

## Synthesis of Bioactive Compounds. Substituted Biphenyls as Juvenile Hormone Mimics

Several substituted biphenyls have been synthesized as a new class of potential insect growth regulators. One of these, ethyl 4-(4-isopropylphenyl)benzoate, had the same order of juvenile hormone activity as methyl juvenate (JH-III) when tested relative to preventing diapause in the adult cereal leaf beetle.

In the past, virtually all juvenile hormone (JH) mimics had a monoterpene or sesquiterpene residue or homologation thereof as part of their structures. Many of these also contain an aromatic group, usually a benzene ring. One early exception was the "peptide" mimic reported by Babu and Slama (1972), while the recent literature reports JH mimics having a pyridine ring (Solli et al., 1975), a pyrimidine ring (Moore, 1974), and a dihydrothiine *S*-oxide ring (Hainant and Toromanoff, 1974). Pallos et al. (1976) report some nonterpene heteroacyclic JH mimics and an extensive compilation by Henrick et al. (1976) lists a diphenyl ether and a diphenylmethane mimic discovered at Ciba-Geigy. In line with these "nonclassical" JH mimics, we wish to report a nonterpene derived (but terpene inspired) substance with considerable juvenile hormone mimicking activity which is a 4,4'-disubstituted biphenyl. This compound, prepared in one step from commercially available materials, represents a new variety of JH mimics.

### EXPERIMENTAL SECTION

<sup>1</sup>H NMR spectra were determined in CD<sub>3</sub>SOCD<sub>3</sub> on a Varian T-60 spectrometer. Mass spectra were determined at 70 eV on a DuPont 21-490 instrument via the direct inlet probe. Probe and source temperatures were 200–250 °C. Preparative thin-layer chromatography employed 20 × 20 × 0.15 cm plates of Merck GF-254 silica gel.

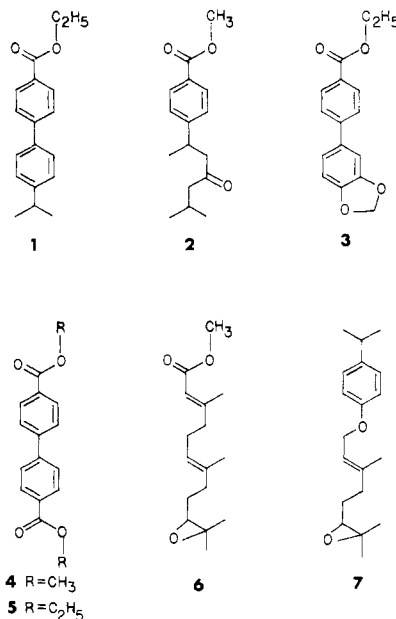
**Ethyl 4-(4-Isopropylphenyl)benzoate (1).** Using as a guide Cadogan's method (1962), a mixture of 12.0 g (0.100 mol) of cumene and 4.95 g (0.030 mol) of ethyl *p*-aminobenzoate was stirred and heated at 70 °C under nitrogen while 5.85 g (0.050 mol) of isoamyl nitrite was added dropwise during 30 min.

The mixture was cooled to 25 °C and stirred 2 h and 100 ml of ether was added. The solution was extracted with two 100-ml portions of 5% HCl and dried with Na<sub>2</sub>SO<sub>4</sub>, and the ether was removed. The residue was distilled (150 °C, 0.3 Torr) to remove ethyl benzoate, cumene, and isopropyl alcohol. The pot residue was purified by preparative TLC, eluting with 3:1 hexane–methylene chloride. The product, 469 mg (1.75 mmol, 5.8%), was a liquid at room temperature: MS, *m/e* 268 (M<sup>+</sup>). The <sup>1</sup>H NMR of the aromatic region consisted of multiplets in the region δ 7.1–8.0, theoretically two overlapping AA'BB' systems. Further confirmation of structure 1 was accomplished by chemical degradation. A portion of 1 was saponified by Claisen's alkali (Tarbell et al., 1955) followed by acidification and recrystallization from ethanol. The melting point of this compound was identical with that reported by Byron et al. (1966) for 4-(4-isopropylphenyl)benzoic acid.

**Ethyl 4-(3,4-Methylenedioxyphenyl)benzoate (3).** The procedure used to prepare mimic 1 was repeated substituting 1,2-methylenedioxybenzene for cumene. The residue after vacuum distillation workup was purified by preparative TLC using a 1:1 mixture of hexane–methylene chloride as eluent. The band at *R<sub>f</sub>* 0.7 was rechromatographed using 3:1 hexane–ether to give three products.

Only the band at *R<sub>f</sub>* 0.5 had the correct parent peak in the mass spectrum at *m/e* 270. Integration of the <sup>1</sup>H NMR spectrum gave the expected ratio of aliphatic to aromatic protons. The yield was 196 mg (0.73 mmol, 2.4%) of the liquid ester.

