Synthesis of cyclic *N*-(aryloxyacetyl)-X-dicarboximides and their pesticidal activity

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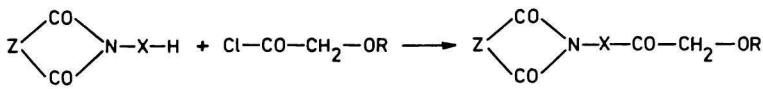
Dedicated to Professor RNDr. V. Sutoris, CSc., in honour of his 60th birthday

Seven types of cyclic *N*-aryloxyacetyl-X-dicarboximides were synthesized by acylation of cyclic *N*-hydroxy-, *N*-amino-, *N*-methylhydroxy-, *N*-ethylhydroxy-, and *N*-phenylhydroxydicarboximides. These compounds were found to have a high and selective herbicidal activity and most of them also reveal a 25—50 % growth inhibition of *Tilletia caries*.

Посредством ацилирования циклических *N*-гидрокси-, *N*-амино-, *N*-метилгидрокси-, *N*-этилгидрокси- и *N*-фенилгидроксидикарбоксиимидов было синтезировано 7 типов циклических *N*-арилоксиацетил-X-дикарбоксиимидов. Полученные соединения обладают высокой селективной гербицидной активностью, и большинство из них проявляет также 25—50 % ингибирование роста *Tilletia caries* в фунгицидных опытах.

Chlorine-substituted aryloxyacetic acids have been used for more than three decades as herbicides [1]. Cyclic dicarboximides, as *e.g. N*-substituted 3,4,5,6-tetrahydrophthalimides [2, 3] are efficient and selective pesticides, *N*-arylamino-1,4-epoxy-5-cyclohexene-2,3-dicarboximides [4] reveal a herbicidal activity, the latter inhibit the growth of *Sinapis alba* and *Pisum sativum* in a 3 g m^{-2} surface concentration by 90—100 %. Esters of *N*-bicyclo[2.2.1]-5-heptene-2,3-dicarboximidoacetic acid inhibit the growth of *Fagopyrum vulgare*, *Sinapis alba*, and *Beta vulgare* in a 1.5 g m^{-2} surface concentration [5]. The importance of this group of compounds has recently been growing for their ability to regenerate damages of cultural plants after application of pesticides [6]. Both types of the starting compounds are known to be biologically active and therefore, we synthesized aryloxy derivatives of cyclic dicarboximides and tested their herbicidal, fungicidal and insecticidal efficacies.

Starting compounds for the synthesis of title products were *N*-hydroxyphthalimide, *N*-hydroxymethylphthalimide, *N*-hydroxyethylphthalimide, *N*-(4-hydroxyphenyl)phthalimide, *N*-hydroxy-1,4-epoxy-5-cyclohexene-2,3-dicarboximide, *N*-hydroxy- and *N*-aminobicyclo[2.2.1]-5-heptenedicarboximides, which are not phytotoxic in herbicidal tests. These were acylated with aryloxyacetic chlorides in dimethylformamide in the presence of pyridine (Scheme 1). Reaction temperatures were kept in the 25—80 °C temperature range depending on the type of the substrate. Those having a hydroxyl group at the amide nitrogen atom required 70—80 °C, the *N*-phenyloxy derivative 50—60 °C, and *N*-amino derivatives and those having an alkyl group between the hydroxyl and nitrogen atom 25—35 °C. Yields of this reaction vary between 70 % and 80 %. The products are relatively difficultly soluble, solvents suitable for crystallization are dimethyl sulfoxide, dimethylformamide, and acetic acid. The ^{1}H NMR spectra (Table 1) were in favour of the presumed structure; measured were the saturated dimethyl sulfoxide solutions.



