Arch Pharm Res Vol 22, No 5, 502-506, 1999 Medicinal Chemistry

Juvenile Hormone Analogs Active on Mosquitoes: Synthesis and Juvenile Hormonal Activity of Newly Synthesized Long Chain Alkoxy Alkyl Phenyl Ethers

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(Received Jaunary 20, 1999)

Different 2-(8,12 dimethyl-5-oxa-7(E), 11-tridecadienyl)-alkyl phenyl ethers, their mono oxirane and thirane derivatives were synthesized and tested on *Culex pipiens quinquefasciatus* Say for their juvenile hormone activity.

Key words : *Culex pipiens quinquefasciatus Say, 2-(8,12-Dimethyl-5-oxa-7(E),11-tridecadienyl) -alkyl phenyl ether, Juvenile hormone activity*

INTRODUCTION

The biological profile of natural products and their synthetic analogues served to formulate the early ideas about possible relationship between chemical structure and biological activity. This provided a guiding principle for designing compounds with hopefully more potent, more specific and less toxic character. As bioanalogues of insect juvenile hormone, several alkoxyalkyl phenyl ethers with various number of carbon atoms in the alkoxy alkyl chain and various substituents in the para position of the phenyl residue (Jarolim *et al.*, 1976) have been synthesized. Aromatic ethers with more than one etheric oxygen atom also showed activity in Tenebrio and few other insects. Certain geraniol based diethers (Phadnis *et al.*,1987; Phadnis *et al.*,1988; Powar *et al.*,1995) reportedly have been found to possess activity against mosquitoes.

Such findings prompted us to design and synthesize similar type of compounds as well as their derivatives and test their juvenile hormone activity against mosquitoes.

MATERIALS AND METHODS

Progress of all the reactions was monitored by TLC using silica gel impregnated with 13% calcium sulfate. Silica gel (100-200 mesh) was used for column chromatography. PMR spectra (in $CC1_4$) were obtained on Varian 90 MHz spectrometer using TMS as internal standard (chemical shift expressed in d ppm and J values in Hz). IR spectra (neat, n_{max}. in cm^{-1}) were run on Perkin-Elmer 1430 spectrometer. Unless otherwise stated, all organic extracts were dried over anhydrous sodium sulfate.

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8, 12-Dimethyl-5-oxa-7 (*E*), 11-tridecadien-2-ol (2)

To the suspension of lithium aluminium hydride (1.52 g, 40 mmol) in dry ether (50 ml), solution of 8,12-dimethyl-5-oxa-7(E), 11-tridecadiene-2-one (**1**) (11.20 g, 50 mmol) in dry ether (50 ml) was added drop wise at 0°C and the mixture was stirred for 12 h at room temperature. To the reaction mixture was added water (1.5 ml) drop wise followed by 15% sodium hydroxide (1.5 ml) and water (4.5 ml) at 0°C. The precipitated solid was filtered off and washed with ether (2 × 20 ml). Solvent was evaporated to yield 9.62 g (85.3%) of pure alcohol (**2**). IR, 3400, 2920, 1670, 910, 830 and 790 cm^{-1}; PMR ($CC1_4$) δ 5.0-5.5 (2H, m, olefinic protons), 4.0 (3H, d, J=8Hz,-C=C-CH_2O,-CH-O), 3.55 (2H, t, J= 12Hz, -CH_2-O-), 3.2 (1 H, -OH, D_2O exchangeable), 2.1 (4H, allylic methylenes), 1.7 (11H, allylic methyls, saturated methylene), 1.18 (3H, saturated methyl).

2-(8,12-Dimethyl-5-oxa-7(*E*),11-tridecadienyl)-*p*-toluene sulfonate (3)

To a mixture of alcohol **2** (2.25 g, 10 mmol) and dry pyridine (1.60 g, 20 mmol) at -5°C was added *p*-toluene sulfonyl chloride (2.10 g, 11 mmol) in one portion. The suspension was stirred at same temperature for 4 h. and then left at 0°C for 12 h. The reaction mixture was then poured on crushed ice and extracted with ether. The organic extract was washed with ice cold dilute sulfuric

acid (2 × 10 ml), water, saturated sodium hydrogen carbonate solution (3 × 10 ml) and dried. Removal of solvent at reduced pressure afforded TLC pure tosylate **3** (92.9%); IR, 2920, 1680, 1600, 910, 820, 760 and 670 cm^{-1}., PMR (CCl_4) δ 7.8 (2H, d, J=8 Hz, aromatic protons), 7.3 (2H, d, J=10 Hz, aromatic protons), 5.0-5.4 (2H, m, olefinic protons), 4.8(1H, m,. -CH-O-SO_2), 3.8 (2H, d, J=8Hz, -C=C-CH_2-O-), 3.3 (2H, t, J=12 Hz,-CH_2-O-), 2.5 (3H, s, benzylic methyl), 2.1 (4H, s, allylic methylenes), 1.68 (11H, allylic methyls, saturated methylene), 1.23 (3H, saturated methyl).

