Synthesis of 1,4,5-Trisubstituted Imidazoles as Juvenile Hormone Analogues

Silvana Bernasconi, Giancarlo Jommi*, Roberto Pagliarin and Paolo Tavecchia

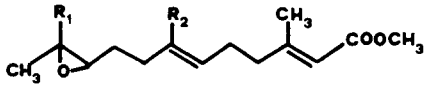
Università degli Studi di Milano,
Dipartimento di Chimica Organica ed Industriale,
Facoltà di Scienze, Via G. Venezian, 21,
20133-Milano, Italy

Received April 23, 1987

Eight compounds containing *N*- or *N'*-alkylated imidazole rings have been synthesized and their structures have been chemically and spectroscopically demonstrated. These molecules, submitted to biological tests in order to evaluate their activity as juvenile hormones, provoke morphological changes in the pupae of *Tenebrio Molitor.*

J. Heterocyclic Chem., **25**, 725 (1988).

With the object of finding new juvenile-hormone-like substances [1,2] and carefully examining the parameters between the biological activity and the chemical structure a few compounds, juvenile hormone bioanalogues, have been synthesized and biologically tested.



I

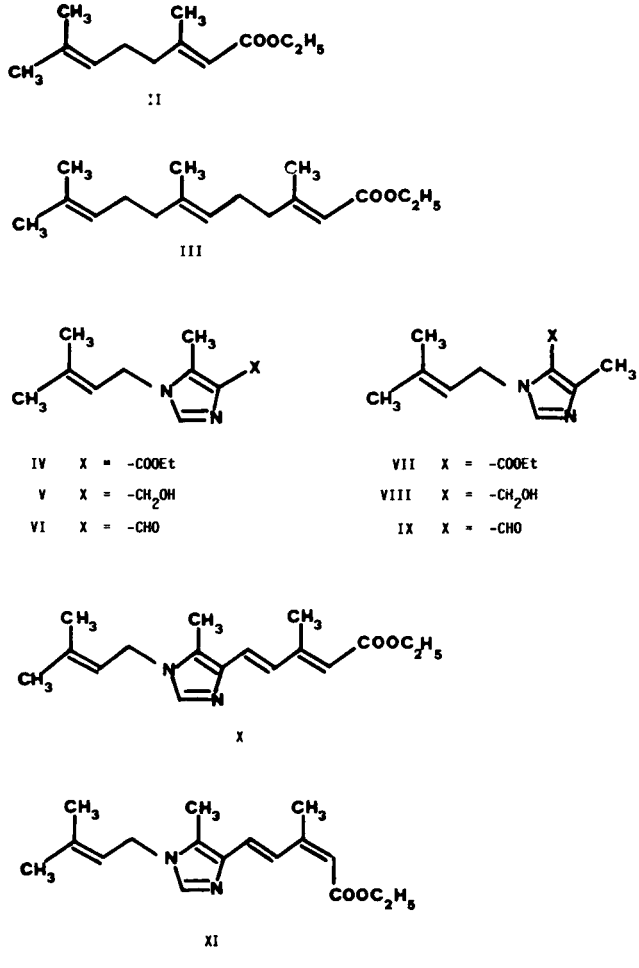
$R_1 = R_2 = Et$ (J.H. I)

$R_1 = Et$ $R_2 = Me$ (J.H. II)

$R_1 = R_2 = Me$ (J.H. III)

Figure 1

The biological activity of these compounds (J.H.) depends on the presence of the α,β-unsaturated ester group, while the alkyl groups in positions 3,7,11 can be modified without any loss of activity; in fact both the geranic and the farnesic acid derivatives show a biological activity similar to juvenile hormones [3]. Some synthetic analogues of **I** prove that the substitution of a methylene group in the chain with an heteroatom such as oxygen, nitrogen, and sulphur can influence the biological activity against specific insects; it has also been verified in many works that alicyclic and aromatic compounds exhibit a considerably high and specific biological activity [3]. We carried out the synthesis of juvenile hormone analogues containing an imidazole ring; the substitution of the carbon in the position 8 with a nitrogen atom [4] and the formation of the imidazole ring, which includes atoms C-6, C-7, C-8 of the farnesoate chain III, should have permitted the locking of the rotation around the bond C-7, C-8, thus reducing the innumerable conformations. The introduction of the imidazole should also have given the possibility of verifying the influence of a polarity increase on the biological activity: we took into consideration that, besides the shape and size of the molecule, exists a clear correlation between water and lipid solubility, and juvenile activity.



