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Synthesis and Morphogenetic Activity of Derivatives and Analogs of Aryl Geranyl Ether Juvenoids

Bruce D. Hammock, Sarjeet S. Gill, and John E. Casida*

1-(4′-Ethylphenoxy)-3,7-dimethyl-6,7-epoxy-*trans*-2-octene (the ethyl epoxide juvenoid) and its nonepoxidized intermediate (the ethyldiene) were used to prepare compounds involving 34 modifications of the geranyl moiety including 13 mono- and bicyclic derivatives. Mechanisms are proposed for tetrahydrofurandiol formation on oxidative cyclization of the ethyldiene, ethyl epoxide, and their 6,7-diol derivative. Additional syntheses yielded analogs involving 17 modifications in the aryl moiety. The ethyl epoxide is more active in the *Tenebrio molitor* juvenoid assay than any of its chemical degradation products. Some 7-alkoxide derivatives are more potent than the ethyl epoxide in *Tenebrio* assays but they are less active in the ecdysone-stimulated *Drosophila* imaginal disk evagination assay. High potency in the *Tenebrio* test may depend, in part, on structural features appropriate to enter a pool or combine with a site in the insect where the juvenoid is refractory to degradation.

Several substituted-phenyl epoxy geranyl ether juvenoids are potent morphogenetic agents on a variety of pest insects. One of the most effective compounds of this type in *Tenebrio molitor* pupal assays and *Culex pipiens quinquefasciatus* larval assays is 1-(4′-ethylphenoxy)-3,7-dimethyl-6,7-epoxy-*trans*-2-octene (R 20458 of Stauffer Chemical Co.; the ethyl epoxide) (Jacobson *et al.*, 1972; Pallos and Menn, 1972; Pallos *et al.*, 1971; Walker and Bowers, 1973). Any potential use of this compound or related ones in insect control requires an understanding of their metabolism and environmental degradation. Accordingly, a series of unlabeled degradation products and derivatives was made for use in comparing with radioactive metabolites and photoproducts (Gill *et al.*, 1974; Hammock, 1973; Hammock *et al.*, 1974; Singh, 1973). Several additional reactions were carried out on the degradation products in order to characterize them and to obtain additional compounds for bioassay. Other aryl geranyl ethers are included to examine structure–activity relationships in light of recent findings on the metabolism of juvenoids.

MATERIALS AND METHODS

Chemicals. The ethers examined include 18 variations in the aryl group (**A**–**R**) and 39 modifications in the aliphatic moiety (**1**–**39**). Figure 1 gives the structures for these compounds and their code designations. Some of the compounds are given trivial names which refer to the 4 substituent of the phenyl group and the nature of the geranyl-derived moiety; thus, **1A** is the ethyldiene, **2A** is the ethyl epoxide, **3A** is the ethyl diepoxide, and **17A** is the ethyldiol. The synthesis of each compound is stated briefly in this report and given in detail by Hammock (1973) or Singh (1973).

Chromatography. The conditions for thin-layer chromatography (tlc) and gas–liquid chromatography (glc) are given elsewhere (Gill *et al.*, 1974; Hammock, 1973; Hammock *et al.*, 1974). Column chromatography was used to purify 1–10-g amounts of the ethyldiene, ethyl epoxide, ethyl diepoxide, and ethyldiol used as starting materials in many reactions. For example, dry column chromatography with alumina (activity grade III, Woelm, Eschwege, Germany) gives R_f values of 0.88 for the ethyldiene, 0.40 for the ethyl epoxide, and 0.08 for the ethyl diepoxide on development with carbon tetrachloride. A dry packed column of Florisil (60–100 mesh, Floridin Co., Berkeley Springs, W. Va.) separates the ethyldiene, ethyl epoxide, ethyl diepoxide, and ethyldiol, the first three being eluted in sequence with a hexane–ether gradient and the last compound with an ether–methanol gradient. These compounds are also separated on columns prepared from slurries of Florisil or silicic acid in hexane with development using the solvent gradients indicated above.

Chromogenic Agents, Functional Group Tests, and Spectroscopy. The compounds were detected on silica gel F_{254} tlc plates (EM Laboratories, Inc., Elmsford, N. Y.) by their quenching of gel fluorescence when viewed under short-wavelength uv light (254 mμ) or with one of the following reagents: iodine vapor, molybdophosphoric acid, anisaldehyde, vanillin, and isatin as relatively nonspecific reagents (Stahl, 1969); diazotized benzidine for phenols and lead tetraacetate for vicinal diols (Stahl, 1969); diphenylamine (7% w/v in acetone) followed by exposure to uv for aliphatic chlorides and bromides; 2,6-dibromo-*N*-chloro-*p*-benzoquinone imine for sulfur-containing compounds (Menn *et al.*, 1957); and 4-(*p*-nitrobenzyl)pyridine (2% w/v in acetone) and heat and then tetraethylenepentamine (10% v/v in acetone) for epoxides. This latter reagent which detects 1–10 μg of unhindered epoxides (Hammock, 1973) proved very useful in these studies and in related investigations on pyrethroids (Ueda *et al.*, 1974).

The following functional group tests assisted in charac-

Division of Entomology and Parasitology, University of California, Berkeley, California 94720.

