Synthesis and Laboratory Evaluation of New Aryl Chloroalkenyl Ether Juvenoids

Paolo Piccardi,* Angelo Longoni, Pietro Massardo, and Francesco Corda

A new class of aryl alkenyl ethers with juvenile hormone activity, containing a dichlorovinyl group at the end of the aliphatic chain, has been synthesized. Bioassay data on yellow mealworm (*Tenebrio molitor*) and large cabbage white (*Pieris brassicae*) for these compounds are given. Variation of activity as a function of structure is briefly discussed.

Since the elucidation of the structure of the natural juvenile hormones, several workers have focused their attention on the synthesis of related compounds. Numerous excellent reviews (Menn and Beroza, 1972; Sláma et al., 1974; Menn and Pallos, 1975; Staal, 1975; Henrick et al., 1976) have appeared in which the chemistry and biological activity of juvenile hormone analogues (JHAs) have been discussed.

This interest may be ascribed to the great selectivity of action of these compounds, which appear to fulfill some of the requirements for third generation pesticides. Our laboratory has been engaged in the synthesis of technically accessible substances that would be satisfactorily active as JHAs and could be used in practice in the control of insect pests. In our search we decided to substitute chlorine for the two methyl groups of the isoprene unit carrying the epoxy function of the natural hormone JH III. By this structural modification, we hoped to obtain compounds having a better field stability than the parent epoxidized analogues. Accordingly, we have prepared several aromatic and nonaromatic JHAs, and in the present communication we report the synthesis and some structure–biological activity relationships of compounds of the former type.

RESULTS AND DISCUSSION

Synthesis. The starting material for the synthesis of the new JHAs were the ketones **3**, **4**, **6**, **9**, **16**, **17** obtained as shown in Scheme I. Carbon tetrachloride was condensed (Asscher and Vofsi, 1963) with ethylene to give the 1,1,1,3-tetrachloropropane (**1**) that was selectively dehydrochlorinated (Fujimori et al., 1974) to 1,1,3-trichloropropene (**2**) using $FeCl_3$ as catalyst. Compound **2** was converted to the ketones **3** and **4** via β-keto esters. Chlorination of **2** in carbon tetrachloride at room temperature gave the pentachloroderivative **5**, which was dehydrochlorinated (Nesmeyanov et al., 1951) and condensed with ethyl acetoacetate.

To synthesize **9**, carbon tetrachloride was added to methyl vinyl ketone in the presence of metal halides to afford the corresponding 1:1 adduct **7**. The treatment of **7** with triethylamine in ether gave 5,5,5-trichloropent-3-en-2-one (**8**), which was smoothly hydrogenated to **9**. In order to clarify the effect of the chain lengthening by an ethenylene unit on biological activity, we decided to prepare the ketones **16** and **17**. Thus carbon tetrachloride was added to butadiene (Asscher and Vofsi, 1963) to give the 1,4 adduct only. The ^1H NMR spectrum of **10** showed a value of $J = 15$ Hz for the trans coupling of the vinylic protons. GLC confirmed that the contamination with the *Z* form was slight. The reaction of isoprene with carbon tetrachloride gave a mixture (68 and 32%) of two structural isomers **11** and **12**. We have attempted to raise the yield of the 1,4-adduct **11** by varying the reaction conditions, but with no success. The dehydrochlorination of **10–12** in a two-phase organic aqueous system gave the conjugated dienes **13–15** in high yield. The ^1H NMR spectra of these compounds did not reveal any appreciable (>8%) amounts of other geometric isomers.

Compound **13** was converted in the usual way to the ketone **16**. The two products **14** and **15** could not be completely separated by fractional distillation, and the ketone **18** was the main by-product in the preparation of **17** via β-keto ester. It was further ascertained that the 1,4-adduct **12** reacted more slowly than **11** during the C-alkylation of acetoacetic ester, so there was no advantage in using pure **11** to prepare the β-keto ester ethyl 2-acetyl-7,7,7-trichloro-5-methylhept-4-enoate. The latter was hydrolyzed and dehydrochlorinated in one step under conditions of the phase-transfer catalysis to give **17**. This reaction was carried out in an aqueous sodium hydroxide–1,2-dichlorobenzene system using tetrabutylammonium iodide as the catalyst.

