

carbofuran, nearer to the site of action. Liberation of carbamate could also occur by hydrolysis of the sulfinamide or the corresponding sulfonamide, produced by oxidation of the sulfenamide sulfur atom, path (d). In either case, predominance of paths (c) and (d) in insects leads to intoxication by carbofuran. The selectivity between mammal and insect is the net result of the relative rates at which these processes occur in each species.

Work on the comparative metabolism of the 2-toluene-sulfonyl derivative of carbofuran (5) in houseflies and mice is in progress.

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Received for review April 6, 1973. Accepted June 16, 1973. This investigation was supported by a Research Training Grant from The Rockefeller Foundation, New York, N. Y.

Preparation of Tritium-Labeled Disparlure, the Sex Attractant of the Gypsy Moth

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Tritium-labeled disparlure (*cis*-7,8-epoxy-2-methyloctadecane-7,8-*t*), the sex attractant of the gypsy moth (*Porthetria dispar* (L.)), and the olefin precursor ((*Z*)-2-methyl-7-octadecene-7,8-*t*) were

synthesized. An improved method was devised for preparing the intermediate, 2-methyl-7-octadecyne.

Although many theories relating to the mechanism of olfaction have been advanced, none has been generally accepted, and it is apparent that more scientific data are needed to aid in solving this difficult problem. Toward this end, we synthesized tritium-labeled disparlure (*cis*-7,8-epoxy-2-methyloctadecane) (Bierl *et al.*, 1970, 1972), the sex attractant pheromone of the gypsy moth (*Porthetria dispar* (L.)), to gather information about the mechanism of olfaction in the gypsy moth and to determine means of utilizing the pheromone effectively. A pioneer study of the olfactory process of the silkworm moth (*Bombyx mori* (L.)) along similar lines has been underway for some time (Schneider and Kasang, 1971; Schneider *et al.*, 1968).

The synthesis of disparlure, outlined in Figure 1, is a modification of the method of Eiter (1972) that utilized simpler conditions and produced a higher yield (80%) of the acetylene intermediate, 2-methyl-7-octadecyne (I). Tritiation of I with a modified Lindlar catalyst gave (*Z*)-2-methyl-7-octadecene-7,8-*t* (II). Epoxidation of II with *m*-chloroperbenzoic acid gave disparlure labeled with tritium in the 7 and 8 positions (III). A procedure in which peracetic acid was used for epoxidation is described and suggested for commercial production of disparlure because of the low cost of the peracetic acid.

EXPERIMENTAL SECTION

Reagent-grade solvents and chemicals were used. For column chromatography, silica gel (J. T. Baker Company, no. 3405) and Adsorbosil-CABN (60/100 mesh, 25% silver nitrate on silica gel, Applied Science Laboratories, State College, Pa.) were used as received. For thin-layer chromatography (tlc), Brinkmann plates (5 × 20 cm, precoated 0.25-mm thick silica gel F254) were used. For AgNO₃ tlc, the Brinkmann plates were dipped in a solution of 10% AgNO₃ in 75% ethanol in water and dried. Spots were made visible by spraying the plates with a solution of 2% cupric acetate in 8% phosphoric acid and heating them at 110° for ½ hr. For gas chromatographic (glc) analysis, a Hewlett-Packard model 7620A instrument equipped with a flame ionization detector was used with a 50-ft × 0.02-in. i.d. SCOT column containing Carbowax 20M operated at 180° with a helium carrier gas flow rate of 4 ml/min. Infrared spectra were recorded on a Perkin-Elmer model 457A grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined with a Varian T-60 instrument; tetramethylsilane (TMS) was used as the internal standard.

Synthesis of 2-Methyl-7-octadecyne (I). Anhydrous HBr was added to a solution of 5-methyl-1-hexene (Chemical Samples Company, Columbus, Ohio, 26.2 g, 0.267 mol) and recrystallized benzoyl peroxide (1.5 g, 0.0062 mol) in 160 ml of hexane at 10–20° until the olefin content (measured by glc) was negligible. The hexane solution was washed successively with water and aqueous solutions of saturated sodium bisulfite, 7% sodium bicarbonate, and saturated sodium chloride; it was then dried over magne-

