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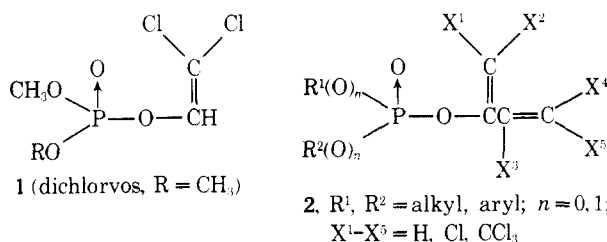
Novel Phosphate Anthelmintics. 3. Alkyl and Aryl 1-Methyleneallyl Phosphates, Phosphonates, and Phosphinites

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A series of new highly chlorinated 1-methyleneallyl ("butadienyl") dialkyl phosphates and related phosphonates and phosphinites 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-dichloro-methyleneallyl ("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 anthelmintic³ properties of dichlorvos, 2,2-dichlorovinyl dimethyl phosphate (1, R = CH₃). 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 -dichlorovinyl 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.



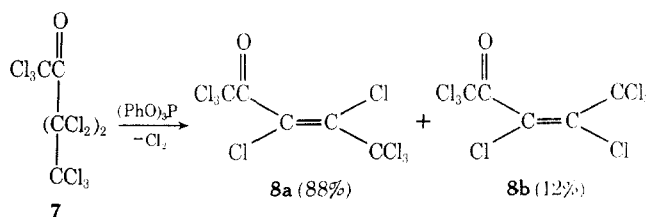
The first reported synthesis of dialkyl 1-methyleneallyl phosphates highly chlorinated in the methyleneallyl moiety was from these laboratories.⁴ In 1967,⁵ we reported on the potent insecticidal activity for a number of these highly chlorinated dialkyl 1-methyleneallyl phosphates and related phosphonates. 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 ap-

proach was also used to prepare dimethyl ethylphosphonite⁷ and diethyl ethylphosphonite⁷ from ethyldichlorophosphine and methanol and ethanol, respectively. Dimethyl phenylphosphonite,⁸ diethyl phenylphosphonite,⁸ and diisopropyl phenylphosphonite⁹ were prepared analogously by the reaction of phenyldichlorophosphine¹⁰ with the respective alcohol. This procedure was also used to prepare methyl diphenylphosphinite¹¹ from diphenylchlorophosphine¹² and methanol.

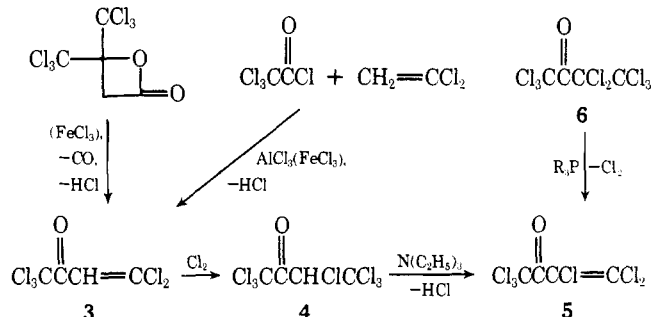
Chloro Ketones (Table I). 1,1,4,4,4-Pentachloro-1-buten-3-one (3) was readily prepared by the ferric chloride catalyzed fragmentation of β,β -bis(trichloromethyl)- β -propiolactone.¹³ An alternate process in which 3 is obtained by treatment of vinylidene chloride with trichloroacetyl chloride in the 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-one¹³ (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 phosphite¹⁶ (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-ones¹⁶ (8a and 8b).