The remaining steps of our synthesis are the same as those described (cf. Bowers, 1969; Krimer et al., 1974) for the preparation of many other aromatic terpenoid ethers.

Thus, the Grignard reaction of vinyl bromide with the appropriate ketones (**3**, **4**, **6**, **9**, **16**, **17**) in tetrahydrofuran afforded vinyl carbinols, which gave the corresponding allylic bromides (**19–24**) in nearly quantitative yield on treatment with 40% hydrobromic acid in the molar ratio 1:3 between −5 and −10 °C for 1–2 h. A study of the relationship between the isomeric composition and the reaction temperature showed that in the range of −10–25 °C the ratio *E*/*Z* remains, almost constantly, 70/30. The JHAs were prepared by stirring the appropriate bromide with a phenol in an anhydrous solvent, using an excess of an acidic acceptor. All compounds were purified by distillation, or by column chromatography, and obtained as mixtures of *E* (70%), *Z* isomers with a purity greater than 95%. Chemical structures were confirmed by the elemental analysis and spectroscopic methods.

Biological Activity. Table I presents the results of the bioassays. The data for a synthetic sample of the known natural juvenile hormone JH III and for some reference substances are included for comparison purpose. With the preparation of aromatic ethers bearing vinylic chlorine atoms at the end of a geranilic chain, our aim was to obtain a new class of compounds lacking the labile epoxide function and yet retaining some important biological properties of the JHAs. When compared with that of the corresponding epoxidized geranyl ethers, the biological activity of the new compounds was found to be lower on *Tenebrio molitor* but not significantly so on *Pieris brassicae*. This insect is not very important from an economic point of view, but it is often taken as a model of Lepidoptera pests. Actually, while the activity on this

Montedison S.p.A., Istituto Ricerche Donegani, Via del Lavoro 4, 28100, Novara, Italy (P.P., P.M.) and Montedison, Centro Ricerche Antiparassitari, Via Bonfadini 148, 20128, Milano, Italy (A.L., F.C.).

Scheme I

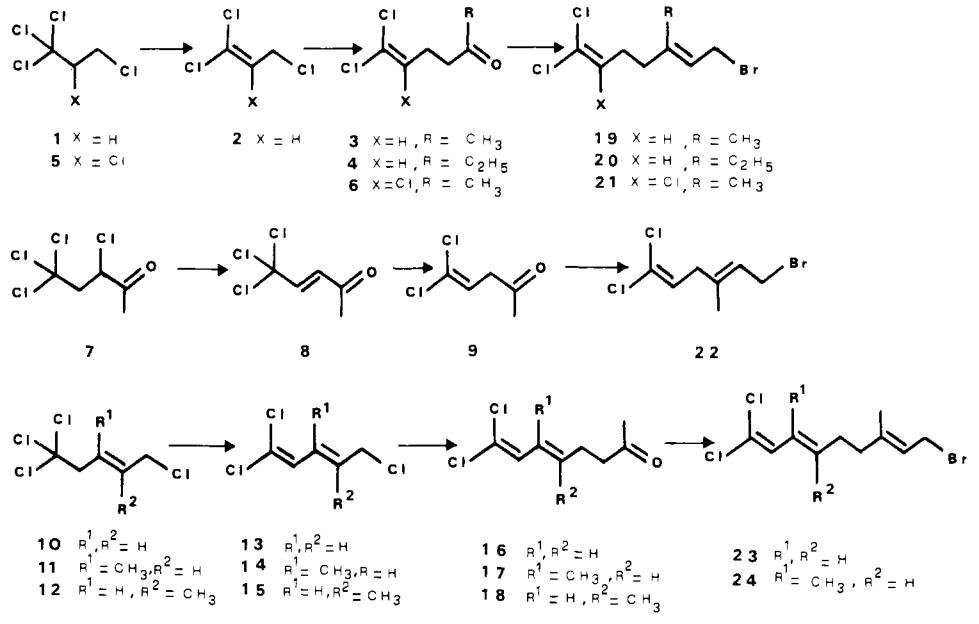
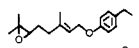
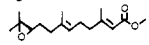
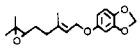
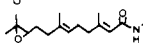


Table I. Juvenile Hormone Activity[a] of Test Compounds on *Tenebrio molitor* (A) and *Pieris brassicae* (B).

