Ratcliff, M. W., "Citrus Science and Technology", Vol. 2, Nagy, S., Shaw, P. E., Veldhuis, M. K., Ed., Avi Publishing Co., Westport, CT, 1977, p 546.
"Standard Methods", 12th ed, American Public Health Association, Inc., New York, 1965, pp 304, 383, 534.
Ting, S. V., *J. Agric. Food Chem.* **4**, 262 (1956).
U.S. Department of Agriculture, "Soil, The Yearbook of Agriculture", U.S. Government Printing Office, Washington, DC., 1957, p 155.
VanOlephen, H., "An Introduction to Clay Colloid Chemistry", Wiley, New York, 1965, p 31.
Waksman, S. A., "Humus Origin, Chemical Composition, and Importance in Nature", Williams & Wilkins, Co., Baltimore, MD, 1938, pp 95, 421.
Waksman, S. A., Stevens, K. R., *Soil Sci.* **26**, 113 (1928).

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1-Phenylcarbamoyl-2-pyrazolines, a New Class of Insecticides. 3. Synthesis and Insecticidal Properties of 3,4-Diphenyl-1-phenylcarbamoyl-2-pyrazolines

Arnold C. Grosscurt, Roelof van Hes,* and Kobus Wellinga

The syntheses and biological activities of 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines are discussed. The structures of these compounds have been confirmed by nuclear magnetic resonance. The insecticidal properties were evaluated with the larval stages of *Aëdes aegypti* L., *Pieris brassicae* L., and *Leptinotarsa decemlineata* Say. The compounds out of this group of pyrazolines have a much higher insecticidal activity than those of the 3-phenyl-1-phenylcarbamoyl-2-pyrazolines and the 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines, which were discussed in part 1 and part 2, respectively.

In this article we report the synthesis and biological evaluation of the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines. These 3,4-diphenyl derivatives give rise to products with much better insecticidal properties than those with phenyl substitution at only the 3 position mentioned in part 1 (Wellinga et al., 1977) or even those with 3,5-diphenyl substitution mentioned in part 2 (van Hes et al., 1978). Although the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines also are active on adult insects, just as the 3-phenyl-substituted compounds and the 3,5-diphenyl-substituted compounds, only the larvicidal activities on *Aëdes aegypti* L., *Pieris brassicae* L., and *Leptinotarsa decemlineata* Say are discussed. The phenomena observed after intoxication are similar to those described for the 3-phenyl-substituted pyrazolines.

CHEMICAL METHODS

Microanalyses were carried out in the Analytical Department of the Institute for Organic Chemistry TNO, Utrecht, Netherlands, under the supervision of W. J. Buis. Nuclear magnetic resonance spectra were recorded on a Varian HA 100 spectrometer with tetramethylsilane as the internal reference. The melting points are uncorrected.

The compounds mentioned in Tables I and II were prepared by one general method, which is outlined in Scheme I.

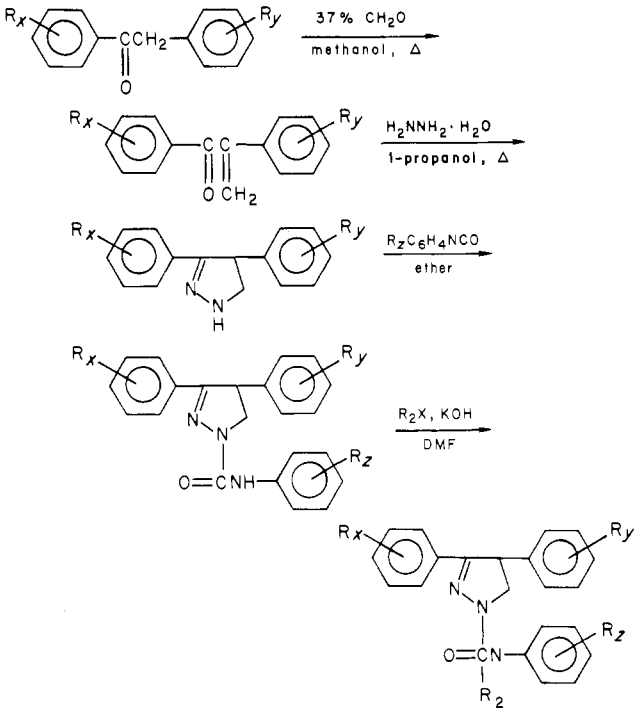
4′-Chloro-2-phenylacrylophenone. To a solution of 41.5 g of 4′-chloro-2-phenylacetophenone (0.18 mol) (Curtin et al., 1954) in 450 mL of methanol, 2 mL of piperidine, 2 mL of acetic acid, and 54 mL of formalin (37%) were added. After refluxing for 3 h, 200 mL of methanol was distilled off. After cooling, the reaction mixture was poured into 500 mL of ice–water and the resulting solid was collected and dried. Yield 42.7 g (98%), mp 45–47 °C.