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

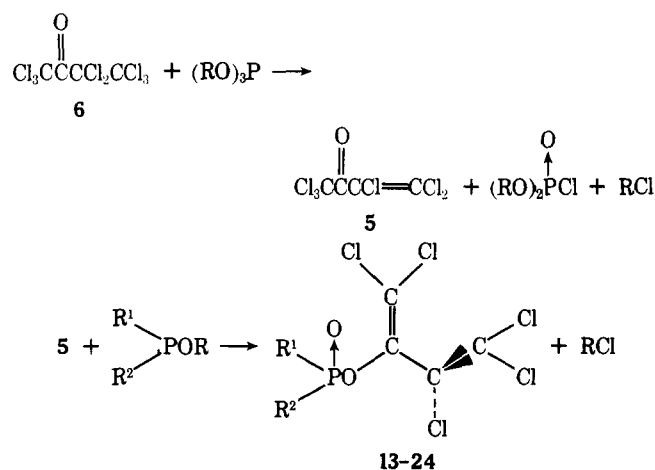
Scheme I



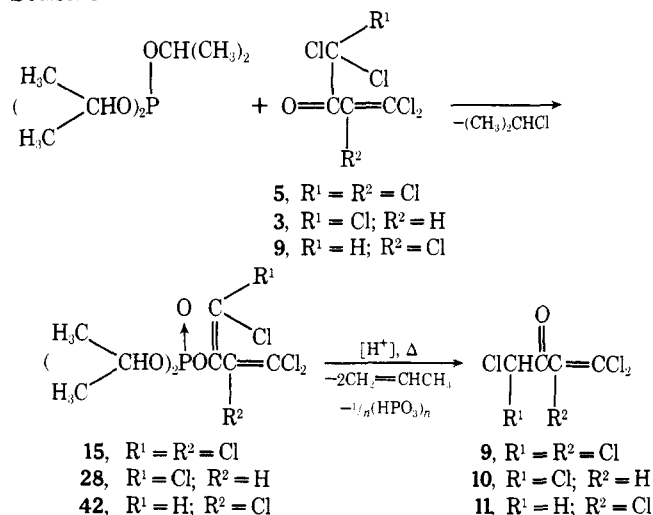
via the Perkow reaction.¹⁸ The method is convenient in that intermediate diisopropyl esters such as 15, 28, and 42 or their di(*sec*-butyl) homologs, such as 31 (Table III), may be thermolyzed without prior purification. In fact, attempted purification of these esters by distillation is usually accompanied 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-one¹⁹ (12).

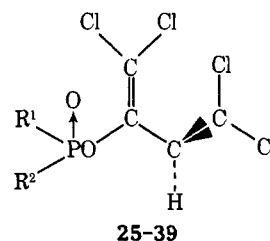
Chlorobutadienyl Phosphates and Related Esters. The Perkow reaction was used to prepare the compounds listed in Tables II-VII. Trialkyl phosphites, dialkyl ethylphosphonites, dialkyl phenylphosphonite, and methyl diphenylphosphinite were allowed to react with a 4-chloro-1-buten-3-one in the usual manner.²⁰ 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 ir²⁴) and in 1,1,2,3,4-pentachloro-1,3-butadiene (uv²²), 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)R¹R²], 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.



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_D^{20} | d_4^{20} | Formula | Analyses |
|-----|--|--------|----------|----------------------|---------------------|------------|---|----------|
| 5 | $\text{Cl}_3\text{CC}(=\text{O})\text{CCl}=\text{CCl}_2$ | 4, 13 | 96.5 | 34 (0.01) | 1.5300 | 1.6979 | $\text{C}_4\text{Cl}_6\text{O}$ | C, H, Cl |
| 3 | $\text{Cl}_3\text{CC}(=\text{O})\text{CH}=\text{CCl}_2$ | 13, 14 | 98.3 | 95-96 (13) | 1.5423 | 1.6493 | $\text{C}_4\text{HCl}_5\text{O}$ | C, H, Cl |
| 9 | $\text{Cl}_3\text{CHC}(=\text{O})\text{CCl}=\text{CCl}_2$ | 4, 17 | 96.3 | 87-88 (10) | 1.5421 | 1.6643 | $\text{C}_4\text{HCl}_5\text{O}$ | C, H, Cl |
| 10 | $\text{Cl}_2\text{CHC}(=\text{O})\text{CH}=\text{CCl}_2$ | 14, 17 | 74.5 | 77 (10) | 1.5371 | 1.5736 | $\text{C}_4\text{H}_2\text{Cl}_4\text{O}$ | C, H, Cl |
| 12 | $\text{ClCH}_2\text{C}(=\text{O})\text{CH}=\text{CHCl}$ | 19 | 86.3 | 82-83 (24) | 1.5020 ^a | | $\text{C}_4\text{H}_4\text{Cl}_2\text{O}$ | Cl |
| 11 | $\text{ClCH}_2\text{C}(=\text{O})\text{CCl}=\text{CCl}_2$ | 17 | 86.6 | 46-47 (0.02) | 1.5386 ^b | | $\text{C}_4\text{H}_2\text{Cl}_4\text{O}$ | Cl |
| 8 | $\text{Cl}_3\text{CC}(=\text{O})\text{CCl}=\text{CClCl}_3$ | 4 | 67.6 | 88-89 (0.02) | | | $\text{C}_5\text{Cl}_8\text{O}$ | Cl |
| 4 | $\text{Cl}_3\text{CC}(=\text{O})\text{CHClCCl}_3$ | 13 | 97.8 | 110 (9) ^c | 1.5271 | 1.7561 | $\text{C}_4\text{HCl}_7\text{O}$ | C, H, Cl |

^a24°, ^b18°, ^cMp 16°.Table II. Physical and Anthelmintic Properties of $\text{R}^1\text{R}^2\text{POCCl}=\text{CCl}_2$ 