R	A	B	A	B	A	B	A	B	A	B	A	B
CH_3CH_2	0.2	2	0.2	20	20	In	200	200	200	In	0.2	20
CH_3S	2	≥20			≥2	In	≥2	In			≥0.2	≥20
CH_3CO	2	20			200	In	In	200			2	20
3,4-OCH_2O	2	20	2	≥20	200	In	In	In			0.2	2
	0.02	A	≥2	B								
	20	A	In	B								
	0.02	A	≥2	B								
	0.02	A	In	B								

[a] *Tenebrio molitor*: effective dose in μg/pupa, resulting in abnormal development of 95% of treated pupae. *Pieris brassicae*: lowest dose in μg/larva causing the 95% of mortality up to and during pupation or abnormal pupation. In indicates that the compound is inactive, or has ID_{95} larger than 200 μg/pupa or larva.

insect was nearly the same under laboratory conditions, it was found to be even better than the reference compounds in small pilot field tests at economic rates. However, it may prove difficult to control in practice such a voracious phytophagous with compounds mainly active during the last larval instar.

Since comparative data from the literature are based mainly on observations made on *Tenebrio molitor*, we summarize our results on this insect. With respect to phenyl ring substitutions, our data, part of which are reported in Table I, support previous findings indicating that JH phenyl ethers with substituents in the para position possess considerably more activity than meta substituted analogues.

Electron-donating substituents give the more active compounds (see also Hammock et al., 1974). However, the *p*-acetyl substitution also confers activity, rather unexpectedly. With the exception of *p*-ethylphenyl and 3,4-methylenedioxyphenyl ethers, the presence of chlorine atoms at C-7 of the aliphatic chain does not seem to cause any special change in activity when compared with corresponding methyl-containing homologues. The introduction of an additional chlorine atom at C-6 leads to reduction or loss of JH activity. The same happens when the chain is shortened by one C atom between the position C-3 and C-7 or is lengthened by two carbon atoms. In the latter case, the introduction of an additional methyl group at C-7 enhances activity. Thus, high morphogenetic potency in *Tenebrio* assay requires a chain bearing a methyl or a chlorine substituent in the C-7 position.

In general, compounds found active against *Tenebrio* are active against *Pieris brassicae*. However, the degree of activity of a given product against these two species is different. Many of the compounds synthesized show appreciable activity on mosquito larvae and ovicidal activity on *Tetranychus urticae*. The oral toxicities to rats are low for the more effective compounds, the acute oral LD_{50} being generally >2000 mg/kg. From the group described, 4-(7,7-dichloro-3-methylhepta-2,6-dienyloxy)-ethylbenzene and 3,4-methylenedioxy-1-(9,9-dichloro-3,7-dimethylnona-2,6,8-trienyloxy)benzene were chosen for further work on physicochemical and biological aspects. Their field performance, problems, and prospects in selective insect control are under consideration. We are confident that this work will give a positive answer to our main hypothesis that the dichlorovinyl JHAs have a better stability than the previously described epoxidized analogues.

BIOASSAY PROCEDURES

Tenebrio Molitor **(Yellow Mealworm).** Aliquots (2 μL) of acetone containing respectively 200, 20, 2, 0.2 etc. μg of the compound were applied to the ventral abdomen of 0–4 h old *Tenebrio molitor* pupae. Twenty insects were treated with each dose and then incubated at 25 °C and 70% relative humidity until they normally molted or showed signs of adult developmental abnormalities typical of those caused by juvenile hormone compounds (Slâma et al., 1974). However, the results were expressed as the minimum amount of material that produced abnormal development in the 90–100% of the treated pupae. The results obtained in our laboratory are shown (Table I) beside those of some reference compounds.

