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Some 4-Oxa-farnesane Insect Juvenile Hormone Mimics†

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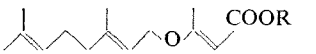
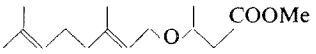
Synthesis of twentyone 4-oxa-farnesane derivatives with a variety of substituents at C_1 and C_{11} is described. Some of these compounds are more active than farnesyl methyl ether against *Dysdercus koenigii* nymphs.

Eversince the possibility,[1] that insect hormones may be harnessed to control their populations, came to be recognized, there has been intense activity in the area of synthesis of *Cecropia* juvenile hormones (JH) and their mimics.[2] Though, the question of structure-activity relationship in the area of JH mimics is very complex because of a large number of variables,[3] the compounds with optimum activity are, as a rule, based on farnesane skeleton. Oxa-analogues of these compounds can be synthesised more easily and economically and the present work was undertaken to assess the activity of such compounds.**

Of the various possible oxa-analogues with farnesane skeleton, the 4-oxa-series (I, III and their derivatives) appeared of special interest to us, since such compounds, should be easily accessible by simple reactions from readily available raw materials.



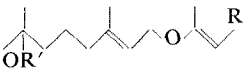
I: R=Et
II: R=Me



III

3,7,11-Trimethyl-4-oxa-2,6,10-dodecatrienoic acid and 3,7,11-trimethyl-4-oxa-6,10-dodecadienoic acid series

Compound I was easily prepared in over 70% yield by the mercuric acetate-catalyzed exchange reaction[9] between geraniol and ethyl 3-ethoxycrotonate.[10] In a similar manner and by employing 7-methoxy- or 7-ethoxy-geraniol, compounds II, IV～VII were prepared. 7-Methoxy- and 7-ethoxy-geraniol were readily prepared by solvomercuration-demercuration.[11]



IV: R=COOEt, R′=Me
V: R=COOEt, R′=Et
VI: R=COOMe, R′=Me
VII: R=COOMe, R′=Et

The structures of these compounds are fully borne out by their spectral characteristics (IR, NMR and Mass) which have been summarised in Table I. In each of these compounds, in the PMR spectrum, one can see only one signal for C_3-Me and C_2-H (Table I), indicating configurational homogeneity of Δ^2, as one would expect different chemical shifts for these signals for the E- and Z-isomers.[12,13] By a comparison of the chemical shift value for C_2-H (δ 4.85, Table I) with those calcu-

† Compounds with Insect Juvenile Hormone Activity. Part I.

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** Since the publication (1974) of the book by Slama, Romanuk and Sorm[2b] it has become known that a variety of oxa derivatives have been synthesised and Patent applications filed by Jarolim *et al.*[4] Recently papers by Jarolim and Sorm describing synthesis of some 5-oxa and 6-oxa analogues have also appeared.[5] Though, undoubtedly a few of the compounds described by us in the present communication must have been covered by these authors in their Patents, there is no description of any of these compounds in the corresponding entries in the *Chemical Abstracts*.[6,7] Compound I has been reported earlier.[8]

TABLE I. SPECTRAL CHARACTERISTICS OF 3,7,11-TRIMETHYL-4-OXA-2,6,10-DODECATRIENOIC ACID AND 3,7,11-TRIMETHYL-4- OXA-2,6-DODECADIENOIC ACID DERIVATIVES

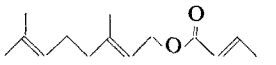
		PMR[a]							IR[c]		Mass[d]
Compound		C_{11}–Me's (s)	C_7–Me (s)	C_3–Me (s)	C_5–H_2 (d, J= 6 Hz)	C_{10}–H (t)[b]	C_6–H (t, J= 6 Hz)	C_2–H (s)	C=O	Vinyl ether	*m/e*
1	I	1.60 1.67	1.67	2.23	4.28	5.05	5.33	4.90	1700	1625, 1270, 1050	—
2	II	1.60 1.66	1.66	2.23	4.25	5.00	5.30	4.86	1700	1618, 1270, 1047	2.52 (6%, M^+), 69, 81, 137, 95, 145
3	IV	1.08 1.08	1.65	2.21	4.20	—	5.33	4.80	1698	1615, 1268, 1047	298 (1%, M^+), 81, 73, 137, 85, 131
4	V	1.16 1.16	1.70	2.23	4.23	—	5.36	4.85	1700	1618, 1270, 1050	—
5	VI	1.16 1.16	1.66	2.23	4.24	—	5.36	4.83	1702	1621, 1270, 1047	81, 73, 137, 85, 95
6	VII	1.11 1.12	1.67	2.23	4.26	—	5.36	4.83	1701	1618, 1270, 1047	81, 87, 59, 85, 137