| No. | R^1 | R^2 | Yield, % | Purity, % | Method of prepn | Bp, °C (mmHg) | n_D^{20} | d_4^{20} | Formula | Analyses | Mouse | | |
|-----|-------------------------------------|-------------------------------------|----------|-----------|-----------------|--------------------------|------------|------------|---|--------------------------|------------|-------------------|------|
| | | | | | | | | | | | MTD, mg/kg | TR (MTD/MED) H.n. | S.o. |
| 13 | CH_3O | CH_3O | 95.5 | 95.5 | A | 85-86 (0.01) | 1.5163 | 1.5899 | $\text{C}_6\text{H}_6\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | 31 | 0 | 2 |
| 13 | CH_3O | CH_3O | 76.0 | 99+ | B | 88-89 (0.01) | 1.5173 | 1.5869 | $\text{C}_6\text{H}_6\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | | | |
| 14 | $\text{C}_2\text{H}_5\text{O}$ | $\text{C}_2\text{H}_5\text{O}$ | 96.8 | 97.5 | A | 98-99 (0.01) | 1.5056 | 1.4775 | $\text{C}_8\text{H}_{10}\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | 62 | 1 | 125 |
| 14 | $\text{C}_2\text{H}_5\text{O}$ | $\text{C}_2\text{H}_5\text{O}$ | 83.0 | 98 | B | 98-99 (0.01) | 1.5054 | 1.4769 | $\text{C}_8\text{H}_{10}\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | | | |
| 15 | $(\text{CH}_3)_2\text{CHO}$ | $(\text{CH}_3)_2\text{CHO}$ | 94.5 | 95 | A | 99-100 (0.01) | 1.4890 | 1.3737 | $\text{C}_{10}\text{H}_{14}\text{Cl}_5\text{O}_4\text{P}$ | <i>b</i> | 500 | 0 | 0 |
| 15 | $(\text{CH}_3)_2\text{CHO}$ | $(\text{CH}_3)_2\text{CHO}$ | 96.2 | 92 | B | 108 (0.03) | 1.4901 | 1.3759 | $\text{C}_{10}\text{H}_{14}\text{Cl}_5\text{O}_4\text{P}$ | <i>b</i> | | | |
| 16 | $\text{CH}_2=\text{CHCH}_2\text{O}$ | $\text{CH}_2=\text{CHCH}_2\text{O}$ | 75.2 | 99+ | A | 108-109 (0.03) | 1.5164 | 1.4490 | $\text{C}_{10}\text{H}_{14}\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | 62 | 0 | 1 |
| 17 | $\text{C}_4\text{H}_9\text{O}$ | $\text{C}_4\text{H}_9\text{O}$ | 74.0 | 98 | B | 121-122 (0.004) | 1.4950 | 1.3411 | $\text{C}_{12}\text{H}_{18}\text{Cl}_5\text{O}_4\text{P}$ | C, H, Cl, P | 500 | 1 | 0 |
| 18 | $\text{C}_5\text{H}_{11}\text{O}$ | $\text{C}_5\text{H}_{11}\text{O}$ | 31.0 | 95 | B | 104-110 (0.001) | 1.4880 | 1.2759 | $\text{C}_{14}\text{H}_{22}\text{Cl}_5\text{O}_4\text{P}$ | C, H, P; Cl ^c | 125 | 0 | 0 |
| 19 | $\text{C}_6\text{H}_{13}\text{O}$ | $\text{C}_6\text{H}_{13}\text{O}$ | 86.0 | 91 | A | 170 (0.004) | 1.4865 | 1.2383 | $\text{C}_{16}\text{H}_{26}\text{Cl}_5\text{O}_4\text{P}$ | H, P; C, Cl ^d | 125 | 0 | 0 |
| 20 | CH_3O | $\text{C}_2\text{H}_5\text{O}$ | 84.5 | 96.5 | A | 98-99 (0.002) | 1.5233 | 1.5208 | $\text{C}_7\text{H}_8\text{Cl}_5\text{O}_3\text{P}$ | C, H, Cl, P | 8 | 0 | 2 |
| 21 | $\text{C}_2\text{H}_5\text{O}$ | $\text{C}_2\text{H}_5\text{O}$ | 85.5 | 97.5 | A | 100-101 (0.005) | 1.5149 | 1.4595 | $\text{C}_8\text{H}_{10}\text{Cl}_5\text{O}_3\text{P}$ | C, H, Cl, P | 31 | 0 | 31 |
| 22 | CH_3O | $\text{C}_2\text{H}_5\text{O}$ | 94.5 | 98 | A | 150 (0.005) | 1.5661 | 1.5129 | $\text{C}_{11}\text{H}_{16}\text{Cl}_5\text{O}_3\text{P}$ | C, H, Cl, P | 250 | 1 | 1 |
| 23 | $\text{C}_2\text{H}_5\text{O}$ | $\text{C}_2\text{H}_5\text{O}$ | 94.0 | 94 | A | 160-170 (0.005) | 1.5582 | 1.4676 | $\text{C}_{12}\text{H}_{16}\text{Cl}_5\text{O}_3\text{P}$ | C, H, Cl, P | 250 | 1 | 4 |
| 24 | C_6H_5 | C_6H_5 | 86.0 | 98 | A | 190 (0.008) ^a | | | $\text{C}_{16}\text{H}_{10}\text{Cl}_5\text{O}_2\text{P}$ | C, H, Cl, P | 500 | 2 | 1 |

^aMp 89-90°. ^bCalcd: 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. ^cCalcd: Cl, 38.3. Found: Cl, 36.8. ^dCalcd: C, 39.2; Cl, 36.2. Found: C, 40.5; Cl, 33.4.

