# New Types of Insect Chemosterilants. Benzylphenols and Benzyl-1,3-benzodioxole Derivatives as Additives to Housefly Diet

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Benzyl and cinnamyl derivatives of 2,4-di-*tert*-butylphenol and of 1,3-benzodioxoles sterilize mixed sexes of houseflies when fed at concentrations as low as 0.025% in the diet. Several of the compounds are also active against males, the most effective male sterilants being 2,4-bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)methyl]phenol (**1c**), 5-propoxy-6-[(4-methoxyphenyl)methyl]-1,3-benzodioxole (**9d**), and 5-ethoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (**10c**) at concentrations of 0.25, 0.1, and 0.05%, respectively. Benzyl-2,6-di-*tert*-butylphenols are generally inactive. Structure–activity correlations suggest that sterilant activity is due to in vivo oxidation of the compounds to reactive quinone methides. **1c** (and other benzylphenols) is only slightly toxic to mice and is nonmutagenic in standard Ames bacterial tests.

Although TEPA [tris(1-aziridinyl)phosphine oxide] is a highly effective insect chemosterilant, the possible mutagenic and carcinogenic properties of this and similar aziridinyl compounds have limited its application and led to a continuing search for new types of sterilants which may be safely used under field conditions (Chang et al., 1964; Bořkovec, 1966). Subsequent studies led to the recognition of new sterilants such as HEMPA (hexamethylphosphoric triamide), dithiazolium salts, and other nitrogenous alkylating agents (Terry and Bořkovec, 1970; Oliver et al., 1973; Fye and Oliver, 1974; Fye et al., 1966). It was observed, however, that few nonaziridine alkylating agents showed sterilizing activity (against the housefly, screwworm, fly, and Mexican fruit fly) and that this activity was highly erratic and difficult to reproduce.

Some years ago a program was begun in these laboratories to determine whether biologically active constituents isolated from plant materials could serve as models for the synthesis and development of new classes of possibly safer insect control agents. As one aspect of this work we have now established that a variety of simple benzylphenols and benzyl-1,3-benzodioxole derivatives are potent insect chemosterilants against the housefly. To determine the sterilizing properties of these substances they were tested as additives to the diet of adult houseflies (*Musca domestica* L.). The sterilant activities of active compounds against mixed sexes, and in some cases, males, are listed in Table I. A limited number of representative inactive compounds are included in Table I and mentioned in the text to illustrate the effects of structural variation upon biological activity.

It is particularly noteworthy that a number of these sterilants have been shown to be nonmutagenic in the Ames test with three *Salmonella* tester strains. Furthermore, studies in progress indicate that these sterilants are toxic or otherwise biologically active against other insect pests.

## EXPERIMENTAL SECTION

All boiling points and melting points are uncorrected. $^1$H NMR spectra were determined in $CDCl_3$ with a $Me_4Si$ internal standard on a modified Varian HA-100 instrument. **5** was provided by Monsanto Co. With the exception of **1b** and **2b** the following compounds have not previously been described. General procedures for the preparation of phenolic benzodioxoles and their alkyl ethers are illustrated by the synthesis of **10a** and its derivatives. Detailed descriptions of other benzodioxoles listed in Table I are given in the Supplementary Material (see Supplementary Material Available paragraph). Satisfactory elemental analyses (C, H) were obtained on all compounds.

**2,4-Bis(1,1-dimethylethyl)-6-(1-phenylethyl)phenol (1b).** **1b** has previously been prepared by reaction of 2,4-di-*tert*-butylphenol and styrene in the presence of concentrated $H_2SO_4$ (Spacht, 1959). In this investigation it was conveniently synthesized in high yield by the following process: A solution of 2,4-di-*tert*-butylphenol (51 g) and 1-phenylethanol (31 g) in acetic acid (40 mL) and formic acid (80 mL) was refluxed for 6 h and diluted with water. Distillation of the oily product gave **1b** as a colorless oil: bp 157–158 °C (2 mm) (71.5 g); meas. mass = 310.2308, calcd for $C_{22}H_{30}O$ = 310.2296; $^1$H NMR $\delta$ 1.34 (9 H, s), 1.55 (9 H, s), 1.65 (3 H, d, $J$ = 7.5 Hz), 4.22 (1 H, q, $J$ = 7.5 Hz), 4.53 (1 H, s), 7.20 (7 H, m). The benzylphenol **1a** was prepared as previously described (Green, 1965).

**2,4-Bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)-methyl]phenol (1c).** A solution of 2,4-di-*tert*-butylphenol (57.5 g), 4-methoxybenzyl alcohol (34.5 g), and oxalic acid (2 g) in acetic acid (80 mL) and water (2 mL) was refluxed for 7 h, diluted with water, and extracted with chloroform. Distillation of the chloroform extract gave an oil, bp 200–210 °C (2 mm), which crystallized (58 g, 71.4%). Recrystallized from methanol, **1c** was obtained as colorless needles: mp 84–85 °C; $^1$H NMR $\delta$ 1.30 (9 H, s), 1.38 (9 H, s), 3.79 (3 H, s), 3.83 (2 H, s), 4.62 (1 H, s), 6.84 (2 H, d, $J$ = 8 Hz), 7.03 (1 H, d, $J$ = 2 Hz), 7.14 (2 H, d, $J$ = 8 Hz), 7.23 (1 H, d, $J$ = 2 Hz).

**2,4-Bis(1,1-dimethylethyl)-6-[1-(4-methoxyphenyl)ethyl]phenol (1d).** A solution of 2,4-di-*tert*-butylphenol (51.5 g) and 1-(4-methoxyphenyl)ethanol (43 g) in acetic acid (40 mL) and formic acid (40 mL) was refluxed for 5 h, diluted with water, and extracted with chloroform. Distillation of the chloroform extract gave a yellow oil, bp 180 °C (1.0 mm), which crystallized (54 g). Recrystallized from methanol, **1d** separated as colorless needles which melt at room temperatures: $^1$H NMR $\delta$ 1.35 (9 H, s), 1.37 (9 H, s), 1.63 (3 H, d, $J$ = 7 Hz), 3.78 (3 H, s), 4.17 (1 H, q, $J$ = 7 Hz), 4.62 (1 H, s), 6.84 (2 H, d, $J$ = 8 Hz), 7.10–7.30 (4 H, m).

**2,6-Bis(1,1-dimethylethyl)-4-(1-phenylethyl)phenol (2b).** **2b** has previously been prepared by reaction of

Western Regional Research Center, U.S. Department of Agriculture, Science and Education Administration, Berkeley, California 94710 (L.J.) and the Insects Affecting Man and Animal Research Laboratory, Southern Region, Agricultural Research, U.S. Department of Agriculture, Gainesville, Florida 32601 (R.L.F., J.M.).

