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Novel Phosphate Anthelmintics. 1. Alkyl 2,2-Dichlorovinyl Methyl Phosphates and Related Alkoxyalkyl and Cycloalkyl Analogs of Dichlorvos

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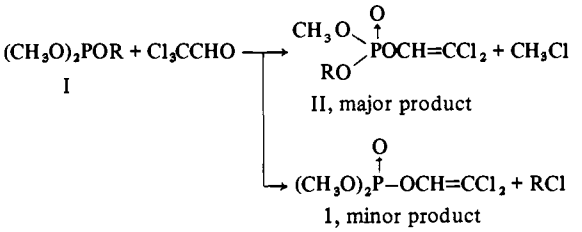
A series of new alkyl 2,2-dichlorovinyl methyl phosphates and related alkoxyalkyl and cycloalkyl analogs of dichlorvos, 2,2-dichlorovinyl dimethyl phosphate (**1**), having a high order of anthelmintic activity, has been synthesized. Novel vinyl pyrophosphates, obtained by treatment of vinyl phosphoric acids with $SOCl_2$ or diphenylcarbodiimide, facilitated the preparation of the asymmetric esters. The activity of these compounds has been assessed in rats and mice against the roundworm *Nippostrongylus brazilensis*, the tapeworm *Hymenolepis nana*, and the pinworm *Syphacia obvelata*.

The broad anthelmintic and insecticidal properties of dichlorvos,[1,2] 2,2-dichlorovinyl dimethyl phosphate (**1**), prompted investigation of possible ways of producing related compounds having improved therapeutic values either by increasing their toxicity toward target organisms, reducing their mammalian toxicity or both. Spontaneous reactivation of phosphorylated cholinesterase has been shown to depend on the structure of the phosphoryl residue and has led to the concept that the rate constant for reactivation decreases with increasing size of the alkoxyl radicals.[3] This concept is only partly correct considering the work of Berry and Davis[4] who have shown that the spontaneous reactivation of alkyl methylphosphonyl acetylcholinesterases shows the expected decrease when the alkyl group changes from Me to Pr, but an increase in spontaneous reactivation above that of the Me homolog, as the alkyl group increases from butyl through hexyl. Since increase in the rate of spontaneous reactivation should decrease toxicity, ways are then suggested for reduction of mammalian toxicity in other phosphates. The same structural modifications that may lead to reduction of mammalian toxicity may also serve to increase toxicity toward target organisms. Enzyme-substrate affinity studies of Hofstee,[5] Lewis,[6] and Bracha and O'Brien[7,8] have shown that the affinity of various esterases toward certain substrates increases to a maximum with increasing length of *n*-alkyl chains in *n*-fatty acid esters, *n*-acyl methylcarbamates, alkyl phosphates, and *S*-alkyl phosphorothiolates. Indeed, the compilation of Dixon and Webb[9] indicates that this is a common property of various substrates toward a variety of bifunctional esterases. In these examples the rate of reaction depends greatly on the presence and length of *n*-hydrocarbon chains in the substrates and often shows a definite maximum for a particular chain length for a particular esterase. Thus, replacement of one of the methyl groups in **1** by larger alkyl groups or other radicals was considered a likely route toward attainment of the desired goals. Several asymmetric esters of vinyl phosphates have been described,[10-12] but their pharmacological utility remained unappreciated until recently, perhaps due to the complexity of the products arising from conventional synthesis routes that were not fully appreciated when the early preparations were evaluated biologically. This paper describes methods for the preparation of asymmetric ester (II) analogs of dichlorvos,[13] their anthelmintic properties,[14] and their structure-activity correlations, and a new class of vinyl phosphates, vinyl pyrophosphates,[15] that greatly facilitated the synthesis work. After completion of this project four patents[16-19] were issued claiming synthesis processes (Schemes III and IV) and/or insecticidal and fungicidal properties for some of the compounds described in this paper. These compounds are referred to in the tables. A fifth patent claims compound **14** as an anthelmintic.[20]

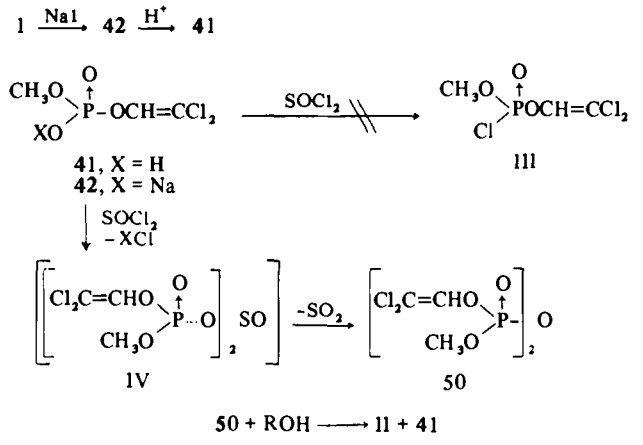
Chemistry. The synthesis of the asymmetric esters II was carried out initially by the reaction discovered by Whetstone[1] and Perkow,[21] Scheme I.

