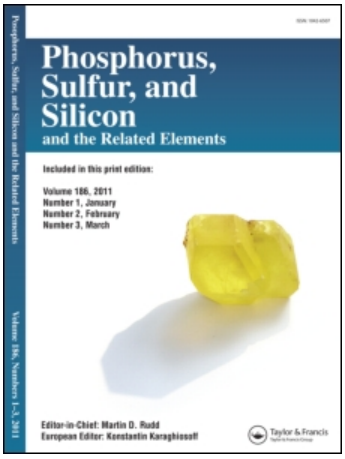

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Synthesis and Pesticidal Activities of O,O-Dialkyl-N-[(4-aryl)-2-thiazolyl] Phosphoramidothioates

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Several fluorine-containing O,O-dialkyl-N-[(4-aryl)-2-thiazolyl] phosphoramidothoiates were synthesized as possible antifungal and insecticidal agents by treating appropriate 2-amino-4-aryl-thiazoles with O,O-dialkyl phosphorochloridothioates. The latter were obtained by the reaction of dry alcohol on thiophosphoryl chloride in the presence of sodium metal. Some of the synthesized compounds exhibited significant antifungal activity against Aspergillus species. In insecticidal activity, compounds possessing a methyl group along with fluorine exhibited enhanced effect. It was also noted that the activity increased with the size and branching of alkyl group.

Keywords 2-Amino-4-aryl thiazoles; fungicidal activity; insecticidal activity; O,O-dialkyl-N-[(4-aryl)-2-thiazolyl]phosphoramidothioates.

INTRODUCTION

Biological activity of organo-phophorus esters is well known.[1,2] Various esters and thioesters of O,O-dialkyl phosphoric acid and thiophosphoric acid are being successfully used as agricultural and household insecticides.[3,4] Study of the structure and activity in the ester series reveals a correlation between toxicity, activity and branching of the alkylgroup through steric and inductive effect.[5] In view of these facts, some ethyl and isopropyl analogs of the title compounds were synthesized by treating appropriate 2-amino-4-fluoroarylthiazoles with

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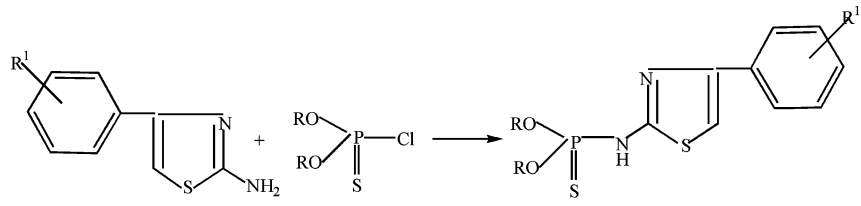

1 **2** **3**

SCHEME 1

O,O-dialkylphosphorochloridothioates (Scheme 1). The role of fluorine in heterocyclic compound is noteworthy in view of profound changes which are produced in biological activities on introduction of fluorine.[6] Some of the compounds have been found to exhibit significant insecticidal and antifungal activity.

EXPERIMENTAL

Melting points were taken in open capillary tubes using an electrical apparatus and are uncorrected. Infrared spectra (ν_{max} cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer as potassium bromide pellets. Proton and phosphorus-magnetic resonance spectra were recorded at 89.99 MHz and 36.23 MHz, respectively, on a JEOL (model FX-90Q) machine using hexadeutero dimethylsulfoxide as solvent. Chemical shifts (δ) are in parts per million downfield to the internal standard tetramethylsilane (TMS). The purity of the compounds was checked on silica gel G plates using iodine vapours as the detecting agent.

Synthesis of 2-Amino-4-aryl-thiazole (1) and O,O-Dialkyl Phosphorochlorido-thioates (2)

These compounds were prepared according to the published procedure.[7,8]

Synthesis of O,O-Diethyl-N-[(4-phenyl)-2-thiazolyl]-phosphoramidothioate (3a)

To an ice cold ethereal solution of O,O-dialkyl phosphorochloridothioate (5.6 g, 30 mmol) was gradually added with stirring an ethereal solution (50 cc) of 2-amino-4- Phenyl-thiazole (10.5 g, 60 mmol), the mixture was then kept at 0°C for 24 h. The solid that separated out was washed

several times with cold water to remove the amine hydrochloride. The residual mass was extracted with ether and this was mixed with the original ether solution. After removing ether the compound was obtained as a red coloured solid, which was recrystallized with pet. ether : benzene (1:3).

