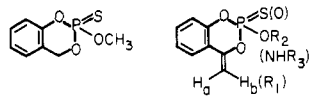
Insecticidal 4-Alkylidene-1,3,2-benzodioxaphosphorinane Derivatives

2-Alkoxy-4-alkylidene-1,3,2-benzodioxaphosphorin 2-sulfides and related compounds are obtained from *o*-hydroxyacetophenone and other *o*-alkylketophenols by several routes, usually involving thermal cyclization of the appropriate phosphorochloridate intermediates. ^1H and ^{31}P NMR and HPLC studies assign the higher 4-alkylidene derivatives as the *Z*-form configuration. As in the salithion series, cyclic phosphorus esters with lower 2-alkoxy or 2-alkylamino and 4-alkylidene substituents are potent insecticides.

The potency of salithion (1) (Eto et al., 1963) and related



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saligenin cyclic phosphorus esters (Eto, 1974) as insecticides prompted synthesis and bioassay of analogous compounds (**2**, R_1, R_2, and R_3 = lower alkyl) with 4-alkylidene substituents.

Preparation of Cyclic Phosphorus Esters. Synthesis routes are given in Figure 1 with examples of the products in Table I. Compound **3** (R_1 = H, CH_3) from commercial sources was converted to **4** (R_1 = H, CH_3) and **5** (R_1 = H, CH_3; R_2 = CH_3, C_2H_5) by a reported procedure (Cragg et al., 1977). Cyclic phosphates **6** and **7** were obtained by reaction of **5** (R_1 = H; R_2 = CH_3, C_2H_5) with equimolar *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at −50 °C with product isolation by preparative TLC (silica gel; hexane–acetone, 7:2). Cyclic phosphorothionates **9**–**11** were prepared by stirring a mixture of **5** and equimolar elemental sulfur in carbon disulfide for 5 h at 50 °C and isolating the products by distillation. Two other routes also provided the cyclic phosphorothionates. Compounds **12** and **14** were obtained by mixing equimolar **3** (R_1 = CH_3, C_2H_5) with *O*-ethyl thionophosphoryl dichloridate in 20% NaOH at 10 °C, followed by stirring for 2 h at 25 °C and recovery by extraction into chloroform. Slow distillation under reduced pressure converted the intermediate **8** (R_1 = CH_3, C_2H_5; R_2 = C_2H_5) to **12** and **14**. The Schotten-Baumann procedure as above but with thiophosphoryl trichloride gave **15** (R_1 = H, CH_3) which was converted to **16** (R_1 = H, CH_3) on distillation (~135 °C/0.1 mmHg). This was a very useful intermediate, providing **13** on reaction with equimolar propanol and triethylamine in benzene and giving **17** and **18** by addition of excess amine to the chloridate in benzene at 25 °C. Compounds **13**, **17**, and **18** were isolated by preparative TLC as above. The

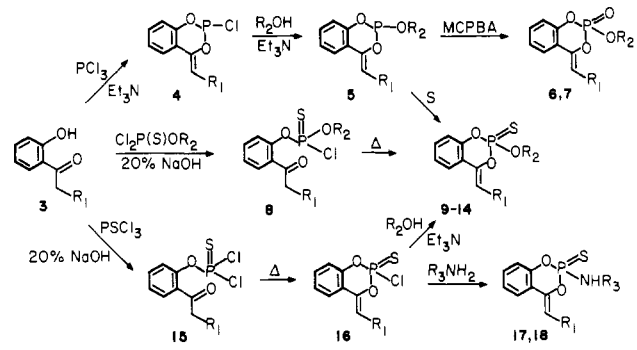

Figure 1

reported yields refer to the final step in the reaction sequence.

Purity and Structure. All compounds (including **4**, **5**, **8**, **15**, and **16**) appeared to be pure by TLC and gave appropriate chemical ionization quasi-molecular ions $(M + 1)^+$ and the anticipated ^1H NMR spectra in $CDCl_3$ (tetramethylsilane). ^{31}P NMR spectra were obtained for solutions in $CDCl_3$, reporting chemical shifts as positive when downfield of 1% trimethyl phosphate in $CDCl_3$ (^{31}P = 0). The higher alkylidene derivatives **11**–**14** each gave a single spot on TLC and a single peak on HPLC (μPorasil; hexane–chloroform, 4:1). ^1H NMR and ^{31}P NMR (**16**, R_1 = CH_3; ^{31}P = 46.5 ppm; see also Table I) further supported the presence of a single isomer. ^1H NMR assigned the *Z*-form configuration. The signals for H_a (5.64–5.76 ppm) appeared as a double quartet (R_1 = CH_3; $J_{H_a\text{-}CH}$ = 7 Hz) or a double triplet (R_1 = C_2H_5; $J_{H_a\text{-}CH}$ = 7 Hz) because of the coupling with phosphorus ($^4J_{P\text{-}H_a}$ = 5 Hz for phosphates and 3 Hz for phosphorothionates) [*W* effect (Cooper, 1980)]. It seems likely that a high degree of stereoselectivity is involved in the enolization and cyclization reaction sequence.