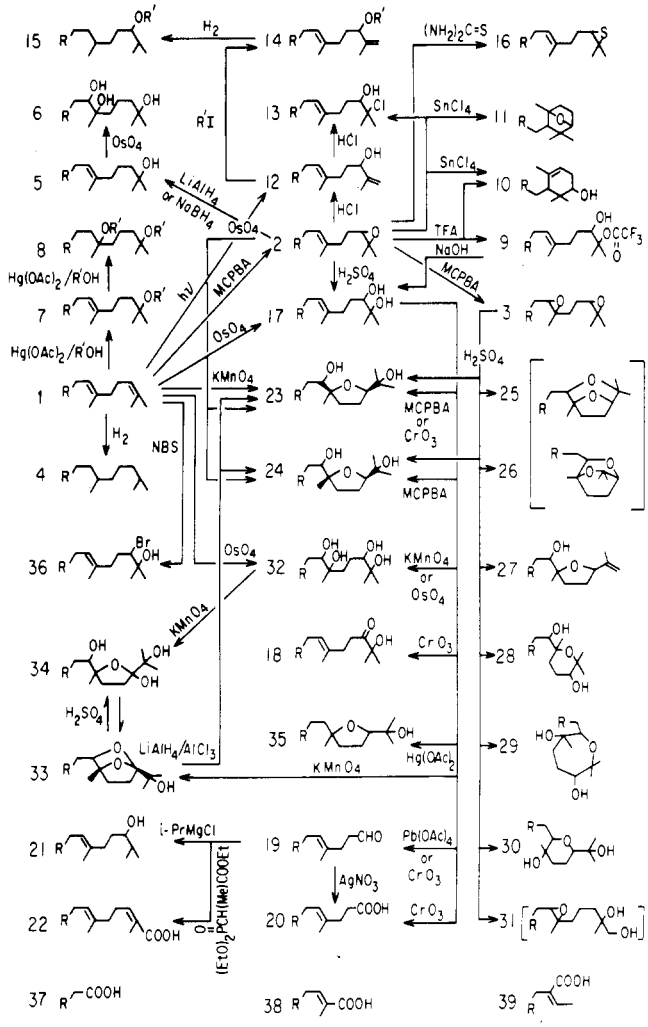
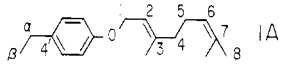


Figure 1. Reactions leading to modifications of the geranyl moiety of aryl geranyl ethers. The nomenclature is based on the ethyldiene (**1A**) which is converted to the 6,7-epoxide (**2A**), the 2,3-6,7-diepoxide (**3A**), or the 6,7-diol (**17A**) as starting materials for syntheses in the ethylphenyl series



R is 4-substituted phenoxy with para substituents as follows: **A**, CH_3CH_2; **B**, $CH_3C(O)$; **C**, CH_3CHOH; **D**, $HOCH_2CH_2$; **E**, $HOC(O)CH_2$ or its methyl ester; **F**, CH_3; **G**, HO; **H**, HOC(O) or its methyl ester; **K**, H; **L**, F; **M**, Cl; **N**, Br; **O**, I. Other R groups are aryloxy or arylthio as follows: **I**, 3-OH-4-$CH_3CH_2C_6H_3O$; **J**, 3-OH-4-$CH_3C(O)C_6H_3O$; **P**, 2-naphthoxy; **Q**, 3,4-methylenedioxyphenoxy; **R**, 4-$CH_3CH_2C_6H_4S$. In the alkoxide series (**7**, **14**, and **15**) and dialkoxide series (**8**), R′ is methyl, ethyl, *n*-propyl, or isopropyl with suffixes to the code designations of **Me**, **Et**, **Pr**, and ***i*-Pr**, respectively. The structures of compounds in brackets are tentative.

terization of most of the compounds shown in Figure 1; the results of these tests are tabulated by Hammock (1973). Epoxides were reduced to the tertiary alcohol derivatives with $NaBH_4$ or $LiAlH_4$ or cleaved to the corresponding diols with 0.05 *N* H_2SO_4 in 40% aqueous tetrahydrofuran. Primary and secondary but not tertiary alcohols were either acetylated with acetic anhydride–pyridine (Bush, 1961) or oxidized with Sarett reagent (CrO_3–pyridine complex; Fieser and Fieser, 1967). Vicinal diols were converted to their boronic acid esters on reaction with *n*-butylboronic acid (BBA) (Oesch *et al.*, 1971) or cleaved to the corresponding aldehydes with lead tetraacetate. Benzylic alcohols were oxidized to the corresponding ketones with lead tetraacetate. Ketones were either converted to their semicarbazones with semicarbazide or reduced with $NaBH_4$ (Bush, 1961); with appropriate mild conditions, the reduction of the ketone group was achieved without cleaving epoxide functionalities. Ketals were cleaved to diols with $AlCl_3$–$LiAlH_4$. Carboxylic acids were methylated with diazomethane. Olefins were either oxidized with OsO_4–pyridine for analysis as the pyridine-stabilized diesters or as the diols after transesterification or they were oxidized with *m*-chloroperoxybenzoic acid (MCPBA).

The compounds are identified by their infrared (ir), proton magnetic resonance (pmr, with decoupling and shift reagents, as appropriate), and mass spectral (electron impact and chemical ionization) characteristics. They are also characterized by conversion to appropriate derivatives (Figure 1). All relevant data, which are given in detail by Hammock (1973) and Singh (1973), support the proposed structure for each compound. The spectral data for two of the compounds (**33A** and **34A**) are given later. In these cases, the ir spectra were determined with a Perkin-Elmer Model 456 grating spectrophotometer using neat samples between AgCl plates. The pmr spectra were obtained with the Perkin-Elmer Model R12B 60-MHz instrument using $CDCl_3$ solutions with tetramethylsilane (TMS) as an internal standard and chemical-shift values are reported in parts per million (δ) downfield from TMS. To determine labile protons the samples were rerun after treatment with D_2O. Eu(fod)$_3$ [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium(III)] was used as the shift reagent. Electron impact mass spectra were obtained on a CEC 211003-C mass spectrometer using a direct introduction probe and an ionization voltage of 70 eV.

Bioassays. Ten pupae of the mealworm (*Tenebrio molitor* L.; 1 to 24 hr after the larval-pupal molt; average weight 136 mg; Sure Live Mealworm Co., Los Angeles, Calif.) were separated from the culture medium by a convenient technique (Hammock, 1973) and placed on a filter paper in a petri dish. Each pupa was treated with the test compound in methanol (1 μl) applied to the ventrum of the last three abdominal segments. The effective dose of compound (ED_{50}, micrograms/pupa) to produce 50% pupal-adult intermediates or more severe responses (Bowers, 1969; Jacobson *et al.*, 1972; Zeikus and Steinhaus, 1968) after 7 to 10 days was determined from log dose–probit effect (LDP) plots (Finney, 1952) with at least four doses yielding between 20 and 80% effect and with three replicates of ten insects for each dose. The ethyl epoxide served as the standard in all tests involving different populations of *T. molitor*. Three variations of this assay were used in special tests. One involved the use of previously sexed pupae (Konok, 1955). Another utilized pupae pretreated 1 hr earlier with a candidate synergist in solvent or with solvent alone (control) applied to the dorsum of the first three abdominal segments. The third compared the sensitivity of 1–24-hr pupae held at 25° after treatment with "chilled" pupae held for 24 hr at 5° after treatment and then at 25° for the remainder of the assay. The emergence time was delayed about 24 hr as a result of chilling, indicating that the pupae did not undergo significant maturation during the period they were held at 5°.