[a] Chemical shifts in ppm; s (singlet), d (doublet), t (triplet), dd (double doublet), q (quartet); [0], not clear, overlapped by other signals; ?, assignment not clear. [b] ill-defined.
[c] Liquid film, values in cm^{-1}. [d] Five most abundant ions (decreasing abundance), besides molecular ion, if observed.

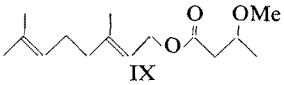
lated[13] for E- (δ 4.86) and Z-isomers (δ 4.44) it becomes obvious that in all these compounds Δ^2 is E-configurated.

3,7,11-Trimethyl-4-oxa-6,10-dodecadienoic acid and 3,7,11-trimethyl-4-oxa-6-dodecenoic acid series

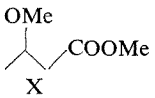
To obtain III, base-catalyzed addition of geraniol to methyl crotonate was investigated, such reactions having been reported earlier.[14] Of the various catalysts investigated (dry sodium methoxide, Triton B, KF) best results were obtained with a methanolic solution of sodium methoxide. Besides III, as expected, geranyl crotonate (VIII), IX and X are also formed as a result of ester exchange and competitive methanol addition. The required product (III) was easily separated as the parent acid XI after alkali hydrolysis of the mixture. By suitable reactions (*vide* EXPERIMENTAL) compounds XII ~ XIX were prepared from XI. The amides (XV ~ XIX) were specially synthesised as in the farnesane series, such compounds showed enhanced activity.[15]



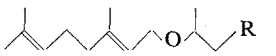
VIII



IX



X



XI: R=COOH
XII: R=CH_2OH
XIII: R=CH_2OAc
XIV: R=CH_2OMe
XV: R=CONHMe
XVI: R=CONHEt
XVII: R=CONHPr^i
XVIII: R=$CONMe_2$
XIX: R=$CONEt_2$

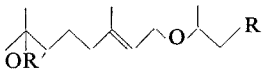
Likewise, starting with 7-methoxy- and 7-ethoxy-geraniol, compounds XX ~ XXIII were synthesised.

It is known that in the farnesane series JH activity is greatly enhanced by the presence of oxirane ring at C_{10}-C_{11}.[16] In view of this compounds XXIV, XXV were synthesised

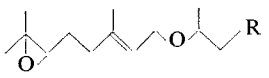
TABLE II. SPECTRAL CHARACTERISTICS OF 3,7,11-TRIMETHYL-4-OXA-6,10-DODECADIENOIC ACID AND 3,7,11-TRIMETHYL-4-OXA-6-DODECENOIC ACID DERIVATIVES[a)]

