Registry No. *trans,trans*-1, 103836-71-1; *cis,trans*-1, 103836-73-3; *cis,cis*-1, 103836-74-4; 2, 455-24-3; 3, 2062-26-2; 4, 103836-72-2; AMDRO, 67485-29-4; H_2O, 7732-18-5.

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Bioactive Aziridine Derivatives of Chrysanthemate Insecticides

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(1*R*,*trans*)-Phenothrin (1) and (1*R*,*trans*,α*RS*)-cyphenothrin (1-CN) are converted to their aziridine derivatives (2, 2-CN) by oxidation of the 2-methyl-1-propenyl substituent to give a 1,2-diol, conversion to the unstable dimesylate, and reaction with aqueous ammonia. Lead tetraacetate catalyzed addition of *N*-aminophthalimide to the double bond of 1 and 1-CN gives the *N*-phthalimidoaziridines (4, 4-CN) which cleave with ethanolic hydrazine hydrate to generate the *N*-aminoaziridines (3, 3-CN). The potency of these pyrethroids to houseflies, cockroaches, and mosquito larvae, both alone and with piperonyl butoxide, is generally 1 > 2 ≥ 3 > 4 for the phenothrin series and 1-CN > 2-CN ~ 3-CN > 4-CN for the more toxic cyphenothrin series. Only 1-CN and 3-CN are toxic when administered intracerebrally to mice. In contrast, the potency in inducing repetitive discharges in the abdominal nerve cord of the American cockroach is 2 and 3-CN ≥ 3 > 1 ~ 4 > 2-CN ≥ 1-CN and 4-CN. The high neuroactivity of the aziridines makes them candidate derivatizing agents to probe the target site.

The 2-methyl-1-propenyl substituent of chrysanthemates is important to their insecticidal activity and their metabolic and photochemical lability (Elliott and Janes, 1978). Derivatization of chrysanthemates to the corresponding epoxides, episulfides, and cyclopropanes generally reduces their insecticidal activity (Ueda et al., 1974; Ruzo et al., 1984) but enhances their in situ potency on the cockroach cercal sensory nerve (Gammon et al., 1983; Ruzo et al., 1984). The corresponding aziridinochrysanthemates are not reported, even though the aziridine functionality confers unique biological properties in several types of compounds, e.g. juvenile hormone mimics (Riddiford et al., 1971; Siddall et al., 1971), inhibitors of sterol biosynthesis (Corey et al., 1967), and antineoplastic agents such as the mitomycins (Lown, 1983; Danishefsky et al., 1985) and tetramin (Oettel, 1959). The present report considers the aziridine, *N*-aminoaziridine, and *N*-phthalimidoaziridine derivatives of phenothrin and cyphenothrin relative to toxicity and neurophysiological activity.

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MATERIALS AND METHODS

Spectroscopy. Chemical ionization mass spectrometry (CI-MS) utilized a Hewlett-Packard 5985B system with methane (0.8 torr) and ionization at 230 eV. Masses are given for the quasi-molecular ions $(M + 1)^+$. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker WM-300 instrument operated at 300 MHz using deuteriochloroform as solvent. Chemical shifts (δ) are reported downfield from tetramethylsilane.

Chromatography. Column chromatography on Kieselgel 60 F_{254} and preparative TLC on silica gel F_{254} chromatoplates utilized hexane–ethyl acetate (1:1) or chloroform–methanol (99:1) with detection by both viewing under ultraviolet light (254 nm) and coloration induced by standing in an iodine atmosphere. Product recovery (preparative TLC) involved gel extraction with ethyl acetate and filtration through fine sintered glass.

Chemicals. Structures, designations, and syntheses for the compounds are given in Figure 1. The required diols (**A**) were prepared by reacting (1*R*,*trans*)-phenothrin and (1*R*,*trans*,α*RS*)-cyphenothrin with a catalytic quantity of osmium tetroxide (5 mol %) with *N*-methylmorpholine

