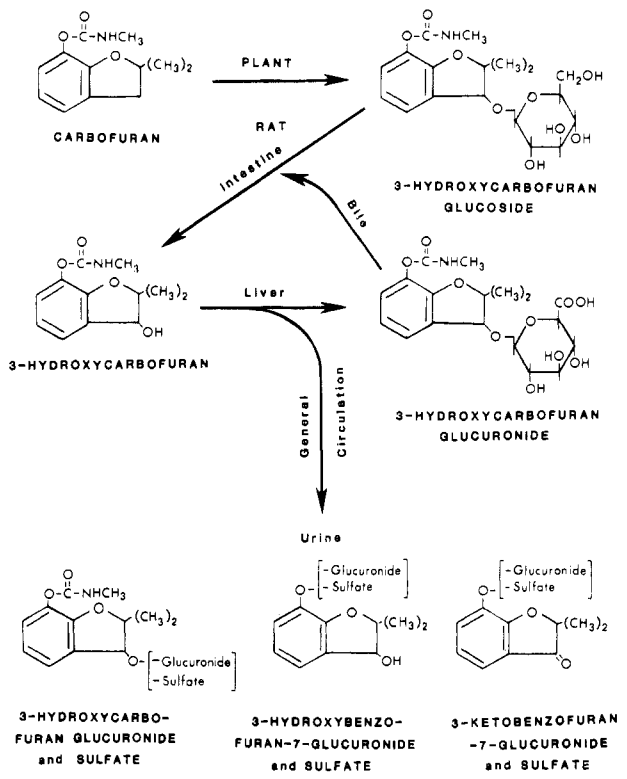

Figure 3. Major metabolic pathway of 3-hydroxycarbofuran glucoside (a plant metabolite of carbofuran) in rats.

esterase agent and any process that increases its residency time in the body could prove detrimental. Fortunately, 3-OH-C-Glu is included in the analysis used to monitor carbofuran residues in plants and is included in the acceptable level of residues established for this insecticide by the regulatory authorities. However, it is not known for certain whether this or any other pesticide conjugate is as safe as the parent compound when consumed in the diet on a chronic basis.

Registry No. 3-OH-C, 16655-82-6; 3-OH-C-Glu, 30368-38-8; 3-hydroxycarbofuran glucuronide, 53305-32-1; 3-hydroxycarbofuran sulfate, 70988-90-8; 3-hydroxybenzofuran 7-glucuronide, 90433-37-7; 3-hydroxybenzofuran 7-sulfate, 90433-38-8; 3-ketobenzofuran 7-glucuronide, 70988-93-1; 3-ketobenzofuran 7-sulfate, 70988-94-2; 3-hydroxybenzofuran glucoside, 30368-38-8.

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Structural Systematics for 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane-Type Compounds: Crystal Structures of Five Analogues and Comments on Mode of Action

Colin H. L. Kennard,* Graham Smith, Tor-Björn Palm, Sven Hovmöller, and Agneta Sjögren

The crystal structures of five 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) analogues are reported. They are 1,1,1-trichloro-2,2-bis(phenyl)ethane, bis(4-chlorophenyl)methane, 9-(trichloromethyl)-9,10-dihydroanthracene, 1-chloro-2,2-bis(4-chlorophenyl)ethene, and 1,1,1-trichloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane. Holan's DDT mode of action theory is analyzed in terms of available crystallographic data.

1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) has been the most widely used and effective insecticide so far developed. The structural criteria among the various DDT analogues for optimum activity are well documented (Riemschneider and Otto, 1954; Metcalf and Fukuto, 1968; Fahmy et al., 1973; Metcalf, 1973). The majority of the theories proposed, regardless of their generation, attempt to relate toxicity with molecular shape and size (derived from structural models) in order to get a hypothetical molecular site model (Gunther et al., 1954; Mullins, 1956; Rogers et al., 1953; Holan, 1969). More recently, Fahmy et al. (1973) reviewed the available theories on structure–activity relationships for the DDT analogues and introduced a more precise theoretical model based on Taft steric substituent parameters (Taft, 1956).

By analyzing data collected from several hundred DDT analogues, it is possible to determine specifications for an active DDT-type insecticide. They are a diphenylmethane

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Table I. DDT Analogues for Which Crystal Data Are Known

systematic name	common or given name	reference
1,1,1-trichlorobis(phenyl)ethane	DTE, 1	this work
bis(4-chlorophenyl)methane	DCM, 2	this work
9-(trichloromethyl)-9,10-dihydroanthracene	VING, 3	this work
1-chloro-2,2-bis(4-chlorophenyl)ethene	DDD-olefin, 4	this work
1,1,1-trichloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane	POP-DDT, 5	this work
1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane	*p,p'*-DDT or DDT	DeLacy and Kennard (1972a)
1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane	*o,p'*-DDT	DeLacy and Kennard (1972a)
(−)-1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane	(−)-*o,p'*-DDT	Smith and Bennett (1977)
1,1,1-trichloro-2,2-bis(4-methoxyphenyl)ethane	Methoxychlor	Smith et al. (1976)
1,1,1-tribromo-2,2-bis(4-chlorophenyl)ethane	Br-DDT	Hovmöller et al. (1978a)
1,1,1,2-tetrachloro-2,2-bis(4-chlorophenyl)ethane	Cl-DDT	Hovmöller et al. (1978a)
1,1-bis(4-methoxyphenyl)-2,2-dimethylpropane	Rogers	Smith et al. (1980)
1,1-bis(4-ethoxyphenyl)-2,2-dimethylpropane	GH44	Delacy and Kennard (1972b)
1,1-bis(4-chlorophenyl)-2,2-dichlorocyclopropane	DCC	Delacy and Kennard (1972b)
2,2-bis(4-ethoxyphenyl)-3,3-dimethyloxetane	Oxetane	Holan et al. (1973)
1,1-dichloro-2,2-bis(4-chlorophenyl)ethane	*p,p'*-DDD or DDD	Shields et al. (1977)
1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane	*o,p'*-DDD	Arora and Bates (1976)
1,1-dichloro-2,2-bis(4-ethoxyphenyl)ethane	Perthane	Hovmöller et al. (1978b)
1,1-dichloro-2,2-bis(4-fluorophenyl)ethane	DFDD	Smith et al. (1977)
1-chloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethene	CDE	Hovmöller and Göthe (1978)
1,1-dichloro-2,2-bis(4-chlorophenyl)ethene	DDE	Shields et al. (1977)
1,1-bis(4-chlorophenyl) acetic acid	DDA	Shields and Kennard (1977) Hovmöller et al. (1977)
4,4'-dichlorobenzophenone	DBP	Shields and Kennard (1977)
1,1-dichloro-2,2-diphenylcyclopropane	DCPC	Lauher and Ibers (1975)
1,1-dibromo-2,2-diphenylcyclopropane	DBPC	Lauher and Ibers (1975)
1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol	Dicofol	Smith et al. (1978)
1,1-bis(4-chlorophenyl)-3-pyridinemethanol	Parinol	Kennard et al. (1981)

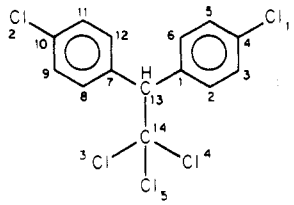
group with electronegative atoms in the para positions and a bulky group attached to the central carbon, e.g., $-CCl_3$ in *p,p'*-DDT.