The second type of bioassay determined the *in vitro* potency (EC_{50}) of the juvenoid (micrograms/milliliter) in giving 50% reduction of the β-ecdysone-induced evagination of *Drosophila melanogaster* imaginal disks (Chihara *et al.*, 1972).

SYNTHESES

Several of the dienes (**1**), epoxides (**2**), diepoxides (**3**), and 7-alkoxides (**7**) are known compounds (Bowers, 1969; Jacobson *et al.*, 1972; Pallos and Menn, 1972; Pallos *et al.*, 1971; Sarmiento *et al.*, 1973; Sláma, 1971; Šorm, 1971; Walker and Bowers, 1973) but they were prepared in this

laboratory to facilitate comparison of bioassay data in the present study with those from other laboratories.

Modifications in the Aryl Group. Sixteen aryloxy (**A, B, E–Q**) or arylthio (**R**) compounds in the *trans*-diene series (1) were prepared in 33–87% yield by reaction of equimolar pure *trans*-geranyl bromide and the appropriate phenol or ethylthiophenol (Newman and Karnes, 1966) by the Williamson synthesis. Digeranoxy compounds are sometimes obtained when dihydroxyphenols are used; their yields are 9, 15, and 0%, respectively, in preparing dienes **1G, 1I,** and **1J.** Reduction of the acetodiene (**1B**) with $NaBH_4$ in methanol and of the methyl ester of the β-carboxymethyldiene (**1E**) with $LiAlH_4$ in ether gave the α-hydroxyethyldiene (**1C,** 91%) and the β-hydroxyethyldiene (**1D,** 85%), respectively. The appropriate methyl esters were saponified with NaOH in methanol to give the carboxymethyldiene (**1E,** 95%) and the carboxydiene (**1H,** 73%).

Reactions of the 6,7-Epoxide Substituent. The 6,7-epoxides **2A–Q** are obtained in 53–90% yield on treating the corresponding dienes **1A–Q** with equimolar MCPBA in dichloromethane. The ethylthiodiene (**1R**) epoxidation with MCPBA gives only 5% epoxide **2R,** the major product being the ethylthiodiene sulfoxide. The ethyldiene is oxidized to the ethyl epoxide with excess H_2O_2 in ethanol buffered with $NaHCO_3$ in the presence but not in the absence of Na_2WO_4; the use of pyridine as the solvent (Saindane *et al.*, 1972) is not appropriate since the ethyldiene does not react and pyridine *N*-oxide is formed when Na_2WO_4 is added. The ethyl epoxide (**2A**) is also obtained in 72% yield on addition of K_2CO_3 to a methanol solution of the bromohydrin (**36A**), prepared in 61% yield by reaction of *N*-bromosuccinimide (NBS) with the ethyldiene (**1A**) in aqueous 1,2-dimethoxyethane. The diols (**17A,B,G,** and the methyl ester of **17H**) are produced in 57–86% yield from the corresponding dienes (**1A,B** and the methyl ester of **1H**) *via* the osmate esters or in 9–91% yield on treating the epoxides (**2A,B,G**) with H_2SO_4 in aqueous tetrahydrofuran. Reduction of the acetodiol (**17B**) with $NaBH_4$ gives the α-hydroxyethyldiol (**17C,** 91%) and saponification of the carbomethoxydiol gives the carboxydiol (**17H,** 79%). The ethyl epoxide (**2A**) is quite stable in alcoholic alkaline media even under oxygenation conditions but it undergoes minor cleavage to the ethyldiol (**17A**) within 24 hr at 60°. Treatment of the ethyl epoxide (**2A**) with KOH in methanol (Cochrane and Chau, 1968) gives the ethyl allylic alcohol (**12A**) among several products without apparent polymerization as a trisubstituted epoxide is involved. Better routes to the allylic alcohols **12A,N** are Rose Bengal photosensitized oxygenation of the diene **1A** in pyridine and isomerization of the corresponding epoxides **2A,N** with HCl in ethyl acetate, giving yields of 35 and 50–75%, respectively. A by-product in conversion of the ethyl epoxide to the ethyl allylic alcohol (**12A**) is the corresponding chlorohydrin (**13A,** 18%) formed by the Markovnikov addition of HCl to the allylic alcohol. Reaction of the ethyl epoxide (**2A**) with lithium diethylamide (Cope and Heeren, 1965; Crandall and Chang, 1967) is not an appropriate route to the allylic alcohol (**12A**) because there is extensive ether cleavage.

Trifluoroacetic acid (TFA) converts the ethyl epoxide (**2A**) to the trifluoroacetate ester of the diol **9A** (63%), the cyclohexenol **10A** (4%), and the diol **17A** (8%), but not to the allylic alcohol **12A.** Saponification of the trifluoroacetate **9A** gives the diol **17A.** Treatment of the ethyl epoxide (**2A**) with $SnCl_4$ gives the cyclohexenol **10A** (9%), the cyclohexane oxide (**11A,** 22%), and the chlorohydrin (**13A,** 6%). Similar cyclic products are formed on treating the ethyl epoxide (**2A**) or other terpene oxides with BF_3 (Sonnet *et al.*, 1969; Trost, 1970). Reductive opening of the 6,7-epoxides **2A,N** with excess $LiAlH_4$ in ether or $NaBH_4$ in ethanol yields the corresponding tertiary alchols **5A,N** in essentially quantitative yields.

Acid-catalyzed isomerization of the ethyl epoxide (**2A**) with thiourea in aqueous dioxane gives the ethylthiarane (**16A,** 23%).

Oxidation or Cleavage of the Diol Moiety. The ethyldiol (**17A**) reacts with Jones reagent (Fieser and Fieser, 1967) in acetone to give the ethyl α-hydroxy ketone (**18A,** 12%) with increased yield on addition of Mn^{2+} (Walker, 1967), the major product in each case being the hexenoic acid (**20A,** 81%) formed on cleavage of the diol. Dicyclohexylcarbodiimide (DCC) and anhydrous H_3PO_4 in dimethyl sulfoxide (Me_2SO) do not oxidize the diol to a significant extent. The use of Me_2SO solutions of DCC with pyridine-stabilized acids, including pyridine–H_3PO_4 and pyridine–TFA, completely oxidizes the ethyldiol without formation of the α-hydroxy ketone. The mild oxidizing reagent, acetic anhydride and Me_2SO, led to acetylation of the 6-hydroxyl group.