Table I. Sterilizing and Toxic Effects of Compounds Added to the Diet of Mixed Sexes of Houseflies

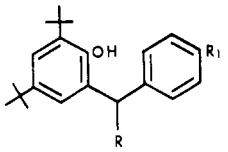
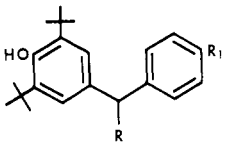
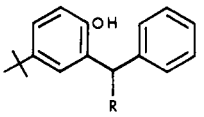
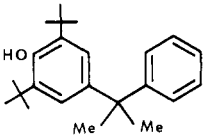
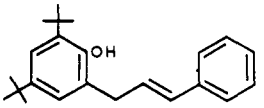
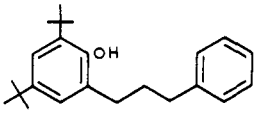
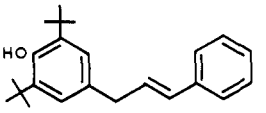
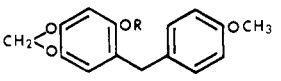
| | compound | concn, % | mortality, % | hatch,[d] % |
|---|---|---|---|---|
| |  | | | |
| 1a | $R = R_1 = H$ | 1.0[a] | 0 | 0 |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 0 |
| | | 0.05 | 0 | 90 |
| 1b | $R = CH_3$, $R_1 = H$ | 1.0 | 100 | |
| | | 0.5 | 78 | 0 |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 0 |
| | | 0.025 | 0 | 28 |
| 1c | $R = H$, $R_1 = OCH_3$ | 1.0 | 0 | NO[c] |
| | | 0.5 | 0 | NO |
| | | 0.25[a] | 0 | 0 |
| | | 0.1[b] | 0 | 0 |
| | | 0.025 | 0 | 0 |
| | | 0.01 | 0 | 45 |
| 1d | $R = CH_3$, $R_1 = OCH_3$ | 1.0[a] | 0 | 0 |
| | | 0.5[b] | 0 | 0 |
| | | 0.25 | 0 | 18 |
| |  | | | |
| 2b | $R = CH_3$, $R_1 = H$ | 1.0[b] | 0 | 0 |
| | | 0.25 | 0 | 0 |
| | | 0.1 | 0 | 36 |
| 2c | $R = H$, $R_1 = OCH_3$ | 1.0 | | normal |
| 2d | $R = CH_3$, $R_1 = OCH_3$ | 1.0 | | normal |
| |  | | | |
| 3 | R = H | 1.0 | | normal |
| 4 | $R = CH_3$ | 1.0 | | normal |
| 5 |  | 1.0 | | normal |
| 6 |  | 1.0 | 0 | NO |
| | | 0.5 | 0 | 0 |
| | | 0.25 | 0 | 0 |
| | | 0.1 | 0 | 21 |
| 7 |  | 1.0 | 0 | NO |
| | | 0.5 | 0 | NO |
| | | 0.25 | 0 | NO |
| | | 0.1 | 0 | 64 |
| 8 |  | 1.0 | | normal |
| |  | | | |
| 9a | R = H | 1.0 | | normal |
| 9b | $R = CH_3$ | 1.0 | 100 | |
| | | 0.5 | 96 | NO |
| | | 0.25 | 60 | NO |
| | | 0.1[b] | 0 | 0 |

Table I (*Continued*)

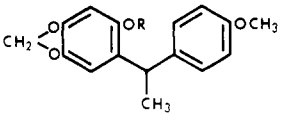
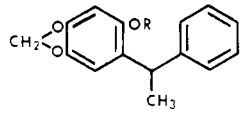
| | compound | concn, % | mortality, % | hatch,[a] % |
|---|---|---|---|---|
| | | 0.05 | 0 | 0 |
| | | 0.01 | 0 | 91 |
| 9c | R = $CH_2CH_3$ | 1.0 | 100 | |
| | | 0.5 | 100 | |
| | | 0.25 | 80 | NO |
| | | 0.1[b] | 0 | NO |
| | | 0.05 | 0 | 0 |
| | | 0.025 | 0 | 0 |
| | | 0.01 | 0 | 19 |
| 9d | R = $CH_2CH_2CH_3$ | 1.0 | 100 | |
| | | 0.5 | 89 | NO |
| | | 0.25 | 75 | NO |
| | | 0.1[a] | 0 | 0 |
| | | 0.05 | 0 | 33 |
| 9e | R = $CH(CH_3)_2$ | 1.0 | 95 | NO |
| | | 0.5 | 80 | NO |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 0 |
| | | 0.05 | 0 | 48 |
| 9f | R = $CH_2(CH_2)_2CH_3$ | 1.0 | 100 | |
| | | 0.5[b] | 0 | 0 |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 10 |
| 9g | R = $CH_2CH(CH_3)_2$ | 1.0 | 0 | 0 |
| | | 0.5 | 90 | NO |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 0 |
| | | 0.05 | 0 | 28 |
| 9h | R = $CH_2(CH_2)_3CH_3$ | 1.0 | 100 | |
| | | 0.5 | 40 | 14 |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 31 |
| 9i | R = $CH_2CH_2CH(CH_3)_2$ | 1.0 | 80 | 0 |
| | | 0.5[b] | 0 | 0 |
| | | 0.25 | 0 | 0 |
| | | 0.1 | 0 | 6 |
| |  | | | |
| 10a | R = H | | | |
| 10b | R = $CH_3$ | 1.0 | 100 | |
| | | 0.5 | 100 | |
| | | 0.25 | 100 | |
| | | 0.1 | 96 | NO |
| | | 0.05 | 92 | NO |
| | | 0.025 | 0 | 45 |
| 10c | R = $CH_2CH_3$ | 1.0[a] | 0 | NO |
| | | 0.5 | 98 | NO |
| | | 0.25 | 96 | NO |
| | | 0.1 | 98 | NO |
| | | 0.05[a] | 0 | NO |
| | | 0.025 | 0 | 83 |
| 10d | R = $CH_2CH_2CH_3$ | 1.0[a] | 0 | NO |
| | | 0.5[a] | 80 | NO |
| | | 0.25[a] | 82 | 0 |
| | | 0.1[b] | 70 | 0 |
| | | 0.05[b] | 60 | 0 |
| | | 0.025 | 0 | 38 |
| 10e | R = $CH_2(CH_2)_2CH_3$ | 1.0 | 60 | 0 |
| | | 0.5 | 38 | 0 |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 2 |
| |  | | | |
| 11a | R = H | | | |
| 11b | R = $CH_3$ | 1.0 | | normal |
| 11c | R = $CH_2CH_2CH_3$ | 1.0 | 100 | |
| | | 0.5[b] | 42 | 0 |
| | | 0.25 | 60 | 56 |

Table I (*Continued*)