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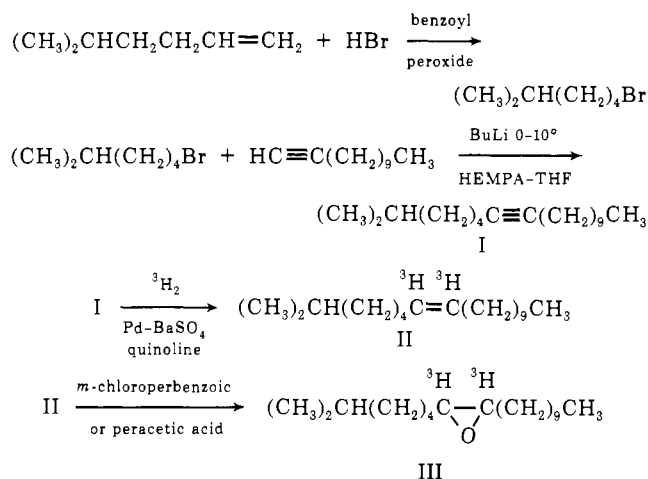


Figure 1. Synthesis of disparlure (III) with tritium in 7 and 8 position.

sium sulfate. Distillation yielded 40.9 g (0.228 mol) of 1-bromo-5-methylhexane (86% yield); bp 68–70° at 14 mm; $n_D^{25} = 1.4455$; lit. bp 83° at 45 mm (Cason, 1942).

Butyllithium in hexane (Foote Mineral Company, 28 ml, 0.044 mol) was added dropwise with stirring to a solution of 1-dodecyne (Chemical Samples Company, 6.65 g, 0.04 mol) in 56 ml of dry tetrahydrofuran at 0–10° under nitrogen. After the lithium acetylide suspension was stirred for 2 hr, a solution of 1-bromo-5-methylhexane (7.85 g, 0.044 mol) in 40 ml of dry hexamethylphosphoramide was added to the suspension at 0–5°. The reaction mixture was stirred 2 hr, allowed to warm to room temperature overnight, and then poured into ice water. The acetylene product was extracted into pentane, washed with water and saturated aqueous sodium chloride, and dried (MgSO_4). Distillation yielded 8.5 g (0.032 mol) of 2-methyl-7-octadecyne in 80% yield: bp 123–125° at 0.6 mm; $n_D^{25} = 1.4405$; tlc $R_f = 0.35$ on silica gel (cyclohexane); peaks in the nmr spectrum (carbon tetrachloride) were: δ 2.05 (m, 4 H, CH_2 groups adjacent to triple bond), 1.25 (broad peak, 23 H, CH_2 and CH), 0.90 (d, 6 H, CH_3), 0.80 (unresolved m, 3 H, CH_3); glc of the product (retention time, 8.8 min) indicated 98% purity; the infrared spectrum exhibited characteristic absorptions at 725, 1335, 1370, 1385, 1465, 2860, and 2930 cm^{-1} .

Anal. Calcd for $\text{C}_{19}\text{H}_{36}$: C, 86.28; H, 13.72. Found: C, 86.42; H, 13.53.

Synthesis of (Z)-2-Methyl-7-octadecene. Hydrogen slightly above atmospheric pressure was introduced into a flask containing 2-methyl-7-octadecyne (1.0 g, 3.78 mmol) dissolved in 20 ml of hexane in the presence of 50 mg of 5% palladium on barium sulfate (Engelhard Industries, Newark, N. J.) which had been deactivated by the addition of 50 mg of quinoline. The solution was magnetically stirred at room temperature, and the immediate and rapid uptake of hydrogen was measured. After 1 hr, when a total 89 ml of hydrogen had been consumed (theory: 85 ml at STP), the uptake of hydrogen ceased and none of the starting acetylene was present, as determined by tlc on silica gel (cyclohexane) and by glc. The solution was filtered to remove the catalyst, washed sequentially with 20 ml of 5% HCl, 20 ml of water, 20 ml of 7% sodium bicarbonate, and 20 ml of saturated sodium chloride solution, and then dried (MgSO_4). Removal of solvent left 0.94 g, 93.5% yield of a clear odorless liquid: $n_D^{25} = 1.4456$; tlc R_f on AgNO_3 -silica gel (methylene chloride) = 0.60 and 0.70 for the (Z) and (E) isomers, respectively. The isomers in a 0.2-g portion were separated (twice) by column chromatography on 2 g of silica gel impregnated with 25% silver nitrate, with hexane as the eluant. Weights of the isolated isomers indicated that the original product was 96% (Z)- and 4% (E)-2-methyl-7-octadecene.

Glc of the purified (Z) olefin indicated 99% purity with a retention time of 6.2 min; it was identical in all tests (tlc and glc) with an authentic specimen (Bierl *et al.*, 1970, 1972). Anal. Calcd for $\text{C}_{19}\text{H}_{38}$: C, 85.63; H, 14.37. Found: C, 85.83; H, 14.26. Characteristic infrared absorption bands were found at 722, 1368, 1382, 1468, 2830, 2930, 2980, and 3005 cm^{-1} .

