(Table III, C). This increased persistence of [^{14}C]paraoxon due to anethole could, therefore, be related to the increased toxicity of paraoxon.

In summary, four major results should be mentioned. (1) Topically applied anethole and anisaldehyde increased the toxicity of several classes of topically applied synthetic insecticides to houseflies (Table I). (2) The presence of anethole in the housefly diet increased the toxicity of topically applied parathion or paraoxon to houseflies. (3) The presence of anethole in the diet resulted in an increased penetration of [^{14}C]paraoxon derived radiocarbon into the housefly body (Table II). (4) The presence of anethole in the housefly diet reduced the degradation of [^{14}C]paraoxon by a cell-free supernatant prepared from houseflies fed anethole for 3 days (Table III). It appears, therefore, that the increased mortalities of houseflies fed anethole in their diet for 3 days prior to topical application of paraoxon was due to an increased penetration of paraoxon into the insect body and an increased stability of paraoxon due to a reduction in the degradation of paraoxon to nontoxic, water-soluble metabolites. Both of these effects would increase the amount of toxic paraoxon within the houseflies and hence increase mortalities.

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Stability of Epoxide-Containing Juvenoids to Dilute Aqueous Acid

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The morphogenetic activity on *Tenebrio molitor* and the stability in weak aqueous acid of 13 *p*-bromophenyl geranyl ether epoxides containing juvenile hormone mimics, radiolabeled juvenile hormone, and three additional nonhalogenated hormone mimics were examined. Although changes in the molecule remote to the epoxide caused variations in hydrolytic stability, major changes resulted from varying the substituents on the epoxide. Increasing the size of alkyl substituents on the epoxide resulted in increased hydrolytic stability, and mono- and disubstituted epoxides were more stable than tri- and tetrasubstituted epoxides. As a derivatization technique, conversion of a trisubstituted epoxide to its diol proved unreliable when sulfuric acid in aqueous tetrahydrofuran was used but quantitative when dilute aqueous buffers were used.

The high biological activity of some insect growth regulators with juvenile hormone-like activity (juvenoids) has resulted in a great deal of synthetic effort leading toward the development of juvenoids as pesticides. Two juvenoids are currently marketed in the United States and several others are under development for U.S. and/or world markets. These and other juvenoids have been found to have very low acute and chronic mammalian toxicity, high specificity for many target vs. nontarget organisms, and favorable environmental properties. As a class of compounds, juvenoids also possess limitations. These limitations often include the appearance of cross-resistance and resistance in target insects (for literature see Vinson and Plapp, 1974; Hammock and Quistad, 1976; Georghiou et al., 1978), a limited spectrum of biological activity, and such rapid environmental degradation that asychronous pest populations are not adequately controlled.

Various functionalities at the isopropylidene end of juvenoid molecules have been explored, and the epoxide, as in the natural hormone, was found to have high biological activity. Epoxide-containing juvenoids have received some attention for commercial development, but

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Table I. Hydrolytic Stability and Morphogenetic Activity of Model Juvenoids

compd	epoxide isomer	R_1	R_2	GLC retention time, min[a] epoxide	GLC retention time, min[a] diol diester	$t_{1/2}$, days 21 °C	$t_{1/2}$, days 40 °C	ED_{50}(μg)[b] *T. molitor*	log *P*
				2,3 Unsaturated 6,7-Epoxides					
1		CH_3	CH_3	1.65	3.62	0.17		0.1	3.50
2	*c/t*	CH_3	C_2H_5	2.07	4.41	1.1		0.1	3.97
3	*c/t*	CH_3	*n*-C_3H_7	2.52	5.05	1.5		0.002	4.46
4	*c/t*	C_2H_5	H	2.06[e]	4.43[c]	12	2.0	0.5	3.71
5 + 6	*c/t*	*n*-C_3H_7	H	2.50[e]	5.14[c] 5.37[d]		2.4	4	4.25
5	*c*	*n*-C_3H_7	H	2.52	5.14[c]		1.5	2	4.25
6	*t*	H	*n*-C_3H_7	2.35	5.37[d]		6.5	5	4.25
				2,3 Saturated 6,7-Epoxides					
7		CH_3	CH_3	1.51	3.12	0.28		0.3	4.00
8		H	H	1.38	3.30		1.3	>10	3.48
9	*c*	CH_3	H	1.52	3.02		0.41	>10	3.82
10	*c*	*n*-C_3H_7	H	2.22	4.37		3.0	>10	4.37
				2,3-Epoxides					
11	*t*	CH_3	CH_3	1.53	2.93	27	3.0	>10	4.06
12	*t*	C_2H_5	H	1.78	3.28		5.5	1	4.16
13	*t*	*n*-C_3H_7	H	2.15	4.02		11	10	4.76