II

III

IV X = -COOEt
V X = $-CH_2OH$
VI X = -CHO

VII X = -COOEt
VIII X = $-CH_2OH$
IX X = -CHO

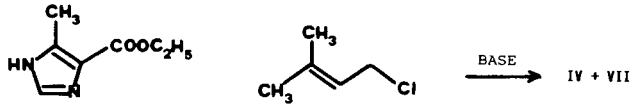
X

XI

Figure 2

The synthetic scheme includes the study of *N*-alkylation of 4(5)-methyl-5(4)-ethoxycarbonylimidazole **XII** to obtain the ethyl geraniate analogues **IV** and their transformation

into the farnesoate analogues **X** and **XI**. The literature describes several methods to prepare *N*-alkylimidazoles, starting from either the open chain [5], or by the alkylation of the substituted imidazoles with bases [6], or Lewis acids [7], or in the presence of transfer phase catalysts [8]. In our work compounds **IV** and **VII** were obtained from compound **XII**, (easily prepared as indicated in the literature [9]), by alkylation with 1-chloro-3-methyl-2-butene [10], under different experimental conditions as reported in Table 1.



XII

Figure 3

Table 1

	T (°C)	Yield %	Ratio **IV/VII**
a) NaH, DMF	25	84	1.7/1
b) NaOH, benzene, tetrabutylammonium bromide	70	72	1/1
c) KOH, CH_3CN tetrabutylammonium bromide	25	57	1/4.5
d) KOH, CH_3CN tetrabutylammonium bromide	−10	81	1/1.3
e) "	−15	81	1/1.9
f) "	−50	no reaction	
g) KOH, CH_3CN HMPA/tetrabutylammonium bromide	−40	43	1/1.1

Under experimental conditions, a variable ratio between the two alkylated molecules has been observed but never the exclusive formation of only one product. The same result has been reported by Lam *et al.* [11] in the alkylation of **XII** in dimethylformamide or methoxyethanol, using triethylamine as the base. The only case of regioselective alkylation is the glycosylation of persilylated **XII** with an opportune sugar in dry dichloroethane and tin tetrachloride as the Lewis acid [7d]. As indicated in Table 1 isomer **IV** is the main product only in case a), while under transfer phase conditions [12] (c, d, e), isomer **VII** is predominant even with a change in temperature. In case g) the addition of cosolvent does not produce a regioselectivity of the alkylation reaction. Regioisomers **IV** and **VII** can be easily separated by column chromatography with silica gel, and the attribution of the structure is performed by ^1H nmr spectroscopy. The ^1H nmr chemical shifts of the 4(5)-5(4)-disubstituted -*N*-alkylated imidazoles are known from the literature [13]: the aliphatic hydrogens of the carbon bound to the nitrogen atom, have a different chemical shift in the two regioisomers. As reported in Table 2 are found for resonance at lower fields those hydrogens of the compound which possesses the alkylated nitrogen closer to either the ethoxycarbonyl, the hydroxymethylene, or the formyl group.

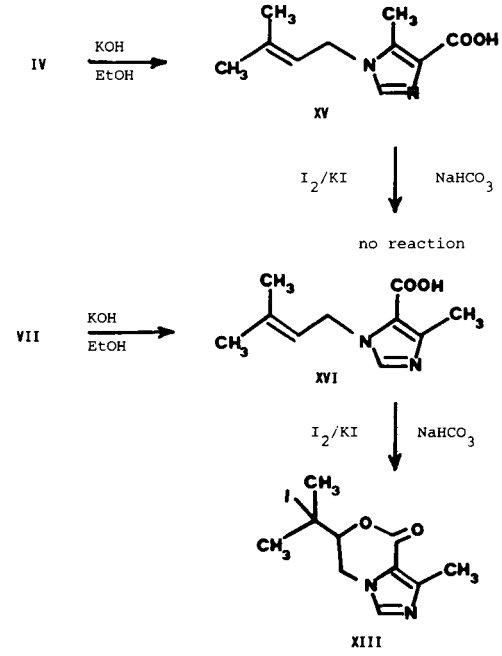
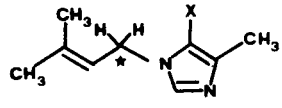
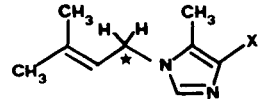


