SYNTHESIS AND FUNGICIDAL ACTIVITY OF ISOXAZOLINES FUSED TO 3,5-DICHLOROMALEIMIDE*

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3-Phenyl-5-(3,5-dichlorophenyl)-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles (*III*, R = H) and 3-phenyl-5-(3,5-dichlorophenyl-6a-methyl-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles (*IV*, R = CH_3) were prepared by 1,3-dipolar cycloaddition of substituted benzonitrile oxides *I* to N-(3,5-dichlorophenyl)maleimide (*I*, R = H), or its methyl derivative *II*, (R = CH_3). Cycloaddition to compound *II* (R = CH_3) proceeded regiospecifically. Reduction of *IVg* with $NaBH_4$ was regio- and stereoselective to yield the hydroxylactams *VIIg*, *VIIIg* and *IXg*. Antifungal activity of several products was worse than that of commercial preparations.

Some compounds of dicarboximide type are reported[1-4] to reveal effective systemic activity against *Botrytis cinerea, Cochliobolus miyabeanus* and *Pellicularia sasaci*. In continuation of our project to utilize products of 1,3-dipolar cycloadditions to heterocyclic compounds we described the preparation and antifungal properties of fused isoxazolines based on substituted maleimides[5,6]. The aim to synthesize isoxazolines fused to 3,5-dichlorophenylmaleimide was stimulated by the finding that the parent derivative – N-(3,5-dichlorophenyl)pyrrolidine-2,5-dione (Dimetachlon) – is being used as a protective and curative fungicide[2] and the cycloadduct of N-(3,5-dichlorophenyl)maleimide to furan[7] and its derivatives have also considerable fungicidal properties.

Substituted 3-phenyl-5-(3,5-dichlorophenyl)-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *III* were obtained by a 1,3-dipolar cycloaddition of substituted benzonitrile oxides *I* to N-(3,5-dichlorophenyl)maleimide (*II*) (Scheme 1, Table I).

Compounds *III* were assigned the structure according to analysis of their NMR spectral data (Tables III and IV) and comparison with analogous derivatives as prepared in ref.[5,6]. The unstable benzonitrile oxides (Scheme 1) were generated in situ from

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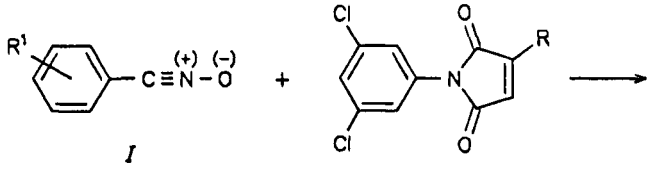
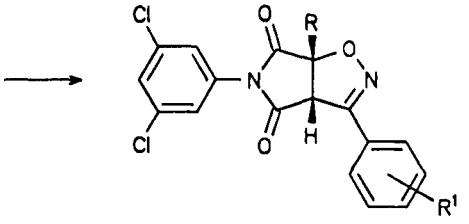
the corresponding benzenehydroximic chlorides and triethylamine[8]. Another method[9] for preparation of benzonitrile oxides used benzaldoximes and sodium hypochlorite; nonetheless, yields are low, because opening of the pyrrolidinedione ring took place under the given reaction conditions. This finding is in agreement with that[10] reporting that *II* (R = H) was the most reactive of substituted maleimides on reactions with a nucleophile. We found that *II* (R = H) was unstable even when crystallized from ethanol affording ethyl 3-(3,5-dichlorophenylcarbamoyl)propenoate. This property made it different from other compounds of type *III*, where 3,5-dichlorophenyl grouping was



I *II*



III, R = H
IV, R = CH_3

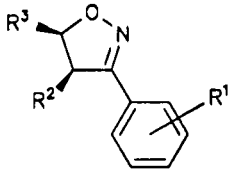
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
R^1	H	4–CH_3	4–OCH_3	2–NO_2	3–NO_2	4–NO_2	2–F	4–F

	i	*j*	*k*	*l*	*m*	*n*	*o*	*p*
R^1	2–Cl	3–Cl	4–Cl	2,4–diCl	2,6–diCl	3,4–diCl	2–Br	3–Br

	q	*r*	*s*
R^1	4–Br	2–OCH_3–3,5–diCl	2–CF_3

SCHEME 1

substituted by another aryl group; these compounds were opened only by methanolysis in ultraviolet light or in the presence of a catalytical amount of an acid[11]. Compound *IIIi* afforded 3-(2-chlorophenyl)-4-(3,5-dichlorophenylcarbamoyl)-5-methoxycarbonylisoxazoline (*Vi*) and the regioisomeric 3-(2-chlorophenyl)-4-methoxycarbonyl-5-(3,5-dichlorophenylcarbamoyl)isoxazoline (*VIi*) even on a short reflux in methanol. The enhanced reactivity of *IIIi* on reaction with a nucleophile is in line with the already mentioned finding[10]. The structure of isoxazolines *Vi* and *VIi* was evidenced from the NMR data; compound having the higher chemical shift value for H-5 was ascribed structure *Vi*.



