# Synthesis and Activity of Juvenile Hormone Analogues (JHA), Part II

Juan B. Rodriguez[a], Eduardo G. Gros*[,a], and Angel M. Stoka[b]

[a] Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

[b] Instituto Nacional de Diagnóstico e Investigación de la Enfermedad de Chagas "Dr. M. Fatala Chaben" (INDIECH), Paseo Colón 568, 1063 Buenos Aires, Argentina

Z. Naturforsch. **44b**, 983–987 (1989); received December 5, 1988

Juvenile Hormone Analogues, Activity, Synthesis

Several derivatives of 4-phenoxyphenoxy-ethyl and 4-phenoxyphenylethyl bearing carbonate and thiolcarbonate as functional groups were synthesized. The products were tested for their respective juvenile hormone activity for *Triatoma infestans*. None of them showed an activity comparable to that of Fenoxycarb which was used as the standard control. The synthetic procedures and the biological results are discussed.

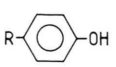
## Introduction

Juvenile hormone (JH) activity is a characteristic property of certain organic compounds that can act as insect growth regulators. By analogy with natural JHs, a great variety of terpenoid JH analogues have been synthesized and tested with variable results [1].

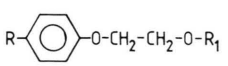
Since the biological activity of the JH analogues could not be attributed to any particular substructure but to the shape of the whole molecule [2], another class of JH analogues having a nonisoprenic structure, albeit important insect growth regulation activities, have been prepared [3–5]. Among them, various (4-phenoxyphenoxy)-alkyl substituted derivatives have shown to be most effective as insect growth regulators [5].

We have recently reported the synthesis and biological activity of several JH analogues featuring isoprenic moieties and carbonate, carbamate, thiolcarbonate, thiolcarbamate, carbonyloxyimino, and thiolcarbonyloxyimino as functional groups [6].

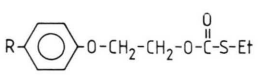
In order to test a new type of structure as insect growth regulators, we prepared a series of compounds bearing carbonate and thiolcarbonate functions attached to 4-phenoxyphenoxy-ethyl and 4-phenylphenoxy-ethyl moieties. Compounds **2a–b, 3a–b, 4a–b, 5a–b, 6a–b** and **7a–b** were synthesized following the sequence depicted in Scheme 1, and characterized by their respective IR, $^1$H NMR, $^{13}$C NMR, and mass spectra.



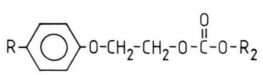
**1a**: R = OPh
**1b**: R = Ph



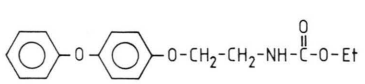
**2a**: R = OPh; $R_1$ = THP
**2b**: R = Ph; $R_1$ = THP
**3a**: R = OPh; $R_1$ = H
**3b**: R = Ph; $R_1$ = H



**4a**: R = OPh
**4b**: R = Ph



**5a**: R = OPh; $R_2$ = Me
**5b**: R = Ph; $R_2$ = Me
**6a**: R = OPh; $R_2$ = Et
**6b**: R = Ph; $R_2$ = Et
**7a**: R = OPh; $R_2$ = i-Bu
**7b**: R = Ph; $R_2$ = i-Bu



**8**

## Results

### *Synthetic procedures*

4-Phenoxyphenol (**1a**) and 4-phenylphenol (**1b**) were condensed with 2-(2-chloroethoxy)-tetrahydropyran [7] to afford 2-(4-phenoxyphenoxy)-ethoxytetrahydropyran (**2a**) and 2-(4-phenoxyphenyl)-ethoxytetrahydropyran (**2b**), respectively. Acid hydrolysis gave the respective free alcohols, namely, 2-(4-phenoxyphenoxy)-ethanol (**3a**) and 2-(4-phenoxyphenyl)-ethanol (**3b**). In separate experiments,

* Reprint requests to Prof. Dr. E. G. Gros.

Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen
0932–0776/89/0800–0983/$ 01.00/0

compounds **3a** and **3b** were condensed with ethyl chlorothioformate giving S-ethyl-[2-(4-phenoxyphenoxy)-ethoxy]-thiolcarbonate (**4a**) and S-ethyl-[2-(4-phenoxyphenyl)-ethoxy]-thiolcarbonate (**4b**), respectively. Besides, compound **3a** was treated with methyl chloro formate, ethyl chloroformate, and isobutyl chloroformate to give methyl-[2-(4-phenoxyphenoxy)-ethyl]-carbonate (**5a**), ethyl-[2-(4-phenoxyphenoxy)-ethyl]-carbonate (**6a**), and isobutyl-[2-(4-phenoxyphenoxy)-ethyl]-carbonate (**7a**), respectively. When the same reactions were performed on compound **3b,** the respective methyl-[2-(4-phenoxyphenyl)-ethyl]-carbonate (**5b**), ethyl-[2-(4-phenoxyphenyl)-ethyl]-carbonate (**6b**), and isobutyl-[2-(4-phenoxyphenyl)-ethyl]-carbonate (**7b**) were obtained. The new products were characterized by IR, $^{1}H$ NMR, $^{13}C$ NMR, and mass spectra.

*Biological assays*

The *Triatoma infestans* eggs were taken from laboratory colonies maintained at the INDIECH. The amount of the employed doses of JHA varies from 0.5 to 1.5 $\mu$g in 0.1 ml of acetone. Each dose of JHA was assayed on groups of thirty eggs which were kept at 30 °C and 55–70% r.h. The effect of JHA on the eggs was measured by their ability to prevent eclosion. After six weeks the percentage of hatchability was calculated. Control eggs were treated with 0.3 $\mu$l of acetone. In the control-treated eggs not all of them hatched; corrections were made to allow for this fact. Corrected percentages of hatchability were plotted against dose of JHA and the ID-50 (doses to inhibit eclosion of 50% of the eggs) were calculated for the tested JHA [8]. The results are presented in Table II.

## Discussion

Although the structures of the synthetic JHA were not quite different from that of Fenoxycarb (ethyl-2-(4-phenoxyphenoxy)-ethyl-carbamate) (**8**), which was tested as a control compound, the activity values presented in Table II show that none of the new products (**2a–7a**) present a value comparable to that of Fenoxycarb. The remarkable structural similarity between Fenoxycarb and compound **6a,** which has an oxygen atom instead of a NH group, and the difference in their respective biological activity indicated the important role that the nitrogen

Table I. $^{13}C$ NMR spectral data for compounds **2a–7a** and **2b–7b** (25.2 MHz; $C_6D_6$-TMS).