The ethyldiol (**17A**) is cleaved to the ethylaldehyde or hexenal (**19A**) on treatment with lead tetraacetate or Sarett reagent in 100 and 50% yields, respectively. Another major product in the Sarett reagent oxidation, the *cis*-ethyltetrahydrofurandiol (**23A**), is discussed later. The ethylaldehyde is not obtained on attempted oxidation of the ethyldiene (**1A**) with $KMnO_4$, $NaIO_4$, $NaIO_4$–OsO_4, and $NaIO_4$–$KMnO_4$, the starting material being almost completely recovered in most cases. The hexenoic acid (**20A**) is obtained in 81% yield from the ethyldiol (**17A**) with Jones reagent and in 79% yield from the hexenal (**19A**) with Tollens reagent (Vogel, 1970). Reaction of the hexenal (**19A**) with isopropylmagnesium chloride gives the 6-hydroxy analog **21A** (64%) and with a phosphonate it gives the trans acid **22A** (65%).

Reactions at the 2,3 Double Bond. The diepoxides **3A,B,K,L,M,N** are obtained in 10–81% yield on epoxidation of the monoepoxides **2A,B** or dienes **1A,B,K,L,M,N** with 1 or 2 molar equiv, respectively, of MCPBA in chloroform. Reduction of the acetodiepoxide (**3B**) with $NaBH_4$ in methanol gives the α-hydroxyethyl diepoxide (**3C,** 100%). Fenton's reagent (modified after Marshall and Wilkinson, 1970) converts the ethyldiene to many products including the ethyl epoxide and diepoxide and converts the epoxide to the diepoxide and many other products. The epoxide does not react with activated MnO_2 in refluxing benzene but it is converted to many products when exposed to SeO_2.

The tertiary alcohols **5A,N** give the corresponding triols **6A,N** in quantitative yields on OsO_4–pyridine oxidation.

Reaction of the ethyldiol (**17A**) with suitable oxidants and of the ethyl diepoxide (**3A**) with acid gives two major products, the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A**); under certain conditions a great variety of other mono- and bicyclic compounds are also generated.

Treatment of the ethyl diepoxide (**3A**) for 15 min with 0.05 *N* H_2SO_4 in 40% aqueous tetrahydrofuran gives the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A,** combined yield 52%) as major products along with the following minor products; three cyclic diols (**28A,** 2%; **29A,** 5 and 7% yields for the two isomers; **30A,** 3%), two bicyclic ethers (**25A** and **26A,** combined yield 2%), the tetrahydrofuran alcohol (**27A,** 2%), and an acyclic epoxydiol (**31A,** 2%). The ratio of the products is probably kinetically determined. Not any of the ethyltetraol (**32A**) is detected, indicating that reaction with an internal nucleophile leading to cyclization is favored over reaction with the aqueous solvent; the tetraol was erroneously reported as a product of diepoxide cleavage under these conditions (Gill *et al.*, 1972) but the product suggested to be the tetraol was in fact a mixture of several of the products indicated above but not including the tetrahydrofurandiols. The product obtained from the analogous diepoxide of the C_{18}-cecropia hormone by an identical procedure (Ajami and Riddiford, 1973) is also probably not a tetraol. Treatment of the acetodiepoxide (**3B**) under similar conditions

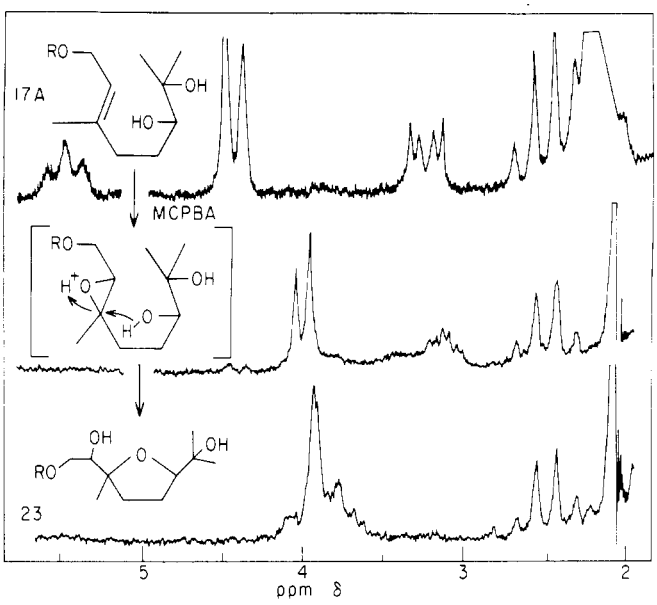


Figure 2. Proton magnetic resonance spectra (60 MHz) of the ethyldiol (**17A**), the diol epoxide "intermediate" (2 min after addition of MCPBA), and the ethyltetrahydrofurandiols (**23A** and **24A**) (90 min after addition of MCPBA).

gives the *cis*- and *trans*-acetotetrahydrofurandiols (**23B, 24B**) as the major products.

Reaction of the ethyldiol (**17A**) with equimolar MCPBA in chloroform gives almost equal amounts of the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A,** combined yield 97%), possibly being formed *via* a reactive 2,3-epoxy-6,7-diol since pmr evidence (Figure 2) indicates the formation and further reaction of this compound. This transition occurs more rapidly if the chloroform pmr solvent is saturated with D_2O, as expected on the basis of destabilizing the 2,3-epoxide. No compound with characteristics appropriate for the epoxydiol was found on tlc, further indicating its reactive nature. These findings strongly suggest that the epoxydiol actually exists for a measurable time before cyclization to the two tetrahydrofurandiols (**23A** and **24A**) and support the cyclization mechanism for 1,5-diepoxides suggested by Wiggins and Wood (1950) based on their studies with 1,2,5,6-diepoxyhexane. None of the other products (**25A–31A**) found on acid cleavage of the diepoxide (**3A**) are detected on MCPBA oxidation of the ethyldiol (**17A**). Possibly the presence of water is required for cyclization to the six- and seven-membered cyclic ethers. These findings indicate that in general compounds containing 1,2-diol–5,6-epoxide moieties are very unstable, tending to cyclize to tetrahydrofurandiols. Thus, there is reason to doubt the structure of such a diol–epoxide assigned to a metabolite (**5f** of Hoffman *et al.*, 1973) of the ethyl epoxide (**2A**) in rats. The mass spectrum published for this metabolite is very similar if not identical with that of a mixture of the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A**). Attempted synthesis of the ethyl-2,3-diol–6,7-epoxide by OsO_4–pyridine oxidation of the ethyl epoxide in benzene resulted in its quantitative conversion to approximately equal amounts of the *cis*- and *trans*-ethyltetrahydrofurandiols. Similarly, epoxidation of the acetodiol (**17B**) gives almost equal amounts of the *cis*- and *trans*-acetotetrahydrofurandiols (**23B** and **24B,** combined yield 48%).