3-(4-Chlorophenyl)-4-phenyl-2-pyrazoline. A mixture of 121.3 g of 4′-chloro-2-phenylacrylophenone (0.5 mol) and 50 mL of hydrazine hydrate in 280 mL of 1-propanol was refluxed for 3 h. After cooling, 200 mL of ice-cold methanol was added. The precipitate was collected and washed with cold methanol and ether. Yield 96.5 g (75%), mp 164–167 °C (dec).

Anal. Calcd for $C_{15}H_{13}ClN_2$ (M_r, 256.74): C, 70.17; H, 5.11; Cl, 13.81; N, 10.91. Found: C, 70.2; H, 5.2; Cl, 13.7; N, 11.0.

3-(4-Chlorophenyl)-1-(4-chlorophenylcarbamoyl)-4-phenyl-2-pyrazoline [Table I, Compound 13 (I,13)]. To

Scheme I. Preparation of Substituted 3,4-Diphenyl-1-phenylcarbamoyl-2-pyrazolines



Research Laboratories, Philips-Duphar B.V., Weesp, 1230, Netherlands.

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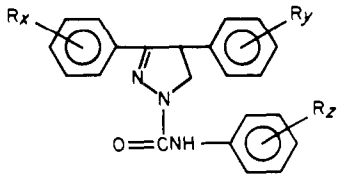
Table I. Insecticidal Activities of



