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

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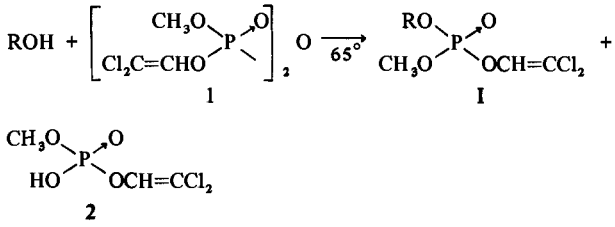
A series of aralkyl and aralkenyl analogs of the phosphate anthelmintic dichlorvos has been synthesized and found to have good anthelmintic activity in mice and rats. One compound, 2,2-dichlorovinyl methyl 4-phenylbutyl phosphate (**8**), is extremely active against the rodent parasites *Hymenolysis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

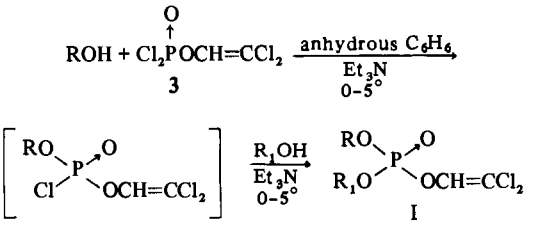
Route A. Eight aralkyl phosphates (I) were prepared by heating the appropriate alcohol with *P,P'*-bis(2,2-dichlorovinyl) *P,P'*-dimethyl pyrophosphate (**1**)[13] as illustrated in Scheme I.

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

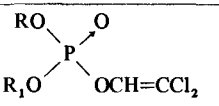


hydrogen chloride scavenger to reduce acid-catalyzed transesterification of the product. The main reaction by-products are dichlorvos, **4**, and the bisaralkyl (alkenyl) 2,2-dichlorovinyl phosphate. Initial reaction of the longer chain alcohol affords maximum product yields by reducing the amounts of 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.