[a] All compounds were assayed simultaneously with those compounds of similar stability. Standard deviations between runs were 10% or less of the reported values. [b] For reference ED_{50} R-20458 = 0.002 μg. For additional biological data on compounds 1, 2, and 7, see Jacobson et al. (1972), Pallos and Menn (1972), Hammock et al. (1974), and included references. [c] Threo-diol boronic diester. [d] Erythro-diol boronic diester. [e] Geometrical isomers not resolved at this column temperature when coinjected.

they have generally been replaced by alkoxides. Possibly the decision to replace epoxides with alkoxides in commercial juvenoids was based in part on the hydrolytic instability of epoxides.

Alkoxides are readily metabolized by microsomal mixed function oxidases, so the discovery of high levels of cross-resistance and resistance to alkoxide containing juvenoids was not surprising (Cerf and Georghiou, 1972). As expected for alkoxide containing juvenoids, NADPH dependent, microsomal O-dealkylation was found to be a major route of metabolism in resistant housefly strains (Hammock et al., 1975a, 1977). The ultimate development of resistance to a pesticide by target species under heavy selection pressure is expected, but resistance due to O-dealkylation is disturbing because it indicates that in many target populations cross-resistance will already exist due to previous selection with other pesticides.

Based on the lack of increased levels of the enzymes necessary to cause epoxide hydrolysis (epoxide hydrases) in several insecticide resistant strains of the housefly, *Musca domestica* (Hammock et al., 1977), and the report by Hangartner et al. (1976) that some epoxide-containing juvenoids could be relatively stable to aqueous acid, a synthetic study was initiated to examine the stability of aliphatic epoxides to dilute acid and to provide model compounds for future studies on the stability of the epoxide moiety in model ecosystems and in target and nontarget organisms. This study was designed to provide part of a theoretical basis for the future synthesis of juvenoids which will be of the appropriate environmental stability and which will be active on insects which are juvenoid-resistant due to oxidative mechanisms.

Alternatively, the quantitative hydration of JH or epoxide-containing juvenoids to their respective diols is important for the production of radiolabeled metabolites, for microchemical derivatization procedures, and for potential analytical methods for JH and some juvenoids. The classical procedure of using sulfuric acid in aqueous tetrahydrofuran (Slade and Zibitt, 1972; Gill et al., 1972) has serious limitations if performed on a microscale. This study also provides the methodology needed to derivatize the epoxide of JH and some juvenoids successfully on a microscale.

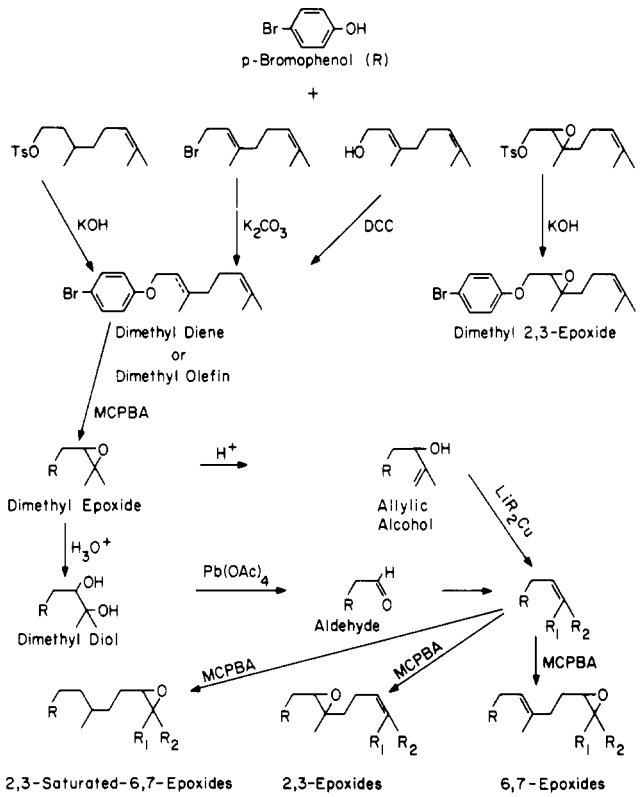
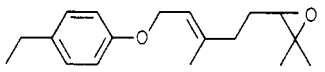
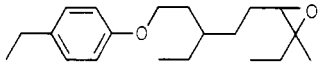
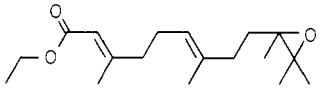
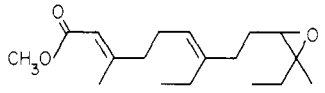