Scheme I



Alkyl dimethyl phosphites (I)[22] were allowed to react with chloral in a usual manner.[23] The product contained from 5 to 15% of **1** and required purification by distillation and column chromatography. Because products obtained by Scheme I required lengthy purification to remove related phosphates, an alternate procedure *via* III was sought. Attempts to prepare III by treatment of **41** or **42**[24] with a 10 *M* excess of thionyl chloride at reflux gave instead **50**. This pyrophosphate may arise through intermediacy of a mixed anhydride IV, as reported for similar reactions of

Scheme II

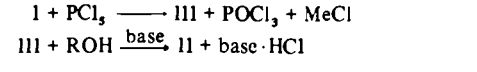


orthophosphate esters with phosgene and oxalyl chloride.[25] Alcoholysis of **50** proceeded spontaneously to give II free of dichlorvos, Scheme II.

The purity and yield of products obtained by Scheme II depended on the stability of the asymmetric esters II under the reaction conditions. Primary alcohols gave undistilled II of 87-95% purity in 80-95% yield. The lower purity, 85-90%, and yield, 70-90%, of undistilled products obtained from secondary alcohols are apparently due to acid-catalyzed decomposition of II by **41**. Incomplete removal of **41** before distillation of **4** caused gradual and complete decomposition of this ester under distilling conditions to give pure dichloroacetaldehyde† and an unidentified gas which may be isopropylene and methane as reported for similar cleavage of other vinyl phosphates.[27]

The preparation of II by alcoholysis of the phosphochloridate III has been recently disclosed in the patent literature, Scheme III. It is reported that III forms readily

Scheme III



and gives II of excellent purity and yield. In our hands III was obtained in 40% yield after repeated distillation to remove by-products **1** and V.

An alternate process in which **1** is converted to the dichloridate V by treatment with thionyl chloride in the presence of DMF, Scheme IV, has been described recently[18] in the patent literature. Scheme IV was used for the preparation of compounds **9**, **35**, **39**, **48**, and **49** of types II or VII.

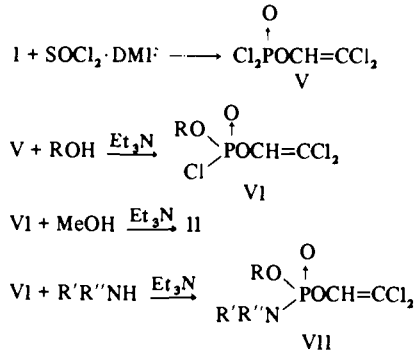
Distilled products II or VII prepared by Scheme IV contained from 2 to 5% of the dialkyl dichlorovinyl phosphates formed by the reaction of V with 2 moles of ROH in the second reaction of Scheme IV.

The preparation of other compounds following published methods is given in the Experimental Section.

Biological Evaluation. The compounds were tested for anthelmintic activity against experimental infections of the intestinal roundworm *Nippostrongylus braziliensis* in albino (Sprague-Dawley) rats and the tapeworm *Hymenolepis nana* and the pinworm *Syphacia obvelata* in albino (Swiss Webster) mice.[28]

All the asymmetric esters were liquids miscible with corn oil vehicle. The salts **42** and **45** were suspended in 1% aqueous methylcellulose. Both solutions and suspensions were administered intragastrically to the test animals *via* a blunt-tipped needle. The corn oil solutions contained 50 mg/ml of the test compound so that a 0.25-ml dose delivered a 500-mg/kg dose to a 25-g mouse. Groups of five mice and two rats were treated initially at 500 mg/kg orally. Efficacy was determined 24 hr after therapy by direct count of helminths in the excised intestine.[28] The minimum effective dose (MED) (defined as the dose that gave complete clearance of the parasite species in three of five mice and a 75% clearance in the rat as compared to infected nontreated controls) of active or toxic compounds was determined by administration of doses decreasing in 0.3 log intervals from 500 mg/kg. Relative activities of the compounds against *H. nana*, *S. obvelata*, and *N. braziliensis* are expressed in the tables in terms of maximum tolerated dose (MTD) or 500 mg/kg and MED. Nonmedicated control animals were used in each assay.

Scheme IV



The acetylcholinesterase inhibitory activity of selected compounds was determined by continuous electrometric titration method[29] using fly-head cholinesterase as the enzyme source.

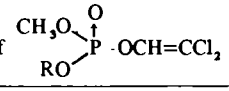
Results

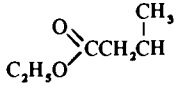
For the purpose of studying the structure-activity relationships of the compounds prepared, structurally related compounds have been grouped into Tables I-III. Miscellaneous compounds and some intermediates included in the anthelmintic evaluation are found in Table IV. The anthelmintic properties for each parasitism (*i.e.*, pinworm, tapeworm, and roundworm) and the *in vitro* cholinesterase activity determined for some of the most active compounds are included in the tables.

