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(9) (a) D. C. Dyer and D. W. Gant, *J. Pharmacol. Exp. Ther.*, 184, 366 (1973); (b) D. W. Gant and D. C. Dyer, *Life Sci.*, 10, 235 (1971); (c) D. C. Dyer, *J. Pharmacol. Exp. Ther.*, 188, 336 (1974).

Novel Phosphate Anthelmintics. 3. Alkyl and Aryl 1-Methyleneallyl Phosphates, Phosphonates, and Phosphinates

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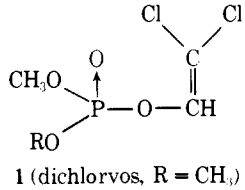
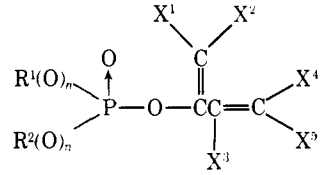
A series of new highly chlorinated 1-methyleneallyl ("butadienyl") dialkyl phosphates and related phosphonates and phosphinates has been synthesized and assessed for anthelmintic activity in mice against the tapeworm *Hymenolepis nana* and the pinworm *Syphacia obvelata*. Highest activity was observed with diethyl 2,3,3-trichloro-1-dichloromethyleneallyl ("perchlorobutadienyl") phosphate (**14**), while replacement of both ethoxy groups by methoxy and larger alkoxy or phenyl groups gave less efficacious compounds. In general, chlorine depletion of the 1,3-butadien-2-yl moiety or saturation of one double bond reduced anthelmintic responses.

Scores of 2,2-dichlorovinyl phosphates have been synthesized and many were found effective anthelmintics[1,2] since the discovery of the broad anthelmintic[3] properties of dichlorvos, 2,2-dichlorovinyl dimethyl phosphate (**1**, R = CH_3). Generally, a variety of alkyl, aralkyl, and aralkenyl groups have been used as substituents, R, to modify the biological activity of dichlorvos. It was of interest to determine the anthelmintic properties arising from **1** by the formal attachment of an unsaturated, highly chlorinated, group to the α-carbon atom of the β,β-dichlorvinyl moiety. 1-Methyleneallyl esters of general structure **2** were chosen for study since the influence on activity of both methylene groups could be studied independently in relation to their degree of chlorination. This study was facilitated by the development in these laboratories of general methods for the preparation of a series of highly chlorinated butenones.



1 (dichlorvos, R = CH_3)



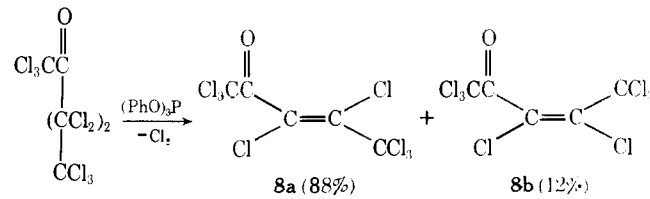
2. R^1, R^2 = alkyl, aryl; $n = 0, 1$; X^1-X^5 = H, Cl, CCl_3

The first reported synthesis of dialkyl 1-methyleneallyl phosphates highly chlorinated in the methyleneallyl moiety was from these laboratories.[4] In 1967,[5] we reported on the potent insecticidal activity for a number of these highly chlorinated dialkyl 1-methyleneallyl phosphates and related phosphonates. Insecticidal activity is largely due to the presence of the 1-methyleneallyl group and we have found it to be highly dependent upon the degree of chlorination. We now wish to describe the synthetic procedures used to prepare these compounds and to relate other details of their properties. Throughout this paper, the term "chlorobutadienyl" refers to chlorination in the 1-methyleneallyl group.

Chemistry. Phosphites, Phosphonites, and Phosphinites. Trialkyl phosphites were purchased from commercial sources or were prepared by the reaction of phosphorus trichloride and the appropriate alcohol in ether in the presence of pyridine or *N,N*-diethylaniline.[6] The latter approach was also used to prepare dimethyl ethylphosphonite[7] and diethyl ethylphosphonite[7] from ethyldichlorophosphine and methanol and ethanol, respectively. Dimethyl phenylphosphonite,[8] diethyl phenylphosphonite,[8] and diisopropyl phenylphosphonite[9] were prepared analogously by the reaction of phenyldichlorophosphine[10] with the respective alcohol. This procedure was also used to prepare methyl diphenylphosphinite[11] from diphenylchlorophosphine[12] and methanol.

Chloro Ketones (Table I). 1,1,4,4,4-Pentachloro-1-buten-3-one (**3**) was readily prepared by the ferric chloride catalyzed fragmentation of β,β-bis(trichloromethyl)-β-propiolactone.[13] An alternate process in which **3** is obtained by treatment of vinylidene chloride with trichloroacetyl chloride in the presence of anhydrous aluminum chloride containing 1% of ferric chloride has recently been described.[14] Addition of chlorine to the double bond of **3** afforded 1,1,1,3,4,4,4-heptachlorobutan-2-one (**4**) which was readily dehydrochlorinated with triethylamine in ether to give 1,1,2,4,4,4-hexachloro-1-buten-3-one[13] (**5**). Compound **5** was also readily prepared by the dechlorination of octachlorobutanone,[15] (**6**). The dechlorination has also been effected using triphenyl phosphite, triphenylphosphine, or a trialkyl phosphite[16] (Scheme I).

