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Insecticides. Part 10. Crystal Structures of Homoendrin, Homoisodrin, and Homoisodrin Acetate

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The crystal structures of three "cyclodiene" analogues, homoendrin (1), homoisodrin (2), and homoisodrin acetate (3), have been determined by X-ray diffraction. The structures found for 1 and 2 confirm those previously proposed but homoisodrin acetate (3) is different with respect to the point of attachment of the acetate group. Comparative structural features are also presented for the cyclodiene series.

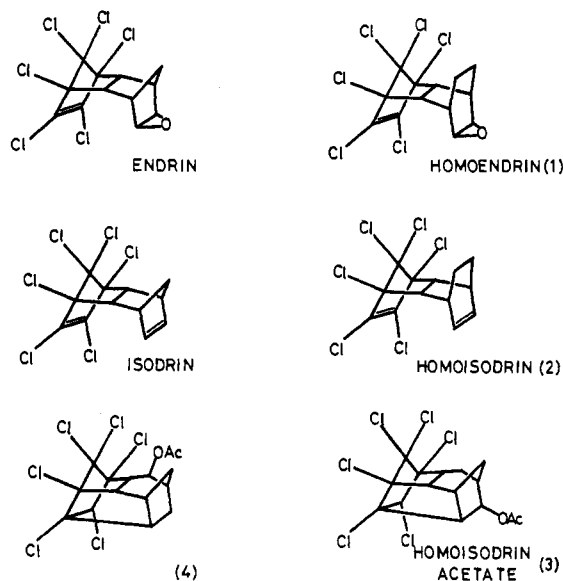
The structural aspects of "cyclodiene" insecticides have been reviewed by Riemschneider (1963), Soloway (1965), Brooks (1966), and Matsumura (1975). So far, a number of crystal structures of compounds containing the hexachloronorbornene nucleus have been determined. They are endrin, aldrin (DeLacy and Kennard, 1972), dieldrin

oxide (Hovmöller et al., 1978), 1-hydroxychlorodene (Kennard et al., 1978), Alodan (Kennard et al., 1981), two different forms of β -endosulfan (Smith et al., 1977; Byrn and Siew, 1977), isobenzan [Telodrin (Smith and Kennard, 1977)], and α - and β -chlordane (Knox et al., 1979). A number of structures of the photodecomposition products of the cyclodienes are also known. In these, the double bond of the cyclopentadiene group is often lost along with bridge bond formation. Examples are α - and β -photochlordane (Knox et al., 1979), photoaldrin (Khan et al., 1972), and dihydrophotoaldrin acetate (Kennard et al., 1983). The structures reported here are homoendrin (1) [5,6,7,8,9-hexachloro-2,3-epoxy-1,2,3,4,4a,5,8,8a-octahydro-*endo*-5,8-*endo*-1,4-ethano-5,8-methanonaphthalene (IUPAC name), homoisodrin (2) [5,6,7,8,9-hexachloro-1,4,4a,5,8,8a-hexahydro-*endo*-5,8-*exo*-1,4-ethano-5,8-methanonaphthalene (IUPAC name), and homoisodrin acetate (3).

1 and 2 are related to endrin and isodrin via an expansion of the ring system attached to the hexachloronorbornene nucleus by a methylene group. These compounds are less toxic to *Musca domestica* than the parent compounds endrin and isodrin (Brooks and Harrison, 1964). Homoisodrin acetate (3) is one of the products formed by treating homoisodrin with sulfuric acid in boiling acetic acid. The structure 4 was assigned by Bird and Yeung (1981) on the basis of ^1H NMR spectroscopy.