V, R^2 = 3,5–dichlorophenylcarbamoyl
R^3 = CH_3OCO
VI, R^2 = CH_3OCO
R^3 = 3,5–dichlorophenylcarbamoyl

for R^1 see Scheme 1

Cycloaddition of nitrile oxides to N-(3,5-dichlorophenyl)methylmaleimide (*II*, R = CH_3) can yield two regioisomers *IV* and *III* possessing the methyl group in position 3a. The frontier orbital theory[12 - 14] predicted formation of the cycloadduct *IV* having the oxygen atom of the nitrile oxide attached to carbon substituted by a methyl group. In fact, only derivatives *IV* were formed (Table II); their structures – 3-phenyl-5-(3,5-dichlorophenyl)-6a-methyl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles – were deduced from the presence of a singlet at δ 4.87 – 5.32 (H-3a) and especially from the doublet at δ 59.47 – 63.43 (C-3a) and the singlet at δ 88.92–90.46 (C-6a) in their NMR spectra (Tables III and V). The regioisomer with the methyl group in position 3a should have the chemical shift values and multiplicity quite opposite in the ^{13}C NMR spectra (the C-6a doublet at δ ≈ 80, the C-3a singlet at δ ≈ 60). Formation of the second regioisomer could be excluded because none of the characteristic signals could be recognized in the NMR spectra of the crude reaction mixture. Cycloaddition to acetonitrile oxide proceeded similarly; only product analogous to that of the cycloadducts *IV* was formed.

Recently, an increasing interest for the synthesis of hydroxylactams has emerged, because these are valuable precursors for obtaining pharmacologically active compounds[15] and also for aza analogues of fused heterocyclic systems[16]. Partial reductions of imides with $NaBH_4$ to the corresponding hydroxylactams are well investigated[17,18], but regio- and chemoselectivities of these nonsymmetric imides are rarely encountered[19,20]. Stereoselectivity of these reactions has virtually not been investigated[21].

TABLE I
Characteristic data for 3-phenyl-5-(3,5-dichlorophenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *III*, R = H

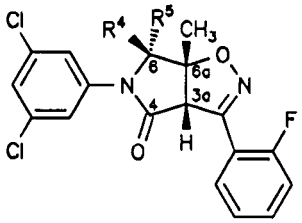
Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found % C	% H	% N	λ_{max}, nm log ε
IIIa	$C_{17}H_{10}Cl_2N_2O_3$	171 – 173	56.52	2.79	7.75	255
	(361.2)	85	56.32	2.80	7.71	2.69
IIIb	$C_{18}H_{12}Cl_2N_2O_3$	185 – 187	57.61	3.22	7.46	255
	(375.2)	88	57.65	3.36	7.54	2.70
IIIc	$C_{18}H_{12}Cl_2N_2O_4$	213 – 215	55.25	3.09	7.16	273
	(391.2)	52	55.18	3.01	7.12	2.58
IIId	$C_{17}H_9Cl_2N_3O_5$	252 – 254	50.26	2.23	10.34	250
	(406.2)	74	50.42	2.36	10.44	2.63
IIIe	$C_{17}H_9Cl_2N_3O_5$	197 – 199	50.26	2.23	10.34	254
	(406.2)	79	50.35	2.35	10.11	2.81
IIIf	$C_{17}H_9Cl_2N_3O_5$	209 – 212	50.26	2.23	10.34	297
	(406.2)	74	50.14	2.60	10.51	2.48
IIIg	$C_{17}H_9Cl_2FN_2O_3$	167 – 169	53.84	2.39	7.38	252
	(379.2)	42	53.93	2.36	7.69	2.67
IIIh	$C_{17}H_9Cl_2FN_2O_3$	194 – 196	53.84	2.39	7.38	254
	(379.2)	42	54.05	2.41	7.39	2.62
IIIi	$C_{17}H_9Cl_3N_2O_3$	180 – 182	51.60	2.29	7.08	251
	(395.6)	78	51.82	2.45	7.18	2.57
IIIj	$C_{17}H_9Cl_3N_2O_3$	160 – 162	51.60	2.29	7.08	255
	(395.6)	55	51.35	2.35	7.01	2.66
IIIk	$C_{17}H_9Cl_3N_2O_3$	224 – 226	51.60	2.29	7.08	258
	(395.6)	68	51.51	2.38	7.07	2.72
IIIl	$C_{17}H_8Cl_4N_2O_3$	242 – 245	47.47	1.87	6.51	249
	(430.1)	92	47.42	2.05	6.62	2.52
IIIm	$C_{17}H_8Cl_4N_2O_3$	243 – 245	47.47	1.87	6.51	248
	(430.1)	67	47.52	2.12	6.65	2.56
IIIn	$C_{17}H_8Cl_4N_2O_3$	191 – 192	47.47	1.87	6.51	259
	(430.1)	42	47.30	1.92	6.47	2.68
IIIo	$C_{17}H_9BrCl_2N_2O_3$	186 – 188	46.39	2.06	6.36	249
	(440.1)	65	46.32	2.06	6.32	2.62

