed as percent control: preemergence-postemergence

Compound	Plant species[a]						
	A	B	C	D	E	F	G
XIII	0–70	20–0	0–30	0–30	0–50	0–40	0–30
XIV	0–30	0–20	0–30	0–50	0–50	0–60	0–90
XV	0–30	0–30	20–30	0–30	30–30	0–60	0–50
XVI	0–0	0–0	0–0	0–0	0–0	0–0	0–0
XVII	0–0	0–0	0–0	0–0	0–0	0–0	0–0
XVIII	0–0	0–0	0–0	0–0	0–0	0–20	0–60
XIX	0–0	0–0	0–0	0–0	0–0	0–0	0–0
XX	0–0	0–10	0–20	0–10	0–10	0–50	0–30
XXI	0–20	0–40	0–20	0–30	0–30	0–50	0–90
XXII	20–10	20–10	30–10	10–20	95–20	0–0	0–20
XXIII	0–10	0–10	0–20	0–0	0–0	0–40	0–30

[a] A Soybean (*Glycine max.*), B Corn (*Zea mays*), C Wheat (*Triticum aestivum*), D Morningglory (*Ipomoea spp*), E Velvetleaf (*Abutilon theophrasti*), F Barnyardgrass (*Echinochloa crus-galli*), G Foxtail green (*Setaria viridis*).

of petroleum ether–acetone in various proportions. The IR spectra were recorded in Nujol on a Perkin–Elmer 298 and are given in cm^{-1}. The ^{1}H NMR spectra were recorded on a Varian EM390 (90 MHz) using TMS as an internal standard and are given in δ ppm. The solvent was deuterated trifluoroacetic acid for compound *XXIII* and hexadeuteriodimethyl sulfoxide for all the others.

6(2-Chlorophenyl)imidazo[2,1-*b*]thiazole (*VIII*)

o-Chloroacetophenone (10·8 g, 70 mmol) was dissolved in $CHCl_3$ and treated dropwise, under stirring at 0—5°C, with the equivalent of bromine dissolved in $CHCl_3$ (10 ml). The reaction mixture was then maintained at room temperature for 30 min and evaporated under reduced pressure. The resulting oil (crude 2-bromo-*o*-chloroacetophenone) was reacted, without further purification, with 2-aminothiazole (7 g, 70 mmol) dissolved in acetone (100 ml). The mixture was refluxed for 20 min and the resulting precipitate was collected, washed with acetone and refluxed for 1 h with 300 ml of 2M-HBr. Before cooling, the solution was cautiously treated under stirring with 15% NH_4OH until basic. The precipitate of 6(2-chlorophenyl)imidazo-[2,1-*b*]thiazole *VIII* was collected and crystallized with a yield of 50%; m.p. 88—90°C (ethanol). IR spectrum: 1 195, 1 030, 757, 641. ^{1}H NMR spectrum: 7·30 d, 1 H (th, J = 4·5); 7·45 m, 3 H (ar); 8·0 d, 1 H (th, J = 4·5); 8·20 m, 1 H (ar); 8·43 s, 1 H (H-5). For $C_{11}H_7ClN_2S$ (234·7) calculated: 56·29% C, 3·01% H, 11·94% N; found: 56·65% C, 2·99% H, 12·14% N.

5-Chloro-6-phenylimidazo[2,1-*b*]thiazole (*XIV*)

6-Phenylimidazo[2,1-*b*]thiazole (*III*, ref.[2]) (15 mmol) was dissolved in 100 ml of $CHCl_3$ and treated with 18 mmol of NCS. The reaction mixture was refluxed for 10 min, washed with 10% Na_2CO_3 and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was crystallized with a yield of 60% (see Tables I, II).

5-Bromo-6-phenylimidazo[2,1-*b*]thiazoles *XV*—*XXIII*

The starting compounds *III*—*XII* (refs[1–8]) (10 mmol) were dissolved in $CHCl_3$ (50 ml) and treated dropwise, under stirring and cooling (10—15°C), with a solution of bromine (10 mmol) in $CHCl_3$ (5 ml). The resulting salt was collected, washed with $CHCl_3$ and stirred for 2 h at room temperature with 150 ml of 0·5M-NaOH. The precipitate thus formed was collected, washed with water and crystallized (see Tables I, II), with an approximate yield, calculated on the starting compound, of 45% (*XVIII*, *XXII*), 75% (*XV*, *XIX*, *XXI*) and 90% (*XX*).

Biology

Compounds *XIII*—*XXIII* were tested against seven species at an application rate of 8 kg/ha with two procedures (see Table III):

a) *Preemergence*: seeds were planted and the soil was sprayed with a solution of the compound under test. Results were recorded 10—14 days after the treatment and are reported as percent control, so the effect may be absent (0), slight (10—30), moderate (40—60), severe (70—90) or complete (100).

b) *Postemergence*: a solution of the compound under test was sprayed onto 10—14 day old plants. After additional 10—14 days, results were recorded as in the preemergence test.

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REFERENCES

1. Pyl T., Giebelmann R., Beyer H.: Justus Liebigs Ann. Chem. *643*, 145 (1961).
2. Kickhöfen B., Kröhnke F.: Chem. Ber. *88*, 1109 (1955).
3. Werbel L. M., Zamora M. L.: J. Heterocycl. Chem. *2*, 287 (1965).
4. Kondo H., Nagasawa F.: J. Pharm. Soc. Jpn. *57*, 1050 (1937); Chem. Abstr. *32*, 3398 (1938).
5. Kochergin P. M., Shchukina M. N.: Zh. Obshch. Khim. *26*, 458 (1956); Chem. Abstr. *50*, 13883b (1956).
6. Andreani A., Rambaldi M., Andreani F., Bossa R., Galatulas I.: Eur. J. Med. Chem. *23*, 385 (1988).
7. Pyl T., Bülling L., Wünsch K., Beyer H.: Justus Liebigs Ann. Chem. *643*, 153 (1961).
8. Matsukawa T., Ban S.: J. Pharm. Soc. Jpn. *71*, 756 (1951); Chem. Abstr. *46*, 8094b (1952).
9. Saldabols N., Lando O. E.: Khim. Geterotsikl. Soedin. *1978*, 258; Chem. Abstr. *88*, 190733d (1978).