Synthesis of (Z)-2-Methyl-7-octadecene-7,8-t (II). By the hydrogenation procedure given, 1.0 g (3.78 mmol) of 2-methyl-7-octadecyne was tritiated by Amersham/Searle Corporation (Arlington Heights, Ill.) to give a 94% yield of 2-methyl-7-octadecene-7,8-t. By radiochromatogram scanning, the product was found to contain 92% (Z) isomer, 4% (E) isomer, and 4% of the saturated compound 2-methyloctadecane. The crude material had a specific activity of 55,000 mCi/mmol. Chromatography of 0.2 g of the crude product on a column of 2 g of silica gel impregnated with 25% silver nitrate with hexane as the eluant yielded a total of 40 mg of pure (Z) isomer, identical by tlc with the nonradioactive preparation.

Synthesis of Disparlure (cis-7,8-Epoxy-2-methyloctadecane). The epoxide was prepared by using *m*-chloroperbenzoic acid (Bierl *et al.*, 1970, 1972) or peracetic acid (Korach *et al.*, 1960). In the first procedure, (Z)-2-methyl-7-octadecene (200 mg, 0.75 mmol) dissolved in 50 ml of methylene chloride was treated with *m*-chloroperbenzoic acid (Aldrich Chemical Company, 180 mg, 1.0 mmol), stirred at room temperature for 2 hr, and worked up as described by Bierl *et al.* (1970, 1972). In tlc on silica gel (benzene), the product gave only one spot at R_f 0.35 (R_f of olefin = 0.70). The yield of epoxide, after purification by column chromatography on 2 g of silica gel with 5% ether-hexane as the eluant, was 200 mg (93%), $n_D^{25} = 1.4450$.

In the second procedure, peracetic acid (FMC Corporation; 1 ml of a 38% soln, 5.0 mmol) which had been pretreated with sodium acetate trihydrate to neutralize excess sulfuric acid was added dropwise with stirring to an ice-cold mixture of (Z)-2-methyl-7-octadecene (0.93 g; 3.5 mmol) and anhydrous sodium carbonate (5 g) in 30 ml of methylene chloride. The solution was stirred and allowed to warm to room temperature overnight. Then it was treated with solid sodium bisulfite (1 g) and filtered, and the residue was washed three times with 10-ml portions of methylene chloride. The methylene chloride solution was washed sequentially with 20 ml of water, 20 ml of saturated sodium bisulfite, 20 ml of 7% sodium bicarbonate, and 20 ml of saturated sodium chloride solution and then dried (MgSO_4). Removal of the solvent left 0.81 g (82%) of a clear colorless liquid ($n_D^{25} = 1.4443$). Tlc of the product, as described, resulted in only one spot at R_f 0.35 (benzene). Products from the two procedures were identical (tlc and glc) to authentic material (Bierl *et al.*, 1970, 1972). The glc indicated that the product was 99% pure; retention times were 21.2 min (cis isomer, 96%) and 19.7 min (trans isomer, 4%). Anal. Calcd for $\text{C}_{19}\text{H}_{38}\text{O}$: C, 80.78; H, 13.56. Found: C, 80.91; H, 13.64. Characteristic infrared absorption bands were found at 725, 828, 1170, 1270, 1365, 1385, 1460, 2860, and 2935 cm^{-1} .

Synthesis of cis-7,8-Epoxy-2-methyloctadecane-7,8-t (III). *m*-Chloroperbenzoic acid (Aldrich Chemical Company, 51 mg, 0.3 mmol) was added to a solution of (Z)-2-methyl-7-octadecene-7,8-t (II, 50 mg, 0.185 mmol) in 40 ml of methylene chloride, and the mixture was stirred at room temperature for 2 hr. The solution was evaporated and the residue was chromatographed on a 1-g silica gel column by using 5% ether-hexane as the eluant. The product obtained (40 mg, 76% yield) was identical by tlc to the nonradioactive preparation. The radioactive material was diluted with hexane for storage and biological testing.

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Received for review March 9, 1973. Accepted April 5, 1973. Mention of a proprietary product in this paper does not constitute an endorsement of this product by the U. S. Department of Agriculture.

Insect Chemosterilants. 1,2,4-Dithiazolium Salts and Related Compounds as Additives to Housefly Diet

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A number of 1,2,4-dithiazolium salts and 2,4-dithiobiurets sterilize houseflies when fed as a diet additive. Only 3,5-bis(dialkylamino)-1,2,4-dithiazolium salts were active against male flies, but some less highly substituted analogs and a num-

ber of dithiobiurets were effective against mixed sexes. The results are compared to those obtained by injecting many of the compounds directly into the flies.

