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Insect Juvenile Hormone Mimics Based on Bakuchiol[†]

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Several derivatives of bakuchiol, a meroterpenoid from *Psoralea corylifolia* Linn., have been prepared and evaluated for insect juvenile hormone activity against *Dysdercus koenigii* nymphs. Almost all of these were found to be more active than the standard farnesyl methyl ether, while some of these proved to be many times more potent.

Bakuchiol (**1**),[1~3] a meroterpenoid from the seeds of *Psoralea corylifolia* Linn., has a structure reminiscent of certain synthetic juvenile hormone (JH) mimics (*e.g.* **5**,[4] **6**,[4] **7**,[5] **8**[6]) incorporating a benzene ring in the structure and hence it appeared worthwhile to synthesise some of its derivatives for evaluating their JH activity. This excercise appeared all the more purposeful as bakuchiol is relatively easily accessible[1] and preliminary investigations had revealed*[1] that the compound exhibits JH activity more potent than that exhibited by the naturally occurring JH mimic, juvabione (**9**).[9]

Keeping in view structural modifications which tend to enhance JH activity, such as incorporation of oxirane, methoxyl, ethoxyl or halogen functions,[10] eleven such derivatives (**2**~**4**, **10**~**17**), based on bakuchiol (**1**), and four each (**19**~**22**; **24**~**27**), derived from 7,8-dihydrobakuchiol methyl ether (**18**) and 7,8,16,17-tetrahydrobakuchiol methyl ether (**23**) have been synthesised and evaluated for JH activity.

Though, preparation of 7,8-dihydrobakuchiol required for methylation to **18** has been described earlier (H_2/Pd–C/EtOH),[1] it was more conveniently obtained by Na-*t*-BuOH–NH_3 reduction[11] of bakuchiol. 7,8,16,17-Tetrahydrobakuchiol, required for preparation of **23**, was obtained by hydrogenation of bakuchiol in EtOH over 5% Pd-$CaCO_3$ catalyst.[1] Alkylation of phenols was carried out by sodium hydride and the appropriate alkyl iodide.[12] Selective epoxidation of 2,3-olefinic linkage was readily achieved by the action of a molar equivalent of perbenzoic acid in benzene solution.[13] 2-Hydroxy derivatives (**14**, **16**, **17**, **21**, **26**) were synthesised from the corresponding 2,3-epoxy derivatives by reduction with lithium aluminium hydride in tetrahydrofuran[14]; the corresponding 2-methoxy derivatives were then obtained by methylation of C–2 hydroxyl with NaH/CH_3I. The 2-chloro derivatives (**13**, **20**, **25**) were easily obtained by addition of the calculated amount of hydrogen chloride to the substrate. The structures of compounds, thus synthesised, are fully borne out by their spectral (UV, IR, PMR, Mass) and analytical data.

Juvenile hormone activity

JH activity of these compounds has been tested on 4 hr old last instar nymphs of red cotton bug, *Dysdercus koenigii*, using 10, 1.0 and 0.1 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*[2] of the results is given

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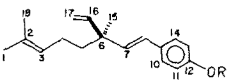
[†] Products Active on Arthropod—II. Insect Juvenile Hormone Mimics (Part 2). Paper appearing in *Agric. Biol. Chem.*, **40**, 697 (1976) to be treated as Part I. MRC Communication No. 21.

[*1] This aspect was first brought to our attention by Dr. M. S. Chadha, who also made available two communications[7,8] of his colleagues describing these results.

[*2] Bio-assay were carried out by Drs. N. K. Joshi and H. B. Mansukhani, through the courtesy of Dr. M. S. Chadha, at Bhabha Atomic Research Centre (Bio-organic Division). Authors would like to place on record their grateful thanks for this help from his group.