It is now generally believed that the primary effects of DDT are on the nervous system (O'Brien, 1967; Gardner and Vincent, 1978), based upon the fact that DDT poisoning causes tremor, so-called DDT jitters. This effect, which is related to neuroexcitation (repetitive firing in the abdominal nerve cord), may be studied on isolated nerves. Mitochondrial ATPase systems are found to be affected by DDT-type compounds, but whether the primary effect is inhibition of the oligomycin-sensitive Mg^{2+}-ATPase (Cutkomp et al., 1971), uncoupling of the oxidative phosphorylation in mitochondria (Byczkowski et al., 1973), or neither of these (Nelson, 1975) needs further investigation. Furthermore, it is not certain that all DDT analogues have the same primary target (Sawicki, 1978). Of course, one possibility is that all the different insecticides inhibit (or stimulate) various enzyme systems in membranes, and differences are due to the relative effects of any one insecticide on the different enzymes. In the absence of detailed knowledge about the mode of action of DDT at a molecular level, hypotheses have been developed around the conformational requirements of the molecule with toxicity data for a large number of DDT analogues.

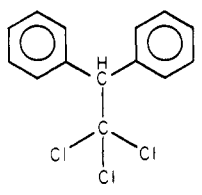
Mullins (1955) has suggested that membranes are composed of "cylindrical lipoprotein macromolecules arranged in regular hexagonal packing". On the basis of the active and inactive compounds, he concluded that "membrane molecules" had a diameter of 40 Å and a separation from each other of 2 Å. "The interspaces between these macromolecules are then the pores of the membrane into which various solutes can be introduced". "Distortion of the position of these molecules may lead to local regions of instability and to ion leaks that are a prelude to excitation".

Holan (1969) proposed a modification of Mullins' theory. This theory is based on the unit membrane hypothesis, where the membrane is composed of protein and lipid layers with a distance of about 5 Å between the protein and the lipid. Holan suggests that there are 5 Å diameter pores within the lipid structure. The DDT molecule would fit into this gap between the protein layer and the pore within the lipid structure, keeping "the pore or receptor open to sodium ions". The lipoprotein has two conformations: a compressed and an expanded form. "The compressed form is selective to non-solvated potassium ions and in its expanded form is selective to hydrated sodium ions. Based on this hypothesis, the insecticides then act by keeping the spring in an expanded sodium ion position".

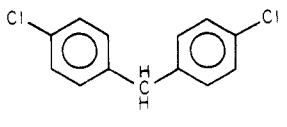
Precise molecular parameters have now been determined for 27 compounds by using X-ray diffraction. This method enables the relationship between two or three atoms (bond distances and bond angles) and between two bonds with respect to one another about a bond vector (the torsion angle from a Newman projection) to be determined with a high degree of accuracy. Thus, the conformation of these DDT analogues are known in the crystalline state. A preliminary survey of the available data derived by this method has already been made (Kennard and Smith, 1980). Further data are now available (Table I) so that a more meaningful review of the structural systematics of the DDT analogues is possible. The five structures reported, 1,1,1-trichloro-2,2-bis(phenyl)ethane (1) bis(4-chlorophenyl)methane (2), 9-(trichloromethyl)-9,10-dihydroanthracene (3), 1-chloro-2,2-bis(4-chlorophenyl)-ethene (4), and 1,1,1-trichloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane (5), provide a somewhat fuller picture of the cross section of structural possibilities within the series. These compounds differ as follows: (a) 1 has the basic $-CX_3$ group but lacks parasubstituents in the rings; this compound, isomorphous with *p,p'*-DDT, but having greater stability in the X-ray beam, gives more precise structural data than from the parent *p,p'*-DDT. During the data collection period, the latter compound suffered a 20% loss in diffraction intensity due to decomposition (DeLacy and Kennard, 1972a). (b) 2 has no basic $-CX_3$ group but has *p*-chloro substituents; this helps to identify the effect the $-CX_3$ group has on conformational aspects of the two phenyl rings. (c) 3 has two ring systems



p,p'-DDT[a]



1



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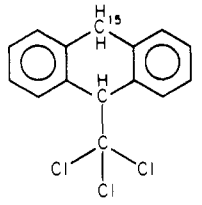

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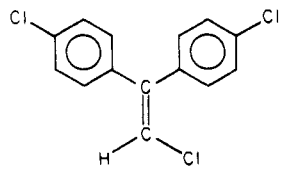

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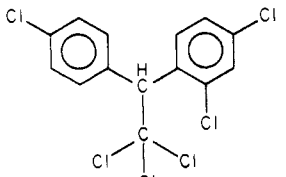

5

[a] Atom numbering for the series follows the convention used for p,p'-DDT (DeLacy and Kennard, 1972a).

constrained by a bridging bond (Vingiello and Newallis, 1960). (d) 4 is an analogue of DDE. The absence of a single terminal chlorine provides a comparison with the parent DDE (Shields et al., 1977) and with the asymmetrically substituted analogue CDE (Hovmöller and Göthe, 1978). (e) 5 is an o-chloro-substituted p,p'-DDT. The Holan theories have been reexamined with the hindsight of current knowledge on the three-dimensional structure of membranes (Singer, 1976).

EXPERIMENTAL SECTION

Samples of 1 and 2 were prepared by Dr. Norman Sharpless of the U.S. National Institutes of Health, Bethesda, MD, in 1944 and were kindly provided. Crystals suitable for X-ray analysis were obtained from a mixture of isopropyl alcohol and water. Compound 3 was supplied by Professor Frank Vingiello, Northeast Louisiana University, Monroe, LA, and suitable crystals were obtained from ethanol. Compound 4, a DDT metabolite, was supplied as an analytical reference standard from the U.S. Environmental Protection Agency, Bethesda, MD (catalog name p,p'-DDD-olefin). Compound 5 was provided by Professor J. N. Smith, Victoria University, Wellington, New Zealand. Unit cell data and details of data collection and structure refinement are given in Table II. Intensity data were collected on a Philips PW1100 four-circle diffractometer at the Arrhenius Laboratory, University of Stockholm, Sweden. The cell parameters and space group for 1 indicated that it was isomorphous and probably isostructural with p,p'-DDT (DeLacy and Kennard, 1972a). The isostructurality of 1 and p,p'-DDT was confirmed by inserting the atomic coordinates for the latter in a Fourier analysis, which gave an initial agreement factor (R) of 0.44. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic subsequently reduced R to a final value of 0.054. Compounds 2 and 5 were solved by the automatic centrosymmetric direct method procedure of SHELX-76 (Sheldrick, 1976). Because of the small number of observed data available for 2, only the p-chlorines were refined anisotropically. With 3 and 4 the positions of the three chlorine atoms were located from sharpened Patterson maps, while the remaining atoms were found in difference Fourier analyses. Full-matrix least-squares refinement was used with 3–5 with anisotropic thermal parameters for all heavy atoms. No corrections were made for absorption.