Figure 4

Table 2



	X =	σ_{CH_2}	4.75
IV	-COOEt		
V	$-CH_2OH$	"	4.65
VI	-CHO	"	4.85



			$\Delta\sigma\ -CH_2-$
VII	σ_{CH_2}	4.40	0.35
VIII	"	4.30	0.30
IX	"	4.50	0.35

This fact, already reported by Cook [7a] and ascribed to the anisotropic effect of the carboxy group, is on the contrary, significant, even when the substituent is the hydroxymethylene group: as a consequence it is possible to calculate the relative composition of **IV** and **VII** directly from the crude reaction material. The structures of the two isomers have also been chemically confirmed: only one of the two compounds **IV** and **VII** in the acid forms **XV** and **XVI** undergo a iodo-lactonization reaction.

After the alkaline hydrolysis of the ester group in **IV** and **VII** the corresponding acids **XV** and **XVI**, were separately treated with a solution of iodine, potassium iodide and sodium bicarbonate for 24 hours at room temperature [14]. In fact only compound **XVI** was transformed into the compound **XIII**, whereas the other was recovered unchanged. The reduction of the ethoxycarbonyl group of the molecules **IV** and **VII** with lithium aluminium hydride in tetrahydrofuran at room temperature provides respectively the alcohol **V** as a white solid after recrystallization and the alcohol **VIII** as an oil after purication by chromatography on silica gel. Aldehydes **VI** and **IX** are obtained in good yield by allylic oxidation of **V** and **VIII** with manganese bioxide and methylenechloride [15]. The aldehyde **VI** is subsequently transformed to synthesize the derivatives of ethyl farnesoate, following the scheme shown in Figure 5.

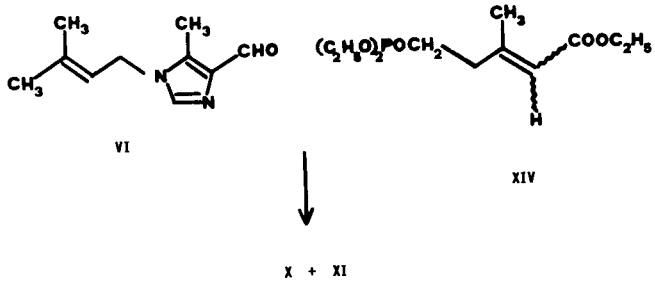


Figure 5

The Wittig-Horner reaction [16] between the aldehyde **VI** and the phosphonate **XIV** [17] (mixture *E* + *Z*) furnishes the polyunsaturated compound **X** (2*E*,4*E*) and **XI** (2*Z*,4*E*) with a ratio 8:2 (total yield 70%). The structures have been assigned with ^{1}H nmr spectroscopy in accordance with the literature data [18]; note also that, in our case, the new double bond ($\Delta_{4\text{-}5}$ = *E*) has been stereospecifically produced. Compounds **IV-XI** have been submitted to biological tests on the species of Tenebrio Molitor and Musca Domestica, but no juvenile activity has been observed.

EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Nuclear Magnetic Resonance spectra were determined on Hitachi-Perkin-Elmer R 24 (60 MHz) and Varian XL 200 instruments using tetramethylsilane as internal standard. Mass spectral analyses were performed on a 7070 EQ instrument. Distillation under vacuum refers to bulb-to-bulb method using a Büchi GKR-50 apparatus. Compound **XII** were purified by sublimation (150°/0.8 mm Hg).

1-(3-Methylbut-2-enyl)-4-carbetoxy-5-methylimidazole **IV** and 1-(3-Methylbut-2-enyl)-4-methyl-5-carbetoxyimidazole **VII** Table I-a).

To a magnetically stirred solution of **XII** (6.5 g, 42.2 mmoles) in dry *N*,*N*-dimethylformamide (20 ml) at 0° was slowly added sodium hydride (1.27 g, 80% in oil, 42.2 mmoles) under nitrogen atmosphere. After ten minutes, 1-chloro-3-methylbut-2-ene (5.25 g, 50 mmoles) was added and then the cooling bath was removed. After 24 hours *N*,*N*-dimethylformamide was distilled under reduced pressure, water (30 ml) was added and the mixture was extracted with ethyl acetate (3 x 15 ml). The organic layer was dried with sodium sulphate and evaporated to give a thick oil (9.74 g) which was chromatographed through a column of silica gel using ethyl acetate-petroleum ether as eluents (1:1) to give **IV** (4.99 g, 53%, oil) and **VII** (2.88 g, 31%, oil).