EXPERIMENTAL SECTION

Crystals of 1 (mp 201–203 °C), 2 (mp 171–172 °C), and 3 were kindly supplied by Dr C. W. Bird, Queen Elizabeth College, London. Unit cell dimensions and intensity data were obtained on an Enraf-Nonius CAD-4 Kappa diffractometer at Rothamsted Experimental Station. Trial structures were obtained by using the EEES centrosymmetric direct methods of SHELX-76 (Sheldrick, 1976) and refined on the PRIME 550 computer at Rothamsted. In



(Gress and Jacobson, 1973), isodrin (Kennard et al., 1979), heptachlor (Shields and Kennard, 1973), heptachlor ep-

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Table I. Crystal Data

	homoendrin (1)	homoisodrin (2)	homoisodrin acetate (3)
formula	C ₁₃ H ₁₀ Cl ₆ O	C ₁₃ H ₁₀ Cl ₆	C ₁₆ H ₁₄ Cl ₆ O ₂
M _r	394.9	378.9	438.8
crystal class	monoclinic	orthorhombic	monoclinic
space group	P2 ₁ /n	Pbca	P2 ₁ /n
a, Å	11.541 (1)	14.988 (2)	12.235 (3)
b, Å	14.584 (3)	13.277 (1)	11.538 (6)
c, Å	8.888 (1)	14.999 (2)	12.232 (2)
β, deg	92.88 (1)		101.60 (2)
V, Å ³	1494.1	2984.7	1691.5
Z	4	8	4
D _{calcd} , g cm ⁻³	1.76	1.69	1.72
F(000)	792	1520	888
μ(Mo Kα), cm ⁻¹	11.32	11.24	10.15
recrystallized from	isopropyl alcohol-water	toluene-hexane	isopropyl alcohol-water
size of crystal, mm	0.24 × 0.23 × 0.11	0.40 × 0.25 × 0.08	0.38 × 0.25 × 0.12
standards used during collection	200, 111, 002	0.20, 104, 104	200, 002, 020
total no. of reflections	1985	2625	2090
no. observed	1309	1127	1980
I > nσ(I) where n =	2.5	2.5	2.5
reflections suffering from extinction		200, 040, 021	
2θ _{max} , deg	50	50	50

ENRAF-NONIUS CAD-4 Diffractometer, Graphite Crystal Monochromatized Mo Kα Radiation [λ_{Kα1} = 0.70926 Å], No Corrections for Absorption, No Significant Changes in Intensities of Standards

structure solution	direct methods	direct methods	direct methods
R [=Σ F _o - F _c /Σ F _o]	0.035	0.033	0.037
R _w [=((wΣ F _o - F _c) ² /Σw F _o ²) ^{1/2}]	0.043	0.037	0.041
weight A/(σ ² F _o + B)			
A	2	1	1
B	5 × 10 ⁻⁵	3 × 10 ⁻³	2 × 10 ⁻³
max ht in final difference synthesis, eÅ ⁻³	0.18	0.12	0.23