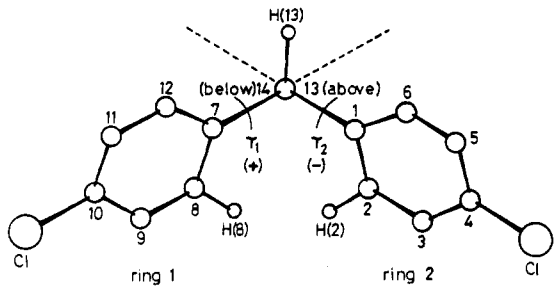

Figure 1. Standard numbering scheme and convention used for comparison of ring torsion angles in DDT analogues [after Hovmöller et al. (1977).

Lists of atomic coordinates and anisotropic thermal parameters are given in the supplementary material (see paragraph at end of paper regarding supplementary material). Observed and calculated structure factors are available from the authors. Comparative bond distances and angles are given in Table III.

The atom-naming convention used is illustrated in Figure 1. The comparative molecular configurations for compounds 1–5 and the packing of the molecules in their unit cells are shown in Figures 2 and 3, respectively. Torsion angles C(7)–C(13)–C(1)–C(2), C(7)–C(13)–C(1)–C(6), C(1)–C(13)–C(7)–C(8), and C(1)–C(13)–C(7)–C(12) are first calculated. The torsion angle τ_1 represents the largest angle and is given a positive sign. τ_2 is the torsion angle for the other phenyl ring with the opposite sign to the largest angle. τ_2 is made negative.

DISCUSSION OF THE STRUCTURES

Compound 1 (Figure 2a) is isostructural with p,p'-DDT, the difference between the two being in the volumes of the unit cells. The increased cell volume in the case of p,p'-DDT [a = 9.963 (2) Å, b = 19.200 (2) Å, c = 7.887 (1) Å, V = 1509 Å^3, D_{calcd} = 1.56 g cm^{-3}] (DeLacy and Kennard, 1972a) is due primarily to an increase in one cell parameter from 16.593 to 19.200 Å (volume increase 158 Å^3) and is consistent with the introduction of two additional chlorine substituents per molecule. The same agreement may be made for 1,1,1-trichloro-2,2-bis(4-bromophenyl)ethane [orthorhombic, cell dimensions a = 9.99, b = 19.60, and c = 7.92 Å (Wild and Brandenberger, 1946)]. Isostructurality and isomorphism are relatively common among sets of benzene derivatives and their 4-chloro-substituted analogues, e.g., 2-phenoxypropionic acid and 2-(4-chlorophenoxy)propionic acid (Kennard and Smith, 1982). The structure of 1 has been determined with considerably higher precision than that of p,p'-DDT so that distance and angular parameters are of correspondingly higher precision. Of particular interest in this study are the relative torsion angles τ_1 and τ_2, which are +131.8° and −92.9° compared with +134.3° and −94.8° for p,p'-DDT.

Barnes et al. (1981) list five molecular conformations for diphenylmethane. They are as follows: C_{2v}, angles of twist $\varphi_A = \varphi_B = 0°$ (planar); C_{2v}, $\varphi_A = \varphi_B = 90°$ (gable); C_2, $0° < \varphi_A = \varphi_B < 90°$ (helical); C_s, $0° < \varphi_A = -\varphi_B < 90°$; C_s, $\varphi_A = 0°$, $\varphi_B = 90°$ (perpendicular). For diphenylmethane at −70 °C, they found the helical arrangement with φ_A = 63.9° and φ_B = 71.1°. The dihedral angles φ_A and φ_B were defined as the angles subtended between least-squares planes of the two rings A and B and the central plane defined by C_A, CH_2, and C_B.

Table II. Comparative Crystallographic Data for Compounds 1-5

	1	2	3	4	5
mol. formula	$C_{14}H_{11}Cl_3$	$C_{13}H_{10}Cl_2$	$C_{15}H_{11}Cl_3$	$C_{14}H_9Cl_3$	$C_{14}H_8Cl_6$
M_r	285.6	235.6	297.4	283.6	388.9
a, Å	16.593 (6)[a]	26.620 (8)	15.732 (5)	15.163 (7)	11.621 (3)
b, Å	10.237 (4)	7.222 (3)	14.611 (2)	5.824 (2)	11.895 (3)
c, Å	7.955 (2)	5.988 (2)	5.928 (1)	7.452 (3)	12.455 (5)
β, deg		91.40 (2)		100.12 (3)	115.60 (8)
V, Å^3	1351	1151	1363	648	1553
Z	4	4	4	2	4
D_{calcd}, g cm^{-3}	1.403	1.368	1.450	1.453	1.663
space group	$Pbc2_1$ (no. 29)	$P2_1/a$ (no. 15)	$Cmc2_1$ (no. 36)	$P2_1$ (no. 4)	$P2_1/c$ (no. 15)
radiation used	Mo Kα	Mo Kα	Cu Kα	Mo Kα	Mo Kα
λ, Å	0.7107	0.7107	1.5418	0.7107	0.7107
μ, cm^{-1}	6.50	5.25	58.7	6.77	10.80
F(000)	584	488	608	288	776
$2\theta_{max}$, deg	60	60	150	60	60
reflections collected					
total	3007	2399	688	3243	2557
used	688	333	511	1052	1759
diffractometer	PW1100	PW1100	PW1100	PW1100	PW1100
discrimination	$I > 2.5\sigma(I)$	$I > 1.5\sigma(I)$	$I > 2.5\sigma(I)$	$I > 2.5\sigma(I)$	$I > 2.5\sigma(I)$
crystal size, mm	0.15 × 0.30 × 0.50	0.05 × 0.08 × 0.16	0.16 × 0.21 × 0.42	0.50 × 0.40 × 0.50	0.50 × 0.20 × 0.10
final residuals					
unweighted R	0.054	0.113	0.066	0.038	0.088
weighted R_w	0.047	0.096	0.068	0.037	0.094
weight $[A/(\sigma^2F + B\sigma F^2)]$					
A	1.6	1.3	0.55	1.70	0.7
B	4.7×10^{-4}	8.5×10^{-4}	9.4×10^{-3}	5.0×10^{-4}	1.5×10^{-2}

[a] a = 16.56, b = 10.34, and c = 8.04 (Wild and Brandenberger, 1946).

