room temperature, the liquid monomer deposited a solid, which was collected by filtration and dried (P_2O_5) *in vacuo*. Since the Cl content of the solid (found, 24.1) was the same as that of the liquid (found, 24.0; theory, 24.2), the solid is presumably a *dimer* or higher intermolecular coordination polymer of If.

2-Diethylamino-1,3,2-diheteroboracycloalkanes (IIIa–f).—The appropriate 2-chloro derivative (Ia–f) was cooled to −70° and treated dropwise with excess Et_2NH. The mixture was allowed to warm to room temperature, stirred cautiously until the exothermic reaction subsided and, then, vigorously for 1 hr, and filtered to remove a precipitate. Distillation of the appropriate filtrate gave the products IIIa–f (Table III).

Acknowledgment.—The authors express their appreciation to Drs. W. J. Barrett, W. C. Coburn, Jr., P. D. Sternglanz, and associates for microanalytical and spectral determinations and to Mrs. Martha Thorpe for nmr data. Some of the analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Compounds Related to Insect Juvenile Hormone. IV

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Received February 28, 1969

The juvenile hormone[1,2] and most compounds that have JH activity by the bioassay with *Tenebrio molitor* L.[3] are acyclic sesquiterpenes or modified sesquiterpenes[3–7] with an array of trisubstituted double bonds every fourth carbon. The purpose of the present work was to assess the JH activity of compounds in which some or all of the double bonds and/or alkyl side chains were eliminated to discover easily preparable JH mimics.

Table I lists the compounds and the minimum weight (ng) that caused detectable retention of juvenile characteristics. The cecropia JH and methyl farnesate 10,11-epoxide are included as references. The removal of either unsaturation caused a drastic reduction of activity.[9]

The conversion of squalene *via* its epoxide to cholesterol and the facile transformations of model acyclic terpenoids to cyclic, bicyclic, and polycyclic materials have been well documented. These results prompted us to heat our mixture of the synthetic JH isomer and the closely related methyl farnesate 10,11-epoxide with acid while conditions were controlled so as to produce mixtures rich in either mono- or bicyclic compounds. These materials were quite inactive.[10] Therefore, since the results of the present test also suggest that the double bonds must be present in the acyclic materials, one is tempted to speculate that the process of cyclization may itself be a key step in the biological scheme of juvenilization involving the cecropia-type hormone. The tenfold reduction in activity from epoxide to olefin may merely reflect a somewhat lessened proclivity for cyclization due to the lower nucleophilicity of a double bond compared with an epoxide oxygen atom, or to a requirement for prior conversion to an epoxide as in the case of the squalene–cholesterol conversion.

Recently, activity was reported in compounds of the sesamex-type,[7] and this family of materials was claimed as "synergists" for insecticidal activity. However, they seemed to function as JH materials in the *T. molitor* test rather than as synergists because they produced their effects on segments of insects that would presumably not have any JH titer, *i.e.*, no *corpora allata*. If both classes of compounds produce their action by the same general biochemical mechanism, a requirement for cyclization would appear to be remote, and a new approach to mechanism is necessary.

Experimental Section

When analyses[11] are indicated in Table I only by symbols of the elements, the analytical results obtained were within ±0.2% of the theoretical values. The identity of all new compounds was confirmed by ir spectra, and samples of >99% purity were obtained by glpc collection for analyses and testing. Ir spectra were recorded with a Perkin-Elmer 137 NaCl spectrophotometer and gas chromatograms were obtained with an Aerograph Model A-700 instrument. Methyl 10-undecenoate and its epoxide were obtained from Eastman Organic Chemicals and Aldrich Chemical Co., Inc., respectively. Company and trade names are given for identification only and do not constitute endorsement by the U. S. Department of Agriculture. The bioassay was performed on *T. molitor*[3] with Mrs. R. Henegar of this Division assisting.