2-(8,12-Dimethyl-5-oxa-7 (*E*), 11-tridecadienyl)-*p*-ethyl phenyl ether (4)

To the suspension of sodium hydride (0.48 g, 20 mmol, 50% dispersion) in DMSO (5 ml) was added a solution of 4-ethylphenol (1.22 g, 10 mmol) in DMSO (5 ml) and the mixture was stirred at room temperature for 1 h. To the resulting mixture compound **3** (3.79 g, 10 mmol) in DMSO (5 ml) was added dropwise. After stirring for 15 h, the reaction mixture was poured into cold water and extracted with ethyl acetate (4 × 20 ml). The extract was washed with water (2 × 10 ml), 10% sodium hydroxide (4 × 10 ml), water and dried. The removal of solvent followed by purification by column chromatography over silica gel using pet. ether: ether (9:1) as eluent afforded 1.98 g, (60.2%) of **4** as colourless liquid; [R_f=0.45 in pet. ether : ether (9:1)]; IR, 2940, 1670, 1620, 930 and 830 cm^{-1}; PMR (CCl_4) d 6.6-7.0 (4 H, aromatic protons), 5.0-5.4 (2H, m, olefinic protons), 4.3-4.6 (1H, q, J=18 Hz, -CH-O-), 3.9 (2H, d, J=8Hz, C=C-CH_2-O-), 3.5 (2H, t, J=12Hz,-O-CH_2-), 2.5-2.8(2H,q, J=22Hz,-O-Ph-CH_2-), 2.0 (4H, s, allylic methylenes), 1.68(11H, allylic methyls, saturated methylene), 1.23 (6H, saturated methyl, -O-Ph-CH_2CH_3). (Found : C, 79.83%; H, 10.24%. calculated for $C_{22}H_{34}O_2$:C, 79.94%; H, 10.37%).

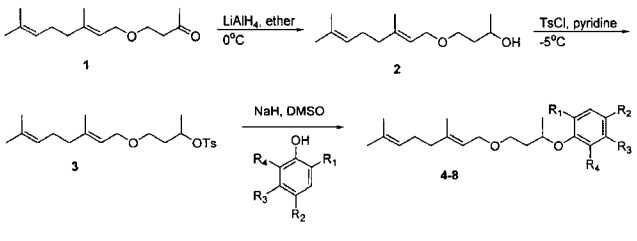
Compounds **5-8** were prepared in the similar way as described for **4** by the reaction of tosylate (3.79 g) with 2-isopropylphenol (1.36 g)/2-methylphenol (1.08 g)/2,6-dimethylphenol (1.22 g)/2,5-dimethylphenol (1.22 g) respectively in the presence of sodium hydride as a base in DMSO. Spectral data of compounds **5-8** are given in Table I.

2- (8,12-Dimethyl-5-oxa-11,12-epoxy-7(*E*)-tridecenyl)-*p*-ethyl phenyl ether (9a)

To the ice cold solution of ether **4** (0.33 g, 1 mmol) in dry methylene chloride (10 ml) was added dropwise solution of *m*-chloroperoxybenzoic acid (0.19 g, 1.1 mmol) in dry methylene chloride (5 ml). The reaction mixture was stirred for 45 min at 0°C and 30 min at room temperature. The resulting solution was decomposed with water, extracted with methylene chloride (3 × 15 ml) washed with 5% sodium hydrogen carbonate solution (25 ml), brine and dried. Evaporation of solvent followed by column chroma-tography over neutral alumina using pet. ether as eluent gave 0.30 g (87%) of **9a** as pale yellow liquid; [Rf=0.62 in pet ether: ethyl acetate (8:2)]; IR, 2940, 1680, 1620, 880, 830, and 680 cm^{-1}; PMR (CCl_4) d 6.63-7.1 (4H, aromatic protons), 5.3 (1H, t, J=12 Hz, olefinic proton), 4.33-4.65 (1H, q, J=18Hz, -CH-O), 3.9 (2H, d, J=8Hz, -C=C-CH_2-O), 3.5 (2H, t, J=12Hz, -CH_2-O-), 2.6 (3H,-OCH of oxirane ring, -O-Ph-CH_2), 1.66-2.20 (9H, allylic methyl, saturated methylenes, allylic methylene) 1.26 (12H, saturated methyls, -O-Ph-CH_2Ch_3). (Found: C, 76.15%; H,9.77% calculated for $C_{22}H_{34}O_3$:C, 76.25%; H, 9.89%). In the similar way, compounds **9b-9e** were prepared from compounds **5-8**. Their spectral data are summarized in Table I.

