Synthesis and Biological Activity of Optically Active Heptachlor, 2-Chloroheptachlor, and 3-Chloroheptachlor

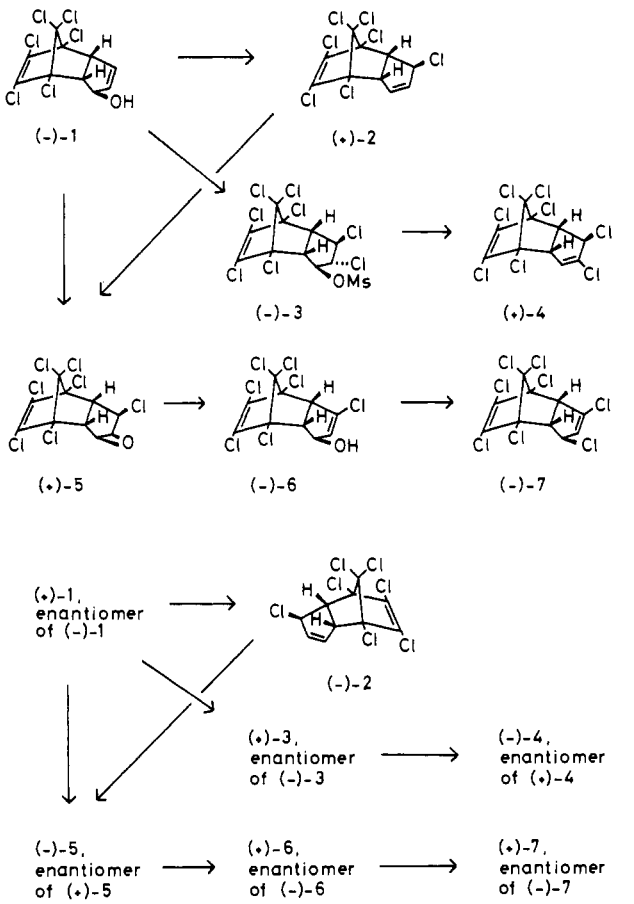
Both enantiomers, optically pure, of heptachlor (2), 2-chloroheptachlor (4) and 3-chloroheptachlor (7) with the known absolute stereochemistry were synthesized starting from optically pure 1-hydroxychlordene (1). The insecticidal activity of these chiral cyclodienes was measured on male adults of German cockroaches, revealing that the racemic form of 2 exhibited a stronger activity than either of its enantiomers, while the (+) enantiomer of 4 was more insecticidal than its (−) antipode as well as the racemate; however, neither optically active nor racemic 7 showed the activity.

We have recently reported (Miyazaki et al., 1978) that a considerable difference of insecticidal activity was found between the enantiomers of some cyclodiene insecticides. The (+) enantiomer of chlordene and the (−) one of chlordene epoxide, whose absolute stereochemistries were the same, exhibited the insecticidal activity, whereas their optical antipodes did not show appreciable toxicity. The (+) enantiomer of heptachlor epoxide, whose absolute stereochemistry was the same as those of the toxic enantiomers of the above two chemicals, similarly showed a stronger activity than the corresponding optical antipode; however, the difference of toxicity between the enantiomers was small (ca. 2.3 times). We have subsequently shown by comparative metabolic studies (Miyazaki et al., 1979) that only the (−) enantiomer of chlordene epoxide was insecticidal without any bioactivation, whereas the (+) enantiomer of chlordene became toxic as a result of biochemical transformation into the corresponding (−)-chlordene epoxide. Since a specific absolute stereochemistry was required for production of toxicity, the optical antipodes such as (+)-chlordene epoxide and (−)-chlordene did not show the activity. In the present communication we synthesized further three kinds of optically active cyclodiene insecticides, i.e., heptachlor (2), 2-chloroheptachlor (4), and 3-chloroheptachlor (7), and their insecticidal activity was measured. We found that the racemic form of heptachlor exhibited a stronger activity than either of its enantiomers, suggesting that a synergistic action must be operating between the enantiomers in the toxicity-inducing processes.