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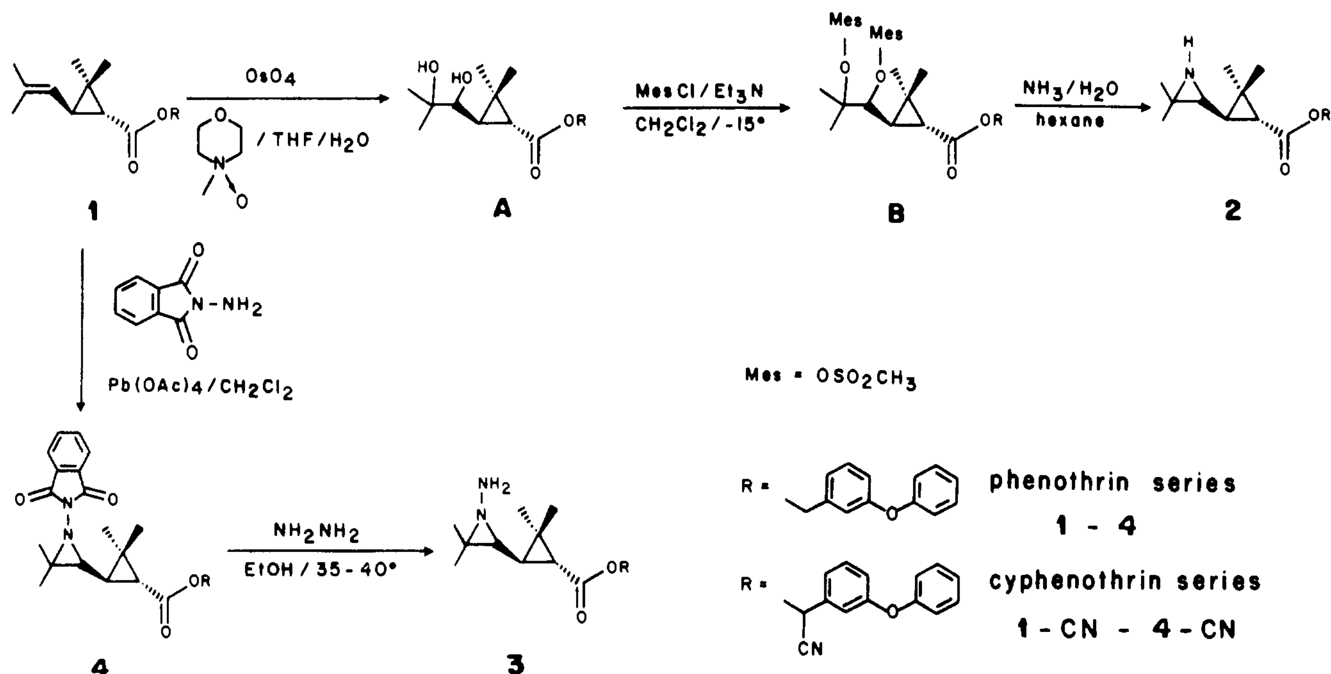

Figure 1. Synthesis of the aziridine (**2**, **2**-CN), *N*-aminoaziridine (**3**, **3**-CN), and *N*-phthalimidoaziridine (**4**, **4**-CN) derivatives of phenothrin (**1**) and cyphenothrin (**1**-CN) including structures and designations for the compounds.

N-oxide (1.1 equiv) as co-oxidant in tetrahydrofuran–water (3:1) as solvent (VanRheenen et al., 1976). After stirring for ~40 h, the black solution was treated with acidic sodium metabisulfite solution and extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to leave, in both cases, viscous yellow oils. Column chromatography (chloroform–methanol, 99:1) gave both diols as colorless oils in yields of 68–71%. Phenothrin diol: $[(M + 1) - H_2O]^+$ *m/e* 367; ^{1}H NMR δ 6.88–7.45 (9 H, m), 5.08 (2 H, s), 3.06 (1 H, m), 2.61–2.98 (2 H, br), 1.71 (1 H, d), 1.49 (1 H, m), 1.07–1.38 (12 H, m). Cyphenothrin diol: $[(M + 1) - H_2O]^+$ *m/e* 392; δ 6.85–7.49 (9 H, m), 6.41 (1 H, s), 3.04 (1 H, m), 2.47–2.77 (2 H, br), 1.74 (1 H, d), 1.51 (1 H, m), 1.05–1.39 (12 H, m). Resonances at δ 2.61–2.98 (phenothrin diol) and 2.47–2.77 (cyphenothrin diol) disappeared on shaking with deuterium oxide.