2-(8,12-Dimethyl-5-oxa-11,12-epithio-7 (*E*) tridecenyl)-*p*-ethyl phenyl ether (10a)

Compound **9a** (0.35 g, 1 mmol) was stirred with potassium thiocyanate (0.10 g, 1 mmol), water (0.01 g, 0.55 mmol) and ethanol (5 ml) at room temperature for 24 h. The reaction mixture was filtered and the residue was concentrated, diluted with ether (20 ml) to precipitate the remaining potassium oxycyanate, filtered and the solvent was evaporated to give 0.29 g (79.1%) of 10a; [R_f=0.70 in pet. ether: ethyl acetate (4:1)], IR, 2940, 1670, 1610, 920 and 830 cm^{-1}, PMR (CCl_4) δ 6.7-7.1 (4H, aromatic protons), 5.3 (1H, olefinic proton), 4.4-4.7 (1H, -CH-O-), 3.9 (2H, d , J= 6 Hz, -C=C-CH_2-O-), 3.4-3.7 (2H,-CH_2-O-), 2.45-2.70 (2H, q, J=16Hz, -O-Ph-CH_2-), 1.6-2.3 (10H, allylic methyl, allylic methylene, -SCH-, saturated methylenes), 1.3 (12H, saturated methyls, -O-Ph-CH_2CH_3). (Found: C, 72.69%; H, 9.33%; S, 8.67%.



	R_1	R_2	R_3	R_4	Compound
4	H	C_2H_5	H	H	9a, 10a
5	$CH(CH_3)_2$	H	H	H	9b, 10b
6	CH_3	H	H	H	9c, 10c
7	CH_3	H	H	CH_3	9d, 10d
8	CH_3	H	CH_3	H	9e, 10e