We recently reported that a number of substituted dimino-1,2,4-dithiazolium salts (Chang *et al.*, 1972; Oliver *et al.*, 1972b) and similarly substituted 2,4-dithiobiurets (Oliver *et al.*, 1971) are sterilants of male houseflies, *Musca domestica* L. The activities of the compounds against female flies, however, were not studied except for the observation that 3,5-bis(dimethylamino)-1,2,4-dithiazolium chloride sterilized mixed sexes of houseflies at substantially lower doses than those required to sterilize the males (Fye *et al.*, 1969). Furthermore, most of the male sterilants in the former reports were tested by injecting them into the flies' bodies. This is a useful technique for quantitative laboratory studies, but not one that could easily be adapted to the sterilization of thousands of millions of insects. Therefore, to determine the effects of these chemosterilants on both sexes, and to compare the results of the injection and feeding techniques, we tested these compounds as additives to the diet of adult houseflies. We have synthesized and screened well over a hundred dithiobiurets, dithiazolium salts, and related compounds, but only compounds that were active are included in Tables I and II; a few examples of inactive compounds will be mentioned in the text to illustrate the effects of varying structure upon biological activity.

Biological Tests. Details of the procedure were described previously (Fye *et al.*, 1966). Briefly, each compound was added on a w/w basis to a diet of sucrose, non-fat dry milk, and powdered egg yolk (6:6:1). Flies that were kept on the medicated diets were allowed to mate and their reproductive performance was evaluated and compared with that of control flies. To assess the effects on males, the treated males were crossed with virgin untreated females and the fertility of the mated females was again evaluated. The concentrations of the compounds were decreased in successive tests from 1% to levels causing less than 50% sterility, but only the lowest concentration causing 95-100% in one of the dietary media was recorded

as the "sterilizing concentration." See Supplementary Material Available paragraph at the end of article.

EXPERIMENTAL SECTION

Physical data have been reported for most of the dithiazolium salts (Oliver *et al.*, 1972a,b) and dithiobiurets (Oliver *et al.*, 1971). Previously undescribed compounds were prepared as follows.

3,5-Bis(dimethylamino)-1,2,4-dithiazolium Iodide (2). This compound was obtained by oxidizing 1,1,5,5-tetramethyl-2,4-dithiobiuret (23) with iodine in absolute ethanol, mp 263° dec (from acetonitrile).

Anal. Calcd for C₆H₁₂IN₃S₂: C, 22.72; H, 3.81; N, 13.25; S, 20.22. Found: C, 22.74; H, 3.68; N, 13.31; S, 20.21.

3-(Dimethylamino)-5-[(2-hydroxyethyl)methylamino]-1,2,4-dithiazolium Iodide (5). A mixture of potassium thiocyanate (10 g) and dimethylthiocarbamoyl chloride (12.4 g) in acetone (115 ml) was refluxed for 0.5 hr, cooled, and filtered. The filtrate was treated dropwise with *N*-methylethanolamine (7.5 g); then the resulting solution was evaporated and the residue was dissolved in absolute ethanol (60 ml). A solution of iodine (12.7 g) in absolute ethanol (100 ml) was added dropwise to the stirred solution. The iodide salt separated and was collected by filtration and recrystallized from absolute ethanol to give 10.5 g of 5, mp 181-183°.

Anal. Calcd for C₇H₁₄IN₃OS₂: C, 24.21; H, 4.06; N, 12.10; S, 18.47. Found: C, 24.07; H, 4.02; N, 12.23; S, 18.21.

3-(Cyclohexylamino)-5-(dimethylamino)-1,2,4-dithiazolium Bromide (18). A mixture of potassium thiocyanate (0.2 mol) and dimethylthiocarbamoyl chloride (0.2 mol) in acetonitrile (200 ml) was refluxed for 15 min, cooled, and filtered. The filtrate was cooled and stirred and treated dropwise with cyclohexylamine (0.2 mol), 48% hydrobromic acid (0.2 mol), and 30% hydrogen peroxide (0.2 mol), in that order. Filtration provided 15.7 g of 18, mp 237-240° dec, and a second crop was obtained by concentrating the filtrate and adding acetone (31.9 g, mp 243-245° dec, total yield 74%). Recrystallization from 95% ethanol gave pure 18, mp 249-251° dec.

Anal. Calcd for C₁₀H₁₇BrN₃S₂: C, 37.04; H, 5.59; N, 12.96. Found: C, 37.28; H, 5.58; N, 13.09.

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