Dichlorvos (**1**) is relatively soluble in water (1.6% at 23°) and readily miscible with vegetable oils. Replacing a methyl group of **1** by a longer alkyl group resulted in compounds having greater hydrophobic character (alkyl compounds in Table I). R_m values,[34] shown in Table V, for some of the alkyl homologs of **1** show the decreasing water partitioning of these compounds with each methylene group introduced into the alkyl chain. Dichlorvos **1** has a higher water-lipid partition coefficient than would be found by extrapolation from its higher homologs. This is a common occurrence for the lowest member of a homologous series.

The increase in hydrophobicity of the *n*-alkyl homologs of **1** is accompanied by an improvement of their therapeutic index relative to the mouse pinworm and tapeworm infections, as shown in Figure 1. The therapeutic indexes become maximum with the *n*-heptyl homolog **13** for the pinworm and with the *n*-decyl homolog **18** for the tapeworm. The I_{50} values for *in vitro* inhibition of fly-head cholinesterase show a similar behavior, maximum inhibition occurring with the

†The acid-catalyzed decomposition of II or **1** offers a more convenient laboratory route to the preparation of pure Cl_2CHCHO than the usual chlorination method.[26]

Table I. Physical and Anthelmintic Properties of 

Compd	R	Yield, %	Purity,[a] %	Method of prepn[b]	Bp (mm),[c] °C	$n^{25.5}$D	Formula	Anal.	Cholinesterase inhibition,[d] I_{50}	MTD,[e] mg/kg	MED[f] Mice Hn	MED[f] Mice So	MED[f] Rats Nb
1	Me	90	99	A	59 (0.1)	1.4518	$C_4H_7Cl_2O_4P$	Cl, P	6.9×10^{-9}	62, 162[g]	>62	62	>62
2	Et		99	A	72–83 (0.06)		$C_5H_9Cl_2O_4P$	Cl, P	3.99×10^{-9}	16, 34[g]	>16	>16	>16
3	*n*-Pr	63	97	B	78–80 (0.1)	1.4497	$C_6H_{11}Cl_2O_4P$	Cl, P	6.20×10^{-10}	125	16	5	62
4	*i*-Pr[p]		90	A	79 (0.04)	1.4463	$C_6H_{11}Cl_2O_4P$	Cl, P	3.80×10^{-9}	62, 74[g]	31	31	>62
5	Bu[q]	75	98	B	70 (0.02)	1.4509	$C_7H_{13}Cl_2O_4P$	Cl,[h] P	3.21×10^{-9}	16, 28[g]	16	1	8
6	*i*-Bu	57	95	B	95–97 (0.02)	1.4481	$C_7H_{13}Cl_2O_4P$	Cl,[i] P	8.84×10^{-10}	125	8	1	31
7	*sec*-Bu[p]	54	95	B	85 (0.0001)	1.4497	$C_7H_{13}Cl_2O_4P$	Cl, P	1.0×10^{-9}	31	8	1	>31
8	Am	72	92	B	100 (0.0001)	1.4518	$C_8H_{15}Cl_2O_4P$	Cl, P	5.32×10^{-10}	62	31	1	>62
9	$(CH_3)_2CH(CH_2)_2$		95	B	75 (0.0001)	1.4506	$C_8H_{15}Cl_2O_4P$	Cl, P		62	16	2	>62
10	$(CH_3)_3CCH_2$	50	94	B	87–90 (0.0001)		$C_8H_{15}Cl_2O_4P$	Cl, P		16	8	12	>16
11	$CH_3(CH_2)_3$[q]	75	95	B	Undistilled	1.4532	$C_9H_{17}Cl_2O_4P$	Cl, P		250	31	4	62
12	C_6H_5[q,r]	76	95	A	90 (0.0005)	1.5132	$C_8H_9Cl_2O_4P$	Cl, P		500, 733[g]	>500	>500	>500
13	$CH_3(CH_2)_6$	66	95	B	125 (0.0001)	1.4515	$C_{10}H_{19}Cl_2O_4P$	Cl, P	2.50×10^{-10}	500, 508[g]	125	2	250
14	c-$C_6H_{10}CH_3$	71	94	B	100 (0.0001)	1.4747	$C_{10}H_{17}Cl_2O_4P$	Cl, P	6.98×10^{-10}	31	16	2	>31
15	$CH_3(CH_2)_7$[q]	82	97	B	135 (0.001)	1.4536	$C_{11}H_{21}Cl_2O_4P$	Cl,[j] P	5.23×10^{-10}	500	62	32	250
16	$CH_3(CH_2)_5CHCH_3$	21	95	B	135 (0.0001)	1.4509	$C_{11}H_{21}Cl_2O_4P$	Cl, P		500	125	32	>500
17	$CH_3(CH_2)_8$	80	96	B	150 (0.001)	1.4571	$C_{12}H_{23}Cl_2O_4P$	Cl, P	6.41×10^{-10}	500	62	16	250
18	$CH_3(CH_2)_9$	92	95	B	160 (0.0001)	1.4555	$C_{13}H_{25}Cl_2O_4P$	Cl, P		500	16	>500	>500
19	$CH_3(CH_2)_{10}$	74	97	B	125 (0.0001)	1.4569^{25}	$C_{14}H_{27}Cl_2O_4P$	Cl. P	3.75×10^{-9}	500	32	>500	250
20	$CH_3(CH_2)_{11}$[q]	89	95	B	175 (0.001)	1.4590^{25}	$C_{15}H_{29}Cl_2O_4P$	Cl, P	4.65×10^{-8}	500	125	>500	>500
21	$CH_3(CH_2)_{15}$	43	95	B	175 (0.0001)	1.4581	$C_{19}H_{37}Cl_2O_4P$	Cl, P	2.57×10^{-7}	500	>500	>500	>500
						Alkoxyalkyls							
22	$CH_3OC_2H_4$[q]	56	95	B	106–108 (0.05)	1.4559	$C_6H_{11}Cl_2O_5P$	Cl,[k] P	7.66×10^{-10}	4	>4	4	>4
23	$CH_3OCHC_2H_6$ (CH$_3$)	74	93	B	120 (0.0005)	1.4535^{25}	$C_8H_{15}Cl_2O_5P$	Cl,[l] P		16	>16	8	>16
24	$CH_3OC_2H_4OC_2H_4$	74	95	B	Undistilled	1.4588	$C_5H_{13}Cl_2O_6P$	Cl,[m] P	1.54×10^{-9}	8	>8	>8	>8
25	$C_2H_5(OC_2H_4)_2$	26	98	B	Undistilled	1.4569^{25}	$C_9H_{17}Cl_2O_6P$	Cl, P		16	8	2	>16
26		20	95	B	130 (0.0001)		$C_9H_{15}Cl_2O_6P$	Cl,[n] P		31	>31	8	>31
						Chloroalkyls							
27	$Cl(CH_2)_2$	26	95	A	116 (0.2)	1.4710	$C_5H_6Cl_5O_4P$	Cl, P		62	2	2	31
28	$Cl(CH_2)_3$	43	92	B	110 (0.0001)	1.4651	$C_6H_{10}Cl_3O_4P$	Cl, P[o]		31, 31[g]	4	4	16
29	$Cl(CH_2)_4$	46	95	B	45 (0.0001)	1.4690^{25}	$C_7H_{12}Cl_3O_4P$	Cl, P		250	16	2	>250