TABLE I
(*Continued*)

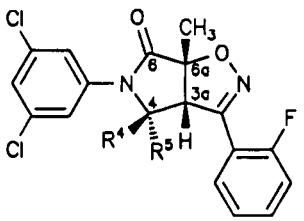
Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found % C	% H	% N	λ_{max}, nm log ε
IIIp	$C_{17}H_9BrCl_2N_2O_3$	159 – 161	46.39	2.06	6.36	256
	(440.1)	68	46.58	2.20	6.50	2.70
IIIq	$C_{17}H_9BrCl_2N_2O_3$	225 – 226	46.39	2.06	6.36	263
	(440.1)	75	46.40	2.10	6.17	2.70
IIIr	$C_{18}H_{10}Cl_4N_2O_4$	185 – 187	46.98	2.19	6.89	253
	(460.1)	78	47.02	2.25	6.89	2.62
IIIs	$C_{17}H_9Cl_2F_3N_2O_3$	182 – 183	50.37	2.11	6.52	258
	(429.2)	54	50.19	2.25	6.60	2.58

As found, reduction chemoselectivity of imides with $NaBH_4$ could be controlled by temperature; thus, at –20 °C only hydroxylactams were produced, whilst at ≥ 50 °C exclusively hydroxymethyl derivatives[15] were obtained. This is why we turned our attention to investigation of regio- and stereoselectivity of reduction of imides *IVg* with $NaBH_4$ as far as the reaction conditions and complexation are concerned (Table VI). Reduction of compounds *III*, having a little different course, was examined separately[22].

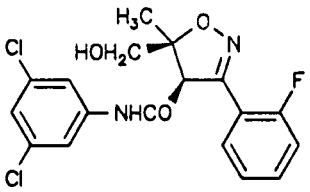
Two regioisomeric pairs of diastereomers *VIIg* and *VIIIg* can originate by reduction of *IVg* to the first step by reducing the C-6 carbonyl group, or derivatives *IXg* and *Xg* by reducing the C-4 carbonyl group; both differ in arrangement of the hydroxyl group with respect to the angular methyl group and H-3a, respectively. Similar course can also be expected with reduction to the second step giving rise to two isoxazolines *XIg* and the corresponding regioisomer.



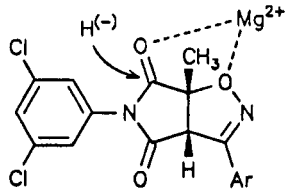
VIIg, R^4 = OH; R^5 = H
VIIIg, R^4 = H; R^5 = OH



IXg, R^4 = OH; R^5 = H
Xg, R^4 = H; R^5 = OH



XIg



XIIg

Reduction of *IVg* with $NaBH_4$ in methanol furnished regio- and stereoisomeric hydroxylactams *VIIg*, *VIIIg* and *IXg* at −20 °C and 0 °C, respectively; compounds *VIIg* and *VIIIg* were obtained in pure form. Their structures were ascribed from the chemical shift data and multiplicity of signals in the ^1H and ^{13}C NMR spectra (Tables VII and VIII). All hitherto known 1,3-dipolar cycloadditions of nitrile oxides as concerted reactions are characterized by a cis-stereospecificity, which means that the angular methyl group and the H-3a atom in compound *IV* have to be in a cis arrangement[12,13]. Nevertheless, all compounds lacked the doublet with a higher coupling constant value about 8 Hz for the H-3 proton which excluded structure *Xg*. Reduction in the presence of magnesium perchlorate resulted in a higher proportion of products *VIIg* and *VIIIg* which indicated the reduction of the C-6 carbonyl group. The chelate *XIIg* arising through coordination of the Mg^{2+} ion with the isoxazoline oxygen and the C-6 carbonyl group activated this carbonyl group in reduction with $NaBH_4$ with respect to the non-chelated C-4 carbonyl group[15]. The cis configuration of the C-6 hydroxy group in *VIIg* was deduced from appearance of the H-3a singlet at δ 4.72 and the trans configuration of the C-6 hydroxy group in *VIIIg* from the presence of an H-3a doublet at δ 4.36 and coupling constant $J(3a,6) = 3.3$ Hz in ^1H NMR spectra. Interaction between H-3a and H-6 can take place in a mutual syn arrangement only, this being evidenced by coupling constant typical of W-interaction. Different chemical shift values for H-3a proton in *VIIg* (syn regarding the OH group) and *VIIIg* (anti with respect to the 6-OH) proved the suggested stereochemical arrangement. Compound *IXg* cannot be obtained in a pure form, only as a mixture with *VIIIg*. The ^1H and ^{13}C NMR spectra enabled us to read the relevant signals for the H-3a singlet at δ 4.74, H-4 and OH doublets at δ 5.49 and 5.85, respectively, and doublets associated with C-3a (δ 62.26) and C-4 (δ 89.74) typical of the cis arrangement of the C-4 hydroxy group in compound *IXg*.

