N-PHENYL-N,N″-GUANIDINEDICARBOXYLIC ACID ESTERS. SYNTHESIS, ANTHELMINTIC AND PESTICIDAL EFFECTS

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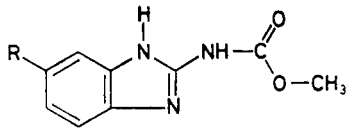
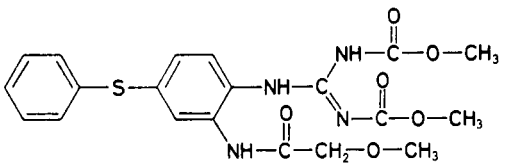
Substituted phenylammonium chlorides react with cyanamide to give the corresponding phenylguanidines which on treatment with chloroformate esters give N-subst.phenyl-N,N″-guanidinedicarboxylic acid esters. All substances prepared have been tested for their anthelmintic activity against the model helminths *Nippostrongylus brasiliensis* and *Hymenolepis nana* var. *fraterna*. The most significant activity has been found with diethyl N-(4-nitrophenyl)-N,N″-guanidinedicarboxylate. In pesticidal screening the compounds have shown fungicidal activity and particularly ovicidal activity against *Tetranychus urticae* which activity is increased with the compounds having a nitro group in the benzene ring.

In the 60's and 70's a group of new anthelmintics[1] were introduced into practice, viz. methyl 5(6)-substituted benzimidazol-2-ylcarbamates (*I*).



I

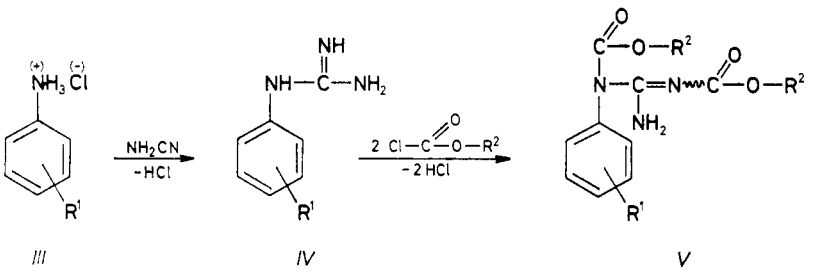


II

Substances with analogous structures were also applied as fungicides, e.g. carbendazim (*I*, R = H), methyl ester of 1*H*-benzimidazol-2-ylcarbamic acid[2]. On the basis of this structure another new anthelmintic was developed – febantel[3] (*II*), dimethyl ester of [[2-[(methoxyacetyl)amino]-4-(phenylthio)phenyl]carbonimidoyl]-biscarbamic acid, which – in fact – was derived by opening of the imidazole cycle.

The compounds of this type are usually prepared[4] by the reaction of the respective substituted phenylamine with dialkyl S-alkyl-N,N′-isothioureadicarboxylates.

Therefore, we decided to prepare a series of compounds with different substituents on the guanidine skeleton and to verify their anthelmintic and pesticidal activity. We started from the respective substituted phenylammonium chlorides (*III*, R^1 = H, 2-NO_2, 3-NO_2, 4-NO_2) which react with cyanamide either in the melt (a modified procedure by Arndt[5,6]) or in ethanol solution under pressure[7] to give the corresponding phenylguanidines *IV* which were mostly isolated as the nitrates. In the subsequent phase these intermediates were submitted to the reaction with chloroformate esters to give the required esters of N-phenyl-N,N″-guanidinedicarboxylic acids *V* (see Scheme 1 and Table I). The positions of substituents on the guanidine



SCHEME 1

skeleton were determined[8] by means of ^1H, ^{13}C, and ^{15}N NMR spectroscopy using the ^{15}N labelled substances.