compd no.	R_x	R_y	R_z	lowest test concentration with ≥90% mortality[a] *Leptinotarsa decemlineata* Say	*Pieris brassicae* L.	*Aëdes aegypti* L.	mp, °C
		a. R_x = Hydrogen; R_y = Hydrogen, Halogen; R_z = Miscellaneous					
1	H	H	H	10	>300	>1	185
2	H	H	4-Cl	0.3	30	0.1	167
3	H	H	4-C_2H_5	3	100	0.1	154
4	H	H	4-NO_2	1	100	1	190
5	H	4-Cl	H	10	>300	>1	224
6	H	4-Cl	4-Cl	0.3	10	0.03	137
7	H	4-Cl	3,4-Cl_2	0.3	10	0.1	170
8	H	4-Cl	4-C_2H_5	1	30	0.1	140
		b. R_x = Halogen; R_y = Hydrogen; R_z = Miscellaneous					
9	4-F	H	H	30	300	>1	161
10	4-F	H	4-Cl	1	1	0.1	158
11	4-Cl	H	H	10	100	>1	157
12	4-Cl	H	2-Cl	>300	>300	>1	195
13	4-Cl	H	4-Cl	0.3	1	0.1	177
14	4-Cl	H	4-Br	0.3	1	0.03	182
15	4-Cl	H	3-CF_3	3	10	>1	151
16	4-Cl	H	4-CF_3	0.1	0.3	0.1	178
17	4-Cl	H	4-C_2H_5	1	10	0.1	158
18	4-Cl	H	4-*n*-C_4H_9	10	10	>1	170
19	4-Cl	H	4-*n*-C_8H_{17}	>300	>300	>1	135
20	4-Cl	H	4-O-*i*-C_3H_7	1	3	0.1	149
21	4-Cl	H	4-CN	1	3	0.1	202
22	4-Br	H	4-Cl	1	1	0.03	178
		c. R_x = R_y = Halogen; R_z = Miscellaneous					
23	4-Cl	4-Cl	H	3	100	1	141
24	4-Cl	4-Cl	4-F	1	1	0.03	146
25	4-Cl	4-Cl	2-Cl	>300	300	>1	204
26	4-Cl	4-Cl	3-Cl	3	10	0.1	158
27	4-Cl	4-Cl	4-Cl	0.3	0.3	0.03	174
28	4-Cl	4-Cl	4-Br	1	1	0.03	174
29	4-Cl	4-Cl	4-I	1	1	0.3	189
30	4-Cl	4-Cl	4-CF_3	0.1	0.3	0.01	152
31	4-Cl	4-Cl	4-C_2H_5	3	3	0.03	172
32	4-Cl	4-Cl	4-OCH_3	1	30	0.1	158
33	4-Cl	4-Cl	4-OCH_3, 3-NO_2	10	300	>1	216
34	4-Cl	4-Cl	4-O-*i*-C_3H_7	3	3	0.03	166
35	4-Cl	4-Cl	3-NO_2	1	10	0.3	165
36	4-Cl	4-Cl	4-NO_2	1	1	0.03	204
37	4-Cl	4-Cl	4-SO_2CH_3	3	1	0.01	>240
		d. R_x = R_y = R_z = Miscellaneous					
38	4-Cl	4-NO_2	H	10	30	>1	192
39	4-Cl	4-NO_2	4-Cl	1	1	0.03	200
40	4-CH_3	4-Cl	4-Cl	0.1	100	0.1	167
41	4-C_2H_5	4-OCH_3	4-Cl	1	30	0.3	124
42	4-OCH_3	4-Cl	4-Cl	1	30	0.1	156
43	4-O-*i*-C_3H_7	H	4-Cl	1	3	0.1	145
44	4-O-*i*-C_3H_7	H	4-C_2H_5	1	10	0.3	97
45	4-O-*i*-C_3H_7	H	4-O-*i*-C_3H_7	1	10	0.1	154
46	4-NO_2	H	4-Cl	3	30	>1	201

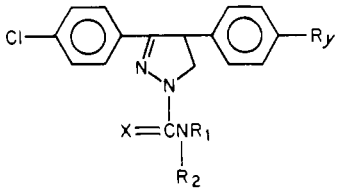
[a] Applied concentrations in parts per million: *Aëdes aegypti* L.; 1, 0.3, 0.1, 0.03, . . .; *Pieris brassicae* L., 300, 100, 30, 10, 3, . . .; *Leptinotarsa decemlineata* Say, 300, 100, 30, 10, 3, . . .

a stirred suspension of 14.8 g of 3-(4-chlorophenyl)-4-phenyl-2-pyrazoline (0.058 mol) in 150 mL of dry ether, 8.9 g of 4-chlorophenyl isocyanate (0.058 mol) was added. The solution became clear and a precipitate of the reaction product appeared. After stirring for 2 h, the precipitate was collected and dried, yielding 19.6 g (82%) of compound I,13; mp 175–177 °C.

Anal. Calcd for $C_{22}H_{17}Cl_2N_3O$ (M_r, 410.32): C, 64.40; H, 4.18; Cl, 17.28; N, 10.24. Found: C, 64.3; H, 4.2; Cl, 17.4; N, 10.2.

3-(4-Chlorophenyl)-1-[*N*-(4-chlorophenyl)-*N*-methyl]carbamoyl-4-phenyl-2-pyrazoline (II,1). To a solution of 4.1 g of 3-(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-4-phenyl-2-pyrazoline (0.01 mol) in 25

Table II. Insecticidal Activities of



compd no.	X	R_1	R_2	R_y	lowest test concentration with ≥90% mortality[a]: *Leptinotarsa decemlineata* Say	*Pieris brassicae* L.	*Aëdes aegypti* L.	mp, °C
1	O	4-ClC_6H_4	CH_3	H	3	1	0.1	144
2	O	4-ClC_6H_4	C_2H_5	H	1	3	0.03	oil
3	O	4-ClC_6H_4	n-C_4H_9	H	3	3	0.1	oil
4	O	4-ClC_6H_4	n-C_8H_{17}	H	3	3	0.1	oil
5	O	CH_3	H	Cl	300	>300	>1	oil
6	O	n-C_4H_9	H	Cl	100	300	1	oil
7	O	c-C_6H_{11}	H	Cl	10	10	>1	188
8	O	n-$C_{11}H_{23}$	H	Cl	>300	>300	>1	oil
9	S	4-ClC_6H_4	H	H	3	3	1	196
10	S	4-ClC_6H_4	H	Cl	3	3	1	147