Z		X	
C_6H_4	(*I–XIII*)	O	(*I–III, XIV–XXI*)
	(*XIV–XVII*)	CH_2O	(*IV–VII*)
		CH_2CH_2O	(*VIII–XI*)
	(*XIX–XXIV*)	$4\text{-}C_6H_4O$	(*XII, XIII*)
		NH	(*XXII–XXIV*)

R	
phenyl	(*I, V, XI, XIII, XXI, XXIV*)
2-naphthyl	(*IV, XII, XVI*)
4-chlorophenyl	(*II, VI, VIII, XIV, XX, XXII*)
2-methyl-4-chlorophenyl	(*III, X, XVI, VII*)
2,4,5-trichlorophenyl	(*VII, IX, XIII, XV, XIX, XXIII*)

Scheme 1

Herbicidal tests of these products showed a great phytotoxicity and selectivity (Table 2). Comparison with 2-methyl-4-chlorophenoxyacetic acid, employed as a standard, disclosed a very close effect: these compounds are either equally effective and more selective or even more effective and have a similar spectrum of

Table 1

N-Aryloxyacetyl-X-dicarboximides

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Cl	Yield %	θ(reaction) °C	M.p. °C	^{1}H NMR δ/ppm
I	$C_{16}H_{11}NO_5$	64.60	3.70	4.71	—	54	80	141—145	5.02 (s, 2H), 6.31—7.62 (m, 9H)
	297.2	64.88	3.49	4.70					
II	$C_{16}H_{10}ClNO_5$	57.94	3.02	4.28	10.35	52	80	147	4.57 (s, 2H), 6.75—7.82 (m, 8H)
	331.0	57.81	3.12	4.48	10.35				
III	$C_{17}H_{12}ClNO_5$	59.07	3.48	4.05	10.25	54	80	125	
	345.6	59.26	3.24	3.94	10.12				
IV	$C_{21}H_{15}NO_5$	70.76	4.05	3.75	—	86	35	148	4.87 (s, 2H), 5.72 (s, 2H), 6.75—7.77 (m, 7H),
	373.4	70.81	4.16	3.52					7.82 (s, 4H)
V	$C_{17}H_{13}NO_5$	65.57	4.18	4.50	—	84	35	113	4.72 (s, 2H), 5.67 (s, 2H), 6.75—7.30 (m, 5H),
	311.3	65.42	4.01	4.44					7.78 (s, 4H)
VI	$C_{17}H_{12}ClNO_5$	59.04	3.47	4.05	10.27	87	35	164—166	4.75 (s, 2H), 5.70 (s, 2H), 6.83—7.25 (q, 4H),
	345.6	59.18	3.21	4.22	10.40				7.87 (s, 4H)
VII	$C_{17}H_{10}Cl_3NO_5$	49.24	2.43	3.38	25.65	90	35	183	5.00 (s, 2H), 5.70 (s, 2H), 7.37 (s, 1H),
	414.6	49.34	2.12	3.18	26.05				7.60 (s, 1H), 7.87 (s, 4H)
VIII	$C_{18}H_{14}ClNO_5$	60.12	3.89	3.89	9.85	80	40	97—98	3.75—3.90 (t, 2H), 4.24—4.37 (t, 2H), 4.62 (s, 2H),
	359.6	60.34	3.91	3.87	9.84				6.70—7.22 (m, 4H), 7.80 (s, 4H)
IX	$C_{18}H_{12}Cl_3NO_5$	50.40	2.80	3.26	24.82	82	40	141	3.77—3.90 (t, 2H), 4.25—4.40 (t, 2H), 4.82 (s, 2H),
	428.5	50.57	2.82	3.28	24.45				7.37 (s, 1H), 7.55 (s, 1H), 7.77 (s, 4H)
X	$C_{19}H_{16}ClNO_5$	61.08	4.28	3.74	9.48	80	40	146	2.05 (s, 3H), 3.75—3.90 (t, 2H), 4.25—4.40 (t, 2H),
	373.6	61.31	4.45	3.88	9.11				4.65 (s, 2H), 6.61—7.00 (m, 3H), 7.77 (s, 4H)

Table 1 (Continued)