| Compound Carbon | **2a** | **3a** | **4a** | **5a** | **6a** | **7a** | **2b** | **3b** | **4b** | **5b** | **6b** | **7b** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 61.5 | 61.2 | 65.1 | 66.0 | 65.8 | 65.9 | 62.0 | 61.4 | 66.2 | 65.8 | 65.9 | 65.8 |
| 2 | 67.6 | 69.9 | 66.0 | 66.1 | 66.2 | 66.2 | 67.4 | 69.2 | 65.7 | 66.1 | 65.9 | 65.9 |
| 3 | 156.2 | 155.2 | 154.8 | 154.9 | 155.0 | 154.9 | 158.2 | 156.2 | 158.8 | 158.2 | 158.3 | 158.2 |
| 4 | 117.8 | 117.8 | 117.8 | 117.8 | 117.8 | 117.8 | 114.9 | 114.7 | 115.6 | 115.0 | 115.0 | 115.0 |
| 5 | 121.0 | 120.9 | 120.9 | 120.9 | 120.9 | 120.9 | 128.5 | 128.5 | 129.4 | 128.8 | 128.8 | 128.8 |
| 6 | 150.5 | 150.7 | 150.8 | 150.8 | 150.8 | 150.8 | 133.7 | 134.0 | 134.9 | 134.4 | 134.4 | 134.3 |
| 7 | 159.0 | 158.7 | 158.8 | 158.9 | 158.9 | 158.8 | 140.6 | 140.5 | 141.5 | 141.1 | 141.0 | 141.1 |
| 8 | 115.8 | 115.8 | 115.8 | 115.8 | 115.8 | 115.8 | 126.5 | 126.5 | 127.4 | 127.9 | 126.9 | 126.8 |
| 9 | 129.7 | 129.7 | 129.7 | 129.7 | 129.8 | 129.7 | 127.8 | 128.0 | 128.8 | 128.3 | 128.3 | 128.2 |
| 10 | 122.4 | 122.5 | 122.5 | 122.5 | 122.5 | 122.5 | 126.5 | 126.5 | 127.3 | 126.9 | 126.8 | 126.7 |
| 1′ | 98.6 | – | – | – | – | – | 98.8 | – | – | – | – | – |
| 2′ | 30.8 | – | – | – | – | – | 30.5 | – | – | – | – | – |
| 3′ | 19.3 | – | – | – | – | – | 19.3 | – | – | – | – | – |
| 4′ | 25.8 | – | – | – | – | – | 25.4 | – | – | – | – | – |
| 5′ | 65.9 | – | – | – | – | – | 65.7 | – | – | – | – | – |
| $S-CH_2\underline{C}H_3$ | – | – | 15.1 | – | – | – | – | – | 15.7 | – | – | – |
| $S-\underline{C}H_2CH_3$ | – | – | 25.4 | – | – | – | – | – | 26.0 | – | – | – |
| C=O | – | – | 170.8 | 155.8 | 155.3 | 155.5 | – | – | 171.5 | 155.9 | 155.3 | 155.5 |
| $O-CH_3$ | – | – | – | 54.2 | – | – | – | – | – | 54.3 | – | – |
| $O-CH_2\underline{C}H_3$ | – | – | – | – | 14.1 | – | – | – | – | – | 14.2 | – |
| $O-\underline{C}H_2CH_3$ | – | – | – | – | 63.8 | – | – | – | – | – | 63.8 | – |
| $O-\underline{C}H_2CH[CH_3]_2$ | – | – | – | – | – | 73.9 | – | – | – | – | – | 73.6 |
| $O-CH_2\underline{C}H[CH_3]_2$ | – | – | – | – | – | 30.0 | – | – | – | – | – | 28.0 |
| $O-CH_2CH[\underline{C}H_3]_2$ | – | – | – | – | – | 18.8 | – | – | – | – | – | 18.8 |

Table II. Biological activity of the synthetic JH analogues on *Triatoma infestans* eggs.

| Compound | Dose of JH analogues that inhibited eclosion of eggs ID-50 ($\mu$g) |
|---|---|
| Fenoxycarb* | 4.2 ± 0.5 |
| S-Ethyl-[6,10-dimethyl-undeca-5E,9-dien-2(R,S)-yl]-thiolcarbonate** | 6.0 ± 1.5 |
| S-Ethyl-[6,10-dimethyl-undeca-5E,9-dien-2(S)-yl]-thiolcarbonate** | 9.8 ± 1.6 |
| **2a** | 13.5 ± 2.2 |
| **2b** | >15 |
| **4a** | 9.0 ± 2.5 |
| **4b** | >15 |
| **5a** | >15 |
| **5b** | >15 |
| **6a** | >15 |
| **6b** | >15 |
| **7a** | 8.8 ± 1.9 |
| **7b** | >15 |

* Commercial product; ** see reference [6].

atom plays in this case. A better result though lower than the activity of Fenoxycarb was obtained when the synthetic product has a sulfur atom in its molecule as it is in the case of compound **4a.**

The activity of compounds **2b–7b** in which the phenoxyphenoxy group has been replaced by the phenylphenyl one, was much lower than that of the control compound; this result could be attributed to the different molecular shape of these products.