Table III. Physical and Anthelmintic Properties of $R^1R^2POCCH=CCl_2$

| No. | R ¹ | R ² | Yield, % | Purity, % | Method of prepn | Bp, °C (mmHg) | n _D ²⁰ | d ₄ ²⁰ | Formula | Analyses | Mouse | | |
|-----|--------------------------------------|--------------------------------------|----------|-----------|-----------------|-----------------|------------------------------|------------------------------|--|--------------------------|------------|-----------|-----------|
| | | | | | | | | | | | MTD, mg/kg | TR | |
| | | | | | | | | | | | | (MTD/MED) | H.n. S.o. |
| 25 | CH ₃ O | CH ₃ O | 78.0 | 99+ | C | 91-92 (0.001) | 1.5142 | 1.5381 | C ₆ H ₇ Cl ₄ O ₄ P | C, H, Cl, P | 62 | 0 | 4 |
| 26 | C ₂ H ₅ O | C ₂ H ₅ O | 88.5 | 99+ | C | 97-98 (0.07) | 1.4995 | 1.4192 | C ₈ H ₁₁ Cl ₄ O ₄ P | C, H, Cl, P | 31 | 0 | 1 |
| 27 | C ₃ H ₇ O | C ₃ H ₇ O | 74.0 | 92.5 | C | 99-100 (0.01) | 1.4951 | 1.3437 | C ₁₀ H ₁₅ Cl ₄ O ₄ P | C, H, Cl, P | 125 | 0 | 0 |
| 28 | (CH ₃) ₂ CHO | (CH ₃) ₂ CHO | 69.2 | 95 | C | 94-95 (0.005) | 1.4873 | 1.3250 | C ₁₀ H ₁₅ Cl ₄ O ₄ P | C, H, Cl, P | 125 | 0 | 0 |
| 29 | CH ₂ =CHCH ₂ O | CH ₂ =CHCH ₂ O | 36.3 | 98 | C | 120-121 (0.005) | 1.5151 | 1.3969 | C ₁₀ H ₁₁ Cl ₄ O ₄ P | C, H, Cl, P | 31 | 0 | 0 |
| 30 | C ₄ H ₉ O | C ₄ H ₉ O | 68.0 | 93 | C | 121 (0.008) | 1.4909 | 1.2883 | C ₁₂ H ₁₉ Cl ₄ O ₄ P | C, H, Cl, P | 125 | 0 | 0 |
| 31 | s-C ₄ H ₉ O | s-C ₄ H ₉ O | 11.2 | 90 | C | 125 (0.01) | 1.4879 | 1.2654 | C ₁₂ H ₁₉ Cl ₄ O ₄ P | C, H, Cl, P | 500 | 0 | 0 |
| 32 | C ₅ H ₁₁ O | C ₅ H ₁₁ O | 63.6 | 98 | C | 136 (0.005) | 1.4824 | 1.2147 | C ₁₄ H ₂₃ Cl ₄ O ₄ P | C, H, Cl, P | 125 | 0 | 0 |
| 33 | C ₆ H ₁₃ O | C ₆ H ₁₃ O | 64.5 | 96 | C | 160-163 (0.005) | 1.4750 | 1.1473 | C ₁₆ H ₂₇ Cl ₄ O ₄ P | C, H, Cl, P | 500 | 0 | 0 |
| 34 | CH ₃ O | C ₂ H ₅ | 91.3 | 97 | C | 88 (0.005) | 1.5206 | 1.4679 | C ₇ H ₉ Cl ₄ O ₃ P | C, H, Cl, P | 8 | 0 | 1 |
| 35 | C ₂ H ₅ O | C ₂ H ₅ | 89.5 | 98 | C | 90 (0.01) | 1.5130 | 1.4103 | C ₈ H ₁₁ Cl ₄ O ₃ P | C, H, Cl, P | 62 | 0 | 16 |
| 36 | CH ₃ O | C ₆ H ₅ | 66.5 | 99+ | C | 150 (0.01) | 1.5660 | 1.4639 | C ₁₁ H ₉ Cl ₄ O ₃ P | C, H, Cl, P | 125 | 0 | 16 |
| 37 | C ₂ H ₅ O | C ₆ H ₅ | 65.0 | 95 | C | 150 (0.08) | 1.5555 | 1.2056 | C ₁₂ H ₁₁ Cl ₄ O ₃ P | C, H, Cl, P | 125 | 0 | 16 |
| 38 | (CH ₃) ₂ CHO | C ₆ H ₅ | 78.0 | 93 | C | 170-180 (0.008) | 1.5468 | 1.3749 | C ₁₃ H ₁₃ Cl ₄ O ₃ P | H, P, C, Cl ^b | 500 | 0 | 0 |
| 39 | C ₆ H ₅ | C ₆ H ₅ | 69.0 | 99+ | C | ^a | | | C ₁₆ H ₁₁ Cl ₄ O ₂ P | C, H, Cl, P | 250 | 1 | 0 |