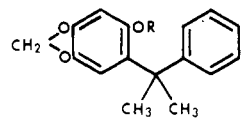
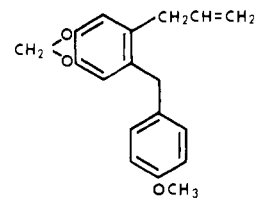
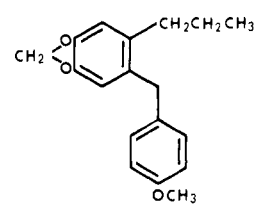
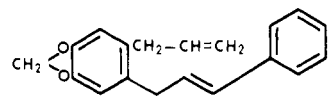
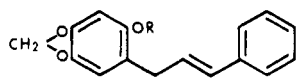
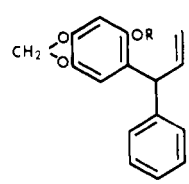
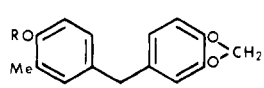
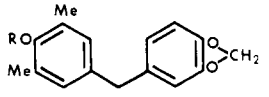
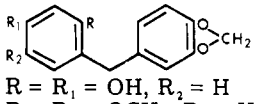
| | compound | concn, % | mortality, % | hatch,[d] % |
|---|---|---|---|---|
| 11d | R = $CH_2(CH_2)_2CH_3$ | 1.0[b] | 0 | 0 |
| | | 0.05 | 0 | 0 |
| | | 0.025 | 0 | 42 |
| 11e | R = $CH_2(CH_2)_3CH_3$ | 1.0 | 100 | |
| | | 0.5 | 0 | 34 |
| |  | | | |
| 12a | R = H | | | |
| 12b | (R = Me), **12c** (R = Et), **12d** (R = Pr), **12e** (R = *n*-Bu), **12f** (R = $CH_2(CH_2)_3CH_3$) | 1.0 | | normal |
| 13 |  | 1.0 | 100 | |
| | | 0.5 | 90 | NO |
| | | 0.25[b] | 50 | NO |
| | | 0.1 | 0 | NO |
| | | 0.05 | 0 | NO |
| | | 0.025 | 0 | 0 |
| | | 0.01 | 0 | 15 |
| 14 |  | 1.0 | 100 | |
| | | 0.5 | 80 | NO |
| | | 0.25[b] | 0 | NO |
| | | 0.1 | 0 | 0 |
| | | 0.05 | 0 | 0 |
| | | 0.025 | 0 | 7 |
| 15 |  | 1.0 | 95 | NO |
| | | 0.5[b] | 0 | 0 |
| | | 0.25 | 0 | 77 |
| |  | | | |
| 16a | R = H | 1.0 | | normal |
| 16b | R = $CH_3$ | 1.0 | 100 | |
| | | 0.5 | 100 | |
| | | 0.25 | 80 | 0 |
| | | 0.1 | 0 | 9 |
| 16c | R = $CH_2CH_3$ | 1.0 | 100 | |
| | | 0.5 | 90 | NO |
| | | 0.25 | 75 | 0 |
| | | 0.1 | 0 | 80 |
| 16d | R = $CH_2CH_2CH_3$ | 1.0 | 90 | NO |
| | | 0.5[b] | 0 | 0 |
| | | 0.25 | 0 | 86 |
| 16e | R = $CH_2(CH_2)_2CH_3$ | 1.0[b] | 0 | 0 |
| | | 0.5 | 0 | 0 |
| | | 0.25 | 0 | 84 |
| |  | | | |
| 17a | R = H | | | |
| 17b | (R = Me), **17c** (R = Et), **17d** (R = Pr) | 1.0 | | normal |
| |  | | | |
| 18a | R = H | | | |
| 18b | R = $CH_3$ | 0.5 | 100 | |
| | | 0.25 | 80 | NO |
| | | 0.1 | 0 | 82 |
| 18c | R = $CH_2CH_3$ | 1.0 | 100 | |

Table I (*Continued*)

| | compound | concn, % | mortality, % | hatch,[d] % |
|---|---|---|---|---|
| | | 0.5 | 80 | NO |
| | | 0.25 | 0 | 50 |
| |  | | | |
| 19a | R = H | | | |
| 19b | R = $CH_3$ | 1.0 | 100 | |
| | | 0.5 | 70 | NO |
| | | 0.25[b] | 0 | 0 |
| | | 0.1 | 0 | 6 |
| 19c | R = $CH_2CH_3$ | 1.0 | 100 | |
| | | 0.5 | 85 | NO |
| | | 0.25 | 0 | 85 |
| |  | | | |
| 20a | R = $R_1$ = OH, $R_2$ = H | | | |
| 20b | R = $R_1$ = $OCH_3$, $R_2$ = H | 0.5 | 100 | |
| | | 0.25 | 60 | NO |
| | | 0.1 | 0 | 76 |
| 20c | R = OH, $R_1$ = H, $R_2$ = $CH_3$ | | | |
| 20d | R = $OCH_3$, $R_1$ = H, $R_2$ = $CH_3$ | 1.0 | 100 | |
| | | 0.5 | 100 | |
| | | 0.25 | 70 | 74 |
| 20e | R = OH, $R_1R_2$ = $OCH_2O$ | | | |
| 20f | R = $OCH_3$, $R_1R_2$ = $OCH_2O$ | 1.0 | | normal |
| 20g | R = $OCH_2CH_3$, $R_1R_2$ = $OCH_2O$ | 0.5 | 100 | |
| | | 0.25 | 90 | |
| | | 0.1 | 0 | 0 |
| | | 0.05 | 0 | 2 |

[a] Sterilization of males (100%) occurs at this concentration. [b] Ineffective against males at this concentration. [c] NO = no oviposition. [d] In all cases number of $F_1$ surviving = % hatch.

4-(1-phenylethyl)phenol with isoprene and sulfuric acid (Holcik and Karvas, 1973). It was now prepared by refluxing 2,6-di-*tert*-butylphenol (51 g) and 1-phenylethanol (31 g) in acetic acid (40 mL) and formic acid (75 mL) as described for **1b**. **2b** was obtained as a colorless oil: bp 166–168 °C (1.0 mm) (62 g); meas. mass = 310.2309, calcd for $C_{22}H_{30}O$ = 310.2296; $^1H$ NMR $\delta$ 1.40 (18 H, s), 1.61 (3 H, d, $J$ = 8 Hz), 4.06 (1 H, q, $J$ = 8 Hz), 5.02 (1 H, s), 7.01 (2 H, s), 7.22 (5 H, s).

**2,6-Bis(1,1-dimethylethyl)-4-[(4-methoxyphenyl)-methyl]phenol (2c).** A mixture of 2,6-di-*tert*-butylphenol (51.5 g), 4-methoxybenzyl alcohol (34.5 g), formic acid (100 mL), and acetic acid (100 mL) was refluxed for 5 h, diluted with water, and extracted with chloroform. Evaporation of the chloroform gave an oil which crystallized. **2c** was recrystallized from methanol, forming colorless needles: mp 139 °C (58 g); $^1H$ NMR $\delta$ 1.42 (18 H, s), 3.79 (3 H, s), 3.86 (2 H, s), 3.79 (3 H, s), 3.86 (2 H, s), 5.04 (1 H, s), 6.83 (2 H, d, $J$ = 8 Hz), 6.98 (2 H, s), 7.12 (2 H, d, $J$ = 8 Hz).

Oxidation of **2c**: (a) A solution of **2c** (10 g) in acetone (50 mL) was stirred overnight with silver oxide (40 g). The filtered reaction solution was concentrated, diluted with methanol, and reconcentrated until yellow crystals separated (6.1 g). The quinone methide **23b** was recrystallized from acetone–methanol and separated as golden yellow needles: mp 125 °C; $^1H$ NMR $\delta$ 1.32 (9 H, s), 1.34 (9 H, s), 3.88 (3 H, s), 6.97 (2 H, d, $J$ = 8.5 Hz), 7.00 (1 H, d, $J$ = 2 Hz), 7.12 (1 H, s), 7.44 (2 H, d, $J$ = 8.5 Hz), 7.56 (1 H, d, $J$ = 2 Hz). (b) A solution of **2c** (6.52 g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.54 g) in acetone was allowed to react until the initial deep green color changed to yellow (10 min). Skellysolve F (400 mL) was added and the precipitated quinol was filtered (4.20 g). The filtrate was evaporated to a gum which was redissolved in Skellysolve F. This solution was concentrated to about 20 mL whereupon the quinone methide **23b** separated, mp and mmp 125 °C (6.13 g).