[a]Characterization and purity criteria were based on nmr,[30,31] ir,[32] and tlc.[33] [b]A = Reaction of corresponding phosphite with chloral. B = Reaction of **50** or **52** with corresponding alcohol. C = Reaction of V with corresponding alcohol and/or amine and Et_3N. D = Acidolysis of corresponding sodium salt. E = Dealkylation of corresponding phosphate with NaI. F = Reaction of **41** with $SOCl_2$. G = Bromination of corresponding dichlorovinyl compound. H = Reaction of **44** with diphenylcarbodiimide. [c]Most of these esters were distilled in a falling film molecular still. [d]Using fly-head cholinesterase. [e]Max tolerated dose oral to mice. Max dose tested was 500 mg/kg. [f]Dose that gives complete clearance in 3 of 5 mice and a 75% clearance in the rat as compared to infected nontreated controls. Hn = *Hymenolepis nana*. So = *Syphacia obvelata*. Nb = *Nippostrongylus brazilensis*. [g]LD_{50} acute oral in male mice. [h]*Anal.* Calcd: Cl, 27.0. Found: Cl, 26.5. [i]*Anal.* Calcd: Cl, 27.0. Found: Cl, 26.3. [j]*Anal.* Calcd: Cl, 22.3. Found: Cl, 21.7. [k]*Anal.* Calcd: Cl, 26.8. Found: Cl, 26.3. [l]*Anal.* Calcd: Cl, 24.2. Found: Cl, 23.7. [m]*Anal.* Calcd: Cl, 23.0. Found: Cl, 22.4. [n]*Anal.* Calcd: Cl, 22.1. Found: Cl, 21.5. [o]*Anal.* Calcd: P, 10.9. Found: P, 10.2. [p]See ref 16. [q]See ref 17. [r]See ref 18 and 20.