^aMp 107.5-108°. ^bCalcd: C, 36.1; Cl, 38.8. Found: C, 36.7, Cl, 38.2.Table IV. Physical and Anthelmintic Properties of $R^1R^2POCCH=CCl_2$

| No. | R ¹ | R ² | Yield, % | Pur-ity, % | Meth-od of prepn | Bp, °C (mmHg) | n _D ²⁰ | d ₄ ²⁰ | Formula | Analyses | Mouse | | |
|-----|--------------------------------------|--------------------------------------|----------|------------|------------------|----------------|------------------------------|------------------------------|--|-------------|------------|-----------|-----------|
| | | | | | | | | | | | MTD, mg/kg | TR | |
| | | | | | | | | | | | | (MTD/MED) | H.n. S.o. |
| 40 | CH ₃ O | CH ₃ O | 96.7 | 99+ | D | ^a | | | C ₆ H ₇ Cl ₄ O ₄ P | C, H, Cl, P | 16 | 0 | 1 |
| 41 | C ₂ H ₅ O | C ₂ H ₅ O | 88.0 | 96 | D | 104 (0.003) | 1.4976 | 1.4243 | C ₈ H ₁₁ Cl ₄ O ₄ P | 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 ₄ O ₄ P | Cl, P | 500 | 0 | 0 |
| 43 | CH ₃ O | C ₆ H ₅ | 97.0 | 95 | D | 150 (0.02) | 1.5627 | 1.4869 | C ₁₁ H ₉ Cl ₄ O ₃ P | C, H, Cl, P | 125 | 1 | 0 |
| 44 | C ₂ H ₅ O | C ₆ H ₅ | 93.0 | 98 | D | 140 (0.04) | 1.5473 | 1.4085 | C ₁₂ H ₁₁ Cl ₄ O ₃ P | C, H, Cl, P | 125 | 0 | 2 |
| 45 | C ₂ H ₅ O | C ₂ H ₅ | 86.6 | 99+ | D | 105 (0.15) | 1.5108 | 1.4181 | C ₈ H ₁₁ Cl ₄ O ₃ P | C, H, Cl, P | 16 | 4 | 4 |
| 46 | C ₆ H ₅ | C ₆ H ₅ | 44.1 | 99+ | D | ^b | | | C ₁₆ H ₁₁ Cl ₄ O ₂ P | C, H, Cl, P | 250 | 0 | 0 |

^aMp 66-67°. ^bMp 62-63°.

$$\begin{array}{c} \text{O} \quad \text{CHCl} \\ \uparrow \quad \parallel \\ \text{R}^1\text{R}^2\text{POCCH}=\text{CCl}_2 \end{array}$$

Table V. Physical and Anthelmintic Properties of $\text{R}^1\text{R}^2\text{POCCH}=\text{CCl}_2$

| No. | R^1 | R^2 | Yield, % | Pur-ity, % | Meth-od of prepn | Bp, °C (mmHg) | n_D^{20} | d_4^{20} | Formula | Analyses | Mouse | | |
|-----|--------------------------------|--------------------------------|----------|------------|------------------|---------------|------------|------------|---|------------------------|------------|---------------------|------|
| | | | | | | | | | | | MTD, mg/kg | TR (MTD/MED) $H.n.$ | S.o. |
| 47 | CH_3O | CH_3O | 92.0 | 99 | E | 82–83 (0.001) | 1.5085 | 1.4719 | $\text{C}_6\text{H}_8\text{Cl}_3\text{O}_4\text{P}$ | C, H, Cl, P | 125 | 0 | 0 |
| 48 | $\text{C}_2\text{H}_5\text{O}$ | $\text{C}_2\text{H}_5\text{O}$ | 94.6 | 99+ | E | 112 (0.05) | 1.4929 | 1.3590 | $\text{C}_8\text{H}_{12}\text{Cl}_3\text{O}_4\text{P}$ | C, H, P; Cl^a | 125 | 0 | 0 |
| 49 | $\text{C}_2\text{H}_5\text{O}$ | C_6H_5 | 92.7 | 98 | E | 136 (0.06) | 1.5557 | 1.1370 | $\text{C}_{12}\text{H}_{12}\text{Cl}_3\text{O}_3\text{P}$ | C, H, Cl, P | 500 | 0 | 31 |
| 50 | CH_3O | C_6H_5 | 66.0 | 99+ | E | 145 (0.05) | 1.5639 | 1.4062 | $\text{C}_{11}\text{H}_{10}\text{Cl}_3\text{O}_3\text{P}$ | C, H, Cl, P | 500 | 2 | 2 |
| 51 | $\text{C}_2\text{H}_5\text{O}$ | C_2H_5 | 80.9 | 99+ | E | 91 (0.03) | 1.5087 | 1.3432 | $\text{C}_8\text{H}_{12}\text{Cl}_3\text{O}_3\text{P}$ | C, H, Cl, P | 62 | 0 | 2 |
| 52 | C_6H_5 | C_8H_5 | 89.0 | 99+ | E | <i>b</i> | | | $\text{C}_{18}\text{H}_{12}\text{Cl}_3\text{O}_2\text{P}$ | C, H, Cl, P | 500 | 0 | 0 |

^aCalcd: Cl, 34.4. Found: Cl, 33.9. ^bMp 82.5°.