**2,6-Bis(1,1-dimethylethyl)-4-[(4-methoxyphenyl)-ethyl]phenol (2d).** Condensation of 2,6-di-*tert*-butylphenol (80 g) and 1-(4-methoxyphenyl)ethanol (40 g) in acetic–formic acid solution as described for **2c** gave, on distillation of the product, a colorless oil, bp 196–201 °C (2.0 mm) (74 g). The oil crystallized from methanol to give **2d** as glistening, colorless needles: mp 83–84 °C (49 g); $^1H$ NMR $\delta$ 1.42 (18 H, s), 1.59 (3 H, d, $J$ = 7.5 Hz), 3.77 (3 H, s), 4.03 (1 H, q, $J$ = 7.5 Hz), 5.02 (1 H, s), 6.81 (2 H, d, $J$ = 8.5 Hz), 7.01 (2 H, s), 7.14 (2 H, d, $J$ = 8.5 Hz).

A solution of **2d** (20 g) in acetone (150 mL) was warmed with silver oxide (50 g) for 30 min. Evaporation of the filtered reaction solution gave an oil which crystallized from Skellysolve F (14.1 g). **23c** was recrystallized from acetone–methanol as yellow prisms: mp 89–90 °C; $^1H$ NMR $\delta$ 1.22 (9 H, s), 1.38 (9 H, s), 2.54 (3 H, s), 3.89 (3 H, s), 6.96 (2 H, d, $J$ = 8 Hz), 7.10 (1 H, d, $J$ = 2 Hz), 7.25 (2 H, d, $J$ = 8 Hz), 7.51 (1 H, d, $J$ = 2 Hz).

**2,4-Bis(1,1-dimethylethyl)-6-(3-phenyl-2-propenyl)phenol (6).** A solution of 2,4-di-*tert*-butylphenol (51 g) and cinnamyl alcohol (33.5 g) in acetic acid (40 mL) and formic acid (80 mL) was refluxed for 6 h and diluted with water. Distillation of the oily product gave **6** as an oil, bp 190–195 °C (0.5 mm) (47 g), which crystallized from methanol and from Skellysolve F to give colorless needles: mp 89 °C; $^1H$ NMR $\delta$ 1.31 (9 H, s), 1.42 (9 H, s), 3.55 (2 H, d, $J$ = 6 Hz), 5.09 (1 H, s), 6.20–6.67 (2 H, m), 7.03 (1 H, d, $J$ = 3 Hz), 7.13–7.37 (6 H, m).

Hydrogenation of **6** (20 g) in tetrahydrofuran (100 mL) in the presence of 5% palladium–carbon catalyst and distillation of the product gave **7** as a colorless oil: bp 183–184 °C (0.5 mm); $^1H$ NMR $\delta$ 1.30 (9 H, s), 1.43 (9 H, s), 2.01 (2 H, m), 2.64 (4 H, m), 4.58 (1 H, s), 6.99 (1 H,

d, $J$ = 2 Hz), 7.13–7.36 (6 H, m).

**2,6-Bis(1,1-dimethylethyl)-4-(3-phenyl-2-propenyl)phenol (8).** Cinnamyl alcohol (134 g) was added to a suspension of 2,6-di-*tert*-butylphenol (206 g) in formic acid (470 mL) and acetic acid (200 mL). After heating for 1.5 h, the oily product obtained on adding water was distilled. A fraction, bp 190–200 °C (0.5 mm) (179 g), crystallized from Skellysolve F and from methanol to give **8** as colorless needles: mp 93 °C; $^1$H NMR $\delta$ 1.41 (9 H, s), 1.45 (9 H, s), 3.48 (2 H, d, $J$ = 5 Hz), 5.07 (1 H, s), 6.18–6.58 (2 H, m), 6.96–7.47 (7 H, m).

A solution of **8** (10 g) in ether (100 mL) was stirred overnight with silver oxide. Yellow crystals separated. The solid was filtered and extracted with warm acetone. The combined ether solution and acetone extracts were concentrated until yellow crystals began to separate (9.5 g). Recrystallized from acetone, the quinone methide **24** was obtained as flat, yellow needles: mp 193–194 °C; $^1$H NMR $\delta$ 1.34 (9 H, s), 1.39 (9 H, s), 6.74–7.08 (3 H, m), 7.24–7.62 (7 H, m).

**5-Hydroxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole (10a).** A solution of sesamol (27.6 g), 1-(4-methoxyphenyl)ethanol (30.4 g), and oxalic acid (2 g) in glacial acetic acid (60 mL) and water (10 mL) was refluxed for 7 h, diluted with water, and extracted with ether. Distillation of the ether extract gave an oil, bp 235–237 °C (5 mm) (53 g), which crystallized from benzene–Skellysolve F to yield **10a** as glistening, colorless needles: mp 93–94 °C; $^1$H NMR $\delta$ 1.53 (3 H, d, $J$ = 7 Hz), 3.77 (3 H, s), 4.21 (1 H, q, $J$ = 7 Hz), 4.58 (1 H (OH), s), 5.86 (2 H, s), 6.35 (1 H, s), 6.70 (1 H, s), 6.81 (2 H, d, $J$ = 9 Hz), 7.17 (2 H, d, $J$ = 9 Hz). With acetic anhydride and pyridine the product formed *monoacetate*, colorless needles from methanol: mp 76 °C; $^1$H NMR $\delta$ 1.50 (3 H, d, $J$ = 7 Hz), 2.18 (3 H, s), 3.77 (3 H, s), 4.13 (1 H, q, $J$ = 7 Hz), 5.92 (2 H, s), 6.52 (1 H, s), 6.66 (1 H, s), 6.79 (2 H, d, $J$ = 9 Hz), 7.08 (2 H, d, $J$ = 9 Hz). *10a monobenzoate*, formed by reaction with benzoyl chloride and pyridine, crystallized from acetone–methanol as colorless plates: mp 127–128 °C; $^1$H NMR $\delta$ 1.51 (3 H, d, $J$ = 7 Hz), 3.74 (3 H, s), 4.20 (1 H, q, $J$ = 7 Hz), 5.92 (2 H, s), 6.63 (1 H, s), 6.70 (1 H, s), 6.74 (2 H, d, $J$ = 9 Hz), 7.06 (2 H, d, $J$ = 9 Hz), 7.50 (3 H, m), 8.10 (2 H, m).

