Boeseken, J., Tellegen, F., Cohen Henriquez, P., *Recl. Trav. Chim.* **50**, 909 (1931).
Casida, J. E., Ahmed, M. K., *J. Econ. Entomol.* **52**, 111 (1959).
Chamberlain, W. F., Gatterdam, P. E., Hopkins, D. E., *J. Econ. Entomol.* **53**, 672 (1960).
Diveley, W. R., Haubein, A. H., Lohr, A. D., Moseley, P. B., *J. Am. Chem. Soc.* **81**, 139 (1959).
Krishna, J. G., Casida, J. E., *J. Agric. Food Chem.* **14**, 98 (1966).
Mastin, T. W., Norman, G. R., Weilmuenster, E. A., *J. Am. Chem. Soc.* **67**, 1662 (1945).
Plapp, F. W., Jr., Bigley, W. S., Darrow, D. I., *J. Econ. Entomol.* **53**, 60 (1960).
Stahl, E., Ed., "Thin-Layer Chromatography", 2nd ed, Springer-Verlag, New York, N.Y., 1969.
Ueda, K., Gaughan, L. C., Casida, J. E., *Pestic. Biochem. Physiol.* **5**, 280 (1975).
Weinhouse, S., in "Amino Acid Metabolism", McElroy, W. D., Glass, H. B., Ed., The Johns Hopkins Press, Baltimore, Md., 1955, pp 637–657.

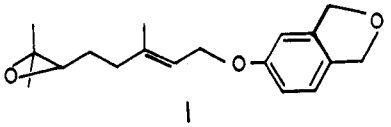
Received for review January 23, 1976. Accepted April 2, 1976. This study was supported in part by grants from The National Institutes of Health (2 PO1 ES00049), The Rockefeller Foundation, and Hercules Inc., Wilmington, Del.

Synthesis of Bioactive Compounds. A Structure-Activity Study of Aryl Terpenes as Juvenile Hormone Mimics

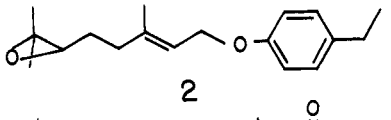
George P. Nilles, Matthew J. Zabik,* Richard V. Connin,[1] and Robert D. Schuetz

A series of aryl terpene ethers has been synthesized and bioassayed for juvenile hormone (JH) activity by induction of oviposition in the adult prediapause cereal leaf beetle [*Oulema melanopus* (L.), Chrysomelidae]. The selection of these JH mimics was based on bit by bit variations on the structure of 6,7-epoxygeranyl 4-ethylphenyl ether. Hansch type quantitative structure–activity relationships were investigated using polar, lipophilic, and steric parameters. Multiple regression analysis indicated that lipophilic and steric factors alone are responsible for the observed biological activity of these compounds. A hypothetical receptor site and its dimensions for these JH mimics are inferred from qualitative observations of the steric effect on JH response. Complete oviposition and mortality data upon treatment of the beetles are given for all compounds.

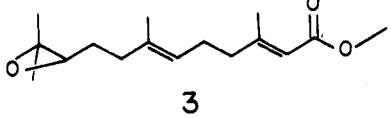
Of the hundreds of chemicals that have been investigated as to their juvenile hormone mimicking properties, probably the largest single group of these is the aryl acyclic monoterpenes. Two of these, namely (*E*)-6,7-epoxy-3,7-dimethyl-1-[3,4-(methylenedioxy)phenoxy]-2-octene (**1**, Bowers, 1969) and (*E*)-6,7-epoxy-1-(*p*-ethylphenoxy)-3,-7-dimethyl-2-octene (**2**, Pallos et al., 1971), have high orders of activity in many insect species. It was the latter of these which attracted our attention in an earlier study (Nilles et al., 1973) since this compound and C-16 juvenile hormone (**3**) have virtually the same order of activity with regard to diapause prevention in the adult cereal leaf beetle, *Oulema melanopus* (L.).



1



2



3

The Pesticide Research Center and the Departments of Chemistry and Entomology (M.J.Z.), and the Agricultural Research Service, U.S. Department of Agriculture, Michigan State University, East Lansing, Michigan 48824.
[1]Present address: U.S. Department of Agriculture Plant Introduction Station, Georgia Experiment Station, Experiment, Georgia 30212.

Large numbers of analogues of **2** have been bioassayed (Jacobsen et al., 1972). Results of these studies indicate that the maximum juvenile hormone (JH) like response was obtained when the benzene ring was para substituted and the terminal double bond was epoxidized.

Quantitative structure–activity relationships (QSAR) have been modestly successful in predicting substituent effect on biological response in many series of pharmaceuticals (Dunn, 1973; Hansch et al., 1973). Metcalf (1974) has used QSAR in his studies of DDT analogues. Such correlations, if extended to JH mimics, should prove useful in the design of new hormonal materials.

If we make the somewhat liberal assumption that the variation in the number and position of introduced alkyl groups on or near the aryl portion of **2** will not greatly affect JH response arising from lipophilicity, electronic factors, or secondary structure in the molecule, then what effect remains should be due to steric factors, i.e., the bit by bit introduction and variation in the position of a methyl group, e.g., could give us a rough picture of the steric requirements of a hypothetical receptor site for **2** and its analogues.

Earlier (Nilles et al., 1973) we had postulated that one requirement for biological response in the JH molecule or its mimics was the placement of a group with a certain π-electron density 11 ± 1 Å away from the epoxy oxygen, assuming conformations in which hydrogen–hydrogen repulsions were minimized. Alternatively, we felt that the requirement may be only for a group having the approximate steric parameters of the *p*-ethylphenyl residue. We now wish to indicate that it is primarily the later alternative which prevails in analogues of **2**. In addition, correlations between JH response in terms of induced oviposition and diapause prevention and lipophilicity, steric parameters, and polar effects of the mimics will be

discussed in quantitative terms.

SYNTHETIC DISCUSSION AND PROCEDURES

Proton magnetic resonance spectra (^{1}H NMR) were run as 20% solutions in carbon tetrachloride on a Varian T-60 instrument using tetramethylsilane as the internal standard (τ scale). Mass spectra and GC–mass spectra were determined using a DuPont 21-490 instrument. Samples were introduced via the direct inlet probe at ambient temperature. The mass spectra were recorded at 70 eV ionization potential and a source temperature of 220–250 °C. Gas chromatography was conducted on two instruments. A Beckmann GC-65 (interfaced to the mass spectrometer) was equipped with a 6 ft × $^1/_8$ in. i.d. glass column packed with 2% DEGS on 100–120 mesh Gas-Chrom Q. The operating temperatures were: oven, 175 °C; injector, 270 °C; flame ionization detector, 310 °C. The carrier gas was 99.997% pure helium at a flow rate of 30 ml/min. These conditions were found to be optimal for analysis of the phenol and alcohol starting materials. The second instrument, used for the epoxy compounds and their olefin precursors, was a Varian 600D gas chromatograph employing a 10 ft × $^1/_8$ in. i.d. glass column packed with 4% XE-60 on 80–100 mesh Gas-Chrom Q and using 99.996% pure nitrogen at 40 ml/min as the carrier gas. The operating temperatures were: oven and flame ionization detector, 150–240 °C, and the injector, 290 °C. Integration of the GC traces was by the cut and weigh method. Analytical thin-layer chromatography utilized 20 × 20 cm Analtech "Uniplates" of 0.25-mm silica gel GF. The solvent was 3:1 hexane–ether. Regression analysis was carried out on a Digital PDP 11/40 computer.