## Experimental

*2-(4-Phenoxyphenoxy)-ethyl-tetrahydropyranyl-ether* (**2a**)

For general procedures see ref. [6]. To a stirred solution of KOH (4 mmol) in DMSO (5 ml), 4-phenoxyphenol (1 mmol) was added. After 5 min, tetrahydropyranyl derivative of ethyl chlorohydrine (2 mmol) was added, and the mixture was stirred overnight at room temperature. It was poured into water (50 ml) and extracted with $CH_2Cl_2$ (3×30 ml). The organic phase was washed with a saturated NaCl solution and dried over $MgSO_4$. Removal of the solvent afforded a residue that was purified by column chromatography (silica gel, hexane–EtOAc 8:2) yielding **2a** in 71% yield. IR (film) ($cm^{-1}$): 2950, 1580, 1470, 1200, 1000. $^1H$ NMR ($CDCl_3$): $\delta$ 1.40–1.90 (m, 6H, H-2′, H-3′, H-4′), 3.60–4.20 (m, 6H, H-1, H-2, H-5′), 3.68 (t, $J$ = 4 Hz, 1H, H-1′), 6.80–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 314 ($M^+$, 78), 230 (65), 186 (72), 185 (72), 85 (82), 77 (100).

*2-(4-Phenylphenoxy)-ethyl-tetrahydropyranyl-ether* (**2b**)

Following a procedure similar to that described for compound **2a** but using 4-phenylphenol, compound **2b** was obtained in 96% yield. Pure **2b** had m.p. 174–175 °C. IR (Nujol) ($cm^{-1}$): 1470, 1440, 1330, 1230, 1100, 1060, 960. $^1H$ NMR ($CDCl_3$): $\delta$ 1.42–2.05 (m, 6H, H-2′, H-3′, H-4′), 3.39–4.25 (m, 6H, H-1, H-2, H-5′), 4.72 (t, $J$ = 4 Hz, 1H, H-1′), 6.89–7.60 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 298 ($M^+$, 75), 214 (14), 170 (100), 85 (74).

*2-(4-Phenoxyphenoxy)-ethanol* (**3a**)

Compound **2a** (1 mmol) in MeOH (10 ml) was treated with *p*-toluensulphonic acid (1 M in $CH_2Cl_2$) (1 ml) and stirred overnight at room temperature. The MeOH was removed and the residue taken in $CH_2Cl_2$ (30 ml). The solution was washed with saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent gave a residue that was purified by column chromatography (silica gel, hexane–EtOAc 9:1) affording **3a** of m.p. 65–66 °C (EtOH–$H_2O$) in 95% yield. IR (Nujol) ($cm^{-1}$): 3060, 1570, 1470, 1220. $^1H$ NMR ($CDCl_3$): $\delta$ 4.05–4.20 (m, 4H, H-1, H-2), 6.82–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 230 ($M^+$, 100), 186 (67), 109 (53), 84 (91), 77 (89), 45 (13).

*2-(4-Phenylphenoxy)-ethanol* (**3b**)

Compound **2b** (1 mmol) was treated with as indicated for the preparation of compound **3a.** In this

case, compound **3b** was obtained in 89% yield. M.p. 137–138 °C (EtOH). IR (Nujol) ($cm^{-1}$): 3350, 2950, 1440, 1240. $^1H$ NMR ($CDCl_3$): $\delta$ 4.05–4.15 (m, 4H, H-1, H-2), 6.95–7.59 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 214 ($M^+$, 100), 170 (89), 169 (65), 153 (62), 45 (55).

*Preparation of carbonate and thiolcarbonate derivatives; general procedure*

The alcohol (**3a** or **3b**) (0.5 mmol) was dissolved in pyridine (3 ml) and treated dropwise with 0.5 ml of ethyl chlorothioformate or methyl, ethyl or isobutyl chloroformate and stirred at room temperature for 14 h. After addition of $CH_2Cl_2$ (30 ml) the solution was washed with 10% HCl (3×15 ml), with saturated $NaCO_3H$ solution (2×15 ml), and with $H_2O$ (2×15 ml), and dried ($MgSO_4$). The residue obtained for evaporation of the solvent was purified by column chromatography (silica gel, solvent indicated in each case).