Compound **2** (Figure 2b) has the "helical" conformation previously described. The comparative angles are +64.9 and +87.5° compared with +63.9 and +71.1° for DPM and +49.4 for both angles in bis(4-aminophenyl)methane (DAM) (Swardstrom et al., 1972). The associative influence of the amino substituents in DAM tends to preclude the usage of this compound in a comparison with the first two, where no intermolecular associative relationships are expected or found. However, the size of the two chlorine atoms in **2** significantly alters the molecular packing in the unit cell (Figure 3b). **2** has a low melting point (49 °C) and the refinement lacks the precision of the other determinations being reported.

Compound **3** has the two phenyl ring systems constrained into an integral part of a six-membered ring system (Figure 2c) while the molecular mirror symmetry is coincident with the crystallographic mirror plane. This places atoms C(13), C(14), H(14), and Cl(1) in the mirror plane and makes torsion angles τ_1 and τ_2 equal (±144.9). The overall conformation of the "part-unsaturated" six-membered ring system is a distorted boat. In terms of bond distances and angles, **1** and **3** are comparable with *p,p'*-DDT and Methoxychlor (Smith et al., 1976), the C(13)–C(1), C(13)–C(7), and C(13)–C(14) distances and the angle C(1)–C(13)–C(7) being of the same order: **1**, 1.512 (12), 1.476 (13), and 1.566 (11) Å and 114.7 (8)°; **3**, 1.505 (8), 1.505 (8), and 1.575 (8) Å and 111.5 (9)°; *p,p'*-DDT, 1.52 (2), 1.57 (2), and 1.51 (2) Å, and 113.6 (10)°; Methoxychlor, 1.525 (10), 1.532 (10), and 1.526 (12) Å and 111.8 (4)°. However the dihedral angle λ for **3** is different: **1**, 70.5°; **3**, 35.6°; *p,p'*-DDT, 64.9°; Methoxychlor, 77.8°. The toxicities of these compounds are quite different (Table IV) with **1** being relatively inactive. Therefore, the difference in the overall width for **1** must be a significant factor determining activity. Because of the restriction of C(15), **3** has different torsion angles with C(15) still behaving as a normal sp^3 carbon. No toxicity data are available for **3**, but the properties for the *p,p'*-DDT equivalent, 2,7-dichloro-9-(trichloromethyl)-9,10-dihydroanthracene (Vingiello and Newallis, 1960) have been referred to by Metcalf (1973), who indicates that the compound (LC_{50} = 0.35 ppm) approaches DDT (LC_{50} = 0.66 ppm) in toxicity to *Culex pipiens* larvae but has very low activity to *Musca domestica*. It might be expected that this compound would have the same stereochemistry as **3**, suggesting possible different modes of action for these two species.

1-Chloro-2,2-bis(4-chlorophenyl)ethene (**4**) is a DDT metabolite. It is also formed when DDE in *n*-hexane is exposed to UV light (Kerner et al., 1972). **4** is compared with other metabolites, DDE and 1-chloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethene. The torsion angles for C(14)–C(13)–C(1)–C(6) and C(14)–C(13)–C(7)–C(8) are +104 (1)° and −38 (1)° for **4**, +127 (1)° and −52 (1)° and +121.0 (1)° and −48.3 (1)° for the two DDE molecules, and +115 (1)° and −34 (1)° for CDDE. The single chlorine substituent at C(14) appears to significantly change this torsion angle.

The last member of this group, **5**, has some unusual properties as an insecticide. It is toxic to both susceptible and DDT-resistant flies (Table V). Therefore, it is probably relatively stable toward the enzyme fly DDT dehydrochlorinase. However, the equivalent enzyme in *Aedes aegypti* actively dechlorinates it (Hennessy et al., 1961). The torsion angles τ_1 and τ_2 (+130.4°, −77.3°) and dihedral angle λ (87.0°) are comparable to those of *o,p'*-DDT (+133.4°, −85.7°, 80.3° and +147.7°, −76.3°, 88.9°) for the two independent molecules and to *p,p'*-DDT (+134.3°, −94.8°, 64.9°) (DeLacy and Kennard, 1972a).

Using structure–insecticidal activity studies with cyclopropanes, Holan (1969) noted two significant structural features: the first, "the state of substitution in the phenyl rings" and, the other, a restrictive one, "the size of the cyclopropane ring". In the case of isosteric compounds, the substituents on the phenyl rings had to be electron donating, although negative atom dipoles were not necessary. Other structural limitations said to be important were "the overall length of the phenyl ring and its substituent (limit 8.0 Å)" and "the distance between the atoms acting as dipoles on the phenyl rings, when those were in their most restricted rotations (limit 11 Å)". The ring size of the most active substituted cyclopropanes had a diam-