The ethyl-*cis*-tetrahydrofurandiol (**23A**) is selectively formed in 57% yield with no detectable trans isomer (**24A**) on treating the ethyldiol (**17A**) with Sarett reagent. This same selectivity is achieved on treating the dienes (**1A,B**) with $KMnO_4$ in cold aqueous acetone buffered with carbon dioxide (Kötz and Steche, 1924; Klein and Rojahn, 1965); the *cis*-ethyltetrahydrofurandiol (**23A**) forms in 73% yield. Since only the cis isomer is formed, the mechanism proposed for $KMnO_4$ oxidation of 1,5-dienes to the *cis*-tetrahydrofurandiols (Klein and Rojahn, 1965; Powell *et al.*, 1972) is probably also applicable to $KMnO_4$ oxidation of the ethyl- and acetodienes (**1A,B**) and an analogous mechanism involving an intermediate CrO_3–pyridine complex with the diol and olefin group simultaneously is probably involved with the Sarett reagent reacting with the ethyldiol (**17A**).

The tetraols (**32A,B,C**) are obtained on oxidation of the diols (**17A,B,C**) with OsO_4–pyridine in benzene with yields of 91, 22, and 40%, respectively. Minor products from the ethyldiol (**17A**) are the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A,** combined yield 1%). Similar oxidation of the ethyldiene (**1A**) by adding it to OsO_4–pyridine in benzene gives the ethyltetraol (**32A,** 85%) along with trace amounts of the ethyldiol (**17A**) and the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A**). The ethyltetraol (**32A**) is also obtained in 16% yield on $KMnO_4$ oxidation of the ethyldiol (**17A**), the major product (59%) being the bicyclic ketal (**33A**); neither the *cis*- nor *trans*-ethyltetrahydrofurandiol (**23A** or **24A**) is detected as a product by tlc.

There are two types of interconversion reactions supporting the structure of the bicyclic ketal (**33A**). First, a cyclic hemiketal (**34A**) is found in equilibrium with the bicyclic ketal (**33A**). This cyclic hemiketal is not detected in the bicyclic ketal by pmr but it appears as a very minor impurity or degradation product at a low R_f value on tlc analysis. Aqueous acid partially converts the bicyclic ketal to the cyclic hemiketal (ir and pmr evidence) which, although stable enough to be isolated at 22°, reverts back to the bicyclic ketal within a few hours when held without solvent. Acetylation of the 2-position hydroxyl prevents this rearrangement permitting pmr studies that establish a 1:1 cis:trans ratio of the cyclic hemiketals (**34A**). Second, the bicyclic ketal is converted in 78% yield on treating with $LiAlH_4$–$AlCl_3$ to the *cis*- and *trans*-tetrahydrofurandiols (**23A** and **24A**) in a 9:2 ratio indicating that in their formation a trans attack of the hydride on the bicyclic ketal-$AlCl_3$ complex is preferred.

Spectral data supporting the structures of compounds **33A** and **34A** are as follows.

Bicyclic ketal (33A): ir (cm^{-1}) 3450 (OH); pmr ($CDCl_3$) δ 1.13 (t, 3, $CH_3CH_2C_6H_4$), 1.27 (s, 6, $COH(CH_3)_2$), 1.45 (s, 3, CCH_3), 1.82 (m, 4, $(CH_2)_2$), 2.52 (q, 2, $CH_2C_6H_4$), and 3.8 ppm (m, 3, OCH_2CH); loss of one proton at 2.30 ppm with D_2O; the multiplet at 3.8 ppm was not coupled elsewhere in the spectrum and could be resolved by $Eu(fod)_3$ addition into an upfield single proton sextet and a downfield two-proton multiplet which were coupled; mass spectra (70 eV) *m/e* (rel intensity) 306 (70), 185 (69), 122 (62), 107 (76), 81 (85), 59 (83), 43 (100), and 41 (75).

Cyclic hemiketals (34A): ir (cm^{-1}) 3420 (OH); pmr ($CDCl_3$) δ 1.27 (m, 12, all CH_3's), 1.8 (m, 4, $(CH_2)_2$), 2.50 (q, 2, $CH_2C_6H_4$), and 3.9 ppm (m, 3, OCH_2CH) with loss of three protons at 3.1 ppm with D_2O; mass spectrum, identical with that of the bicyclic ketal (**33A**).

Acetates of cyclic hemiketals (34A acetate): ir (cm^{-1}) 3470 (OH) and 1730 (C=O); pmr ($CDCl_3$) δ 1.12 (t, 3, $CH_3CH_2C_6H_4$), 1.17 (br s, ~7.5, $COH(CH_3)_2$ and *cis*-CCH_3), 1.39 (s, ~1.5, *trans*-CCH_3), 2.05 (s, 3, OAc), 2.50 (q, 2, $CH_3CH_2C_6H_4$), 4.00 (m, 2, OCH_2), and 5.24 ppm (d of t, 1, OCH_2CH); loss of 0.6 proton at 3.4 ppm and 1.4 protons at 2.8 ppm with D_2O; and decoupling at 4.0 yields two singlets each integrating at 0.5 proton at 5.15 and 5.34 ppm; mass spectra (70 eV) *m/e* (rel intensity) 366 (8), 348 (13), 330 (7), 307 (20), 306 (12), 301 (11), 219 (49), 149 (60), 123 (70), 122 (51), 91 (100), 81 (54), 69 (52), 59 (53), 57 (70), and 55 (81).