The substances synthetized were tested for their anthelmintic activity using the sewer-rats of Wistar strain with model helminth *Nippostrongylus brasiliensis* and the mice of NMRI strain with the model helminth *Hymenolepis nana*, var. *fraterna* at a dose of 150 mg/kg × 2. In the former case the activity of the substances tested was compared with that of levamisole, in the latter case with that of piperazine salt of niclosamide (TAENIFUGIN). The highest activity (see Table II) against both helminths was found with diethyl N-(4-nitrophenyl)-N,N″-guanidinedicarboxylate (*Vm*). The highest activity against the worm *N. brasiliensis* was found with dibenzyl N-phenyl-N,N″guanidinedicarboxylate (*Vc*). Most substances tested are more efficient against this helminth than against the tapeworm tested. Introduction of a nitro group into benzene ring does not increase the activity as compared with the unsubstituted compounds; from among the nitro derivatives the 4-nitro isomers exhibit a slightly higher activity. Surprisingly, the highest activity is not shown by the methyl esters (in contrast to the applied substances, 2-benzimidazolylcarbamates and febantel) but, instead, by ethyl esters of 4-nitrophenyl derivatives (*Vm*) and by benzyl ester (*Vc*) from among the group with unsubstituted benzene ring.

Moreover, the substances were tested for pesticidal activity (herbicidal, fungicidal, insecticidal, and acaricidal) and as growth regulators. Interesting results were only

TABLE I

Yields, melting points, and analytical data of N-phenyl-N,N″-guanidinedicarboxylates *Va*—*Vo*

Compound	R^1	R^2	Yield %	M.p., °C Solvent[a]	Mol. formula M.w.	Calculated/Found		
						% C	% H	% N
Va	H	$-CH_3$	70	180·0—182·5 benzene + PE	$C_{11}H_{13}N_3O_4$ 251·24	52·59 52·56	5·22 5·33	16·72 16·53
Vb	H	$-CH(CH_3)_2$	62	92·5—94·5 PE	$C_{15}H_{21}N_3O_4$ 307·35	58·62 58·34	6·89 6·88	13·67 13·69
Vc	H	$-CH_2-C_6H_5$	87	103·5—106·0 benzene + PE	$C_{23}H_{21}N_3O_4$ 403·44	68·47 68·51	5·25 5·25	10·42 10·51
Vd	2-NO_2	$-CH_3$	61	178·0—180·0 benzene + PE	$C_{11}H_{12}N_4O_6$ 296·24	44·60 44·66	4·08 4·19	18·91 19·16
Ve	2-NO_2	$-C_2H_5$	76	102·5—104·0 CCl_4 + PE	$C_{13}H_{16}N_4O_6$ 324·29	48·15 48·22	4·97 4·97	17·28 17·28
Vf	2-NO_2	$-CH(CH_3)_2$	97	116·0—117·5 CCl_4 + PE	$C_{15}H_{20}N_4O_6$ 352·35	51·13 51·25	5·72 5·54	15·90 15·69
Vg	2-NO_2	$-CH_2-C_6H_5$	62	103·5—106·0 benzene + PE	$C_{23}H_{20}N_4O_6$ 448·43	61·60 61·75	4·50 4·54	12·49 12·43
Vh	3-NO_2	$-CH_3$	60	191·0—192·0 benzene + PE	$C_{11}H_{12}N_4O_6$ 296·24	44·60 44·39	4·08 3·98	18·91 18·83
Vi	3-NO_2	$-C_2H_5$	88	138·5—140·0 CCl_4 + PE	$C_{13}H_{16}N_4O_6$ 324·29	48·15 47·97	4·97 5·19	17·28 17·38
Vj	3-NO_2	$-CH(CH_3)_2$	84	122·5—123·5 CCl_4 + PE	$C_{15}H_{20}N_4O_6$ 352·35	51·13 50·96	5·72 5·93	15·90 15·95
Vk	3-NO_2	$-CH_2-C_6H_5$	85	133·5—135·0 benzene + PE	$C_{23}H_{20}N_4O_6$ 448·43	61·60 61·47	4·50 4·58	12·49 12·33
Vl	4-NO_2	$-CH_3$	68	188·5—189·5 benzene + PE	$C_{11}H_{12}N_4O_6$ 296·24	44·60 44·52	4·08 4·10	18·91 19·09
Vm	4-NO_2	$-C_2H_5$	75	117·0—118·5 CCl_4 + PE	$C_{13}H_{16}N_4O_6$ 324·29	48·15 48·18	4·97 4·87	17·28 17·23
Vn	4-NO_2	$-CH(CH_3)_2$	80	150·0—152·0 CCl_4 + PE	$C_{15}H_{20}N_4O_6$ 352·35	51·13 51·21	5·72 5·69	15·90 15·84
Vo	4-NO_2	$-CH_2-C_6H_5$	87	154·0—157·5 CCl_4	$C_{23}H_{20}N_4O_6$ 448·43	61·60 61·43	4·50 4·53	12·49 12·71

[a] PE petrolether (B.p. 60—70°C).

found (see Table III) in the fungicidal and acaricidal-ovicidal tests using ova of the mites *Tetranychus urticae*. The highest acaricidal effect was found with the substances having a nitro group bound to the benzene ring.

