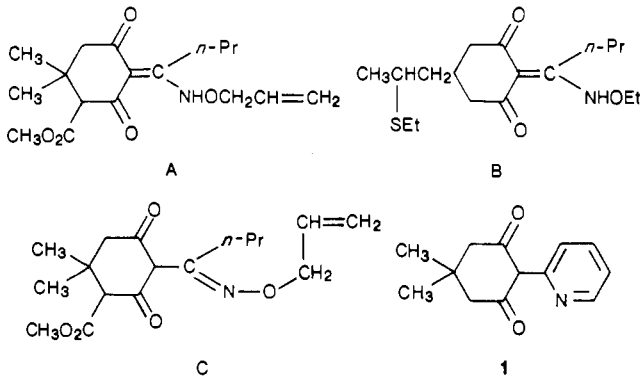
Synthesis and Herbicidal Activity of Pyridinyl-Substituted 1,3-Cycloalkanediones

David T. Manning,* Anson R. Cooke, and Richard D. Gruenhagen[1]

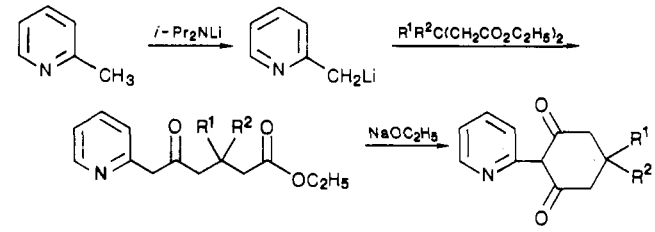
A series of pyridinyl-substituted 1,3-cycloalkanediones and derived enol esters was synthesized for herbicidal evaluation. 5,5-Dimethyl-2-(2-pyridinyl)-1,3-cyclohexanedione showed high post- and preemergence activity, particularly against annual broadleaf species. Significant activity against the seedlings was seen only with 2-(2-pyridinyl) compounds; 2-(4-pyridinyl) 1,3-diones were inactive. 1,3-Cyclohexanediones with nitrogen at the heterocyclic 2-position appear to exist in intramolecularly hydrogen-bonded ring forms, and modifications preventing this bonding such as a methyl at pyridine position 3 or N-oxidation decreased or abolished activity. Alkyl groups at pyridine positions 5 or 6 or benzo ring fusion decreased or eliminated activity while methyl or methoxy at position 4 increased activity in certain cases. Highest activity was seen with 1,3-cyclohexanediones; 1,3-cyclopentanediones, indanediones, and hexahydroindanediones were less active.

2-Phenyl-1,3-indanediones (Durden, 1974), 2-phenylhexahydro-1,3-indanediones (Wheeler, 1982), 2-phenyl-1,3-cyclohexanediones, and their enol esters (Wheeler, 1980) and 2-phenyl-1,3-cyclopentanediones (Wheeler, 1982), in all cases bearing appropriate phenyl ortho substituents, display high levels of miticidal activity and are also significantly toxic, in both pre- and postemergence applications, to various grass species. Plans to explore less conventional modifications of the 2-aryl-1,3-cyclodiones suggested examination of compounds with 2-heteroaryl substituents. In this connection it was interesting to note the grass herbicide activity of various O-substituted oximes of 2-acyl-1,3-cyclohexanediones such as alloxydim (A) and sethoxydim (B), in which miticidal properties are also reported for the latter case (Iwataki et al., 1981). While the latter compounds lack 2-aryl substituents, the [(allyloxy)amino]butylidene substituent of alloxydim may be drawn in the hypothetical tautomeric form C, suggesting the 2-(2-pyridinyl) compound 1 of our present investigation.



Our attention was thus directed to 1,3-cycloalkanediones substituted at the 2-position with pyridinyl groups. Among this compound class are the well-known 2-pyridinyl-1,3-indanediones or "pyrophthalones" (Ploquin et al., 1974). While 5,5-dimethyl-2-(2-pyridinyl)-1,3-cyclohexanedione (Yousif et al., 1982), its 3-carboxy analogue (Ames and Dodds, 1972), and certain quinolinyl dione derivatives (Douglass and Fortner, 1973; Yousif et al., 1982) have also been described, no study of the biological properties or systematic investigation of pyridinyl-1,3-cycloakanediones has been reported.

Scheme I



METHODOLOGY

Synthesis. *2-(2-Pyridinyl)- and 2-(4-Pyridinyl)-1,3-cyclodiones.* Synthesis of the 2-(2-pyridinyl)- and 2-(4-pyridinyl)-1,3-cyclohexanediones generally began with preparation of (lithiomethyl)pyridine derivatives, based upon a reported procedure (Edwards and Teague, 1949). In most cases the lithium salts were then condensed with 3-substituted glutaric esters to give 6-pyridinyl-5-oxohexanoates, which were cyclized by heating with ethanolic sodium ethoxide (Scheme I). The single 3a,4,5,6,7,7a-hexahydroindane-1,3-dione **23** was also prepared by this method.

Preparation of 4-alkyl-2-pyridinyl diones required a modification of the above procedure. With 2,4-dimethylpyridine, lithiation by lithium diisopropylamide occurred selectively at the 4-methyl, leading to the 2-(4-pyridinyl) dione **30**. The alternate use (Arens et al., 1950; Kaiser et al., 1973) of *n*-butyllithium or phenyllithium, however, gave selective 2-methyl lithiation, leading to the 2-(2-pyridinyl) product **2** as shown in Scheme II.

