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Products Active on Mosquitoes, IV [1]: Synthesis and Biological Activity of 8-Propargyloxy-3,7-dimethyl-2,6-octadienyl/6-octenyl Ethers [2]

Anil P. Phadnis, Bharati Sinha, Bhagbat Nanda, Sarita A. Patwardhan*, J. Venkatesh Rao, and **Ravindra N. Sharma**

National Chemical Laboratory, Pune 411 008, India

Summary. A series of 8-propargyloxy-3,7-dimethyl-2,6-octadienyl and 8-propargyloxy-3,7-dimethyl-6-octenyl ethers were prepared from 8-hydroxygeranyl and 8-hydroxycitronellyl ethers, respectively. Almost all compounds showed high toxicity to *Culex quinquefaciatus* larvae at 1 $mg\,l^{-1}$ dose level.

Keywords. Culex quinquefaciatus; Larval toxicity; 8-Propargyloxy-3,7-dimethyl-2,6-octadienyl/6-octenyl ethers.

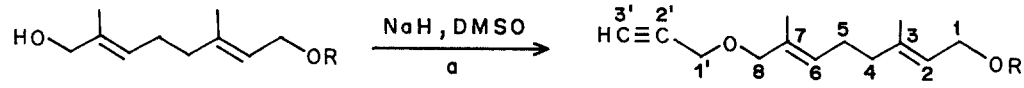
Gegen Mücken aktive Produkte, 4. Mitt. [1]: Synthese und biologische Aktivität von 8-Propargyloxy-3,7-dimethyl-2,6-octadienyl/6-octenyl-ethern [2]

Zusammenfassung. Eine Reihe von 8-Propargyloxy-3,7-dimethyl-2,6-octadienyl- und 8-propargyloxy-3,7-dimethyl-6-octenyl-ethern wurden aus 8-Hydroxygeranyl- bzw. 8-Hydroxycitronellyl-ethern hergestellt. Fast alle Verbindungen zeigten hoch Toxizität gegenüber Larven von *Culex quinquefaciatus* in einer Dosierung von 1 $mg\,l^{-1}$.

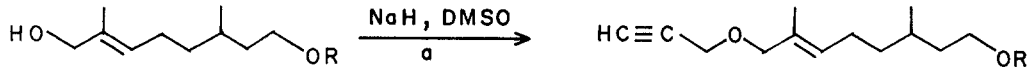
Introduction

Presence of heteroatoms such as oxygen or nitrogen in terpene molecules is known to enhance its juvenile hormonal (JH) activity, inhibiting the metamorphosis and development of insects. Compounds structurally related to natural insect hormones with ether function in the molecule also possess JH activity [3].

In continuing our work on the synthesis of JH mimics active on mosquitoes we have synthesized 3,7-dimethyl-2,6-octadienes with ether functions at C-1 and C-8 positions [4]. These compounds exhibited JH and higher order of developmental inhibition activity in mosquitoes [4]. Here we report the synthesis of some 3,7-dimethyl-2,6-octadienyl (**I**) and 3,7-dimethyl-6-octenyl (**II**) ethers with a propargyloxy group at C-8 position. Compounds from series **I** and **II** exhibited fairly high insect growth regulatory activity resulting in overall target population mortality in *Culex quinquefaciatus*.



III Ia – Ii



IV IIa – IIf

a : Propargyl bromide

Experimental

IR spectra, as smears, were recorded on a Perkin-Elmer 588B infrared spectrophotometer and ^{1}H NMR spectra on a Varian T-60 spectrometer using CCl_4 as a solvent and *TMS* as internal standard. Mass spectra were recorded on a CEC-2-110B Mass spectrometer at 70 eV using direct inlet.

8-Propargyloxy-3,7-dimethyl-2,6-octadienyl ethers (**Ia–Ii**) were prepared by alkylation, with propargyl bromide, of the corresponding 8-hydroxy-3,7-dimethyl-2,6-octadienyl ether (**III**) which was obtained from the respective geranyl ether on oxidation with selenium dioxide [4]. Similarly, 8-propargyloxy-3,7-dimethyl-6-octenyl ethers (**IIa–IIf**) were synthesized from the respective 8-hydroxy-3,7-dimethyl-6-octenyl ether (**IV**) which in turn was prepared from the corresponding citronellyl ether [5].