EXPERIMENTAL SECTION

Both enantiomers of heptachlor and those of 2- and 3-chloroheptachlor were prepared by starting from optically pure 1-hydroxychlordene as follows. (−)-1-Hydroxychlordene [(−)-1] (Miyazaki et al., 1978) afforded upon chlorination ($SOCl_2$–pyridine) (+)-heptachlor [(+)-2] (quantitative): mp 96 °C; $[\alpha]_D$ + 214° (*c* 0.52, $CHCl_3$). (+)-1 was similarly converted to (−)-2 (quantitative): mp 96 °C; $[\alpha]_D$ −217° (*c* 0.52, $CHCl_3$). (−)-1 was chlorinated (Cl_2 in $CHCl_3$–CCl_4) and then mesylated (MsCl in pyridine) to produce the (−)-dichloromesyl derivative [(−)-3]: mp 160 °C; MS *m/e* 500 (M^+); $[\alpha]_D$ −2.1° (*c* 0.33, $CHCl_3$). On treatment with base (*t*-BuOK in diethyl ether), (−)-3 gave (+)-2-chloroheptachlor [(+)-4] [42% from (−)-1]: mp 89 °C; $[\alpha]_D$ +75.1° (*c* 0.35, $CHCl_3$). (+)-1 was similarly converted via (+)-3 [$[\alpha]_D$ +1.5° (*c* 0.37, $CHCl_3$)] into (−)-4 [46% from (+)-1]: mp 89 °C; $[\alpha]_D$ −74.4° (*c* 0.41, $CHCl_3$). Both enantiomers of heptachlor epoxide [(+)-5 and (−)-5], previously prepared from (−)-1 and (+)-1, respectively (Miyazaki et al., 1978), were treated with methanolic NaOMe (Cochrane and Chau, 1968) to give allyl alcohols (−)-6 [55%; mp 163 °C; $[\alpha]_D$ −15.1° (*c* 0.66, $CHCl_3$)] and (+)-6 [52%; mp 163 °C; $[\alpha]_D$ +15.2° (*c* 0.63, $CHCl_3$)], respectively. Chlorination ($SOCl_2$ in diethyl ether) of (−)-6 and (+)-6 produced (−)-3-chloroheptachlor [(−)-7] [68%; mp 96 °C; $[\alpha]_D$ −109° (*c* 0.70, $CHCl_3$)] and (+)-7 [48%; mp 96 °C; $[\alpha]_D$ +107° (*c* 0.69, $CHCl_3$)], respectively.

Scheme I



The bioassay methods are described in the footnotes of Table I.

RESULTS AND DISCUSSION

The absolute stereochemistry of synthetic chiral heptachlor was determined by converting (+)- and (−)-heptachlor (2) upon oxidation with CrO_3 (Singh, 1969) into the corresponding epoxy compounds (+)-5 [$[\alpha]_D$ +95.9 ± 0.7° (*c* 0.38, $CHCl_3$)] and (−)-5 [$[\alpha]_D$ −96.4 ± 0.6° (*c* 0.48, $CHCl_3$)], respectively. The optical rotations of these oxidation products were compatible with those of chiral heptachlor epoxide [(+)-5, $[\alpha]_D$ +92.8 ± 1.4°; (−)-5, $[\alpha]_D$ −94.1 ± 1.4°], whose absolute stereochemistry and optical purity were previously established (Miyazaki et al., 1978). The data show that the chlorination reaction with $SOCl_2$–pyridine proceeds stereospecifically with a double-bond migration from the 2,3 to the 1,2 position, thus inverting the absolute stereochemistry of the chlorination

0021-8561/80/1428-1310$01.00/0 © 1980 American Chemical Society

Table I. Insecticidal Activity of the Enantiomers of Heptachlor and 2-Chloroheptachlor[a]

	dose, μg/g						
	18.0	10.8	6.48	3.88	2.32	1.39	LD_{50}, μg/g
(+)-heptachlor, (+)-**2**	93.3	66.7	43.3	0	0	0	3.38[b]
racemic heptachlor, (±)-**2**	86.7	93.3	60.0	25.0	0	0	2.64
(−)-heptachlor, (−)-**2**	90.0	46.7	36.7	0	0	0	5.32
	dose, μg/g						
	200	100	50	25	12.5		LD_{50}, μg/g
(+)-2-chloroheptachlor, (+)-**4**	100	100	100	60	40		20[c]
racemic 2-chloroheptachlor, (±)-**4**	100	80	50	10	10		50
(−)-2-chloroheptachlor, (−)-**4**	40	40	0	0	0		100

[a] A sample dissolved in 0.52 μL of acetone was applied topically to 10–30 insects per dose. The toxicity was expressed as percentage mortality at 24 h after application of the sample, and the control insects treated with acetone only showed 0% mortality under these experimental conditions. The bioassay was carried out once, and these results were confirmed by repeated experiments. [b] LD_{50} was determined by probit analysis of percentage mortality at 48 h after application of chemicals and is significantly different at the 5% level. [c] LD_{50} was calculated from percentage mortality at 24 h after application of chemicals.

products, as shown in Scheme I. The absolute stereochemistry of 2- and 3-chloroheptachlor was reasonably concluded to be the same as that of 1-hydroxychlordene, judging from the chemical reactions employed for these transformations. The synthetic chemicals should be optically pure, because the optically pure 1-hydroxychlordene was used as a starting material and no racemization could occur during chemical derivation except an enantiomeric inversion of 1-hydroxychlordene with the chlorination reaction ($SOCl_2$–pyridine).

