

Note

Synthesis and Biological Activity of Some Dibromoalkadienyl Ether Analogs of Juvenile Hormone[†]

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Received June 15, 1981

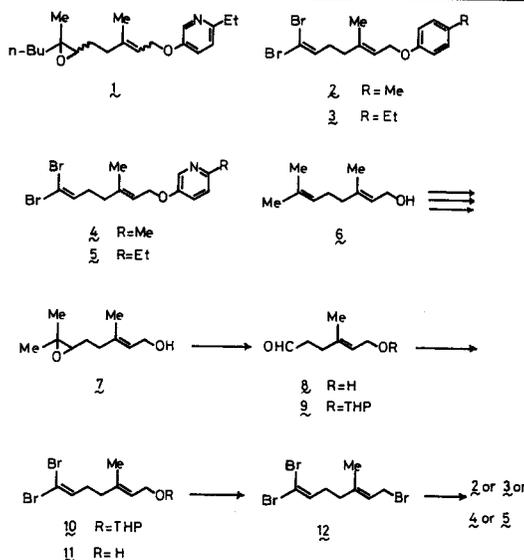
We recently synthesized some pyridyl terpenoid ether analogs of juvenile hormone (JH) such as **1** which showed strong insect-growth regulating activities comparable to methoprene.¹⁾ The fact that pyrethroid analogs with dichlorovinyl or dibromovinyl groups are very effective insecticides²⁾ prompted us to synthesize some dibromoalkadienyl ether analogs of JH, **2**~**5** and determine their bioactivity.

Geraniol **6** was converted to epoxygeraniol **7** in the usual manner.³⁾ Cleavage of the epoxide **7** with periodic acid yielded a hydroxy aldehyde **8**. After protecting the hydroxyl group as tetrahydropyranyl ether **9**, the dibromovinyl moiety was attached by a Wittig reaction⁴⁾ using carbon tetrabromide, triphenylphosphine, and zinc in methylene chloride to give **10**. The protective group was removed to afford a dibromovinyl alcohol **11**. This was treated with phosphorus tribromide. The resultant bromide **12** was coupled with *p*-cresol, *p*-ethylphenol, 2-methyl-5-pyridinol and 2-ethyl-5-pyridinol to give **2**, **3**, **4** and **5**, respectively.

The susceptibility of stored-product insects to these brominated juvenile hormone analogs was determined at the U. S. Grain Marketing Research Laboratory. We assayed for inhibitory effects against progeny development at 0.1, 1, 10 and 100 ppm, in wheat media using Indian meal moth (*Plodia interpunctella*), confused flour beetle (*Tribolium confusum*) and rice weevil (*Sitophilus oryzae*) as test insects according to the published procedure.⁵⁾ Only at 100 ppm was significant suppression of adult progeny observed as shown in Table I. These JH analogs were expected to be more active on the basis of the bioisosterism theory, since the van der Waals radius of a bromine atom (1.95 Å) is quite similar to that of a methyl group (2.0 Å). The disappointing result may be due to the reduced

TABLE I. INHIBITION OF PROGENY DEVELOPMENT CAUSED BY JH MIMICS

Compound	Adult progeny reduced at 100 ppm (%)		
	Indian meal moth	Confused flour beetle	Rice weevil
2	47	15	51
3	39	85	59
4	38	77	40
5	100	97	16



electron density at the terminal double bond caused by two electronegative bromine atoms.

EXPERIMENTAL

IR spectra refer to films. NMR spectra were recorded at 60 MHz in CCl_4 with TMS as internal standard.

(*E*)-6-Hydroxy-4-methyl-4-hexenal **8**. 6,7-Epoxygeraniol (8.5 g) in ether (81 ml) was added during 1 hr to a solution of periodic acid hexahydrate (14.8 g) in THF (65 ml) with stirring and ice-cooling. The stirring was continued for 2 hr. Subsequent work-up gave 6.7 g of crude **8**, $\text{IR}_{\text{max}} \text{cm}^{-1}$: 3400, 1710; $\text{NMR } \delta$ 1.68 (3H, s), 4.05 (2H, t, $J=6\text{Hz}$), 9.84 (~1H, t, $J=2\text{Hz}$).

(*E*)-6-Tetrahydropyranyloxy-4-methyl-4-hexenal **9**. The above aldehyde **8** (5.84 g) in dichloromethane (153 ml) was mixed with dihydropyran (6.01 g) and pyridinium *p*-toluenesulfonate (2.35 g). The mixture was left to stand overnight at room temperature. Subsequent work-up gave 4.14 g of **9** after chromatographic purification over silica gel, $\text{IR}_{\text{max}} \text{cm}^{-1}$: 1720, 1110, 1080, 1020. This was em-

[†] Synthesis of Compounds with Juvenile Hormone Activity, Part XXIV. For Part XXIII, see ref. 1.