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%				Yield	θ(reaction)	M.p.	^{1}H NMR
		C	H	N	Cl	%	°C	°C	δ/ppm
XI	$C_{18}H_{15}NO_5$	66.46	4.61	4.31	—	77	40	93—94	3.77—3.90 (t, 2H), 4.27—4.40 (t, 2H), 4.62 (s, 2H),
	325.1	66.60	4.43	4.52					6.67—7.27 (m, 5H), 7.80 (s, 4H)
XII	$C_{26}H_{17}NO_5$	73.75	4.02	3.30	—	60	60	203	
	423.3	73.68	4.11	3.21					
XIII	$C_{22}H_{12}Cl_3NO_5$	55.40	2.52	2.93	22.35	63	60	280	
	476.5	55.69	2.24	3.24	21.85				
XIV	$C_{16}H_{12}ClNO_6$	54.94	3.43	4.00	10.14	58	70	156	3.05 (s, 2H), 5.20 (s, 2H), 5.27 (s, 2H),
	349.5	55.24	3.62	4.28	10.04				6.50 (s, 2H), 6.92—7.37 (m, 4H)
XV	$C_{16}H_{10}Cl_3NO_6$	45.87	2.40	3.34	25.44	60	70	171	3.05 (s, 2H), 5.20 (s, 2H), 5.45 (s, 2H),
	418.5	45.48	2.69	3.71	25.82				6.52 (s, 2H), 7.47 (s, 2H), 7.65 (s, 1H)
XVI	$C_{17}H_{14}ClNO_6$	56.15	3.85	3.85	9.77	57	70	149	2.15 (s, 3H), 3.02 (s, 2H), 3.25 (s, 2H),
	363.3	56.32	3.52	3.61	9.38				5.17 (s, 2H), 6.50 (s, 2H), 6.87—7.25 (m, 3H)
XVII	$C_{20}H_{15}NO_6$	65.73	4.10	3.83	—	56	70	129	3.02 (s, 2H), 5.20 (s, 2H), 5.35 (s, 2H),
	365.1	65.52	4.33	4.02					6.50 (s, 2H), 7.05—7.87 (m, 7H)
XVIII	$C_{16}H_{13}NO_6$	58.71	3.97	4.28		58	70	128—129	3.05 (s, 2H), 5.20 (s, 4H), 6.47 (s, 2H),
	327.1	58.89	4.07	4.44					6.82—7.40 (m, 5H)

Table 1 (Continued)

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Cl	Yield %	θ(reaction) °C	M.p. °C	^{1}H NMR δ/ppm
XIX	$C_{17}H_{12}Cl_3NO_5$	49.03	2.88	3.36	25.54	63	70	192	1.52 (s, 2H), 3.17—3.42 (m, 4H), 4.92 (s, 2H),
	416.4	49.22	2.64	3.15	25.53				6.02 (s, 2H), 7.32 (s, 1H), 7.66 (s, 1H)
XX	$C_{17}H_{14}ClNO_5$	58.70	4.04	4.04	10.20	59	70	154—156	1.55 (s, 2H), 3.15—3.50 (m, 4H), 5.10 (s, 2H),
	347.5	58.54	3.86	3.99	10.14				6.05 (s, 2H), 6.82—7.37 (m, 4H)
XXI	$C_{17}H_{15}NO_5$	63.74	4.98	4.65	—	61	70	132—133	1.55 (s, 2H), 3.32 (s, 2H), 3.45 (s, 2H),
	313.1	63.62	4.87	4.43					5.12 (s, 2H), 6.07 (s, 2H), 6.75—7.42 (m, 5H)
XXII	$C_{17}H_{15}ClN_2O_4$	58.87	4.35	8.87	10.57	84	30	198	1.50 (s, 2H), 3.00—3.50 (m, 4H), 4.62 (s, 2H),
	346.5	58.78	4.36	8.51	10.40				6.02 (s, 2H), 6.62—7.37 (q, 4H)
XXIII	$C_{17}H_{13}Cl_3N_2O_4$	49.10	3.13	6.74	25.61	86	30	158	1.50 (s, 2H), 3.00—3.47 (m, 5H), 4.82 (s, 2H),
	415.4	48.92	3.01	6.62	26.06				6.02 (s, 2H), 7.27 (s, 1H), 7.65 (s, 1H)
XXIV	$C_{17}H_{16}N_2O_4$	63.97	5.33	9.33	—	84	30	184	1.52 (s, 2H), 3.00—3.50 (m, 4H), 4.62 (s, 2H),
	312.1	63.75	5.23	9.12					6.02 (s, 2H), 6.75—7.37 (m, 5H), 10.57 (s, 1H)