Table II. Comparative Bond Distances and Angles and Torsion Angles

	homoendrin	endrin ^a	homoisodrin	isodrin ^b	homoisodrin acetate
(a) Distances (Å)					
Cl(1)-C(11)	1.757 (4)	1.766 (5)	1.779 (5)	1.8 (2)	1.759 (4)
Cl(2)-C(11)	1.785 (4)	1.775 (5)	1.765 (5)	1.75 (2)	1.780 (4)
Cl(3)-C(3)	1.746 (5)	1.762 (5)	1.752 (5)	1.74 (2)	1.755 (3)
Cl(4)-C(4)	1.682 (6)	1.694 (5)	1.695 (5)	1.70 (2)	1.773 (3)
Cl(5)-C(5)	1.703 (5)	1.695 (5)	1.707 (5)	1.69 (2)	1.779 (3)
Cl(6)-C(6)	1.742 (6)	1.765 (5)	1.751 (5)	1.74 (2)	1.757 (3)
C(1)-C(2)	1.544 (9)	1.55 (1)	1.557 (7)	1.53 (2)	1.572 (5)
C(2)-C(3)	1.567 (6)	1.57 (1)	1.558 (7)	1.57 (2)	1.532 (5)
C(3)-C(4)	1.523 (6)	1.48 (1)	1.513 (7)	1.43 (2)	1.585 (5)
C(4)-C(5)	1.315 (10)	1.33 (1)	1.317 (7)	1.34 (2)	1.568 (5)
C(5)-C(6)	1.517 (7)	1.52 (1)	1.505 (7)	1.46 (2)	1.532 (5)
C(6)-C(1)	1.559 (6)	1.52 (1)	1.552 (7)	1.58 (2)	1.563 (5)
C(1)-C(7)	1.547 (5)	1.55 (1)	1.550 (7)	1.64 (2)	1.539 (5)
C(7)-C(8)	1.527 (7)	1.51 (1)	1.503 (8)	1.50 (2)	1.532 (5)
C(8)-C(9)	1.456 (10)	1.52 (1)	1.310 (8)	1.30 (2)	1.525 (6)
C(9)-C(10)	1.452 (6)	1.48 (1)	1.505 (8)	1.45 (2)	1.525 (5)
C(10)-C(2)	1.549 (7)	1.55 (1)	1.554 (7)	1.59 (2)	1.521 (5)
C(3)-C(11)	1.546 (7)	1.57 (1)	1.555 (7)	1.48 (2)	1.528 (5)
C(11)-C(6)	1.552 (6)	1.53 (1)	1.556 (7)	1.51 (2)	1.544 (5)
C(7)-C(12)	1.542 (6)	1.56 (1)	1.541 (8)	1.44 (2)	
C(12)-C(13)	1.545 (10) }	1.55 (1)	1.550 (8) }	1.44 (2)	
C(13)-C(10)	1.548 (6) }		1.548 (7) }		
C(8)-O	1.452 (6)	1.44 (1)			
O-C(9)	1.447 (6)	1.46 (1)			
C(4)-C(13)					1.569 (5)
C(8)-C(12)					1.539 (5)
C(12)-O(121)					1.466 (4)
O(121)-C(122)					1.330 (4)
O(122)-O(123)					1.202 (5)
C(122)-C(124)					1.502 (4)
(b) Angles (deg)					
C(2)-C(1)-C(6)	103.3 (4)	104.1 (5)	103.3 (4)	103.5 (18)	103.3 (3)
C(2)-C(1)-C(7)	110.9 (4)	103.9 (5)	110.0 (4)	100.1 (18)	116.1 (3)
C(6)-C(1)-C(7)	119.2 (3)	126.0 (5)	119.0 (4)	127.0 (19)	116.1 (3)
C(1)-C(2)-C(3)	102.7 (4)	101.2 (5)	102.2 (4)	101.6 (18)	101.2 (3)
C(1)-C(2)-C(10)	110.4 (4)	103.3 (5)	108.7 (4)	104.7 (18)	114.4 (3)
C(3)-C(2)-C(10)	120.6 (4)	125.5 (5)	119.8 (4)	124.3 (19)	104.4 (3)
Cl(3)-C(3)-C(2)	114.3 (3)	114.4 (5)	114.4 (3)	112.0 (11)	114.2 (2)
Cl(3)-C(3)-C(4)	115.6 (4)	115.4 (5)	115.2 (4)	116.2 (11)	115.4 (2)

Table II (Continued)