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ployed for the next step without further purification.

(*E*)-7,7-Dibromo-3-methyl-2,6-heptadien-1-ol tetrahydro-pyranyl ether **10**. A mixture of triphenylphosphine (2.61 g), carbon tetrabromide (3.32 g) and zinc dust (0.654 g) in dichloromethane (15 ml) was stirred for 24 hr at room temperature under nitrogen. A solution of the aldehyde (**9**, 1.06 g) in a small amount of dichloromethane was added to the stirred mixture and the stirring was continued for 2 hr. The mixture was diluted with pentane and filtered. The residue on the filter was triturated with dichloromethane, diluted with pentane and filtered again. This was repeated several times. The combined filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel (Kieselgel 60, Art 7734, 40 g). Elution with *n*-hexane-ethyl acetate-triethylamine (89.1:9.9:1) yielded 696 mg of crude **10**. This was employed for the next step without further purification.

(*E*)-7,7-Dibromo-3-methyl-2,6-heptadien-1-ol **11**. Pyridinium *p*-toluenesulfonate (270 mg) was added to a solution of **10** (3.59 g) in ethanol (80 ml). The mixture was stirred and heated at 50~55°C (bath temperature) for 3 hr. After the removal of the solvent, the residue was chromatographed over silica gel (Kieselgel 60, Art 7734, 75 g). Elution with *n*-hexane-ethyl acetate (3:1) gave 1.01 g (36%) of **11**, with 1.82 g of the recovered **10**. The bromo alcohol **11** showed the following properties: n_D^{23} 1.5421; IR $_{\text{max}}$ cm $^{-1}$: 3300 (s), 2920 (s), 2850 (s), 1670 (w), 1620 (w), 1450 (m), 1385 (m), 1065 (m), 1010 (s), 805 (s), 785 (s); NMR δ 1.65 (3H, s), 2.15 (4H, m), 3.10 (1H, s, OH), 4.05 (2H, d, $J=6$ Hz), 5.40 (1H, t, $J=6$ Hz), 6.40 (3H, dt, $J_1=6$ Hz, $J_2=1$ Hz); *Anal.* Found: C, 34.00; H, 4.44; Calcd. for C $_8$ H $_{12}$ OBr $_2$: C, 33.84; H, 4.26%.

(*E*)-1,1,7-Tribromo-5-methyl-1,5-heptadiene **12**. Phosphorus tribromide (0.31 ml) was slowly added to a stirred and ice-salt-cooled solution of **11** (284 mg) in dry ether (15 ml) at -14~-16°C. The mixture was stirred at -15~0°C for 1 hr, poured into ice-water and extracted

with ether. The ether solution was washed with water, sodium bicarbonate solution and brine, dried over calcium chloride and concentrated *in vacuo* to give 244 mg of crude **12**, IR $_{\text{max}}$ cm $^{-1}$: 2900 (m), 2840 (m), 1650 (m), 1620 (w), 1445 (m), 1380 (m), 1200 (s), 800 (s), 780 (s).

(*E*)-7,7-Dibromo-3-methyl-2,6-heptadienyl 2-ethyl-5-pyridyl ether **5**. Powdered potassium hydroxide (42 mg) was added to a solution of 5-ethyl-3-pyridinol (86.5 mg) in dry DMF (10 ml) and the mixture was stirred for 1 hr at room temperature. A solution of **12** (244 mg) in dry DMF (5 ml) was added and the mixture was stirred overnight at room temperature. Then it was diluted with water and extracted with ether. The ether solution was washed with water, dried over sodium sulfate and concentrated *in vacuo*. After chromatographic purification over silica gel, 124 mg (32%) of **5** was obtained, n_D^{23} 1.5615; IR $_{\text{max}}$ cm $^{-1}$: 3010 (w), 2950 (m), 2910 (m), 2850 (m), 1660 (w), 1620 (w), 1590 (w), 1565 (s), 1495 (s), 1480 (s), 1390 (m), 1280 (s), 1270 (s), 1245 (s), 1020 (m), 995 (m), 830 (m), 805 (m), 780 (m); NMR δ 1.25 (3H, t, $J=7.5$ Hz), 1.70 (3H, s), 2.15 (4H, m), 2.70 (2H, q, $J=7.5$ Hz), 4.50 (2H, d, $J=6$ Hz), 5.40 (1H, t, $J=7$ Hz), 6.25 (1H, m), 7.00 (2H), 8.15 (1H, br. s). In the same manner **2**, **3**, and **4** were prepared.

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