Methyl 10-Oxodecanoate.—Methyl undecenoate (50.0 g, 0.252 mole) was dissolved in 200 ml of 97% HCO_2H, and the solution was warmed to 35–40°. The temperature was maintained at this level while 28.0 g (0.257 mole) of 30% H_2O_2 was added dropwise. The resulting solution was allowed to remain at 40° overnight. Then the solvent was removed, the product was taken up in Et_2O and washed with aqueous Na_2CO_3, and the ethereal phase was dried ($MgSO_4$). After removal of the solvent, the crude product was dissolved in 400 ml of MeOH containing 0.07 mole of NaOMe and heated under reflux for 3 hr. The solvent was removed, and the product was taken up in Et_2O and washed with H_2O. After drying ($MgSO_4$), the solvent was removed, and the crude diol was dissolved in 550 ml of C_6H_6. To this solution was added in one portion 78.0 g (0.167 mole, 95% purity) of $Pb(OAc)_4$. After a mild exothermic reaction, the mixture was held at 35–45° for 1 hr, poured into 800 ml of 20% AcOH, and extracted with Et_2O. The combined organic phase was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated, and distilled to give 25.9 g (51%) of colorless liquid, bp 93–97° (0.14–0.19 mm). The semicarbazone was then prepared, mp 100–102° (MeOH–H_2O) (lit.[12] mp 100–101°).

Methyl 11-Methyl-10-dodecenoate.—NaH (0.26 g, 0.011 mole) was added to dry DMF under N_2, and 0.38 ml of MeOH was added thereto. After 15 min, 4.94 g (0.0114 mole) of isopropyltriphenylphosphonium iodide was added. The mixture was cooled in an ice bath, and 1.50 g (0.00714 mole) of methyl 10-oxodecanoate was added. Then the mixture was stirred at ambient temperature for 18 hr, diluted with cold H_2O, and extracted with Et_2O. The organic phase was washed (H_2O), dried ($MgSO_4$), concentrated, and finally extracted with boiling petroleum ether (bp 30–60°). The extract was concentrated

(1) H. Röller, K. H. Dahm, C. C. Sweely, and B. M. Trost, *Angew. Chem.*, **79**, 190 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 179 (1967).

(2) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Natl. Acad. Sci. U. S.*, **60**, 853 (1968).

(3) W. S. Bowers and M. J. Thompson, *Science*, **142**, 1469 (1963).

(4) P. Schmialek, *Z. Naturforsch.*, **B18**, 516 (1963).

(5) H. A. Schneiderman, A. Krishnakumaran, V. E. Kulkarni, and L. Friedman, *J. Insect Physiol.*, **11**, 1641 (1965).

(6) W. S. Bowers, M. J. Thompson, and E. C. Uebel, *Life Sci.*, **4**, 2323 (1965).

(7) Recently, compounds unrelated to sesquiterpenes that have high JH activities were reported.[8]

(8) W. S. Bowers, *Science*, **161**, 895 (1968).

(9) The slight activity of methyl 3,7,11-trimethyldodecanoate may be the result of an undetectable amount of methyl farnesate that survived hydrogenation.

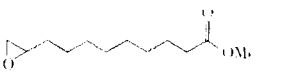
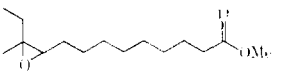
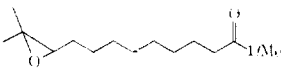
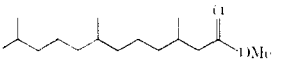
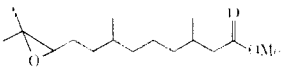
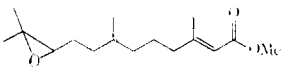
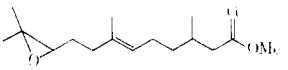
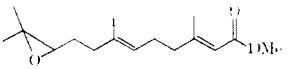
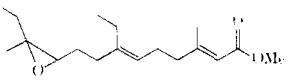
(10) P. E. Sonnet, B. H. Braun, M. Schwarz, N. Wakabayashi, R. M. Waters, and M. Jacobson, *Ann. Entomol. Soc. Amer.*, in press.

(11) Microanalyses were done by Galbraith Laboratories, Knoxville, Tenn.

(12) F. C. Pennington, W. D. Celmer, W. M. McLamore, V. V. Bogert, and I. A. Solomons, *J. Amer. Chem. Soc.*, **75**, 109 (1953).