The insecticidal activity of chiral cyclodiene insecticides thus synthesized was measured on male adults of German cockroaches. The results are shown in Table I. The (+) enantiomer of heptachlor was more insecticidal than the (−) antipode, just as in the case of heptachlor epoxide (Miyazaki et al., 1978). The weaker activity of (+), (−), and racemic heptachlors, compared with that of heptachlor epoxide, may support the hypothesis (Perry, 1960) that heptachlor becomes insecticidal as a result of bioactivation to heptachlor epoxide. Quite interestingly, racemic heptachlor was more insecticidal than either of its enantiomers. Although the difference of toxicity between the racemate and the enantiomers was small, a statistical evaluation concluded it to be significant. These data were rather unexpected, differing entirely from those of other cyclodiene insecticides so far examined, such as heptachlor epoxide, chlordene, chlordene epoxide, and *cis*- and *trans*-chlordanes. In all of these cases, the toxicity of racemates was intermediate between the enantiomers. In heptachlor, a synergistic action must be operating between the enantiomers in the toxicity-inducing processes, either by promoting a metabolic activation or by suppressing a detoxification reaction. The relationship between biological activity and stereochemistry has been extensively investigated in insect pheromone chemistry, and there have been many examples reported to show an enantiomeric interaction of chiral pheromone molecules. Among them, a synergistic action of both enantiomers was found in female sex pheromone mimics of redbanded leaf rollers (Chapman et al., 1978). Our present findings on the synergistic action between the heptachlor enantiomers are the first example to be found in synthetic insecticide chemicals.

In 2-chloroheptachlor, the (+) enantiomer with the same absolute stereochemistry as the more toxic (+)-heptachlor exhibited a stronger activity than the (−) antipode and that of the racemate was intermediate between them. On the other hand, neither optically active nor racemic 3-chloroheptachlor showed the activity at a 200 μg/g dose. The absence of toxicity in **7** was curious from its close structural similarity to 2-chloroheptachlor. The reason may be ascribed to the different susceptibility of **7** for an in vivo epoxidation which should be essential for becoming insecticidal. Tashiro and Matsumura (1977) found the production of 2-chloroheptachlor in a metabolism of *cis*- and *trans*-chlordanes by rats, suggesting the product to be still an intermediate finally transformed to more toxic 2-chloro-2,3-epoxyheptachlor (oxychlordane), whose toxicity was shown by a mosquito larva bioassay. Our present studies with optically active 2-chloroheptachlor revealed that the (+) enantiomer afforded upon epoxidation (CrO_3 in H_2O–AcOH) (+)-oxychlordane, $[\alpha]_D$ +23 ± 4°.

Comparative metabolic studies on the (+), (−), and racemic heptachlors, which are now under way, are particularly necessary for investigating the synergistic interaction of toxicity between the enantiomers of heptachlor.

LITERATURE CITED

Chapman, O. L., Mattes, K. C., Sheridan, R. S., Klun, J. A., *J. Am. Chem. Soc.* **100**, 4878 (1978).
Cochrane, W. P., Chau, A. S., *Chem. Ind. (London)*, 1696 (1968).
Miyazaki, A., Hotta, T., Marumo, S., Sakai, M., *J. Agric. Food Chem.* **26**, 975 (1978).
Miyazaki, A., Sakai, M., Marumo, S., *J. Agric. Food Chem.* **27**, 1403 (1979).
Perry, A. S., *J. Agric. Food Chem.* **8**, 266 (1960).
Singh, J., *Bull. Environ. Contam. Toxicol.* **4**, 77 (1969).
Tashiro, S., Matsumura, F., *J. Agric. Food Chem.* **25**, 872 (1977).

Akio Miyazaki*[1]
Michihiko Sakai[2]
Shingo Marumo[3]

[1]Osaka Agricultural Research Center
Shakudo, Habikino-shi
Osaka 583, Japan
[2]Agricultural Chemicals Division
Takeda Chemical Industries, Ltd.
Kyoto 606, Japan
[3]Department of Agricultural Chemistry
Nagoya University
Nagoya 464, Japan

Received for review March 7, 1980. Accepted June 3, 1980.