Figure 1. Synthetic pathways to and trivial names of compounds used in this study. MCPBA is *m*-chloroperoxybenzoic acid while DCC is dicyclohexylcarbodiimide.

MATERIALS AND METHODS

Trivial names refer to the 6,7 substituents of the geranyl moiety; examples include: the dimethyl diene [Figure 1, (2*E*)-1-(4′-bromophenoxy)-3,7-dimethyl-2,6-octadiene] and *cis*-propyl proton epoxide [Figure 1, Table I, (2*E*)-1-(4′-bromophenoxy)-3-methyl-*cis*-6,7-epoxy-2-decene]. Trivial

Table II. Hydrolytic Stability of Radiolabeled Juvenoids and JH

structure	designation	$t_{1/2}$, days, at 21 °C	log P
	R-20458[a]	0.083	3.66
	Ro 10-3108[b]	0.46	5.18
	Ro 8-4374[b]	0.17	3.44
	JH I	0.48	3.71

[a] Courtesy of Stauffer Chemical Company, Mountain View, CA. [b] Courtesy of Hoffman LaRoche Chemical Company, Basle, Switzerland.

names are referenced to the structures shown in Figure 1, Table I, and/or Table II.

Synthesis. Most synthetic methods (Figure 1) are modifications of published procedures and are illustrated in the supplementary material (Mechoulam and Sondheimer, 1958; Hauser et al., 1963; Seyferth and Fogel, 1966; Henrick et al., 1972; Kamimura et al., 1972; Sharpless and Michaelson, 1973; Hammock et al., 1974; Mori et al., 1975; Hangartner et al., 1976; Henrick et al., 1978). All chemicals and radiochemicals were handled according to recommended procedures of laboratory safety (Steere, 1967; Green and Turk, 1978). Compounds with 2,3-unsaturation are >99% 2*E* (trans). The synthetic procedures used led to cis-rich mixtures of the 6,7-epoxide isomers. The 6,7-geometrical isomers of the disubstituted epoxides were purified by high-pressure liquid chromatography (LC) and were in each case >65% cis before LC and >99% geometrically pure after LC, while the 6,7-geometrical isomers of the trisubstituted epoxides or their precursors could not be separated by thin-layer chromatography (TLC), gas–liquid chromatography (GLC), or LC. Based on model syntheses the isomeric ratios are expected to be >60% cis (Hauser et al., 1963). Otherwise all compounds were pure by TLC in several solvent systems by reversed-phase LC and by GLC. The assigned structures were substantiated by their infrared (Beckman Model 4240) and ^{1}H NMR (Varian EM-390) spectra and occasionally by their ultraviolet (Beckman Model 24-25), mass (Finnigan Model 1015 interfaced with System 150), and ^{13}C NMR (Bruker WH90-P) spectra. The *cis*- and *trans*-propyl proton epoxides (Table I, compounds **5**, **6**) were separated by preparative LC, and subsequently found to be pure isomers by TLC, LC, and GLC. The geometrical structures of the propyl proton epoxides are assigned based on ^{1}H and ^{13}C NMR of the isomers (Jackman and Sternhell, 1969; Solli et al., 1976; Rakoff and Emken, 1977), synthetic methods, chromatographic behavior, and the conversion of the cis epoxide to the threo diol by acid cleavage and the threo diol to the trans olefin and the erythro diol to the cis olefin by a modification of the triethyl orthoformate method of Rakoff and Emken (1977).