Analysis of the ^1H NMR spectra of crude reaction mixtures revealed population of individual products at various conditions (Table VI).

Reductions of *IVg* with $NaBH_4$ were found to proceed with a good regioselectivity in favour of the C-6 carbonyl (78 : 22 or 91 : 9, respectively), which means that they are chemoselective, giving rise only to hydroxylactams *VIIg*, *VIIIg* and *IXg*, and also stereoselective (cf. Table VI) this being manifested by an enhanced production of the C-6

cis-hydroxy derivative *VIIg* when compared with the C-6 trans-hydroxy derivative *VIIIg*. Complexation with magnesium perchlorate improved a little the regioselectivity. This phenomenon can be rationalized by application of the complexation model *XIIg* with a preferential attack of the hydride ion from the bottom side of the "bent" arrangement of the fused system.

TABLE II
Characteristic data for 3-phenyl-5-(3,5-dichlorophenyl)-6a-methyl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *IV*, R = Me

Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found % C	% H	% N	λ_{max}, nm log ε
IVa	$C_{18}H_{12}Cl_2N_2O_3$	237 – 239	57.61	3.22	7.46	257
	(375.2)	59	57.79	3.36	7.58	2.54
IVb	$C_{19}H_{14}Cl_2N_2O_3$	177 – 179	58.62	3.62	7.19	267
	(389.2)	64	58.53	3.72	7.29	2.49
IVd	$C_{18}H_{11}Cl_2N_3O_5$	216 – 218	51.44	2.63	10.00	256
	(420.2)	74	51.52	2.69	9.89	2.70
IVe	$C_{18}H_{11}Cl_2N_3O_5$	210 – 213	51.44	2.63	10.00	256
	(420.2)	83	51.54	2.84	10.16	2.76
IVf	$C_{18}H_{11}Cl_2N_3O_5$	216 – 218	51.44	2.63	10.00	267, 333
	(420.2)	71	51.48	2.72	10.01	2.15, 2.18
IVg	$C_{18}H_{11}Cl_2FN_2O_3$	208 – 211	54.97	2.82	7.12	255
	(393.2)	95	55.12	2.90	7.24	2.51
IVi	$C_{18}H_{11}Cl_3N_2O_3$	205 – 206	52.77	2.70	6.83	249
	(409.6)	86	52.89	2.84	6.92	2.11
IVk	$C_{18}H_{11}Cl_3N_2O_3$	217 – 219	52.77	2.70	6.83	264
	(409.6)	85	52.81	2.85	6.86	2.65
IVl	$C_{18}H_{10}Cl_4N_2O_3$	177 – 179	48.67	2.26	6.30	249
	(444.1)	73	48.76	2.40	6.43	2.57
IVm	$C_{18}H_{10}Cl_4N_2O_3$	213 – 215	48.67	2.26	6.30	250
	(444.1)	73	48.72	2.36	6.36	2.08
IVo	$C_{18}H_{11}BrCl_2N_2O_3$	203 – 204	47.60	2.44	6.17	249
	(454.1)	72	47.82	2.56	6.21	2.00
IVs	$C_{19}H_{11}Cl_2F_3N_2O_3$	179 – 181	51.48	2.50	6.32	250
	(443.2)	45	51.57	2.55	6.35	2.00

TABLE III

^{1}H NMR data (δ, ppm and *J*, Hz) of 3-phenyl-5-(3,5-dichlorophenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *III*, R = H and *IV*, R = CH_3