	homoendrin	endrin ^a	homoisodrin	isodrin ^b	homoisodrin acetate
Cl(3)-C(3)-C(11)	116.5 (3)	114.8 (5)	115.9 (3)	118.2 (12)	115.6 (2)
C(2)-C(3)-C(4)	109.7 (3)	113.2 (5)	110.3 (4)	108.9 (18)	99.7 (3)
C(2)-C(3)-C(11)	100.3 (4)	99.4 (5)	100.2 (4)	96.8 (18)	104.0 (3)
C(4)-C(3)-C(11)	98.5 (4)	97.5 (5)	98.9 (4)	103.7 (17)	106.2 (3)
Cl(4)-C(4)-C(3)	124.6 (5)	125.9 (5)	124.6 (4)	127.7 (11)	113.6 (2)
Cl(4)-C(4)-C(5)	128.5 (4)	125.6 (5)	128.0 (4)	124.2 (12)	112.9 (2)
C(3)-C(4)-C(5)	106.9 (5)	108.5 (5)	107.0 (4)	108.1 (17)	102.4 (3)
Cl(5)-C(5)-C(4)	127.5 (4)	129.4 (5)	127.5 (4)	128.6 (11)	117.3 (2)
Cl(5)-C(5)-C(6)	123.7 (5)	124.3 (5)	123.5 (4)	124.4 (12)	116.5 (2)
C(4)-C(5)-C(6)	108.8 (4)	106.2 (5)	108.7 (4)	107.0 (19)	101.3 (3)
Cl(6)-C(6)-C(1)	114.2 (4)	114.7 (5)	114.5 (3)	111.9 (11)	112.9 (2)
Cl(6)-C(6)-C(5)	115.9 (4)	114.0 (5)	116.1 (3)	119.1 (12)	114.7 (2)
Cl(6)-C(6)-C(11)	116.9 (3)	115.6 (5)	115.9 (3)	117.9 (12)	115.4 (2)
C(1)-C(6)-C(5)	110.5 (4)	112.0 (5)	110.0 (4)	109.5 (19)	104.1 (3)
C(1)-C(6)-C(11)	99.6 (3)	101.2 (5)	99.9 (4)	93.4 (17)	102.0 (3)
C(5)-C(6)-C(11)	97.5 (4)	97.5 (5)	98.3 (4)	101.7 (16)	106.4 (3)
C(1)-C(7)-C(8)	109.8 (4)	110.5 (5)	112.0 (4)	105.8 (14)	116.7 (3)
C(1)-C(7)-C(12)	104.7 (3)	97.6 (5)	104.2 (4)	98.6 (16)	
C(8)-C(7)-C(12)	107.9 (4)	100.6 (5)	106.0 (4)	96.9 (16)	
C(7)-C(8)-C(9)	112.8 (4)	105.2 (5)	115.1 (5)	107.1 (17)	109.4 (3)
C(8)-C(9)-C(10)	112.8 (5)	104.4 (5)	115.0 (5)	109.0 (17)	100.8 (3)
C(2)-C(10)-C(9)	110.7 (4)	110.5 (5)	112.3 (4)	111.9 (15)	111.1 (3)
C(2)-C(10)-C(13)	104.1 (4)	97.7 (5) ^e	104.5 (4)	96.3 (15) ^e	102.9 (3)
C(9)-C(10)-C(13)	107.5 (4)	102.9 (5) ^e	105.4 (4)	96.7 (17) ^e	105.9 (3)
Cl(1)-C(11)-Cl(2)	107.4 (2)	106.5 (5)	106.8 (3)	107.6 (8)	107.4 (2)
Cl(1)-C(11)-C(3)	114.9 (3)	114.0 (5)	114.3 (3)	109.2 (12)	114.3 (2)
Cl(1)-C(11)-C(5)	115.0 (3)	115.0 (5)	114.0 (3)	108.2 (12)	117.0 (3)
Cl(2)-C(11)-C(3)	113.0 (3)	114.6 (5)	115.2 (3)	119.3 (12)	112.6 (2)
Cl(2)-C(11)-C(6)	113.2 (3)	106.5 (5)	114.0 (3)	116.4 (12)	112.0 (2)
C(3)-C(11)-C(6)	93.0 (3)	92.1 (5)	92.2 (4)	95.3 (18)	93.2 (3)
C(7)-C(12)-C(13)	110.3 (4)	94.4 (5) ^d	109.3 (4)	101.1 (18) ^d	
C(10)-C(13)-C(12)	111.0 (4)		109.8 (4)		104.0 (3)
C(7)-C(8)-O	116.5 (3)	115.8 (5)			
C(9)-C(8)-O	59.7 (3)	59.3 (5)			
C(8)-O-C(9)	60.3 (4)	62.9 (5)			
C(8)-C(9)-O	60.0 (3)	57.9 (5)			
C(10)-C(9)-O	116.9 (3)	114.1 (5)			
Cl(4)-C(4)-C(13)					110.0 (2)
C(3)-C(4)-C(13)					104.8 (3)
C(5)-C(4)-C(13)					112.7 (3)
C(7)-C(8)-C(12)					114.0 (3)
C(9)-C(8)-C(12)					100.9 (3)
C(4)-C(12)-C(10)					105.9 (3)
C(4)-C(13)-C(12)					118.3 (3)
C(8)-C(12)-C(11)					104.7 (3)
C(8)-C(12)-O(121)					104.4 (3)
C(13)-C(12)-O(121)					108.3 (3)
C(12)-O(121)-C(122)					117.4 (3)
O(121)-C(122)-O(123)					123.2 (3)
O(121)-C(122)-C(124)					110.9 (3)
O(123)-C(122)-C(124)					125.9 (4)
(c) Torsion Angles (deg)					
C(1)-C(2)-C(10)-C(13)	+61 (1)		-63 (0)		+67 (0)
C(2)-C(10)-C(13)-C(12)	-61 (1)	<i>e</i>	+63 (1)		-106 (0)
C(10)-C(13)-C(12)-C(7)	0 (1)		+1 (1)		
C(13)-C(12)-C(7)-C(1)	+61 (1)		-64 (1)		
C(12)-C(7)-C(1)-C(2)	-61 (1)	-37 (1)	+63 (1)	-30	
C(2)-C(1)-C(7)-C(8)	+55 (1)	+68 (1)	-51 (1)	+69	-15 (1)
C(1)-C(7)-C(8)-C(9)	-56 (1)	-67 (1)	+54 (1)	-74	+46 (0)
C(7)-C(8)-C(9)-C(10)	+1 (1)	-2 (1)	+1 (1)	+5	-73 (0)
C(8)-C(9)-C(10)-C(2)	+55 (1)	+71 (1)	-55 (1)	+64	+74 (0)
C(9)-C(10)-C(2)-C(1)	-54 (1)	-69	+59 (1)	-61	-46 (0)

