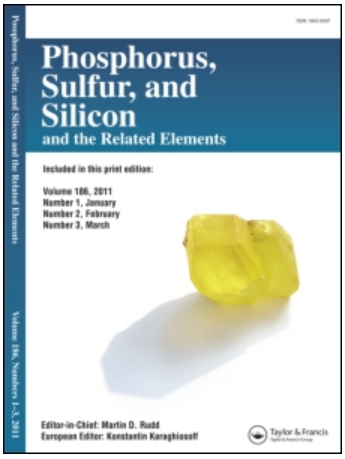

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SYNTHESIS OF THE TERTIARY PHOSPHINE OXIDES POSSESSING JUVENILE HORMONE ACTIVITY

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SYNTHESIS OF THE TERTIARY PHOSPHINE OXIDES POSSESSING JUVENILE HORMONE ACTIVITY

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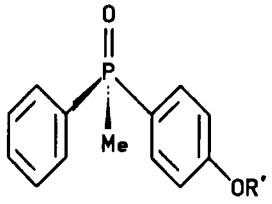
The synthesis of the first organophosphorus compounds (**1a–d**) possessing insect juvenile hormone activity is described. The structure of the compounds (**1a–d**) is confirmed by IR and NMR spectra.

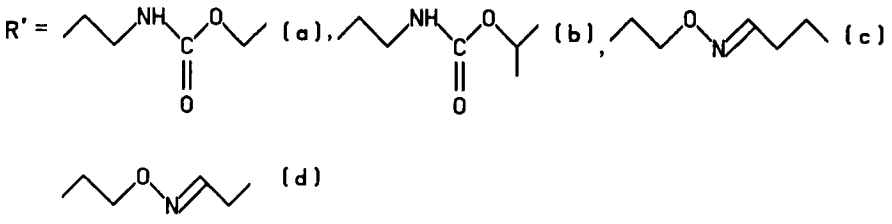
Key words: Tertiary phosphine oxides; phenols phosphorylated; phosphinites; NMR spectra; mimetic insect juvenile hormones; biological activity.

INTRODUCTION

In search for new kinds of biological activity of the organophosphorus compound we found that the tertiary phosphine oxides (**1a–d**) are insect juvenile hormone (JH) mimics, in spite of their structural differences from the naturally occurring JHs. These compounds are the first organophosphorus mimetics of insect juvenile hormones,[1–3] unlike the terpenoid and aromatic juvenoids that are known and have practical application.[4–6] In this paper we report on the synthesis and characterization of new bioactive compounds (**1a–d**).

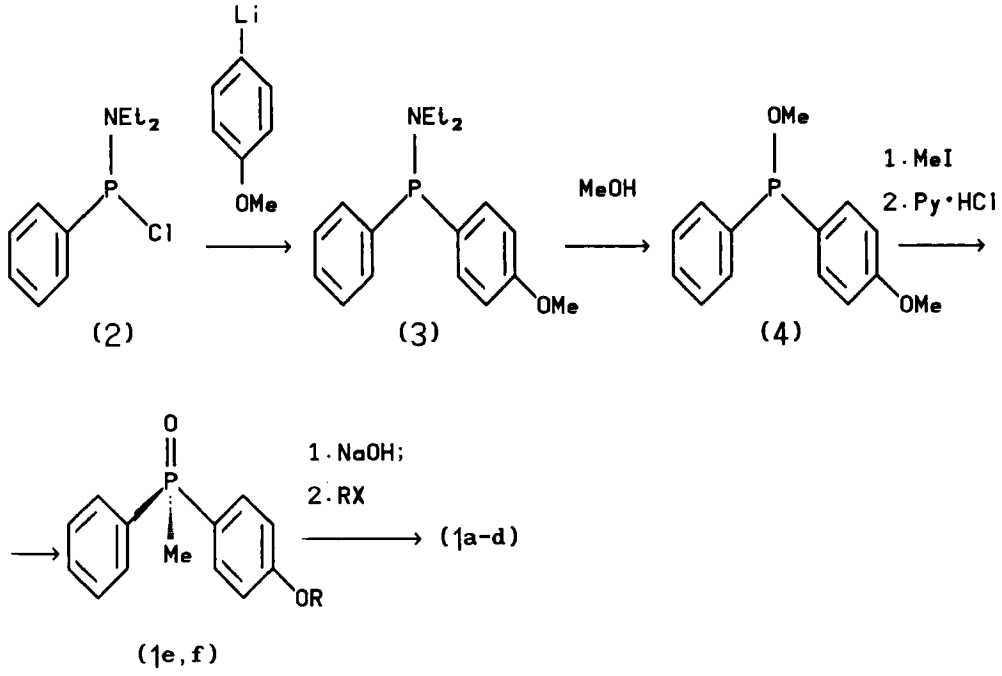


(1a-d)



RESULTS AND DISCUSSION

The synthesis of the compounds (**1a–d**) was carried out as shown in the Scheme.