Table I. Aralkyl and Aralkenyl Analogs of Dichlorvos



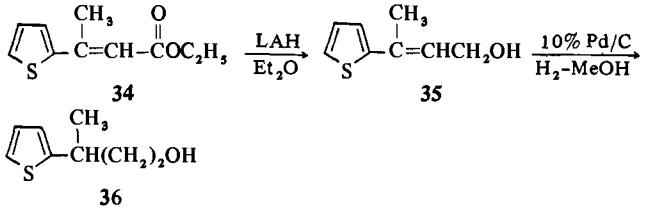
No.	R	R_1	Preparative route	Molecular still temp, °C (pressure, μ)	Yield, %	Purity, %[a]	Formula	Anal.	Mouse MTD,[b] mg/kg	Mouse MED,[b] mg/kg H.n.[c]	Mouse MED,[b] mg/kg S.o.[d]	Rat MTD, mg/kg	Rat MED, mg/kg N.b.[e]
4	CH_3	CH_3							62	*g*	62	62	*g*
5	C_6H_5-CH_2	CH_3	A	135 (0.2)	60	96	$C_{10}H_{11}Cl_2O_4P$	Cl, P	32	16	4	32	*g*
6	C_6H_5-C_2H_4	CH_3	A	130 (0.2)	91	95	$C_{11}H_{13}Cl_2O_4P$	Cl, P	125	62	4	62	*g*
7	C_6H_5-C_3H_6	CH_3	A	130 (0.2)	90	95	$C_{12}H_{15}Cl_2O_4P$	Cl. P	125	62	8	250	125
8	C_6H_5-C_4H_8	CH_3	A	160 (0.4)	86	94	$C_{13}H_{17}Cl_2O_4P$	Cl, P	500	4	2	250	125
9	C_6H_5-C_5H_{10}	CH_3	A	135 (0.6)	85	95	$C_{14}H_{19}Cl_2O_4P$	Cl, P	250	31	62	500	250
10	4-FC_6H_4-C_4H_8	CH_3	A	140 (0.4)	86	96	$C_{13}H_{16}Cl_2FO_4P$	Cl, P	250	31	31	250	31
11	4-ClC_6H_4-C_4H_8	CH_3	A	135 (0.5)	70	94	$C_{13}H_{16}Cl_3O_4P$	Cl, P	500	31	16	250	31
12	2,4-$CH_3C_6H_3$-C_4H_8	CH_3	A	150 (0.2)	87	95	$C_{15}H_{21}Cl_2O_4P$	Cl, P	125	31	125	125	*g*
13	*trans*-C_6H_5CH=CHC_2H_4	CH_3	B	145 (0.1)	80	95	$C_{13}H_{15}Cl_2O_4P$	Cl, P	500	31	31	500	62
14	*cis*-C_6H_5CH=CHC_2H_4	CH_3	B	145 (0.1)	66	96	$C_{13}H_{15}Cl_2O_4P$	Cl, P	250	31	16	125	62
15	C_6H_5-$CH(CH_3)C_2H_4$	CH_3	B	165 (0.3)	63	95	$C_{13}H_{17}Cl_2O_4P$	Cl, P	125	31	8	125	125
16	$C_6H_{11}C_4H_8$	CH_3	B	180 (500)	38	95	$C_{13}H_{23}Cl_2O_4P$	Cl, P	500	250	500	500	250
17	$C_6H_5C_4H_8$	C_3H_7	B	150 (0.1)	64	90	$C_{15}H_{21}Cl_2O_4P$	Cl, P	125	8	62	125	31
18	$C_6H_5C_4H_8$	$C_6H_5C_4H_8$	B	*f*	77	95	$C_{22}H_{27}Cl_2O_4P$	Cl, P	62	31	*g*	125	*g*
19	*cis*-C_6H_5CH=CH_2H_4	*cis*-C_6H_5CH=CHC_2H_4	B	*f*	95	95	$C_{22}H_{23}Cl_2O_4P$	Cl, P	31	*g*	*g*	125	*g*
20	*cis*-C_6H_5CH=CHC_2H_4	*trans*-C_6H_5CH=CHC_2H_4	B	*f*	85	95	$C_{22}H_{23}Cl_2O_4P$	Cl, P	125	*g*	125	250	*g*
21	*trans*-C_6H_5CH=CHC_2H_4	*trans*-C_6H_5CH=CHC_2H_4	B	*f*	84	95	$C_{22}H_{23}Cl_2O_4P$	Cl, P	500	500	250	500	500
22	2-C_4H_3S-C_2H_4	CH_3	B	150 (0.5)	78	98	$C_9H_{11}Cl_2O_4PS$	Cl, P, S	16	*g*	4	*h*	*h*
23	2-C_4H_3S-C_3H_6	CH_3	B	150 (0.15)	90	97	$C_{10}H_{13}Cl_2O_4PS$	Cl, P	250	62	4	250	62
24	2-C_4H_3S-C_4H_8	CH_3	B	150 (0.1)	88	96	$C_{11}H_{15}Cl_2O_4PS$	Cl, P, S	250	62	8	250	31
25	2-C_4H_3S-C_5H_{10}	CH_3	B	*f*	20	90	$C_{12}H_{17}Cl_2O_4PS$	Cl, P	250	250	16	500	250
26	2-C_4H_3S-CH=CHC_2H_4 [i]	CH_3	B	150 (0.3)	89	94	$C_{11}H_{13}Cl_2O_4PS$	Cl, P	250	250	8	250	31
27	2-C_4H_3S-$CH(CH_3)C_2H_4$	CH_3	B	*f*	73	90	$C_{11}H_{15}Cl_2O_4PS$	Cl, P, S	125	16	8	250	125
28	2-C_4H_3S-C_4H_8	C_2H_5	B	180 (5)	57	95	$C_{12}H_{17}Cl_2O_4PS$	Cl, P, S	125	31	2	62	16
29	2-C_4H_3S-C_4H_8	C_4H_9	B	170 (5)	67	96	$C_{14}H_{21}Cl_2O_4PS$	Cl, P, S	125	16	16	62	31
30	2-C_4H_3S-C_4H_8	2-C_4H_3S-C_4H_8	B	*f*	91	97	$C_{18}H_{23}Cl_2O_4PS$	Cl, P	125	62	62	125	62
31	2-C_4H_3O-C_3H_6	CH_3	B	150 (0.3)	65	94	$C_{10}H_{13}Cl_2O_5P$	Cl, P	125	125	4	125	125
32	2-C_4H_3O-C_4H_8	CH_3	B	*f*	45	95	$C_{11}H_{15}Cl_2O_5P$	Cl, P	250	62	4	125	16
33	2-C_4H_3O-CH=CHC_2H_4	CH_3	B	150 (0.1)	24	95	$C_{11}H_{13}Cl_2O_5P$	Cl, P	500	125	16	250	31