Pieris brassicae L. **(Large Cabbage White).** The larvae were of a laboratory strain that is not under insecticide pressure. Aliquots (2 μL) of acetone containing respectively 200, 20, 2, 0.2 etc. μg of the compound were applied to the first abdominal segment of the last instar larvae. The treated larvae were placed in groups of ten in plastic cylinders containing cabbage leaves and kept at 25 °C and 70% relative humidity. The conventional toxic activity was recorded every day.

The cumulative percentage of mortality up to and during the pupal stage plus the percentage of abnormal pupae was calculated.

EXPERIMENTAL SECTION

General. Products were identified by elemental analysis, IR spectroscopy (Perkin-Elmer 225 grating spectrophotometer), NMR spectroscopy (Bruker WH 90 instrument), and mass spectrometry (Varian MAT CH5 instrument coupled with a Hewlett Packard 5750 gas-chromatograph). Analytical GLC was carried out with a glass column packed (10%) with UCC W 982 on 100–120 mesh Chromosorb W or a column packed (20%) with Carbowax 20M on Chromosorb; temperatures were 80–200 °C, 2.5 °C min^{-1}. Analytical TLC utilized E. Merck silica gel GF-254 (10–40 μ), with a hexane–ether eluent. Column chromatography utilized E. Merck silica gel, 0.05–0.2 mm, with a weight ratio of 25–30:1 (support to compound). The solvent systems employed were those optimized by analytical TLC.

6,6-Dichlorohex-5-en-2-one (3). Compound **2** (90 g) was added at 5–10 °C to a solution of sodioacetic ester, prepared from NaH (14.9 g) and ethyl acetoacetate (80.6 g) in 200 mL of THF. The reaction mixture was refluxed, with stirring, for 8 h and left overnight at room temperature. Workup and distillation gave ethyl-2-acetyl-5,5-dichloropent-4-enoate (90.8 g, 61.4%), bp 85–87 °C (0.1 mm). This compound (78.4 g) was dissolved in 400 mL of 5% potassium hydroxide solution. The solution was stirred for 4 h at room temperature, acidified with H_2SO_4 (50%), and refluxed until the evolution of CO_2 had ceased. Workup and distillation gave the ketone **3** (45.4 g, 83%): IR 1730 (C=O), 1620 (C=C), and 880 cm^{-1} (CCl_2); NMR ($CDCl_3$) δ 2.17 (s, 3, CH_3), 2.35–2.7 (m, 4, CH_2CH_2), and 5.88 (t, 1, J = 7 Hz, CH=CCl_2). Anal. Calcd for $C_6H_8Cl_2O$: Cl, 42.45. Found: Cl, 41.9.

7,7-Dichlorohept-6-en-3-one (4) [bp 57–59 °C (0.07 mm) (Anal. Calcd for $C_7H_{10}Cl_2O$: Cl, 39.16. Found: Cl, 39.4)], **5,6,6-trichlorohex-5-en-2-one (6)** [bp 67.5 °C (0.15 mm) (Anal. Calcd for $C_6H_7Cl_3O$: Cl, 52.79. Found: Cl, 52.5)], and **8,8-dichloroocta-5,7-dien-2-one (16)** [bp 75–77 °C (0.2 mm) (Anal. Calcd for $C_8H_{10}Cl_2O$: Cl, 36.73. Found: Cl, 37.0)] were prepared (≃65% yield) by the same method as described in the preparation of **3**.