Table III

	1	2	3	4	5
		Bond Distances (Å)			
Cl(1)–C(4)		1.65 (3)		1.738 (7)	1.741 (9)
Cl(2)–C(10)		1.80 (3)		1.752 (8)	1.732 (9)
Cl(3)–C(14)	1.780 (10)		1.772 (6)	1.714 (9)	1.769 (9)
Cl(4)–C(14)	1.768 (9)				1.780 (9)
Cl(5)–C(14)	1.774 (9)		1.744 (6)		1.768 (9)
Cl(6)–C(8)					1.770 (9)
C(1)–C(2)	1.368 (15)	1.49 (5)	1.385 (12)	1.364 (13)	1.388 (11)
C(2)–C(3)	1.410 (15)	1.43 (5)	1.439 (14)	1.383 (13)	1.402 (10)
C(3)–C(4)	1.402 (16)	1.43 (5)	1.333 (34)	1.358 (13)	1.384 (12)
C(4)–C(5)	1.363 (18)	1.40 (4)	1.370 (32)	1.362 (12)	1.368 (12)
C(5)–C(6)	1.388 (15)	1.42 (5)	1.383 (16)	1.408 (10)	1.401 (9)
C(6)–C(1)	1.389 (13)	1.34 (5)	1.409 (14)	1.372 (10)	1.366 (10)
C(1)–C(13)	1.512 (12)	1.53 (5)	1.505 (8)	1.515 (8)	1.539 (8)
C(13)–C(14)	1.566 (11)		1.575 (8)	1.296 (11)	1.552 (12)
C(13)–C(7)	1.476 (13)	1.45 (4)	1.505 (8)	1.483 (9)	1.553 (12)
C(7)–C(8)	1.390 (15)	1.44 (5)		1.390 (9)	1.358 (9)
C(8)–C(9)	1.460 (17)	1.44 (5)		1.391 (12)	1.381 (10)
C(9)–C(10)	1.366 (22)	1.37 (3)		1.358 (12)	1.361 (10)
C(10)–C(11)	1.355 (22)	1.33 (3)		1.378 (11)	1.386 (10)
C(11)–C(12)	1.399 (17)	1.41 (4)		1.395 (12)	1.354 (13)
C(12)–C(7)	1.388 (15)	1.43 (4)		1.378 (11)	1.418 (10)
C(2)–C(15)			1.498 (14)		
		Bond Angles (deg)			
C(6)–C(1)–C(2)	118.2 (9)	122 (3)	121.3 (8)	118.9 (7)	120.1 (6)
C(1)–C(2)–C(3)	121.3 (9)	116 (3)	116.5 (11)	120.7 (9)	120.1 (7)
C(2)–C(3)–C(4)	118.9 (9)	123 (3)	122.0 (17)	119.9 (9)	118.2 (8)
C(3)–C(4)–Cl(1)		121 (2)		119.5 (6)	118.5 (6)
C(5)–C(4)–Cl(1)		124 (2)		119.1 (6)	119.0 (6)
C(3)–C(4)–C(5)	120.0 (10)	115 (3)	120.2 (12)	121.3 (7)	122.4 (6)
C(4)–C(5)–C(6)	119.9 (11)	125 (3)	121.3 (15)	118.2 (8)	118.4 (7)
C(5)–C(6)–C(1)	121.7 (10)	119 (3)	118.4 (14)	120.9 (8)	120.8 (8)
C(2)–C(1)–C(13)	121.5 (8)	122 (3)	119.4 (8)	122.2 (7)	120.6 (6)
C(6)–C(1)–C(13)	120.3 (9)	115 (3)	119.2 (9)	118.8 (7)	119.1 (7)
C(1)–C(13)–C(7)	114.7 (8)	110 (3)	111.5 (9)	116.4 (5)	110.3 (6)
C(13)–C(7)–C(8)	125.7 (9)	118 (3)	119.4 (8)	120.8 (6)	119.7 (6)
C(12)–C(7)–C(8)	117.3 (9)	114 (3)		117.7 (7)	115.5 (7)
C(7)–C(8)–C(9)	118.0 (10)	123 (3)		121.3 (7)	124.4 (7)
C(8)–C(9)–C(10)	122.3 (12)	112 (3)		119.3 (7)	117.9 (7)
C(9)–C(10)–Cl(2)		113 (2)		119.6 (6)	119.2 (7)
C(11)–C(10)–Cl(2)		114 (2)		118.9 (6)	120.1 (6)
C(9)–C(10)–C(11)	118.8 (12)	131 (3)		121.5 (8)	120.6 (6)
C(10)–C(11)–C(12)	120.0 (12)	113 (3)		118.5 (8)	119.9 (7)
C(11)–C(12)–C(7)	123.5 (10)	125 (3)		121.8 (7)	121.6 (6)
C(12)–C(7)–C(13)	116.8 (9)	114 (3)		121.5 (6)	124.8 (6)
C(7)–C(13)–C(14)	114.3 (8)		113.1 (9)	122.2 (6)	115.5 (5)
C(1)–C(13)–C(14)	111.6 (8)		113.1 (9)	121.5 (7)	113.3 (5)
C(13)–C(14)–Cl(3)	109.6 (6)		110.0 (8)	125.3 (7)	108.5 (5)
C(13)–C(14)–Cl(4)	110.4 (6)				114.1 (5)
C(13)–C(14)–Cl(5)	113.5 (6)		112.8 (7)		110.1 (5)
C(1)–C(2)–C(15)			121.2 (8)		
C(3)–C(2)–C(15)			122.3 (11)		
C(2)–C(15)–C(8)			112.5 (10)		
C(7)–C(8)–Cl(6)					119.7 (6)
C(9)–C(8)–Cl(6)					115.9 (6)

eter limit of 6.1–6.3 Å with 50–60 Å^2 for the projected area of the ring. A later paper (Holan, 1971) stated that the apex for active compounds had a projected maximum van der Waals' diameter of 6 ± 0.5 Å. Holan's Figure 2 specified a number of additional dimensional parameters for DDT-type molecules. These parameters define the overall height of the molecule (9.0 Å), a width limit (14.0 Å), and van der Waals' limits of negative atom dipoles (11.5 Å).

In most of these theoretical models it is assumed that the molecule has mirror symmetry between the two phenyl rings. However, it should be noted that in most determinations, the DDT molecules are found to be highly asymmetrical, i.e., $|\tau_1| \neq |\tau_2|$.

In order to check Holan's specifications, the intramolecular distances were calculated by using atomic parameters obtained from X-ray studies. The parameters measured have been defined as follows: (1) Apex width is the largest distance (l) between any two terminal α-carbon substituent atoms. This distance is then converted into an overall diameter of the base. (2) Overall height is from the plane containing the three α-carbon substituent groups to the furthest atoms away. It should be noted, especially with ethoxy groups, that the para groups are not necessarily the farthest away from this plane. (3) Estimated width limits due to the length of the phenyl ring substituents are the distance from C(1) or C(7) to the farthest substituent atom. This definition becomes a problem with ethoxy substituents. (4) Distance between dipoles is taken from negative centers on phenyl ring substituents. No distance is given for the p-ethyl compound (Perthane).

Table V lists all this information together with τ_1, τ_2, and λ. For a DDT analogue to be active, it must at least have certain specifications. The results show no real surprises although active lengths will depend on definitions and effective van der Waals' distance added.

Table IV. Raw Data without van der Waals' Corrections

	apex width	overall height	estim width	distance between dipoles	τ_1, deg	τ_2, deg	λ, deg
DTE	2.9	4.6			+132	−93	71
DCM			4.6	10.2	+114	−88	71
VING	2.9	3.9			+145	−145	35
DDD-olefin			4.5	10.2	+143	−77	85
POP-DDT	2.9	5.2	4.5	9.8	+130	−77	87
p,p'-DDT	2.9	4.9	4.5	10.3	+134	−95	65
o,p'-DDT	2.9	4.8	4.5	7.1	+133	−85	80
	2.9	4.9	4.5	6.7	+142	−76	89
(−)-*o,p'*-DDT	2.9	4.8	4.5	6.9	+131	−83	78
Methoxychlor	2.9	5.0	5.0	9.4	+137	−88	77
Br-DDT	3.1	5.4	4.5	9.9	+131	−81	83
	3.1	5.5	4.6	9.7	+127	−87	79
Cl-DDT	2.9	5.1	4.5	9.7	+149	−74	90
Rogers	2.6	4.8	5.6	9.9	+124	−121	50
GH44	2.5	4.3	6.4	10.1	+132	−119	52
DCC	2.8	4.8	4.5	10.0	+98	−95	69
	2.9	4.6	4.5	10.1	+99	−97	66
p,p'-DDD	2.9	4.5	4.5	9.6	+105	−93	75
o,p'-DDD	2.9	4.8	4.5	7.1	+114	−86	74
Perthane	2.9	4.8	5.0		+106	−97	75
DFDD	2.9	4.1	4.0	9.3	+119	−104	70
CDE			4.5	10.1	+150	−70	94
DDE			4.5	9.9	+127	−53	98
			4.5	10.6	+127	−53	84
DDA			4.5	10.0	+131	−85	74
DBP			4.6				
DCPC	2.9	4.0			+104	−99	71
DBPC	3.1	4.0			+105	−98	71
Dicofol	2.9	5.5	4.5	9.8	+126	−59	86
	2.9	5.1	4.5	9.9	+142	−93	77
Parinol			4.6	10.0	+139	−93	77