[a] Determined by nmr. [b] MTD = maximum tolerated dose; MED = minimum effective dose following oral administration. [c] H.n. = *Hymenolepsis nana* (mouse tapeworm). [d] S.o. = *Syphacia obvelata* (mouse pinworm). [e] N.b. = *Nippostrongylus braziliensis* (rat roundworm). [f] Sample chromatographed through silica gel G (Grace Grade 950; 60-200 mesh) using Et_2O as eluent. [g] Inactive at the MTD. [h] Not tested. [i] Contains trans and cis isomers in a 60/40 ratio.

The 4-aryl-3-buten-1-ols for the synthesis of **13**, **14**, **19**, **20**, **21**, **26**, and **33** were prepared from 2,2,2-triphenyl-1,2-oxaphospholane and an aldehyde as described by Hands and Mercer[15] for the phenyl and furyl alcohols. As previously reported,[15] the product was a mixture of isomeric alcohols consisting of approximately 60% trans and 40% cis. Samples of *cis*- and *trans*-4-phenyl-3-buten-1-ol were obtained by spinning band distillation. Hydrogenation over W-2 Raney nickel of the mixture of 4-(2-furyl)-3-buten-1-ols afforded the alcohol for the synthesis of **32**.

Ethyl 2-thiopheneacrylate,[16] obtained by the Wittig reaction between 2-thiophenecarboxaldehyde and (ethoxycarbonylmethyl)triphenylphosphonium bromide,[17] was reduced with LAH to 2-thiophenepropanol,[18] the intermediate for the synthesis of **23**. 3-Phenylbutanol, the intermediate for the synthesis of **15**, was synthesized by the procedure of Heilmann and Glenat.[19] γ-Methyl-2-thiophenepropanol (**36**), the starting alcohol for **27**, was prepared from ethyl β-methyl-β-(2-thienyl)acrylate (**34**)[20] as shown in Scheme III. In contrast to the previously described reduc-

Scheme III



tion of ethyl 2-thiopheneacrylate, LAH did not reduce the double bond of **34**, as evidenced by nmr, presumably due to the increased steric hindrance of the methyl group. The hydrogenation of **35** was carried out on the crude material due to its relative instability to distillation. This hydrogenation proceeded slowly presumably due to catalyst poisoning by the divalent sulfur as reported for thiophene containing compounds.[21] However, after hydrogenation at 3-4 atm for 24 hr **36** was obtained.

2-Furanpropanol was synthesized from 2-furanacrolein by the method of Ponomarev.[22] Cyclohexanebutanol[23] was prepared by the LAH reduction of cyclohexanebutanoic acid.

Biological Results and Discussion. The phosphates in Table I were tested for anthelmintic activity in parasitized Swiss-Webster derived white mice and Sprague-Dawley derived white rats. The mice were exposed to a mixed culture of infective larvae and eggs of the roundworm *Nematosphiroides dubius*, tapeworm *Hymenolysis nana*, and pinworm *Syphacia obvelata* 15 days pretreatment, while the rats were infected with the roundworm *Nippostrongylus braziliensis* 8 days before chemotherapeutic dosing.§ The compounds were dissolved in corn oil at 50 mg/ml 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. Twenty-four hours after therapy the animals were sacrificed and evaluated for efficacy. Active or toxic compounds were tested subsequently at lower doses to establish a minimum effective dose (MED), *i.e.*, that dose which effected complete clearance of the parasite species in three of five mice and a 75% clearance in the rat as compared to infected nontreated controls. Relative activities of the compounds against *H. nana*, *S. obvelata*, and *N. braziliensis* are expressed in Table I in terms of their maximum tolerated dose (MTD) (or 500 mg/kg) and minimum effective dose.