4-(2-Pyridinyl)-1,3-cyclohexanediones. Condensation of ethyl 2-pyridinylacetate with appropriate vinyl methyl ketones, in the presence of ethoxide, gave the desired compounds as indicated in Scheme III. Spectroscopic evidence suggests the formation of the bisenol tautomer shown.

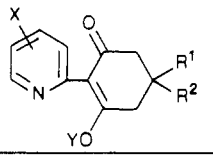
Enol Esters. Treatment of the dry potassium salts of various diones with 1 equiv of acid chloride and a small amount of crown ether in dry THF gave the enol esters in satisfactory yield.

Research and Development Department, Rhône-Poulenc Ag Company, Research Triangle Park, North Carolina 27709.

[1]Present address: New Jersey Department of Agriculture, Trenton, NJ 08625.

0021-8561/88/1436-0169$01.50/0

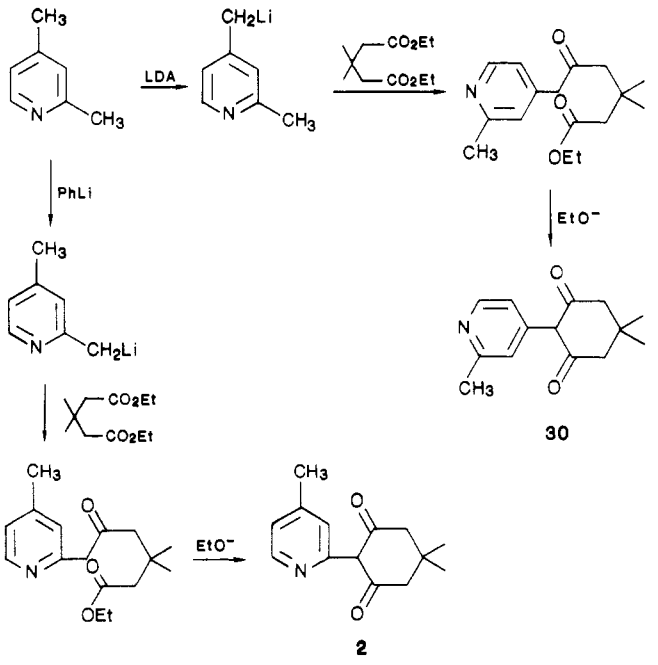
Table I. Pyridinyl 1,3-Diones



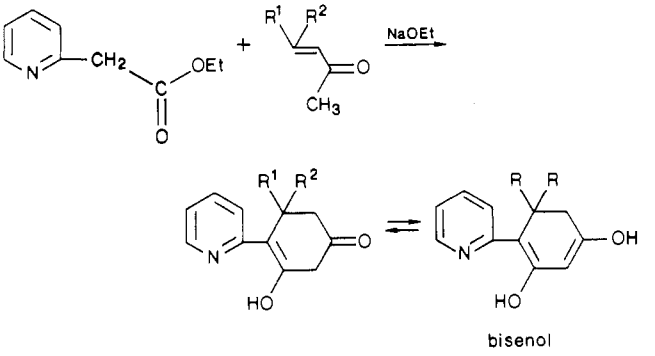
no.	X	R^1, R^2	Y	mp, °C	analysis calculated C	calculated H	calculated N	found C	found H	found N	postemergence herbicidal act., % control (8 lb AI/acre) broadleaves[a]	grasses[b]
1	H	Me, Me	H	163–165.5	71.86	6.96	6.45	71.71	7.00	6.64	88	90
2	4-Me	Me, Me	H	122–123.5	72.70	7.41	6.06	72.32	7.47	6.04	100	100
3	H	*i*-Pr, H	H	110–112	72.70	7.41	6.06	72.59	7.57	5.92	96	100
4	4-Me	*i*-Pr, H	H	104–106.5	73.44	7.81	5.71	73.34	7.79	5.62	93	96
5	4-MeO	*i*-Pr, H	H	152–154.5	68.94	7.33	5.36	69.30	7.43	5.41	100	100
6	H	2-Bu, H	H	69–72	73.44	7.81	5.71	73.47	7.82	5.65	100	79
7	4-Et	*i*-Pr, H	H	74.5–77.5	74.10	8.16	5.40	73.98	8.24	5.39	100	90
8	H	Et_2CH, H	H	93.5–95	74.10	8.16	5.40	73.33	8.19	5.25	76	34
9	H	$-(CH_2)_4-$	H	170–171.5	74.05	7.04	5.76	73.75	6.98	5.76	93	100
10	H	Me_3C, H	H	145.5–148.5	73.44	7.81	5.71	73.31	7.86	5.78	95	77
11	H	Me, Et	H	121–122.5	72.70	7.41	6.06	72.85	7.49	6.11	91	67
12	6-Me	Me, Me	H	88.5–90.5	72.70	7.41	6.06	72.74	7.57	6.14	84	17
13	compound 12 *N*-oxide			127–129	68.00	6.93	5.66	68.07	6.73	5.71	28	0
14	3-Me	Me, Me	H	238 dec	62.80	6.78	5.23	61.84	6.79	5.25	0	0
15	3,5-Me_2	Me, Me	H	222–228.5	63.94	7.15	4.97	63.48	7.20	4.88	0	4
16	5-Et	Me, Me	H	154.5–156.5	73.44	7.81	5.71	73.52	7.72	5.78	0	0
17	5-Et	Me, Me	MeCO	oil	71.06	7.37	4.87	70.92	7.90	5.12	54	10
18	5-Me	*i*-Pr, H	H	132.5–135	73.44	7.81	5.71	73.11	7.96	5.69	27	0
19	6-Cl	Me, Me	H	76–78	62.03	5.61	5.56	61.97	5.55	5.65	4	14
20[c]	H	H, H	H	152–172	58.54	5.36	6.21	58.45	5.48	6.16	89	32
21	H	C_6H_5, H	H	144.5–146.5	76.96	5.70	5.28	76.90	5.60	5.24	18	6
22	H	C_6H_{11}, H	H	181–182.5	75.24	7.80	5.16	75.25	7.76	5.21	8	0