Table V. Toxicity of Some DDT Analogues

	Metcalf and Fukuto (1968), *Musca domestica*, topical LD_{50}, μg/female			Metcalf et al. (1971) and Coats et al. (1977), *Musca domestica*, topical LD_{50}, (μg/g)				LC_{50}					
								Phormia regina		*Culex fatigans*		*Anopheles albimanus*	
	S_{NAIDM}	R_{SP}	R_{SC}	S_{NAIDM} alone	with p.b.[a]	R_{sp} alone	with p.b.	alone	with p.b.	larvae, ppm	adults, μg/cm²	larvae, ppm	adults, μg/cm²
DTE	>10	>10	>10	2900	575	>2500	>2500	>1250	>1250	1.1	>16	1.9	>16
POP-DDT	0.22	0.72	0.43							0.054	>16	0.019	6.2
p,p'-DDT	0.04	>100	>100	14.0	5.5	170	40	11.5	8.25	0.07	6.9	0.015	0.23
o,p'-DDT	3.66	>10	>10										
Methoxychlor	0.18	>10	>10	45	3.5	48	4.6	10	4.6	0.067	>16	0.18	13
Br-DDT	0.078	>10	>10							0.074	>16	0.018	>16
Rogers				480	36	>500	120	122.5	95	0.48	>160	>1	27
GH44				21.5	3.5	38	12.5	14.5	6.7	0.08	14.3	0.028	9.5
DCC	0.24	2.1	0.53							0.042	320	0.014	70
p,p'-DDT	0.39	>10	>10	72.5	35	>500	>500	15.25	9	0.038	>16	0.01	1.4
Dicofol	>10	>10	>10							5.8	>16	>1	>16

[a] p.b. = piperonyl butoxide.

Questions that must be raised, considering the limited amount of comparable toxicity data available in the general literature (Table V) are as follows: (1) Is the apex width so critical to make Br-DDT less effective than *p,p'*-DDT? The difference is small. Is this confirmed by the difference between GH44 and Rogers? (2) Overall height is smaller than predicted but does not vary very much. (3) Width limits do not seem to mean much. They generally break the group into those with *p*-halogen substituents or those with *p*-alkyl/alkoxy substituents. (4) Once again, the distance between dipoles does not vary very much. Perhaps an insecticidal DDT analogue must obey all these conditions. Although DTE is similar in stereochemistry to *p,p'*-DDT, it has limited width limits and distance between *p,p'*-chlorine atoms. It is also ineffective as an insecticide.

Dicofol, Cl-DDT, and Parinol are not insecticides in their own right although their geometry is comparable to that of the other analogues. Substitution for H(13) at C(13) by a larger atom or group of atoms significantly alters τ_1 and τ_2, and perhaps these should also be included in the molecular specification.

Figure 4 plots τ_1/τ_2 for all the published crystal structures. These may be classified into the following groups: (a) $(Ph)_2CHCX_3$, 135°, −90°; (b) $(Ph)_2CHCHX_2$, 110°, −95°; (c) $(Ph)_2CHC(CH_3)_3$, 128°, −120°; (d) nonactive compounds, outside this general area. Parinol and DDA are within the area but may be rejected because they do not meet the apex width and C(13) nonsubstitution specifications.

There is an interesting group of compounds having $|\tau_1| = |\tau_2|$. These mirror-related compounds are DCC, Rogers, and VING.

There seems to be a relationship between τ_1 and τ_2 for *p,p'*-DDT (+134.3°, −94.7°), *o,p'*-DDT (+133.4°, −85.7°), *p,p'*-DDD (105.3°, −92.8°), and *o,p'*-DDD (113.5°, −86.1°); i.e., ortho substitution changes τ_2, and changing the terminal $-CCl_3$ group to $-CHCl_2$ changes τ_1.

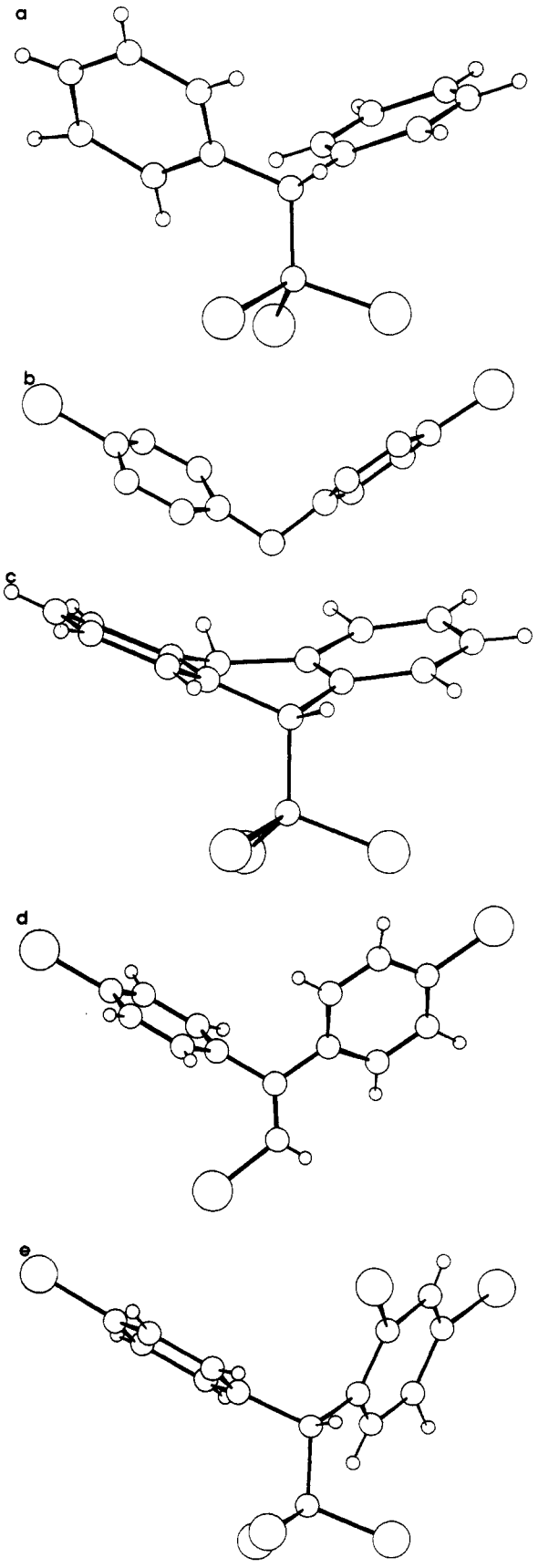

Figure 2. (a) General view of 1,1,1-trichloro-2,2-bis(phenyl)-ethane, 1. Unless otherwise indicated, atoms are carbons with hydrogens taking the number of the parent carbon. (b) General view of bis(4-chlorophenyl)methane, 2. (c) General view of 9-(trichloromethyl)-9,10-dihydroanthracene, 3. (d) General view of 1-chloro-2,2-bis(4-chlorophenyl)ethene, 4. (e) General view of 1,1,1-trichloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane, 5.