In general, the phosphates in Table I were inactive against the mouse roundworm *N. dubius*. Only **13**, **14**, **23**, and **32** at their maximum tolerated doses and **33** at 250 mg/kg were active against *N. dubius*. Therefore, the following structure-activity discussion will consider only activity against the mouse pinworm and tapeworm and rat roundworm.

All the compounds, except **19**, had activity equal to or better than technical dichlorvos (**4**) against all the parasites. The anthelmintic activity of the phenylbutyl ester, **8**, was greatly superior to any of the other analogs against the mouse tapeworm and pinworm but had only a low level of activity against the rat roundworm. Whether the high activity of **8** can be attributed to increased hydrophobic bonding of the phenylbutyl group, as in the *O*-alkyl *S*-phenylbutyl methylthiophosphonate inhibition of butyryl cholinesterase,[8] is uncertain since enzyme binding studies have not been done with these compounds.

In the phenylbutyl ester series, ring substitution of fluorine (**10**), chlorine (**11**), or methyl (**12**), unsaturation in the side chain (**13** and **14**), or replacement of the methyl ester with propyl (**17**) resulted in large decreases in activity against the mouse pinworm and tapeworm, but gave variable responses against the rat roundworm. Phosphates **10**, **11**, **13**, and **17** were more active than **8** against the rat roundworm. Compounds **12** and **17** also appeared slightly more toxic to the mouse. In the rat the *cis*-butenyl (**14**) is less active and more toxic than the trans isomer (**13**).

Replacement of the phenyl ring with thienyl (**24**) or furyl (**32**) again resulted in a large decrease in activity against the mouse pinworm and tapeworm, but afforded an increase in activity against the rat roundworm. Replacement with the cyclohexyl ring (**16**) nearly abolished activity against the mouse parasites.

In the phenyl series, both decreases (**5**, **6**, and **7**) and an increase (**9**) in the alkyl chain length from four carbons (**8**) afforded less active compounds against the tapeworm and pinworm. In the thienyl and furyl compounds a decrease in the alkyl chain length from four carbons (**24**, **32**) to three carbons (**23**, **31**) or an increase to give carbons (**25**) caused essentially no change against the pinworm. Against tapeworms, **24** and **23** were equal in activity, but **31** and **25** were less active than **32** and **24**. Against the rat roundworm **23**, **24**, and **25** were essentially equal in activity, but **32** was more potent than **31**. Decreasing the chain length two carbons (**22**) resulted in lower activity against both mouse parasites and a marked increase in toxicity.

In the thienyl series replacement of the methyl ester in **24** with ethyl (**28**) and butyl (**29**) afforded more toxic compounds. Compound **28** had a similar spectrum of activity, but **29** was considerably less active against the mouse pinworm. Replacement of the tetramethylene chain of **24** and **32** with a butenylene chain (**26** and **33**) afforded essentially no change in toxicity or efficacy against the mouse pinworm or rat roundworm. Both **26** and **33** were less active against the mouse tapeworm.

Alteration of the aryl ring from the 4 position on the alkyl chain to the 3 position again resulted in a decrease in mouse parasite activity in the phenyl series, **8** *vs.* **15**, and a variable response in activity against the rodent parasites in the thienyl series, **24** *vs.* **27**.

The bisaralkyl or aralkenyl esters, **18**, **19**, **20**, **21**, and **30**, were either devoid, or possessed only low levels, of activity.

§ For procedures see ref 24.

Of interest is the significantly greater toxicity of **19** (cis alkenyl) compared to **21** (trans) against both rodent species.