EXPERIMENTAL

The melting points were determined with a Boëtius PHMK 05 apparatus and were not corrected. For analyses, the samples were dried at 62°C at a pressure of ca 20 Pa over paraffin. The purity of the products was checked by TLC (Silufol UV 254/366, Kavalier Votice; benzene–ethanol–triethylamine 8 : 2 : 1), the IR spectra were measured in KBr pellets using a Perkin–Elmer 577 apparatus.

Phenylguanidine (*IV*, R^1 = H)

A mixture of 13·0 g (100 mmol) aniline hydrochloride and 6·3 g (150 mmol) cyanamide was heated at 85–100°C 15 min, whereafter the mixture was cooled, dissolved in 180 ml water, alkalized with saturated potassium hydroxide solution, and the separated crystalline solid was

TABLE II
Anthelminthic activity of N-phenyl-N,N″-guanidinedicarboxylates *V*

Compound	Effect in %	
	Hymenolepis nana	*Nippostrongylus brasiliensis*
Va	0	0
Vb	0	59·4
Vc	0	75·9
Vd	0	14·8
Ve	23·5	0
Vf	0	0
Vg	15·5	3·7
Vh	0	25·9
Vi	0	37·9
Vj	8·8	18·7
Vk	0	0
Vl	13·4	14·8
Vm	52·9	68·8
Vn	7·2	0
Vo	0	0
Levamisole	—	100·0
TAENIFUGIN	100·0	—

collected by suction. The product was recrystallized from benzene. Yield 9·6 g (71%), m.p. 64—67°C; ref.[9] gives m.p. 66—67°C.

The procedure described in ref.[7] gave the title compound in a yield of 58—100%.

General Procedure for Preparation of Nitrophenylguanidinium Nitrates (*IV*, $R^1 = NO_2$)

A mixture obtained by addition of 6·3 g (150 mmol) cyanamide to 17·5 g (100 mmol) respective nitroanilinium chloride and by thorough mixing was heated at 120—140°C 15 min. After cooling, the melt was dissolved and suspended in hot water, the mixture was filtered, the filtrate was extracted with benzene (toluene for the 4-nitro derivative), and the aqueous layer was acidified with concentrated nitric acid and cooled. The separated crystalline solid was collected by filtration and recrystallized from water.

2-*Nitrophenylguanidinium nitrate*. Yield 11·9 g (49%), m.p. 156—158·5°C (decomp.); ref.[10] gives m.p. 159°C:

3-*Nitrophenylguanidinium nitrate*. Yield 15·6 g (64%), m.p. 208—211°C (decomp.); ref.[6] gives m.p. 203°C.

4-*Nitrophenylguanidinium nitrate*. Yield 14·8 g (61%), m.p. 223—225°C (decomp.); ref.[11] gives m.p. 219—220°C.

General Procedure for Preparation of
N-Phenyl-N,N″-guanidinedicarboxylic Acid Esters *Va*—*Vc*

A solution of 2·0 g (15 mmol) phenylguanidine in 25 ml hot water was cooled and treated with 0·7 g (18 mmol) magnesium oxide and 100 ml dichloromethane. The mixture was intensively

TABLE III

Fungicidal and acaricidal-ovicidal effects of compounds *V* (for the method of estimation see Experimental)