^aDeLacy and Kennard (1972). ^bKennard et al. (1979). ^cC(12) replaces C(13). ^dC(10) replaces C(13). ^eTorsion angles (deg) are as follows (angle for endrin and angle for isodrin): C(1)-C(2)-C(10)-C(12), +38 (1), +38; C(2)-C(10)-C(12)-C(7), -61 (1), -61; C(10)-C(12)-C(7)-C(1), +60 (1), +59.

all cases, blocked anisotropic thermal parameters were used for all non-hydrogen atoms. Hydrogen atoms were located in difference Fourier syntheses and included in the refinements with their positional and isotropic thermal parameters fixed. Final difference Fourier revealed no significant features. Atomic scattering factors were those of

Cromer and Mann (1968) for non-hydrogens and of Stewart et al. (1965) (hydrogen). Table I gives complete details of crystal data, methods of data acquisition, and structure refinement for compounds 1-3. Lists of atomic coordinates and anisotropic parameters are given in the supplementary material (see paragraph at end of paper regarding sup-

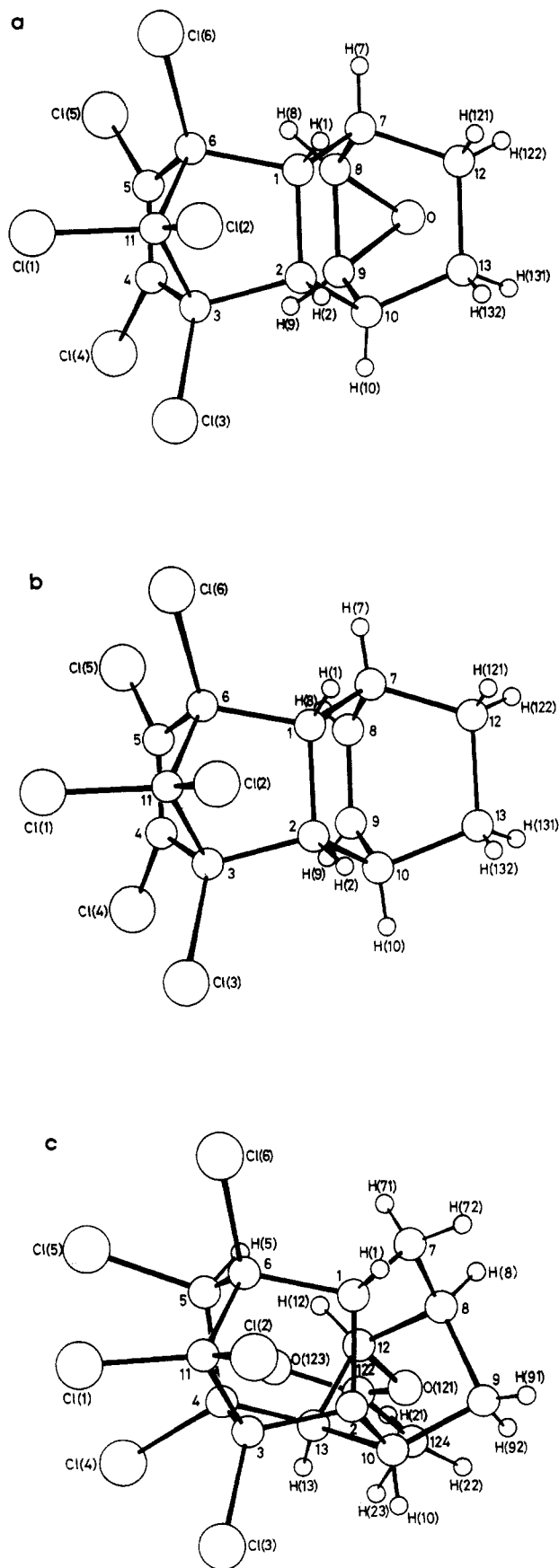


Figure 1. Molecular configuration and atom numbering scheme for (a) homoendrin (1), (b) homoisodrin (2), and (c) homoisodrin acetate (3). Unless otherwise indicated, atoms are carbons. [The numbering convention follows that of DeLacy and Kennard (1972).]

plementary material). Observed and calculated structure factors are available from the authors.

DISCUSSION

The molecular stereochemistries of homoendrin (1) and homoisodrin (2) (Figure 1) do not change significantly from those of the parent compounds endrin (DeLacy and Kennard, 1972) and isodrin (Kennard et al., 1979). Although the relative precisions of the determinations of 1 and 2 are considerably better than those for the parent compounds, the introduction of the additional carbon into the ring has little effect upon the comparative bond distances for the whole series (Table II). Differences in the bond angles are a direct consequence of the relief of the steric strain in the ring via the presence of the additional carbon, e.g., the angles C(6)–C(1)–C(7) and C(3)–C(2)–C(10) in endrin and isodrin contract from 126.0 (5)° and 127.0 (19)° and 125.5 (5)° and 124.3 (19)° respectively to 119.2 (3)° and 119.0 (4)° and 120.6 (4)° and 119.8 (4)° in 1 and 2. These angular differences are also reflected in the torsion angles [Table II (c)].