The unstable dimesylates (**B**) were prepared by reacting the diols with methanesulfonyl chloride in the presence of triethylamine (Crossland and Servis, 1970). Thus, the diols were stirred at −15 °C in dry dichloromethane (N_2 atmosphere) containing triethylamine (1 equiv), and methanesulfonyl chloride (1.5 equiv, freshly distilled) was added dropwise. After 30 min at −15 °C the reaction mixture was poured onto ice–water and extracted with dichloromethane. The combined organic extracts were washed with cold dilute HCl, dried ($MgSO_4$), and evaporated to leave the crude dimesylates as slightly yellow pungent oils that were used immediately for the next reaction without purification. In both cases NMR revealed the disappearance of resonances due to OH protons and new resonances due to OSO_2CH_3 at δ 3.04–3.14. Mass spectroscopy (direct probe) gave ions due to $[M - OSO_2CH_3]^+$ (no $[M + 1]^+$).

The aziridines (**2**, **2**-CN) were obtained by rapidly stirring the dimesylates with excess aqueous ammonia as an emulsion in hexane at room temperature overnight (Felix et al., 1972). The hexane layer was separated, washed with water, dried ($MgSO_4$), and evaporated to leave a yellow oil in each case. The pure aziridines were isolated by preparative TLC (ethyl acetate–hexane, 1:1) as colorless oils typically in 28–32% yield. **2**: R_f 0.32; $[M + 1]^+$ *m/e* 366, $[(M + 1) - NH]^+$ 351, $[(M + 1 - NH_3]^+$ 349; ^{1}H NMR δ 6.89–7.43 (9 H, m), 5.32–5.48 (1 H, br), 5.08 (2 H, s) 2.49 (1 H, dd), 1.74 (1 H, m), 1.44 (1 H, m), 1.02–1.42 (12 H, m). **2**-CN: R_f 0.30; $[M + 1]^+$ *m/e* 391, $[(M + 1) - NH]$ 376, $[(M + 1) - NH_3]^+$ 374; ^{1}H NMR δ 6.90–7.45 (9 H, m), 6.36 (1 H, s), 5.14–5.31 (1 H, br), 2.51 (1 H, dd), 1.74 (1 H, m), 1.46 (1 H, m), 1.02–1.44 (12 H, m).

Preparation of the *N*-phthalimidoaziridines (**4**, **4**-CN) involved slow addition of lead tetraacetate (2 equiv) to a stirred solution of **1** or **1**-CN (1 equiv) and *N*-aminophthalimide (2 equiv) in dry dichloromethane under N_2 (Felix et al., 1972). After stirring at room temperature overnight, the solution was filtered through sintered glass to remove the majority of the lead salts. Column chromatography followed by preparative TLC in each case with ethyl acetate–hexane (1:1) gave slightly yellow semisolids in 48–51% yields. **4**: R_f 0.16; $[M + 1]^+$ *m/e* 511; ^{1}H NMR δ 6.88–7.92 (13 H, m), 5.07 (1 H, s), 2.66 (1 H, dd), 1.73 (1 H, m), 1.48 (1 H, m), 1.04–1.46 (12 H, m). **4**-CN: R_f 0.12; $[M + 1]^+$ *m/e* 536; δ 6.91–7.94 (13 H, m), 6.37 (1 H, s), 2.67 (1 H, dd), 1.74 (1 H, m), 1.50 (1 H, m), 1.07–1.44 (12 H, m).

The *N*-aminoaziridines (**3**, **3**-CN) were obtained by dissolving **4** or **4**-CN in absolute ethanol, addition of an excess of hydrazine hydrate, and heating the contents of the flask at 35–40 °C for 30 min (Felix et al., 1972). Ice was added to the solution and the whole mixture extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated to leave colorless oils. Preparative TLC (ethyl acetate–hexane, 1:1) gave **3** and **3**-CN typically in yields of 54–59% as colorless oils. **3**: R_f 0.24; ^{1}H NMR δ 6.91–7.43 (9 H, m), 5.16–5.39 (2 H, br), 5.07 (2 H, s), 2.42 (1 H, dd), 1.76 (1 H, m), 1.49 (1 H, m), 1.06–1.46 (12 H, m). **3**-CN: R_f 0.23; ^{1}H NMR δ 6.89–7.46 (9 H, m), 6.37 (1 H, s), 4.97–5.28 (2 H, br), 2.43 (1 H, dd), 1.78 (1 H, m), 1.48 (1 H, m), 1.07–1.45 (12 H, m).