^{1}H NMR of the starting dicarboximides δ(DMSO)/ppm: 2-hydroxyphthalimide 7.75 (s, 4H); 2-hydroxymethylphthalimide 5.00 (s, 2H), 7.77 (s, 4H); 2-hydroxyethylphthalimide 3.75—4.00 (t, 2H), 4.16—4.37 (t, 2H), 7.55 (s, 1H), 7.77 (s, 3H); *N*-hydroxy-1,4-epoxy-5-cyclohexene-2,3-dicarboximide 2.77 (s, 2H), 5.10 (s, 2H), 6.47 (s, 2H); *N*-hydroxybicyclo[2.2.1]-5-heptene-2,3-dicarboximide 1.50 (s, 2H), 3.20 (s, 4H), 6.00 (s, 2H), 10.37 (s, 1H); *N*-aminobicyclo[2.2.1]-5-heptene-2,3-dicarboximide 1.50 (s, 2H), 3.17 (s, 4H), 4.72 (s, 2H), 5.96 (s, 2H).

Table 2

Inhibition tests of the studied compounds*

Compound	Conc.**	*Echinochloa crus-galli*	*Beta vulgare*	*Pisum sativum*	*Avena fatua*	*Vicia sativa*	*Sinapis alba*	*Amaranthus retroflexus*	*Linum usitatissimum*	*Zea mays*	*Triticum sativum*	*Fagopyrum vulgare*
II	*a*	4	5	5	3	5	5	5	5	2	3	4
	c	2	5	5	0	5	5	5	2.5	1	1	2.5
III	*a*	0	0	4	0	4	4.5	3	1.5	0	0	2
	c	0	0	2	0	3	2	0	0	0	0	0
IV	*a*	5	5	5	3	4	4.5	5	5	2.5	0	1
	c	5	5	5	0	2	3	5	5	0	0	0
VI	*a*	—	5	5	5	4	5	5	5	0	3	4
	c	—	5	5	2	1	5	5	5	0	1	2
VIII	*a*	—	5	5	3	5	5	—	5	1.5	3.5	4
	c	—	2	5	1	2.5	5	—	5	0	2	2
IX	*a*	—	1	1	0	3	0	—	3	2	0	2
X	*a*	—	5	1	0	2	5	5	5	0	0	2
	c	—	2	0	0	0	2.5	0	0	0	0	0
XIII	*a*	—	5	2	3	5	5	5	5	2.5	1.5	5
	c	—	2	0	2	2	2	3	5	1.5	0	3
XIV	*a*	4	5	5	3	5	5	5	5	1	3	4.5
	c	0	2	1.5	1	4	5	5	5	0	0	1
XV	*a*	4.5	5	5	4.5	5	5	5	5	0	0	4.5
	c	1	4.5	0	0	1	5	5	5	0	0	1

Table 2 (Continued)

Compound	Conc.**	*Echinochloa crus-galli*	*Beta vulgare*	*Pisum sativum*	*Avena fatua*	*Vicia sativa*	*Sinapis alba*	*Amaranthus retroflexus*	*Linum usitatissimum*	*Zea mays*	*Triticum sativum*	*Fagopyrum vulgare*
XVI	*a*	1	5	5	1	5	5	5	5	2	2.5	5
	c	0	5	1.5	0	5	5	5	5	0	0	3
	f	0	5	0	0	5	5	5	5	0	0	0
XVII	*a*	1	5	5	1	5	5	5	5	1	0	2
	c	0	5	5	0	3	5	5	5	1	0	2
	f	0	5	5	0	0	5	5	5	0	0	0
XIX	*a*	5	5	5	2.5	4.5	5	5	5	0	0	0
	c	3.5	5	3	0	4	5	5	5	0	0	0
XX	*a*	5	5	4	3	4	5	5	5	1.5	2	1
	c	2.5	5	1	0	1.5	4	5	5	0	0	0
XXII	*a*	3	5	5	1	5	5	5	5	3	2	1
	c	0	5	2	0	2.5	5	5	5	0	0	0
XXIII	*a*	0	5	5	0	5	5	5	5	0	0	1
	c	0	5	5	0	5	5	5	5	0	0	0
	f	0	5	5	0	0	5	1	4	0	0	0
MCPA	*a*	1	5	5	0	5	5	5	5	1	2	5
	c	1	5	5	0	3	5	5	5	0	0	3
	f	0	5	2	0	0	5	3	0	0	0	0