Compound	H-3a	H-6a *J* (3a, 6a)	H_{arom}	Compound	H-3a CH_3-6a	H_{arom}
IIIa	5.40	5.84 10.00	7.45 – 8.00	*IVa*	5.15 1.87	7.50 – 8.02
IIIb[a]	5.38	5.80 9.60	7.30 – 7.92	*IVb*	5.12 1.86[e]	7.31 – 7.90
IIIc[b,c]	5.37	5.73 10.00	7.00 – 7.94	*IVd*	5.32 1.92	7.51 – 8.86
IIId[b]	5.31	5.93 10.00	7.40 – 8.16	*IVe*	5.32 1.91	7.52 – 8.82
IIIe[b]	5.56	5.89 10.00	7.51 – 8.79	*IVg*	5.17 1.91	7.28 – 7.97
IIIg	5.48	5.82 10.00	7.28 – 7.56	*IVi*	5.15 1.90	7.30 – 7.65
IIIh	5.39	5.84 13.00	7.26 – 8.16	*IVk*	5.18 1.88	7.53 – 8.03
IIIi	5.39	5.71 9.60	7.25 – 7.54	*IVl*	5.17 1.92	7.46 – 7.86
IIIj	5.43	5.87 13.00	7.49 – 8.04	*IVm*	4.87 1.97	7.47 – 7.65
IIIk[b]	5.42	5.80 10.00	7.48 – 8.01	*IVo*	5.12 1.91	7.47 – 7.85
IIIl	5.18	6.06 9.60	7.44 – 7.63	*IVs*	4.96 1.92	7.48 – 7.95
IIIm	5.15	6.04 10.00	7.41 – 7.62			
IIIn	5.43	5.95 10.00	7.47 – 8.22			
IIIo	5.44	5.90 10.00	7.43 – 7.59			
IIIp	5.43	5.87 13.00	7.34 – 8.18			
IIIq	5.40	5.85 10.00	7.48 – 8.02			
IIIr[d]	5.46	5.88 10.00	7.41 – 7.70			
IIIs	5.28	5.91 9.00	7.39 – 7.88			

[a] 2.39 s, CH_3; [b] in CD_3SOCD_3; [c] 3.82 s, OCH_3; [d] 3.96 s, OCH_3; [e] 2.40 s, OCH_3.

TABLE IV
^{13}C NMR data (δ, ppm) of 3-phenyl-5-(3,5-dichlorophenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]-isoxazoles *III*, R = H

Compound	C-3	C-3a	C-4 C-6	C-6a	C_{arom}		
IIIa	153.73	56.09	170.98 172.00	82.16	126.41 129.31 134.86	128.31 129.38 135.42	128.70 131.52
IIIb[a]	153.60	56.24	171.06 172.05	82.06	125.62 129.31 135.46	126.47 130.02 141.85	128.73 135.02
IIIc[b]	152.52	55.35	170.42 170.95	80.62	114.09 128.65 142.40	119.47 129.59	126.14 134.09
IIId	151.58	58.14	169.97 171.97	81.07	121.30 125.82 132.12 134.45	125.11 129.01 134.22 134.51	125.16 131.56 134.27 148.15
IIIe	152.65	55.89	169.93 170.45	82.92	123.40 129.43 135.51	125.86 131.00 149.20	126.50 134.46
IIIf	152.20	54.57	170.07 171.18	81.97	123.74 133.39 148.37	126.08 133.80	129.06 134.04
IIIg	150.66	57.17	170.61 172.02	81.80	125.39 129.37 133.75	125.51 131.59 134.98	126.44 133.40 135.51
IIIh	152.88	56.24	171.08 171.96	82.39	116.03 126.50 131.36	116.91 129.43 135.04	124.98 131.00 135.51
IIIi	152.51	56.14	168.53 170.21	79.95	124.52 129.39 132.13 135.53	125.43 130.76 132.36	127.38 131.37 133.17
IIIj	152.83	55.89	170.90 171.78	82.56	126.50 129.37 131.30	127.14 130.54 134.87	128.49 131.18 135.45
IIIk	152.35	55.12	170.25 171.42	81.38	126.14 133.86	128.77 134.09	129.59 135.50

TABLE IV
(*Continued*)

Compound	C-3	C-3a	C-4 C-6	C-6a	C_{arom}		
IIIl	151.02	58.32	169.90 172.14	81.83	126.00 133.71	129.46 134.65	129.59 135.75
IIIm	150.32	57.52	169.54 171.65	80.94	125.09 129.07 134.54	125.51 133.39	128.83 133.48
IIIn	152.28	55.85	170.97 171.77	82.80	126.51 129.44	128.44 130.56	129.11
IIIo	154.11	58.40	170.20 172.13	81.75	122.76 129.43 134.22	126.32 132.58 134.81	128.66 132.76 135.57
IIIp	152.77	55.95	170.96 171.84	82.62	122.93 129.43 134.28	126.50 130.77 134.98	127.61 131.41 135.51
IIIq	153.06	56.00	170.96 171.84	82.51	125.33 129.37 134.98	126.44 130.54 135.45	127.73 132.58
IIIr[c]	151.34	57.21	170.50 171.93	81.96	125.47 129.91 134.80	126.30 130.12 135.48	129.35 132.85 154.54
IIIs[d]	152.55	59.85	170.26 172.13	81.81	123.00 129.56 133.41	126.25 131.64 134.83	127.65 132.10 135.69

[a] 21.32 q, CH_3; [b] 45.75 q, OCH_3; [c] 62.22 q, OCH_3; [d] 46.39 s, CF_3.