A relatively inflexible unit in these structures and in fact among the entire cyclodiene series is the hexachloronorborene moiety. This has previously been observed from crystallographic parameters for a series of seven cyclodienes. (Smith, 1978). There is relatively constant ortho Cl–Cl separation (mean, 3.42 Å) which is of the same order as the mean separation (3.41 Å) for the vicinal chlorines [Cl(4)–Cl(5)] where the angles are constrained by a fixed double-bond system. Of greater significance is the meta Cl–Cl separations, which comprise the “pentagonal system” of Busvine (1954). The overall range of distances for the series is 5.46–5.55 Å compared with the individual mean values of 5.54 Å [Cl(4)–Cl(4)], 5.55 Å [Cl(2)–Cl(5)], 5.47 Å [Cl(3)–Cl(5)], and 5.46 Å [Cl(4)–Cl(6)]. Similar dimensional features are found for 1,2,3,4,5,6-hexachlorocyclohexane (lindane) which shares similar toxicological properties with the cyclodienes and possibly the same mode of action. Considering that both active and inactive cyclodiene analogues share the same basic hexachloronorborene nucleus, other factors must be important in governing activity. The molecular thickness, i.e., the distance between Cl(1) of the norbornene nucleus and the “active site” (the functional group centre) on the side cage, can be accurately determined from X-ray structures. Quite a range is observed, e.g., 5.69 Å in isobenzan to 7.46 Å in dieldrin. Since the homoanalogues (1 and 2) are dimensionally similar, other factors must be important in accounting for the lesser activities of these two compared with endrin and isodrin and indeed for the other members of the cyclodiene series. While a “thickness” range of 5.6–7.5 Å is essential, factors such as the nature of the breakdown product or intermediate, the rate of breakdown, and the breakdown mechanism must be considered. Some of the products formed in the breakdown of the dienes are known to be more insecticidally active than the parent compounds, e.g., both photodieldrin and photoaldrin (Brooks, 1974). Furthermore, a compound such as lindane, which possesses the ideal structural features for insecticidal potency, undergoes *in vitro* dehydrohalogenation to varying degrees in different insects. This reduces its toxicity to a level comparable in many cases with cyclodienes where similar breakdown is not possible.