Radioactive Samples. The following radiolabeled juvenoids were used: R-20458 (Stauffer Chemical Co., uniform ^{14}C ring, 17 mCi/mmol, >96% 2*E*), Ro 10-3108 (Hoffman-LaRoche Chemical Co., 2,3-^{3}H, 2.3 Ci/mmol, isomer mixture), Ro 8-4374 (Hoffman-LaRoche Chemical Co., 1-^{14}C, 11 mCi/mmol, isomer mixture), and juvenile hormone (JH) I (New England Nuclear Corp., 10-^{3}H, 10Ci/mmol, >98% 2*E*,6*E*,10cis) (Table II).

Mineral Acid Hydrolysis of R-20458. R-20458 was converted to its diol in inorganic acid by dissolving 1 mg of pure, radiolabeled R-20458 in 1 mL of a solution of cold 0.05 N H_2SO_4 in 40% aqueous, peroxide-free tetrahydrofuran (Slade and Zibitt, 1972; Gill et al., 1972). The reactions were sonicated and allowed to reach room temperature (22 °C) in the dark, under N_2 in siliclad treated glassware (Hammock et al., 1975b, 1976). As variables, 5 mg each of ten salts were added to the aqueous, acidic tetrahydrofuran before it was, in turn, added to the R-20458. After 8 h the reactions were saturated with sodium chloride, extracted three times with peroxide-free ether, the ether dried with sodium sulfate, and the sample concentrated and spotted on TLC. The plates were developed halfway in benzene/propanol (10:1) and then in hexane/ether (4:1). Similar resolution can be obtained when toluene is substituted for benzene in the above system. The TLC plates were exposed to Blue Brand X-ray plates to detect radioactive spots.

Weak Acid Hydrolysis of R-20458. For complete hydrolysis of R-20458, 2.7-ng samples of radiolabeled epoxide were added to clean, silylated tubes, the solvent evaporated, and sodium acetate buffer (0.2M) with or without 10% methanol added. After sonication, the samples were stored at 22 °C under N_2 in the dark and aliquots were periodically removed for analysis by TLC and liquid scintillation counting. The structure of the product diol was confirmed by LC and microchemistry (Hammock et al., 1974).

Comparative Acid Hydrolysis of Epoxide-Containing Juvenoids. All glassware and solvents used in this experiment were kept separate from other laboratory glassware to avoid troublesome contamination by electron-capturing material. Carefully cleaned culture tubes were heated at 400 °C for 6 h before each use, while the sodium sulfate was washed with ether and dried (110 °C). The candidate juvenoid (10 μg, ~30 nmol) in spectral grade isooctane (1 μL) was added to a 10 × 75 mm culture tube and the solvent evaporated. Glass distilled ethanol (10 μL) was then added to insure solution of the epoxide before the addition of sodium acetate buffer (1 mL, 0.1 M, pH 4 unless otherwise noted) to give a concentration of ~3×10^{-5} M, assuming that the juvenoid is in solution. The samples were held in the dark at either 21 or 40 °C for varying times. The starting epoxide and product diol

were extracted with ether (2×, 0.75 mL, either freshly distilled in the laboratory or from Burdick and Jackson), the ether dried with sodium sulfate, evaporated, and butaneboronic acid (BBA) in isooctane (20 μg, 50 μL) added to the residue before covering, vortexing, and allowing the tube to stand for 30 min to derivatize the diol to its BBA diester. The epoxide–diol diester mixture (1 μL) was injected directly onto a silane-treated glass column (1.5 mm i.d. × 6 ft, 2% OV-101 on Gas-Chrom Q, 100/120 mesh) in a Hewlett Packard 5710A GLC with 5% methane in argon as carrier gas (14 mL/min). The injection port and electron-capture detector were kept at 300 °C and the column at 250 °C. An integrator (Hewlett Packard 3380A) was used to determine the relative amounts of epoxide and diol diester present in the sample by internal normalization of the peak areas. The procedure was verified by injecting known amounts of standards. Incubation of the epoxides in acetate buffer resulted in only one product peak except in the case of the geometrical mixtures of disubstituted epoxides (**4**, **5**, **6**, Table I) which resulted in separate peaks for the threo and erythro diesters. The use of BBA to derivatize the diols improves the sharpness and reproducibility of the product peaks, but the injection of boronic acids onto a GLC column results in a column residue which may affect the behavior of subsequent diols if they are not derivatized. The sole hydrolysis product from dimethyl epoxide (1, Table I) cochromatographed with the authentic dimethyl diol on GLC before and after derivatization.