Experimental Section#

The following known compounds, whose general synthesis was described in the test, had physical constants and spectral features in agreement with reported values: *p*-fluorobenzoylpropionic acid,[25] *p*-fluorophenylbutyric acid,[25] ethyl *p*-fluorophenylbutyrate,[25] *p*-chlorobenzoylpropionic acid,[26] *p*-chlorophenylbutyric acid,[26] ethyl *p*-chlorophenylbutyrate,[27] 2,4-xyloylpropionic acid,[28] 2,4-xylylbutyric acid,[28] 2,4-xylylbutanol,[29] 3-(2-thenoyl)propionic acid,[26] 2-thiophenebutyric acid,[26] ethyl 2-thiophenebutyrate,[30] 2-thiophenebutanol,[31] 4-(2-thenoyl)butyric acid,[32] 2-thiophenevaleric acid,[33] and methyl 2-thiophenevalerate.[33]

p-**Fluorophenylbutanol** was synthesized in a 97% yield of crude product by the LAH (Et_2O) reduction of the corresponding Et ester.[25] *Anal.* ($C_{10}H_{13}FO$) H, C: calcd, 71.4; found, 69.3.

Ethyl 2,4-xylylbutyrate was synthesized in a 98% yield of crude product by the HCl-catalyzed esterification of the corresponding acid.[28] The product, showing essentially a single peak of glc, was reduced without further purification to the known 2,4-xylylbutanol.[29]

cis- **and** *trans*-**4-Phenyl-3-buten-1-ols.**[15] The cis isomer had bp 88° (0.6 mm), the trans isomer bp 96° (0.6 mm). *Anal.* ($C_{10}H_{12}O$) C, H.

cis- **and** *trans*-**4-(2-thienyl)-3-buten-1-ols** were prepared by the method of Hands and Mercer[15] in an 82% yield of an isomeric mixture consisting of approx 60% trans and 40% cis (glc), bp 95–98° (0.35 mm). *Anal.* ($C_8H_{10}OS$) S.

γ-Methyl-2-thiophenepropanol (36) had bp 86–88° (0.1 mm). *Anal.* ($C_8H_{12}OS$) S.

The following are representative of the routes used to prepare the phosphates.

Phosphoric Acid 2,2-Dichlorovinyl Methyl 4-Phenylbutyl Ester (8). Route A. To 9.9 g (0.065 mole) of stirred 4-phenylbutanol was added 27.2 g (0.065 mole, 95% purity) of **1**.[13] After an initial exothermic reaction, the mixt was heated at 65° for 3 hr, cooled, and diluted with 300 ml of CH_2Cl_2. This soln was washed successively with H_2O, saturated $NaHCO_3$, and saturated NaCl, dried (Na_2SO_4), and concentrated. The residue was distilled through a wiped-film molecular still at 160° (0.4 μ) to give 18.9 g (86%) of light yellow **8**.

Phosphoric Acid 2,2-Dichlorovinyl Methyl 4-(2-Thienyl)butyl Ester (24). Route B. To a stirred anhydrous C_6H_6 soln of 135 g (0.58 mole) of 2,2-dichlorovinyl phosphorodichloridate (**5**)[12] at 0–10° was added dropwise an anhydrous C_6H_6 solution of a mixt of 91.2 g (0.58 mole) of 2-thiophenebutanol[30] and 59 g (81 ml, 0.58 mole) of Et_3N (KOH dried). After stirring at 5–10° for 2.5 hr, an anhydrous C_6H_6 soln of a mixt of 18.7 g (0.58 mole) of anhydrous MeOH and 59 g (81 ml, 0.58 mole) of Et_3N was added dropwise at 8°. The reaction mixt was stirred for 2 hr, and the solids were filtered and washed with C_6H_6. The combined filtrates were concentrated, and the residue was taken up in CH_2Cl_2, washed (H_2O), dried ($MgSO_4$), and stripped to give 206 g of crude **24**. The crude **24** was distilled through a wiped-film molecular still at 175° (0.1 μ) to give 190 g of **24** which was redistilled at 150° (0.3 μ) to afford 180 g (88%) of **24** as a light yellow oil.

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#Structure determinations were based on microanalysis and comparison of ir and nmr spectral features. Since no unusual spectral features were observed for these compounds, no absorption peaks are listed in the Experimental Section. Where analyses are represented only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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