The phrase "the solvent was dried" refers to equilibration with anhydrous sodium sulfate. Solvents used in reaction workups were removed by rotary evaporator at a bath temperature less than 50 °C. Most of the hormone mimic starting materials were purchased: *p*-ethylphenol, 2,4,6-trimethylphenol, geraniol (gold label), *p*-bromoethylbenzene, 5-methyl-2-thiophenecarbaldehyde, and *p*-methylbenzyl bromide from Aldrich Chemical Co., Milwaukee, Wis.; *p*-cresol, 2-phenylethanol, 3,4-dimethylphenol, and *p*-phenylphenol from Eastman Kodak Co., Rochester, N.Y.; phenol from Mallinckrodt Chemical Works, St. Louis, Mo.; 3,4,5-trimethylphenol and *p*-methylacetophenone from K&K labs., Inc., Plainview, N.Y.; *p-tert*-butylphenol and 1-naphthol from MCB Manufacturing Chemists, Norwood, Ohio; 2-naphthol from Fisher Scientific Co., Pittsburgh, Pa.; *cis*-4-ethylcyclohexanol and *trans*-4-ethylcyclohexanol from Chemical Samples Co., Columbus, Ohio. These phenols and alcohols as well as those whose syntheses are given below were purified, when necessary, by distillation or recrystallization to at least 98% isomeric purity as indicated by GC and ^{1}H NMR spectra. The 4-ethylcyclohexanols were at least 99% geometrically pure by GC (2% DEGS column described above, 15 ml/min flow rate; oven at 100 °C). *p-n*-Propylphenol and *p-n*-butylphenol were prepared in 22 and 11% yields, respectively, after distillation, by the method of Niederl et al. (1937). *p*-Isopropylphenol was prepared from cumene in 23% yield by the KOH fusion of sodium *p*-isopropylbenzenesulfonate according to Frank et al. (1949). Geranic acid was prepared as described previously (Nilles et al., 1973). New syntheses are described below.

***p*-Ethylbenzoic Acid.** A solution of the Grignard reagent prepared from 9.25 g (0.050 mol) of *p*-bromoethylbenzene and 1.20 g (0.050 mol) of magnesium turnings in 100 ml of dry ether was poured into approximately 50 g of dry solid carbon dioxide. After stirring and warming to room temperature, 20 ml of 50% aqueous HCl was cautiously added. The layers were separated, and the aqueous layer was extracted with 50 ml of ether. The combined extracts were washed with 30 ml of 10% NaOH. The aqueous extract was shaken with Norit, filtered, and acidified to pH 1 with concentrated HCl. The precipitated acid was crystallized from 200 ml of 10% aqueous ethanol to give 3.66 g (0.0244 mol, 49%) of the acid, mp 109–110 °C; reported (Fittig and Konig, 1867), 110–111 °C.

1-(*p*-Methylphenyl)ethanol. A stirred suspension of 1.9 g (0.050 mol) of lithium aluminum hydride in 50 ml of dry ether was treated during 30 min with a solution of 13.4 g (0.100 mol) of *p*-methylacetophenone in 100 ml of dry ether. After stirring overnight at room temperature, 50 ml of 5% aqueous NH_4Cl was cautiously added. The layers were separated, and the aqueous material was extracted by stirring and decantation with three 100-ml portions of ether. The combined, dried ether extracts were stripped to give 13.2 g (0.097 mol, 97%) of crude alcohol: ^{1}H NMR 2.9 (s, 4 H's), 5.3 (q, 1 H, J = 6.5 Hz), 7.7 (s, 3 H's), 8.7 (d, 3 H's, J = 6.5 Hz).

5-Methyl-2-thienylmethanol. A solution of 5.0 g (0.0397 mol) of 5-methyl-2-thiophenecarbaldehyde in 25 ml of 95% 2-propanol was treated at 0 °C in one portion with 1.52 g (0.040 mol) of $NaBH_4$. After stirring overnight at room temperature and then recooling in an ice bath, 2 N H_2SO_4 was added to pH 7. Most of the 2-propanol was then removed by rotary evaporator. The residue was extracted with 50 ml of hexane. Removal of the dried hexane gave 6.11 g (0.0397 mol, 99%) of the crude alcohol which was used directly to prepare the corresponding chloride.

5-Methyl-2-thienylchloromethane. A solution of 1.28 g (0.010 mol) of the above alcohol in 15 ml of dry hexane containing one drop of pyridine was stirred and maintained at 20 °C by occasional cooling. A solution of 1.31 g (0.011 mol) of thionyl chloride in 10 ml of dry hexane was then added over a period of 30 min followed by an additional 15 min of stirring. The solvent was removed and the crude chloride (0.81 g, 0.055 mol, 55%) was used directly in the preparation of the geranyl ether leading to **22**. This procedure is virtually the same as that of Emerson and Patrick (1949).

2-(4-Methylphenyl)ethanol. This alcohol was prepared by reduction of *p*-tolylacetic acid which was prepared by hydrolysis of the thiomorpholide resulting from the Willgerodt–Kindler reaction on *p*-methylacetophenone.

A mixture of 26.8 g (0.200 mol) of *p*-methylacetophenone, 26.1 g (0.300 mol) of morpholine, and 9.6 g (0.300 mol) of sulfur was refluxed for 12 h and then poured into 200 ml of cold water. After 12 h, the semicrystalline mass was collected, washed well with water, and then refluxed 6 h with 200 ml of 10% aqueous NaOH. The cooled solution was washed with three 100-ml portions of ether and then acidified with concentrated HCl. After cooling in the ice box, the precipitated acid was collected and dried over P_2O_5 in a vacuum dessicator for 2 days. The yield was 22.3 g (0.149 mol, 74%); mp 80–83 °C; reported, 90–91 °C (Schorigin, 1910).

A 6.0-g (0.040 mol) quantity of the above acid in 50 ml of dry ether was added dropwise to a suspension of 3.8 g (0.100 mol) of lithium aluminum hydride in 100 ml of dry ether. The mixture was refluxed 24 h, cooled, and added very slowly to 100 ml of water. The pH was adjusted to 1 with concentrated HCl, and extracted with three 150-ml portions of ether. The combined extracts were washed with two 50-ml portions of 10% aqueous NaOH, 100 ml of water, and 100 ml of salt solution, and then dried.

Removal of the solvent gave 5.06 g (0.0372 mol, 92%) of the alcohol: ^{1}H NMR 3.1 (s, 4 H's), 6.4 (t, 2 H's, J = 6 Hz), 7.0 (br s, 1 H), 7.3 (t, 2 H's, J = 6 Hz), 7.7 (s, 3 H's).

4,4-Diethylcyclohexanol. This alcohol was prepared by catalytic hydrogenation of 4,4-diethylcyclohex-2-en-1-one, itself prepared by the method of Bordwell and Wellman (1963) substituting 2-ethylbutyraldehyde for isobutyraldehyde. The yield of this ketone was 47%; bp 80–90 °C (4 Torr).

A solution of 6.08 g (0.040 mol) of this ketone was dissolved in 50 ml of glacial HOAc. About 200 mg of platinum oxide was added and the mixture shaken in a Parr apparatus in an atmosphere of 45 psi of hydrogen until the theoretical amount of hydrogen had been absorbed (about 5 h). After filtering, most of the HOAc was removed by rotary evaporator and the residue made strongly basic with 5% KOH. This solution was extracted with two 50-ml portions of hexane, the layers separated, and the extract dried. Removal of the solvent and vacuum distillation of the residue gave 5.87 g (0.0376 mol, 94%) of the saturated alcohol, bp 125–130 °C (7 Torr): ^{1}H NMR 6.4 (br s overlapping a multiplet centered at 6.5, total 2 H's), 8.2–9.3 (m, with triplet centered at 9.2, J = 7 Hz, total 12 H's).

8-Bromo-2,6-dimethyl-2-octene. A solution of 5.88 g (0.0377 mol) of 3,7-dimethyl-6-octenol in 25 ml of hexane containing 2.4 ml of pyridine was cooled to 0 °C and treated dropwise during 45 min with a solution of 5.42 g (0.020 mol) of phosphorous tribromide in 20 ml of hexane. After stirring 3 h at room temperature, the reaction mixture was poured into 100 g of crushed ice, and the organic phase separated. It was washed with three 100-ml portions of water and dried and the solvent was removed. The yield of crude citronellyl bromide (99% pure by GC) was 7.16 g (0.0327 mol, 87%).