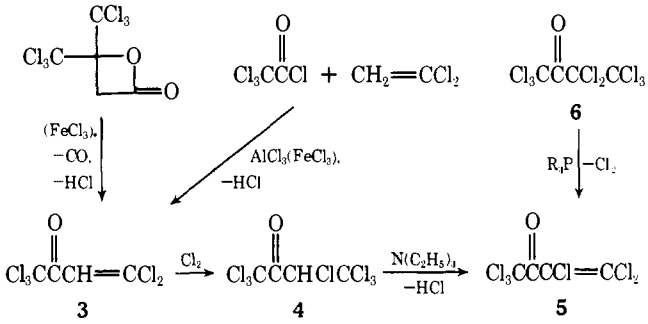
Decachloro-2-pentanone (**7**) reacted analogously with triphenyl phosphite to give a mixture of the two geometrically isomeric 1,1,1,2,3,5,5,5-octachloro-2-penten-4-ones[16] (**8a** and **8b**).



7 → **8a** (88%) + **8b** (12%)

The facile acid-catalyzed thermolysis of the phosphates **15**, **28**, and **42** leading to 1,1,2,4,4-pentachloro-1-buten-3-one (**9**), 1,1,4,4-tetrachloro-1-buten-3-one (**10**), and 1,1,2,4-tetrachloro-1-buten-3-one (**11**) has been described.[17] This technique, which is outlined in Scheme II, represents a valuable preparative method for the selective mono-α-dechlorination of α-chlorocarbonyl compounds originally used in the preparation of the vinyl phosphates

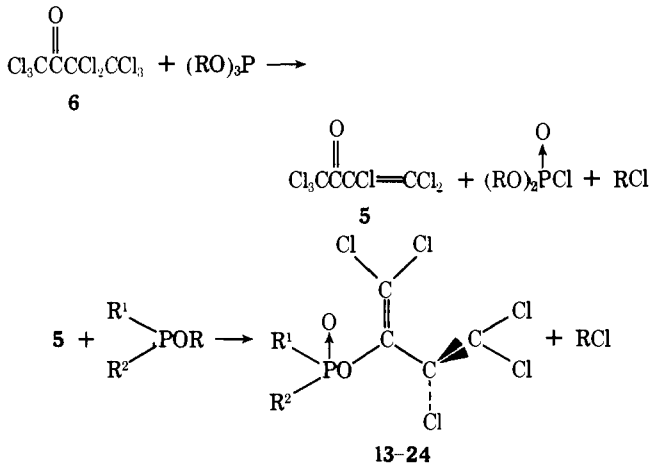
Scheme I



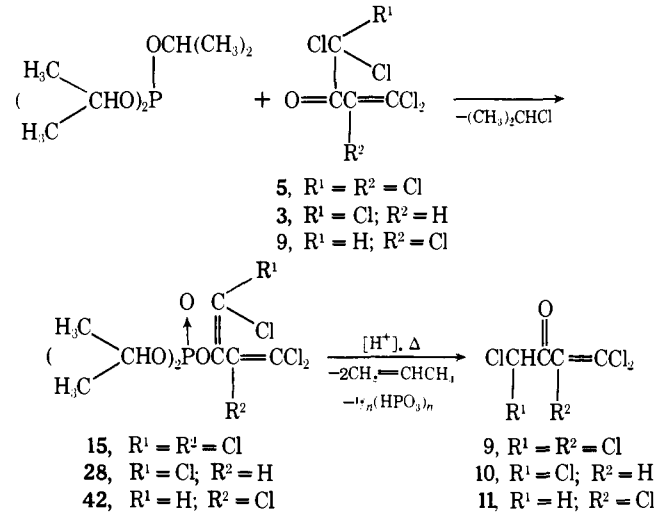
via the Perkow reaction.[18] The method is convenient in that intermediate diisopropyl esters such as **15, 28, and 42** or their di(*sec*-butyl) homologs, such as **31** (Table III), may be thermolyzed without prior purification. In fact, attempted purification of these esters by distillation is usually accompanied by decomposition, thus making it difficult to prepare analytically pure isopropyl and *sec*-butyl esters of this type.

Reaction of chloroacetyl chloride with acetylene in the presence of anhydrous aluminum chloride afforded 1,4-dichloro-1-buten-3-one[19] (**12**).

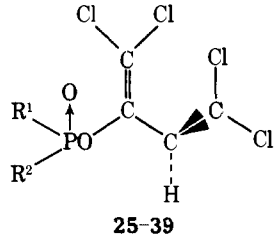
Chlorobutadienyl Phosphates and Related Esters. The Perkow reaction was used to prepare the compounds listed in Tables II–VII. Trialkyl phosphites, dialkyl ethylphosphonites, dialkyl phenylphosphonite, and methyl diphenylphosphinite were allowed to react with a 4-chloro-1-buten-3-one in the usual manner.[20] The resulting 1-methyleneallyl (1,3-butadien-2-yl) esters were purified by distillation or crystallization techniques. Structures and purities were determined by GC, TLC, NMR, and ir spectral analyses. Details of representative reactions are presented in the Experimental Section. Trialkyl phosphites, dialkyl phosphonites, and methyl diphenylphosphinite reacted exothermically with perchloro-1-buten-3-one (**5**) to give the desired pentachlorobutadienyl esters **13–24** in high yield (procedure A). When perchloro-2-butanone (**6**) is utilized, 2 equiv of trialkyl phosphite is necessary for successful reactions (procedure B). In this reaction sequence, the first equivalent of trialkyl phosphite dechlorinates **6** to give **5**, dialkyl phosphorochloridate, and alkyl chloride. A second equivalent reacts subsequently with **5** via the Perkow reaction to give the pentachlorobutadienyl phosphates **13–15, 17, and 18** in addition to alkyl chloride. Procedure B is the most versatile of the available synthetic techniques for the preparation of pentachlorobutadienyl esters due to the availability of perchloro-2-butanone (**6**) which is readily prepared by chlorination of 2-butanone as described by Geiger et al.[15]