[a] Average for morningglory, mustard, black nightshade, teaweed, and velvetleaf. [b] Average for downy brome, wild oats, crabgrass, barnyardgrass, and giant foxtail. [c] HCl salt.

Scheme II



Scheme III

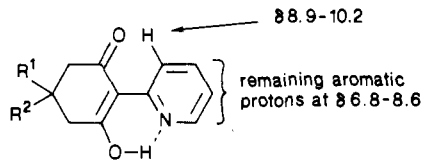


Postemergent Herbicidal Evaluation. The test plants were morningglory (*Ipomoea purpurea*), mustard (*Brassica kaber*), black nightshade (*Solanum nigrum*), teaweed (*Sida spinosa*), velvetleaf (*Abutilon theophrasti*), jimsonweed (*Datura stramonium*), downy brome (*Bromus tectorum*), wild oats (*Avena fatua*), crabgrass (*Digitaria sanguinalis*), barnyardgrass (*Echinochloa crus-galli*), giant foxtail (*Setaria faberi*), annual ryegrass (*Lolium multiflorum*), and seedling johnsongrass (*Sorghum halepense*). Test chemicals were dissolved in 50:50 (v/v) acetone–water and applied in a spray volume equivalent to 100 GPA. The soil and developing plants were sprayed at the one- to two-leaf stage at rates of 8, 2, 1, and 0.5 lb AI/acre, as indicated in the tables. The postemergence activity, as estimated percent control, is reported in Tables I–III.

RESULTS AND DISCUSSION

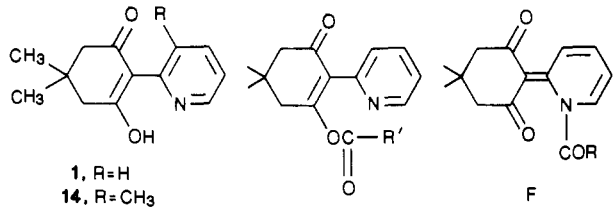
Physical Properties and Spectroscopic Evidence. The heterocyclic diones are amphoteric compounds, soluble in water at both low and high pH values. While many of the compounds precipitated as crystalline solids in the approximate range pH 5.5–10.5, others were highly water soluble, as in the case of the free base of hydrochloride 27.

The 2-(2-pyridinyl) 1,3-diones appear to exist as enols in intramolecularly hydrogen-bonded ring forms such as D. Molecular models show the N- - -HO— ring of D to be fairly rigid, with the proton at pyridine ring position 3 approaching the dione oxygen. In all pyridine-substituted diones where a chelate ring is possible, this 3-proton



D

was isolated and shifted downfield to 8.9–10.2 ppm by the deshielding carbonyl oxygen, an observation also reported in the case of the 2-(2-quinolinyl) dione **29** (Douglass and Fortner, 1973). Enol esterification of D (as in **17**) or conversion to the *N*-oxide (**13**) disrupts the chelate ring and shifts the 3-proton resonance upfield markedly. In the case of 2-(2-pyridinyl) diones such as **1** the intramolecular proton binding was indicated by the inability to titrate the compounds to an inflection point, similar to the observation for the corresponding indanedione (Lombardino, 1967). In their syntheses from 2,4-dimethylpyridine, the isomeric diones **30** and **2** (see Scheme II) were distinguishable by the titrateability of **30** and by its lack of the isolated, low-field 3-proton seen in **2**. Disruption of the chelate ring in **14** by its 3-methyl substituent enables its titration (enol pK_a ~6.9).



E F

IR spectra of acyl derivatives of these diones show ester-like carbonyls (1750–1770 cm^{-1}) as in E, and further evidence for E, as opposed to amide isomer F, is given by the aromatic ^1H NMR spectra. In comparison of ^1H NMR spectra of dione enol esters and the corresponding keto ester synthesis precursors the aromatic regions were found to be essentially identical.