Scheme. 1. Synthetic scheme for alkoxyalkyl phenyl ethers

Table I. Spectral data of synthesized compounds

Compound No.	% Yield	IR	PMR (CCl_4) δ values
5	64	2940, 1680, 1600, 930, 790, 750	6.8-7.3 (4H, m, aromatic protons), 5.1-5.45 (2H, m, olefinic protons), 4.5-4.8 (1H, q, J=18 Hz, -CH-O-), 3.93 (2H, d, J=8Hz, -C=C-CH_2-O-), 3.1-3.65 (3H, -CH_2O-, $CH(CH_3)_2$), 2.1 (4H, s, allylic methylenes), 1.68 (11H, allylic methyls, saturated methylene), 1.3 (9H, -$CH(CH_3)_2$, saturated methyl)
6	63	2900, 1670, 1590, 920, 780, 740	6.6-7.2 (4H, aromatic protons), 5.0-5.4 (2H, m, olefinic protons), 4.4-4.7 (1H, q, J=18 Hz, -CH-O-), 3.9 (2H, d, J=8Hz, -C=C-CH_2-O), 3.5 (2H, t, J=12Hz, -CH_2-O-), 2.0-2.2 (7H, allylic methylenes, benzylic methyl), 1.68 (11H, allylic methyls, saturated methylene), 1.33 (3H, saturated methyl)
7	60	2900, 1670, 1590, 900, 820, 760	6.76 (3H, s, aromatic protons), 5.0-5.35 (2H, m, olefinic protons), 4.1-4.4 (1H, q, J=18Hz, -CH-O-), 3.87 (2H, d, J=8Hz, -C=C-CH_2O-), 3.5 (2H, -CH_2-O-), 2.0-2.2 (10H, allylic methylenes, benzylic methyls), 1.68 (11H, allylic methyls, saturated methylene), 1.18 (3H, saturated methyl)
8	61	2900, 1670, 1610, 790	6.9 (1H, aromatic proton), 6.57(2H, aromatic protons), 5.0-5.4 (2H, m, olefinic protons) 4.35-4.7 (1H, q, J=18Hz, -CH-O-), 3.9 (2H, d, J=8Hz, -C=C-CH_2O), 3.5 (2H, t, J=12Hz, -CH_2O-), 1.9-2.23 (10H, m, allylic methylenes, benzylic methyls), 1.6 (11H, allylic methyls, saturated methylene), 1.23 (3H, saturated methyl)
9 b	82	2920, 1680, 930, 880, 750, 680	6.7-7.15 (4H, m, aromatic protons), 5.25 (1H, t, J=12 Hz, olefinic proton), 4.3-4.7 (1H, m, -CH-O-), 3.8 (2H, d, J=8Hz, -C=C-CH_2-O-), 3.0-3.6 (3H, -CH_2O-, $CH(CH_3)_2$), 2.5 (1H, t, J=12Hz, OCH of oxirane ring), 1.9-2.1 (2H allylic methylene), 1.6(7H, s, allylic methyl, saturated methylenes), 1.2 (15H, saturated methyls -CH-$(CH_3)_2$)
9 c	79	2900, 1660, 920, 860, 740, 670	6.7-7.2 (4H, m, aromatic protons), 5.3 (1H, t, J=14 Hz, olefinic proton), 4.4-4.73 (1H, q, J=18z -CH-O-), 3.9(2H, d, J=8Hz, -C=C-CH_2-O-), 3.5 (2H, t, J=12 Hz, -CH_2O-), 2.56(1H, t, J=12Hz, OCH of oxirane ring), 2.2 (5H,s, benzylic methyl allylic methylene), 1.68 (7H, s, allylic methyl, saturated methylenes), 1.3 (9H, saturated methyls).
9 d	84	2900, 1670, 1590, 900, 870, 760, 670	6.9 (3H, s, aromatic protons), 5.35 (1H, t, J=12Hz, olefinic proton), 4.1-4.47 (1H, q, J=18Hz -CH-O-), 3.9 (2H, d, J=8Hz, -C=C-CH_2-O-), 3.53 (2H, t, J=12Hz, -CH_2O-), 2.56 (1H, t, J=12Hz, OCH of oxirane ring), 2.26 (8H, s, benzylicmethyls, allylic methylene), 1.68 (7H, s, allylic methyl, saturated methylene), 1.2 (9H, saturated methyls).
9 e	80	2900, 1660, 1600, 890, 790, 670	6.9 (1H, aromatic proton), 6.5 (2H, aromatic protons), 5.3(1H, t, J=12Hz olefinic proton), 4.35-4.7 (1H, q, J=18Hz -CH-O-), 3.9 (2H, d, J=8Hz, -C=C-CH_2-O-), 3.5 (2H, t, J=12 Hz, -CH_2O-), 2.56 (1H, t, J=12Hz, OCH of oxirane ring), 2.1-2.3 (8H, m, benzylic methyl, allylic methylene), 1.68 (7H, s, allylic methyl, saturated methylenes), 1.3(9H, saturated methyls).
10 d	79	2940, 1680, 1120-1090, 870, 770	6.9 (3H, s, aromatic protons), 5.3 (1H, olefinic proton), 4.1-4.4 (1H, -CH-O-), 3.9(2H, d, J= 6Hz, -C=C-CH_2-O-), 3.4-3.7 (2H, -CH_2-O-) 2.1-2.5 (9H, benzylic methyls, allylic methylene, -SCH-), 1.6(7H, s, allylic methyl, saturated methylene), 1.23 (9H, saturated methyls).
10 e	78	2940, 1670, 1020, 810	6.8(1H, aromatic proton), 6.5 (2H, aromatic protons), 5.25 (1H, olefinic proton), 4.3-4.6 (1H, q, J=12Hz, -CH-O-), 3.85 (2H, d, J=6Hz -C=C-CH_2O-). 3.4 (2H, t, J=10Hz, -CH_2-O-), 1.95-2.3 (9H, benzylic methyls, allylic methylene, -SCH-), 1.6 (7H, allylic methyl, saturated methylenes), 1.2 (9H, saturated methyls)