Scheme II



All pentachlorobutadienyl esters absorb in the ultraviolet near 210 and 250 nm. In all cases, the shape of the absorption curves is identical. The position and intensity of the bands are similar to the absorption of hexachloro-1,3-butadiene[21,22] and 1,1,2,3,4-pentachloro-1,3-butadiene.[22] Evidence has been presented that a non-s-trans conformation predominates in hexachloro-1,3-butadiene (uv,[22] Raman,[23] ir[24]) and in 1,1,2,3,4-pentachloro-1,3-butadiene (uv[22]), which points to and is consistent with a skew form. It appears that interaction between bulky substituents in the 1,1,3 positions of 1,3-butadiene (1,1,3 type of interaction) is necessary for twisting the molecule out of the s-trans conformation.[25] For hexachloro-1,3-butadiene there is strong evidence (ir, Raman) for a cisoid structure.[24,26] The unlikelihood of a completely s-cis structure due to halogen–halogen overlap supports this view.[27] Hexachloro-1,3-butadiene and the pentachlorobutadienyl esters **13–24** have in effect two 1,1,3 interactions, strongly suggesting that they too exist in a cisoid conformation as indicated. Compounds **25–39** were readily synthesized by reaction of the appropriate trialkyl phosphite, dialkyl phosphonite, or methyl diphenylphosphinite with 1,1,1,4,4-pentachloro-3-buten-2-one (**3**) in ether. In the NMR spectra, the olefinic proton for all 1,1,4,4-tetrachlorobutadienyl esters has a relatively constant chemical shift (δ 6.45–6.73 ppm) and the coupling constant (J = 1–2 Hz) is consistent with previously reported values.[28–30] The fact that 1,1,3 type of interaction destabilizes the s-trans form, and that this factor is present in the esters **25–39** [e.g., Cl, Cl, OP(O)R^1R^2], is indicative that in these esters a single rotamer, namely a cisoid form, predominates. The available evidence[22,25] indicates that the similarly constituted 1,1,2,3,4-pentachloro-1,3-butadiene exists in a cisoid (non-s-cis) conformation.



25–39

1,1,3,4,4-Pentachloro-3-buten-2-one (**9**) and a series of alkyl phosphites, phosphonites, and one phosphinite were utilized to prepare the 1,1,2,4-tetrachloro-1,3-butadien-2-yl compounds **40–46** listed in Table IV. 1,1,4,4-Tetrachloro-3-buten-2-one (**10**) reacted analogously to give the

Table I. Chloro Ketones

No.	Structure	Ref	Yield, %	Bp, °C (mmHg)	$n^{20}D$	d^{20}_4	Formula	Analyses
5	$Cl_3CC(=O)CCl=CCl_2$	4, 13	96.5	34 (0.01)	1.5300	1.6979	C_4Cl_6O	C, H, Cl
3	$Cl_3CC(=O)CH=CCl_2$	13, 14	98.3	95–96 (13)	1.5423	1.6493	C_4HCl_5O	C, H, Cl
9	$Cl_2CHC(=O)CCl=CCl_2$	4, 17	96.3	87–88 (10)	1.5421	1.6643	C_4HCl_5O	C, H, Cl
10	$Cl_2CHC(=O)CH=CCl_2$	14, 17	74.5	77 (10)	1.5371	1.5736	$C_4H_2Cl_4O$	C, H, Cl
12	$ClCH_2C(=O)CH=CHCl$	19	86.3	82–83 (24)	1.5020[a]		$C_4H_4Cl_2O$	Cl
11	$ClCH_2C(=O)CCl=CCl_2$	17	86.6	46–47 (0.02)	1.5386[b]		$C_4H_2Cl_4O$	Cl
8	$Cl_3CC(=O)CCl=CClCCl_3$	4	67.6	88–89 (0.02)			C_5Cl_8O	Cl
4	$Cl_3CC(=O)CHClCCl_3$	13	97.8	110 (9)[c]	1.5271	1.7561	C_4HCl_7O	C, H, Cl

[a] 24°. [b] 18°. [c] Mp 16°.