*S-Ethyl-2-(4-phenoxyphenoxy)-ethyl-thiolcarbonate* (**4a**); *from* **3a**

After elution with hexane-EtOAc it was obtained in 80% yield as a syrup. IR (film) ($cm^{-1}$): 2950, 1710, 1490, 1210, 1130. $^1H$ NMR ($CDCl_3$): $\delta$ 1.33 (t, $J$ = 7 Hz, 3H, S–$CH_2C\underline{H}_3$), 3.90 (q, $J$ = 7 Hz, 2H, S–$C\underline{H}_2CH_3$), 4.10–4.26 (m, 2H, H-2), 4.50–4.62 (m, 2H, H-1), 6.88–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 318 ($M^+$, 37), 186 (14), 185 (65), 133 (61), 105 (100), 89 (51).

*S-Ethyl-2-(4-phenylphenoxy)-ethyl-thiolcarbonate* (**4b**); *from* **3b**

Eluted with hexane–EtOAc (9:1) in 86% yield. It was recrystallized from EtOH to m.p. 76–77 °C. IR (Nujol) ($cm^{-1}$): 1730, 1440, 1220. $^1H$ NMR ($CDCl_3$): $\delta$ 1.32 (t, $J$ = 7 Hz, 3H, $CH_2C\underline{H}_3$), 2.89 (q, $J$ = 7 Hz, 2H, $C\underline{H}_2CH_3$), 4.16–4.32 (m, 2H, H-2), 4.52–4.66 (m, 2H, H-1), 6.94–7.60 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 302 ($M^+$, 68), 170 (64), 169 (70), 152 (100), 105 (87), 89 (83).

*Methyl-2-(4-phenoxyphenoxy)-ethyl-carbonate* (**5a**); *from* **3a**

After elution with hexane–EtOAc (85:15), compound **5a** (80%) was recrystallized from EtOH. M.p. 114–116 °C. IR (Nujol) ($cm^{-1}$): 2950, 1740, 1460, 1180. $^1H$ NMR ($CDCl_3$): $\delta$ 3.82 (s, 3H, O–$CH_3$), 4.17 (t, $J$ = 5 Hz, 2H, H-2), 4.50 (t, $J$ = 5 Hz, 2H, H-1), 6.86–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 288 ($M^+$, 59), 213 (28), 186 (55), 185 (72), 103 (100), 59 (76).

*Methyl-2-(4-phenylphenoxy)-ethyl-carbonate-*(**5b**); *from* **3b**

Elution with hexane–EtOAc (9:1) afforded compound **5b** in 64% yield. It was recrystallized from EtOH to m.p. 110–111 °C. IR (Nujol) ($cm^{-1}$): 1740, 1440, 1200. $^1H$ NMR ($CDCl_3$): $\delta$ 3.83 (s, 3H, O–$CH_3$), 4.18–4.34 (m, 2H, H-2), 4.44–4.60 (m, 2H, H-1), 6.92–7.60 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 272 ($M^+$, 54), 197 (80), 170 (67), 169 (58), 153 (59), 103 (56), 59 (100).

*Ethyl-2-(4-phenoxyphenoxy)-ethyl-carbonate* (**6a**); *from* **3a**

After elution with hexane-EtOAc compound **6a** was obtained as a syrup in 99% yield. IR (film) ($cm^{-1}$): 2950, 1740, 1470, 1240, 1200, 1000. $^1H$ NMR ($CDCl_3$): $\delta$ 1.33 (t, $J$ = 7 Hz, 3H, $CH_2C\underline{H}_3$), 4.18 (t, $J$ = 5 Hz, 2H, H-2), 4.24 (q, $J$ = 7 Hz, 2H, $C\underline{H}_2CH_3$), 4.50 (t, $J$ = 5 Hz, 2H, H-1), 6.80–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 302 ($M^+$, 81), 213 (9), 186 (91), 185 (13), 117 (85), 89 (100).