**Alkyl Ethers of 10a.** **10a** was alkylated by refluxing its solution in acetone with potassium carbonate and excess (2 mol equiv) of an appropriate alkylating agent, viz., methyl iodide, ethyl iodide, or alkyl bromides in the presence of small amounts of potassium iodide, e.g., for the *propyl ether* **10d**, a solution of **10a** (13.6 g, 0.05 mol), 1-bromopropane (12.3 g, 0.1 mol), and potassium iodide (3 g) in acetone (50 mL) was refluxed with potassium carbonate (25 g) for 20 h, diluted with 5% aqueous NaOH (100 mL), and extracted with ether. Distillation of the ether extract gave a colorless oil, bp 191–192 °C (1.0 mm), which rapidly crystallized (13.1 g). **10d** was recrystallized from methanol to give colorless needles, mp 84 °C; $^1$H NMR $\delta$ 0.97 (3 H, t, $J$ = 7 Hz), 1.50 (3 H, d, $J$ = 7 Hz), 1.70 (2 H, m, $J$ = 7 Hz), 3.73 (3 H, s), 3.78 (2 H, m), 4.49 (1 H, q, $J$ = 7 Hz), 5.81 (2 H, s), 6.46 (1 H, s), 6.64 (1 H, s), 6.78 (2 H, d, $J$ = 9 Hz), 7.13 (2 H, d, $J$ = 9 Hz). The following compounds were prepared similarly: *methyl ether* **10b**, colorless oil, bp 184 °C (1.0 mm); $^1$H NMR $\delta$ 1.49 (3 H, d, $J$ = 7 Hz), 3.69 (3 H, s), 3.74 (3 H, s), 4.46 (1 H, q, $J$ = 7 Hz), 5.82 (2 H, s), 6.48 (1 H, s), 6.62 (1 H, s), 6.78 (2 H, d, $J$ = 9 Hz), 7.03 (2 H, d, $J$ = 9 Hz); *ethyl ether* **10c**, colorless needles from methanol: mp 95 °C; $^1$H NMR $\delta$ 1.28 (3 H, t, $J$ = 7 Hz), 1.45 (3 H, d, $J$ = 7 Hz), 3.72 (3 H, s), 3.85 (2 H, q, $J$ = 7 Hz), 4.44 (1 H, q, $J$ = 7 Hz), 5.80 (2 H, s), 6.32 (1 H, s), 6.60 (1 H, s), 6.75 (2 H, d, $J$ = 9 Hz), 7.12 (2 H, d, $J$ = 9 Hz); *butyl ether* **10e**, colorless oil, bp 202–203 °C (1.5 mm), $^1$H NMR $\delta$ 0.93 (3 H, t, $J$ = 7 Hz), 1.48 (3 H, d, $J$ = 8 Hz), 1.55 (4 H, m), 3.76 (3 H, s), 3.80 (q, $J$ = 7 Hz), 4.48 (1 H, q, $J$ = 8 Hz), 5.83 (2 H, s), 6.47 (1 H, s), 6.63 (1 H, s), 6.78 (2 H, d, $J$ = 9 Hz), 7.12 (2 H, d, $J$ = 9 Hz).

**5-(2-Propenyl)-6-(4-methoxyphenyl)methyl-1,3-benzodioxole (13).** Safrole (34.4 g), 4-methoxybenzyl alcohol (34.4 g), and oxalic acid (3 g) were refluxed in acetic acid (100 mL) and water (5 mL) for 6 h. The oily product obtained on adding excess of water was extracted with ether, dried and distilled to give **13** as a colorless oil: bp 165–167 °C (0.5 mm) (35 g); $^1$H NMR spectrum: $\delta$ 3.26 (2 H, dt, $J$ = 7, 1.5 Hz), 3.77 (3 H, s), 3.85 (2 H, s), 4.93 (1 H, d of dd, $J$ = 9.3, 1.5 Hz), 5.07 (dd, $J$ = 3, 1.5 Hz); 5.81 (1 H, m), 5.88 (2 H, s), 6.58 (1 H, s), 6.67 (1 H, s), 6.80 (2 H, d, $J$ = 9 Hz), 7.02 (2 H, d, $J$ = 9 Hz).

Catalytic hydrogenation of **13** in acetic acid in the presence of palladium charcoal gave the dihydro derivative **14** as a colorless oil, bp 169–170 °C (0.5 mm); $^1$H NMR spectrum $\delta$ 0.92 (3 H, t, $J$ = Hz), 1.51 (2 H, m), 2.50 (2 H, t, $J$ = 7 Hz), 3.77 (3 H, s), 3.86 (2 H, s), 5.86 (2 H, s), 6.55 (1 H, s), 6.67 (1 H, s), 6.80 (2 H, d, $J$ = 9 Hz), 7.03 (2 H, d, $J$ = 9 Hz).

**6-(3-Phenyl-2-propenyl)-5-(2-propenyl)-1,3-benzodioxole (15).** A solution of safrole (40.5 g), cinnamyl alcohol (33.5 g), and oxalic acid (140 mL) in acetic acid (140 mL) and water (10 mL) was refluxed for 3 h, diluted with water and extracted with chloroform. Evaporation of chloroform and distillation of the residue gave **15** as a colorless oil, bp 188–189 °C (1.0 mm) (13.0 g); $^1$H NMR $\delta$ 3.32 (2 H, dt, $J$ = 7, 1.5 Hz), 3.43 (2 H, d, $J$ = 6 Hz), 4.95 (1 H, d of dd, $J$ = 9.3, 1.5 Hz), 5.09 (1 H, dd, $J$ = 3, 1.5 Hz), 5.91 (2 H, s), 5.94 (1 H, m), 6.28 (2 H, m), 6.67 (1 H, s), 6.70 (1 H, s), 7.20 (5 H, m).

**Sterilant Tests.** Details of the testing procedure were described previously (Fye et al., 1966). Briefly, immediately upon eclosion, adult flies from 100 pupae were offered the candidate sterilant in a diet of sucrose, nonfat dry milk, and powdered egg yolk (6:6:1). Oviposition medium was provided 7 days posttreatment; if no eggs were laid, the medium was offered every 3 days. Sterilizing activity was based on the proportion of progeny reaching the pupal stage from 100 eggs. Males (10) surviving a treatment with an effective sterilant were crossed with virgin females (10), and the fertility of these females was determined. Normal egg hatch equals 80–95%.

**Mutagenicity Tests.** The mutagenic activity of the benzylphenols **1a**, **1b**, and **1c** and benzodioxoles **9c**, **10d**, and **13** have been tested by the standard Ames *Salmonella*/microsome procedure (Ames et al., 1975; McCann et al., 1975). Tester strains TA-100, TA-98, and TA-1537 and the plate test method were used, employing concentrations of 10, 100, 1000, and 10000 $\mu$g of compound per plate. The metabolic activation mixture (S-9 mix) used the 9000*g* supernatant of Arochlor-1254-induced rat liver homogenate at a level of 100 $\mu$g/mL of S-9 mix.

**Oral $LD_{50}$ Measurements.** Four, log spaced dosage levels of each of the compounds, dissolved in corn oil, were fed to male mice. Ten mice, 15–20 g body weight, were used per dose, and the animals were observed for a 2-week period after dosing. $LD_{50}$'s were estimated from a plot of percent deaths vs. log dosage. A corn oil control which was run simultaneously resulted in no deaths.