(*E*)-1-Bromo-3,7-dimethyl-2,6-octadiene. This compound was prepared by a variation on the procedure of Corey et al. (1972). A solution of 1.08 g (6.00 mmol) of *N*-bromosuccinimide in 15 ml of CH_2Cl_2 was treated dropwise at 0 °C with 0.62 g (7.00 mmol) of tetrahydrothiophene. The bright yellow suspension was cooled to −20 °C and treated dropwise with a solution of 0.62 g (4.00 mmol) of geraniol in 2 ml of CH_2Cl_2 at such a rate that the temperature was maintained below −15 °C. The resulting pink suspension was then stirred at 5 °C until the solution became colorless and all of the precipitate had dissolved (about 30 min). The solution was poured into 50 ml of water and 50 ml of hexane was added. The organic phase was separated and the aqueous phase was washed with 20 ml of hexane. The combined extracts were back washed with 50 ml of water and 50 ml of 10% salt solution and dried and the solvent was removed to give 0.65 g (3.0 mmol, 75%) of geranyl bromide completely free of starting material by GC. This product contained less than 3% neryl bromide (the *Z* isomer) by GC–mass spectra.

General Ether Synthesis. The ethers leading to compounds **2**, **4–6**, **8–21**, and **23** were prepared by procedure A.

Procedure A. A 10-mmol quantity of the appropriate phenol or alcohol was dissolved in 15 ml of dry ether and treated with 0.25 g (10.4 mmol) of sodium hydride. The mixture was stirred under nitrogen until hydrogen evolution had ceased. To this, 2.17 g (10 mmol) of geranyl bromide was injected through a septum cap in one portion, followed by 4 ml of dimethyl sulfoxide previously dried by distillation from calcium hydride. The mixture was stirred at room temperature for 2 days, then poured into 30 ml of water, and 50 ml of hexane was added. The shaken layers were separated and the aqueous layer was washed with 30 ml of hexane. The combined hexane extracts were washed with 20 ml of 10% NaOH. This wash was omitted if the starting material was an alcohol. After separating and drying, the solvent was removed.

Procedure B. The ethers leading to compounds **7** and **22** were prepared in the same manner as in A, except that geraniol was the starting alcohol, and after treatment with sodium hydride, the appropriate halide was added. Procedure A gave consistently inferior yields for these two ethers.

These diolefinic ethers, as well as the olefins leading to compounds **24–27** were purifed by means of a Varian 4000 liquid chromatograph using a 25 mm i.d. glass column packed with 80 g of E. Merck 70–325 mesh silica gel, packed as a slurry in the solvent used for elution. The eluting solvent was 4:1 hexane–ether with a flow rate of 2–5 ml/min at atmospheric pressure. The eluent was monitored at 254 nm in the nonlinear mode. The product was always the second substance eluted. The yield of the diolefinic ethers after purification was in the range of 65–95%.

Geranyl *p*-Ethylphenyl Sulfide. The Grignard reagent prepared from 3.70 g (0.020 mol) of *p*-bromoethylbenzene and 0.48 g (0.020 mol) of magnesium in 80 ml of dry ether was treated with 0.48 g (0.015 mol) of sulfur. This initially exothermic reaction was stirred at room temperature for 90 min and 2.17 g (0.0100 mol) of geranyl bromide was added followed by 10 ml of dry dimethyl sulfoxide. This mixture was stirred 36 h and poured into water. The layers were separated and the aqueous layer extracted with two 50-ml portions of hexane. The combined extracts were washed with 100 ml of water, 20 ml of saturated salt solution, separated and dried. The solvent was removed and the residue purified to give 2.74 g (0.0094 mol, 94%), of the sulfide.

The procedure of Staab and Mannschreck (1962) was used as a guide in the preparation of the following two esters.

Geranyl *p*-Ethylbenzoate. A solution of 0.50 g (3.3 mmol) of *p*-ethylbenzoic acid in 15 ml of dry ether was treated in one portion with 0.81 g (5.0 mmol) of 1,1′-carbonyldiimidazole (CDI) and stirred at room temperature for 4 h. A solution of 0.51 g (3.3 mmol) of geraniol in 10 ml of dry ether was treated with about 20 mg of sodium hydride. This solution was added in one portion to the imidazolide solution and stirred 20 h. Water, 10 ml, followed by 50 ml of hexane was added and the layers were separated. The organic phase was washed with three 20-ml portions of water. After separating and drying, the solvent was removed. The residue was subjected to liquid chromatography to give 0.682 g (2.38 mmol, 74%) of the ester.

***p*-Ethylphenyl Geraniate.** A solution of 1.68 g (0.010 mol) of geranic acid in 30 ml of dry benzene was treated in one portion with 2.00 g (0.0123 mol) of CDI and stirred at room temperature for 8 h. After refluxing for 15 min and recooling to room temperature, a solution prepared by treating 1.22 g (0.010 mol) of *p*-ethylphenol in 20 ml of dry ether with about 50 mg of sodium hydride was added. The entire mixture was allowed to stir for an additional 14 h and then added to a mixture of 50 ml of water and 100 ml of hexane. After separation of the layers, the organic phase was washed with three 100-ml portions of water and dried and the solvent was removed. The purified yield was 0.825 g (3.06 mmol, 31%).

General Procedure for Epoxidation. All of the compounds in Table I, with the exceptions of **25** and **28**, were prepared from their olefin precursors by epoxidation with *m*-chloroperbenzoic acid in CH_2Cl_2. While it would appear to be more convenient to first epoxidize the geranyl bromide and use it in the above Williamson synthesis (Pallos et al., 1971) we found that this procedure led to a greater percentage and number of side products. These possibly arise from concomitant attack by the more nucleophilic alcoholates and phenolates on the epoxide ring.

A 2.0-mmol quantity of the olefin was dissolved in 15 ml of CH_2Cl_2 and cooled to 0–5 °C. To this, a solution of 0.361 g (2.1 mmol) of purified *m*-chloroperbenzoic acid (Schwartz and Blumbergs, 1964) in no more than 10 ml of CH_2Cl_2 was added in one portion. The mixture was stirred 45 min, during which time considerable *m*-chlorobenzoic acid precipitated. The reaction mixture was poured into 20 ml of 5% aqueous Na_2CO_3, shaken well for 10 min, and then separated. The aqueous phase was extracted with 20 ml of CH_2Cl_2. The extracts were combined and dried and the solvent was removed. The residue was purified by preparative thin-layer chromatography. This employed 20 × 20 cm plates coated with a 1.5-mm layer of E. Merck silica gel GF-254. The elution solvent was 2:1 hexane–ether. About 300 mg could be purified at one time. Purity was further checked by GC, which indicated that the hormone mimics were at least 97% pure.

Since epoxidation of the sulfide leading to compound **25** by *m*-chloroperbenzoic acid would lead to oxidation of the sulfur atom (cf. Hlavacek et al., 1972) the epoxide was prepared by base-catalyzed ring closure of the 6,7-bromohydrin following the procedure of Coates and Melvin (1970).

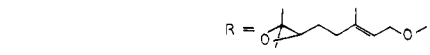
Compound **28** was furnished by Dr. Richard Bagley of Hoffman-LaRoche, Nutley, N.J. Dr. Julius Menn of Stauffer Chemical Co., Mountain View, Calif., gave us a comparison sample of mimic **2**. We express our appreciation to these two gentlemen for these compounds.

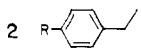
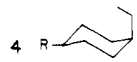
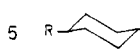
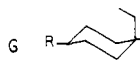
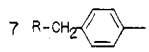
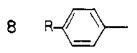
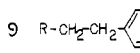
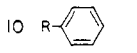
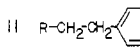
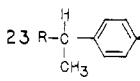
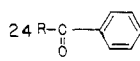
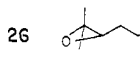
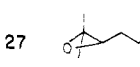
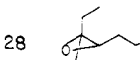
The structures of all of the compounds in Table I as well as their olefin precursors were readily confirmed by: mode of synthesis, observation of the correct *m/e* peak for the parent ion in the mass spectrum, and the correct integration ratio for olefinic to aryl or alkyl protons in the ^1H NMR spectrum. The epoxy proton showed up as a triplet between τ 7.2 and 7.5. Overall yields are given in Table I for both the coupling step (Williamson ether or Staab ester) and the epoxidation step. R_f values are from the analytical thin-layer system.