Compound	Fungicidal effect evaluation 1·0—4·0		Acaricidal effect evaluation 0—10·0
	cont.	syst.	
Va	—	—	2·0
Vb	2·0	2·0	5·5
Vc	2·0	1·5	2·5
Vd	1·0	2·0	10·0
Vf	2·0	1·0	10·0
Vg	2·0	1·0	2·5
Vj	1·0	1·0	10·0
Vk	2·0	1·5	0·5
Vl	1·0	1·0	0
Vm	1·5	1·0	6·0
Vn	1·5	1·0	1·5
Vo	1·0	1·0	6·0

stirred at room temperature, and 31 mmol respective chloroformate ester was added drop by drop. The reaction mixture was stirred 2·5 h (4·5 h in the case of benzyl chloroformate), whereafter the layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried with sodium sulfate, and the solvent was distilled off in vacuum. The product was repeatedly recrystallized from the solvent given. The yields, solvents, and results of elemental analyses of the products are given in Table I, the IR spectra are given in Table IV.

General Procedure for Preparation of N-(Nitrophenyl)-N,N″-guanidinedicarboxylic Acid Esters *Vd*— *Vo*

A solution of 2·0 g (8·2 mmol) respective nitrophenylguanidinium nitrate in 35 ml hot water was cooled and treated with 0·6 g (14 mmol) magnesium oxide and 140 ml dichloromethane. The mixture was intensively stirred at room temperature, and 17 mmol respective chloroformate was added drop by drop. The further procedure was the same as that used for N-phenyl-N,N″-guanidinedicarboxylic acid esters (see above). The yields, solvents used for recrystallizations, and elemental analyses of the products are given in Table I. The IR spectra are given in Table IV.

Methods Used for Determination of Acaricidal-Ovicidal Effect upon Ova of *Tetranychus urticae*

Circular filter papers of 9 cm diameter were placed on a circular PVC support and wetted with water. A bean leaf was placed on the paper with the upper side down, and a square of 2·5 cm side was drawn on the leaf. In this square, 12—15 female *Tetranychus urticae* species were located and transferred into a recreation room (24°C, humidity 60—90%). After 24 h, the females

TABLE IV
Characteristical vibrations (cm^{-1}) in the IR spectra of N-phenyl-N,N″-guanidinedicarboxylates *V*

Compound	ν(NH)	ν(C=O)	δ(NH_2), ν(C=N)	ν(C—O)
Va	3 350, 3 220	1 705	1 620, 1 600	1 260
Vb	3 370, 3 260	1 710	1 625	1 270
Vc	3 405, 3 265	1 700	1 640, 1 585	1 250
Vd	3 360, 3 260	1 740	1 640, 1 600	1 270
Ve	3 370, 3 260	1 725	1 640, 1 615	1 260
Vf	3 380, 3 270	1 715	1 620	1 270
Vg	3 360, 3 260	1 710	1 610	1 250
Vh	3 380, 3 270	1 710	1 630, 1 610, 1 595	1 250
Vi	3 410, 3 300	1 725	1 640, 1 615	1 250
Vj	3 480, 3 260	1 720	1 630	1 270
Vk	3 420, 3 300	1 730	1 650, 1 630	1 255
Vl	3 360, 3 250	1 720	1 650, 1 615, 1 600	1 250
Vm	3 390, 3 280	1 715	1 640, 1 620, 1 605	1 260
Vn	3 360, 3 230	1 720, 1 700	1 625, 1 595	1 255
Vo	3 380, 3 230	1 710	1 640, 1 600	1 255, 1 249

were removed from the squares, and the leaves were treated with solutions of the substances tested (concentrations of 500 and 5 000 ppm, volume of 2 ml per 2 leaves) using an atomizer in a vertical toximeter. After a two-minute sedimentation time, the treated leaves were put back into the recreation room for 7—9 days at sufficient humidity. From the number of non-hatched ova the percentage of dead species was calculated to give the respective point evaluation. The resulting point evaluation is equal to the sum of points obtained with the two concentrations.

Determination of Activity against *Erysiphe graminis* on Barley

The barley plants in the phase of two leaves were treated with the tested substances in gradually increasing concentrations (the contact effect) using a volume corresponding to 400 l/ha. After 24 h they were artificially infected by powdering with spores of *Erysiphe graminis*. The effect was evaluated after 6 day incubation in a vegetation chamber at standard conditions (15—18°C, humidity 90—95%) by estimation of the attacked leaf area which corresponds to the respective point evaluation.

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