Prior to bioassay, compounds **2**, **2**-CN, **3**, and **3**-CN were held up to 3 days at 0 °C in the dark, without any evidence (NMR) of decomposition.

Toxicity. Houseflies (*Musca domestica* L., SCR strain, adult females, 3–5 days after emergence, ~20 mg each) were treated with the test compound in tetrahydrofuran

(0.5 μL) by topical application to the ventrum of the abdomen. American cockroaches (*Periplaneta americana* L., adult males, ~1 g each) were administered the pyrethroid in methoxytriglycol (1 μL) by injection into the abdomen. With both species the synergist piperonyl butoxide (PB) was applied topically at 250 μg/g, with acetone (0.5 μL) as the carrier vehicle, 1 h prior to administration of the pesticide. Mosquitoes (*Culex pipiens* L.) were tested by placing 20 early- to mid-fourth instar larvae in 100 mL of water and adding the test compounds as ethanol solutions. PB was added (2 mg/L) in the same manner, and at the same time as the test compound. In all cases the final concentration of ethanol did not exceed 0.6%. Intracerebral treatments of male albino mice (17–21 g, Simonsen Laboratories, Gilroy, CA) were performed by injection of the pyrethroid in 1 μL of methoxytriglycol (Lawrence and Casida, 1982) with a 10-μL syringe. Toxicity was evaluated after 24 h at 24 °C and analyzed by a computer Probit analysis program based on that of Finney (1952) to give LD_{50} and 95% confidence interval (CI) values. Three or more doses giving >0% and <100% mortality were involved in each determination. At least 50 houseflies and mosquito larvae and 6 cockroaches or mice were used at each dose.

Neurophysiological Activity. Studies were conducted on the intact abdominal nerve cord of male American cockroaches, exposed by opening the dorsal side and removing the digestive tract, fat bodies, tracheae, and sex organs. Dissections and recordings were made in dishes containing Sylgard 184 resin. These dishes were washed with acetone and water between experiments, and separate dishes were used for each compound. The spontaneous activity was monitored with a suction electrode placed between the fifth and sixth abdominal ganglia. The saline contained 210 mM NaCl, 3.1 mM KCl, 1.8 mM Na_2HPO_4, 1.8 mM $CaCl_2$, and 0.2 mM NaH_2PO_4 with a final pH of 7.4 (Yamasaki and Narahashi, 1959). Pyrethroids were dissolved in ethanol and added to the saline (<0.1% ethanol). Saline was profused over the preparation at a rate of 1 mL/min. All nerve cords were examined for 15 min in saline before pesticides were added. Cockroaches were profused with a given dose for 10 min, and if no effects were observed, the next highest concentration was used. Thresholds were measured as the concentration to cause repetitive discharges as defined previously (Scott and Matsumura, 1981).

RESULTS

Insecticidal Activity (Table I). Phenothrin is 10–12-fold more toxic than 2 and 3 and 25-fold more toxic than 4 on topical application to houseflies. In the cyphenothrin series, 1-CN is 2–3-fold more toxic than 3-CN and 20–40-fold more toxic than 2-CN and 4-CN to houseflies. The cyano compounds are 2–10-fold more toxic than the noncyano compounds. All pyrethroids are highly synergized by PB with factors of 18–54-fold.

The structure–activity patterns observed with cockroaches are similar to those with houseflies, i.e. 1 > 2 > 3 > 4 and 1-CN > 2-CN ~ 3-CN > 4-CN, with the latter series being 8–30-fold more toxic than their noncyano counterparts. The synergistic ratios do not significantly vary from one compound to another; however, they are significantly lower than the values obtained with houseflies or mosquitoes.

Mosquitoes give a similar relationship of structure to activity with a potency order of 1 > 2 > 3 > 4, paralleled by the cyano compounds, which are equivalent to 9-fold more toxic. With PB synergism, 2 is slightly more toxic than 1, and 3-CN is only 3-fold less toxic than 1-CN.