Table II. Physical and Anthelmintic Properties of $R^1R^2POC(Cl)=CCl_2$

No.	R^1	R^2	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	$n^{20}D$	d^{20}_4	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H. n.*	Mouse TR (MTD/MED) *S. o.*
13	CH_3O	CH_3O	95.5	95.5	A	85–86 (0.01)	1.5163	1.5899	$C_6H_6Cl_5O_3P$	C, H, Cl, P	31	0	2
13	CH_3O	CH_3O	76.0	99+	B	88–89 (0.01)	1.5173	1.5869	$C_6H_8Cl_5O_4P$	C, H, Cl, P			
14	C_2H_5O	C_2H_5O	96.8	97.5	A	98–99 (0.01)	1.5056	1.4775	$C_8H_{10}Cl_5O_4P$	C, H, Cl, P	62	1	125
14	C_2H_5O	C_2H_5O	83.0	98	B	98–99 (0.01)	1.5054	1.4769	$C_8H_{10}Cl_5O_4P$	C, H, Cl, P			
15	$(CH_3)_2CHO$	$(CH_3)_2CHO$	94.5	95	A	99–100 (0.01)	1.4890	1.3737	$C_{10}H_{14}Cl_5O_4P$	*b*	500	0	0
15	$(CH_3)_2CHO$	$(CH_3)_2CHO$	96.2	92	B	108 (0.03)	1.4901	1.3759	$C_{10}H_{14}Cl_5O_4P$	*b*			
16	$CH_2=CHCH_2O$	$CH_2=CHCH_2O$	75.2	99+	A	108–109 (0.03)	1.5164	1.4490	$C_{10}H_{10}Cl_5O_4P$	C, H, Cl, P	62	0	1
17	C_4H_9O	C_4H_9O	74.0	98	B	121–122 (0.004)	1.4950	1.3411	$C_{12}H_{18}Cl_5O_4P$	C, H, Cl, P	500	1	0
18	$C_5H_{11}O$	$C_5H_{11}O$	31.0	95	B	104–110 (0.001)	1.4880	1.2759	$C_{14}H_{22}Cl_5O_4P$	C, H, P; Cl[c]	125	0	0
19	$C_6H_{13}O$	$C_6H_{13}O$	86.0	91	A	170 (0.004)	1.4865	1.2383	$C_{16}H_{26}Cl_5O_4P$	H, P; C,[d] Cl[d]	125	0	0
20	CH_3O	C_2H_5	84.5	96.5	A	98–99 (0.002)	1.5233	1.5208	$C_7H_8Cl_5O_3P$	C, H, Cl, P	8	0	2
21	C_2H_5O	C_2H_5	85.5	97.5	A	100–101 (0.005)	1.5149	1.4595	$C_8H_{10}Cl_5O_3P$	C, H, Cl, P	31	0	31
22	CH_3O	C_6H_5	94.5	98	A	150 (0.005)	1.5661	1.5129	$C_{11}H_8Cl_5O_3P$	C, H, Cl, P	250	1	1
23	C_2H_5O	C_6H_5	94.0	94	A	160–170 (0.005)	1.5582	1.4676	$C_{12}H_{10}Cl_5O_3P$	C, H, Cl, P	250	1	4
24	C_6H_5	C_6H_5	86.0	98	A	190 (0.008)[a]			$C_{16}H_{10}Cl_5O_2P$	C, H, Cl, P	500	2	1

[a] Mp 89-90°. [b] Calcd: C, 29.5; H, 3.4; Cl, 43.8; P, 7.6. Found: C, 31.3, 30.1; H, 4.0, 3.9; Cl, 42.4, 41.9; P, 8.2, 8.5. [c] Calcd: Cl, 38.3. Found: Cl, 36.8. [d] Calcd: C, 39.2; Cl, 36.2. Found: C, 40.5; Cl, 33.4.

Table III. Physical and Anthelmintic Properties of $R^1R^2POCCH{=}CCl_2$ (O and CCl_2)

No.	R^1	R^2	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	n^{20}_D	d^{20}_4	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
25	CH_3O	CH_3O	78.0	99+	C	91–92 (0.001)	1.5142	1.5381	$C_6H_7Cl_4O_4P$	C, H, Cl, P	62	0	4
26	C_2H_5O	C_2H_5O	88.5	99+	C	97–98 (0.07)	1.4995	1.4192	$C_8H_{11}Cl_4O_4P$	C, H, Cl, P	31	0	1
27	C_3H_7O	C_3H_7O	74.0	92.5	C	99–100 (0.01)	1.4951	1.3437	$C_{10}H_{15}Cl_4O_4P$	C, H, Cl, P	125	0	0
28	$(CH_3)_2CHO$	$(CH_3)_2CHO$	69.2	95	C	94–95 (0.005)	1.4873	1.3250	$C_{10}H_{15}Cl_4O_4P$	C, H, Cl, P	125	0	0
29	$CH_2{=}CHCH_2O$	$CH_2{=}CHCH_2O$	36.3	98	C	120–121 (0.005)	1.5151	1.3969	$C_{10}H_{11}Cl_4O_4P$	C, H, Cl, P	31	0	0
30	C_4H_9O	C_4H_9O	68.0	93	C	121 (0.008)	1.4909	1.2883	$C_{12}H_{19}Cl_4O_4P$	C, H, Cl, P	125	0	0
31	*s*-C_4H_9O	*s*-C_4H_9O	11.2	90	C	125 (0.01)	1.4879	1.2654	$C_{12}H_{19}Cl_4O_4P$	C, H, Cl, P	500	0	0
32	$C_5H_{11}O$	$C_5H_{11}O$	63.6	98	C	136 (0.005)	1.4824	1.2147	$C_{14}H_{23}Cl_4O_4P$	C, H, Cl, P	125	0	0
33	$C_8H_{13}O$	$C_8H_{13}O$	64.5	96	C	160–163 (0.005)	1.4750	1.1473	$C_{16}H_{27}Cl_4O_4P$	C, H, Cl, P	500	0	0
34	CH_3O	C_2H_5	91.3	97	C	88 (0.005)	1.5206	1.4679	$C_7H_9Cl_4O_3P$	C, H, Cl, P	8	0	1
35	C_2H_5O	C_2H_5	89.5	98	C	90 (0.01)	1.5130	1.4103	$C_8H_{11}Cl_4O_3P$	C, H, Cl, P	62	0	16
36	CH_3O	C_6H_5	66.5	99+	C	150 (0.01)	1.5660	1.4639	$C_{11}H_9Cl_4O_3P$	C, H, Cl, P	125	0	16
37	C_2H_5O	C_6H_5	65.0	95	C	150 (0.08)	1.5555	1.2056	$C_{12}H_{11}Cl_4O_3P$	C, H, Cl, P	125	0	16
38	$(CH_3)_2CHO$	C_6H_5	78.0	93	C	170–180 (0.008)	1.5468	1.3749	$C_{13}H_{13}Cl_4O_3P$	H, P; C,[b] Cl[b]	500	0	0
39	C_6H_5	C_6H_5	69.0	99+	C	*a*			$C_{16}H_{11}Cl_4O_2P$	C, H, Cl, P	250	1	0

[a] Mp 107.5–108°. [b] Calcd: C, 36.1; Cl, 38.8. Found: C, 36.7, Cl, 38.2.