Duplicate samples were assayed at a minimum of four time points to determine the stability of each epoxide. The half-life ($t_{1/2}$) of each epoxide was calculated by extrapolating to 50% the line generated from a plot of the log of percent epoxide remaining vs. time. Each epoxide was run or rerun in an experiment with epoxides of similar hydrolytic stability to facilitate close comparison.

The hydrolytic stability of the radiolabeled epoxides (Table II) was determined similarly except that the reactions were scaled down tenfold, taking place in 6 × 50 mm culture tubes and 100 μL of buffer. Analysis was by TLC (developed in benzene/propanol, 10:1) and autoradiography with unlabeled standards visualized by their quenching of gel fluorescence under ultraviolet light. The epoxide and diol regions of the TLC plate were scraped and quantified by liquid scintillation counting, and the sole products of hydrolysis were confirmed by microchemistry.

Partition Coefficients. As an indication of lipophilicity, the partition coefficients (P) of Fujita et al. (1964) were used. The P values for the compounds investigated (Tables I and II) were determined on 5-μg samples injected on a reversed-phase LC column (Dupont, 5 μm ODS, 2 mm × 250 mm) and eluted with 25% double distilled HOH in methanol (Burdick and Jackson) delivered at 0.366 ± 0.002 mL/min, 5010 ± 10 psi (Spectra Physics M-3500B pump) and detected by their absorbance at 254 nm (Spectra Physics Model 230 UV detector). P values were calculated from retention times of the compounds (±0.02 min) by a modification of the methods of Carlson et al. (1975) and Hulshoff and Perrin (1976) based on $\log P = \log k' - \log r$. The $\log r$ value [(stationary phase)/(mobile phase)] for the reversed-phase column was determined experimentally from the P values found by octanol/water partition (Fujita et al., 1964) utilizing radiolabeled JH I. The k' value = [(retention time of compound) − (retention time of unbound material)] ÷ retention time of unbound material. The log P value for R-20458 determined chromatographically (3.66, Table II) compared favorably with that determined by octanol/water partitioning of the radiolabeled material (3.68). The π values from the chromatographic method for the addition of methylenes in a homologous series are close but not identical with those found by other workers using classical methods (Fujita et al., 1964; Fahmy et al., 1978). Poor correlations were obtained with compounds from other series, such as phenols and substituted benzenes. These correlations illustrate Carlson et al. (1975) caution that factors other than P are involved in retention times on reversed-phase LC. The exceedingly limited solubility of the juvenoids in aqueous systems prevented reliable determination of P values by UV or GLC analysis of the aqueous phase.

Bioassays. Morphogenetic activity was determined by assaying the compounds using topical application to the ventral surface of 0–24-h old pupae of the yellow mealworm (*Tenebrio molitor* L.) as described earlier by Hammock et al. (1974). The pupae were obtained by rearing last instar larvae purchased from California Worm Warehouse (Riverside, CA).

RESULTS AND DISCUSSION

Quantitative Epoxide Hydration. When 1 mg of R-20458 (Table II) was converted to its diol in 1 mL of acidic, aqueous tetrahydrofuran, the diol was the only product detected. Several workers have found that when the reaction is run on the microgram scale or below with epoxide-containing juvenoids or JH that production of the diol is erratic even when carefully cleaned glassware and purified solvents are used (Schooley et al., 1976; Schooley, 1977). Even at the 1-mg level, the addition of several salts led to greatly reduced yield of the diol. For instance, addition of ferric chloride led to a major product with a TLC R_f just below R-20458, while zinc and magnesium sulfate led to an unknown product chromatographing just above the diol on TLC. Results with JH were similar except that numerous products were sometimes obtained. Due to the difficulty of removing all traces of interfering substances, especially when samples with high biomass but low levels of terpenoid epoxides are to be analyzed, epoxide hydration using enzymatic mechanisms (Hammock et al., 1976) or weak acid (Kramer et al., 1974) seems preferable to strong acid. The latter procedures result in essentially quantitative conversion to the diol, although longer reaction times are required (Figure 2). The inclusion of 10% methanol in the reaction mixture helps to solubilize terpenoid epoxides in samples with high biomass, and methanol only slightly slows the reaction, in part, by reducing the effective hydrogen ion concentration (Figure 2). Addition of a number of inorganic salts as above had no detectable effect on epoxide hydrolysis, and addition of lipid fractions from *T. molitor* pupal homogenates (0.5 pupal equivalent/mL) failed to reduce the yield of diol when 10% methanol was included. Weak acid hydrolysis should be applicable to analytical procedures for JH or juvenoid analysis involving derivatization to the corresponding diol. Even with picogram levels of JH I, conversion to the diol led to practically quantitative yield if done in the dark, in silane or carbowax treated glassware, under N_2 and with a trace of antioxidant (2,4-di-*tert*-butyl-*p*-cresol) in the buffer system. Traces of JH, JH acid, and JH diol acid may be removed by partition methods (Hammock and Sparks, 1977; Mumby and Hammock, 1979).