Table I. Insecticidal Activity of Phenothrin (1), Cyphenothrin (1-CN), and Their Aziridine (2, 2-CN), *N*-Aminoaziridine (3, 3-CN), and *N*-Phthalimidoaziridine (4, 4-CN) Derivatives

compd	LD_{50} or LC_{50} (95% CI) alone	piperonyl butoxide	synerg ratio[a]
	M. domestica L. Adults (μg/g), Topical Application		
1	0.36 (0.31–0.42)	0.015 (0.014–0.017)	24
2	3.7 (2.9–4.5)	0.16 (0.13–0.20)	23
3	4.0 (3.3–4.9)	0.22 (0.18–0.26)	18
4	11 (9–13)	0.40 (0.32–0.49)	28
1-CN	0.12 (0.10–0.14)	0.006 (0.004–0.007)	20
2-CN	3.6 (3.2–4.3)	0.066 (0.033–0.097)	54
3-CN	~0.3[b]	~0.01[b]	~30[b]
4-CN	5.5 (4.6–6.5)	0.14 (0.12–0.16)	39
	P. americana L. Adults (μg/g), Injection		
1	0.33 (0.22–0.59)	0.15 (0.10–0.23)	2.2
2	0.50 (0.31–0.86)	0.27 (0.09–0.50)	1.9
3	1.1 (0.70–1.8)	0.43 (0.16–0.92)	2.6
4	>10 (33)[c]	1.6 (0.2–5.0)	>6
1-CN	0.024 (0.014–0.087)	0.004 (0.001–0.007)	6.0
2-CN	0.17 (0.08–0.25)	0.032 (0.016–0.071)	5.3
3-CN	0.17 (0.02–0.40)	0.059 (0.028–0.092)	2.9
4-CN	0.88 (0.60–1.30)	0.19 (0.12–0.33)	4.6
	C. pipiens L. Larvae (μg/L), Treatment of Aqueous Media		
1	35 (31–40)	2.0 (1.8–2.3)	17
2	71 (63–78)	1.5 (1.3–1.7)	47
3	830 (660–1000)	29 (23–35)	29
4	1400 (700–2300)	45 (39–50)	31
1-CN	7.5 (6.5–8.8)	0.22 (0.19–0.26)	34
2-CN	17 (15–19)	1.5 (1.4–1.7)	11
3-CN	30 (26–36)	0.58 (0.37–0.79)	52
4-CN	710 (600–850)	14 (12–16)	51

[a] LD_{50} alone/(LD_{50} + PB). [b] Approximation from single experiment. [c] Percentage mortality at 10 μg/G.

Table II. Neuroactivity in the Cockroach Abdominal Nerve Cord of Phenothrin (1), Cyphenothrin (1-CN), and Their Aziridine (2, 2-CN), *N*-Aminoaziridine (3, 3-CN), and *N*-Phthalimidoaziridine (4, 4-CN) Derivatives

compd	threshold concn,[a] nM
1	300, 100, 300, 300
2	100, 30, 100, 30
3	300, 100, 30, 100
4	100, 300, 300
1-CN	>1000 (n = 4)
2-CN	>1000, >1000, 100, >1000
3-CN	30, 100, 30
4-CN	>1000 (n = 3)

[a] Each preparation was exposed to the test compound sequentially for 10 min at 3, 10, 30, 100, 300, and 100 nM to determine the lowest concentration eliciting repetitive discharges.

Neuroactivity in the Cockroach Abdominal Nerve Cord (Table II). Potency in causing repetitive discharges in the cockroach abdominal nerve cord is in the order 2 and 3-CN > 3 > 1 ~ 4 > 2-CN > 1-CN and 4-CN. The high potency of 3-CN is of particular interest, both as the only highly active cyano derivative and because it produces repetitive discharges that are notably longer than those caused by any other compound tested, with several bursts lasting >10 s. The potency of the aziridine derivatives of phenothrin (2–4) on the abdominal nerve cord generally parallels their toxicity to cockroaches, but overall the potency in causing repetitive discharges is not correlated with the toxicity results.

Intracerebral Toxicity to Mice. Only 1-CN and 3-CN are toxic by intracerebral injection to mice, with 1-CN being 16-fold more toxic than 3-CN, i.e. LD_{50} (μg/g brain weight) and 95% CI values of 3.0 (2.3–3.9) and 47 (27–84), respectively. Mortality occurs at 0.5–5 h posttreatment.