[a] Applied concentrations in parts per million: *Aëdes aegypti* L., 1, 0.3, 0.1, 0.03, . . .; *Pieris brassicae* L., 300, 100, 30, 10, 3, . . .; *Leptinotarsa decemlineata* Say, 300, 100, 30, 10, 3, ...

mL of dimethylformamide, 0.7 g of powdered potassium hydroxide (0.0125 mol) was added, followed after 15 min by 1.42 g of methyl iodide (0.01 mol). After being stirred for 0.5 h, the reaction mixture was poured into ice–water. The resulting precipitate was stirred for another 2 h and then collected and washed with methanol and petroleum ether. Yield 3.1 g (73%), mp 142–144 °C.

Anal. Calcd for $C_{23}H_{19}Cl_2N_3O$ (M_r, 424.34): C, 65.10; H, 4.51; Cl, 16.71; N, 9.90. Found: C, 64.8; H, 4.5; Cl, 16.8; N, 9.8.

1-(n-Butylcarbamoyl)-3,4-bis(4-chlorophenyl)-2-pyrazoline (II,6). To a suspension of 2.91 g of 3,4-bis-(4-chlorophenyl)-2-pyrazoline (0.01 mol) in 50 mL of dry ether, three drops of triethylamine and 1 g of n-butyl isocyanate (0.01 mol) were added. After stirring for 16 h, the solvent was evaporated in vacuum and the residue was chromatographed over a silica gel column, with chloroform as an eluant. The reaction product failed to crystallize. Yield 2.2 g (56%).

Anal. Calcd for $C_{20}H_{21}Cl_2N_3O$ (M_r, 390.33): C, 61.54; H, 5.42; Cl, 18.17; N, 10.77. Found: C, 61.1; H, 5.3; Cl, 18.3; N, 10.3.

3,4-Bis(4-chlorophenyl)-1-cyclohexylcarbamoyl-2-pyrazoline (II,7). To a suspension of 2.91 g of 3,4-bis(4-chlorophenyl)-2-pyrazoline (0.01 mol) in 30 mL of dry ether, three drops of triethylamine and 1.25 g of cyclohexyl isocyanate (0.01 mol) were added. After stirring for 16 h, the precipitate was collected and dried. Yield 2.1 g (50%), mp 185–188 °C.

Anal. Calcd for $C_{22}H_{23}Cl_2N_3O$ (M_r, 416.36): C, 63.46; H, 5.57; Cl, 17.03; N, 10.09. Found: C, 63.5; H, 5.7; Cl, 16.6; N, 10.1.

3-(4-Chlorophenyl)-1-(4-chlorophenylthiocarbamoyl)-4-phenyl-2-pyrazoline (II,9). Prepared according to the procedure described for compound I,13, except that now the reaction mixture was stirred for 20 h. Yield 92%, mp 194–196 °C.

Anal. Calcd for $C_{22}H_{17}Cl_2N_3S$ (M_r, 426.38): C, 61.97; H, 4.02; Cl, 16.63; N, 9.86; S, 7.52. Found: C, 62.0; H, 4.2; Cl, 16.7; N, 9.8; S, 7.7.

4′-Chloro-3-dimethylamino-2-phenylacrylophenone. A mixture of 23.1 g of 4′-chloro-2-phenylacetophenone (0.1 mol) and 17.2 mL of *N,N*-dimethylformamide diethylacetal (0.1 mol) in 250 mL of dry tetrahydrofuran was stirred at room temperature for 24 h and then refluxed for 6 h. The solvent was distilled off at reduced pressure and the residue was chromatographed over a silica gel column, with ether as an eluant. Yield 5.6 g (20%), mp 101–110 °C.