TABLE I

JUVENILE HORMONE ACTIVITY OF VARIOUS COMPOUNDS IN *Tenebrio molitor*

Name	Structure	Activity[a]	Remarks
Methyl laurate		—	
Methyl 10,11-epoxyundecanoate		—	
Methyl 10,11-epoxy-11-methyltridecanoate		—	
Methyl 10,11-epoxy-11-methyldodecanoate		—	
Methyl 3,7,11-trimethyldodecenoate		10,000	
Methyl 10,11-epoxy-3,7,11-trimethyldodecanoate		—	
Methyl 10,11-epoxy-3,7,11-trimethyl-2-dodecenoate		*c*	3:7 *cis trans* mixture
Methyl 10,11-epoxy-3,7,11-trimethyl-6-dodecenoate		—	*trans* component
Methyl 10,11-epoxy-3,7,11-trimethyl-2,6-dodecadienoate (methyl farnesate 10,11-epoxide)		31	Ref 6
Juvenile hormone (methyl 10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate)		10[d]	*e*

[a] This column gives the minimum weight of material in nanograms that caused detectable retention of juvenile characteristics when it was injected into pupae of *T. molitor* in 1 μl of hexane. [b] — denotes inactivity at 10,000 ng. [c] Activity at 30,000 ng. [d] Calculated from reported activity compared with farnesyl methyl ether. [e] H. Röller, B. S. Bjerke, and W. H. McShan, *J. Insect Physiol.*, 11, 1185 (1965).

and distilled to give 6.51 g (62%) of liquid, bp 125–160° (0.05 mm). Glpc (152 cm × 3.2 mm silicone gum rubber SE-30 on base-washed Chromosorb P) revealed the material to be 91–92% pure. *Anal.* ($C_{14}H_{26}O_2$) C, H.

Methyl 11-Methyl-10-tridecenoate.—To 50 ml of dry THF was added 3.99 g (0.010 mole) of *sec*-butyltriphenylphosphonium bromide (prepared by alkylation of ethylidenetriphenylphosphorane with ethyl bromide[13]). Then 6.3 ml of 1.6 *M* *n*-BuLi was added to this suspension. After 10 min, the mixture was cooled in an ice bath, and 1.80 g (0.0090 mole) of methyl 10-oxodecanoate was added. The mixture was stirred without cooling for 1.5 hr and then worked up in the usual manner. The product was distilled to give 0.91 g (42%) of liquid, bp 170–185° (10 mm). Glpc indicated 85% purity. *Anal.* ($C_{15}H_{28}O_2$) C, H.

Methyl 10,11-Epoxy-11-methyldodecanoate.—Methyl 11-methyl-10-dodecenoate was epoxidized with *m*-chloroperbenzoic acid in the usual manner to give 60% of the epoxide. The product was purified by molecular distillation before glpc collection. *Anal.* ($C_{14}H_{26}O_3$) C, H.

Methyl 10,11-Epoxy-11-methyltridecanoate.—Methyl 11-methyl-10-tridecenoate was epoxidized in like manner to give the epoxide in 75% yield after molecular distillation. This epoxide was not separable by glpc with the columns at our disposal. *Anal.* ($C_{15}H_{28}O_3$) C, H.

Methyl 3,7,11-Trimethyldodecanoate.—Methyl farnesate (0.5 g, 0.002 mole) was hydrogenated at atmospheric pressure in MeOH by using 25 mg of PtO_2 as catalyst. The product, after filtering and concentrating, had essentially one peak on glpc. The ir was as expected.

Methyl Laurate.—A mixture of lauric acid (5.0g), concentrated H_2SO_4 (0.25 g), and 10 ml of MeOH was refluxed for 6 hr, diluted with H_2O, and extracted with hexane. The hexane phase was extracted with aqueous $NaHCO_3$ and then with H_2O, dried ($MgSO_4$), filtered, and distilled. The product (4.27 g, 80%) had bp 94–95° (0.2 mm).

Methyl 3,7,11-Trimethyl-2,10-dodecadienoate.—8-Bromo-2,6-dimethyl-2-octene (citronellyl bromide) was prepared in 70% yield from citronellol by the method of Wagner-Jauregg and Arnold,[14] and used without distillation. 6,10-Dimethyl-9-undecen-2-one (citronellylacetone) was prepared from the bromooctane by the method of Renfro and Renfro[15] in 75% yield.