The cyphenothrin LD_{50} reported here is not significantly different from that reported previously (Lawrence and Casida, 1982). The other compounds show no toxicity at 500 (**2**) and 1000 μg/g brain weight (**1**, **3**, **4**, **2**-CN, **4**-CN).

DISCUSSION

Conversion of **1** and **1**-CN to their aziridine derivatives (**2**, **2**-CN) is readily achieved by the Eschenmosher procedure (Felix et al., 1972) from available starting materials, although in only moderate yields. Alternative methods involving ring opening of epoxides with various nucleophiles proved to be less satisfactory. Ring opening with lithium azide and reduction of the resulting β-hydroxy azides with Raney nickel and other reagents is used to form β-hydroxy amines that undergo ring closure with base (Riddiford et al., 1971; Anderson et al., 1972). However, in the present series only poor yields of azido alcohols were obtained even with the use of hexamethylphosphoramide as solvent, and reduction with Raney nickel did not proceed cleanly. Ring opening of epoxides with ammonia (McManus et al., 1973) gave very little of the intermediate β-hydroxy amines useful for aziridine synthesis. Prolonged heating of the epoxide in aqueous ammonia gave no isolable products, and pressure reaction with liquid ammonia at 100 °C gave only small amounts of required intermediates. Addition of iodine isocyanate to olefins is a general method for introducing the β-iodo isocyanate functionality into the parent pyrethroids (Hassner et al., 1967), and conversion to aziridines is reported to be mild and high yielding. Unfortunately, the starting iodo isocyanate was never obtained in reasonable yield even when the reagent was generated from freshly prepared silver cyanate.

Aziridines are far more reactive than ordinary amines, because of the favorable release of ring strain energy associated with ring opening. It is to be expected that aziridines undergo extensive ring opening in both a nucleophilic and electrophilic sense. Protonated aziridines are exceptionally reactive toward nucleophiles, and attempts to prepare them generally result in ring cleavage (Paquette, 1968). In the present study, the aziridine derivatives were quickly isolated, chromatographed, and bioassayed to prevent decomposition on exposure to light and air.

Addition of *N*-H, *N*-amino, or *N*-phthalimido to the chrysanthemate 2-methyl-1-propenyl double bond generally reduces insecticidal activity, while increasing in situ potency in causing repetitive discharges in the cockroach ventral nerve cord, in agreement with earlier results on the cyclopropyl, episulfide, and epoxide analogues (Ruzo et al., 1984). The aziridine compounds, more than the other analogues, are candidate derivatizing agents to probe the target site. The synergistic ratios are lower in cockroaches than in houseflies or mosquitoes, suggesting that the cockroaches less readily detoxify the pyrethroids by cytochrome P_{450} mediated oxidation. The PB effect indicates that all of the compounds examined undergo substantial oxidative detoxification in each insect species.

There are two unusual findings on the biological activity of the aziridine derivatives. First, as α-cyano compounds generally do not cause repetitive discharges in cockroach nerve preparations (Gammon et al., 1981; Scott and Matsumura, 1983; Ruzo et al., 1984), it is surprising to find the high potency of **3**-CN and the possible activity of **2**-CN. Second, **2**-CN and **4**-CN are not toxic intracerebrally in mice in contrast to previously reported insecticidal α-cyano pyrethroids (Lawrence and Casida, 1982). Pyrethroids administered in this way probably act locally in the brain and before significant detoxification (Lawrence and Casida, 1982). These findings, and preliminary but unsuccessful attempts to synergize **2**-CN with PB, suggest that the receptor responsible for toxicity in mouse brain interacts with **1**-CN and **3**-CN but not with **2**-CN, **4**-CN, or the noncyano compounds.

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Registry No. 1, 26046-85-5; α*R*-1-CN, 64312-68-1; α*S*-1-CN, 64312-65-8; **2**, 104576-63-8; α*R*-**2**-CN, 104576-64-9; α*S*-**2**-CN, 104640-87-1; **3**, 104598-40-5; α*R*-**3**-CN, 104576-65-0; α*S*-**3**-CN, 104640-88-2; 4, 104576-66-1; α*R*-**4**-CN, 104598-41-6; α*S*-4-CN, 104641-35-2; *N*-aminophthalimide, 1875-48-5; piperonyl butoxide, 51-03-6.

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