$$\begin{array}{c} \text{O} \quad \text{CH}_2 \\ \uparrow \quad \parallel \\ (\text{R}^1\text{O})_2\text{POCC}(\text{R}^2)=\text{CClR}^3 \end{array}$$

Table VI. Physical and Anthelmintic Properties of $(\text{R}^1\text{O})_2\text{POCC}(\text{R}^2)=\text{CClR}^3$

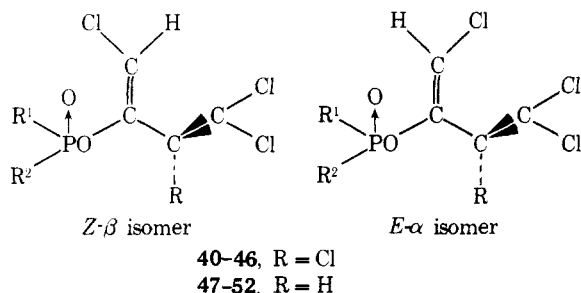
| No. | R^1 | R^2 | Yield, % | Pur-ity, % | Meth-od of prepn | Bp, °C (mmHg) | n_D^{20} | Formula | Anal-yses | Mouse | | |
|-----|------------------------|--------------|----------|------------|------------------|----------------|--------------|--|-----------|------------|---------------------|------|
| | | | | | | | | | | MTD, mg/kg | TR (MTD/MED) $H.n.$ | S.o. |
| 53 | CH_3 | H | 35.3 | 95 | F | 88–92 (0.02) | 1.4715 (25°) | $\text{C}_6\text{H}_{10}\text{ClO}_4\text{P}$ | Cl, P | 31 | 0 | 0 |
| 54 | C_2H_5 | H | 85.3 | 99 | F | 92–93 (0.02) | 1.4646 (25°) | $\text{C}_8\text{H}_{14}\text{ClO}_4\text{P}$ | Cl, P | 31 | 0 | 0 |
| 55 | CH_3 | Cl | 74.7 | 99 | G | 100–101 (0.04) | 1.4938 (18°) | $\text{C}_6\text{H}_8\text{Cl}_2\text{O}_4\text{P}$ | Cl, P | 125 | 0 | 0 |
| 56 | C_2H_5 | Cl | 81.6 | 92 | G | 110 (0.03) | 1.4844 (18°) | $\text{C}_8\text{H}_{12}\text{Cl}_2\text{O}_4\text{P}$ | Cl, P | 31 | 0 | 1 |

$$\begin{array}{c} \text{O} \quad \text{CCl}_2 \\ \uparrow \quad \parallel \\ (\text{RO})_2\text{POCCCl}=\text{C}(\text{Cl})\text{CCl}_2 \end{array}$$

Table VII. Physical and Anthelmintic Properties of $(\text{RO})_2\text{POCCCl}=\text{C}(\text{Cl})\text{CCl}_2$

| No. | R | Yield, % | Purity, % | Method of prepn | Bp, °C (mmHg) | n_D^{21} | Formula | Analyses | Mouse | | |
|-----|------------------------|----------|-----------|-----------------|----------------|------------|--|----------|------------|---------------------|------|
| | | | | | | | | | MTD, mg/kg | TR (MTD/MED) $H.n.$ | S.o. |
| 57 | CH_3 | 71.5 | 95 | H | 137 (0.02) | 1.5271 | $\text{C}_7\text{H}_8\text{Cl}_7\text{O}_4\text{P}$ | Cl, P | 250 | 1 | 16 |
| 58 | C_2H_5 | 58.6 | 95 | H | 145–146 (0.02) | | $\text{C}_9\text{H}_{10}\text{Cl}_7\text{O}_4\text{P}$ | Cl, P | 62 | 0 | 2 |

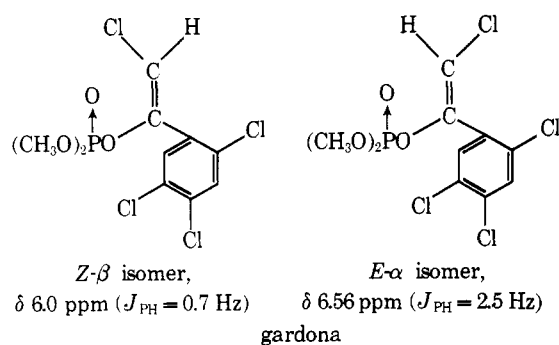
1,1,4-trichloro-1,3-butadien-3-yl esters 47–52 in high yield (Table V).