Structure–Activity Relationships. Various 5-alkyl-substituted 2-(2-pyridinyl)-1,3-cyclohexanediones showed high postemergent herbicidal activity. The activity of 29 pyridinyl diones at 8 lb/acre is shown in Tables I and II. Table III shows a comparison of nine of the most active compounds at rates of 2.0, 1.0, and 0.5 lb/acre. Significant activity was seen only with 2-(2-pyridinyl) compounds. 2-(4-Pyridinyl) 1,3-diones, with or without an ethyl substituent at the ortho pyridine 3-position, and 4-(2-pyridinyl)-1,3-diones were inactive. Highest activity was seen with 1,3-cyclohexanediones; 1,3-cyclopentanediones, indanediones, and hexahydroindanediones were much less active, with activity decreasing in the cyclodione order cyclohexanedione > hexahydroindanedione > cyclopentanedione ~ indanedione. Herbicidal activity of the 2-(2-pyridinyl)-1,3-cyclohexanediones was sensitive to substitution in the pyridine ring. Alkyl substituents at ring positions 3 (ortho), 5, or 6 were detrimental, particularly at positions 3 or 5 which abolished activity. Enol esterification of the 5-ethyl compound **16** resulted, however, in some activity at the 8-lb rate (compound **17**). Chlorine at position 6 (**19**) and *N*-oxide (**13**) nearly eliminated activity. Activity was also lost upon benzo ring fusion to pyridine (**29**). Broad-spectrum activity was highest with 5-isopropyl, 5-(2-butyl), or 5,5-dimethyl substituents on the dione nucleus but diminished abruptly with 5,5-dihydrogen, 5-(2-pentyl), 5-cyclohexyl, and 5-phenyl substitutuents. A 5-spirocyclopentano substituent, however, gave an active compound (**9**).

Alkyl or methoxy substituents at the 4-position of the pyridine increased activity in certain cases, and the 4-methoxy compound **5** showed the highest postemergent activity at 0.5 lb/acre of compounds tested at that rate. The 5-isopropyl-2-(4-methyl-2-pyridinyl) compound **4** appeared to be as active on broadleaves as the 4-methoxy compound **5**. The 4-ethyl substituent (**7**) was less effective. The highest grass activity was shown by compounds (**3**, **5**, **6**) with isopropyl or 2-butyl substituents at the dione 5-position and H, methyl, or methoxy at pyridine position 4 (Table III). None of the pyridinyl 1,3-diones showed potentially useful selectivity patterns.

Certain observations support the thesis that activity is dependent upon the presence of the 2-pyridinyl N---HO— chelate ring. In the inactive **14**, methyl at the pyridine 3-position sterically disrupts this ring and this bonding is also precluded in the nearly inactive *N*-oxide **13** and 2-(4-pyridinyl) compounds (**26**, **27**, **30**). Inactivation by 5-methyl (**18**) and 5-ethyl (**16**) substituents, in sharp contrast to the effects of these groups at the pyridine 4-position, is less readily explained. It is possible that 5-alkyls are vulnerable to metabolic oxidation or cause the molecules to exceed a "length" requirement that might also be the case when large groups such as 3-pentyl, cyclohexyl, or phenyl are present at the 5-position of the nucleus.

The various pyridinyl-substituted 1,3-cycloalkanediones were inactive on insects and mites.

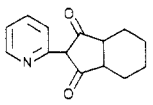
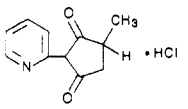
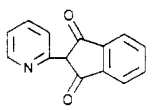
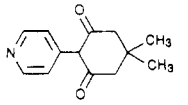
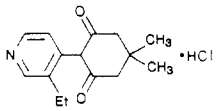
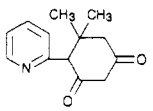
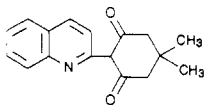
EXPERIMENTAL CHEMISTRY SECTION

Melting points are uncorrected. ^1H NMR spectra were obtained with a Varian EM-360A spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 197 or Beckman Acculab 2 spectrometer. Elemental analyses were performed by the Union Carbide Analytical Group at the South Charleston, WV, Technical Center. Potentiometric pH measurements were performed on a Beckman Zeromatic pH meter equipped with manual temperature control, fiber junction calomel reference, and glass silver–silver chloride electrodes. The reference electrode contained saturated aqueous potassium chloride solution. The instrument was standardized with commercial aqueous buffer systems. pK_a values were determined by titration in 70% ethanol–30% water (v/v) and extrapolated to 100% aqueous values by graphical relations to values determined in aqueous solutions containing decreasing concentrations of ethanol.

Special Starting Materials. 4-Ethyl-2-methylpyridine was prepared by the procedure of Kaiser et al. (1973). 4-Methoxy-2-picoline 1-oxide was prepared according to the general procedures of Profft et al. (1969). The crude 1-oxide was reacted directly with PCl_3 in chloroform to give the known 4-methoxy-2-picoline, based upon the general method of Herz and Tsai (1954). 2,3,5-Trimethylpyridine was synthesized by the procedure of Bohlmann et al. (1955).