Table II. Physical and Anthelmintic Properties of $(RO)_2POCH{=}CCl_2$

Compd	R	Yield, %	Purity,[a] %	Method of prepn[b]	Bp (mm),[c] °C	n^tD	Formula	Anal.	MTD,[d] mg/kg	MED, mg/kg[e] Mice Hn	MED, mg/kg[e] Mice So	MED, mg/kg[e] Rats Nb
30	Et	90	98	A	67–68 (0.1)	1.4457[25]	$C_6H_{11}Cl_2O_4P$	Cl, P	31	16	2	>31
31	*n*-Pr	76	95	A	95 (0.0001)		$C_8H_{15}Cl_2O_4P$	Cl,[f] P	125	4	1	>125
32	*n*-Bu	95	99	A	128 (1.0)	1.4527[20]	$C_{10}H_{19}Cl_2O_4P$	Cl, P	62	4	2	>62
33	Am	76	99	C	140 (0.005)		$C_{12}H_{23}Cl_2O_4P$	Cl, P	62	62	2	>62
34	n-C_6H_{10}	67	98	A	115 (0.001)	1.4525[25]	$C_{14}H_{27}Cl_2O_4P$	Cl, P	250	>250	>250	>250
35	n-C_7H_{15}	86	99	C	140 (0.005)		$C_{16}H_{31}Cl_2O_4P$	Cl, P	125	>125	>125	>125
36	n-$C_{10}H_{22}$	79	99	A	160 (0.001)	1.4610[25]	$C_{22}H_{43}Cl_2O_4P$	Cl, P	250	>250	>250	>250
37	$ClCH_2CH_2$	77	99	A	115 (0.0001)		$C_6H_9Cl_4O_4P$	Cl, P	125	31	8	>125

[a]As defined in Table I. [b]As defined in Table I. [c]As defined in Table I. [d]Same as *e* in Table I. [e]Same as *f* in Table I. [f]*Anal.* Calcd: Cl, 25.6. Found: Cl, 26.2.

Table III. Physical and Anthelmintic Properties of $(RO)(R_1)P(O){-}OCH{=}CCl_2$

Compd	R	R_1	Yield, %	Purity,[a] %	Method of prepn[b]	Bp (mm)[c] or mp, °C	Formula	Anal.	MTD,[d] mg/kg	MED, mg/kg[e] Mice Hn	MED, mg/kg[e] Mice So	MED, mg/kg[e] Rats Nb
38	Me	Me	84	95	A	85–97 (3.0)	$C_4H_7Cl_2O_3P$	Cl, P	4	>4	>4	>4
39	Me	c-C_3H_5NH	32	95	C	56–58	$C_6H_{10}Cl_2NO_3P$	Cl, N, P[f]	31	>31	>31	>31
40	Me	$(Me)_2N$	76	98	A	80 (0.002)	$C_5H_{10}Cl_2NO_3P$	Cl, N, P	62	>62	>62	>62
41	Me	HO	90	97	D	Undistilled	$C_3H_5Cl_2O_4P$	Cl, P, neut equiv	500	>500	>500	>500
42	Me	NaO	90	99	E	200 dec	$C_3H_4Cl_2O_4P{\cdot}Na$	Cl, P	500	>500	>500	>500
43	Me	$EtS(CH_2)_2$	10	98	B	135 (0.0002)	$C_7H_{13}Cl_2O_4PS$	Cl, P	62	62	62	>62
44	Et	HO	71	97	D	Undistilled	$C_4H_7Cl_2O_4P$	Cl,[g] P	500	>500	>500	>500
45	Et	NaO	90	99	E	185 dec	$C_4H_6Cl_2O_4P{\cdot}Na$	Cl, P	500	>500	>500	>500
46	Et	*n*-BuO	47	97	B	100–102 (0.01)	$C_8H_{15}Cl_2O_4P$	Cl, P	31	31	1	>31
47	Et	$MeO(C_2H_4O)_2$	48	99	B	125 (0.0004)	$C_9H_{17}Cl_2O_6P$	Cl, P	16	4	4	>16
48	*n*-Pr	n-$C_7H_{15}O$	68	98	C	140 (0.005)	$C_{12}H_{23}Cl_2O_4P$	Cl, P	125	31	4	62
49	*n*-Bu	n-$C_7H_{15}O$	65	97	C	140 (0.005)	$C_{13}H_{25}Cl_2O_4P$	Cl, P	31	>31	>31	16

[a]As defined in Table I. [b]As defined in Table I. [c]As defined in Table I. [d]Same as *e* in Table I. [e]Same as *f* in Table I. [f]*Anal.* Calcd: P, 12.6. Found: P, 12.0. [g]*Anal.* Calcd: Cl, 32.1. Found: Cl, 31.6.

Table IV. Physical and Anthelmintic Properties of Miscellaneous Phosphates

Compd	Structure	Yield, %	Purity,[a] %	Method of prepn[b]	Bp (mm)[c] or mp, °C	Formula	Anal.	MTD,[d] mg/kg	MED, mg/kg[e] Mice Hn	Mice So	Rats Nb
50	$[ClC{=}CHO{-}\overset{\overset{O}{\uparrow}}{P}{-}MeO]_2O$	90	98	F	100 (0.0001)	$C_6H_6Cl_4O_7P_2$	Cl,[f] P	500	>500	>500	>500
51	$[Cl_2BrCCBrHO{-}\overset{\overset{O}{\uparrow}}{P}{-}MeO]_2O$	98	95	G	Undistilled	$C_6H_6Br_4Cl_4O_7P_2$	Cl,[g] Br, P	500	>500	500	>500
52	$[Cl_2C{=}CHO{-}\overset{\overset{O}{\uparrow}}{P}{-}EtO]_2O$	99	90	H	Undistilled	$C_8H_{12}Cl_4O_7P_2$	[h]	500	250	>500	>500
53		58	99	A	21-25	$C_3H_7Cl_2O_4P$	Cl, P	500	>500	>500	>500

[a] As defined in Table I. [b] As defined in Table I. [c] As defined in Table I. [d] Same as *e* in Table I. [e] Same as *f* in Table I. [f] *Anal.* Calcd: Cl, 35.8. Found: Cl, 35.1. [g] *Anal.* Calcd: Cl, 19.8. Found: Cl, 20.9. [h] Characterized by spectral analysis.