In addition to being mixtures of rotamers, tetrachlorobutadienyl esters 40–46 and trichlorobutadienyl compounds

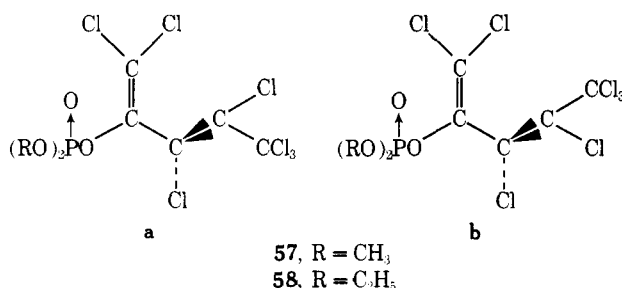
47–52 allow for *cis*–*trans* isomerism around the olefinic [chloromethylene ($\text{CHCl}=\text{}$)] bond. For example, in the NMR spectrum compound 41 shows two doublets (δ 6.52 and 6.62 ppm) in an 80:20 ratio. By analogy with the literature data,^{28–30} the 6.52 bond would be attributed to the *Z* 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 ($-\text{C}(\text{Cl})=\text{CCl}_2$) 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



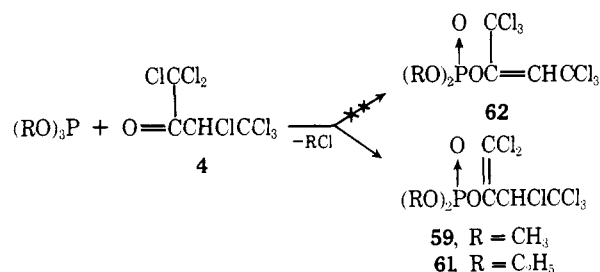
The 1,1,2,4-tetrachlorobutadienyl portion of the esters 40–46 may exist in a cisoid conformation (see above) and cause steric hindrance in the α isomer causing a preference for production of *Z* isomer. Compounds 40 (obtained from 9 and trimethyl phosphite) and 46 (purified by recrystallizations of the 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-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.

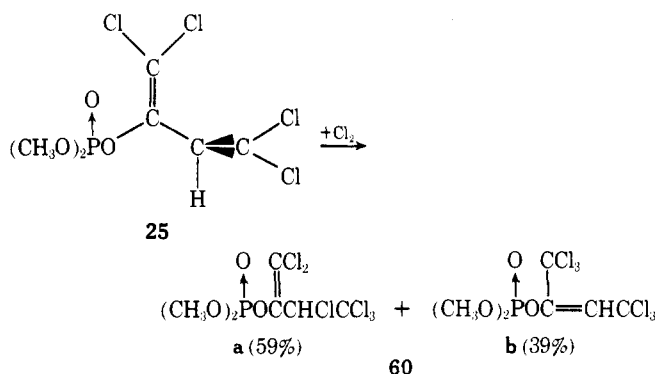


The key intermediate for the preparation of the dialkyl hexachlorobutenyl phosphates 59 and 61 was 1,1,1,3,4,4,4-heptachlorobutan-2-one (4). Both trimethyl and triethyl phosphite reacted uniformly with 4. Isomers such as 62 were not formed as evidenced by the chemical shift values of the reaction products. 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 correspond-

ing chemical shift of the olefinic proton would be expected near 6.6 ppm.



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 ($n^{20\text{D}}$, 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.



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,

$$\begin{array}{c} \text{O} \quad \text{CCl}_2 \\ \uparrow \quad \parallel \\ (\text{RO})_2\text{POCCHClCCl}_3 \end{array}$$

Table VIII. Physical and Anthelmintic Properties of $(\text{RO})_2\text{POCCHClCCl}_3$

| No. | R | Yield, % | Purity, % | Method of prepn | Bp, °C (mmHg) | n_D^{20} | d_4^{20} | Formula | Analyses | Mouse | | |
|-----|-------------------------------|-------------|--------------|--------------------|-----------------|------------|------------|---|---------------------------------------|---------------|-----------------|-------|
| | | | | | | | | | | MTD, mg/kg | TR (MTD/MED) | |
| | | | | | | | | | | | H. n. | S. o. |
| 59 | CH ₃ | 84.7 | 99 | I | 127 (0.02) | 1.5176 | 1.6475 | C ₆ H ₇ Cl ₆ O ₄ P | C, H, Cl, P | 31 | 0 | 2 |
| 60 | CH ₃ | 60.0 | 95 | J | 110–120 (0.01) | 1.5161 | 1.6439 | C ₆ H ₇ Cl ₆ O ₄ P | H, P; C, ^a Cl ^a | 31 | 0 | 2 |
| 61 | C ₂ H ₅ | 72.2 | 99+ | I | 110–111 (0.005) | 1.5035 | 1.5177 | C ₈ H ₁₁ Cl ₆ O ₄ P | C, H, Cl, P | 125 | 1 | 16 |