**Dimethyl and Diethyl 4,4'-Biphenyldicarboxylate.** The diesters 4 and 5 were prepared from 4,4'-dibromobiphenyl (Aldrich Chemical Co.). This was converted, in 41% yield, to 4,4'-diphenic acid by successive treatment with *n*-butyllithium at room temperature, anhydrous solid CO<sub>2</sub>, and 5% HCl. Fisher esterification of the diacid failed to give either diester. The diacid was converted quantitatively to the diacid chloride upon metathesis with PCl<sub>5</sub> at 200 °C for 4 h. Reaction of the diacid chloride with anhydrous methanol gave 4 in 57% yield, mp 214–215 °C.



Reaction of the diacid chloride with anhydrous ethanol gave 5 in 49% yield, mp 110–111 °C. The reported mp (Heilbron, 1965) are 214 and 112 °C, respectively. Methyl juvenate (6, JH-III) was prepared by our reported method (Nilles et al., 1973). No attempt was made to optimize yields in any of these syntheses.

Bioassay for juvenile hormone activity was based on diapause prevention and induced oviposition in laboratory reared adult cereal leaf beetles (*Oulema melanopus* (L); Connin et al., 1967; Connin and Hoopingarner, 1971). The procedure was as described in Nilles et al. (1973). A test colony consisted of ten male and ten female prediapause insects. All 20 insects were treated with topical solutions of a given compound at 100 μg/insect or at 50 μg/insect levels. The bioassay data are given in Table I and include the number of days following treatment before oviposition began, the total number of eggs deposited in 14 days posttreatment, the vitality, i.e., the percent of the total number of treated insects alive after 14 days, and the

Table I. Bioassay Data

Compd	Dose, $\mu\text{g}$	Days to 1st egg	Total eggs 14 days	Vitality, % <sup>g</sup> alive	AR <sup>g</sup>
1	100	8	176	30	73
	50	8	204	65	39
3	100		0	10	0
	50		0	10	0
4 <sup>a</sup>	50		0	55	0
5 <sup>a</sup>	50		0	40	0
6 <sup>b</sup>	100	6	154	40	65
	50	6	193	70	46
6 <sup>c</sup>	100	6	217	55	66
	50	8	43	60	21
7 <sup>d</sup>	100	8	156	40	53
	50	8	93	35	36
Post-diapause check		5 <sup>e</sup>	438	80	114 <sup>f</sup>

<sup>a</sup> Not soluble at 100  $\mu\text{g}/\mu\text{l}$ . <sup>b</sup> In acetone. <sup>c</sup> In dimethyl sulfoxide. <sup>d</sup> Data from Nilles et al. (1976). <sup>e</sup> Following normal diapause. <sup>f</sup> Gravimetric factor = 1. <sup>g</sup> See text (activity rating).

activity rating, AR (Nilles et al., 1976). AR values typically range from 0 to just over 100. The postdiapause check was determined on laboratory reared insects after normal diapause.

#### RESULTS AND DISCUSSION

Dimethyl sulfoxide replaced our usual solvent, acetone, in the administration of the candidate mimics. None of the biphenyls had sufficient solubility in acetone to permit testing at the levels indicated in Table I. Methyl juvenile (6, JH-III) was tested in both acetone and dimethyl sulfoxide to allow comparison with our earlier work. We noted no difference in JH activity or vitality with  $\text{Me}_2\text{SO}$  as a solvent. When treated with blanks of either acetone or  $\text{Me}_2\text{SO}$ , all beetles failed to oviposit by 14 days and exhibited vitalities of at least 80–90%. Most of these insects entered normal diapause during the test period.

Mimic 1 was the only JH active compound. Its activity is of the same magnitude as JH-III 6 and the aryl geranyl ether 7. Insects treated with either of these compounds did not diapause. They fed as normal postdiapause insects and began oviposition by the number of days following treatment as indicated in Table I.

We note that mimic 1 bears at least a superficial resemblance to a possible conformer of the naturally occurring JH mimic, juvabione 2 (Pawson et al., 1970). The intriguing concept that the search for certain JH mimics and other insect growth regulators (IGR's) can be guided by a structural template has been advanced by Pallos et al. (1976). However, it is difficult to reconcile mimic 1 and juvabione 2 to their geranyl and farnesyl inspired template. In addition, compounds 3, 4, and 5, which show reasonable congruency with structures 1 and 2, are either quite toxic or JH inactive. We speculate that the minor structural differences between 1 and the other biphenyls may indicate

the need for one end of these mimics to be rather lipophilic.

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George P. Nilles<sup>1</sup>  
 Matthew J. Zabik\*  
 Richard V. Connin<sup>2</sup>  
 Robert D. Schuetz

The Pesticide Research Center  
 Departments of Chemistry and Entomology (M.J.Z.)  
 Agricultural Research Service  
 U.S. Department of Agriculture  
 Michigan State University  
 East Lansing, Michigan 48824  
<sup>1</sup>Present address: Bennett St.  
 Chisago City, Minnesota 55013  
<sup>2</sup>Present address: U.S. Department of Agriculture  
 Regional Plant Introduction Station  
 Experiment, Georgia 30212

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