R_f values were also determined on a layer of cereal leaf beetle bodies. Approximately 10000 field collected beetles were macerated in a blender for 15 min with 1 l. of $CHCl_3$. After filtration, the filter cake was extracted with CH_2Cl_2 in a Soxhlet apparatus for 72 h. The resulting chitinous mass was air dried and ground to pass an 80 mesh sieve. This material was mixed with 0.5% manganese zinc silicate (254-nm fluorescent indicator) and spread 300 μm thick on 20 × 20 cm TLC plates. After air drying, these were used as TLC plates in the usual manner with hexane as the eluent.

Biological Assay. The mimics were assayed on laboratory reared adult prediapause cereal leaf beetles, *Oulema melanopus* (Connin et al., 1968). They were applied as 5 and 10% solutions (50 or 100 μg per insect) in acetone on the ventral side of the abdomen. Either females alone were treated (designated F in Table II) or both males and females (designated MF in Table II). In the present study only prediapause insects were treated.

Table I. Percent Yield and R_f Values for All Mimics[a]



No.	Structure	% Yield	R_f	R_{fb}	No.	Structure	% Yield	R_f	R_{fb}
2		74	.32	.83	12		63	.41	.81
4		92	.33	.82	13		88	.41	.81
5		83	.28	.77	14		89	.42	.81
6		43	.29	.92	15		48	.23	.84
7		98	.25	.78	16		66	.30	.76
8		24	.23	.84	17		55	.33	.83
9		80	.25	.83	18		76	.41	.77
10		76	.32	.85	19		85	.41	.82
11		88	.24	.83	20		61	.32	.87
23		72	.33	.86	21		57	.41	.88
24		93	.31	.89	22		98	.29	.88
25							24	.31	.78
26							71	.35	.85
27							95	.27	.87
28							–	.34	.83

[a] The column headed R_f was determined on silica gel. The column headed R_{fb} was determined on a thin layer of cereal leaf beetle exoskeleton.

Blank runs in which insects were treated only with acetone consistently gave zero oviposition and insects entered normal diapause toward the end of the test period. Observations were made on feeding and mating activity, number of eggs layed, and cumulative mortality. Other bioassay details are exactly as described earlier (Nilles et al., 1973).

DISCUSSION

The use of the adult prediapause cereal leaf beetle, *Oulema melanopus*, in evaluating juvenile hormone activity of hormone mimics has been described (Nilles et al., 1973, and references therein). The JH activity of the mimic was directly proportional to faster initial oviposition following treatment and to larger numbers of eggs oviposited by the test colony. A compound has maximum JH activity if initiation of oviposition and number of eggs layed in a given time are the same as would be expected from a postdiapause beetle after emerging from over-

Table II. Oviposition, Vitality Data, and Activity Ratings

Compd no.	Dosage, μg	Days to[a] 1st egg		Total eggs in 14 days		Act. rating		Vitality,[b] % alive		Compd no.	Dosage, μg	Days to 1st egg		Total eggs in 14 days		Act. rating		Vitality, % alive	
		MF	F	MF	F	MF	F	MF	F			MF	F	MF	F	MF	F	MF	F
2	100	7	7	139	144	34	28	60	75	17	100	-	-	0	0	0	0	20	35
	50	6	7	78	126	18	22	70	85		50	10	-	22	0	8	0	30	40
3	100	7	7	182	94	87	30	30	45	18	100	13	-	4	0	2	0	20	35
	50	7	7	106	45	38	13	40	50		50	-	-	0	0	0	0	50	40
4	100	8	8	74	87	24	16	40	70	19	100	12	-	14	0	2	0	25	15
	50	14	10	8	34	1	4	50	80		50	-	-	0	0	0	0	90	70
5	100	8	8	304	132	114	29	35	60	20	100	7	7	142	32	38	6	40	20
	50	9	9	192	64	50	19	45	40		50	-	7	0	31	0	5	85	90
6	100	8	-	66	0	24	0	40	45	21	100	-	6	0	15	0	5	55	60
	50	8	-	99	0	29	0	50	45		50	6	-	48	0	15	0	60	80
7	100	6	6	587	125	126	27	80	80	22	100	8	10	21	25	27	3	10	65
	50	6	6	144	315	25	64	100	85		50	0	10	0	9	0	1	75	65
8	100	-	5	0	131	0	36	25	70	23	100	-	-	0	0	0	0	65	40
	50	5	7	24	2	9	0	50	85		50	-	-	0	0	0	0	65	65
9	100	13	11	15	12	5	2	25	55	24	100	10	10	144	51	26	6	60	85
	50	6	-	14	0	16	0	15	15		50	-	-	0	0	0	0	80	80
10	100	-	14	0	7	0	3	20	40	25	100	-	-	0	0	0	0	30	10
	50	13	-	13	0	3	0	35	35		50	12	-	27	0	10	0	25	50
11	100	14	-	9	0	2	0	45	65	26	100	8	8	49	118	21	20	30	75
	50	10	-	18	0	1	0	80	80		50	8	10	68	12	11	18	80	40
12	100	7	7	166	135	73	35	35	60	27	100	8	-	4	0	3	0	20	40
	50	7	6	154	128	40	36	60	65		50	10	-	85	0	11	0	85	70
13	100	6	6	147	58	62	20	45	55	28	100	-	-	0	0	0	0	0	35
	50	8	6	5	6	1	2	50	60		50	-	-	0	0	0	0	5	40
14	100	8	10	156	29	53	16	40	20	Acetone	100	-	-	0	0	0	0	90	85
	50	8	8	93	29	36	7	35	60	check									
15	100	10	-	24	0	12	0	25	40	Untreated		-	-	0	0	0	0	80	80
	50	-	-	0	0	0	0	30	70	Untreated		5		438				75	
16	100	9	11	30	30	13	5	30	60	postdi-									
	50	6	11	59	13	32	2	35	55	apause									
										check									

[a] In columns headed MF, the mimic was applied to both sexes at the indicated dosage; in columns headed F, only the females were treated. Dashes indicate failure of insects to oviposit by 14 days. [b] After 14 days.

wintering or laboratory storage (Connin et al., 1968). Thus, an activity rating for a candidate mimic should be directly proportional to the total number of eggs layed and the molar quantity of the mimic applied. It should be inversely proportional to the number of days following treatment on which oviposition first occurs. A correction for mortality is necessary since, obviously, dead insects cannot lay eggs. Fewer live insects would mean a total egg production which is not due to lower JH activity. Accordingly, we define the activity rating (AR) as in eq 1. In this equation,

$$AR = TG/DV \quad (1)$$

T is the total number of eggs layed by the test colony for 14 days inclusive, following topical application of the mimic; G is a gravimetric factor relative to mimic **3** which allows correction to equimolar treatment; D is the number of days elapsed, following treatment on which oviposition first occurs; and V is the vitality of the test colony after 14 days expressed as a decimal fraction. AR values are rounded to the nearest whole number.

Although this definition of JH activity differs from the oviposition index used in our previous study, values of AR may be calculated for compounds in that paper from the data given therein. Table II gives the complete bioassay results for compounds in the present study as well as activity ratings (AR) for each compound tested.

Basically we had two goals in this study. One was to synthesize and bioassay a number of epoxygeranyl ethers and related compounds for JH activity. Some of these compounds (**1, 2, 3, 8, 10, 12, 14, 16, 19, 26, 28**) were known earlier and their JH activities had been determined in other insects (Jacobsen et al., 1972; Walkers and Bowers, 1973). The second goal of our study, and the design factor in our choice of candidate mimics, was to evaluate the essential three-dimensional parameters of the aryl portion of these mimics, i.e., to determine whether or not it was possible to use small alkyl groups as a steric probe to determine the optimum structure–activity response. In addition we wished to assess the relative importance of steric, electronic, and lipophilic parameters that contribute to JH activity for these compounds.