^aCalcd: 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 | | | | NMR positions (δ) for | | No. | Ultraviolet absorption | | | | NMR positions (δ) for | |
|-----|------------------------|------------------|-------------|------------------|-----------------------|---|-----|------------------------|------------------|-------------|------------------|-----------------------|------------|
| | λ_1 | Log ϵ_1 | λ_2 | Log ϵ_2 | –CH= | Others | | λ_1 | Log ϵ_1 | λ_2 | Log ϵ_2 | –CH= | Others |
| 5 | 245 | 3.871 | 205 | 3.853 | | | 40 | 246 | 3.940 | 205 | 4.189 | | 6.67 |
| 3 | 259 | 4.021 | | | 7.26 | | | | | | | (=CHCl) ^c | |
| 9 | 271 | 3.479 | 212 | 3.901 | | 6.76 (CHCl ₂) | 41 | 243 | 3.894 | 205 | 4.205 | | 6.52, 6.62 |
| 10 | 255 | 4.050 | | | 7.15 | 5.96 (CHCl ₂) | | | | | | (=CHCl) ^d | |
| 12 | <i>a</i> | | | | 6.8 | 4.15 (CH ₂ Cl), 7.5 (=CHCl) | 42 | <i>a</i> | | | | | 6.35, 6.42 |
| | | | | | | 4.5 (CH ₂ Cl) | | | | | | (=CHCl) ^e | |
| 11 | 263 | 3.620 | 205 | 3.780 | | | 43 | 252 | 3.741 | 215 | 4.287 | | 6.36, 6.60 |
| 8 | <i>a</i> | | | | | | | | | | | (=CHCl) ^f | |
| 4 | <i>b</i> | | | | | 5.71 (CHCl) | 44 | 245 | 3.874 | 210 | 4.371 | | 6.39, 6.61 |
| 13 | 247 | 3.868 | 208 | 4.301 | | | | | | | | (=CHCl) ^f | |
| 14 | 249 | 3.858 | 212 | 4.186 | | | 45 | 248 | 3.880 | 206 | 4.154 | | 6.41, 6.63 |
| 15 | 248 | 3.877 | 202 | 4.499 | | | | | | | | (=CHCl) ^g | |
| 16 | 251 | 3.869 | 212 | 4.197 | | | 46 | 252 | 3.833 | 220 | 4.346 | | 6.58 |
| 17 | 247 | 3.840 | 214 | 4.189 | | | | | | | | (=CHCl) ^c | |
| 18 | 248 | 3.888 | 212 | 4.223 | | | 47 | 256 | 4.127 | 200 | 3.656 | 6.78 | 6.48 |
| 19 | 248 | 3.841 | 212 | 4.187 | | | | | | | | (=CHCl) | |
| 20 | 249 | 3.851 | 207 | 4.264 | | | 48 | 257 | 4.107 | | | 6.70 | 6.42 |
| 21 | 249 | 3.845 | 213 | 4.173 | | | | | | | | (=CHCl) | |
| 22 | 251 | 3.822 | 217 | 4.356 | | | 49 | 264 | 4.205 | 216 | 4.224 | 6.67 | 6.43 |
| 23 | 252 | 3.826 | 215 | 4.411 | | | | | | | | (=CHCl) | |
| 24 | 252 | 3.848 | 222 | 4.509 | | | 50 | 259 | 4.133 | 217 | 4.180 | 6.62 | 6.43 |
| 25 | 260 | 4.052 | | | 6.56 | | | | | | | (=CHCl) | |
| 26 | 260 | 4.031 | | | 6.55 | | 51 | 262 | 4.176 | | | 6.76 | 6.46 |
| 27 | 258 | 4.039 | | | 6.60 | | | | | | | (=CHCl) | |
| 28 | 258 | 4.015 | | | 6.58 | | 52 | 261 | 4.092 | 223 | 4.315 | 6.70 | 6.57 |
| 29 | 258 | 4.010 | | | 6.60 | | | | | | | (=CHCl) | |
| 30 | 259 | 3.991 | | | <i>a</i> | | 53 | <i>a</i> | | | | <i>a</i> | |
| 31 | 257 | 4.038 | | | <i>a</i> | | 54 | <i>a</i> | | | | 6.4 | 4.7, 5.2 |
| 32 | 257 | 4.001 | | | <i>a</i> | | | | | | | (=CH ₂) | |
| 33 | 257 | 4.059 | | | <i>a</i> | | 55 | <i>a</i> | | | | 5.2, 5.5 | |
| 34 | 257 | 4.013 | | | 6.73 | | | | | | | (=CH ₂) | |
| 35 | 259 | 4.006 | | | 6.74 | | 56 | <i>a</i> | | | | 5.2, 5.2 | |
| 36 | 257 | 4.040 | 217 | 4.246 | 6.65 | | | | | | | (=CH ₂) | |
| 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 | | | 5.97 (CHCl) | |
| 39 | 260 | 3.939 | 224 | 4.423 | 6.45 | | 61 | 221 | 4.034 | | | 5.84 (CHCl) | |

^aNot determined. ^bNo absorption between 350 and 200 nm. ^cOnly one isomer (β) present. ^d $\alpha:\beta$ = 80:20. ^e $\alpha:\beta$ = 55:45. ^f $\alpha:\beta$ = 72:28. ^g $\alpha:\beta$ = 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 ($\text{CCl}_2=$) containing esters, e.g., 14, have higher therapeutic ratios than the chloromethylene ($\text{CHCl}=$) containing esters, e.g., 41, whereas the methylene ($\text{CH}_2=$) 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 ($-\text{CCl}=\text{CCl}_2$) portion of the butadienyl moiety, e.g., $-\text{CH}=\text{CCl}_2$ and $-\text{CH}=\text{CHCl}$, or saturation to $-\text{CHClCCl}_3$ 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 $\pm 0.4\%$ 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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