3-(4-Chlorophenyl)-4-phenylpyrazole. To a solution of 5 g of 4′-chloro-3-dimethylamino-2-phenylacrylophenone (0.0175 mol) in 50 mL of ethanol, 1.75 mL of hydrazine hydrate (0.035 mol) was added. After refluxing for 3 h, the ethanol was distilled off at reduced pressure. The residue was dissolved in ether and washed with water. Evaporation of the solvent gave an oil, which after solidification could be recrystallized from petroleum ether. Yield 3.6 g (80%), mp 133–135 °C.

3-(4-Chlorophenyl)-1-(4-chlorophenylcarbamoyl)-4-phenylpyrazole. A solution of 0.89 g of 3-(4-chlorophenyl)-4-phenylpyrazole (0.0035 mol) and 0.6 g of 4-chlorophenyl isocyanate (0.0039 mol) in 15 mL of dry ether was refluxed for 7 h. After addition of 15 mL of dry hexane, the precipitate formed was collected. Yield 1.1 g (77%), mp 172–175 °C. NMR (Me_2SO) δ 7.44 (13, m, aromatic), 8.36 (1, s, CH), 9.13 (1, s, NH).

Anal. Calcd for $C_{22}H_{15}Cl_2N_3O$ (M_r, 408.30): C, 64.72; H, 3.70; Cl, 17.37; N, 10.29. Found: C, 64.6; H, 3.7; Cl, 17.2; N, 10.3.

NMR SPECTRA

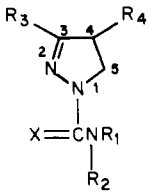
The NMR proton chemical shift data of the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines are summarized in Table III. All the chemical shifts are as may be expected. The N-alkyl derivatives (R_2 = alkyl) have the same anomalous proton chemical shift behavior as the 1-(*N*-alkyl-*N*-phenylcarbamoyl)-3-phenyl-2-pyrazolines (Wellinga et al., 1977).

The proton spin coupling constants of the 2-pyrazoline protons ($J_{4,5}$ = 11 Hz; $J_{4,5'}$ = 5 Hz; $J_{5,5'}$ = −11 Hz) are in accordance with those of the 1,3,4-triphenyl-2-pyrazolines ($J_{4,5}$ = 10 Hz; $J_{4,5'}$ = 6 Hz; $J_{5,5'}$ = −10 Hz; Batterham, 1973).

BIOLOGICAL METHODS

The methods for the insecticidal evaluation are described in part 1 of this series of papers.

Table III. ^{1}H NMR Data in Me_2SO of



					average chemical shifts in δ value[a]												
					pyrazoline			phenyl R_1				phenyl R_3			phenyl R_4		
X	R_1	R_2	R_3	R_4	H_4	H_5	H_5'	ortho	meta	para	R_2	ortho	meta	para	ortho	meta	para
S	phenyl	H	phenyl	phenyl	5.08	4.68	4.22	7.63	7.31		10.15	7.81	7.28		7.20	7.28	
O	phenyl	H	phenyl	phenyl	4.99	4.37	3.87	7.66	7.23	6.93	9.06 5.70[b]	7.77	7.28		7.24	7.27	7.28
O	alkyl	H	phenyl	phenyl	4.93	4.25	3.77				7.09[c]	7.60	7.28		7.18	7.23	
O	phenyl	alkyl	phenyl	phenyl	4.73	4.30	3.86	7.12	7.09			{7.19 7.37	{7.34 7.16		7.06	7.25	

[a] The standard deviation from the average chemical shifts of the pyrazoline protons were H_4, 0.10; H_5, 0.05; H_5', 0.04. The chemical shifts of the phenyl and NH protons are calculated for the unsubstituted derivatives by means of the aromatic substituent shifts (Wellinga et al., 1976, Table IV). The standard deviation of the aromatic protons was 0.05 and of the NH protons 0.09. [b] Cyclohexyl. [c] *n*-Alkyl.