The second-step reduction product *XIg* was formed exclusively in the presence of magnesium perchlorate at 0 °C. Its structure – 5-hydroxymethylisoxazoline (*XIg*) – was proved from the ^{1}H NMR spectral data showing the H-4 as a singlet, whereas in its regioisomer this proton should appear as a triplet.

Structural similarity of these compounds with some fungicidally active derivatives[1–4] prompted us to test their effect on phytopathogenic molds. Derivatives *IIIa*, *IIIf*, *IIIg*, *IIIh*, *IIIj*, *IIIn*, *IIIp* showed activity against *Alternaria species* and *IIIa*, *IIIf*, *IIIg*, *IIIh*, *IIIj*, *IIIp* and *IIIs* against *Botrytis cinerea*; none of compounds tested was of practical use.

TABLE V
^{13}C NMR data (δ, ppm) of 3-phenyl-5-(3,5-dichlorophenyl)-6a-methyl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *IV*, R = CH_3

Compound	C-3	C-3a	C-4 C-6	C-6a	CH_3	C_{arom}	
IVa	153.73	60.01	170.35 173.14	89.39	18.90	126.60 128.92 129.41 135.48	128.76 129.37 131.43
IVb[a]	153.61	60.09	170.36 173.01	89.15	18.88	126.07 128.72 130.01 135.46	126.56 129.34 135.07 141.75
IVd[b]	151.95	58.41	169.36 173.35	89.07	18.38	122.38 126.17 129.29 133.69 147.76	124.98 128.62 130.29 133.96
IVe	152.32	61.61	169.67 173.39	89.28	18.83	126.39 128.50 130.90 134.68 135.57	126.75 129.48 133.65 134.82 137.37
IVf	152.81	59.47	170.20 173.14	90.46	18.94	124.49 129.44 134.91 135.49	126.54 129.79 134.96 149.69
IVg	152.51	60.94	170.31 173.21	88.92	18.84	117.09 126.47 131.36 134.95	125.36 129.35 133.41 135.46
IVi	153.13	61.90	169.66 173.32	89.10	18.80	126.42 128.17 131.11 132.68 134.90	127.87 129.45 132.62 133.62 135.55
IVk	152.96	59.82	170.31 173.37	89.69	18.90	126.56 129.39 130.33 135.47	127.76 129.59 135.00 136.88

TABLE V
(*Continued*)

Compound	C-3	C-3a	C-4 C-6	C-6a	CH_3	C_{arom}	
IVl[b]	151.22	60.53	168.81 172.50	88.07	18.19	125.38 127.62 129.78 133.54 135.78	125.92 128.68 133.17 134.05
IVm	150.92	62.10	169.20 173.46	89.44	18.88	126.15 129.48 133.67 135.72	126.91 129.63 134.70 135.81
IVo	150.60	61.02	169.91 173.44	88.94	18.86	117.40 129.37 133.54 135.49	125.43 131.38 134.98
IVs[c]	152.48	63.43	169.58 173.41	89.15	18.78	126.36 129.53 132.34 134.85	127.67 131.57 133.33 135.63

[a] 21.35 q, CH_3; [b] in CD_3SOCD_3; [c] 69.61 s, CF_3.

TABLE VI
Products of $NaBH_4$ reduction of (2-fluorophenyl)-5-(3,5-dichlorophenyl)-6a-methyl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazole (*IVg*)

Method	Temperature °C	Molar ratio				Regioselectivity[a]
		VIIg	*VIIIg*	*IXg*	*Xlg*	
A	−20	45	33	22	0	78 : 22
A	0	55	36	9	0	91 : 9
B	−20	57	29	14	0	86 : 14
B	0	63	21	5	11	95 : 5

[a] The C-6 : C-4 reduction ratio.

TABLE VII
^{1}H NMR data (δ, ppm and *J*, Hz) of the $NaBH_4$ reduction products of *IVg*

Compound	CH_3	H-3a *J*(3a, 6)	H-6 *J*(6, OH)	OH	H-arom
VIIg	1.62	4.72 0.00	5.88 8.40	6.25	7.24 – 7.98
VIIIg	1.84	4.36 3.30	5.98 4.50	6.52	7.25 – 7.89
XIg[a]	1.88	– –	5.14[b] –	4.29	7.28 – 7.92

[a] 4.21 dd, CH_2; [b] C-4.