Table V. R_m' Values of Some Asymmetric Analogs of Dichlorvos (1)

Compd	PEG 600[a] 30% IPA–isooctane
1	0.342
3	0.164
5	0.128
11	0.090
13	0.069

[a] Silica gel (Grace F254) plates coated with polyethylene glycol 600 (PEG 600) dissolved in CH_2Cl_2. Development was done with 30% IPA in isooctane satd with PEG 600.

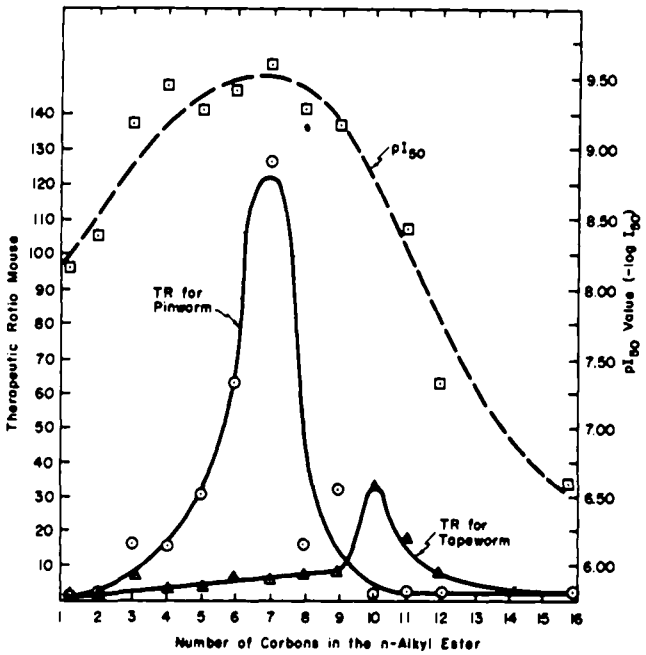


Figure 1. Comparison of therapeutic ratio and the cholinesterase inhibition (pI_{50}) of dichlorvos analogs.

n-heptyl homolog **13**. The difference in carbon chain length required for maximum effect in these organisms may reflect differences in the distance between the esteratic site and the site receiving the hydrophobic group of their cholinesterases, as postulated by Hofstee.[5]

The branched-chain alkyl, alicyclic, and alkoxyalkyl analogs of **1** have lower therapeutic indexes than the *n*-alkyl homologs as a result of increased mouse and rat toxicities. These results were predictable for the branched alkyl and cycloalkyl analogs based on the work of Berry and Davis[4] who have shown that spontaneous reactivation of alkyl methylphosphonyl acetylcholinesterase decreases with branching of the alkyl group.

The ω-chloroalkyl esters **27**, **28**, and **29** have higher therapeutic indexes than the *n*-alkyl analogs **2**, **3**, and **5**. The dialkyl esters, Table II, were ineffective against *N. braziliensis* in the rat at the MTD. The dipropyl (**31**) and dibutyl (**32**) esters also have higher therapeutic indexes relative to the mouse helminths than the asymmetric analogs **3** and **5**.

Replacement of the methoxyl group of II by other radicals gave compounds, Table III, having a broad range of toxicities, MTD of 4–500 mg/kg which, with the exception of **47** and **48**, is equal to or lower than the minimum effective dose.

In general, analogs of **1**, containing groups other than ester functions, were of no anthelmintic interest, either because of severe toxicity, *e.g.*, **38** and **40**, or because of lack of biological activity, *e.g.*, **41** and **42**. Hydrolytic instability

is likely responsible for the lack of anthelmintic properties of the pyrophosphates **50** and **52** which hydrolyze very rapidly ($T_{1/2}$ for **50** is less than 15 min at pH 1.1 or 9.1 at 38°). The cyclic phosphate **53** is interesting because, despite being so closely related to **1**, it is inactive as an anthelmintic and is not toxic to mice at 500 mg/kg; yet it is relatively active as an inhibitor of cholinesterase (I_{50} for **53** = 6.9×10^{-7} using fly-head cholinesterase).