Holan's model has been useful in synthesizing cyclopropane and oxetane-type DDT analogues. However, with a more accurate description of the molecular dimensions of a series of active and inactive insecticides, it is possible to modify this model. This current work has firmly established that most DDT analogues are asymmetric, i.e. $|\tau_1| \neq |\tau_2|$. In studying both Holan's work and this work, two distinct groups of molecules are apparent. They are the *p*-halogen-substituted molecules with short width and the alkyl/alkoxy analogues with a longer one.

Terms such as "butterfly" and "face-to-face" conformations have been used to describe DDT analogues. A strict nomenclature was introduced for bridged biphenyls (van der Heijen et al., 1975) with "planar", "butterfly", "twisted", and "skewed" structures being clearly defined. A more quantitative description (DeLacy and Kennard, 1972a) uses the angles between the three planes defined by the two phenyl groups and the plane through the three central atoms [C(1), C(13), and C(7)]. The λ referred to in Table V is the acute dihedral angle between the two benzene rings. However, this system is limited since two different conformations may have the same set of three angles between the pairs of planes. Torsion angles were used to overcome this ambiguity.

In the cases studied so far, torsion angles τ_1 and τ_2 are interdependent (Figure 4) with the rotations of the two phenyl rings coupled. This means that pairs of torsion angles lie on an ellipse with its origin at ($\tau_1 = +120°$, $\tau_2 = -90°$), with C(13) effectively acting as an asymmetric carbon atom. This effect might be due to a repulsion between the π-electron clouds from the two phenyl rings. Of all the analogues so far studied there is one example, Dicofol, which deviates significantly, and this is considered to be due to intermolecular hydrogen bonding for one of the two molecules in the asymmetric unit of the cell. The other Dicofol molecule, which does not participate in hydrogen bonding, obeys the τ_1/τ_2 relationship.

The τ_1/τ_2 torsion angle relationship may also be interpreted by assuming that all DDT analogues, except those with ortho ring substituents, have phenyl groups that freely rotate about C(13). It would be feasible that in solution the molecule could have any conformations defined by the ellipse. The τ_1/τ_2 relationship found from crystal structure determinations would represent the conformation at the time of crystallization. Four ideal conformations and a possible geometric mechanism are illustrated in Figure 5. A similar interpretation for ribose, deoxyribose, and arabinose compounds has been proposed (Murray-Rust and Motherwell, 1978).

Comments on Mode of Action Hypotheses. It is now believed that membranes are made up of a phospholipid bilayer with hydrophobic proteins inserted into the fluid lipid phase. The long hydrophobic tails of the phospholipids are directed from both sides toward the middle of the membrane. The hydrophilic head groups are facing the exterior water phase. The diameter of each lipid alkyl chain is about 4 Å and it is about 15–20 Å long, making the hydrophobic part of the membrane 30–40 Å thick and the whole membrane, including the hydrophilic head group, about 50 Å thick. Inserted into the phospholipid bilayer are the hydrophobic membrane proteins. The membrane protein would be amphiphilic with hydrophobic amino acids within the lipid bilayer and hydrophilic side chains facing the water.

There have been recent studies by electron microscopy on the three-dimensional structure of membrane proteins. The dimensions of these proteins range from 25 × 35 × 45 Å (M_r 28 000) for bacteriorhodospin to 60 × 80 × 150