Compounds **3b–k** were prepared in a similar manner.

RESULTS AND DISCUSSION

The structure of synthesized compounds were established by analytical and spectral studies. Elemental and physical data of the synthesized compounds are given in Table I.

Infrared Spectra

The infrared spectrum of **1** showed a doublet at 3180 cm^{-1} and 3200 cm^{-1}due to $–NH_2$, its conversion to **3** was confirmed by the

TABLE I New O,O-Dialkyl-N-[(4-aryl)-2-thiazolyl]-phosphoramidothioates

Compound	Substituents R	Substituents R^1	M.P. (°C)	Yield (%)	Molecular formula	Analysis (%) Found (Calcd.) N	S
3a	C_2H_5	H	145	70	$C_{13}H_{17}N_2O_2PS_2$	8.58 (8.53)	19.50 (19.51)
3b	C_2H_5	4-F	211	68	$C_{13}H_{16}FN_2O_2PS_2$	8.05 (8.09)	18.50 (18.49)
3c	C_2H_5	4-F, 3-CH_3	95–97	67	$C_{14}H_{18}FN_2O_2PS_2$	7.75 (7.77)	17.72 (17.77)
3d	C_2H_5	2-F, 5-CH_3	116–18	74	$C_{14}H_{18}FN_2O_2PS_2$	7.73 (7.77)	17.76 (17.77)
3e	C_2H_5	4-F, 3-Cl	160	72	$C_{13}H_{15}ClFN_2O_2PS_2$	7.32 (7.35)	16.80 (16.81)
3f	C_2H_5	4-F, 2-Cl	120	71	$C_{13}H_{15}ClFN_2O_2PS_2$	7.36 (7.35)	16.82 (16.81)
3g	$CH(CH_3)_2$	H	97	75	$C_{15}H_{21}N_2O_2PS_2$	7.85 (7.86)	17.96 (17.97)
3h	$CH(CH_3)_2$	4-F	93–94	80	$C_{15}H_{20}FN_2O_2PS_2$	7.45 (7.48)	17.10 (17.11)
3i	$CH(CH_3)_2$	4-F, 3- CH_3	86–88	69	$C_{16}H_{22}FN_2O_2PS_2$	7.20 (7.21)	16.52 (16.49)
3j	$CH(CH_3)_2$	4-F, 3-Cl	155–57	74	$C_{15}H_{19}ClFN_2O_2PS_2$	6.63 (6.62)	15.12 (15.14)
3k	$CH(CH_3)_2$	4-F, 2-Cl	104–6	81	$C_{15}H_{19}ClFN_2O_2PS_2$	6.68 (6.62)	15.11 (15.14)

disappearance of doublet and appearance of a broad band from 3360–3100 cm^{-1} for >N–H group and an additional absorption band from 760–730 cm^{-1} for P=S.

^{1}H NMR Spectra

The PMR spectrum indicated the formation of compounds **3** where a quartet in the region δ 3.25–3.80 (-CH_2-) and triplet from δ 1.31–1.37 (-CH_3) in compounds **3a-f** and a doublet in the region δ 1.03–1.37 [-CH(C**H**$_3$)$_2$] and a multiplet from δ 3.88–4.70 (-C**H**$(CH_3)_2$] in compounds **3g–k** appeared due to the alkoxy groups. The broad singlet $\approx \delta$ 7.70 which disappeared on deutration indicated the conversion of –NH_2 group to >NH. The other peaks observed were the aromatic protons as a multiplet from δ 7.39–7.68 and an additional singlet in the region δ 2.14–2.30 in compounds **3c**,**d**,**i** due to –CH_3 group attached to phenyl ring.

^{31}P NMR Spectra

The ^{31}P NMR spectrum of compounds also supported the conversion of **1** to **3**. In compounds **3a–f**, a singlet appeared at δ 61.17–62.17, and in compounds **3g–k**, the signal appeared at δ 53.17–55.74—due to a pentavalent phosphorus attached to sulfur, nitrogen and, oxygen.

Pesticidal Activity

The synthesized compounds were tested for antifungal and insecticidal activities.