## RESULTS AND DISCUSSION

**Synthesis of Compounds.** Benzyl- and cinnamyldi-*tert*-butylphenols were prepared by adaptation of a mild,

Table II. Reversion of *Salmonella typhimurium* Strains TA100, TA98, and TA1537 Exposed to Chemosterilants[a]

| | | number of revertants per plate | | | | | |
|---|---|---|---|---|---|---|---|
| | | TA100 | | TA98 | | TA1537 | |
| test compound | μg/plate | with S-9[b] | w/o S-9[b] | with S-9[b] | w/o S-9[b] | with S-9[b] | w/o S-9[b] |
| control (mean ± SD(*n*)) | | 135 ± 12 (5) | 161 ± 15 (5) | 45 ± 4.6 (7) | 28 ± 4.3 (7) | 12 ± 4.4 (6) | 10 ± 3.4 (6) |
| aflatoxin $B_1$ | 1.0 | 1379 ± 258 (5) | | | | | |
| 9-aminoacridine | 0.5 | | | 1271 ± 290 (7) | | | |
| 1a | 100 | | | | | | 1561 ± 502 (6) |
| | 10000 | 81 | 68 | 17 | 17 | 10 | 5 |
| | 1000 | 135 | 138 | 40 | 25 | 10 | 7 |
| | 100 | 160* | 145 | 49 | 29 | 15 | 7 |
| | 10 | 163* | 155 | 47 | 21 | 14 | 7 |
| | 0 | 120[d] | 170[d] | 51 | 32 | 11 | 7 |
| | positive control[c] | 1250[d] | | 930 | | | 1200 |
| 1b | 10000 | 98 | 104 | 37 | 28 | 5 | 5 |
| | 1000 | 113 | 143 | 30 | 23 | 8 | 5 |
| | 100 | 130 | 150 | 53 | 27 | 10 | 5 |
| | 10 | 140 | 143 | 53 | 41* | 12 | 8 |
| | 0 | 125 | 153 | 47 | 23 | 11 | 15 |
| | positive control[c] | 1350 | | 1800 | | | 1300 |
| 1c | 10000 | 152 | 144 | 41 | 22 | 9 | 5 |
| | 1000 | 138 | 145 | 63 | 21 | 14 | 8 |
| | 100 | 140 | 150 | 51 | 29 | 8 | 11 |
| | 10 | 145 | 143 | 56* | 36 | 8 | 5 |
| | 0 | 120[d] | 170[d] | 48 | 34 | 20 | 9 |
| | positive control[c] | 1250[d] | | 1475 | | | 915 |
| 10d | 10000 | 144 | 140 | 41 | 26 | 6 | 7 |
| | 1000 | 151 | 148 | 53 | 40 | 10 | 11 |
| | 100 | 142 | 127 | 53 | 25 | 12 | 13 |
| | 10 | 148 | 143 | 47 | 41 | 9 | 11 |
| | 0 | 134 | 159 | 40 | 26 | 10 | 7 |
| | positive control[c] | 1367 | | 1113 | | | 2250 |
| 9c | 10000 | 150 | 153 | 44 | 21 | 6 | 9 |
| | 1000 | 175** | 183 | 44 | 29 | 10 | 9 |
| | 100 | 143* | 165 | 40 | 27 | 9 | 11 |
| | 10 | 165* | 175 | 38 | 25 | 9 | 11 |
| | 0 | 138 | 183 | 47 | 31 | 11 | 13 |
| | positive control[c] | 1750 | | 1175 | | | 1800 |
| 13 | 10000 | 155 | 153 | 35 | 22 | 6 | 4 |
| | 1000 | 141 | 160 | 46 | 25 | 8 | 11 |
| | 100 | 153 | 148 | 47 | 22 | 9 | 9 |
| | 10 | 140 | 150 | 47 | 30 | 12 | 8 |
| | 0 | 143 | 150 | 46 | 27 | 7 | 8 |
| | positive control[c] | 1063 | | 1290 | | | 1900 |

[a] Values are the mean of duplicate determinations. Values exceeding the mean control value plus two standard deviations (SD) are marked with an asterisk (*); those exceeding the mean control value plus 3SD are marked with a double asterisk (**). [b] S-9 denotes the metabolizing mixture described by Ames et al. (1975) using Arochlor-1254-induced rat liver at 50 μL/plate. [c] The positive controls were: TA100, 1.0 μL/plate aflatoxin $B_1$ with S-9; TA98, 0.5 μL/plate aflatoxin $B_1$ with S-9; TA1537, 100 μL/plate 9-aminoacridine without S-9. [d] Compounds 1a and 1c were tested in TA100 in a single experiment employing the same positive and negative controls.

general method originally used for the synthesis of obtusastyrene, a cinnamylphenol microbicide isolated from *Dalbergia obtusa* (Gregson et al., 1968b; Jurd et al., 1971). 1-Phenylethanol, 4-methoxybenzyl alcohol, and 1-(4-methoxyphenyl)ethanol, like cinnamyl alcohol, readily form resonance stabilized carbonium ions in aqueous organic acid solutions. These allylic alcohols, therefore, condense easily with 2,4-di-*tert*-butylphenol and 2,6-di-*tert*-butylphenol in formic and acetic acid media to give good yields of corresponding phenols, **1b–1d**, **2b–2d**, **6**, and **8** (Table I). Sesamol (3,4-methylenedioxyphenol) reacts similarly with the benzylic alcohols to give the phenolic 1,3-benzodioxoles **9a**, **10a**, and **11a**, which on treatment with alkyl halides and potassium carbonate in acetone form almost quantitatively the alkyl ethers, **9b–9i**, **10b–10e**, and **11b–11e**. Although α,α-dimethylbenzyl alcohol does not react with the di-*tert*-butylphenols in acid solutions, it readily condenses with the more reactive sesamol to give the phenolic 1,3-benzodioxole **12a**. With cinnamyl alcohol sesamol forms a separable mixture of the cinnamylphenol **16a** and its 1-phenyl-2-propenyl isomer **17a**. Safrole, a constituent of plant essential oils, reacts with 4-methoxybenzyl alcohol and with cinnamyl alcohol to give the potent chemosterilants **13** and **15**, respectively. The phenolic 1,3-benzodioxoles **18a**, **19a**, and **20a,d,f,j** were prepared by similar condensations of piperonyl alcohol (3,4-methylenedioxybenzyl alcohol) with appropriate phenols. All structural assignments were confirmed by $^1H$ NMR spectra.

**Toxic and Sterilant Effects on Flies.** With the exception of **1b**, benzyl- and cinnamyldi-*tert*-butylphenols are nontoxic to houseflies at concentrations of 1% in the diet. As shown in Table I, however, all of the benzylphenols (**1a–1d**) in which the benzyl group is ortho to the

phenolic hydroxyl are highly effective chemosterilants, which compare favorably with previously reported chemosterilants tested under similar conditions, e.g., dithiazolium salts. The most active compound **1c** [2,4-bis-(1,1-dimethylethyl)-6-[(4-methoxyphenyl)methyl]phenol] produced 100% sterilization of the mixed sexes without mortality at a concentration of only 0.025% in the diet. In the female flies, sterility is demonstrated primarily in oviposition and egg hatch. When no oviposition occurs, which happened with this sterilant at the higher concentrations, the effects can vary from barely perceptible to complete inhibition of development of ovary, ovariole, oocyte and germarium and in some cases complete resorption of the ovaries. TEPA, used as a standard in these tests, produces 100% sterilization of mixed sexes at a minimal concentration of 0.25%. **1c** is also a male sterilant, 100% sterilization of males being obtained with a concentration of 0.25%.

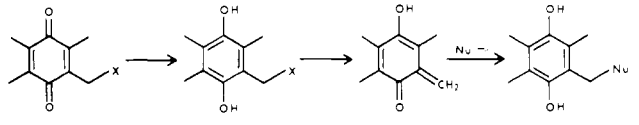
The monomethyl analogue **1d** of **1c** is also active against male and female flies, but considerably less than the unsubstituted benzylic compound. The sterilant activity of these alkylated phenols is primarily governed by the location of the benzyl group relative to the phenolic hydroxyl. Thus, the only *p*-benzylphenol which shows appreciable sterilant activity is **2b**, and this activity is less than that of the isomeric *o*-benzylphenol **1b**. The *p*-benzylphenols **2c** and **2d**, isomeric with the active *o*-benzylphenols **1c** and **1d**, are completely ineffective, as are benzylmono-*tert*-butylphenols **3** and **4**. The same correlation between location of the cinnamyl substituent and sterilant activity was found with cinnamylphenols; the *o*-cinnamyl compound **6** and its dihydro derivative **7** are active, whereas the isomeric *p*-cinnamylphenol **8** and its dihydro derivative are inactive.