Several observations permit speculation on the mechanism for formation of the bicyclic ketal (**33A**). It is not

Table I. Potency (EC_{50} as Micrograms/Pupa) of Some Juvenoids and Their Derivatives or Degradation Products in *Tenebrio* Assays

Dienes and alkanes: **1A**, 0.12; **4A**, 4; Et ester of **22A**, 7; **1H** and sulfoxide of **1R**, >7.5; **1D** and **1G**, >75
Epoxides: **2A**, 0.0046; **2R**, *ca.* 0.1; **2Q**, 0.17; **2O**, 0.23; **2B**, 0.3; **2N**, 0.35; **2F**, 0.38; **2M**, 0.89; **2L**, 4.2; **2J**, *ca.* 10; **2K** and **2P**, 26; **2I**, *ca.* 40; **2C** and **2E**, >1; **2D** and **2G**, >75
Diepoxides: **3A**, 10; **3B**, **3C**, **3K**, **3L**, **3M**, and **3N**, >75
Alkoxides and dialkoxides: **7AEt**, 0.00051; **7APr**, 0.00062; **7NEt**, 0.0022; **7OEt**, 0.0032; **7A-*i*-Pr**, 0.040; **7AMe**, 0.12; **8AEt** and **8NEt**, *ca.* 1; **14AMe**, **14AEt**, **14APr**, **14NMe**, **14NEt**, **14NPr**, **15AMe**, **15AEt**, **15APr**, **15NMe**, **15NEt**, and **15NPr**, >1
Diols and tetraols: Me ester of **17H**, 0.7; **31A**, *ca.* 7; BBA ester of **17A**, *ca.* 30; **17A**, 100; **17B**, **17C**, and **32A**, >75
Cyclic ethers: **25A** + **26A**, 5; **11A** and **28A**, *ca.* 70; **23A**, acetate of **23A**, **23B**, **23B** + **24B**, **24A**, acetate of **24A**, **27A**, **29A**, **33A**, **34A**, and **35A**, >75
Alcohols other than above: **5A** and **13A**, 0.06; **5N** and **13N**, *ca.* 0.2; acetate of **12N**, 0.9; acetate of **12A**, *ca.* 1; **18A**, 10; **10A** and **12N**, >50
Aldehydes, acids, and esters other than above: Me esters of **38A**, **39A**, and **39B**, each 4–8; Me ester of **37A**, 20; Me ester of **20A**, 75; **19A**, *ca.* 80; **20A** and **37A**, >50
Other compounds: **16A**, 0.25; metyrapone, >100; 1,1,1-trichloropropene 2,3-oxide, *ca.* 1000; cyclohexene oxide and 1-octene, >1000

produced from the *cis*-tetrahydrofurandiol (**23A**) on oxidation with either $KMnO_4$ or activated MnO_2. Starting from the tetraol (**32A**), a very large excess of $KMnO_4$ is required to form even a small amount of the cyclic hemiketal (**34A**) which rearranges to give the bicyclic ketal (**33A**) accounting for only some of the reaction products. The reaction occurs more readily starting with the ethyldiol (**17A**) in which case the tetraol is expected as an intermediate undergoing oxidation at the 6-hydroxyl. Possibly on oxidation of the ethyldiol to the tetraol the $KMnO_4$ undergoes an appropriate change in oxidation state necessary for rapid oxidation of the 6-alcohol substituent.

A related bicyclic ketal forms on oxymercuration of geraniol with mercuric acetate (Brieger and Burrows, 1972) but the corresponding cyclic hemiketals are not reported. Attempts to prepare the cyclic hemiketals of geraniol from this bicyclic ketal by treatment with aqueous acid gave only a small amount of compound with appropriate tlc and mass spectral properties, when analyzed as the monoacetate. Other analyses (tlc, glc) without acetylation also indicate that the bicyclic ketal from geraniol is more stable than the ethyl bicyclic ketal (**33A**) from the ethyldiol (**17A**) as expected on the basis of the relative strain in these ring structures.

Another tetrahydrofuran derivative (**35A**) similar to the tetrahydrofurandiols (**23A** and **24A**) but lacking the 2-hydroxyl group is obtained in 60% yield from the ethyldiol (**17A**) by a solvomercuration–demercuration procedure (Brown and Geoghegan, 1970). The diol group is an important feature because the ethyldiene (**1A**) fails to show significant reaction when exposed to mercuric acetate under a variety of aqueous conditions. The reaction of the ethyldiol (**17A**) presumably proceeds by forming the 2-mercuriacetate derivative of the structure shown (**35A**) with the 6-hydroxyl acting as an internal nucleophile followed by demercuration. An analogous internal nucleophilic attack may be involved in formation of a similar tetrahydrofuran alcohol on perchloric acid oxidation of 9,10-dihydroxy-6,10-dimethyl-5-undecen-2-one (Suzuki and Marumo, 1970).

Synthesis of Other Derivatives. The 6-alkoxy derivatives **14A,N** (20–25%) of the 6,7-allylic alcohols (**12A,N**) are obtained on their treatment with the appropriate iodide in dimethylformamide containing NaH. The 7-alkoxy (**7A,N,O**; 31–66%) and the 3,7-dialkoxy (**8A,N,O**; 10–27%) derivatives are obtained by alkoxymercuration of the appropriate diene with equimolar mercuric acetate using Brown and Geoghegan's (1970) procedure modified by Brieger and Burrows (1972) which gives selective Markovnikov addition of alkoxy substituents to the terminal double bond.

The saturated compounds (**4A** and **15A,N**) were made from the olefins (**1A**, **14A,N**) by hydrogenation over Pd on charcoal. The ethyl phenyl ethers of short-chain aliphatic acids (**37A**, **38A,B**, **39A**) were prepared from the appropriate bromides by the Williamson condensation.