The structure of homoisodrin acetate (3) appears to be quite unique. It is different from the structure of photoaldrin acetate (Kennard et al., 1983) and differs from that proposed for this compound by Bird and Yeung

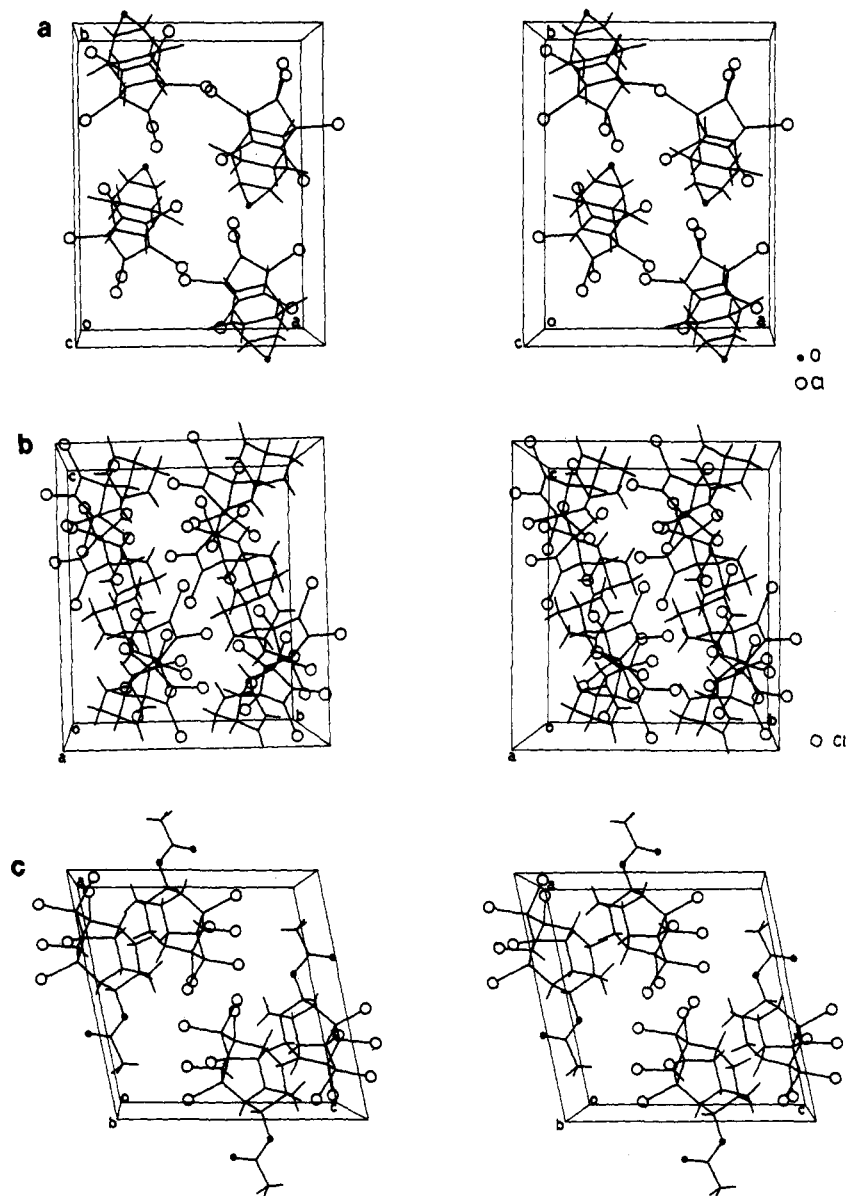


Figure 2. Stereoviews of the packing (a) homoendrin, (b) homoisodrin, and (c) homoisodrin acetate in their respective unit cells.