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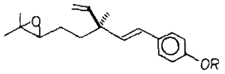
2 : R = Me
3 : R = Et
4 : R = n-Pr



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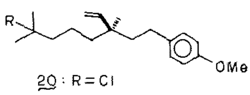

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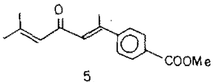

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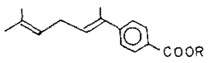

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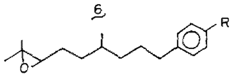

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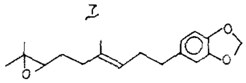

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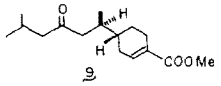

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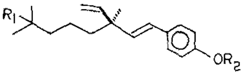
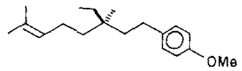


	R_1	R_2
13	Cl	Me
14	OH	Me
15	OMe	Me
16	OH	Et
17	OH	n-Pr



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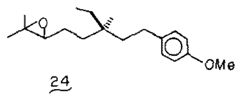

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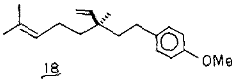

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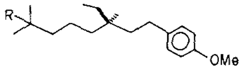

25 : R = Cl
26 : R = OH
27 : R = OMe

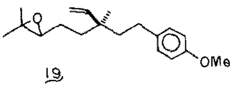

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TABLE I. PHYSICAL PROPERTIES OF BAKUCHIOL DERIVATIVES

Structure	Molecular formula	B.P (°C/mm)	n_D^{25}	$\{\alpha\}_D^{25}$ [c] (conc.)
2	$C_{19}H_{26}O$	133~35/0.4[a]	1.5402[b]	
3	$C_{20}H_{28}O$	144~45/0.1[a]	1.5338	+29.47 (1.7)
4	$C_{21}H_{30}O$	140~42/0.2[a]	1.5294	+26.62 (3.6)
10	$C_{19}H_{26}O_2$	190~95/0.2	1.5300	+33.84 (2.5)
11	$C_{20}H_{28}O_2$	180~98/0.4	1.5314	+34.03 (3.6)
12	$C_{21}H_{30}O_2$	178~84/0.1	1.5228	+25.55 (3.1)
13	$C_{19}H_{27}OCl$	—	1.5341	+15.39 (5.1)
14	$C_{19}H_{28}O_2$	175~80/0.3	1.5340[b]	+35.40 (1.3)
15	$C_{20}H_{30}O_2$	155~66/0.3	1.5231[b]	+33.37 (1.3)
16	$C_{20}H_{30}O_2$	185~90/0.1	1.5324	+43.82 (1.1)
17	$C_{21}H_{32}O_2$	184~90/0.3	1.5292	+29.17 (4.6)
18	$C_{19}H_{28}O$	144~46/0.8[a]	1.5130[b]	+ 9.90 (2.7)
19	$C_{19}H_{28}O_2$	165~70/0.3	1.5076[b]	+16.73 (1.5)
20	$C_{19}H_{29}OCl$	—	1.5078	+11.69 (1.1)
21	$C_{19}H_{30}O_2$	175~80/0.3	1.5095	+21.72 (2.0)
22	$C_{20}H_{32}O_2$	165~70/0.6	1.4964[b]	+14.95 (2.7)
23	$C_{19}H_{30}O$	142~44/1.0[a]	1.5032	±0
24	$C_{19}H_{30}O_2$	140~45/0.2	1.5140	±0
25	$C_{19}H_{31}OCl$	—	1.5015	±0
26	$C_{19}H_{32}O_2$	170~75/0.2	1.5018	±0
27	$C_{20}H_{34}O_2$	140~45/0.1	1.4921	±0

[a] Uncorrected boiling points. The remaining entires indicate the temp. of the bath (bulb distillations).
[b] These measurements are at 30°C.
[c] Specific rotations in chloroform solution.

TABLE II. JUVENILE HORMONE ACTIVITY OF SOME BAKUCHIOL DERIVATIVES

Compound	Dose/nymph		
	10	1	0.1
	Score[a]		
Farnesyl methyl ether	1.5	0.0	—
2	4.0	1.4	—
3	4.0	4.0	1.5
4	4.0	3.4	0.0
10	4.0	4.0	—
11	4.0	4.0	2.0
12	4.0	4.0	2.9
13	4.0	1.5	—
14	4.0	3.7	—
15	4.0	0.7	—
16	4.0	4.0	1.8
17	4.0	4.0	1.2
18	1.5	0.0	—
19	4.0	0.1	—
20	4.0	0.0	—
21	3.1	0.3	—
22	2.7	0.0	—
23	1.5	0.0	—
24	4.0	0.1	—
25	3.0	0.0	—
26	2.5	0.3	—
27	1.8	0.0	—
Bakuchiol[b]	3.0	1.0	—

[a] Score represents the mean of two experiments, each of which was carried out using three replicates of 15 nymphs each. Nymphs which successfully moulted were characterised and scored as: normal adults (0), adult-nymphs (1), intermediates (2), nymph-adults (3), and sixth instar nymphs (4).