Experimental Section‡

Chemistry. Intermediates and products prepared by reported procedures have physical constants in agreement with reported values. Spectral features were in accord with structures. Alkyl dimethyl phosphites used in the preparation of compds **2**, **4**, **12**, and **23** were obtained by refluxing the appropriate alcohol with trimethyl phosphite.[22] The desired phosphite was distilled. The distillate was cooled with Dry Ice–acetone and protected from moisture to minimize disproportionation. 2-Methoxy-1,3,2-dioxaphospholane, used in the prepn of **53**, was prepared by the method of Lucas, *et al.*[35] The following is a representative method for the preparation of II from the above phosphites.

2,2-Dichlorovinyl Isopropyl Methyl Phosphate (4). To a soln of 76 g (0.517 mole) of chloral in 75 ml of CH_2Cl_2 was added dropwise 87 g (0.573 mole) of dimethyl isopropyl phosphite. Both reagents were freshly distilled. Addition over 1.5 hr was adjusted to maintain a moderate reflux, which was continued for an additional 0.5 hr. Solvent and excess phosphite were removed in a rotating evaporator at 60° (25 mm) to give 129 g of a colorless liquid. Analysis was by glpc (F&M 810-29 chromatograph equipped with a thermoconductivity detector; columns 6 ft × 0.125 in. packed with 10% SE-30 on 80–100 mesh Chromosorb P; carrier gas, He, 40 psig; bridge current, 150 mA; program, 30°/min beginning at 110° column temp and terminating at 300°; sample size, 0.2–0.4 μl; attenuation, 32 manual). Under these conditions peak height of this product indicated a composition of 7% 1 (retention time 1.85 min) and 93% 4 (retention time 2.35 min). The product was distilled. Product boiling at 79° (0.04 mm) was collected, 109 g, in four fractions of about equal volume which contained 10, 6, 4, and 4%, respectively, of 1 by glpc analysis. Ten grams of the last fraction containing 4% of 1 was chromatographed through a 2-in. column made with 2 lb of 60–200 mesh deactivated silica gel (Grace 950) and eluted with 2% ether in CH_2Cl_2; 5.76 g of **4**, pure by glpc, was obtained from four 500-ml fractions of eluate. *Anal.* ($C_6H_{11}Cl_2O_4P$) P, Cl.

Sodium 2,2-Dichlorovinyl Methyl Phosphate (42). A stirred soln of 170 g (0.77 mole) of 1 in 2 l. of Me_2CO containing 105 g (0.70 mole) of KI was refluxed vigorously for 0.5 hr when all KI was consumed. **42** crystallized out of the reaction mixture, which in two crops amounted to 147 g (92%) as a white crystalline solid, mp 185–200° dec. *Anal.* ($C_3H_4Cl_2O_4P \cdot Na$) P, Cl, Na equiv. Calcd: Na equiv, 229. Found: Na equiv, 218.

2,2-Dichlorovinylmethylphosphoric Acid (41). Treatment of **42** with 1 mole equiv of HCl in MeOH at 30° (cooling required) gave a 95% yield of **41** as a straw-colored oil after filtration of NaCl and removal of solvent. *Anal.* ($C_3H_5Cl_2O_4P$) Cl, P, neut equiv.

Compds **44** and **45** were obtained in similar respective fashions as **42** and **41**.

***P,P'*-Bis(2,2-dichlorovinyl) *P,P'*-Dimethyl Pyrophosphate (50).** A soln of 793 g (3.38 moles) of **41** in 2760 ml (4550 g, 38.3 moles) of $SOCl_2$ was refluxed (78°) for 5 hr under usual conditions for gas venting and moisture protection. Removal of excess $SOCl_2$ at reduced pressure (terminal conditions 75° (0.0001 mm)) gave 97% yield of **50** as a pale yellow liquid. *Anal.* ($C_2H_8Cl_4O_7P_2$) P, Cl, anhyd equiv. Calcd: anhyd equiv, 198. Found: anhyd equiv, 200.

The pyrophosphate **52** was obtained by the method of Khorana and Todd[36] by treating the acid **44** with diphenylcarbodiimide.

Alcohol intermediates used in Scheme II were purchased. The following is a representative method for the preparation of II by Scheme II.

Butyl 2,2-Dichlorovinyl Methyl Phosphate (5). To 20 g (0.005 mole) of **50** was added 4.3 g (0.006 mole) of *n*-BuOH and the soln was heated at 68° for 3 hr. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried, stripped, and distilled on a falling film molecular still at 115° (0.0004 mm) to give 85% yield of **5** as a colorless liquid. *Anal.* ($C_7H_{13}Cl_2O_4P$) P, Cl. Calcd: Cl, 27.0. Found: Cl, 26.5.

Compound **40** was prepared as reported by Alimov and Cheplanova.[37] The dibromide **51** was obtained by addition of Br_2 in CCl_4 to **50** in the usual manner.

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‡Where analysis are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Boiling points represent conditions for falling film molecular still distillations, unless otherwise indicated. Melting point temperatures are uncorrected.