RESULTS AND DISCUSSION

From the many hundreds of compounds prepared in this series we have made a representative selection. In Table I (subdivided into sections a, b, c, and d) the insecticidal properties are presented of the different types of substituted 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines. Table Ia represents the activities of the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines with an unsubstituted "ring 3" and with an unsubstituted or with a para chloro substituted "ring 4". The phenyl ring in the carbamoyl group, "ring 1", has a miscellaneous substitution pattern. An unsubstituted ring 1 is not favorable, while substitution of that ring with a para chloro atom enhances the activity on all three species involved (**1** vs. **2** and **5** vs. **6**). This also holds true for some other compounds mentioned in Table I (**9** vs. **10**; **11** vs. **13**; **23** vs. **27**; and **38** vs. **39**). Substitution of a chloro atom in one of the phenyl rings by another halogen atom leads to compounds with roughly the same order of activity (**11** vs **9**; **13** vs. **10**, **14** and **22**; **27** vs. **24**, **28**, and **29**). Replacement of a chloro atom by an ethyl group gives a slight reduction in activity (**2** vs. **3**; **6** vs. **8**; **13** vs. **17**; **27** vs. **31**; **43** vs. **44**). A longer alkyl group seems to be even more unfavorable (**17** vs. **18** and **19**). Substitution, at the meta position but especially at the ortho position, causes a decrease in activity (**15** vs. **16**; **35** vs. **36**; **26** and **25** vs. **27**; **12** vs. **13**).

Table II shows some modifications in the carbamoyl moiety of the molecule. N-Alkylation causes only a slight decrease in activity (II:**1**, **2**, **3**, **4** vs. I,**13**). The same happens when the oxygen atom is replaced by a sulfur atom (II:**9** and **10** vs. I:**13** and **27**). A much greater reduction in activity is obtained when the aromatic ring 1 is replaced by a *n*-alkyl group (II:**5**, **6**, **8**). The cyclohexyl group causes less reduction in activity (II,**7**). Finally, replacement of the pyrazoline nucleus of compound I,**13** by a pyrazole nucleus gives rise to a very strong reduction in activity. This compound (not presented in the tables) may be considered as the 4,5-dehydro derivative of I,**13**.

From the data presented (Tables I and II), it appears that there are numerous compounds with a high insecticidal activity, particularly—among others—the para-substituted halogen derivatives and the *p*-trifluoromethyl and *p*-nitro compounds.

Preliminary toxicological data of a number of 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines have been obtained with mice. When administered orally, the following compounds are found to have LD_{50} values higher than 1000 mg/kg: I:**15**, **16**, **21** and II: **5**, **6**. Of the compounds I,**13** and I,**27** the acute LD_{50} values are higher than 3160 mg/kg when administered orally and higher than respectively 3160 and 562 mg/kg upon intraperitoneal application.

CONCLUSION

When comparing the activities of four representatives of the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines (e.g., Table I, **13**, **14**, **27**, **30**) with compounds with the same substitution pattern of the 3-phenyl-1-phenylcarbamoyl-2-pyrazolines (part 1; Table I, **40**, **47**, **40**, **64**) and the 3,5-diphenyl-1-phenylcarbamoyl-2-pyrazolines (part 2; Table I, **15**, **16**, **7**, **9**), it is clear that the 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines are more active on larvae of *Pieris brassicae* L., *Leptinotarsa decemlineata* Say, and *Aëdes aegypti* L. The order of magnitude by which these 3,4-diphenyl derivatives are more active than the 3-phenyl or 3,5-diphenyl analogues is roughly a factor 3–100.

Supplementary Material Available: A listing of microanalyses for compounds I,**30**; I,**31**; I,**33**; and II,**10** (1 page). Ordering information is given on any current masthead page.

LITERATURE CITED

Batterham, T. J., "NMR Spectra of Simple Heterocycles", Wiley, New York, 1973, p 206.
Curtin, D. Y., Crew, M. C., *J. Am. Chem. Soc.* **76**, 3719 (1954).
van Hes, R., Wellinga, K., Grosscurt, A. C., *J. Agric. Food Chem.* **26**, 915 (1978).
Wellinga, K., Grosscurt, A. C., van Hes, R., *J. Agric. Food Chem.* **25**, 987 (1977).

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