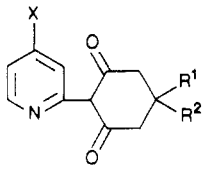
3-Substituted glutaric esters were prepared by three general methods. For the *tert*-butyl, 2-butyl, and 3-pentyl-substituted esters, α,β-unsaturated ketones were first prepared by a procedure similar to that of Drake and Allen (1951) and condensed with malonic ester to give properly substituted 1,3-cyclohexanediones by the method of Shriner and Todd (1950). Oxidation of the cyclodiones then gave the glutarates (Smith and McLeod, 1963). The glutaric esters with 3-isopropyl and 3-cyclohexyl substituents were synthesized from the appropriate aldehydes and cyanoacetamide (Kent and McIlvain, 1955). The esters with 3-cyclopentano and 3-ethyl-3-methyl groups were prepared by the Guareschi synthesis from the corre-

Table II. Additional Pyridinyl 1,3-Diones

no.	structure	mp, °C	analysis: calculated C	calculated H	calculated N	found C	found H	found N	postemergence herbicidal act., % control (8 lb AI/acre): broadleaves[a]	grasses[b]
23		212.5–215	73.34	6.59	6.10	73.55	6.50	6.05	90	69
24		200–205	58.54	5.36	6.21	57.33	5.27	6.10	62	0
25		288–290	75.33	4.06	6.27	75.29	4.34	6.13	43	12
26		242–249 dec	71.86	6.96	6.45	71.87	6.82	6.51	8	0
27		202–205.5	63.94	7.15	4.97	63.92	7.08	4.87	4	16
28		113–116	71.81	6.96	6.45	71.52	6.84	6.35	0	0
29		182–183.5[c]	76.38	6.41	5.24	76.33	6.57	4.98	20	0

[a] Average for morningglory, mustard, black nightshade, teaweed, and velvetleaf. [b] Average for downy brome, wild oats, crabgrass, barnyardgrass, and giant foxtail. [c] Reported mp 188–189 °C (Douglass and Fortner, 1973).

Table III. Postemergence Control Data



no.	X	R^1, R^2	% control of broadleaves[a] 2.0[c]	broadleaves[a] 1.0	broadleaves[a] 0.5	grasses[b] 2.0	grasses[b] 1.0	grasses[b] 0.5
1	H	Me, Me	74	57	41	32	18	0
2	Me	Me, Me	84	67	20	47	37	
3	H	*i*-Pr, H	83	55	4	88	72	28
4	Me	*i*-Pr, H	87	78		50	36	
5	MeO	*i*-Pr, H	85	76	65	88	60	57
6	H	2-Bu, H	93	59		83	60	
7	Et	*i*-Pr, H	46	25	25	0	0	
9	H	$-(CH_2)_4-$	71				16	
10	H	Me_3C, H	43	36		7	0	

[a] Average for morningglory, velvetleaf, black nightshade, teaweed, and jimsonweed. [b] Average for giant foxtail, large crabgrass, wild oats, annual rye, and seedling johnsongrass. [c] Pounds AI/acre.

sponding ketones, cyanoacetic ester, and ammonia (Farmer and Rabjohn, 1963).

Ethyl 3,3-Dimethyl-6-(4-methyl-2-pyridinyl)-5-oxohexanoate. A 1.9 M solution of phenylithium in benzene–ether (95 mL, 0.18 mol) was added, with stirring, to 180 mL of dry tetrahydrofuran in a dry argon-blanketed flask cooled to −10 to −20 °C. Continuing the stirring and cooling to −15 °C, a 27.7-mL portion (0.18 mol) of dry 2,4-lutidine was added over 7 min and the black solution stirred at −15 to −20 °C for 30 min. This solution was then fed, with stirring, to a solution of diethyl 3,3-dimethylglutarate (116.8 g, 0.54 mol) in 230 mL of dry tetrahydrofuran with cooling to −78 °C. The resulting mixture was allowed to warm to 0 °C and held at this temperature for about 16 h. Water (60 mL) was then added, with stirring, to the mixture and gaseous CO_2 fed in until the pH dropped to about 6–8 and a white solid had precipitated. Tetrahydrofuran was evaporated off and the residue slurried with ether, filtering off insolubles. The ether layer was extracted with 6 N HCl (4×), and adjusting the acid extracts to pH 11 caused separation of the oily crude ester. Flash distillation of the latter gave 17.7 g (35.4% yield) of product over the approximate range 120–210 °C (0.2 mm) (Kugelrohr air temperature): IR (smear) 1730 cm^{-1} (ester C=O).

5,5-Dimethyl-2-(4-methyl-2-pyridinyl)-1,3-cyclohexanedione (2). To a refluxing solution of 1.46 g (0.064 mol) of sodium in 200 mL of dry ethanol was added 17.7 g (0.064 mol) of ethyl 3,3-dimethyl-6-(4-methyl-2-pyridinyl)-5-oxohexanoate over a period of a few minutes. Refluxing was continued for 2 h, ethanol was then removed by vacuum stripping, and the orange glassy residue was taken up in water and extracted with ether (3×) to remove water-insoluble materials. The water phase was adjusted to about pH 6 with 6 N HCl, causing the product to separate as a light pink solid. Crystallization from isopropyl ether gave 6.35 g (43.2% yield) of crystals: mp 122–123.5 °C; IR 2700–3000 (H-bonded N or O), 1635 (conj C=O), 1545, 1365 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (s, 6 H, CH_3CCH_3), 2.48 (s, 4 H, CH_2CCH_2), 6.95 (d, 1 H, 5-pyridinyl), 7.86 (d,

1 H, 6-pyridinyl), 9.15 (s, 1 H, 3-pyridinyl). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.32; H, 7.47; N, 6.04. An attempted titration with 0.1 N KOH gave no discernible end point.