Since we used topical application to an adult insect, one might argue that differences in transport properties of the mimics would affect their activities. Solomon et al. (1973) in their study on JH mimics have suggested that structurally similar compounds whose R_f values are nearly the same would have similar uptake through the insect cuticle. It will be noted from Table I that all of the mimics have an R_f value in the range 0.32 ± 0.10 determined with the same TLC system. Of course, beetle exoskeleton is not composed of silica gel. However, R_f values determined on a thin layer of insect bodies (R_{fb}) showed a similar range for all of the mimics, 0.84 ± 0.08. We feel that passive transport through the beetle cuticle should be a relatively constant factor for all of the mimics studied here.

One question from our earlier study was whether or not the mimic needed a π electron center such as a benzene ring in order to be active. The JH response of **5** clearly obviates this requirement. Indeed, this trans cyclohexyl compound is quite a bit more active than its corresponding aryl analogue **2**. We will show later that this increase in activity of **5** is probably due to an increase in lipophilicity for **5** relative to **2**. The markedly diminished activity of **4**, the cis stereoisomer of **5**, indicates that this end of the mimic must be at least roughly planar. Restoring the trans ethyl group to the mimic as in **6** does not restore activity since a planar shape is still not possible. The ball-like shape of **4** or **6** may interfere with approach of the mimic to a receptor site.

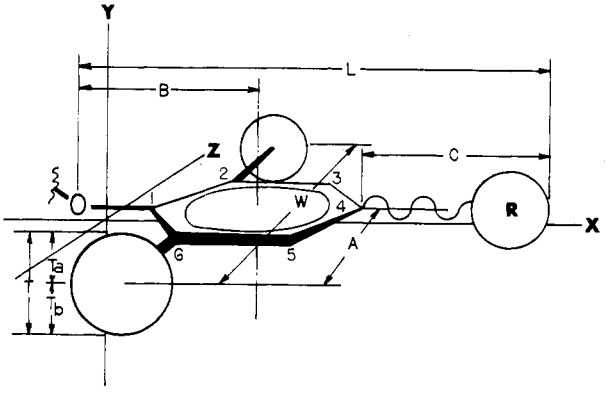


Figure 1. Dimensional symbols and cartesian orientation for all mimics.

Recent advances in quantitative structure–activity relationships (QSAR) have allowed the statistical assessment of the contribution of steric, electronic, and lipophilic parameters on biological activity (Hansch, 1972). This type of analysis has been recently extended to the entomological area by Metcalf and his coworkers (1974), and by Yu and Kuhr (1976). Since these parameters derive from extrathermodynamic relationships, it is important to utilize those that are primary in nature as well as to indicate which chemical system from which they are derived.

For σ values, we have used the excellent compilation of Hansch et al. (1973). σ values are too frequently *not* additive. In those cases where the σ value based on the additivity rule did not agree with the value obtained from direct measurement, we used the directly measured value. The σ value for **19** is based on the ionization constant of 3,4-dimethylbenzoic acid (Table II of the 1973 Hansch study) rather than the sum of σ_m and σ_p for the methyl group. The σ value for **17** was calculated from the pK_a of 2,4,6-trimethylbenzoic acid (Wilson et al., 1967) and for **18** from the ionization constant for 3,4,5-trimethylbenzoic acid (Stone and Pearson, 1961). The σ value for **21** is based on the pK_a of 1-naphthoic acid from the Handbook of Chemistry and Physics (1970).

The lipophilicity parameters (π) are from the study by Hansch et al. (1973) and are based on the benzene system. Certain values not included in this study were calculated. The π values for the cyclohexyl compounds were calculated by taking the value for the ethyl group (1.02) and adding the difference between phenyl and cyclohexyl (0.55). This gives $\pi = 1.57$ for both **4** and **5**. For **6** an additional 1.02 was added for the extra ethyl group making $\pi = 2.59$. The π value for **13** was obtained by adding 0.50 for the extra CH_2 to the value for **12** to total 2.05.

The steric parameter most used in the past in QSAR has been Taft's E_s values (Kutter and Hansch, 1969). Charton (1969) has shown that E_s is a linear function of Van der Waals radii. Thus, substituents that deviate strongly from a spherical shape or multiple spherical substituents that are placed in a nonspherical pattern (e.g., 3,4,5-trimethylphenyl) cause considerable differences between predicted and actual physical or biological properties. Hansch and his coworkers (1973) have suggested that molar refractivity might replace E_s as a steric parameter. He cautions, however, that MR values contain an electronic contribution term and could give rise to erroneous conclusions based on multiple regression analysis.

In the present study, we employed a term ω empirically defined in eq 2. In Figure 1 and Table III, we present the

$$\omega = \frac{(C - 2.08) + (B - 2.75)}{(W - 6.29) + (T_a - 2.00)} \quad (2)$$

Table III. Dimensions (in Angstroms) and Regression Analysis Parameters for All Mimics

Compd no.	Log J/J_0	L	W	A	B	C	T_b	T_a	ω	π	σ
2	1.230	8.45	6.29	3.14	2.75	4.31	3.15	1.72	3.10	1.02	−0.15
4	0.875	7.65[a]	6.68[a]	3.34[a]	2.74	3.31[a]	2.29[a]	4.33[b]	0.331	1.57	
5	1.549	8.88[a]	6.68[a]	3.34[a]	2.74	3.83	3.25[a]	2.29	1.04	1.57	
6	0.946	8.88[a]	6.68[a]	3.34[a]	2.74	3.83	3.25[a]	4.33[b]	0.472	2.59	
7	1.605	7.85	6.29	3.14	3.37	3.07	2.23	1.72	2.24		
8	0.875	7.21	6.29	3.14	2.75	3.07	2.23	1.72	1.38	0.56	−0.17
9	0.584	8.22	7.02	3.88[a,c]	4.75[c]	2.08	3.15	1.72	1.38		
10	0.000	6.22	6.29	3.14	2.75	2.08	1.00	1.00	0.00	0.00	0.00
11	−0.301	9.32	7.02	3.88[a]	4.86[c]	3.07	3.15	1.72	2.14		
12	1.487	9.26	7.78[a]	4.64[c]	2.75	5.12[c]	4.64[a]	1.72	4.23	1.55	−0.13
13	1.152	10.50	8.97[a]	5.83[a,c]	2.75	6.36[c]	5.68[c]	1.72	5.95	2.05	−0.16
14	1.272	8.45	6.29	3.14	2.75	4.31	3.15[d]	2.16[d]	1.92	1.53	−0.15
15	0.301	10.53	6.29	3.14	2.75	6.39	2.00[e]	2.73[e]	2.49	1.96	−0.01
16	0.938	8.45	6.29	3.15	2.75	4.31	3.15[d]	2.44[d]	1.55	1.98	−0.20
17	0.124	7.21	9.07	4.54	2.75	3.07	2.23[b]	1.72	0.283	1.29	+0.75
18	−0.482	7.21	9.07	4.54	2.75	3.07	2.23[b]	1.72	0.283	1.42	−0.39
19	−0.482	7.21	7.68	4.54	2.75	3.07	2.23[b]	1.72	0.469	0.99	−0.30
20	0.912	8.31	7.49	4.35	2.75	4.17	1.00	1.00	1.74	1.32	+0.04
21	0.522	6.22	8.70	5.56	2.75	2.08	1.00	1.00	0.00	1.32	+0.50
22	0.714	7.70[a,f]	6.28[a]	3.14[a]	3.00[a,f]	3.07	2.23	1.72	1.72		
23		7.85	6.44[a]	3.30[a]	3.37	3.07	2.64[a]	2.92[a,g]	0.777		
24	0.727	9.01	6.29	3.14	3.31	4.31	3.15	1.72	3.88		
25	0.223	8.91	6.29	3.14	3.21	4.31	3.15	1.72	3.74		
26	1.068	8.45	6.29	3.14	2.75	4.31	3.15	1.72	3.10		
27	0.369	8.45	6.29	3.14	2.75	4.31	3.15	1.72	3.10		
28		7.57[a]	7.04[a]	3.80[a]	2.75	3.52[a]	2.17	2.17	1.57		