Antifungal Activity Test

The antifungal activity was determined against *Aspergillus flavus, A. niger, Curvularia lunata* and *Fusarium moniliformae* by using the filter paper disc method of Gould and Bowie.[9] Standard size (5-mm diameter) blank Whatman filter paper discs were , sterilized by dry heat at 140°C for 1 h; then they were saturated with the test solution (100 μg $disc^{-1}$) and a known quantity of standard reference (mycostatin 10 μg $disc^{-1}$), separately. These were air-dried at room temperature to remove any residual solvent, which might interfere with the determination. The discs were placed on the surface of a sterilized agar nutrient medium that had been inoculated with the test organism (using a sterile swab) and dried to remove the surface moisture. The thickness of agar medium was kept equal in all petri plates and a standard disc was used in each

plate as a control. Before incubation, the petri dishes were placed in a cold room (5°C) for 1 h to allow diffusion of the compounds from the disc in to the agar plates. These were incubated at 37°C for 20–24 h, after which zones of inhibition or depressed growth could be easily measured. All experiments were in five replicates and the values were then computed. The results are given in Table II.

It is observed that, in general, the compounds were more active against A*spergillus* species, with compounds **3e** and **3g** exhibiting activity comparable to that of mycostatin and compound **3c** having fluoro and methyl group attached to phenyl ring exhibiting much higher activity than the standard (AI = 1.27).

Insecticidal Activity Test

The insecticidal activity was evaluated against the larvae of *Plutella xylostella* (Diamond black moth) which were reared on cauliflower leaves using leaf feeding and direct contact method (Table II). The larvae in the penultimate instar were selected to carry out the tests. Three batches of ten insects each were used in each method.

TABLE II Antifungal and Insecticidal Activity of O,O-Dialkyl-N-[(4-aryl)-2-thiazolyl]phosphoramidothioates

Test compound Test organism		3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
Antifungal activity											
Aspergillus flavus	IZ[a]	8	9	—[c]	—	12	10	12	7	7	10
	AI[b]	0.72	0.81	—	—	1.09	0.90	1.09	0.63	0.63	0.90
A. niger	IZ	7	7	14	—	8	7	10	7	—	8
	AI	0.63	0.63	1.27	—	0.72	0.62	0.90	0.63	—	0.72
C. lunata	IZ	8	—	7	—	8	6	9	6	—	—
	AI	0.72	—	0.63	—	0.72	0.54	0.81	0.54	—	—
F. moniliformae	IZ	10	7	—	7	8	—	—	—	7	8
	AI	0.98	0.63	—	0.63	0.72	—	—	—	0.63	0.72
Insecticidal activity (% mortality)											
P. xylostella	D.C.	20	40	80	40	*[d]	10	20	50	100	*
	L.F.	40	50	60	40	*	40	60	70	80	*

IZ[a]: Inhibition zone (m.m.); AI[b]: Activity index = Inhibition zone of sample/Inhibition zone of standard; -[c]: Not measurable activity; *[d]: Activity not detected; D.C.: Direct contact method ; Standard mortality 100%; and L.F.: Leaf feeding method; Standard mortality 90%.

Leaf Feeding Method

1000 ppm solution of the compound was prepared in 5% ethyl alcohol. Fresh cabbage/cauliflower leaves were taken, each of which was dipped in the solution of the test sample and allowed to dry. The leaves were put in the petri plates and ten larvae of *Plutella* sp. were released in each of them. A control was also taken. Monocrotophos (50 ppm) solution was used for standard evaluation. The larvae were left undisturbed under laboratory condition and observations were taken after 78 h of exposure.

Direct Contact Method

In this method 1000 ppm solution of measured quantity was sprayed on the larvae of *Plutella* sp. and allowed to dry. These larvae were then left undisturbed in petri plates along with the food material. Monocrotophos (50 ppm) solution was used as control. Observations were made after 78 h.

It was observed that compounds **3a** and **3f** were totally inactive, whereas **3b** and **3g** exhibited slight activity, showing that introduction of fluorine brings about a positive change. Promising activity was exhibited by compound **3c** and **3i** by both methods indicating that presence of methyl group at 3-position with fluorine increased the activity. Compound **3i** showed maximum activity nearing to that of standard in both cases indicating that the activity increases with the size and branching of alkyl group.

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