[b] From ref. 8.

in Table II.

From an analysis of the JH activity data (Table II), it is clear that bakuchiol (**1**) provides a valuable model for JH mimics. Ethers (**2**, **3**, **4**) are more potent than the free phenol (**1**). 2,3-Epoxy derivatives (**10**, **19**, **24**) are, in general, more potent than the corresponding 2-chloro (**13**, **20**, **25**), 2-hydroxy (**14**, **21**, **26**) or 2-methoxy (**15**, **22**, **27**) analogues. Both Δ^7 and Δ^{16} appear to be essential for good activity (**2**~**4**, and **10**~**17** as compared to **18**~**27**). 2,3-Epoxybakuchiol propyl ether(**12**) is most potent of the compounds investigated in the present study and deserves further detailed exploration of its activity in other systems.

EXPERIMENTAL

The following instruments were used for spectral/physical data: Perkin-Elmer UV spectrophotometer, model 402; Perkin-Elmer IR spectrophotometer, model 267; Perkin-Elmer, model R32 (90 MHz), NMR spectrometer; Varian Mat CH-7 mass spectrometer (70 eV, direct inlet system); Carl-Zeiss polarimeter, model 31841. Purity of each preparation was ascertained by thin-layer chromatography of the material on 0.3 mm layers of silica gel (solvent: 20% EtOAc in benzene, unless stated to the contrary).

7,8,Dihydrobakuchiol. Sodium pieces (1.3 g; 0.056g atom) were added to a stirred solution of bakuchiol (5.0 g; 19.5 mmol) in *t*-butanol (50 ml) and liquid ammonia (300 ml). The deep blue solution was stirred for 10 mins followed by cautious addition of solid NH_4Cl (2.0 g). Ammonia was allowed to evaporate to half the volume when it was cautiously diluted with water (50 ml). After leaving the solution overnight at room temperature it was extracted with ether (25 ml ×4) and the ether extract washed with water (25 ml×8) and brine (25 ml×2). Solvent removal gave a reddish oil which was distilled to give pure (TLC: solvent, 40% diethyl ether in hexane) 7,8-dihydrobakuchiol[1)] (4.32 g; yield, 86%).

7,8,16,17-Tetrahydrobakuchiol. Bakuchiol (2.77 g) dissolved in absolute ethanol (25 ml) was hydrogenated over 5% Pd-$CaCO_3$ (372 mg) at 730 mm pressure and at 29°C until two equivalent of hydrogen (560 ml) was absorbed. The product which contained some hexahydrobakuchiol was purified by column chromatography (10% $AgNO_3$-SiO_2, 100 g; column, 24.0× 3.5 cm; solvent, pet ether 60~80 containing increasing amounts of diethyl ether) to give hexahydroderivative (0.81 g) and pure (TLC: 5% $AgNO_3$–SiO_2; solvent, 20% Et_2O–hexane) 7,8,16,17-tetrahydrobakuchiol[1)] (1.84 g).

Alkylation of phenols. The following is illustrative of the general procedure followed for alkylation of **1** and its dihydro and tetrahydro derivatives. Bakuchiol (3.2 g; 12.5 mmol) dissolved in dry THF (10 ml) was injected into a suspension of sodium hydride (6.0 g as oil dispersion; washed with ether; NaH, 3.0 g; 130 mmol) in THF (10 ml) and ethyl iodide (20.28 g; 130 mmol). The mixture was stirred at room temperature for 0.5 hr and at reflux for 6 hr. The excess hydride was decomposed by cautious addition of water (20 ml). The organic layer was separated and the aqueous layer extracted with ether (25 ml×3). The combined organic layer was washed with water (20 ml × 3) and brine (15 ml × 2), dried (Na_2SO_4) and freed from solvent to give a residue which on distillation gave bakuchiol methyl ether (3.22 g; yield 91%). Methyl and *n*-propyl iodides were used for the preparation of the corresponding alkyl ethers; yields varied 87 to 91%.