[a] Measured from Dreiding models. [b] Maximum value. [c] Minimum values are: 9, B = 2.19, A = 3.14; 11, B = 2.19; 12, A = 3.14, C = 4.31; 13, A = 3.14, C = 4.31. [d] Methyls in the eclipsed conformation. [e] Dihedral angle between rings = 60°. [f] B maximum is 3.45, L minimum is 7.25. [g] T_a is for methyl aligned with y axis; T_a minimum is 1.72.

dimensional parameters used in calculating ω. All measurements were made with respect to the x, y, and z axes, with the plane of the benzene ring parallel to the xz coordinate plane. In the case of compounds **4–6** the plane defined by C-1, -3, and -5 was placed parallel to the xz plane. The parameters are defined as follows. L is the distance from the oxygen nucleus to the furthest extent of the Van der Waals radius of the para substituent; B is the distance from the oxygen nucleus to the center of the ring; C is the maximum length of the para substituent from the C-4 nucleus to the Van der Waals radius terminal hydrogen of the substituent; W is the width of the group inclusive of the Van der Waals radii; A is the distance in the xz plane perpendicular to the axis joining C-1 and C-4 and measured to the Van der Waals radius of a substituent on C-2 or C-3; T is the thickness of the group; T_a is the distance above the plane defined by C-1, C-3, and C-5; and T_b is the distance below this plane. All measurements are inclusive of the Van der Waals radii (Bondi, 1964). The dimensions of the alkyl substituents were calculated by the method of Charton (1971). Bond lengths are from Sutton (1965). Values with a superscript a were measured from Dreiding models. In all other cases dimensions were both calculated and measured. They agreed with each other within ±2%.

It may be seen from Tables I and II that biological activity is in direct proportion to C and B, and inversely proportional to W and T_a. We have selected mimic **10** as a standard compound. Therefore, ω from eq 2 is a steric factor based on dimensional increases for a given mimic relative to those for **10**, the unsubstituted mimic.

Rather than discuss each of the four runs made on each mimic separately, we will combine them. We introduce the term J, equal to the sum of the four AR values for each mimic. QSAR are, of course, based on linear and parabolic free-energy relationships; consequently, we must use the logarithm of the biological activity. Table III gives $\log J/J_0$ for each mimic, where J_0 is the value for mimic **10**, the arbitrary standard.

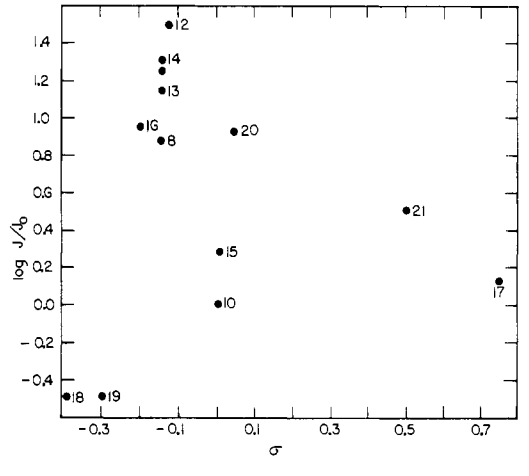


Figure 2. Hammett plot for selected mimics.

In selecting mimic data to include in the regression analysis, we have limited ourselves to those data belonging to the largest single homologous series, namely the epoxygeranyl aryl ethers (**2**, **8**, **10**, **12–21**). The resulting regression equations cannot accommodate the other mimics (except fortuitously) since those mimics belong to chemically different series with probably noncongruent regression coefficients.

Figure 2 shows the Hammett plot for all mimics for which a σ value could be found. No one equation linking σ and $\log J/J_0$ could be found. Mimics **17** and **21** could probably be justifiably eliminated from the plot, since they are ortho substituted and cannot be expected to give good Hammett results. The data of the remaining mimics still show considerable scatter. Biological activity frequently shows a parabolic relationship with a contributing parameter (Hansch, 1967; Kutter and Hansch, 1969). Upon introduction of higher powers of σ into a multiple regression with π and ω, the correlation coefficient decreased. For these reasons we believe that the JH response of this

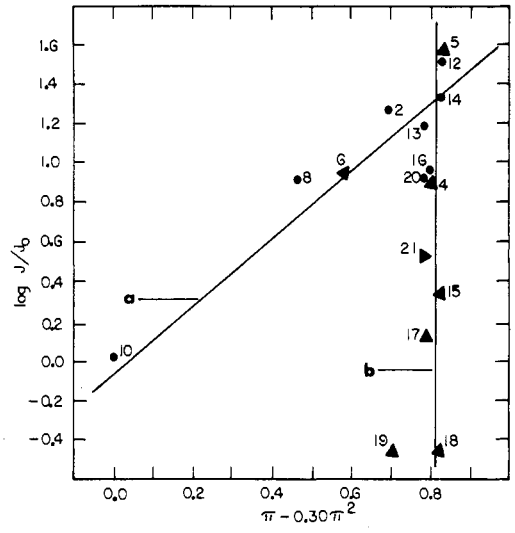


Figure 3. Plot of JH response vs. the lipophilicity parameter, π, for selected mimics.

series of compounds has little dependency on polar effects.

In the above plot and later ones, we wish to caution the reader to judge not harshly deviations from the regression line for those points where the log J/J_0 value is less than zero. A difference of one or two eggs layed by a test colony causes a greatly disproportionate change in log J compared to values where J/J_0 is greater than zero. Mimics **18**, **19**, and **21** fall into this class.

As in the case with σ, no one equation could be found that would linearly relate π, the Hansch lipophilicity parameter, with log J/J_0. However, by adding π^2 terms, the data fall into two linear groups as seen in Figure 3. The data indicated by the solid dots obey eq 3.

$$\log J/J_0 = -0.140 + 1.72\pi - 0.516\pi^2 \quad (3)$$
$$n = 8,\ r = 0.9009,\ s = 0.234,\ F = 25.85,$$
$$F_{2,5}(0.01) = 13.27$$

The para phenyl mimic **15** could not be accommodated by any equation. However, it has been noted in other studies that phenyl as a substituent can give a poor fit in QSAR (Unger and Hansch, 1973).

While the usefulness of eq 3 is rather restricted, it can be used to answer an earlier question. The lipophilicity parameters calculated for mimics **4** and **5** put their respective log J/J_0 values within the range of the regression and do not significantly change the coefficients of eq 3. Put another way, the increase in activity of **5** vs. its phenyl counterpart **2** appears to be due solely to an increase in lipophilicity of the cyclohexyl vs. aryl group.

Only half of the compounds (line a) obey eq 3, while the rest (line b) are invariant with respect to π. The range of π values given by line b is 1.29–1.98, in good agreement with the optimum value 1.67, obtained by setting the first derivative of eq 3 equal to zero. The invarience of lipophilicity on log J/J_0 prompted us to investigate the effect of steric factors on JH response.

Qualitatively, an examination of Tables I, II, and III reveals several steric effects on JH response which lead to a picture of a receptor site as in Figure 4. The shape of this hypothetical receptor site is purely a rationale for the experimental JH activities. We will make the unsubstantiated assumption that the epoxy oxygen is involved in binding that end of the mimic to the receptor. However, we do point out the almost universally noted fact that epoxy mimics are more JH active than the olefins from which they are derived. A second assumption from Figure 4 is that there is a "pouch" at P which holds the para

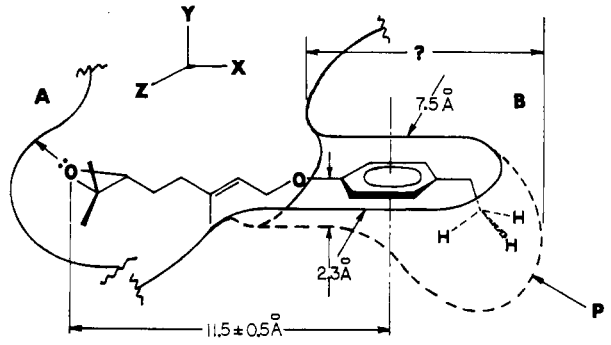


Figure 4. Drawing of a hypothetical receptor site with critical dimensions. Part A of the receptor may or may not be directly connected to Part B.

substituent and "locks in" the aryl end of the mimic. The dimensions in this figure are the averages between the maxima at which JH response is significant (log $J/J_0 >$ 1.00) and the minima at which JH response is seriously diminished (log $J/J_0 <$ 1.00).