Comparative Hydrolytic Stability. The geranyl phenyl ether series of juvenoids was chosen as a source for model compounds because members of this series have been considered for commercial development, epoxide hydration is the only likely route of hydrolytic degradation, and the compounds are relatively stable to light. The *p*-bromophenyl substituent was chosen because the phenol,

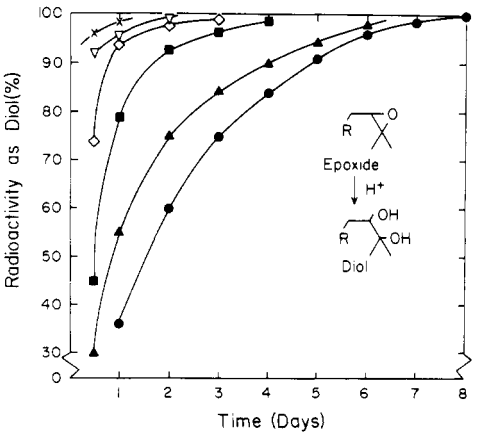


Figure 2. Hydrolysis of the epoxide-containing juvenoid, R-20458, to its diol at various times by 0.2 M sodium acetate buffer of three different pH's with and without 10% methanol. Conditions are: pH 5.0, +MeOH (●); pH 5.0, -MeOH (▲); pH 4.5, +MeOH (■); pH 4.5, -MeOH (◇); pH 4.0, +MeOH (▽); and pH 4.0, -MeOH (×). Only the last point before 100% conversion is shown to simplify the figure. Addition of methanol reduces the pH of the buffer 0.1–0.2 pH units when measured with a Corning AgCl electrode.

diene, and diol (Figure 1) could be purified by crystallization, the series showed moderate morphogenetic activity in the *Tenebrio molitor* bioassay, and the bromine resulted in the compounds being detected at low levels by electron-capture GLC. The pH of 4, chosen for most of the study on relative hydrolytic stability of juvenoids, is clearly in the region of acid hydrolysis, in contrast to the pH region of "water" reaction (neutrality) or base-catalyzed epoxide hydration (Long and Pritchard, 1956; Pritchard and Long, 1956), and mosquito breeding is not likely to occur at significantly lower pH's. Although hydrolysis is the most likely route of degradation of the epoxide of epoxide-containing juvenoids under aqueous field conditions (Gill et al., 1974), the applicability of the weak acid model to complex ecosystems must be tested. The compounds and methods reported in this study have been used to monitor epoxide hydration by mammalian enzymes (Mumby et al., 1978) and similar studies are in progress with enzymes from target and nontarget insects and more complex model ecosystems.

Since very low concentrations of epoxides were used in silylated glassware, micelle formation (critical micelle concentration of R-20458 in distilled water is 1.2×10^{-5} M) and binding to the glassware (Hammock et al., 1976, 1977) probably do not greatly affect hydration rates. The hydration rate of the tetrasubstituted epoxide (Table II, Ro 8-4374) is similar to that of the trisubstituted dimethyl epoxides (Table I, 1 and R-20458). Such a result could be predicted because the formation of a carbonium ion-like intermediate is the rate-limiting step in hydration, and any increase in steric hindrance about the epoxide from a methyl at C-10 is likely to be offset, in part, by increasing the ease of formation of a carbonium ion at C-10 (Pritchard and Long, 1956).