Epoxidation of 2,3-olefinic linkage. Epoxidations were carried out as illustrated below. A chilled solution of perbenzoic acid (0.97 g; 7.0 mmol) in benzene (23 ml) was added dropwise to bakuchiol ethyl ether (2.0 g; 7.0 mmol) and the solution was kept at 0～5°C for 14 hr. The mixture was diluted with ether (10 ml) and washed with water (5 ml), aqueous sodium carbonate (5%; 15 ml × 3), water (25 ml × 4) and brine (25 ml × 2). It was dried (Na_2SO_4), freed from solvent and the residue was purified by IDCC[16] (SiO_2, 250 g; column, 25.0 × 4.7 cm; solvent, 11% EtOAc in benzene) and distilled to give pure 2,3-epoxybakuchiol ethyl ether (1.77 g; yield, 85%).

Reduction of 2,3-epoxy derivatives to 2-hydroxy compounds. The following is illustrative of the general procedure used for the reduction of 2,3-epoxybakuchiol derivatives to the corresponding 2-hydroxy compounds. 2,3-Epoxybakuchiol methyl ether (1.43 g; 5 mmol) in THF (5 ml) was added dropwise to a stirred suspension of LAH (0.19 g; 5 mmol) in THF (5 ml) at 0°C under N_2 blanket and the mixture was stirred for 0.5 hr at 0°C and at reflux for 4 hr. The excess hydride was decomposed with a saturated solution of Rochelle salt (25 ml). The organics were separated and aqueous portion extracted with ether (25 ml × 3). The combined organic layer was washed with water (25 ml × 5) and brine (25 ml × 2) and dried (Na_2SO_4). Removal of solvent gave a colourless viscous residue which was distilled to give pure 2-hydroxybakuchiol methyl ether as a colourless oil (1.22 g; yield, 87%).

O-Methylation of 2-hydroxy derivatives. *O*-methylation of 2-hydroxy derivatives was typically carried out as follows: 2-Hydroxybakuchiol methyl ether (0.288g; 1 mmol) in dry THF (5 ml) was injected slowly (10 min) with stirring to a suspension of sodium hydride (4.8 g, oil dispersion washed with ether; NaH, 2.4 g, 100 mmol) in THF (5 ml) and methyl iodide (2 ml) under N_2 blanket. The mixture was stirred for 1.5 hr at room temperature and 1.0 hr at reflux. The excess hydride was decomposed with water (40 ml) added dropwise. The aqueous layer was separated and extracted with ether (20 ml × 2). The combined organic layers were washed with water (30 ml × 3) and brine (25 ml × 2), dried (Na_2SO_4) freed from solvent and residue distilled to give 2-methoxy bakuchiol methyl ether as a colourless oil (0.274 g; yield, 91%), homogeneous by TLC (solvent: 40% diethyl ether in hexane).

Addition of HCl to bakuchiol derivatives. Addition of HCl across the 2,3-double bond of bakuchiol derivatives was typically carried out as follows: Acetyl chloride (0.39 g; 5.0 mmol) was added to a solution of absolute methanol (0.16 g; 5.0 mmol) in glacial acetic acid (10 ml) at 16～17°C and the mixture was allowed to stand for 0.5 hr. This solution (1 ml: 0.5 mmol HCl) was added to bakuchiol methyl ether (0.135 g; 0.5 mmol) at 0°C and the solution allowed to stand at 0～5°C for 14 hr. The reaction mixture was diluted with water (5 ml) and extracted with ether (10 ml × 3). The ether extract was washed with aqueous sodium bicarbonate (5%; 10 ml × 2), water (20 ml × 6) and brine (10 ml × 2), dried (Na_2SO_4) and freed from solvent. The residue (0.15 g) was purified by IDCC (SiO_2, 20 g; column, 25 × 1.5 cm; solvent, 20% EtOAc in benzene) to give pure (TLC) 2-chlorobakuchiol methyl ether (0.121 g; yield, 79%).

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