Increasing T_a beyond about 2.3 Å (cf. **5** with **4**, **6**, **16**, and **23**) causes a sharp drop in activity. This would occur if it is essential for the ring to approach the receptor site "flat on". Portions of the substrate below the plane of the ring, T_b, would be sterically unencumbered. Increasing the length of the para substituent increases activity linearly in the series **10**, **8**, **2**, and **12**. Differentiation here between a steric effect and a lipophilic effect is difficult. Probably both are operational. The decrease in activity for **13** could be ascribed to the folding of the *n*-butyl group resulting in an increase in W and/or T_a, or rationalized by the normally expected parabolic effect of lipophilicity on activity. The phenyl group **15** and the tolyl **11** are too bulky to fit the pouch. Mimics **10** and **8** give poor response, since the hydrogen and methyl groups, respectively, are too short to lock in the aryl end of the substrate. The cyclohexyl mimics (**4** and **6**) give poor response since the axial ethyl group will not lock in to the pouch and still allow the remainder of the substrate to fit the receptor.

Mimic **7**, which has only a para methyl group, can fit this pouch since the intervening methylene between the oxygen and the ring pushes the methyl group into the pouch. The activity increase of **7** cannot be lipophilic since the π contribution for the methylbenzyl residue should be nearly the same as the ethylphenyl **2**. Mimic **7** is actually about 2.4 times as active as **2**. Let us assume the theory that these mimics are JH active because they inhibit the system responsible for the destruction of endogenous juvenile hormone. Let us also assume that the oxygen at the aryl end of the mimic could bond to a different portion of the receptor which is responsible for the inactivation of natural JH, in a manner suggested by Koshland (1964) for receptor inhibition. This is, of course, purely speculative, but we do note that sterically crowding this oxygen by methyl (**17**, **23**) or by carbonyl (**24**, **27**) results in a sharp decrease in activity. Hlavacek and his coworkers (1972) have noted a loss in activity when the ether oxygen is replaced by sulfur in similar JH mimics. We note the same effect in this study in comparing **25** with **2**. This could be due either to loss of coordinate–covalent bonding due to decreased electron density of sulfur vs. oxygen or change in bond angle. The difference between the average C–O–C bond angle and the average C–S–C bond angle is about 6°. This would result in moving the terminal hydrogen of the para ethyl group about 0.8 Å in the z direction. This may be enough to make a proper fit at P difficult.

The effect of the olefinic bond on activity is revealed by comparing **26** and **2**. Mimic **26** should have shown an

Table IV. Observed and Calculated Values of Log J/J_0

Compd no.	Log J/J_0 Obsd	Calcd	Diff	Compd no.	Log J/J_0 Obsd	Calcd	Diff
2	1.23	1.20	−0.02	14	1.27	1.16	−0.11
4	0.88	0.76	−0.12	15	0.30	1.24	+0.94
5	1.55	0.96	−0.59	16	0.94	1.06	+0.12
6	0.95	0.59	−0.36	17	0.12	0.71	+0.59
8	0.88	0.73	−0.15	18	−0.48	0.73	+1.21
10	0.00	−0.06	−0.06	19	−0.48	0.69	+1.17
12	1.49	1.41	−0.08	20	0.91	1.10	+0.19
13	1.15	1.31	+0.16	21	0.52	0.62	+0.10

increase in activity on the basis of lipophilicity since saturating the double bond should increase π by about 0.45 [$\pi(CH_2CH_2CH_3) = 1.55$, $\pi(CH_2CH{=}CH_2) = 1.10$]. The decrease in activity could be due to steric factors (changing two sp^2 carbons to sp^3) and/or loss of possible bonding of the olefin moiety to the receptor. One might also consider the increase in entropy resulting from constraining the less rigid mimic to the receptor.

Mimic **22**, the thienyl isostere of **7**, has a markedly diminished response, which can be attributed to a slight change in steric parameters since the response falls within the range of regression as in Figure 4. However, some of this decrease may be due to a decrease in lipophilicity (π(phenyl) = 1.96, π(2-thienyl) = 1.61).

Those mimics with a W value above about 7.5 Å show decreased JH activity. From this, we conclude that the receptor slot cannot be much wider than this figure. Mimics **17**, **18**, **19**, and **28** give low activities since they are too wide to fit the slot.

The quantitative results of correlating ω with JH response are shown in Figure 5 and eq 4. Again only the

$$\log J/J_0 = 0.018 + 0.672\omega - 0.0739\omega^2 \quad (4)$$
$$n = 8,\ r = 0.9518,\ s = 0.159,\ F = 57.72,$$
$$F_{2,5}(0.01) = 13.27$$

epoxygeranyl aryl ether data are plotted. The regression analysis includes the same mimics as in eq 3 (solid circles).

That ω gives somewhat better results as a steric factor than molar refractivity is shown by a correlation for the same eight mimics as in eq 4 between log J/J_0 and MR ($r = 0.6568$, $F = 4.551$) and ω ($r = 0.6978$, $F = 5.695$). The absence of parameter mutual dependency is shown by the collinearity matrix.

	σ	π	ω
σ	1.00	0.00	0.22
π		1.00	0.27
ω			1.00

Equation 5 shows the results of combining π and ω in

$$\log J/J_0 = -0.061 + 0.860\pi + 0.336\omega - 0.258\pi^2 - 0.0370\omega^2 \quad (5)$$
$$n = 8,\ r = 0.9622,\ s = 0.140,\ F = 74.81,$$
$$F_{4,3}(0.01) = 28.71$$

a multiple regression. The F test reveals a better correlation than either parameter taken singly. The observed vs. calculated (by eq 5) values of log J/J_0 are given in Table IV.

Regression analysis has revealed that both lipophilicity and steric effects are dominant in the epoxygeranyl aryl ether mimic series. It also appears that since attempts to add σ values to eq 5 resulted in poorer correlations, polar effects are not important. However, since the range of polar substituents that we have tested is rather small, we do not feel that this conclusion can be extended to more polar substituents. We also caution the reader that our analysis and experimental results are only applicable to the cereal leaf beetle due to the well-known variation in structure–activity response in different species of insects.

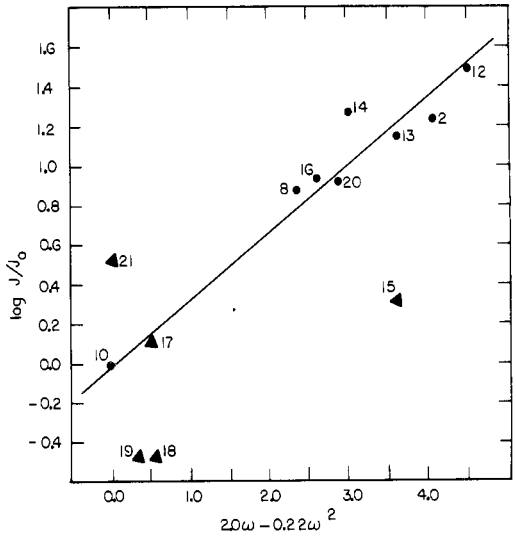


Figure 5. Plot of JH response vs. the steric parameter, ω, for selected mimics.