The phenolic 4-methoxybenzyl-1,3-benzodioxole derivative **9a** is inactive. However, alkyl ethers (**9b–9i**) of this phenol, and of the benzyl, $\alpha$-methylbenzyl, and cinnamylphenols **10a**, **11a**, and **16a**, are toxicants at high concentrations and highly active sterilants at low concentrations, e.g., the ethyl ether **9c** produces 80–100% mortality at concentrations of 0.25–0.5%, whereas at concentrations of 0.025% it gives 100% sterilization without mortality. Although benzodioxole derivatives are generally most effective with mixed sexes, the ethyl ether **10c** (5-ethoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole) and the propyl ethers **9d** (5-propoxy-6-[(4-methoxyphenyl)methyl]-1,3-benzodioxole) and **10d** (5-propoxy-6-[1-(4-methoxyphenyl)ethyl]-1,3-benzodioxole) are also very active against males. Thus, **10c** and **9d** sterilize both mixed sexes and males at concentrations of only 0.05% and 0.1%, respectively; **10d** is active against mixed sexes at 0.05% and males at 0.25%. In contrast to the toxicant and sterilant properties of these ethers, alkyl ethers of the closely related $\alpha,\alpha$-dimethylbenzyl-1,3-benzodioxole **12a** and of the (1-phenyl-2-propenyl)-1,3-benzodioxole **17a**, which is isomeric with **16a**, are completely inactive.

Alkyl ethers of phenolic 1,3-benzodioxoles **18a**, **19a**, **20a**, **20c**, and **20e**, in which the methylenedioxy group is located on a phenyl ring without an ether substituent, proved to be generally less active than benzodioxoles of the type described above. However, 4-methoxybenzyl and cinnamyl derivatives **13**, **14**, and **15**, of safrole (3,4-methylenedioxyallylbenzene), are very active, with concentrations as low as 0.025% of **13** producing 100% sterilization. These three sterilants, which inhibit egg deposition, are effective against the females.

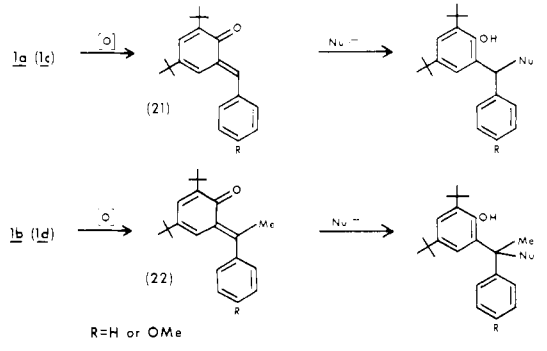
**Structural Basis of Sterilant Action.** In view of the fact that benzyldi-*tert*-butylphenols and nonphenolic benzyl-1,3-benzodioxoles differ markedly in structure, it may not be immediately apparent how structure and sterilant activity can be correlated. However, the activity of these diverse compounds can be readily rationalized by the reasonable assumption that, after translocation to the site of action, they undergo microsomal oxidation to similar, biologically active quinone methides which determine the sterilant activity.

*o*-Quinone and *p*-quinone methides, which are highly reactive, electrophilic molecules, have been implicated as intermediates in oxidative phosphorylation and in many phenol oxidation and elimination reactions (Turner, 1964). Until recently, *o*-quinone methides had not actually been isolated or detected spectroscopically because of the ease with which they dimerize or react with nucleophiles (Schleigh, 1971; Jurd, 1977). *p*-Quinone methides, however, are generally more stable and a number of fungal metabolites, wood and insect pigments possessing this structural unit have been isolated (Brown and Baker, 1971; Edwards, 1972). Furthermore, it has recently been suggested that the antineoplastic properties of some antitumor drugs, e.g., benzoquinones of type A, may be due to their in vivo activation by conversion to *o*-quinone methides of type B (Moore, 1977; Lin et al., 1972) (eq 1).



A B

We now propose that, in addition to structural features necessary for translocation to the action site, two principal factors determine the sterilant properties of benzylphenols and 1,3-benzodioxole derivatives, viz., (a) to be effective sterilants these compounds must possess structural features which allow facile formation of quinone methide intermediates, and (b) the quinone methide must be sufficiently reactive to undergo nucleophilic attack by a cell constituent(s) which is significant in the reproductive process. This theory is based on the observation that the most active chemosterilants are the *o*-benzylphenols **1a–1d** and the *o*-cinnamylphenol **6** (and its dihydro derivative **7**), all of which should form highly unstable *o*-quinone methide intermediates (**21**, **22**) on microsomal oxidation (eq 2).

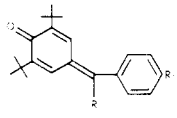


R=H or OMe

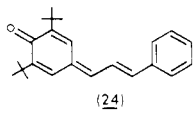
The *p*-quinone methide **23a** is more stable than the isomeric *o*-quinone methide **22** (R = H), and in agreement with this the *p*-benzylphenol **2b** is a less effective sterilant than the ortho isomer **1b**. Furthermore, the *p*-quinone methides **23b** and **23c** possess the additional stabilizing effect of a para methoxyl group. This makes them less reactive than **23a** and accounts for the complete inactivity of **2c** and **2d** as sterilants. Facile formation of quinone

methides requires the presence of at least one hydrogen atom in the benzylic position ortho or para to the phenolic OH. Thus, the inactivity of the $\alpha,\alpha$-dimethylbenzyl phenol **5**, which does not have a benzylic hydrogen, would be expected on the basis of the proposed hypothesis, since a quinone methide could be formed from **5** only after an oxidative demethylation.

Additional strong support for the proposed quinone methide mechanism of sterilant action is provided by correlating the chemical response of the benzyl- and cinnamylphenols to silver oxide oxidation with their sterilant activities. Oxidation of the six active phenols (**1a–1d, 2b, 6**) gives colorless, oily products resulting from the further rapid reaction, e.g., dimerization, of the initially formed, unstable quinone methides. Oxidation of the three inactive phenols **2c, 2d**, and **8**, however, gives high yields of the corresponding crystalline *p*-quinone methides **23b, 23c**, and **24**, which are sufficiently stable to be recrystallized readily without loss, and when tested themselves as chemosterilants are inactive.