Compound **IV**.

This compound had ir (chloroform): 1695, 1565 cm^{-1}; ^{1}H nmr (deuteriochloroform 200 MHz): δ 1.36 (t, 3H, J = 7 Hz), 1.75 (m, 6H), 2.49 (s, 3H), 4.30 (q, 2H, J = 7 Hz), 4.40 (d, 2H, J = 7 Hz), 5.20 (m, 1H), 7.36 (s, 1H); ms: (70 eV) m/z (relative intensity) 222 (M$^+$), 207, 177, 176, 154, 125, 109, 108, 69 (100).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.60. Found: C, 64.46; H, 8.21; N, 12.39.

Compound **VII**.

This compound had ir (chloroform): 1690, 1545 cm^{-1}; ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.29 (t, 3H, J = 7 Hz), 1.65 (m, 6H), 2.39 (s, 3H), 4.24 (q, 2H, J = 7 Hz), 4.75 (d, 2H, J = 7 Hz), 5.28 (m, 1H), 7.39 (s, 1H); ms: (70 eV) m/z (relative intensity) 222 (M$^+$), 207, 177, 176, 155, 154 (100), 149, 136, 135, 69.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.82; H, 8.17; N, 12.60. Found: C, 64.55; H, 8.14; N, 12.43.

Table 1, b).

To the suspension of **XII** (154 mg, 1 mmole), tetrabutylammonium bromide (12.9 mg, 0.04 mmole) 1-chloro-3-methylbut-2-ene (125 mg, 1.2 mmoles) in benzene (3 ml) was added a solution of sodium hydroxide 50% (0.3 ml). The mixture was stirred at 70° for 2.5 hours. After cooling, the suspension was diluted with water and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 5 ml). The combined extracts were dried over sodium sulphate and after a filtration and the removal of the solvent, a residue of **IV** and **VII** (160 mg, 72%) was obtained. From the ^{1}H nmr the ratio between **IV** and **VII** was 1:1.

Table 1, c, d, e, f) General Procedure.

To a solution of **XII** (1.2 g, 7.79 mmoles) in acetonitrile (24 ml) at −15° (or different temperature, as described in Table 1) were added tetrabutylammonium bromide (100 mg, 0.31 mmole) and powdered potassium hyroxide (523 mg, 9.34 mmoles). After 30 minutes, 1-chloro-3-methylbut-2-ene (1.12 g, 10.7 mmoles) in acetonitrile (10 ml) was added dropwise and the reaction was stirred for 30 hours. The solvent was evaporated, water (30 ml) was added and the mixture was extracted with dichloromethane (3 x 10 ml). The organic layer was dried with sodium sulphate and filtered, then the filtrate was distilled; the resulting residue was purified by chromatography with silica gel using ethyl acetate-petroleum ether as eluent (1:1) to give **IV** (0.480 g, 28%) and **VII** (0.92 g, 53%).

Table 1, g).

The suspension of **XII** (154 mg, 1 mmole) and powdered potassium hydroxide (67 mg, 1.2 mmoles) in acetonitrile (4 ml) and hexamethyl phosphoric triamide (1 ml) was stirred at −40° for 30 minutes, then 1-chloro-3-methylbut-2-ene (125 mg, 1.2 mmoles) in acetonitrile (2 ml) was added dropwise. After 24 hours the mixture was worked following the same pro-

cedure described for c, d, e, f, 21% of compound **IV** and 23% of **VII** are recovered.

Iodolactonization of **XVI**. 1-(3-Methylbut-2-enyl)-4-methyl-5-carboxyimidazole.