LITERATURE CITED

Bondi, A., *J. Phys. Chem.* **68**, 441 (1964).
Bordwell, F. G., Wellman, K. M., *J. Org. Chem.* **28**, 1347 (1963).
Bowers, W. S., *Science* **164**, 323 (1969).
Charton, M., *J. Am. Chem. Soc.* **91**, 615 (1969).
Charton, M., *Progr. Phys. Org. Chem.* **8**, 235 (1971).
Coates, R. M., Melvin, L. S., *Tetrahedron* **26**, 5699 (1970).
Connin, R. V., Cobb, D. L., Arnsman, J. C, Lawson, G., *Agric. Res. Bull.* **No. 33-125** (1968).
Corey, E. J., Kim, C. H., Takeda, M., *Tetrahedron Lett.*, 4339 (1972).
Dunn, W. J., *Annu. Rep. Med. Chem.* **8**, 313 (1973).
Emerson, W. S., Patrick, T. M., *J. Org. Chem.* **14**, 790 (1949).
Fittig, R., Konig, J., *Justus Liebigs Ann. Chem.* **144**, 277 (1867).
Frank, R. L., Berry, R. E., Shotwell, D. L., *J. Am. Chem. Soc.* **71**, 3889 (1949).
"Handbook of Chemistry and Physics", 50th ed, Weast, R. C., Ed., The Chemical Rubber Co., Cleveland, Ohio, 1970, p D-118.
Hansch, C., *Annu. Rep. Med. Chem.* **3**, 348 (1967).
Hansch, C., *Adv. Chem. Ser.* **No. 114**, 20–40 (1972).
Hansch, C., Leo, A., Unger, S. H., Kim, K. H., Nikaitani, D., Lien, E. J., *J. Med. Chem.* **16**, 1207 (1973).
Hlavacek, J., Polejs, L., Sorm, F., *Collect. Chem. Commun.* **37**, 3905 (1972).
Jacobsen, M., Beroza, M., Bull, D. L., Bullock, H. R., Chamberlain, W. F., McGovern, T. P., Redfern, R. E., Sarmiento, R., Schwarz, M., Sonnet, D. E., Wakabayashi, N., Waters, R. M., Wright, J. E., in "Insect Juvenile Hormones", Menn, J. J., Beroza, M., Ed., Academic Press, New York, N.Y., 1972, p 249.
Koshland, D. E., *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **23**, 719 (1964).
Kutter, E., Hansch, C., *J. Med. Chem.* **12**, 647 (1969).

Metcalf, R. L., *Annu. Rep. Med. Chem.* **9**, 300 (1974).
Niederl, J. B., Niederl, V., Shapiro, S., McGreal, M. E., *J. Am. Chem. Soc.* **59**, 1113 (1937).
Nilles, G. P., Zabik, M. J., Connin, R. V., Schuetz, R. D., *J. Agric. Food Chem.* **21**, 342 (1973).
Pallos, F. M., Menn, J. J., Letchworth, P. E., Miaullis, J. B., *Nature (London)* **232**, 486 (1971).
Schorigin, P., *Chem. Ber.* **43**, 1938 (1910).
Schwartz, N. N., Blumbergs, J. H., *J. Org. Chem.* **29**, 1976 (1964).
Solomon, K. R., Bowlus, S. B., Metcalf, R. L., Katzenellenbogen, J. A., *Life Sci.* **13**, 733 (1973).
Staab, H. A., Mannschreck, A., *Chem. Ber.* **95**, 1284 (1962).
Stone, R. M., Pearson, D. E., *J. Org. Chem.* **26**, 257 (1961).
Sutton, L. E., Ed., *Chem. Soc. Spec. Publ.* **No. 18** (1965).
Unger, S. H., Hansch, C., *J. Med. Chem.* **16**, 745 (1973).
Walkers, W. F., Bowers, W. S., *J. Agric. Food Chem.* **21**, 145 (1973).
Wilson, J. M., Gore, N. E., Sawbridge, J. E., Cardenas-Cruz, F., *J. Chem. Soc. B*, 852 (1967).
Yu, C.-C., Kuhr, R. J., *J. Agric. Food Chem.* **24**, 134 (1976).

Received for review December 17, 1975. Accepted March 29, 1976. This research was supported in part by the U.S. Department of Agriculture (Cooperative Agreement No. 12-14-100-10418 (33)) and the Environmental Protection Agency (Grant No. 8R01EP00801-06). Reference to a product name or company does not imply endorsement of that product or company to the exclusion of others that may be equally suitable. Michigan Agricultural Experiment Station Journal Article No. 7537.

Ultraviolet Irradiation of Fenitrothion and the Synthesis of the Photolytic Oxidation Products

Roy Greenhalgh* and William D. Marshall

The ultraviolet irradiation of fenitrothion in oxygenated solutions produced isomerization, oxidation, and solvolysis. In hexane, both the P=S and the aryl methyl group were oxidized to give fenitrooxon and formylfenitrothion. Small amounts of denitrofenitrothion were also formed. Irradiation in methanol gave carbomethoxyfenitrothion formed from oxidation followed by solvolysis. Isomerization of fenitrothion to its *S*-methyl isomer took place on a small scale in all solvents; however, no *S*-aryl isomer was detected. Irradiation of hydroxymethylfenitrothion in hexane readily gave formyl- and carboxyfenitrothion. This supports the suggestion that hydroxymethylfenitrothion is a reactive intermediate formed in the photolysis of fenitrothion. Several potential oxidation products, hydroxymethyl, formyl, carboxy, and carbomethoxy analogues of fenitrothion and fenitrooxon were prepared together with the *S*-aryl isomer. The mass spectral (MS) and nuclear magnetic resonance (NMR) data, gas chromatographic (GC), and thin-layer chromatographic (TLC) properties of these compounds and other fenitrothion derivatives are given.

Fenitrothion [*O,O*-dimethyl *O*-(4-nitro-*m*-tolyl) phosphorothioate] (I) is an important insecticide used in many countries for orchard and field crops. In Canada, its main use is to control defoliators in forests.

It is structurally similar to parathion, the ultraviolet (uv) photolysis of which has been extensively studied (Cook and Pugh, 1957; Frawley et al., 1958; Koivistoinen and Merilainen, 1963; El-Rafai and Hopkins, 1966; and Joiner and Baetcke, 1974). In contrast, little work has been carried out on the photolysis of fenitrothion. Brewer et al. (1974) reported the formation of two products on irradiation of fenitrothion with light >300 nm, one of which was identified as 4-nitro-*m*-cresol (II). A more exhaustive investigation was carried out by Ohkawa et al. (1974) who studied the photodecomposition in various solvents and as films by both uv and sunlight. Five products were isolated, resulting from photoinduced isomerization, oxidation, hydrolysis, and solvolysis. The predominant reaction in benzene, acetone, methanol, and aqueous methanol was oxidation of the aryl methyl group to give carboxyfenitrothion and its oxygen analogue, which were characterized by nuclear magnetic resonance (NMR) and infrared (ir) spectroscopy.

Chemistry and Biology Research Institute, Agriculture Canada, Ottawa, Ontario, K1A 0C6 Canada.

It would be expected that oxidation of the aryl methyl group of fenitrothion would also form hydroxymethyl- and formylfenitrothion as precursors to carboxyfenitrothion. Efforts to detect these partially oxidized products of fenitrothion in the past have been hampered by a lack of synthetic standards. To this end, several potential oxidation products and isomers of fenitrothion have been synthesized and details of their chromatographic behavior recorded.

EXPERIMENTAL SECTION

Chemicals. Fenitrothion (99.6%) was obtained by purifying technical grade Sumithion (Sumitomo Chemical Co., ~97%) after the manner of Kovacicova et al. (1971). *S*-Methylfenitrothion [*O,S*-dimethyl *O*-(4-nitro-*m*-tolyl) phosphorothioate] (III) (Kovacicova et al., 1973) and fenitrooxon [*O,O*-dimethyl *O*-(4-nitro-*m*-tolyl) phosphate] (IV) (Marshall et al., 1974) were synthesized according to the procedures referenced. The starting materials 4-nitro-*m*-cresol, 5-hydroxy-2-nitrobenzaldehyde, and *m*-cresol were purchased from Aldrich Chemical Co. (Milwaukee, Wis.).

S-Arylfenitrothion [*O,O*-dimethyl *S*-(4-nitro-*m*-tolyl) phosphorothioate] (V) was synthesized in moderate yield (~35%) by the reaction of trimethyl phosphite (0.85 ml, 8.1 mM) with 4-nitro-*m*-thiocresol (VI) (5.4 g, 32 mM) in the presence of bromotrichloromethane (1.64 ml, 16.2 mM)