Table IV. Physical and Anthelmintic Properties of $R^1R^2POCC(Cl){=}CCl_2$ (O and CHCl)

No.	R^1	R^2	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	n^{20}_D	d^{20}_4	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
40	CH_3O	CH_3O	96.7	99+	D	*a*			$C_6H_7Cl_4O_4P$	C, H, Cl, P	16	0	1
41	C_2H_5O	C_2H_5O	88.0	96	D	104 (0.003)	1.4976	1.4243	$C_8H_{11}Cl_4O_4P$	C, H, Cl, P	62	2	31
42	$(CH_3)_2$-CHO	$(CH_3)_2$-CHO	90.0	92	D	124–125 (0.05)	1.4883		$C_{10}H_{15}Cl_4O_4P$	Cl, P	500	0	0
43	CH_3O	C_6H_5	97.0	95	D	150 (0.02)	1.5627	1.4869	$C_{11}H_9Cl_4O_3P$	C, H, Cl, P	125	1	0
44	C_2H_5O	C_6H_5	93.0	98	D	140 (0.04)	1.5473	1.4085	$C_{12}H_{11}Cl_4O_3P$	C, H, Cl, P	125	0	2
45	C_2H_5O	C_2H_5	86.6	99+	D	105 (0.15)	1.5108	1.4181	$C_8H_{11}Cl_4O_3P$	C, H, Cl, P	16	4	4
46	C_6H_5	C_6H_5	44.1	99+	D	*b*			$C_{16}H_{11}Cl_4O_2P$	C, H, Cl, P	250	0	0

[a] Mp 66–67°. [b] Mp 62–63°.

Table V. Physical and Anthelmintic Properties of $R^1R^2POCCH{=}CCl_2$

No.	R^1	R^2	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	n^{20}_D	d^{20}_4	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
47	CH_3O	CH_3O	92.0	99	E	82–83 (0.001)	1.5085	1.4719	$C_6H_8Cl_3O_4P$	C, H, Cl, P	125	0	0
48	C_2H_5O	C_2H_5O	94.6	99+	E	112 (0.05)	1.4929	1.3590	$C_8H_{12}Cl_3O_4P$	C, H, P; Cl[a]	125	0	0
49	C_2H_5O	C_6H_5	92.7	98	E	136 (0.06)	1.5557	1.1370	$C_{12}H_{12}Cl_3O_3P$	C, H, Cl, P	500	0	31
50	CH_3O	C_6H_5	66.0	99+	E	145 (0.05)	1.5639	1.4062	$C_{11}H_{10}Cl_3O_3P$	C, H, Cl, P	500	2	2
51	C_2H_5O	C_2H_5	80.9	99+	E	91 (0.03)	1.5087	1.3432	$C_8H_{12}Cl_3O_3P$	C, H, Cl, P	62	0	2
52	C_6H_5	C_6H_5	89.0	99+	E	[b]			$C_{18}H_{12}Cl_3O_2P$	C, H, Cl, P	500	0	0

[a] Calcd: Cl, 34.4. Found: Cl, 33.9. [b] Mp 82.5°.

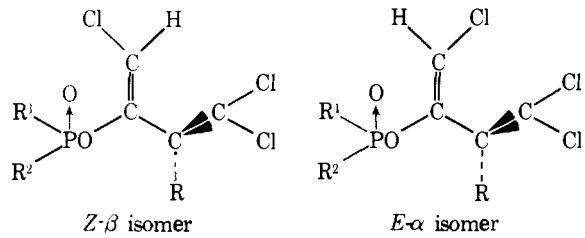
Table VI. Physical and Anthelmintic Properties of $(R^1O)_2POCC(R^2){=}CClR^2$

No.	R^1	R^2	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	n^t_D	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
53	CH_3	H	35.3	95	F	88–92 (0.02)	1.4715 (25°)	$C_6H_{10}ClO_4P$	Cl, P	31	0	0
54	C_2H_5	H	85.3	99	F	92–93 (0.02)	1.4646 (25°)	$C_8H_{14}ClO_4P$	Cl, P	31	0	0
55	CH_3	Cl	74.7	99	G	100–101 (0.04)	1.4938 (18°)	$C_6H_8Cl_3O_4P$	Cl, P	125	0	0
56	C_2H_5	Cl	81.6	92	G	110 (0.03)	1.4844 (18°)	$C_8H_{12}Cl_3O_4P$	Cl, P	31	0	1

Table VII. Physical and Anthelmintic Properties of $(RO)_2POCCCl{=}C(Cl)CCl_3$

No.	R	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	n^{21}_D	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
57	CH_3	71.5	95	H	137 (0.02)	1.5271	$C_7H_6Cl_7O_4P$	Cl, P	250	1	16
58	C_2H_5	58.6	95	H	145–146 (0.02)		$C_9H_{10}Cl_7O_4P$	Cl, P	62	0	2

1,1,4-trichloro-1,3-butadien-3-yl esters **47–52** in high yield (Table V).