TABLE VIII
^{13}C NMR data (δ, ppm) of the $NaBH_4$ reduction products of *IVg*

Compound	CH_3	C-3a C-6a	C-6	C=N C=O	C_{arom}	
VIIg	18.93	61.21 88.44	92.07	154.74 168.29	117.05 121.32 125.31 131.40 132.98 135.55	117.35 125.27 125.91 131.44 133.09 140.67
VIIIg	20.23	61.93 84.51	89.74	153.45 171.64	117.32 122.42 125.99 133.27 135.45	121.44 125.81 130.35 133.38 140.36
XIg[a]	18.86	– –	60.95[b]	– –	117.01 125.40 129.73 131.36 133.40	125.35 126.46 129.58 131.39 135.46

[a] 68.24 t, CH_2, 88.91 s, C-5; [b] C-4.

EXPERIMENTAL

Melting points are not corrected. The ^1H and ^{13}C NMR spectra of deuterioacetone solutions containing tetramethylsilane as internal reference were measured with Tesla BS 487 C (80 MHz) and Varian VXR 300 (300 and 75 MHz) instruments, respectively. The UV spectra were recorded with an M 40 (Zeiss, Jena) spectrophotometer in temperated cells in methanol; the ε values are given in $m^2\ mol^{-1}$. The reaction course and purity of compounds were monitored by thin-layer chromatography on Silufol sheets, detection by UV_{254} light or with iodine vapours.

N-(3,5-Dichlorophenyl)maleimide (*II*, R = H) was obtained from 3,5-dichloroaniline and maleic anhydride according to ref.[23] and 3-methyl-1-(3,5-dichlorophenyl)maleimide (*II*, R = CH_3) from the afore-mentioned aniline and itaconic anhydride followed by a triethylamine-induced rearrangement[24,25].

Testing conditions were reported in ref.[5].

General Procedure for Preparation of 3-Phenyl-5-(3,5-dichlorophenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles *III* and *IV*

Triethylamine (13 mmol) in anhydrous ether (30 ml) was added during 1 h to a stirred and cooled (0 °C) solution of maleimide *II* (10 mmol) and benzenehydroximic chloride (10 ml) in anhydrous ether (40 ml). The product separated after a 24 h-stirring at room temperature was filtered off and washed thoroughly with water and crystallized. Characteristic data of products are listed in Tables I – V.

3,6a-Dimethyl-5-(3,5-dichlorophenyl)-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d]isoxazole. This compound was synthesized from *II*, (R = CH_3) and acetonitrile oxide prepared in situ from nitroethane and phenyl isocyanate under catalysis of triethylamine[26]. Yield 75%, m.p. 236 – 237 °C. For $C_{13}H_{10}Cl_2N_2O_3$ (313.1) calculated: 49.85% C, 3.21% H, 8.94% N; found: 49.93% C, 3.28% H, 8.97% N. ^1H NMR: 1.78 s, 3 H, CH_3; 2.19 s, 3 H, CH_3; 4.01 s, 1 H, H-3a; 7.29 – 7.43 m, 3 H, arom. ^{13}C NMR: 12.21 q, CH_3; 18.95 q, CH_3; 62.33 d, C-3a; 86.17 s, C-6a; 124.69, 129.35, 132.54, 135.52, C-arom; 151.10 s, C=N; 168.72 s, 172.48 s, C=O.

Alcoholysis of Maleimides *II* and *III*

Ethyl 3-(3,5-dichlorophenylcarbamoyl)propenoate was obtained by crystallization of *II* (R = H) in hot ethanol in almost quantitative yield, m.p. 86 – 88 °C. For $C_{12}H_{11}Cl_2NO_3$ (288.1) calculated: 50.01% C, 3.80% H, 4.86% N; found: 49.78% C, 3.71% H, 5.01% N. ^1H NMR: 1.35 t, 3 H, CH_3, $J(CH_3,CH_2)$ = 7.2 Hz; 4.30 q, 2 H, OCH_2; 6.24 d, 1 H, vinyl, $J(2,3)$ = 12 Hz; 6.39 d, 1 H, vinyl; 7.08 – 7.61 m, 3 H, arom. 11.29 s, 1 H, NH.