The *p*-bromodimethyl epoxide (1, Table I) is twice as stable to acid hydrolysis as the *p*-ethyldimethyl epoxide (R-20458, Table II). The 2,3-saturated dimethyl epoxide (7) is, in turn, twice as stable as the 2,3-unsaturated compound (1) to acid hydrolysis. In the case of the 2,3-saturated compounds the relatively polar epoxide is apparently somewhat protected from solvation as evidenced by the increase in the log *P*. These observations indicate that structural changes remote from the epoxide moiety may influence hydrolytic stability, but not as much as structural changes directly on the epoxide.

As earlier illustrated by the work of Hangartner et al. (1976), on Ro 10-3108 (Table II) the methyl ethyl epoxide (2) is about seven times more stable to dilute acid hydrolysis than is the dimethyl epoxide (1). The ethyl substituent would be expected to lead to a slightly more stable carbonium ion than the corresponding methyl substituent due to its superior ability to release electrons, but this very small electronic effect is probably offset by increased hydrophobicity and steric hindrance in the epoxide region. As the C-7 branch is lengthened to propyl (3) with a concomitant increase in log *P*, the stability again increases (~1.5×), but not so dramatically as in going from methyl to ethyl.

The 6,7-disubstituted epoxides (4–6, 9, 10) are much more stable to acid than are the trisubstituted (1–3, 7) probably because a relatively stable tertiary carbonium ion-like intermediate is no longer possible (Pritchard and Long, 1956). As in the case of the trisubstituted epoxides, increasing the chain length of the C-7 alkyl substituent further increases the stability of the epoxide. Hydrolysis of the trans-disubstituted epoxides (4, 6) to their erythro diols occurs more slowly than the hydrolysis of the cis-disubstituted epoxides (4, 5) to their threo diols although the log *P* values for the cis and trans epoxides are indistinguishable by our techniques. Pritchard and Long (1956) observed a similar phenomenom with *cis*- and *trans*-2,3-epoxybutanes and attributed the faster hydrolysis rate of the cis epoxide to a less stable configuration. The monosubstituted epoxide (8) has about the same rate of hydrolysis as the disubstituted epoxides probably because a secondary carbonium ion can still form at C-6. The trans trisubstituted 2,3-epoxides are very stable to hydrolysis in part because they may exist in a more hydrophobic environment as illustrated by higher values for log *P* than similar compounds with a 6,7 epoxide, and they are glycidyl ethers which were earlier reported to be slowly hydrolyzed by aqueous acid (Pritchard and Long, 1956).

Biological Activity. The series of *p*-bromo-substituted compounds chosen for this study has long been known to have only moderate morphogenetic activity on *Tenebrio molitor* (a common insect for laboratory evaluation of juvenile hormone-like activity) (Jacobson et al., 1972; Pallos and Menn, 1972), and it was earlier shown that modifications of the terpenoid moiety resulted in greater effects on the biological activity for geranyl phenyl ethers of the moderately active phenols (*p*-bromo, *p*-nitro) than highly active phenols (*p*-ethyl, *p*-isopropyl) (Hammock et al., 1974; Hammock, 1973). Possibly this trend is again evidenced by the very high activity of the methyl propyl epoxide (3, Table I). Past research has led to juvenoids of improved stability in the environment as recently illustrated by the work of Schwarz et al. (1974) (for the review see Hammock and Quistad, 1976). Similar approaches can be applied to the isopropylidene functionality hopefully without resorting to compounds of enhanced hydrolytic stability at the expense of oxidative lability. With the trisubstituted epoxides, an increase in log *P* results in a slight increase in biological activity and a major increase in hydrolytic stability while saturation of the 2,3 olefin slightly decreases morphogenetic activity while increasing hydrolytic stability (saturation presumably also increases stability to allylic oxidation). At the expense of some biological activity, even greater hydrolytic stability can be obtained with disubstituted epoxides.

A profitable direction for synthetic effort may lie in the production of juvenoids containing the epoxide moiety.

The epoxide will not be susceptible to oxidation in the environment or by target insects resistant by oxidative mechanisms. This study has shown that the epoxide in juvenoids can be stabilized to acid hydrolysis by increasing the hydrophobicity in the region of the epoxide and/or by destabilizing the carbonium ion-like intermediate assumed to be involved in acid hydrolysis of epoxides.

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Supplementary Material Available: Typical syntheses and isolation of substituted epoxides, proton and ^{13}C NMR, and structural proof for the cis and trans propyl proton epoxides (9 pages). Ordering information is given on any current masthead page.

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