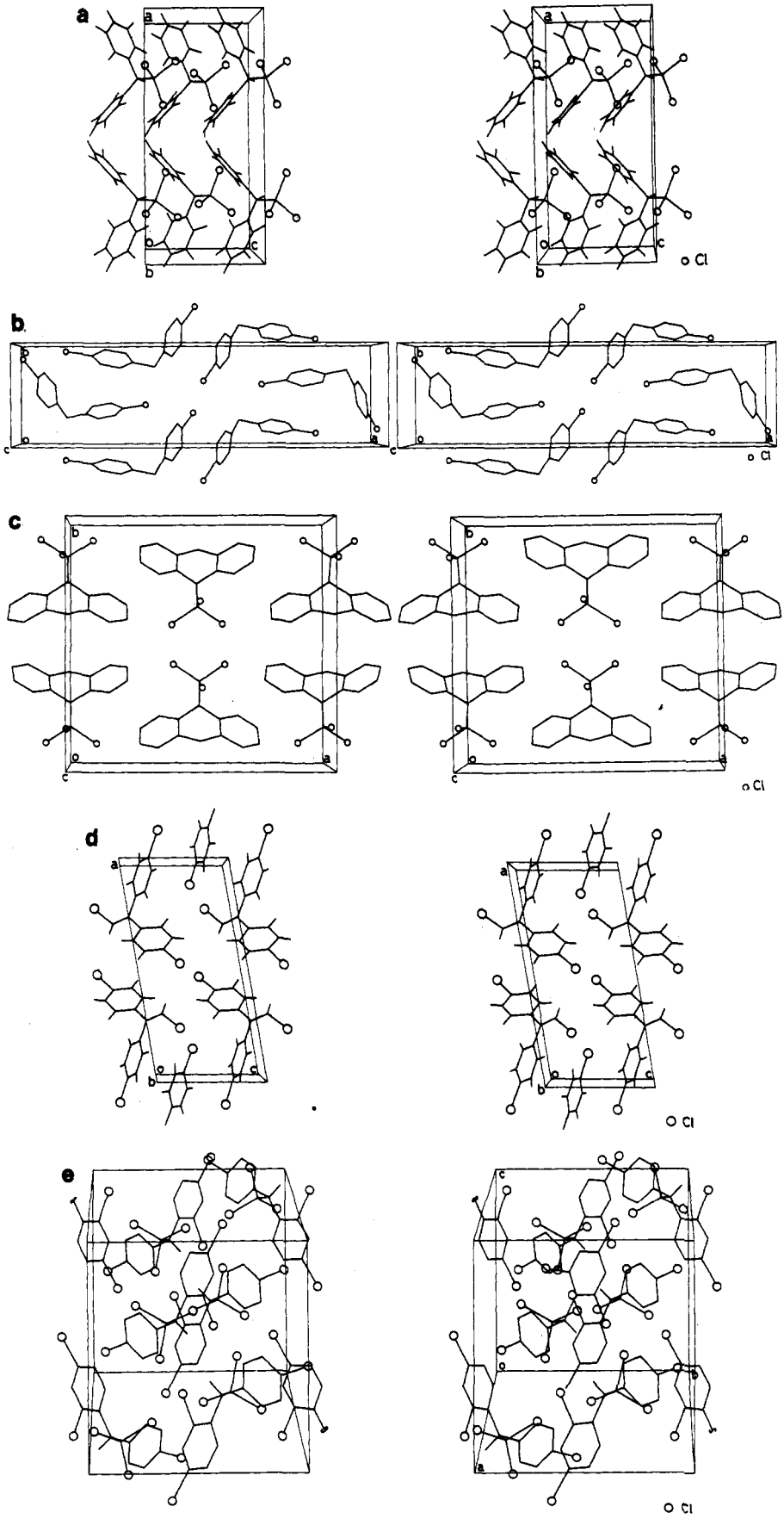

Figure 3. Stereoviews. (a) 1,1,1-Trichloro-2,2-bis(phenyl)ethane, **1**, viewed perpendicular to *ac*. (b) Bis(4-chlorophenyl)methane, **2**, viewed perpendicular to *ab*. (c) 9-(trichloromethyl)-9,10-dihydranthracene, **3**, viewed perpendicular to *ab*. (d) 1-Chloro-2,2-bis-(4-chlorophenyl)ethene, **4**, viewed perpendicular to *ac*. (e) 1,1,1-Trichloro-2-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane, **5**, viewed perpendicular to *bc*.

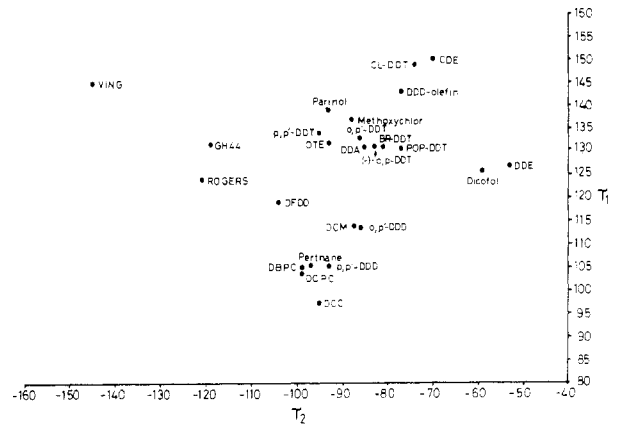

Figure 4. Relationship between τ_1 (torsion angle 1) and τ_2 (torsion angle 2) for the DDT analogues.

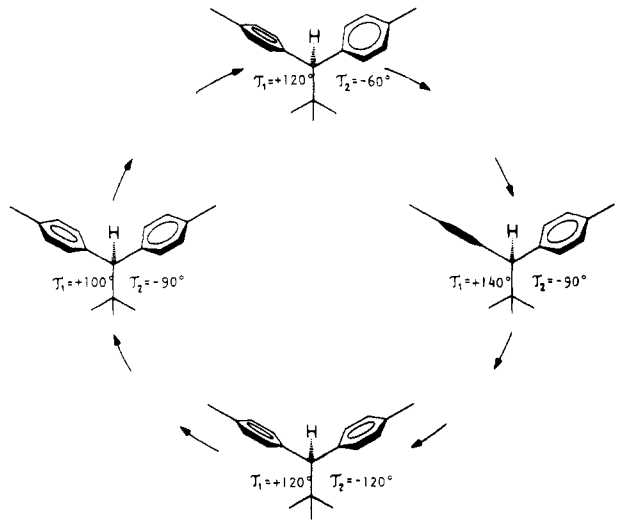

Figure 5. Coupling of the two main torsion angles (τ_1 and τ_2), involving phenyl rings, in DDT analogues.

Å (M_r 550 000) for cytochrome reductase (Unwin and Henderson, 1975; Leonard et al., 1981). The phospholipids are in van der Waals' contact with the amino acid side chains of the proteins. In previous theories the existence of any pore or any channel between the protein and the lipid has not been found experimentally. On the contrary, the phospholipids are believed to be at an unspecified but close van der Waals' distance (3.5 Å) to the protein. Any channel for ions would have to be within the membrane protein molecule, rather than within the lipid phase, or in the hydrophobic interface between lipid and protein. The DDT molecule being highly hydrophobic will interact with hydrophobic regions in the membrane.

One possibility is that DDT interferes with the packing of the lipid molecules, disrupting the membrane and causing a leak. This would be an unspecified interaction. Another possibility would be that DDT binds to a specific place on the surface of the protein by altering the conformation of the protein, which would open up to the Na^+ pump, causing it to leak. Such an interaction would be expected to be more specific than the first possibility.

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Registry No. 1, 2971-22-4; 2, 101-76-8; 3, 89873-34-7; 4, 1022-22-6; 5, 2798-55-2; DDT, 50-29-3.

Supplementary Material Available: Lists of atomic coordinates and anisotropic thermal parameters (9 pages). Ordering information is given on any current masthead page.

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

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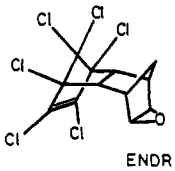
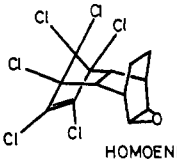
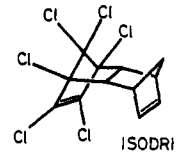
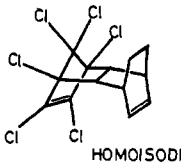
The crystal structures of three "cyclodiene" analogues, homoendrin (1), homoisodrin (2), and homoisodrin acetate (3), have been determined by X-ray diffraction. The structures found for 1 and 2 confirm those previously proposed but homoisodrin acetate (3) is different with respect to the point of attachment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

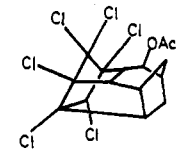
The structural aspects of "cyclodiene" insecticides have been reviewed by Riemschneider (1963), Soloway (1965), Brooks (1966), and Matsumura (1975). So far, a number of crystal structures of compounds containing the hexachloronorbornene nucleus have been determined. They are endrin, aldrin (DeLacy and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

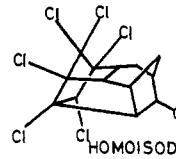

ENDRIN


HOMOENDRIN(1)


ISODRIN


HOMOISODRIN (2)


(4)


HOMOISODRIN ACETATE (3)

(Gress and Jacobson, 1973), isodrin (Kennard et al., 1979), heptachlor (Shields and Kennard, 1973), heptachlor epoxide (Hovmöller et al., 1978), 1-hydroxychlordene (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 ^{1}H 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

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