Biological Activity. The toxicity of the new compounds applied topically to adult female houseflies (*Musca*

Table I. Properties of 4-Alkylidene-1,3,2-benzodioxaphosphorinane Derivatives

no.	phosphorus moiety of 2	H_b or R_1	yield, %	mp, °C, or bp, °C/mmHg	^1H NMR ($CDCl_3$), δ H_a	H_b	^{31}P NMR ($CDCl_3$), δ	fly LD_{50}, μg/g
6	$P(O)OCH_3$	H	80	27-28	5.23	5.00	−15.7	8
7	$P(O)OC_2H_5$	H	85	25-27	5.29	5.04	−16.5	43
9	$P(S)OCH_3$	H	90	125-130/0.1	5.24	5.00	52.0	7
10	$P(S)OC_2H_5$	H	92	134-136/0.1	5.21	4.94	51.0	18
11	$P(S)OCH_3$	CH_3	85	135-137/0.1	5.76		53.6	56
12	$P(S)OC_2H_5$	CH_3	20	140-142/0.1	5.70		51.9	43
13	$P(S)OC_3H_7$	CH_3	20	oil	5.69		51.9	590
14	$P(S)OC_2H_5$	C_2H_5	35	140-142/0.1	5.64		52.0	15
17	$P(S)NHCH_3$	H	90	oil	5.22	4.94	58.2	7
18	$P(S)NHC_3H_7$	H	19	oil	5.24	4.89	61.8	240

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domestica L., SCR strain) was somewhat less than that of salithion and its ethoxy analogue which gave LD_{50} values of 2.5 and 7 $\mu g/g$, respectively. Within the 4-alkylidene series considered here, high toxicity to houseflies was conferred by a phosphate or phosphorothionate moiety, by several small exocyclic substituents (e.g., methoxy, ethoxy, or methylamino), and by R_1 as H, CH_3, or C_2H_5. The potency of compound **6** in inhibiting fly head and electric eel acetylcholinesterase was similar to that of the phosphate analogue of salithion. Several *O*-phenyl cyclic phosphates (R_1 = H, CH_3, or C_2H_5; R_2 = phenyl) administered intraperitoneally were potent synergists for malathion toxicity in mice and were delayed neurotoxicants in hens.

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CORRESPONDENCE

On Globulins of Soybean Seeds

Sir: My colleagues and I at Iowa State University wish to report some serious deletions in the literature citations in a pair of articles appearing in the *Journal of Agricultural and Food Chemistry*. The articles are the following: "2S Globulins of Soybean Seeds. 1. Isolation and Characterization of Protein Components", by I. Koshiyama,* M. Kikuchi, K. Harada, and D. Fukushima, *J. Agric. Food Chem.* **1981**, *29*, 336; "2S Globulins of Soybean Seeds. 2. Physicochemical and Biological Properties of Protease Inhibitors", by I. Koshiyama, M. Kikuchi, and D. Fukushima, *J. Agric. Food Chem.* **1981**, *29*, 340. Nowhere in their literature citations do they cite the original work of others more than 15 years ago. Among the original works are the following.

1. Birk, Y., et al. *Biochem. J.* **1963**, *87*, 281–284.
2. Catsimpoolas, N., et al. *Cereal Chem.* **1969**, *46*, 136–144.
3. Catsimpoolas, N., et al. *Anal. Biochem.* **1969**, *31*, 437–447.
4. Eldridge, A. C.; Wolf, W. J. *Cereal Chem.* **1969**, *46*, 470–478.
5. Frattali, V., et al. *Biochemistry* **1968**, *7*, 521–530.
6. Frattali, V. *J. Biol. Chem.* **1969**, *244*, 274–280.
7. Kunitz, M. *J. Gen. Physiol.* **1946**, *29*, 149–154.
8. Obara, T., et al. *Cereal Chem.* **1970**, *47*, 597–606.
9. Rackis, J. J., et al. *J. Am. Chem. Soc.* **1959**, *81*, 6265–6270.
10. Rackis, J. J., et al. *Arch. Biochem. Biophys.* **1962**, *98*, 471–478.
11. Rackis, J. J., et al. *Biochem. Biophys. Res. Commun.* **1964**, *15*, 230–235.
12. Rackis, J. J., et al. *Arch. Biochem. Biophys.* **1970**, *98*, 471–478.

There have also been a number of excellent reviews on the chemical and physical properties of these soy trypsin inhibitors. Among them are the following.

Birk, Y. *Ann. N.Y. Acad. Sci.* **1968**, *148*, 388–399.
Vogel, R., et al. "Natural Proteinase Inhibitors"; Academic Press: New York, 1968.
Liener, I. E.; Kakade, M. L. In "Toxic Constituents of Plant Foodstuffs"; Liener, I. E., Ed.; Academic Press: New York, 1969.
Kassell, B. *Methods Enzymol.* **1970**, *19*, 839–890.

The failure to cite at least some of these original workers in the newly published articles leads one to believe the work is "new". Careful examination of the literature shows this to be quite the opposite.

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