3-(Acetyloxy)-5,5-dimethyl-2-(5-ethyl-2-pyridinyl)-2-cyclohexenone (17). (*A*) *Dione Potassium Salt.* A 10.0-g (0.041-mol) portion of 5,5-dimethyl-2-(5-ethyl-2-pyridinyl)-1,3-cyclohexanedione was added, with mild agitation at room temperature, to a solution of 2.69 g of KOH (85%, 0.041 mol) in 50 mL of water. The resulting solution was vacuum evaporated, with final vacuum drying at 60 °C, to give the dione potassium salt: 10.9 g (93.7% yield); NMR (D_2O) δ 1.05–1.43 (s and t, 9 H, CH_3CCH_3 and ethyl CH_3), 2.33 (s, 4 H, CH_2CCH_2), 2.44–2.90 (q, 2 H, ethyl CH_2), 7.07–8.47 (m, 3 H, aromatic H).

(*B*) *Acetylation.* To a stirred mixture of 5.0 g (0.018 mol) of 5,5-dimethyl-2-(5-ethyl-2-pyridinyl)-1,3-cyclohexanedione potassium salt, 75 mL of dry tetrahydrofuran, and 1 drop of dicyclohexyl-18-crown-6 was added 1.38 g (0.018 mol) of acetyl chloride at room temperature and the resulting mixture stirred overnight at ambient temperature. Solvent was removed under reduced pressure and the residue taken up in ether. The ether solution was filtered, washed in succession with cold 5% $NaHCO_3$, water, cold 0.25 N NaOH, and water, and then dried over $MgSO_4$. Vacuum removal of solvents gave 2.61 g (51.5% yield) of product as a light orange oil: IR 1768 (ester C=O), 1680 (ketone C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–1.45 (m, 9 H, 3 CH_3), 1.98 (s, 3 H, CH_3CO), 2.20–2.93 (m, 6 H, 3 CH_2), 7.04–8.57 (m, 3 H, aromatic H). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.92; H, 7.90; N, 5.12.

Ethyl 3,3-Dimethyl-6-(2-methyl-4-pyridinyl)-5-oxohexanoate. A 1.6 M solution of *n*-butyllithium in hexane (144 mL, 0.231 mol) was added, with stirring, to a solution of 23.4 g (0.231 mol) of dry diisopropylamine in 180 mL of dry tetrahydrofuran at −10 to −20 °C. 2,4-Lutidine (24.8 g, 0.231 mol) was then added, with stirring, over a 9-min period at the same temperature. The red-orange solution was stirred for 22 min and then fed, over a 1-h period, to a stirred solution of 150 g (0.693 mol) of diethyl 3,3-dimethylglutarate in 230 mL of dry tetrahydrofuran at −78 °C. The resulting mixture was allowed to warm to 0–5 °C and then held at this temperature for a 20-h period. Water (75 mL) was added, followed by a feed of gaseous CO_2, bringing the mixture to pH 7–8. Volatiles were flashed under reduced pressure, and the aqueous residue was extracted with ether. The ether extract was extracted with 3 N HCl (3×), and the aqueous phases were combined and their pH was adjusted to 9–10 by addition of 6 N NaOH. Ether extraction, $MgSO_4$ drying, and solvent evaporation gave the crude ester, which was distilled through a Kugelrohr apparatus to give 29.5 g (46.0% yield) of product: 140–200 °C (0.05–0.10 mm) (distillation air temperature); IR (smear) 1720 cm^{-1} (ester C=O).

5,5-Dimethyl-2-(2-methyl-4-pyridinyl)-1,3-cyclohexanedione (30). To a refluxing solution of 2.4 g (0.10 mol) of sodium in 200 mL of dry ethanol was added 29.01 g (0.10 mol) of ethyl 3,3-dimethyl-6-(2-methyl-4-pyridinyl)-5-oxohexanoate over 3 min. The mixture was heated under reflux for 2.6 h, and ethanol was then flash evaporated to give a dark orange glass. This was dissolved in water, the water solution extracted with ether, and its pH then adjusted to 7, following which water was removed under reduced pressure to give the crude, water-soluble product. Crystallization from acetonitrile gave 13.66 g (56.4% yield) of product as two crops of a yellow powder. Recrystallization (CH_3CN) gave the product: mp 201.5–204.5 °C; ^1H NMR ($CDCl_3$) δ 1.11 (s, 6 H, CH_3CCH_3), 2.45 (s, 4 H, CH_2CCH_2), 2.60 (s, 3 H, pyridine CH_3), 7.75–8.75 (m, 3 H, aromatic H), 15.06 (s, 1 H, OH). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.67; H, 7.17; N, 6.07; Potentiometric titration pK_a (70% EtOH in H_2O) 8.27 (pK_a 6.9, extrapolated to 100% H_2O).