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Novel Phosphate Anthelmintics. 2. Aralkyl and Aralkenyl Analogs of Dichlorvos[1]

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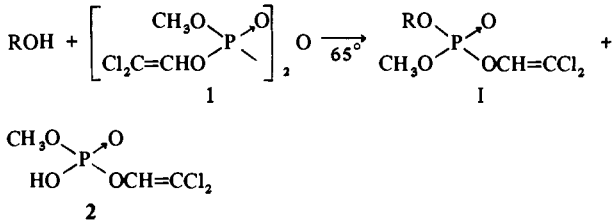
A series of aralkyl and aralkenyl analogs of the phosphate anthelmintic dichlorvos has been synthesized and found to have good anthelmintic activity in mice and rats. One compound, 2,2-dichlorovinyl methyl 4-phenylbutyl phosphate (**8**), is extremely active against the rodent parasites *Hymenolysis nana* and *Syphacia obvelata*. Synthetic methods and structure-activity relationships are discussed.

The broad-spectrum anthelmintic activity of dichlorvos†,‡ in both animals and man has led to the successful investigation of other active 2,2-dichlorovinyl phosphate esters not requiring a resin formulation.[1] Recently, Baker[3] demonstrated substantial increases in the inhibition of dihydrofolic reductase by substrates containing groups capable of hydrophobic bonding at a region of the enzyme near the active site. Particularly high activity was found for the substrate containing a 4-phenylbutyl group. Bracha and O'Brien[4,5] demonstrated the existence of such a hydrophobic binding region in the vicinity of the esteratic site in erythrocyte acetylcholinesterase by measurement of the affinity constants and inhibitory properties of a series of trialkyl phosphates and phosphorothiolates of varying alkyl chain length. These workers found a steadily increasing affinity, attributed to hydrophobic bonding, with increasing alkyl chain length up to six carbons, after which the affinity remained constant through an 11-carbon chain length. Subsequent studies[6] indicated no specifically favorable locations exist for alkyl chain branching; the added methylenes simply contributed to the total hydrophobic bonding. Breskin and coworkers have shown that similar relationships exist for the inhibition of butyrylcholinesterase by a series of *O*-ethyl *S*-alkyl methylphosphonates[7] containing a *tert*-butyl group at various distances from the phosphorus atom and a series of *O*-ethyl *S*-(*w*-phenylalkyl) methylthiophosphonates.[8] These workers found maximum inhibition occurred with a methylene chain length of four or more. Since dichlorvos probably exerts its anthelmintic effect by inhibition of helminth acetylcholinesterase,[9,10] application of hydrophobic bonding concepts by variation of the other ester groups on the 2,2-dichlorovinyl phosphate moiety proved to be a rational approach to compounds of greater activity.[1] This paper reports the extension of this approach by the synthesis of a series of aralkyl and aralkenyl mixed ester analogs of dichlorvos. During the course of this work two Bayer patents were issued claiming synthesis processes[11,12] and insecticidal[12] and fungicidal properties[12] for a related series of alkyl, alkoxyalkyl, and aryl mixed ester analogs of dichlorvos.

Chemistry. The two routes used to synthesize the phosphates in Table I are summarized below.

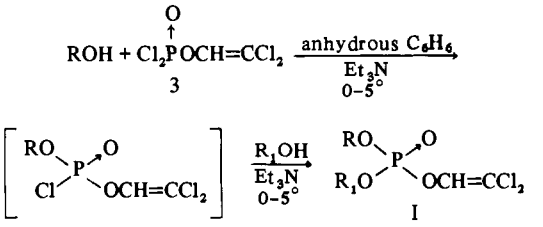
Route A. Eight aralkyl phosphates (I) were prepared by heating the appropriate alcohol with *P,P'*-bis(2,2-dichlorovinyl) *P,P'*-dimethyl pyrophosphate (**1**)[13] as illustrated in Scheme I.

Scheme I



Route B. The remainder of the phosphates (I) were synthesized by the sequential reaction of the appropriate alcohols with 2,2-dichlorovinyl phosphorodichloridate[14] (**3**) as illustrated in Scheme II. Triethylamine is used as a

Scheme II



hydrogen chloride scavenger to reduce acid-catalyzed transesterification of the product. The main reaction by-products are dichlorvos, **4**, and the bisaralkyl (alkenyl) 2,2-dichlorovinyl phosphate. Initial reaction of the longer chain alcohol affords maximum product yields by reducing the amounts of by-products formed. This route allows a variety of mixed esters to be prepared from a common intermediate.

The commercially unavailable alcohols utilized in the preparation of the phosphates in Table I were synthesized by the following methods. The aralkyl alcohols used in the synthesis of **10**, **11**, **12**, **24**, **28**, **29**, and **30** were prepared by the Friedel-Crafts acylation of the appropriate aromatic with either succinic or glutaric anhydride, followed by Wolff-Kishner reduction, esterification, and LAH reduction.

†For a review of the anthelmintic activity of dichlorvos see ref 2.
‡Phosphoric acid 2,2-dichlorovinyl dimethyl ester.