8-Propargyloxy-3,7-dimethyl-2,6-octadienyl (4-ethyl) phenyl ether (**Ig**)

To a solution of NaH (55% suspension in oil, 0.1 g) in *DMSO* (6 ml), **IVg** (0.5 g) in *DMSO* (8 ml) was added with stirring under nitrogen, stirred for 1 h and the solution of propargyl bromide (0.2 g) in *DMSO* (5 ml) was gradually added and stirred overnight. The resulting mixture was poured into cold water and extracted with ether. The ether extract was washed with water, brine and dried over anhyd. Na_2SO_4. The residue obtained after removal of solvent was purified by chromatography over column grade silica gel.

Compounds **Ia–If**, **Ih**, **Ii**, and **IIa–IIf** were similarly prepared.

The preliminary assessment of bioactivity of these compounds was undertaken using IVth instar larvae of *Culex quinquefaciatus*. Concentrations of 3.2 and 1 mg l^{-1} were used as preliminary test doses. The IVth instar larvae were exposed to 50 ml water containing the test compound and mortality after 24–72 h and morphological aberrations, if any, in the surviving pupae or emergent adults, were recorded.

Results and Discussion

The structures of compounds **Ia–Ii** and **IIa–IIf** were mainly confirmed by ^{1}H NMR and mass spectra. In ^{1}H NMR spectra the C-1 methylene protons show a doublet at δ 3.86–4.45 in compounds belonging to series **I** and a triplet at δ 3.3–4 for **II**. When *R* is a phenyl moiety the C-1 methylene signal appears to be shifted upfield (Tables 1 and 2). A sharp singlet at δ 3.6–4.05 is observed due to the C-8 methylene

Table 1. Characteristics of compounds **Ia–Ii**

Compound	*R*	Yield (%)	b. p. (°C[a]/0.3–0.5 mm Hg)	^{1}H NMR data (δ)[b]						
				C_3-*Me* C_7-*Me*	C_1-H_2 (d, $J=6$)	C_2-H C_6-H (br)	C_8-H_2 (s)	$C_{1'}$-H_2 (d, $J=2$)	$C_{3'}$-H (t, $J=3$)	
Ia	CH_3-	38	150–160	1.6	3.81	5.3	3.86	4.0	2.3	—OCH_3 3.23 (s)
Ib	C_2H_5-	25	140–150	1.65	3.86	5.3	3.86	4.01	2.23	—OCH_2 —OCH_2CH_3 3.36 (q, $J=7$); 1.16 (t, $J=7$)
Ic	$C_6H_5CH_2$-	27	180–190	1.6	3.9	5.4	4.05	4.0	2.2	Benzylic CH_2, 4.4 (s)
Id	4-$CH_3C_6H_4CH_2$-	30	180–190	1.63	3.86	5.26	3.8	3.9	2.2	Benzylic CH_2, 4.33 (s)
Ie	C_6H_5-	22	180–190	1.63 1.73	4.43	5.4	3.83	3.95	2.1	
If	4-$CH_3C_6H_4$-	35	185–190	1.63 1.7	4.33	5.3	3.8	4.0	2.2	
Ig	4-$C_2H_5C_6H_4$-	37	208–210	1.61 1.71	4.5	5.46	3.9	4.01	2.25	
Ih	4-$(CH_3)_2CHC_6H_4$-	20	210–215	1.63 1.73	4.45	5.4	3.86	3.98	2.23	
Ii	4-ClC_6H_4-	44	190–195	1.56 1.66	4.36	5.3	3.73	3.91	2.18	

[a] Bath temperature
[b] J in Hz

Table 2. Characteristics of compounds **II a–II f**

Compound	*R*	Yield (%)	b. p. (°C[a]/0.3–0.5 mm Hg)	^{1}H NMR data (δ)[b]							
				C_3-*Me* (d, $J = 6$)	C_6-*Me* (s)	C_1-H_2 (t, $J = 6$)	C_6-H (t, $J = 6$)	C_8-H_2 (s)	$C_{1'}$-H_2 (d, $J = 2$)	$C_{3'}$-H (t, $J = 2$)	
II a	CH_3-	45	120–125	0.91	1.63	3.3	5.33	3.83	4.0	2.25	—OCH_3, 3.26 (s)
II b	C_2H_5-	41	135–140	0.96	1.63	3.33	5.33	3.85	4.0	2.23	—OCH_2CH_3, 3.3 (m) —OCH_2CH_3, 1.16 (t, $J = 6$)
II c	$C_6H_5CH_2$-	27	188–190	0.9	1.6	3.4	5.3	3.8	4.0	2.2	Benzylic CH_2, 4.4 (s)
II d	C_6H_5-	39	165–170	0.98	1.63	3.93	5.36	3.83	3.95	2.23	–
II e	4-$CH_3C_6H_4$-	30	180–185	0.83	1.4	3.66	5.16	3.6	3.76	1.83	–
II f	4-ClC_6H_4-		190–195	1.0	1.68	4.0	5.4	3.9	4.03	2.33	–