3-(2-Chlorophenyl-4-(3,5-dichlorophenylcarbamoyl)-5-(methoxycarbonyl)isoxazoline Vi was obtained by boiling *IIIi* in methanol and purified by chromatography on silica gel, heptane–ethyl acetate (2 : 1) being the eluent. Yield 52%, m.p. 208 – 210 °C. For $C_{18}H_{13}Cl_3N_2O_4$ (427.7) calculated: 50.54% C, 3.06% H, 6.55% N; found: 50.45% C, 2.98% H, 6.51% N. ^1H NMR: 3.67 s, 3 H, OCH_3; 5.36 d, 1 H, H-4, $J(4,5)$ = 4.5 Hz; 5.74 d, 1 H, H-5; 7.24 – 7.93 m, 7 H, arom; 9.81 s, 1 H, NH. ^{13}C NMR: 53.33 d, C-4; 59.32 q, OCH_3; 83.71 d, C-5; 119.19, 124.58, 128.05, 129.36, 130.95, 132.21, 132.47, 135.48, 141.11, arom; 155.13 s, C=N; 168.48 s, 168.61 s, C=O.

3-(4-Chlorophenyl)-4-(3,5-dichlorophenylcarbamoyl)-5-(methoxycarbonyl)isoxazoline (Vk) *and 3-(4-chlorophenyl)-4-(methoxycarbonyl)-5-(3,5-dichlorophenylcarbamoyl)isoxazoline* (VIk) were obtained in the 3 : 1 ratio from compounds *IIIk* by refluxing in methanol; they cannot be isolated in pure form, only as enriched mixtures. ^1H NMR *Vk*: 3.75 s, 3 H, OCH3; 5.17 d, 1 H, H-4, $J(4,5)$ = 4.0 Hz; 5.62 d, 1 H, H-5; 7.18 – 7.89 m, 7 H, arom. *VIk*: 4.08 s, 3 H, OCH_3; 4.98 d, 1 H, H-4, $J(4,5)$ = 4.5 Hz; 5.38 d, 1 H, H-5; 7.18 – 7.87 m, 7 H, arom.

Reduction of Compound *IVg* with Sodium Hydridoborate

Method A: Sodium hydridoborate (4 g, 106 mmol) was added to a stirred solution of *IVg* (71 mmol) in methanol (50 ml) at −20 or 0 °C. A saturated aqueous ammonium chloride was introduced after a 2 h-stirring which was continued for 1 h. Methanol was removed under reduced pressure and the aqueous solution was stepwise extracted with chloroform (3 × 20 ml) and ethyl acetate (3 × 20 ml). The combined organic layers were dried with sodium sulfate and the distillation residue was separated on silica gel column using heptane–ethyl acetate (5 : 1) as eluent.

Method B: Magnesium perchlorate (4.46 g, 20 mmol) was added to a stirred solution of compound *IVg* (10 mmol) in methanol–chloroform (1 : 1, 100 ml) at either 20 or 0 °C. Stirring was continued at the respective temperature for 1 h; sodium hydridoborate (0.57 g, 15 mmol) was then introduced and after the reaction had finished (TLC) the mixture was acidified with hydrochloric acid to pH 2 and after 10 min to pH 11 with aqueous sodium hydroxide. The mixture was afterwards worked up as in the preceding experiment.

3-(2-Fluorophenyl)-5-(3,5-dichlorophenyl)-6-cis-hydroxy-6a-methyl-4-oxo-3a,4,6,6a-tetrahydropyrrolo-[3,4-d]isoxazole (VIIg) was obtained in 50% yield applying method *A* and temperature 0 °C; m.p. 177 – 179 °C. For $C_{18}H_{13}Cl_2FNO_3$ (395.2) calculated: 54.70% C, 3.31% H, 7.08% N; found: 54.81% C, 3.40% H, 7.10% N.

3-(2-Fluorophenyl)-5-(3,5-dichlorophenyl)-6-trans-hydroxy-6a-methyl-4-oxo-3a,4,6,6a-tetrahydropyrrolo[3,4-d]isoxazole (VIIIg) was prepared in 15% yield by method *A* at 0 °C; m.p. 135 – 137 °C. Found: 54.68% C, 3.43% H, 7.32% N.

3-(2-Fluorophenyl)-5-(3,5-dichlorophenyl)-4-cis-hydroxy-6a-methyl-6-oxo-3a,4,6,6a-tetrahydropyrrolo-[3,4-d]isoxazole (IXg) was synthesized with the admixture of *VIIIg* by method *A* at −20 °C. ^{1}H NMR: 4.74 s, 1 H, H-3a; 5.49 d, 1 H, H-4, J(4,OH) = 10.6 Hz; 5.85 d, 1 H, OH. ^{13}C NMR: 62.26 d, C-3a; 88.01 s, C-6a; 89.74 d, C-4.

3-(2-Fluorophenyl-4-(3,5-dichlorophenylcarbamoyl)-5-hydroxymethyl-5-methylisoxazoline (XIg), m.p. 180 – 182 °C was produced by method *B* at 0 °C in 12% yield.

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