Compound **VII** (222 mg, 1 mmole) was refluxed in a 0.5 *N* solution of potassium hydroxide in ethanol (2 ml). After 6 hours the solvent was evaporated, water (5 ml) was added and the solution was adjusted to *p*H 7.5-8 with hydrogen chloride 1 *N*. A solution of sodium hydrogen carbonate 0.5 *M* (15 ml) and a solution of iodine (508 mg, 2 mmoles) and potassium iodide (996 mg, 6 mmoles) in water (4 ml) were added to the mixture. After 24 hours in the dark with stirring the mixture was extracted with methylene chloride (2 x 5 ml). The organic layer was washed with aqueous sodium thiosulphate, dried with sodium sulfate and evaporated to give a solid residue. A sample was crystallized from diisopropyl ether-ethyl acetate to obtain pure **XIII**, mp = 140° dec; ir (nujol): 1715, 1590 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.15 (d, 6H, J = 5 Hz), 2.50 (s, 3H), 4.95-4.15 (m, 3H), 7.65 (s, 1H); ms: 70 eV) m/z (relative intensity) 320 (M^+), 193 (100), 151, 149, 134, 109, 94, 69, 67.

Anal. Calcd. for $C_{10}H_{13}IN_2O_2$: C, 37.51; H, 4.06; N, 8.75. Found: C, 38.07; H, 4.08; N, 8.57.

1-(3-Methylbut-2-enyl)-4-hydroxymethyl-5-methylimidazole **V** and 1-(3-Methylbut-2-enyl)-4-methyl-5-hydroxymethylimidazole **VIII**.

1-(3-Methylbut-2-enyl)-4-carbetoxy-5-methylimidazole **IV** (0.526 g, 2.37 mmoles) in dry tetrahydrofuran (3 ml) was dropped into a suspension of lithium aluminium hydride (0.09 g, 2.37 mmoles) in dry tetrahydrofuran (3 ml) maintained at 0° under nitrogen atmosphere. After 24 hours at 25°, a 10% solution of potassium hydroxide (5 ml) was added and the mixture was stirred for 15 minutes. Tetrahydrofuran was evaporated and the residue was extracted with chloroform (4 x 5 ml); the organic layer was dried over sodium sulphate, filtered and the filtrate was evaporated to give a solid residue. Pure **V** (0.206 g, 49%) was obtained by crystallization from chloroform-diisopropyl ether, mp = 129-130°C; ir (nujol): 3400-3100, 1500 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.75 (s, 6H), 2.22 (s, 3H), 4.38 (d, 2H, J = 7 Hz), 4.55 (s, 2H), 5.28 (b t, 1H), 6.90 (b s, 1H), 7.40 (s, 1H); ms: (70 eV) m/z (relative intensity) 180 (M^+), 112, 111, 95, 94, 83, 69 (100).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.61; H, 8.96; N, 15.54. Found: C, 66.71; H, 9.03; N, 15.55.

1-(3-Methylbut-2-enyl)-4-methyl-5-hydroxymethylimidazole **VIII**.

This compound was obtained with 71% yield. It solidified on standing, mp = 81-82°; ir (nujol): 3700-3100, 1500 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.78 (s, 6H), 2.08 (s, 3H), 4.75-4.45 (m, 5H), 5.35 (b t, 1H), 7.30 (s, 1H); ms: (70 eV) m/z (relative intensity) 180 (M^+), 112, 111, 95, 94, 83, 69 (100).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.61; H, 8.96; N, 15.54. Found: C, 66.72; H, 8.92; N, 15.61.

1-(3-Methylbut-2-enyl)-4-formyl-5-methylimidazole **VI** and 1-(3-Methylbut-2-enyl)-4-methyl-5-formylimidazole **IX**.

To a solution of **V** (0.40 g, 2.22 mmoles) in methylene chloride (15 ml) manganese **IV** oxide activated (1.25 g, 14.3 mmoles) was added and the suspension was stirred for one hour at room temperature. After filtration through celite, the solution was dried over sodium sulphate, filtered and evaporated. The residue was chromatographed over silica gel using chloroform-methanol (gradient to 5%) to give **VI** (0.32 g, 81%) which was recrystallized from cyclohexane/ethyl acetate, mp = 76-77°; ir (nujol): 1670, 1555 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.80 (b s, 6H), 2.55 (s, 3H), 4.55 (d, 2H, J = 7 Hz), 5.30 (m, 1H), 7.53 (s, 1H), 9.95 (s, 1H); ms: (70 eV) m/z (relative intensity) 178 (M^+), 163, 110, 69 (100).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.37; H, 7.93; N, 15.71. Found: C, 67.23; H, 7.87, N, 15.65.