* Inhibition grades 0—5 (0—100 %).

** Surface concentration $a = 0.5$ g m^{-2}, $c = 0.158$ g m^{-2}, $f = 0.05$ g m^{-2} (preemergent application).

— not tested.

action. Bicyclic derivatives were found to be more effective than derivatives having an aromatic ring. Separation of oxygen from nitrogen by a methyl, ethyl or phenyl group does not substantially influence the efficacy. When applied *in vitro* and *in vivo*, these compounds showed in fungicidal tests a 25 % inhibition of growth of *Erisiphe graminis*, *Phytophtora infestans*, *Tilletia caries*, *Botritis cinerea*, *Fusarium avenaceum*, and *Alternaria alternata* at the same reference. Compounds *VIII*, *XV* inhibited the growth of *E. graminis* and compounds *II*, *IV*, *VI*, *XIV*, *XV*, *XXII*, *XXIII* the growth of *Tilletia caries* by 50 %.

The synthesized compounds were ineffective in contact application insecticidal tests against *Musca domestica*, *Calandra granaria*, *Aphis fabae*, and *Tetranychus urticae*. Ovicidal tests against *T. urticae* with compounds *V*—*VII*, *IX*, *XX* showed a 20—30 % activity of the reference.

Experimental

N-Hydroxy-1,4-epoxy-5-cyclohexene-2,3-dicarboximide was prepared according to [7], *N*-hydroxybicyclo[2.2.1]-5-heptene-2,3-dicarboximide and *N*-aminobicyclo[2.2.1]-5-heptene-2,3-dicarboximide according to [8].

The ^{1}H NMR spectra of saturated dimethyl sulfoxide solutions were recorded with a Tesla BS 487 A spectrometer operating at 80 MHz, hexamethyldisiloxane being the internal reference.

Herbicidal tests

The model inhibition test of Hill reaction was carried out according to [9] by the *in vitro* method using pyrazone as the standard. The most active compounds were pre- and postemergently applied to living plants and the effect was contrasted with 2-methyl-4-chlorophenoxyacetic acid (MCPA) as reference substance at a 5.0 kg, 1.58 kg, 0.5 kg, and 0.158 kg per hectare dose and graded 0 — unharmed plants, 1—5 harmed plants (20—100 %).

Fungicidal tests

The fungicidal effect was tested by the *in vitro* method [10] using following references: Vitavax, Euparen, captan, methylenethiocyanate. Evaluation grades: 0 — control, 1—4 — inhibition of the growth of microorganisms (25—100 %).

Insecticidal tests

The insecticidal tests were carried out according to [11] *in vitro*, fenitrothion being the reference. Surface concentration of the compound tested was 5 mg cm^{-3}, 1 mg cm^{-3}, 0.5 mg cm^{-3}, and 0.1 mg cm^{-3}.

N-Aryloxyacetyl-X-dicarboximides

A solution of aryloxyacetic chloride (60 mmol) in anhydrous dimethylformamide (20 cm^3) was dropwise added to a stirred solution of N-hydroxy-X-dicarboximide (50 mmol) in dimethylformamide (20 cm^3) and pyridine (10 cm^3) at 25 °C. The mixture was then stirred for additional 3 h, cooled to 0 °C, poured onto crushed ice (100 g), and the separated precipitate was filtered off. The product was stirred in 2 % $NaHCO_3$ (50 cm^3) for 30 min, filtered and crystallized from acetic acid, dimethylformamide or dimethyl sulfoxide. The products are characterized in Table 1.

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