R= Me (e), H (f).

SCHEME

The diethylamino-phenyl-chlorophosphine (**2**) reacts with lithium anisole to give aminophosphine (**3**) which on treatment with methanol yields phosphinite (**4**). The phosphinite (**4**) reacts with iodomethane to form a tertiary phosphine oxide (**1e**) which on heating with pyridine hydrochloride in dimethylformamide is transformed into a phenol (**1f**). The alkylation of the phenol (**1f**) by N-chloroethylcarbamat or by propionaldoxime-O-2-bromoethylether leads to the tertiary phosphine oxides (**1a–d**), which were purified by silica gel column chromatography. The compounds (**1a–d**) are stable, easily soluble in polar solvents, viscous liquids. The structure of these compounds was determined by elemental analysis. IR and NMR spectra. Their purity was confirmed by the high performance liquid chromatography.

BIOLOGICAL ACTIVITY

All compounds were bioassayed for their hormonomimetic activity against four selected insect species (*Tenebrio molitor*, *Musca domestica*, *Galleria melonella*, *Culex pipiens*). The activity of these mimetics was stronger than that of JH I and comparable to that of methoprene [isopropyl (2*E*, 4*E*)-11-methoxy-3,7,11-tridecadienoate], one of the most active JH-mimetic compounds known.[6] The compounds (**1a–d**) inhibit the development of the first generation of insects at a concentration of 5 ppm. The compounds (**1a–d**) show at a low concentration a high preventive juvenile hormone-like controlling effect and therefore can be used for

the control of insects. The detailed data of biological studies were described in a separate publication.[7]

EXPERIMENTAL

Melting points were uncorrected. The NMR spectra were recorded on a "Varian VXR-300" spectrometer at 300 (^{1}H) and 126.16 MHz (^{31}P). All chemical shifts are expressed in δ (ppm). ^{1}H chemical shifts are expressed relative to Me_4Si as internal standard. ^{31}P NMR spectra are referenced to external 85% H_3PO_4. All manipulations were carried out under an inert atmosphere (N_2 or Ar), solvents were distilled under an inert atmosphere from the following drying agents: diethyl ether, hexane (P_2O_5), methanol (sodium), ethyl acetate ($CaCl_2$). HPLC analyses were performed on a "Millichrom-4A" instrument (UV detector, λ_{max} 270 nm, Silasorb SPH-c_{18} column, 120 mm length and 2 mm diameter, acetonitrile-water 9:1) thin layer chromatography on Silufol UV 254 plates using various solvents as eluent

Diethylamino-p-methoxyphenyl-phenyl-phosphine (**3**). To a solution of 11.5 ml of *p*-bromoanisole in 60 ml of pentane was added with stirring 70 ml of 1.4 N BuLi in hexane. The solution was allowed to stand for 2 hours at room temperature. The solid precipitate of anisyllithium was filtered off and dissolved in 100 ml of ether. 100 ml of a solution of 0.65 N anisyllithium was added with stirring to a solution of 12.6 ml of chloro-N,N-diethylamino-phenylphosphine in 20 ml of ether at −5°C. After heating up to room temperature the reaction mixture was refluxed for 1 hour. The precipitate of LiCl was filtered off and washed with 20 ml of ether. The filtrate was evaporated and the residue was distilled under reduced pressure.
Yield 12.0 g (65%), b.p. 145–146°C (0.02 mm Hg).
NMR spectra (δ, ppm; J, Hz; $CDCl_3$):
δ_H: 0.87 t (J_{HH} 7, 6H, CH_3); 3.00 dq(J_{HH} 7, J_{HP} 10, 4H, CH_2); 3.72 s (1H, CH_3); 6.80–7.30 (9H, C_6H_5 + C_6H_4). δ_P: 61.4. Calcd for the $C_{17}H_{22}NOP$: N 4.78, P 10.65. Found: N 4.87, P 10.85.

Anisyl-methyl-phenylphosphine oxide (**1e**). 12.0 g of diethylamino-*p*-methoxyphenyl-phenyl-phosphine in 25 ml of methanol was refluxed for 4 hours. The yield of methyl anisyl-phenylphosphinite (**4**) determined by ^{31}P NMR spectra is 96%. NMR spectra (δ, ppm; $CDCl_3$): δ_P: 111.8.