Trimethyl phosphonoacetate (40.5 g, 0.222 mole) was added to a suspension of 5.3 g (0.222 mole) of NaH in 150 ml of DMF over 30 min while the temperature was kept between 20 and 25° with an ice bath. The mixture was stirred for 2 hr after the addition was complete; then citronellylacetone (29 g, 0.148 mole) was added for 20 min at 15–20°. At this point, stirring was stopped, and the mixture was allowed to stand overnight at room temperature. The reaction was worked up by diluting with 1500 ml of H_2O and extracting three times with hexane; then the hexane layers were extracted three times with H_2O, dried ($MgSO_4$), filtered, and concentrated. Distillation yielded a mixture of methyl *cis*- and *trans*-3,7,11-trimethyl-2,10-dodecadienoate, bp 90–112° (0.5 mm), yield 32.2 g (86%). *Anal.* ($C_{16}H_{28}O_2$) C, H.

Methyl 10,11-Epoxy-3,7,11-trimethyl-2-dodecenoate.—Methyl 3,7,11-trimethyl-2,10-dodecenoate (*cis* and *trans* mixture) was epoxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 in the usual manner. Analytical and bioassay samples were collected by preparative glpc. *Anal.* ($C_{16}H_{28}O_3$) C, H.

Methyl 3,7,11-Trimethyl-10-dodecenoate.—Methyl 3,7,11-trimethyl-2,10-dodecadienoate (5.8 g) was stirred at room temperature in a solution of NaOH (16 g) in 300 ml of a mixture (1.3 *N*) of 1:2 H_2O–MeOH overnight until a homogeneous solution was obtained. Most of the MeOH was removed under reduced pressure, NaCl was added to the residue to prevent emulsion, and the residue was extracted twice with 100-ml portions of hexane. The aqueous layer was acidified with aqueous HCl and extracted twice with 100-ml portions of Et_2O. The organic phase was extracted with H_2O and dried ($MgSO_4$), and the solvent was removed to give 4.5 g (83%) of 3,7,11-trimethyl-

(13) B. H. Braun, M. Jacobson, M. Schwarz, P. E. Sonnet, N. Wakabayashi, and R. M. Waters, *J. Econ. Entomol.*, **61**, 866 (1968).

(14) T. Wagner-Jauregg and K. Arnold, *Justus Liebigs Ann. Chem.*, **529**, 274 (1937).

(15) W. B. Renfro and A. Renfro, *J. Amer. Chem. Soc.*, **70**, 3957 (1948).

2,10-dodecadienoic acid as a pale yellow oil. The acid was placed in 300 ml of BuOH and heated to 100°, and Na (10 g) was added in lumps during 30 min with stirring. The mixture was cooled, and about 200 ml of BuOH was removed under reduced pressure; then 150 ml of 1:1 MeOH–H_2O was added, and the mixture was refluxed 1 hr and reduced to a volume of about 100 ml at a pressure of 20 mm. The remainder was acidified with aqueous HCl and extracted with Et_2O. The Et_2O phase was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was treated with ethereal CH_2N_2 to give methyl 3,7,11-trimethyl-10-dodecenoate (3.0 g, 52%) which had bp 80–88° (0.5 mm). *Anal.* ($C_{16}H_{30}O_2$) C, H.

Methyl 10,11-Epoxy-3,7,11-trimethyldodecanoate.—Methyl 3,7,11-trimethyl-10-dodecenoate was epoxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 in the usual way. An analytical sample was collected on preparative glpc. *Anal.* ($C_{16}H_{30}O_3$) C, H.

Methyl 10,11-Epoxy-3,7,11-trimethyl-6-dodecenoate.—Methyl *trans*-6-farnesate was hydrolyzed, reduced, and esterified as for the preparation of methyl 3,7,11-trimethyl-10-dodecenoate. The product had bp 97–103° (0.1 mm) and was obtained in 47% yield. *Anal.* ($C_{16}H_{28}O_2$) C, H.

Epoxidation with *m*-chloroperbenzoic acid in CH_2Cl_2 in the usual way followed by purification by preparative glpc gave analytical samples for bioassay. *Anal.* ($C_{15}H_{28}O_3$) C, H.