Compound **IX**.

Compound **VIII** was treated in the same manner to give **IX** (65%). It solidified on standing, mp = 40-41°; ir (nujol): 1670, 1500 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.75 (s, 6H), 2.50 (s, 3H), 4.85 (d, 2H, J = 7 Hz), 5.40 (m, 1H), 7.60 (b s, 1H), 9.90 (s, 1H); ms: (70 eV) m/z (relative intensity) 178 (M^+), 163, 110, 69 (100).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.37; H, 7.93; N, 15.71. Found: C, 67.59; H, 7.96; N, 15.58.

Ethyl 3-Methyl-5-[1-(3-methylbut-2-enyl)-5-methyl-4-imidazolyl]penta-(2*E*,4*E*)dienoate **X**.

A solution of ethyl 3-methyl-4-diethylphosphonobut-2-enoate (*E-Z* mixture 55/45) (0.244 g, 0.92 mmole) in dry tetrahydrofuran (2 ml) was slowly added to a suspension of sodium hydride 60% dispersion in mineral oil (0.037 g, 0.92 mmole) in dry tetrahydrofuran (2 ml) at room temperature. After 15 minutes the mixture was cooled at 0° and the aldehyde **VI** (0.150 g, 0.84 mmole) in dry tetrahydrofuran (2 ml) was added dropwise. After 4 hours at room temperature, the solvent was evaporated, water (10 ml) was added and the reaction mixture was extracted with ethyl acetate (2 x 5 ml). The organic layer was dried over sodium sulphate and evaporated. The residue was subjected to "flash chromatography" using as eluent petroleum ether-ethyl acetate (1:1). The separation was quantitative to give the solid compounds **X** (2*E*,4*E*, 0.135 g, 56%) and **XI** (2*Z*,4*E*, 0.035 g, 14%).

Compound **X**.

This compound had mp = 85-85°; ir (chloroform): 1700, 1625, 1610, 1500 cm^{-1}, ^1H nmr (deuteriochloroform, 200 MHz): δ 1.28 (t, 3H, J = 7 Hz), 1.75 (b s, 6H), 2.22 (s, 3H), 2.38 (d, 3H, J = 1.5 Hz), 4.15 (q, 2H, J = 7 Hz), 4.39 (d, 2H, J = 7 Hz), 5.20 (m, 1H), 5.84 (b s, 1H), 6.78 (d, 1H, J = 15.3 Hz), 6.97 (d, 1H, J = 15.3 Hz), 7.40 (s, 1H); ms: (70 eV) m/z (relative intensity) 288 (M^+), 248, 215, 175, 147 (100), 120, 69.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.78; H, 8.40; N, 9.72. Found: C, 70.68; H, 8.42; N, 9.64.

Compound **XI**.

This compound had mp = 144-146°; ir (chloroform): 1700, 1625, 1610, 1500 cm^{-1}; ^1H nmr (deuteriochloroform, 200 MHz): δ 1.28 (t, 3H, J = 7 Hz), 1.75 (b s, 6H), 2.08 (d, 3H, J = 1.5 Hz), 2.29 (s, 3H), 4.16 (q, 2H, J = 7 Hz), 4.39 (d, 2H, J = 7 Hz), 5.22 (m, 1H), 5.63 (d, 1H, J = 1.5 Hz), 6.85 (d, 1H, J = 16 Hz), 7.40 (s, 1H), 8.25 (d, 1H, J = 16 Hz); ms: (70 eV) m/z (relative intensity) 288 (M^+), 243, 215, 175, 147 (100), 120, 69.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.78; H, 8.40; N, 9.71. Found: C, 70.32; H, 8.18; N, 9.38.

Biological Tests.

The compounds were assayed on the species and by the methods described below. *Tenebrio molitor L.* (*Coleoptera, Tenebrionidae*): administration by contact to 1-20 hour pupae of 200 μg of active substances for individual (2 samples of 30 individuals); *Musca Domestica L.* (*Diptera, Muscidae*): administration has been carried out by ingestion and contact of a solution of active compound (200 ppm for individual) in acetone, to 3 days larvae (2 samples of 100 individuals). The compounds **IV-XI** were found to be inactives on *Musca Domestica L.*, whereas on *Tenebrio Molitor* they give rise to some malformation which cannot be ascribed to a typical activity as juvenile hormones. This research has been supported by the Italian National Research Council (CNR) special "ad hoc" program "Fitofarmaci e Fitoregolatori" Subproject 7.