BIOASSAYS

Effects of Sex, Age, Chilling, and Selected Chemicals on Juvenoid Activity in *Tenebrio* Assays. The pupae were not sexed for routine assays since in a preliminary test the ethyl epoxide was equipotent on males and females (ED_{50} 3.7 and 4.2 ng/pupa, respectively). The routine assays utilized only 0–24-hr pupae since they give a single straight LDP line with the ethyl epoxide (**2A**) whereas 24–48-hr pupae respond as if they consist of two groups, one of similar sensitivity to the younger pupae and a second equal group about one-fourth as sensitive to the juvenoid. A similar age relationship was obtained with the chloroepoxide (**2M**) and the ethyl methoxide and ethoxide (**7AMe** and **7AEt**) (Hammock, 1973). Chilling reduces the sensitivity of the pupae to epoxides (ethyl and chloro derivatives, **2A** and **2M**) by 2.1- to 2.4-fold but not to alkoxides (ethyl methoxide and ethoxide, **7AMe** and **7AEt**) where the effect, if any, is only 1.0- to 1.2-fold.

The morphogenetic activity of the ethyl and chloroepoxides (**2A** and **2M**) is unaffected by pretreating the pupae with any of the following compounds at nonmorphogenetic levels: ethyldiene (**1A**) (0.05 μg), ethylthiarane (**16A**) (0.01 μg), ethyldiol (**17A**, 1 μg), each of the *cis*- and *trans*-ethyltetrahydrofurandiols (**23A** and **24A**) (10 μg), cyclohexene oxide (500 μg), 2,2-dimethyloxetane (500 μg), and 1,1,1-trichloropropene 2,3-oxide (200 μg).

Structure–Activity Relationships in *Tenebrio* Assays. The potencies of the test compounds are given in Table I.

In a series of six dienes, only the ethyl compound (**1A**) shows appreciable activity. The saturated alkane (**4A**) is greatly reduced in activity relative to the analogous diene (**1A**). The diepoxides (**3**) are almost inactive relative to the corresponding monoepoxides (**2**).

The epoxides are usually equal in potency or much more active than the corresponding dienes. Based on the data in Table I and other available results (Hammock, 1973) the potency differential (ED_{50} diene/ED_{50} epoxide) increases from a value of 1–6 for seven compounds active, as the epoxides, at 1 μg or above, to a value of 10–20 for three compounds active at 0.1–1 μg, to a value of 40–100 for two compounds active at 0.03 μg or less. Thus, epoxidation most effectively increases the morphogenetic activity when the other molecular features are at or near the optimum.

The potency of compounds in the epoxide series (**2**) increases as the bond distance of the para hydrogen or halogen substituent from the phenyl group is increased (Table I; see also Jacobson *et al.*, 1972; Pallos and Menn, 1972; Sláma, 1971). These structure–activity relationships do not correlate with the electron-withdrawing ability of the aromatic substituents (see also Jacobson *et al.*, 1972). In

the aromatic derivatives with two ring systems, the methylenedioxyphenyl epoxide (**2Q**) is highly active (Bowers, 1969) whereas the β-naphthyl derivative (**2P**) is not. The thiophenyl ether is of reduced activity compared with the phenoxy ether (**2R** *vs.* **2A**) (see also Sláma, 1971).

In the alkoxide series (**7**) the potency in the *Tenebrio* assay of either the 4-nitro compounds (Šorm, 1971) or the 4-ethyl compounds (**A**) (Table I; Sarmiento *et al.*, 1973) is at an optimum with ethyl or *n*-propyl substituents, whereas methoxides and isopropoxides are much lower in activity. On comparing the epoxides (**2**) and ethoxides (**7Et**) with 4-nitro and chloro (Šorm, 1971) and bromo, iodo, and ethyl substituents (Table I), a potency differential of tenfold is found for the ethoxides with various 4 substituents, whereas the differential is 1000-fold for the epoxides (nitro *vs.* ethyl). Further, the potency difference (ED_{50} epoxide/ED_{50} alkoxide) decreases progressively as the potency of the epoxide is increased; thus, the ratio is 1000 for the nitro and 500 for the chloro derivatives (Šorm, 1971) and 159 for the bromo, 72 for the iodo, and 9 for the ethyl derivatives (Hammock, 1973; Table I). Additional substitution at C-3 by a second alkoxide group (**8AEt, 8NEt**) results in a tremendous decrease in activity. The 6-position alkoxy dienes (**14AMe,Et,Pr; 14NMe,Et,Pr**) are inactive even after hydrogenation of the double bond in each of these compounds (series **15**) as might be expected from an earlier report on compounds of a different series (Jacobson *et al.*, 1972). It is interesting to note that the C-6 acetates (those of **12A** and **12N**) are more active than the corresponding ethers (**14A** and **14N** series).

The diols and tetraols are inactive with one interesting exception, the carbomethoxydiol (**17H**) which is tenfold more active than its diene (**1H**) and is also more active than the previously reported value (Bowers, 1969) for the corresponding epoxide. This is of interest because of the resemblance of the carbomethoxydiol (**17H**) configuration to that of the major ester–diol metabolite of the natural juvenile hormone. The cyclic ethers and their acetates are inactive with the exception of slight activity for the ethylpyrandiol (**28A**) and the two ethyl bicyclic ethers (**25A** and **26A**). Among the other alcohols, the chlorohydrins (**13**) are particularly active, possibly because of cyclization to the epoxides. The tertiary alcohols (**5**) are also moderately active. Three of the esters (**37–39**) show slight but definite activity in contrast to other short chain compounds in this study and others (Jacobson *et al.*, 1972). Moderate activity is found for the compound (**16A**) involving a thiarane replacing the epoxide where the activity loss possibly results from the reduction in electronegativity. The other compounds were essentially inactive.

Structure–Activity Relationships in Ecdysone-Induced *Drosophila* Imaginal Disk Evagination Assays. The high potency of ethyl epoxide (**2A**) and the low potency of the ethyl alkoxides (**7AMe** and **7AEt**) are particularly interesting in this assay. The EC_{50} is 58 μg/ml for the C_{18}-juvenile hormone as compared with the following values for the juvenoids: 11 for the ethyl epoxide (**2A**), 45 for the ethyldiol (**17A**), 65 for the methyl ester of compound **38A**, 130 for the carbomethoxydiol (**17H**), 140 for the ethyl methoxide (**7AMe**), and 450 for the ethyl ethoxide (**7AEt**).