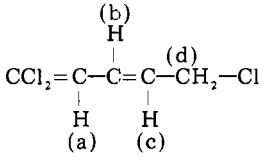
2,5,5,5-Tetrachloropentan-2-one (7). A mixture of methyl vinyl ketone (213 g), acetonitrile (195 g), CCl_4 (925 g), $CuCl_2 \cdot H_2O$ (5.1 g), and n-$BuNH_2$ (5.25 g) was charged in a Pfaudler autoclave (2 L). The autoclave was heated, with stirring, at 120 °C for 5 h. Workup and distillation gave the ketone **7** (290 g, 42.6%): bp 108–110 °C (18 mm); NMR (CCl_4) δ 2.40 (s, 3, CH_3), 3.07 (dd, 1, J = 15.5 and 4.5 Hz), 3.88 (dd, 1, J = 15.5 and 6.5 Hz), and 4.55 (dd, 1, J = 6.5 and 4.5 Hz, CHCl).

5,5,5-Trichloropent-3-en-2-one (8) [bp 95–100 °C (20 mm); NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3), 6.6 and 7.06 (AB, 2, J = 14 Hz, CH=CH)] was prepared (77%) from **7** using an excess of triethylamine in THF at 120 °C for 4 h in an Hastelloy autoclave.

5,5-Dichloropent-4-en-2-one (9). To a well-stirred mixture of **8** (189 g), THF (400 mL), and zinc dust (20–40 mesh; 95 g) gaseous hydrogen chloride was added at 60–65 °C, under reflux for 2 h. Workup and distillation gave the ketone **9** (140 g, 91%), bp 75 °C (15 mm). Anal. Calcd for $C_5H_6Cl_2O$: Cl, 46.35. Found: Cl, 46.0.

1,1,5-Trichloro-3-methylpenta-1,3-diene (14) [NMR ($CDCl_3$) δ 2 (s, 3, CH_3), 4.15 (d, 2, J = 7.5 Hz, CH_2Cl), 5.83 (t, 1, J = 7.5 Hz, C*H*CH_2Cl), and 6 (s, 1, CH=CCl_2)] and **1,1,5-trichloro-4-methylpenta-1,3-diene (15)** [NMR ($CDCl_3$) δ 1.9 (s, 3, CH_3), 4.10 (s, 2, CH_2Cl), 6.15 (d, 1, J = 10.8 Hz, CH=C), and 6.55 (d, 1, J = 10.8 Hz, –CH=CCl_2)] were obtained from **11** and **12** (Tanaka et al., 1969) by the same treatment as described in the preparation of **13**.

1,1,5-Trichloropenta-1,3-diene (13). A mixture of benzene (160 mL), water (160 mL), NaOH (135 g, 3.375 mol), compound **10** (165.95 g, 0.750 mol), and tetrabutylammonium iodide (1 g, 2.7 mmol) was vigorously stirred at 25–30 °C for 4 h. The organic layer was separated, combined with benzene extracts, dried, and distilled to yield **13** (100.3 g, 77%), bp 88–90 °C (20 mm); chemical shifts and coupling constants (Hz) are shown below the formula:



$\delta a = 6.45$, $\delta b = 6.44$, $\delta c = 5.94$, $\delta d = 4.11$

$J_{a,b} = 10$, $J_{b,c} = 15$, $J_{c,d} = 7.5$, $J_{b,d} = 0.7$

8,8-Dichloro-6-methylocta-5,7-dien-2-one (17). A mixture of ethyl 2-acetyl-7,7,7-trichloro-5-methylhept-4-enoate (200 g), water (200 mL), 1,2-dichlorobenzene (200 mL), NaOH (104 g), and tetrabutylammonium iodide (3.25 g) was vigorously stirred at 90 °C for 10 h. The organic layer was separated and the aqueous phase extracted with ether. The combined organic extracts were rinsed with water, dried ($MgSO_4$), and distilled to give the ketone **17** (110 g, 0.531 mol, 79.6%): bp 82–85 °C (0.2 mm); NMR (CCl_4) δ 1.9 (s, 3, CH_3), 2.11 (s, 3, CH_3CO), 2.2–2.7 (m, 4), 5.5 (t, 1, J = 7.5 Hz, =C*H*CH_2), and 6.3 (s, 1, CH=CCl_2). Anal. Calcd for $C_9H_{12}Cl_2O$: Cl, 34.25. Found: Cl, 34.3.

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