[a] Bath temperature

[b] J in Hz

Table 3. Larval toxicity of compounds **Ia–Ii** and **IIa–IIf** to *C. quinquefaciatus*

Compound	Dose ($mg\,l^{-1}$)	%M[a] in h			Compound	Dose ($mg\,l^{-1}$)	%M[a] in h		
		24	48	72			24	48	72
Ia	3	+	++	+++	**If**	3	+++	−	−
	2	++	++	+++		2	+++	−	−
	1	0	++	+++		1	+++	−	−
Ib	3	+++	+++	−	**Ig**	3	+	0	0
	2	++	+++	−		2	+	0	0
	1	++	+++	−		1	0	0	0
Ic	3	+	++	+++	**Ih**	3	+	0	0
	2	+	++	+++		2	+	0	0
	1	+	++	+++		1	0	0	0
Id	3	+	++	+++	**Ii**	3	+	++	+++
	2	+	++	+++		2	+	++	+++
	1	0	++	+++		1	+	++	+++
Ie	3	++	++	+++					
	2	++	++	+++					
	1	0	++	+++					
IIa	3	++	++	+++	**IId**	3	++	+++	
	2	+	++	+++		2	+++	−	
	1	+	++	+++		1	++	+++	
IIb	3	++	++	+++	**IIe**	3	++	++	+++
	2	+	++	+++		2	++	++	+++
	1	+	++	+++		1	+	++	+++
IIc	3	0	++	+++	**IIf**	3	++	+++	
	2	+	++	+++		2	++	+++	
	1	0	++	+++		1	++	+++	

[a] M mortality. Grading for mortality: 0 = 0%; + = 10.50%; ++ = 60–80%; +++ = 90–100%

in **I** and **II**. A well defined doublet at δ 4 corresponds to the C-1′ methylene of the propargyl group while C-3′ methine gives a triplet at δ 2. Olefinic methyls at C-3 and C-7, which appear as a singlet (6H) at δ 1.6 in **Ia–Id** where *R* is benzyl or alkyl, appear as two separate singlets at δ 1.6 and 1.7 when *R* is a phenyl moiety. In the mass spectra of these compounds cleavage of the C_8—0 bond gave rise to an ion *m/z* 55 $[HC{=}CCH_2O]^+$. Allylic cleavage at C_4—C_5 bond resulted in the fragment $[HC{=}CCH_2OCH_2(CCH_3){=}CHCH_2]^+$ with *m/z* 123.

In the series **I** and **II** almost all compounds showed larval toxicity to *C. quinquefaciatus* at 1 $mg\,l^{-1}$ except **Ig** and **Ih** (Table 3) which were found to be inactive. Compounds **Ic** and **Ie** and **IIa–IIc** exhibit 60–80% mortality in 48 h at 1 $mg\,l^{-1}$ while 100% mortality is observed for **Ib**, **IId**, and **IIf** with the same dose and during the same period of time. Compound **IId** with a phenoxy group at C-1 and a double bond at C-6 is fairly active at 2 $mg\,l^{-1}$, however, the presence of an additional double bond at C-2 as in **Ie** reduced the activity where 100% killing is observed in 72 h. Introducing of *p*-chloro in phenyl (**Ii** and **IIf**) did not alter the

activity, whereas, introduction of *p*-methyl (**I f**) considerably enhanced the activity. A similar effect is observed in compounds with ethoxy at C-1 position. **I b** with a C-2 double bond is more active than its counterpart **II b** without a C-2 double bond.

In our earlier series of 3,7-dimethyl-2,6-octadiene-1,8-diol ethers [4] and 3,7-dimethyl-6-octene-1,8-diol ethers [5] it was observed that compounds from the former series with C-2 and C-6 double bonds show higher activity towards mosquitoes [4] whereas for compounds from the latter series with only a C-6 double bond, the activity is considerably reduced. In the present report compounds from geraniol (**I a–I i**) and citronellol (**II a–II f**) appear to be equally active.

References

[1] Part III: Ref. [5]
[2] NCL Commun. No. 4439
[3] Slama K., Romanuk M., Sorm F. (eds.) (1974) Insect Hormones and Bioanalogues. Springer, Wien New York, p. 203
[4] Phadnis A. P., Patwardhan S. A., Gund P., Sharma R. N. (1987) Pesticide Science **21**: 93
[5] Phadnis A. P., Nanda B., Patwardhan S. A., Powar P., Sharma R. N. (1988) Indian J. Chem. **27B:** 867

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