5,5-Dimethyl-4-(2-pyridinyl)-1,3-cyclohexanedione (28). A mixture of ethyl 2-pyridinylacetate (16.6 g, 0.10 mol) and mesityl oxide (9.91 g, 0.10 mol) was fed, dropwise with stirring, to a solution of 2.3 g (0.10 mol) of sodium in 200 mL of dry ethanol over 20 min at room temperature. The mixture was refluxed for 6.5 h, ethanol was vacuum flashed, and the residue was dissolved in 150 mL of water. The water solution was extracted with ether (3×) and then acidified to pH 5, causing the product to precipitate. Ether extraction gave the crude product as a yellow glass after solvent evaporation. The product was crystallized by dissolving in ethyl acetate (70 mL) and adding hexane (50 mL), giving 5.3 g (24.0% yield) of crystals: mp 113–116 °C; after recrystallization from ethyl acetate, mp 112–114 °C; IR (KBr) 2300–2600 (H-bonded N or O), 1600 cm^{-1} (br); ^1H NMR (Me_2SO-d_6) δ 0.72 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.98, 2.68 (AB q, 2 H, J = 17 Hz, CH_2), 3.39 (s, 1 H, =CH), 5.34 (s, 1 H, OH), 7.10–8.63 (m, 4 H, aromatic H), 11.30 (br s, 1 H, OH---N). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.81; H, 6.96; N, 6.45. Found: C, 71.52; H, 6.84; N, 6.35.

ACKNOWLEDGMENT

We thank Harold A. Coleman for assistance in conducting the syntheses and Robert L. Selvey for performing the potentiometric titration studies. Helpful discussions with A. P. Kurtz are also gratefully acknowledged. We also thank a reviewer for suggesting the bisenol tautomer of compound **28**.

Registry No. 1, 111087-23-1; 2, 111087-24-2; 3, 111087-25-3; 4, 111087-26-4; 5, 111087-27-5; 6, 111087-28-6; 7, 111087-29-7; 8, 111087-30-0; 9, 111087-31-1; 10, 111087-32-2; 11, 111087-33-3; 12, 111087-34-4; 13, 111087-35-5; 14, 111087-36-6; 15, 111087-37-7; 16, 111087-38-8; 16-K, 111087-51-5; 17, 111087-39-9; 18, 111087-40-2; 19, 111087-41-3; 20, 111087-42-4; 21, 111087-43-5; 22, 111087-44-6; 23, 111087-45-7; 24, 111087-46-8; 25, 641-63-4; 26, 111087-47-9; 27, 111087-48-0; 28, 111087-49-1; 29, 30389-49-2; 30, 111087-53-7; $Me_2C(CH_2CO_2Et)_2$, 17804-59-0; ethyl 3,3-dimethyl-6-(4-methyl-2-pyridyl)-5-oxohexanoate, 111087-50-4; 2,4-lutidine, 108-47-4; ethyl 3,3-dimethyl-6-(2-methyl-4-pyridinyl)-5-oxohexanoate, 111087-52-6; ethyl 2-pyridinylacetate, 2739-98-2; mesityl oxide, 141-79-7.

LITERATURE CITED

Ames, D. E.; Dodds, W. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 705.

Arens, J. F.; van Dorp, D. A.; van Dijk, G. M. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 287.

Bohlmann, F.; English, A.; Politt, J.; Sander, H.; Weise, W. *Chem. Ber.* **1955**, *88*, 1831.

Douglass, J. E.; Fortner, H. D. *J. Heterocyl. Chem.* **1973**, *10*, 115.

Drake, N. L.; Allen, P., Jr. *Organic Syntheses*; Wiley: New York, 1951; Collect Vol. I; p 77.

Durden, J. A., Jr. *Medicinal Chemistry*, Proceedings of the International Symposium on Medicinal Chemistry, Main Lecture; Maas, J., Ed.; Elsevier: Amsterdam, 1974; p 143.

Edwards, W. M.; Teague, P. C. *J. Am. Chem. Soc.* **1949**, *71*, 3548.

Farmer, H. H.; Rabjohn, N. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 441.

Herz, W.; Tsai, L. *J. Am. Chem. Soc.* **1954**, *76*, 4184.

Iwataki, I.; Shibuya, M.; Ishikawa, H.; Kawana, T. (Nippon Soda Co., Ltd.) U.S. Patent 4 249 937, 1981.

Kaiser, E. M.; Bartling, G. J.; Thomas, W. R.; Nichols, S. B.; Nash, D. R. *J. Org. Chem.* **1973**, *38*, 71.

Kent, R. E.; McIlvain, S. M. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 591.

Lombardino, J. G. *J. Org. Chem.* **1967**, *32*, 1988.
Ploquin, J.; Sparfel, L.; Le Baut, G.; Floc'h, R.; Welin, L.; Petit, J. Y.; Henry, N. *Eur. J. Med. Chem.-Chim. Ther.* **1974**, *9*, 526.
Profft, E.; Krueger, W.; Kuhn, P.; Lietz, W. East German Patent 69 126, 1969; *Chem. Abstr.* **1970**, *72*, 90309w.
Shriner, R. L.; Todd, H. R. *Organic Syntheses*; Wiley: New York, 1950; Collect Vol. II, p 200.
Smith, W. T.; McLeod, G. L. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 345.
Wheeler, T. N. (Union Carbide Corp.) U.S. Patent 4 209 532, 1980; *Chem. Abstr.* **1979**, *91*, 39134a.
Wheeler, T. N. (Union Carbide Corp.) U.S. Patent 4 338 122, 1982; *Chem. Abstr.* **1982**, 96, 6260p.
Yousif, M. M.; Saeki, S.; Hamana, M. *Chem. Pharm. Bull.* **1982**, *30*, 2326.