Synthesis of Some Substituted 5H-Dibenz[*b*,*f*]azepines as Potential Antimalarials[1]

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As part of an investigation of potential novel antimalarials, we have prepared several of the 5-substituted 5H-dibenz[*b*,*f*]azepines for evaluation. The synthetic scheme employed begins with 9-chloroacridines and is essentially as reported by Bergmann, *et al.*[2] The details of the procedures are included in the Experimental Section.

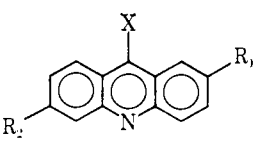
All of the compounds listed in Tables I–III were screened for antimalarial activity against *Plasmodium berghei* in mice by the method of Rane, *et al.*,[3] by the Walter Reed Army Institute of Research. All compounds except **12** and **13** were tested against *Plasmodium gallinaceum* in mosquitos.[4] Production of abnormal oocysts by **15** in the mosquito screen was observed, but no significant activity was noted for it in the mouse screen. None of the other compounds showed any significant activity in either of these tests. We are indebted to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck for these results.

Experimental Section

All melting points were obtained on a Thomas–Hoover Unimelt and are uncorrected. Satisfactory uv, ir, and nmr spectra were recorded for all new compounds. The uv and ir spectra were recorded using a Perkin-Elmer 202 spectrophotometer and a Perkin-Elmer Model 337 spectrophotometer, respectively. Nmr spectra were recorded on a Varian Model A-60A spectrophotometer (TMS internal standard). Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for these elements were within ±0.4% of the theoretical values.

9-Methylacridines.—The 9-chloroacridines used were prepared from the corresponding diphenylaminecarboxylic acids by the published methods.[5] In a typical preparation, to a solution of 35.4 g (0.52 mole) of NaOEt and 88 g (0.55 mole) of diethyl malonate in 350 ml of EtOH, was added 81.2 g (0.35 mole) of 2-fluoro-9-chloroacridine in 350 ml of PhMe, and the mixture was refluxed with stirring for 16 hr. To this mixture was added 800 ml of 18% HCl, the EtOH–PhMe was removed by distillation, and the resultant mixture was refluxed for 4 hr. To this mixture was added 800 ml of H_2O and the solution was filtered hot. The filtrate was cooled, the crystals were collected, and the crystalline material was suspended in 1 l. of H_2O and made alkaline with 10% NaOH solution. Filtration gave the crude 2-fluoro-9-methylacridine which was washed with cold H_2O, dried (30 g crude), and recrystallized from MeCN: yield 22 g (30%).

TABLE I



No.	X	R_1	R_2	Yield, %	Mp, °C[a]	Formula	Analyses	Recrystn solvent
1	CH_3	F	H	30	121–123	$C_{14}H_{10}FN$	C, H, N	MeCN
2	CHO	F	H	65	167–168	$C_{14}H_8FNO$	C, H, N	MeCN
3	CH_3	Cl	H	50	123–124 (124–125)[b]	$C_{14}H_{10}ClN$		EtOH
4	CHO	Cl	H	60	170–171 (169)[c]	$C_{14}H_8ClNO$		PhH
5	CH_3	OCH_3	Cl	65	167–169 (169–170)[d]	$C_{15}H_{12}ClNO$		EtOH
6	CHO	OCH_3	Cl	40	183–185 (185–186)[d]	$C_{15}H_{10}ClNO_2$		PhH

[a] Numbers in parentheses are literature melting points. [b] A. Champbell, C. S. Franklin, E. N. Morgan, and D. J. Tivey, *J. Chem. Soc.*, 1145 (1958). [c] O. Tsuge, M. Nishinohara, and M. Tashiro, *Bull. Chem. Soc. Japan*, **36**, 1477 (1963); *Chem. Abstr.*, **60**, 5455 (1964). [d] T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 583 (1949).

(1) We gratefully acknowledge the support of this investigation by the U. S. Army Medical Research and Development Command under Contract No. DADA17-68-C-8035. This is Contribution No. 592 from the Army Research Program on Malaria.

(2) E. D. Bergmann, M. Rabinovitz, and A. Bromberg, *Tetrahedron*, **24**, 1289 (1968).

(3) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(4) E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **26**, 350 (1966).

(5) A. Albert, "The Acridines," 2nd ed, St. Martin's Press, New York, N. Y., 1966, p 50.