No.	Compound	PMR									Mass
		C_{11}–Me's (s)	C_7–Me (s)	C_8–Me (d, J= 6 Hz)	C_8–H (q, J= 6 Hz)	C_5–H_2 (d, J= 6 Hz)	C_{10}–H (t)	C_6–H (t, J= 6 Hz)	C_1–H_2 (t, J= 6 Hz)	C_2–H_2	m/e
1	III	1.63 1.66	1.66	1.15	3.63[b)]	3.89	5.11	5.29	—	2.36 (t, J=6Hz)	254 (M^+, 16%), 69, 136, 101, 95, 93
2	XII	1.61 1.68	1.68	1.15	3.60	3.95	5.11	5.30	3.60	—	226 (M^+, 15%), 69, 121, 81, 96, 123
3	XIII	1.63 1.68	1.68	1.15	3.50	3.91	5.11	5.30	4.12	—	268 (M^+, 50%), 136, 153, 55, 69, 123
4	XIV	1.60 1.66	1.66	1.11	3.51[b)]	3.85	5.10	5.26	3.38[b)]	—	—
5	XV	1.60 1.66	1.66	1.15	3.82	3.97	5.08	5.28	—	2.27 (dd, J=4Hz)	253 (M^+, 1%), 58, 73, 101, 69, 118
6	XVI	1.60 1.66	1.66	1.12	3.50[b)]	3.96	5.03	5.26	—	2.26 (dd, J=3Hz)	267 (M^+, 16%), 116, 132, 115, 133, 69
7	XVII	1.60 1.66	1.66	1.15	3.83[b)]	3.97	5.08	5.30	—	2.26 (dd, J=4Hz)	281 (M^+, 1%), 129, 69, 114, 86, 146
8	XVIII	1.60 1.65	1.68	1.15	3.82[b)]	3.96	5.08	5.27	—	?	267 (M^+, 4%), 115, 87, 72, 132, 100
9	XIX	1.60 1.63	1.67	1.15	3.82[b)]	3.95	5.08	5.26	—	?	295 (M^+, 4%), 143, 69, 72, 100, 115
10	XX	1.16 1.16	1.70	1.20	3.80[b)]	4.10	—	5.50	—	2.43 (t, J=6Hz)	73, 81, 97, 101, 136
11	XXI	1.10 1.10	1.70	1.10	3.70[b)]	3.90	—	5.25	3.37[b)]	—	—
12	XXII	1.10 1.10	1.66	1.10	3.83[b)]	3.96	—	5.26	—	2.26 (dd, J=3Hz)	299 (M^+, 0.5%), 73, 72, 87, 132, 115
13	XXIII	1.10 1.10	1.66	1.10	?	3.95	—	5.26	—	2.40 (t, J=6Hz)	—
14	XXIV	1.20 1.23	1.66	1.10	3.70[b)]	3.91	—	5.30	—	2.36[b)]	270 (M^+, 1%), 59, 101, 81, 85, 71
15	XXV	1.20 1.23	1.63	1.08	3.65[b)]	3.89	—	5.28	3.36[b)]	—	—

[a)] See footnotes to Table I.



XX: R=COOMe, R′=Me
XXI: R=CH_2OMe, R′=Me
XXII: R=CONHEt, R′=Me
XXIII: R=COOMe, R′=Et



XXIV: R=COOMe
XXV: R=CH_2OMe

from III and XIV respectively, by the bromohydrin route.[17] These compounds are expected to be diastereoisomeric mixtures.

Structures of all these compounds rest securely on their spectral characteristics (Table II) and elemental analysis. Purity of all the compounds was ascertained by GLC.

Juvenile hormone activity

JH activity of these compounds has been tested on last instar nymphs of red cotton bug, *Dysdercus koenigii* using 10 μg of each compound in acetone as a topical application and evaluating the results in terms of inhibition of metamorphosis. Farnesyl methyl ether was used as a reference compound. Summary

TABLE III. JUVENILE HORMONE ACTIVITY OF SOME 4-OXA-FARNESANE DERIVATIVES[a)]

	Compound	Score
1	Farnesyl methyl ether	2.0
2	I	2.5
3	III	2.7
4	IV	3.6
5	XII	1.4
6	XIII	1.6
7	XIV	2.3
8	XX	3.5
9	XXIV	3.3
10	XXV	3.1

a) Test insect: *Dysdercus koenigii*; dose, 10 μg/insect; mode of application, topical (acetone solution); score: normal adult (0), adult-nymph (1), intermediate (2), nymph-adult (3) and, sixth instar nymph (4).

of results with some of these compounds is given in Table III. A detailed report and discussion covering all the compounds will be published elsewhere.*

EXPERIMENTAL

All b.ps are uncorrected. IR spectra were recorded (as smears) with Perkin-Elmer Infracord, model 137E. PMR spectra were determined with a Varian A-60/T-60 spectrometer (in CCl_4 solution and using TMS as internal standard). CEC mass spectrometer, model 21-110B was employed for mass spectral data (at 70 eV, direct inlet system). Thin-layer chromatography (TLC) was carried out on 0.3 mm silica layers.