Received for review December 12, 1986. Accepted August 7, 1987.

Perfluorinated Alkyl Carboxanilides: A New Class of Soil Insecticide

Robert P. Gajewski,* Gary D. Thompson, and Eddie H. Chio

EL-499, a mixture of 2′-bromo-4′-nitro-1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexanecarboxanilide and isomeric (trifluoromethyl)perfluorocyclopentanecarboxanilides, represents a new chemical class of soil insecticide derived from electrochemical fluorination technology. The general structural requirement for the surprising insecticidal activity of the series of carboxanilides is α branching in the perfluorinated alkyl moiety, which reduces hydrolytic lability relative to normal-chain acyclic derivatives.

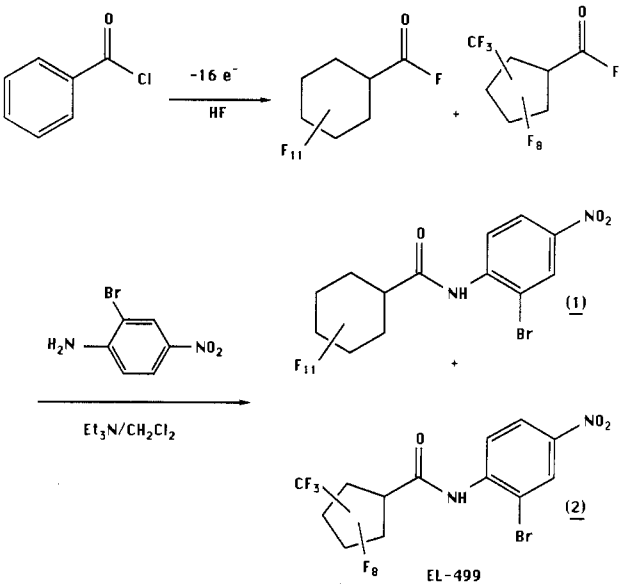
EL-499 (1, 2) is a novel soil insecticide candidate under investigation for the control of soil-borne insects including rootworm larvae in corn (Thompson et al., 1987). It is technically a mixture of isomeric six-carbon perfluorinated cycloalkyl carboxanilides prepared principally from perfluorocyclohexane carbonyl fluoride and 2-bromo-4-nitroaniline (Scheme I). Because of its excellent residual properties (Schultz et al., 1987) and low mammalian acute toxicity relative to many soil-applied phosphates and carbamates, EL-499, which is derived from electrochemical fluorination technology, represents an interesting new chemical class of insecticide. Indeed, these first-order derivatives of perfluorinated cycloalkyl carboxylic acids and acid halides, by virtue of their α branching, exhibit properties differing dramatically from those of similar derivatives of the commercially available normal-chain perfluorinated carboxylic acid halides and anhydrides.

EXPERIMENTAL SECTION

Insecticidal activity was determined by bioassays on southern corn rootworm (*Diabrotica undecimpunctata howardi*) larvae. The test compositions were solubilized in 50:50 acetone–ethanol and pipetted onto a dry, sandy loam soil on a w/w basis. Third instar larvae and corn seedlings were introduced after solvent evaporation with mortality readings taken 4 days post larval introduction.

Substituted anilines, benzoyl chlorides, and perfluorinated normal-chain carboxylic acid halides and anhydrides either were commercially available or were prepared by known methods. Carboxanilides were prepared from substituted anilines and acid halides in the presence of triethylamine and purified by either silica gel chromatography with toluene eluent or recrystallization from toluene or hexane to give satisfactory microanalyses (C, H, N) with yields, except as noted, of greater than 60%. All ^{19}F NMR data were obtained on an IBM NR-80 at 75.26 MHz and are reported (ppm) relative to $CFCl_3$ in chloroform solvent. Capillary GC/MS data were obtained on a Hewlett-Packard 5985B system with a 25-m SE-54 capillary column and temperature programming from 90 to 260 °C at 20 °C/min. Relative isomer peak areas are reported without correction for detector response. Melting points were determined on a Mel-Temp and are uncorrected.

Scheme I. Synthesis of EL-499



EL-499 (1, 2). The crude carboxanilide products derived from 3.2 kg (14.75 mol) of 2-bromo-4-nitroaniline, 8 kg (14.75 mol) of C_6F_{11} carbonyl fluoride mixture, and 2.1 kg (21 mol) of triethylamine in 20 L of ether were triturated with boiling hexane, leaving a sandy, insoluble residue. The hexane solution was evaporated to dryness and recrystallized from toluene to produce two crops: (5.5 kg (71%); combined mp 100–102 °C; capillary GC/MS relative peak area analysis, 90.4% cyclohexyl, 7.3% major (trifluoromethyl)cyclopentyl, 0.9% minor C_6F_{11}.

2′-Bromo-4′-nitro-1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexanecarboxanilide (98%) (1). Crude EL-499 (350 g) was recrystallized twice from 1.6 L of toluene and then once from 1.0 L of toluene. The resultant product (64 g) was chromatographed on 500 g of silica gel with toluene eluent. The product-containing fraction was

Lilly Research Laboratories, Eli Lilly and Company, Greenfield, Indiana 46140.

0021-8561/88/1436-0174$01.50/0