Interpretation of Bioassay Results. The test compounds vary over five orders of magnitude in biological activity so trace impurities could give apparent low activity to otherwise inactive compounds. The active compounds in Table I produce no symptoms of intoxication and the insects molt about 24 hr earlier than untreated pupae. In contrast, the following insecticidal pyrethroids show morphogenetic activity at doses that give symptoms of acute poisoning and the treated pupae frequently molt 24 hr later than normal: allethrin and (+)-*trans*-ethanoresmethrin, each at 0.1 μg; the epoxides of (+)-*trans*- and (+)-*cis*-ethanoresmethrin, each at 1 μg. Other chrysanthemates are known to be active as juvenile hormone mimics in *Dysdercus fasciatus* assays (Punja *et al.*, 1973).

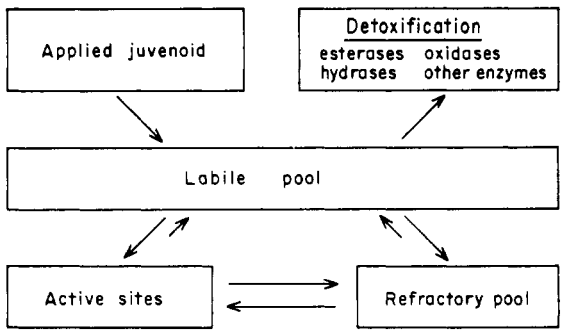


Figure 3. Model illustrating the interactions of labile and refractory pools in the action of juvenoids in *Tenebrio* assays.

The finding that the ethyldiene undergoes biological and environmental oxidation to the more morphogenetically active ethyl epoxide (Gill *et al.*, 1974; Hammock *et al.*, 1974) suggests the epoxidation may be an obligatory activation mechanism for geranyl ethers; however, this is not the case since several 6,7-epoxygeranyl ethers are similar in activity to the unepoxidized compounds and the corresponding saturated alkane (**4A** *vs.* **1A**) which cannot undergo epoxidation also has morphogenetic activity. Although many active juvenoids in this series contain potential alkylating groups (epoxide or *tert*-chloro substituents), others do not (the 7-alkoxides) so the 6,7 substituents are probably important in conferring appropriate steric and polaric properties rather than chemical reactivity.

The identified metabolites and photoproducts of the ethyl epoxide (compounds **2B, 2C, 2D, 3A, 3B, 3C, 17A, 17B, 17C, 23A, 24A, 25A, 26A, 28A, 29A,** and **30A**) (Gill *et al.*, 1974; Hammock *et al.*, 1974) are all less active in *Tenebrio* assays than the precursor compound and are usually inactive; only the acetoepoxide (**2B**) shows significant activity, confirming a previous report on the activity of this compound (Bowers, 1969). Thus, high morphogenetic potency requires fit at the active site for juvenilizing action combined with resistance to detoxification. It is suggested that the high potency of the ethyl epoxide relative to other 4-alkyl analogs is due, in part, to the resistance of the ethyl epoxide to metabolism in insects (Pallos and Menn, 1972). However, the *p*-ethyl moiety itself is biodegraded in some insects, mammals, and their enzyme systems (Gill *et al.*, 1974; Hammock *et al.*, 1974). An alternative hypothesis is that the ethyl epoxide has a favorable configuration for localization at a site ("refractory pool") away from detoxifying enzymes yet available for transfer to the juvenoid receptor to produce abnormal growth (Figure 3). This refractory pool may involve carrier molecules, the hormone receptor sites, or, less likely, lipid depots.

The epoxides (**2**) have a more rigid requirement than the alkoxides (**7**) for a specific 4 substituent to display high morphogenetic activity, yet the optimal compounds in each series are of similar activity, indicating similar ability to fit at the hormone receptor site. Cleavage of the epoxide group, a major detoxification reaction in several insects (Hammock *et al.*, 1974), is precluded by the use of alkoxides which may explain the relatively high potency of alkoxides regardless of the 4 substituent. Therefore, it appears that the ethyl substituent in the epoxide series confers the ability to resist metabolism even though neither the ethyl nor the epoxide moieties are uniquely resistant to either oxidation or hydrase attack. It is conceivable that the ethyl epoxide persists in some insects because of an ability to enter the "refractory pool."

Both low and high potency epoxides (**2M** and **2A**, re-

spectively) which are likely to undergo rapid degradation by epoxide hydrases show lower activity in chilled than in normal *Tenebrio* pupae, while the alkoxides which are less likely to undergo rapid detoxification do not differ in potency with normal and chilled pupae. The rate of juvenoid metabolism, an enzymatic process, should be greatly reduced in the chilled pupae. It seems unlikely that the potency difference is due to varying degrees of retention of the epoxides and alkoxides in the cuticle and epidermis. Tissues of the chilled pupae probably do not undergo extensive reprogramming at low temperature since the development of these pupae is delayed for 24 hr, the same time period as that involved in the chilling process. Possibly the juvenoids enter the insect much more rapidly in chilled than in normal pupae when measured on a developmental time scale. These high levels of epoxides may saturate the "refractory pool" in the chilled pupae leaving the majority of the compound available in the labile pool for degradation. A similar explanation may be applicable to the greater potency of some topically applied juvenoids when compared to injected juvenoids (Bowers *et al.*, 1965) since C_{18}-cecropia hormone persists longer after topical application than injection (Ajami and Riddiford, 1973).

The potency of dienes with low morphogenetic activity is increased only slightly upon epoxidation while analogous oxidation of morphogenetically active dienes leads to a very large increase in activity. These differences may be even larger than indicated by the usual bioassays due to small amounts of diene epoxidation prior to application or penetration, while in solvents or exposed to air, or after entry by the action of insect oxidases. The potency differential of the diene to the epoxide is not likely to be related to differences in their liposolubility or lipid–water partitioning characteristics. Perhaps the dienes and epoxides differ in persistence due to their relative tendencies to associate with a specific site, such as a detoxifying enzyme because of its substrate specificity or a juvenoid carrier (refractory pool). The increase in activity of the epoxide over its diene may be offset in some cases by rapid metabolism of the epoxide to the corresponding diol.

Effective juvenoids persist for a critical period within the insect, usually longer than the cecropia hormone itself (Reddy and Krishnakumaran, 1972). The persistence is achieved by introducing functional groups that resist metabolism, such as an alkoxide instead of an epoxide and suitable phenyl substituents in ethers or suitable alcohols in esters. These structural features allow compounds complementary to the hormone receptor site to maintain the titer necessary for morphogenetic disruption. The present results suggest that a hormone receptor or carrier isolating the juvenoid in a pool refractory to rapid metabolic degradation may also be important.

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