Acknowledgments.

Thanks are due to Professor G. Bolchi Serini for the biological tests.

REFERENCES AND NOTES

[1] S. Bernasconi, A. Corbella, M. Ferrari and M. Sisti, *Experientia*, **35**, 11 (1979).

[2] S. Bernasconi, M. Ferrari, P. Gariboldi, M. Sisti, G. Bolchi Serini and M. Colombo, *Experientia*, **36**, 1337 (1980).

[3] K. Slama, M. Romanuk and F. Sorm, "Insect Hormones and Bioanalogues", Springer-Verlag, Wien and New York, 1974.

[4] N. Wakabayash, M. Schwarz, P. E. Sonnet, R. M. Water, R. E. Redfer and M. Jacobsson, "Compounds Related to Insect Juvenile Hormones", *Mitt. Schweiz. Ent. Ges.*, **44**, 131 (1971).

[5a] P. K. Martin, H. R. Matthews, H. Rapoport and G. Thyagarayan, *J. Org. Chem.*, **33**, 3758 (1968); [b] V. Buran and G. G. Massaroli, *Boll. Chim. Farm.*, **119**, 725 (1980).

[6a] M. Hoffer and E. Grunberg, *J. Med. Chem.*, **17**, 1019 (1974); [b] I. Antonini, G. Cristalli, P. Franchetti, M. Grifantini and S. Martelli, *Synthesis*, 47 (1983); [c] R. P. Gupta, C. A. Larroquette, K. C. Agrawal, J. Grodkowski and P. Neta, *J. Med. Chem.*, **28**, 987 (1985).

[7a] P. D. Cook, R. J. Rousseau, A. Moshin Mian, P. Dea, R. B. Meyer, Jr., and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976); [b] P. D. Cook, L. B. Allen, D. G. Steeter, J. H. Huffman, R. W. Sidwell and R. K. Robins, *J. Med. Chem.*, **21**, 1212 (1978); [c] M. T. Garcia-Lopez and R. Herranz, *J. Heterocyclic Chem.*, **19**, 233 (1982); [d] S. G. Wood, K. G. Upadhya, N. K. Dalley, A. Mckernan, P. G. Canonico, R. K. Robins and G. R. Renvankar, *J. Med. Chem.*, **28**, 1198 (1985); [e] J. A. Montgomery, H. J. Thomas, A. L. Zell, H. M. Einsphar and C. E. Bugg, *J. Med. Chem.*, **28**, 1751 (1985).

[8] H. G. M. Dou and J. Metzger, *Bull. Soc. Chim. France*, 1861 (1976).

[9a] H. Bohme and H. Schneider, *Chem. Ber.*, **91**, 996 (1958); [b] H. Graboyes, T. Y. Kasper, P. D. Vaidya, *Chem. Abstr.*, **97**, 72363w (1982).

[10] W. J. Jones and H. W. T. Chorley, *J. Chem. Soc.*, 832 (1946).

[11] B. L. Lam, G. R. Wellman and C. S. Labaw, *J. Am. Chem. Soc.*, **47**, 144 (1982).

[12] E. V. Dehmlow and S. S. Dehmlov, "Phase Transfer Catalysis", Verlag Chemie Weinheim, Deerfield Beach, Florida, Basel, 1980.

[13] See refs [7a], [7e], [11], [6b] and references therein.

[14] H. O. House, R. G. Carlson and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

[15] E. F. Pratt and J. F. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1979).

[16a] D. Davalian and C. H. Heathcock, *J. Org. Chem.*, **44**, 4458 (1979); [b] M. I. Dawson, P. D. Hobbs, L. S. Chan and W. Chao, *J. Med. Chem.*, **24**, 1214 (1981).

[17] J. B. Davis, L. M. Jachman, P. T. Siddons and B. C. L. Weedon, *J. Chem. Soc. (C)*, 2154 (1966).

[18a] S. Bittner, M. Gorodetsky, I. Har-Paz, Y. Mizrahi and A. E. Richmond, *Phytochemistry*, **16**, 1143 (1977); [b] P. Albaugh Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, **48**, 5288 (1983).