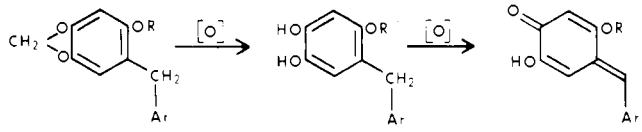


(23) a. R=Me, $R_1$=H
b. R=H, $R_1$=OMe
c. R=Me, $R_1$=OMe

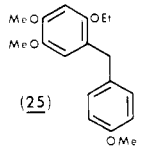


(24)

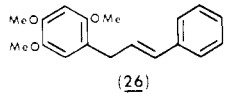
The sterilant activity of the 1,3-benzodioxole derivatives in Table I can be accounted for by a similar theory of in vivo conversion to reactive quinone methides. A number of 1,3-benzodioxole compounds, e.g., piperonyl butoxide and sesoxane, are known to be excellent insecticide synergists (Bowers, 1968). It is believed that this synergistic activity is due to an initial microsomal oxidation of the methylenedioxy group to form a catechol (1,2-dihydroxybenzene), which subsequently inhibits enzymic degradation of the insecticide (Hennessy, 1965). If the sterilant 1,3-benzodioxoles are similarly metabolized, the initially formed catechols may be expected, because of the benzyl substituents, to undergo further oxidation to reactive quinone methides, e.g., for alkyl ethers of phenols of types **9a, 10a**, and **11a** (eq 3). In accord with this proposal



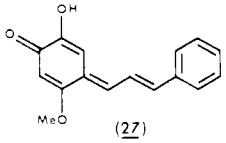
ethers of the $\alpha,\alpha$-dimethyl analogue **12a** would be expected to be inactive, because of the inability of these compounds to be oxidized readily to quinone methides. The importance of the readily removable methylenedioxy group in active compounds was confirmed by the complete absence of sterilant activity in the related compounds, **25** and **26**, in which the methylenedioxy substituent was replaced by two stable methoxy groups.



(25)



(26)



(27)

Table III. Oral $LD_{50}$ Estimation on Insect Chemosterilants

| compd | no. of mice[a] | dosage, mg/kg body wt[b] | % mortal. | estimated $LD_{50}$ mg/kg body wt |
|---|---|---|---|---|
| 1c[c] | 10 | 2510 | 30 | 3550 |
| | 4 | 5010 | 75 | |
| 1b | 10 | 2510 | 60 | 2510 |
| | 10 | 3160 | 70 | |
| | 10 | 3980 | 60 | |
| | 10 | 5010 | 100 | |
| 1a | 10 | 2510 | 30 | 3430 |
| | 10 | 3160 | 30 | |
| | 10 | 3980 | 90 | |
| | 10 | 5010 | 100 | |
| solvent control | 10 | 10 mL/kg | 0 | |

[a] Male Swiss-Webster mice, 15–20 g. [b] Compounds dissolved in 20% $Me_2SO$ in corn oil. Concentration (mg/mL) = dosage × 0.1 kg/mL. Volume dosage = 10 mL/kg body wt. [c] Compound was difficult to keep in solution.

Similar oxidative demethylenation of the active cinnamyl-1,3-benzodioxoles **16b–16f** should give quinone methides which are stabilized by extended conjugation with the phenyl ring, e.g., **16b** → **27**. It is noteworthy that **27** is a biologically active, natural quinone methide which has been isolated from the wood of *Dalbergia retusa*, a timber resistant to attack by marine organisms (Gregson et al., 1968a; Jurd et al., 1972). The inactivity of ethers of the 1-phenyl-2-propenyl isomer **17a** of **16a** is not unexpected since quinone methides formed by oxidation of these compounds would undergo rapid intramolecular cyclization due to the proximity of the side-chain ethylenic group.

**Mutagenicity and Toxicity Data.** Since the practical application of aziridines and similar compounds to natural insect populations is restricted by their suspected toxic and mutagenic properties, the development of nonmutagenic sterilants with low mammalian toxicity would be highly significant (Chang et al., 1964). The mutagenic activity of the benzylphenols **1a, 1b**, and **1c** and representative benzodioxoles **9c, 10d**, and **13** have been tested by the standard Ames *Salmonella*/microsome procedure, which is reported to show a good correlation with development of mammalian cancers (Ames et al., 1975; McCann et al., 1975). The results, provided by Dr. J. T. MacGregor and summarized in Table II indicate that in the strains tested compounds **1a, 1c, 10d** and **13** are nonmutagenic, either without or with metabolic activation. Compounds **1b** and **9c** did exhibit revertant frequencies which exceeded the mean control value plus two or three standard deviations at doses between 10 and 10 000 $\mu$g/plate in TA 100 with S-9. This response is extremely weak relative to known mutagenic agents which revert this strain.

The three benzylphenols were also assayed for oral toxicity in mice. Estimated $LD_{50}$ for **1a, 1b**, and **1c** were 3430, 2510, and 3550 mg/kg body weight, respectively, indicating that these compounds are only slightly toxic (Table III).

If the low mammalian toxicity and nonmutagenicity are confirmed by additional tests, the active compounds, which can be synthesized cheaply from phenol, may provide a practical, safe chemosterilant for use in the field. Although the degree of insect specificity of these sterilants is uncertain at this time, work currently being undertaken indicates that they are effective sterilants for other fly species, e.g., the screwworm fly, and are biologically active against some other pests. Thus, **1a** and **1b** protect wood from attack by marine borers (Jurd and Bultman, 1977)

Table IV. Inhibition of Development of *Anopheles quadrimaculatus*[a]

| compd | lethal concn[b] $LC_{50}$, ppm | $LC_{90}$, ppm |
|---|---|---|
| 1b | 0.02 | 0.04 |
| 1c | 0.12 | 0.22 |
| 6 | 0.035 | 0.15 |
| 9c | 0.10 | 0.35 |
| 9d | 0.03 | 0.04 |
| 9i | 0.02 | 0.03 |
| 10d | 0.02 | 0.04 |
| 10e | 0.01 | 0.02 |

[a] Late third-fourth larval stage in water containing ground hog supplement for larval food. [b] Data based on the percentages of treated insects that fail to complete development to the free-flying adult stage.

and, as previously observed with 5 and other 2,6-di-*tert*-butylphenols (Pridantseva and Volod'kin, 1974), are mosquito juvenile hormone mimics. The inhibitory activity of some representative housefly sterilants on the development of the mosquito (*Anopheles quadrimaculatus*) are shown in Table IV (Dame and Jurd, 1978).

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The authors thank G. Secor and M. Benson for elementary analyses and measurement of $^1H$ NMR spectra, J. T. MacGregor for mutagenic data, and M. Gumbmann for toxicity tests.

**Supplementary Material Available:** The preparation and physical properties of new compounds listed in Table I are given (6 pages). Ordering information is given on any current masthead page.

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# Physical-Chemical and Biological Degradation Studies on DDT Analogues with Altered Aliphatic Moieties

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A series of diethoxy 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) analogues with eight different aliphatic moieties were subjected to photodegradation studies, utilizing a sterile soil, an aqueous solution, and a film on glass. The 2-chloroisobutane analogue, a tertiary chloride, was quite photolabile in all trials. Photolability followed the order of the ease of formation of free radicals by loss of chlorine from the aliphatic moiety: tertiary > secondary > primary ≈ no chlorine. Several series of analogues were evaluated for biological degradation rates and products in the following types of studies: housefly synergistic ratios, housefly penetration–metabolism–excretion, salt marsh caterpillar metabolism, mouse metabolism, and in vitro metabolism by mouse liver microsomes. Both aliphatic and aromatic substituents influence biological degradation of the DDT analogues. In model ecosystem assessments of environmental fate, the two most important factors affecting bioaccumulation in fish were the type of alkyl chloride and water solubility of the molecule.

Biodegradable analogues of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) have been of interest since it was shown by Metcalf et al. (1971a) that replacement of the aromatic chlorine atoms by more degradable groups (alkyl, alkoxy) resulted in molecules that retained insecticidal potency but did not biomagnify or persist in the environment to the extent that DDT did. The possibility of finding analogues that possess the advantages of DDT such as high mammalian $LD_{50}$'s, low cost, and residual activity, but minimize environmental hazards, has inspired

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