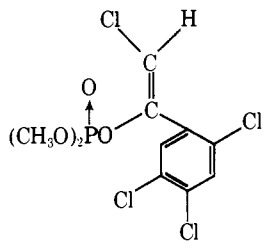


Z-β isomer *E-α* isomer

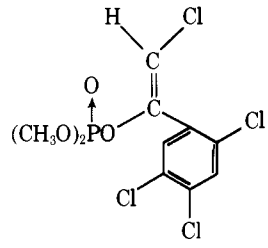
40–46, R = Cl
47–52, R = H

In addition to being mixtures of rotamers, tetrachlorobutadienyl esters **40–46** and trichlorobutadienyl compounds **47–52** allow for cis–trans isomerism around the olefinic [chloromethylene (CHCl=)] bond. For example, in the NMR spectrum compound **41** shows two doublets (δ 6.52 and 6.62 ppm) in an 80:20 ratio. By analogy with the literature data,[28–30] the 6.52 bond would be attributed to the *Z* isomer (*β* isomer). This larger proportion of *Z* isomer is in conflict with the usual Perkow reaction with trimethyl phosphite wherein the *E* isomer (*α* isomer) predominates. Two explanations are possible: (1) the chemical shift values are reversed due to the effect of the trichlorovinyl (-C-Cl=CCl_2) group; (2) the conformation of the molecule involves steric hindrance, which affects the reaction product ratio. There seems to be very little evidence to support the first point and steric effects seem a more likely explanation. These compounds are analogous to the *α*-(polychlorophenyl)vinyl phosphates (e.g., gardona insecticide) wherein

an *o*-chlorine on phenyl results in steric and electronic effects to produce a large portion of the *Z* isomer.[31]



Z-β isomer, δ 6.0 ppm (J_{PH} = 0.7 Hz)

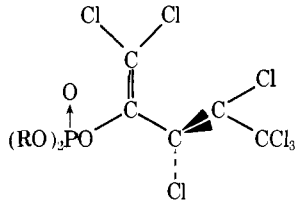


E-α isomer, δ 6.56 ppm (J_{PH} = 2.5 Hz)

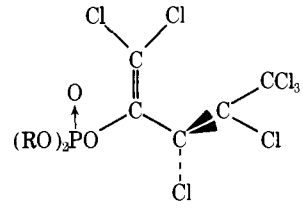
gardona

The 1,1,2,4-tetrachlorobutadienyl portion of the esters **40–46** may exist in a cisoid conformation (see above) and cause steric hindrance in the α isomer causing a preference for production of *Z* isomer. Compounds **40** (obtained from **9** and trimethyl phosphite) and **46** (purified by recrystallizations of the reaction mixture) were obtained as single isomers. NMR data in Table IX confirm the presence of two olefinic protons in the 1,1,4-trichlorobutadienyl esters **47–52**. However, interpretation in these instances does not seem warranted without separation of the geometric isomers. Treatment of 1,4-dichloro-3-buten-2-one (**12**) with trimethyl or triethyl phosphite afforded the dialkyl chlorobutadienyl phosphates **53** and **54** (procedure F). 1,3,4,4-Tetrachloro-3-buten-2-one (**11**) reacted analogously to give the dialkyl trichlorobutadienyl phosphates **55** and **56** (procedure G). The available evidence does not permit the assignment of a single structure (geometrical isomer and/or rotamer) to any of these four esters. Based on the degree and type of substitution of the 1,3-butadiene moiety of **55** and **56** (1,1,2,4-tetrasubstitution), it would appear that in these esters a single rotamer predominates, a skew form. Esters **53** and **54** might exist as a mixture of rotamers.

For the preparation of the heptachloropentadienyl esters **57** and **58**, 1,1,1,3,4,5,5,5-octachloro-3-penten-2-one (**8**, mixture of geometrical isomers) was allowed to react with trimethyl and triethyl phosphite. No effort was made to determine the isomer ratio of the distilled esters **57** and **58**. Based upon the chemical similarity of perchloro-1,3-butadiene with **8** and on the basis of the initial composition of **8** (88% cis and 12% trans), we conclude that **57a** and **58a** are the predominant species in **57** and **58**.



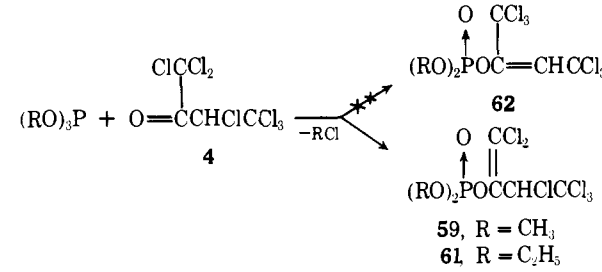
a



b

57, R = CH_3
58, R = C_2H_5

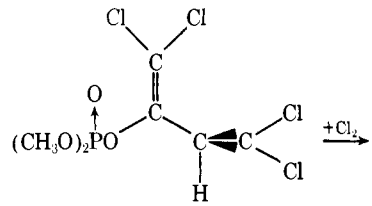
The key intermediate for the preparation of the dialkyl hexachlorobutenyl phosphates **59** and **61** was 1,1,1,3,4,4,4-heptachlorobutan-2-one (**4**). Both trimethyl and triethyl phosphite reacted uniformly with **4**. Isomers such as **62** were not formed as evidenced by the chemical shift values of the reaction products. In **59** and **61**, the chemical shift of the remaining proton of the hexachlorobutenyl group is observed at δ 5.84 and 5.99 ppm, respectively, indicating the presence of a saturated CH linkage. In **62** the corresponding chemical shift of the olefinic proton would be expected near 6.6 ppm.