7-Methoxy-geraniol. To a solution of geraniol (4.77 g, 0.031 mole) in MeOH (45 ml) was added, with stirring and cooling (5~10°C) under N_2, a solution of freshly crystallized Hg $(OAc)_2$ (9.6 g, 0.03 mole) in MeOH (150 ml). After stirring for 30 min at 5~10°C, a solution of KOH (4.6 g) in MeOH (50 ml) was added, followed by addition of solid $NaBH_4$ (400 mg) in portions. The reaction mixture was stirred for another one hour, filtered, the filtrate concentrated to half the volume (under reduced pressure), diluted with water (70 ml) and extracted with ether (30×3 ml). The extract was washed with water, dried (Na_2SO_4) and freed of solvent. The product was chromatographed over silica gel (5 cm×32 cm) and eluted with 4% acetone in benzene to furnish, besides unchanged geraniol (1.0 g), 3.5 g of 7-methoxy-geraniol (bp 108~109°C/1 mm), followed by 0.4 g of 3,7-dimethoxygeraniol (bp 135~138°C/4 mm). NMR, δ ppm: 1.10 (6H, s, $\underline{CH_3}$–C(=O)–$\underline{CH_3}$), 1.66 (3H, d, J= 1.5 Hz, C=C–$\underline{CH_3}$), 3.10 (3H, s, $O\underline{CH_3}$), 4.03 (2H, d, J=7 Hz, C=CH–$\underline{CH_2}$–O), 5.36 (1H, t, J=7 Hz, C=$\underline{CH}$–CH_2–O). *Anal.* Found: C, 71.17; H, 12.39. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%.

7-Ethoxy-geraniol. This was prepared exactly as above, using EtOH in place of MeOH: bp 110~113°C/1.5 mm. NMR δ ppm: 1.10 (6H, s, $\underline{CH_3}$–C(=O)–$\underline{CH_3}$), 1.66 (3H, s, C=C–$\underline{CH_3}$), 4.03 (2H, d, J=7 Hz, C=CH–$\underline{CH_2}$–O), 5.36 (1H, t, J=7 Hz, C=$\underline{CH}$–CH_2–O). *Anal.* Found: C, 71.89; H, 11.54. Cacld. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08%.

Ethyl β-ethoxy-crotonate.[10] A mixture of ethyl acetoacetate (8.0 g), ethyl orthoformate (40 ml) and Amberlyst-15 (2 g) was shaken at 10~20°C (N_2) for 3 hr. The product was decanted from the resin, excess ethyl orthoformate distilled off and the residue distilled over $KHSO_4$ (300 mg): bp 117°C/50 mm, yield 90%.

Methyl β-ethoxy-crotonate was similarly prepared: bp 110~112°C/50 mm.

General procedure for exchange reaction with enol ethers of acetoacetic esters. β-Ethoxycrotonic ester (5.0 g), geraniol (or alkoxygeraniol) (1.0 g) and, Hg $(OAc)_2$ (30 mg) were mixed and heated at 70~75°C for 16~18 hr (N_2). The solution was filtered, the filtrate washed with aq. K_2CO_3 (20%) and, dried over K_2CO_3 (anhyd.). Excess of ethoxycrotonic ester was removed under reduced pressure at a bath temp. below 100°C. The residue was chromatographed over basic Al_2O_3 (1.5 cm×30 cm); light petroleum-benzene (1:1) eluates furnished the required product. The separation was monitored by TLC (solvent: 5% acetone in benzene). The compounds were thermally labile and hence were not distilled.

General procedure for the addition of geraniol and its alkoxy derivatives to methyl crotonate. The procedure is illustrated for condensation of geraniol: To a solution of MeONa in MeOH (from 600 mg of Na and 12 ml MeOH) were added geraniol (20.0 g, 0.13 mole) dissolved in dry ether (200 ml) and a solution of methyl crotonate (37.0 g, 0.37 mole) in dry ether (200 ml). The addition was done rapidly and without external cooling. The reaction mixture was refluxed (N_2) for 15~17 hr, cooled, washed with 10% aq. AcOH, water and dried (Na_2SO_4). Ether and excess methyl crotonate were removed and the residue

* Bioassay was carried out by the Entomological group at Bhabha Atomic Research Centre (Bio-organic Division), Bombay and, the full report will be published in collaboration with this group. Authors are grateful to Dr. M. S. Chadha for this help.