Table II. Juvenile hormone activity of synthesized compounds

Compound No.	Dose in ppm	Different stages (Grades)**				Activity Index
		0	1	2	3	
4	10	0	0	28	72	2.72
	5	0	0	54	46	2.46
5	10	0	0	29	71	2.71
	5	0	16	51	33	2.17
6	10	0	0	39	61	2.61
	5	0	18	40	42	2.24
7	10	0	0	2	98	2.98
	5	0	2	18	80	2.78
8	10	0	0	31	69	2.69
	5	0	5	50	45	2.40
9a	10	0	0	38	62	2.62
	5	0	0	53	47	2.47
9b	10	0	0	14	86	2.86
	5	0	0	37	63	2.63
9c	10	0	0	23	77	2.77
	5	0	1	43	56	2.55
9d	10	0	0	3	97	2.97
	5	0	0	22	78	2.78
9e	10	0	0	11	89	2.89
	5	0	0	24	76	2.76
10a	10	0	0	31	69	2.69
	5	0	0	49	51	2.51
10b	10	0	0	18	82	2.82
	5	0	0	29	71	2.71
10c	10	0	0	18	82	2.82
	5	0	0	29	71	2.71
10d	10	0	0	5	95	2.95
	5	0	0	26	74	2.74
10e	10	0	0	8	92	2.92
	5	0	0	19	81	2.81
Methoprene	5	0	0	0	100	3.00

calculated for $C_{22}H_{34}O_2S$: C, 72.88%; H, 9.45%; S, 8.84 %). Similarly epoxides **9b-9e** on treatment with potassium thiocyanate in ethanol gave mono thirane derivatives **10b-10e** respectively in good yield. The spectral data of **10b-10e** are given in Table I.

Juvenile hormone activity

All the synthesized compounds were screened for their Juvenile hormonal activity against mosquitoes (Busvine *et al* 1976). The fourth instar larvae of mosquitoes were reared in different doses of the compound for overnight. Their mortality at larval, pupal and adult stages was noted. To find out the activity index, different grades** were given to deaths at each stage. The larvae which died at larval stage only i.e. failed to moult to pupae was rated as three. The larvae which succeeded in moulting into a pupa but failed to emerge as an adult, was rated as two and the pupa which did emerge into adult but failed to survive, was rated as one. The larvae which successfully reached the adult stage and survived for one day, was rated as zero. The activity index was determined by multiplying the number of larvae at one stage by its numerical value and dividing it by the total number of larvae taken into account. All the experi-ments were repeated six times to take out the mean mortality at each stage.

RESULTS AND DISCUSSION

The synthesis of diethers *4-8* are outlined in Scheme 1.

Lithium aluminium hydride reduction of 8, 12-dimethyl-5-oxa-7(E), 11-tridecadien-2-one (**1**) (prepared from geraniol and methyl vinyl ketone in the presence of mercuric oxide as catalyst) in dry ether at 0°C gave pure alcohol **2**, which was further converted to tosylate **3** on treatment with *p*-toluene sulfonyl chloride (Tipson *et al.*, 1944) in the presence of pyridine at -5°C. Alkylation (Phadnis *et al.*, 1988) of 4-ethylphenol / 2-isopropylphenol / 2-methylphenol /2,6-dimethylphenol / 2,5-dimethylphenol with tosylate **3** in the presence of sodium hydride in dry DMSO afforded pure ethers **4-8** after column chromatographic purification using pet. ether as eluent. Reaction of parent diethers **4-8** with *m*-chloroperoxybenzoic acid (Fieser *et al.*, 1967) yielded the corresponding epoxides **9a-9e** in 79-87% yields. Monooxirane derivatives **9a-9e** were further converted to monothirane derivatives **10a-10e** upon reacting with potassium thiocyanate (Bouda *et al.*, 1987). The structures of compounds **4-10e** were confirmed by their spectral and analytical analysis. Entomological studies of compounds **4-10e** along with commercially available JHA-methoprene (M) have been reported in Table II.

It has been found that administration of these compounds to the fourth instar larvae killed them at larval or pupal stages, when tested at 5 ppm and 10 ppm concentrations. The unique characteristic of these compounds was their larvicidal activity, although methoprene was a more effective JH mimic. It has been found that thiranes **10a-10e** and oxiranes **9a-9e** are more potent as compared to the parent diethers **4-8**. These compounds can be further tested against anopholes stophensi and aedes aegypti which are medically important mosquito species.

ACKNOWLEDGEMENTS

The authors express their sincere gratitude to Council of Scientific and Technology, DST, UT Chandigarh for the award of fellowship to one of us (RK).

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