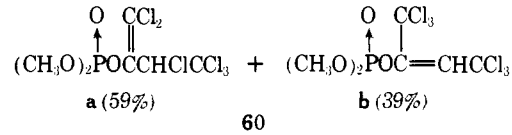
4 **62**

59, R = CH_3
61, R = C_2H_5

Chlorine was allowed to react with the ester **25** in order to prepare adducts that might be active per se or by virtue of their ability to generate a toxic material in situ. Chlorination of **25** proceeded sluggishly in chloroform and was still incomplete (ca. 70%) after 37 hr. However, addition of 1 equiv of chlorine occurred rapidly at 0° in the absence of solvents under irradiation with ultraviolet light to give **60**. Analytical (C, H, Cl, P) and physical ($n^{20}D$, d^{20}_4, uv spectrum) data of **60** agree well with that of **59** (see above). However, the NMR spectrum revealed that **60** was a mixture of two isomers. One isomer, **a**, showed a singlet at δ 5.97 and is obviously identical with **59** (δ 5.99); this is the major isomer. From the position of the CH– signal of the second isomer (δ 6.67), it can be concluded that it is an olefinic proton. On this basis, the second (minor) isomer in **60** has been assigned structure **b**. It is obvious from these data that the addition of chlorine to the 1,1,4,4-tetrachlorobutadienyl group follows two different paths. The major isomer, **a**, is formed by 1,2 addition, whereas the minor (**b**) isomer is the result of 1,4 addition.



25



a (59%) **60** **b** (39%)

Biological Results. Members from this series of organo phosphates were tested for their anthelmintic activity in parasitized mice (see ref 1 and 2 for procedural details). As a point of reference, the known anthelmintic, dichlorvos,[3] has been tested repeatedly in this test system. Nominally, dichlorvos has a therapeutic ratio (TR) of 0:1 for the mouse tapeworm, *Hymenolepis nana*, and a TR of 1:2 for the mouse pinworm, *Syphacia obvelata*.[1]

The anthelmintic activity described for this series of compounds was directed mainly against the pinworm and followed a similar pattern as established for the related dichlorvos analogs.[1] However, none of these chlorobutadienyl esters was effective for the intestinal roundworm, *N. dubius*, and only minimal responses (therapeutic ratios of four or less) were accorded to some of the materials relative to the tapeworm, *H. nana*. Thus, the structure-activity relationships presented below are based upon responses observed with the pinworm.

With these groups of organophosphorus compounds, we have, broadly speaking, two areas of substitution: the alkyl,

Table VIII. Physical and Anthelmintic Properties of $(RO)_2\overset{\uparrow}{P}OC\overset{\|}{C}HClCCl_3$ (O, CCl_2)

No.	R	Yield, %	Purity, %	Method of prepn	Bp, °C (mmHg)	$n^{20}D$	$d^{20}4$	Formula	Analyses	Mouse MTD, mg/kg	Mouse TR (MTD/MED) *H.n.*	Mouse TR (MTD/MED) *S.o.*
59	CH_3	84.7	99	I	127 (0.02)	1.5176	1.6475	$C_6H_7Cl_6O_4P$	C, H, Cl, P	31	0	2
60	CH_3	60.0	95	J	110–120 (0.01)	1.5161	1.6439	$C_6H_7Cl_6O_4P$	H, P; C,[a] Cl[a]	31	0	2
61	C_2H_5	72.2	99+	I	110–111 (0.005)	1.5035	1.5177	$C_8H_{11}Cl_6O_4P$	C, H, Cl, P	125	1	16

[a] Calcd: C, 18.6; Cl, 55.0. Found: C, 19.1; Cl, 54.2.

Table IX. Ultraviolet Absorption and NMR Positions for Chloro Ketones and Vinyl Esters

No.	Ultraviolet absorption λ_1	Log ϵ_1	λ_2	Log ϵ_2	NMR positions (δ) for -CH=	Others	No.	Ultraviolet absorption λ_1	Log ϵ_1	λ_2	Log ϵ_2	NMR positions (δ) for -CH=	Others
5	245	3.871	205	3.853			40	246	3.940	205	4.189		6.67 (=CHCl)[c]
3	259	4.021			7.26								
9	271	3.479	212	3.901		6.76 ($CHCl_2$)	41	243	3.894	205	4.205		6.52, 6.62 (=CHCl)[d]
10	255	4.050			7.15	5.96 ($CHCl_2$)							
12	*a*				6.8	4.15 (CH_2Cl), 7.5 (=CHCl)	42	*a*					6.35, 6.42 (=CHCl)[e]
11	263	3.620	205	3.780		4.5 (CH_2Cl)	43	252	3.741	215	4.287		6.36, 6.60 (=CHCl)[f]
8	*a*												
4	*b*					5.71 (CHCl)	44	245	3.874	210	4.371		6.39, 6.61 (=CHCl)[f]
13	247	3.868	208	4.301									
14	249	3.858	212	4.186			45	248	3.880	206	4.154		6.41, 6.63 (=CHCl)[g]
15	248	3.877	202	4.499									
16	251	3.869	212	4.197			46	252	3.833	220	4.346		6.58 (=CHCl)[c]
17	247	3.840	214	4.189									
18	248	3.888	212	4.223			47	256	4.127	200	3.656	6.78	6.48 (=CHCl)
19	248	3.841	212	4.187									
20	249	3.851	207	4.264			48	257	4.107			6.70	6.42 (=CHCl)
21	249	3.845	213	4.173									
22	251	3.822	217	4.356			49	264	4.205	216	4.224	6.67	6.43 (=CHCl)
23	252	3.826	215	4.411									
24	252	3.848	222	4.509			50	259	4.133	217	4.180	6.62	6.43 (=CHCl)
25	260	4.052			6.56								
26	260	4.031			6.55		51	262	4.176			6.76	6.46 (=CHCl)
27	258	4.039			6.60								
28	258	4.015			6.58		52	261	4.092	223	4.315	6.70	6.57 (=CHCl)
29	258	4.010			6.60								
30	259	3.991			*a*		53	*a*				*a*	
31	257	4.038			*a*		54	*a*				6.4	4.7, 5.2 (=CH_2)
32	257	4.001			*a*								
33	257	4.059			*a*		55	*a*					5.2, 5.5 (=CH_2)
34	257	4.013			6.73								
35	259	4.006			6.74		56	*a*					5.2, 5.2 (=CH_2)
36	257	4.040	217	4.246	6.65								
37	260	4.031	2.7	4.256	6.57		59	221	4.019				5.99 (CHCl)
38	258	3.999	217	4.230	6.64		60	220	4.004			6.67	5.97 (CHCl)
39	260	3.939	224	4.423	6.45		61	221	4.034				5.84 (CHCl)