TABLE IV. ELEMENTAL ANALYSIS OF COMPOUNDS RECORDED IN TABLE II

Compound	Mol. formula	bp (°C/mm)	Analysis Found (%) C	Found (%) H	Calcd. (%) C	Calcd. (%) H
III	$C_{15}H_{26}O_3$	118~120°C/1	70.78	10.40	70.83	10.30
XII	$C_{14}H_{28}O_3$	135~140°C/2.5	73.59	10.54	74.29	11.58
XIII	$C_{16}H_{28}O_3$	130~133°C/2.5	71.78	10.66	71.60	10.52
XIV	$C_{15}H_{28}O_2$	125~126°C/1	74.28	12.21	74.95	11.74
XV	$C_{15}H_{27}O_2N$	160~170°C/1[a]	70.54	10.94	71.10	10.74
XVI	$C_{16}H_{29}O_2N$	160~170°C/1[a]	72.12	11.18	71.87	10.93
XVII	$C_{17}H_{31}O_2N$	160~170°C/1[a]	72.90	10.94	72.55	11.10
XVIII	$C_{16}H_{29}O_2N$	160~170°C/1[a]	72.35	11.29	71.87	10.93
XIX	$C_{18}H_{33}O_2N$	160~170°C/1[a]	72.71	11.37	73.17	11.26
XX	$C_{16}H_{30}O_4$	150°C/1[a]	66.87	11.23	67.10	10.56
XXI	$C_{16}H_{32}O_3$	127~130°C/2	69.77	12.07	70.54	11.85
XXII	$C_{17}H_{33}O_3N$	160~170°C/1[a]	68.25	10.55	68.19	11.11
XXIII	$C_{17}H_{32}O_4$	160~163°C/4	68.23	10.73	67.96	10.74
XXIV	$C_{15}H_{28}O_4$	148~149°C/1	65.97	9.23	66.64	9.69
XXV	$C_{15}H_{28}O_3$	133~135°C/1	70.31	11.32	70.27	11.01

[a] Bath temperature.

(30.0 g) chromatographed over silica gel (8 cm×32 cm) with TLC monitoring (solvent: 5% acetone in benzene):

Frac. 1	50% light petrol in benzene	300 ml×7	3.8 g	geranyl crotonate
Frac. 2	〃	300 ml×12	20.0 g	mixture containing III
Frac. 3	2% acetone in benzene	300 ml×6	6.0 g	geraniol

Fraction 1 (bp 120~123°C/3 mm) from its spectral data was identified as *geranyl crotonate* (VIII). IR $\nu_{max}^{liq.}$ cm^{-1}: 1710 (C=O), 1650 (C=C). NMR, δ ppm: 1.58, 1.70, 1.71 (each 3H, all singlets, C=C-CH_3), 1.90 (3H, dd, J=7 Hz, C=CH-CH_3), 4.53 (2H, d, J=7 Hz, C=CH-CH_2-O), 5.03 (1H, broad triplet, C=CH-CH_2), 5.30 (1H, t, J=7 Hz, C=CH-CH_2-O), 5.71 (1H, dq, J=15 Hz, CH_3-CH=CH-COO), 6.87 (1H, dq, J=2 Hz, CH_3CH=CH-COO). *Anal.* Found: C, 75.26; H, 10.11. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

Fraction 2 was fractionally distilled to furnish: (i) methyl 3-methoxybutyrate (X),[18] bp 85~90°C/10 mm, 7.0 g; (ii) mixture of III and geranyl 3-methoxybutyrate (IX), bp 125~130°C/2 mm, yield 13 g. Fraction (ii) (27 g) was hydrolysed with 3% methanolic KOH (270 ml, 3 hr) at reflux and the acids fractionated to give 3-methoxy-butyric acid[19] (bp 80~85°C/1 mm, 2.44 g) and 3,7,11-trimethyl-4-oxa-6,10-dodecadienoic acid (XI; bp 150~153°C/1 mm, 8.40 g). The latter acid was esterified (CH_2N_2 in ether) to give required compound III (Tables II and IV).

In subsequent experiments the total reaction product from Michael addition was hydrolyzed and worked up to give XI.

Preparation of derivatives. The various derivatives of III, XX were prepared by standard procedures: alcohol XII (LAH reduction of III), acetate XIII (acetic anhydride-pyridine method), ethers XIV, XXI (NaH-DMSO-CH_3I method), amides XV-XIX, XXII (acid chloride-amine method),[20] epoxides XXIV, XXV (bromohydrin route).[17] The relevant spectral and analytical data for these compounds are listed in Tables II and IV.

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