The solution of methyl anisylphenylphosphinite (**4**) was added with stirring to the 25 ml of methyl iodide at 40–45°C. The mixture was stirred 0.5 hour at refluxing temperature and then was concentrated under reduced pressure to dryness. The residue was purified by crystallization from ether-hexane. Yield 10.0 g (91.5%), mp. 120°C.[8]
NMR spectra (δ, ppm; J, Hz; $CDCl_3$):
δ_H: 1.92 d (J_{HP} 13, 3H, CH_3P); 3.77 s (3H, CH_3O); 6.90–7.60 (9H, C_6H_5 + C_6H_4). δ_P: 31.5.

Methyl-4-methoxyphenyl-phenylphosphine oxide (**1f**). A mixture of 6.0 g of anisyl-methyl-phenyl-phosphine oxide (**1e**), 8.4 g pyridine hydrochloride and 1.2 ml of acetic acid was heated for 2 hours at 190°C. After being cooled to room temperature, the mixture was poured into water and dilute hydrochloric acid was added to pH 1–2. The mixture was extracted with ethyl acetate. The ethyl acetate solution was treated with 10% KOH and the aqueous layer was separated. The aqueous layer was acidified with dilute hydrochloric acid to pH 1–2 and extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated solution of NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled in vacuum. Yield 2.5 g (44%), b.p. 260°C (0.01 mm Hg), mp. 67–68°C.
NMR spectra (δ, ppm; J, Hz; $CDCl_3$);
δ_H: 1.89 d (J_{HP} 13, 3H, CH_3P); 6.90–7.60 (9H, C_6H_5 + C_6H_4); 9.8 br (1H, OH). δ_P: 34.0 Calcd for the $C_{13}H_{13}O_2P$: C 67.03, H 5.62, P 13.35. Found: C 67.24, H 5.64, P 13.33.

Tertiary phosphine oxides (**1a–d**). *General procedure*: A solution of 1.0 g of phenol (**1f**) in 5 ml of methanol was treated with sodium methylate (0.1 g sodium in 1 ml of methanol). The solution of sodium phenolate was evaporated in vacuum to dryness, the residue was dissolved in 5 ml of dimethylformamide and then was added to 1.0 g of RX. The mixture was refluxed for 0.5 hours, diluted with water, and extracted with benzene. The benzene layer was washed with 10% NaOH and water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using methanol-chloroform as eluent to give the oily tertiary phosphine oxides (**1a–d**). Yield, physical and spectral data are given in Tables I and II. The purity of the compounds was confirmed by HPLC method.

TABLE I

Characterization data of compounds (**1a–d**)

Compound	R'	Yield, %	R_f*	Molecular formula	Calcd.		Found.	
					N	P	N	P
(1a)	$(CH_2)_2NHCO_2Et$	58	0.47	$C_{18}H_{22}NO_4P$	4.03	8.92	4.14	9.34
(1b)	$(CH_2)_2NHCO_2Pr$-i	56	0.27	$C_{19}H_{24}NO_4P$	3.88	8.57	3.99	8.60
(1c)	$(CH_2)_2N{=}CHPr$	45	0.42	$C_{19}H_{24}NO_3P$	4.06	8.97	4.05	8.73
(1d)	$(CH_2)_2N{=}CHPr$-i	40	0.50	$C_{19}H_{24}NO_3P$	4.06	8.97	4.05	8.96

*Thin layer chromatography was carried out on Silufol UV 254, using chloroform-methanol (9:1) as eluent.

TABLE II

NMR-spectra of the compounds **1a–d**.

Compound	δ_P, ppm	δ_H, ppm (J, Hz, $CDCl_3$)				
		CH_3P	CH_2N	CH_2O	H-Ar	other signals
1a	30.3	1.93(d,13)	3.52(q,5)	4.00(t,5)	6.80-7.60m	1.17(t,7,CH_3), 4.04(q,7,CH_2), 5.20(s,NH)
1b	31.3	1.93(d,13)	3.52(q,5)	4.00(t,5)	6.80-7.60m	1.16(d,6,CH_3), 4.85(sp,6,CH), 5.11(s,NH)
1c	30.3	1.93(d, 9)	4.15m, (CH_2ON)	4.30m	6.90-7.70m	0.87(t,7,CH_3), 1.42(m,7,CH_2), 2.11(m,CH_2) 7.28(t,8,=CH)
1d	30.3	1.93(d,13)	4.15m, (CH_2ON)	4.30m	6.90-7.70m	0.99(t,7,CH_3),2.41(sp,7,CH),7.24(d,5,=CH)

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