*Ethyl-2-(4-phenylphenoxy)-ethyl-carbonate* (**6b**); *from* **3b**

Elution with hexane–EtOAc (7:3) gave compound **6b** in 98% yield. After recrystallization from EtOH it has m.p. 159–161 °C. IR (Nujol) ($cm^{-1}$): 1730, 1440, 1220. $^1H$ NMR ($CDCl_3$): $\delta$ 1.32 (t, $J$ = 7 Hz, 3H, $CH_2C\underline{H}_3$), 4.16–4.20 (m, 2H, H-2), 4.23 (q, $J$ = 7 Hz, 2H, $C\underline{H}_2CH_3$), 4.43–4.52 (m, 2H, H-1), 6.91–7.61 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 286 ($M^+$, 89), 197 (69), 170 (92), 169 (83), 152 (100), 117 (83), 89 (58).

*Isobutyl-2-(4-phenoxyphenoxy)-ethyl-carbonate* (**7a**); *from* **3a**

Eluted with hexane–EtOAc (9:1) in 90% yield as a syrup. IR (film) ($cm^{-1}$): 2950, 1740, 1440, 1350, 1220. $^1H$ NMR ($CDCl_3$): $\delta$ 0.96 (d, $J$ = 6 Hz, 6H, $CH[C\underline{H}_3]_2$), 1.99 (m, 1H, $C\underline{H}[CH_3]_2$), 3.95 (d, $J$ = 7 Hz, 2H, $C\underline{H}_2CH[CH_3]_2$), 4.16 (t, $J$ = 5 Hz, 2H, H-2), 4.48 (t, $J$ = 5 Hz, 2H, H-1), 6.80–7.40 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 330 ($M^+$, 86), 213 (11), 186 (80), 145 (74), 89 (100).

*Isobutyl-2-(4-phenylphenoxy)-ethyl-carbonate* (**7b**); *from* **3b**

Elution with hexane–EtOAc (9:1) afforded compound **7b** in 91% yield. Recrystallized from EtOH, it has m.p. 171–172 °C. IR (Nujol) ($cm^{-1}$): 1740, 1445, 1350, 1210. $^1H$ NMR ($CDCl_3$): $\delta$ 0.95 (d, $J$ = 7 Hz, 3H, $CH[C\underline{H}_3]_2$), 1.99 (m, 1H, $C\underline{H}[CH_3]_2$), 3.95 (d, $J$ = 7 Hz, 2H, $C\underline{H}_2CH[CH_3]_2$), 4.14–4.29 (m, 2H, H-2), 4.40–4.54 (m, 2H, H-1), 6.90–7.60 (m, 9H, aromatic protons). $^{13}C$ NMR (see Table I). MS (*m/z*, %): 314 ($M^+$, 100), 197 (58), 170 (89), 169 (63), 153 (71), 145 (81).

We thank CONICET and The Organization of the American States for partial financial support.

[1] C. A. Henrick, in J. R. Coats (ed.): Insecticide Mode of Action, Academic Press, N.Y. (1982).
[2] A. Nakayama, H. Iwamura, and T. Fujita, J. Med. Chem. **27,** 1493 (1984).
[3] M. Hatakoshi, H. Kisida, I. Fujimoto, N. Itaya, and I. Nakayama, Appl. Ent. Zool. **19,** 523 (1984).
[4] H. Kisida, M. Hatakoshi, N. Itaya, and I. Nakayama, Agric. Biol. Chem. **48,** 2889 (1984).
[5] T. Ohsumi, M. Hatakoshi, H. Kisida, N. Matsuo, I. Nakayama, and N. Itaya, Agric. Biol. Chem. **49,** 3197 (1985).
[6] J. B. Rodriguez, E. G. Gros, and A. M. Stoka, Z. Naturforsch. **43b,** 1038 (1988).
[7] P. M. Frearson, D. G. Hardy, and E. S. Stern, J. Chem. Soc. 2103 (1960).
[8] W. S. Abbot, J. Econ. Ent. **18,** 265 (1985).