[a] Not determined. [b] No absorption between 350 and 200 nm. [c] Only one isomer (β) present. [d] α:β = 80:20. [e] α:β = 55:45. [f] α:β = 72:28. [g] α:β = 85:15.

alkoxy, or phenyl groups on phosphorus on the one hand and the chlorinated butadienyl group bonded via oxygen to phosphorus on the other.

Among the phosphates, highest activity was observed with the dimethyl and diethyl chlorobutadienyl phosphates. Replacing both methoxy and ethoxy groups in a given ester by longer unbranched-chain or branched-chain alkoxy, alkenyloxy, or phenyl groups resulted in esters that were essentially inactive.

Comparison of a chlorobutadienyl phosphate characterized by two ethoxy groups, with a chlorobutadienyl phosphonate, e.g., those having ethoxy/ethyl or ethoxy/phenyl

groups, disclosed that the phosphonates were the more efficacious compounds.

One must, however, also take the chlorobutadienyl moiety into consideration for the overall series. As will be noted, the single most active compound, **14** in Table II, is a diethyl phosphate containing the perchlorobutadienyl group. However, the corresponding ethyl ethylphosphonate, **21**, was only one-fourth as active as **14**. All other combinations containing the pentachlorobutadienyl group demonstrated minimal or no anthelmintic effect.

Of interest is that a high degree of chlorination of the 1-methylene portion of the butadienyl moiety is required for maximum activity. For example, the dichloromethylene (CCl_2=) containing esters, e.g., **14**, have higher therapeutic ratios than the chloromethylene (CHCl=) containing esters, e.g., **41**, whereas the methylene (CH_2=) containing esters, e.g., **56**, were ineffective against *S. obvelata*. With this series of materials, it has been speculated that partitioning between aqueous and lipoidal phases is directly related to anthelmintic activity. Therefore, it is feasible that there is a member from each type of substituted butadienyl group which will demonstrate a specific anthelmintic effect. Alternately, excluding these exceptions, chlorine depletion of the trichlorovinyl (-CCl=CCl_2) portion of the butadienyl moiety, e.g., -CH=CCl_2 and -CH=CHCl, or saturation to -$CHClCCl_3$ may reduce rather than enhance the anthelmintic responses.

Overall, these chlorobutadienyl esters were also moderately toxic with the MTD generally within the range of 31–125 mg/kg. Additional studies with some of the more active materials given to parasitized pigs or sheep demonstrated a good anthelmintic response for ascarids, trichurids, and a variety of trichostrongylid parasites. Once again, however, there was a reduced tolerance to these materials and the safety factors were minimal.

Experimental Section

Intermediates and products prepared by reported procedures had analytical and physical constants in agreement with reported values. Boiling points, melting points, percentage yields, and analytical and physical data are given in Tables I–VIII; spectral data are recorded in Table IX. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical values. The structures assigned to all new compounds were supported by infrared spectra recorded on a Perkin-Elmer Model 21 spectrophotometer, ultraviolet spectra recorded with a Cary 14 spectrophotometer (200–350 nm), and nuclear magnetic resonance spectra recorded on Varian A-60A or KIS-2 (90 MHz) spectrometers.

Reaction of 1,1,1,3,4,4-Hexachloro-3-buten-2-one (5) with Diethyl Phenylphosphonite (Procedure A). To a stirred solution of 13.85 g (0.05 mol) of **5** in 50 ml of ether was added dropwise a solution of 10.9 g (0.055 mol) of diethyl phenylphosphonite. Addition over 15 min was adjusted to maintain a moderate reflux, which was continued for an additional 0.5 hr. The solvent was removed in a rotating evaporator. The residual liquid was distilled in a falling film molecular still at 160–170° (0.005 mm) to give 19.35 g (94%) of **23** as a colorless liquid.

Reaction of Octachlorobutanone (6) with Triethyl Phosphite (Procedure B). To a stirred solution containing 34.8 g (0.1 mol) of **6** in 50 ml of ether was added dropwise 33.2 g (0.2 mol) of triethyl phosphite. Addition was adjusted to maintain a moderate reflux, which was continued for an additional 0.5 hr. The solvent was removed in a rotating evaporator at 35° (20 mm). The residual liquid was distilled under reduced pressure to give 17.4 g (82%) of diethyl phosphorochloridate, bp 74° (8 mm), and 31.45 g (83%) of ester **14**, a colorless liquid.

Chlorination of Dimethyl 3,3-Dichloro-1-(dichloromethylene)allyl Phosphate (25) (Procedure J). Chlorine was introduced into 40 g (0.13 mol) of **25** at 0° in the presence of ultraviolet light. After 3 hr, excess chlorine was removed under vacuum to give 57.1 g of reaction product. Distillation under reduced pressure gave 37.2 g (76%) of **60**, a colorless liquid.

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