(1981). The difference is primarily in the location of the acetate group on the molecular cage [C(8) instead of C(9)]. This difference could arise as the result of a 1,3-hydrogen shift in the molecule. Bond distances and angles for **3** are as expected in a molecule of this type where the double bond has been lost and a bridge bond formed.

Packing of homoendrin and homoisodrin in their respective unit cells (Figure 2a,b) appear to be governed by van der Waals' forces, resulting in discrete nonassociated molecules with intermolecular distances typical of the series, e.g., Cl(2)---O' = 3.339 (3) Å and Cl(1)---Cl(4)' = 3.687 (2) Å. The presence of the acetate group in **3** does not result in any strong hydrogen-bonding associations, Cl---Cl' distances again appear to be important, e.g., Cl(4)---Cl(6)', = 3.490 (2) Å while Cl(1)---O(121)' must be considered weakly interactive.

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Registry No. 1, 73454-25-8; 2, 73454-21-4; 3, 89873-35-8.

Supplementary Material Available: Lists of atomic coordinates and anisotropic thermal parameters (6 pages). Ordering information is given on any current masthead page. Observed and calculated structure factors are available from the authors.

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Methoxychlor Metabolism in Chickens

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[¹⁴C]Methoxychlor [1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane] was given orally to intact, colostomized, and bile-fistulated chickens. Dosages were 0.2, 10, and 100 mg of methoxychlor/day for periods of 1 and 14 days. Recovery of ¹⁴C was greater in carcasses of hens compared to roosters for comparable dosages and time. ¹⁴C in eggs varied with dose and time and was predominantly in yolk. Methoxychlor and 26 metabolites were either identified or characterized: 22 metabolites in feces, 14 in urine, and 6 in bile. Metabolism included demethylation, ring hydroxylation, conjugation with glucuronic acid, dechlorination, dehydrochlorination, and formation of substituted benzophenones.

Methoxychlor [1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane] (1, Table I) is an insecticide used to control flies on livestock and in farm buildings. It has other insecticidal uses, but, for this paper, we are concerned with its direct contact by farm animals.

The metabolism or distribution of methoxychlor or [¹⁴C]methoxychlor has been studied in mice, rats, and goats. Kapoor et al. (1970) reported five metabolites of [¹⁴C]methoxychlor in urine and feces of mice. Woodward et al. (1948) observed no methoxychlor or bis(4-methoxyphenyl) acetic acid in urine of rats fed methoxychlor, and Weikel (1957) observed that ¹⁴C was eliminated predominantly in feces of rats given [¹⁴C]methoxychlor intravenously. We (Davison et al., 1982) identified 17 metabolites of [¹⁴C]methoxychlor in urine and feces of goats and observed that an increase in size of the dose shifted the predominant route for elimination of ¹⁴C-metabolites from urine to feces.

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We now report the metabolism of [¹⁴C]methoxychlor by chickens.

MATERIALS AND METHODS

Chickens. One-year-old white leghorn hens and 4-5-month-old white leghorn roosters were used. Methoxychlor was given once daily in gelatin capsules at 0.2, 10, or 100 mg/chicken for 1 or 14 consecutive days (see Table II). Eight tenths to 6.9 μCi of [¹⁴C]methoxychlor was given in each capsule, and three to six chickens were used in each treatment group. Feed and water were available ad libitum.

Urine and feces were collected from colostomized roosters, and bile was collected from bile-fistulated roosters. All chickens were killed 24 h after the last dose of [¹⁴C]methoxychlor. The chickens were plucked, the feathers were discarded, various tissues were sampled, and then the remainder of the carcasses were ground and sampled. All samples except bile were lyophilized and stored in glass jars. Bile was stored either frozen or at 3 °C.

Methoxychlor and [¹⁴C]Methoxychlor. Purity of