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Synthesis and Herbicidal Activity of the Optical Isomers of O-Ethyl O-2-Nitro-5-methylphenyl N-Isopropyl Phosphoramidothioate

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The toxicity of organophosphorus esters to insects and mammals is greatly affected by asymmetry at phosphorus atom. The levorotatory isomer of O-methyl S-methyl O-4-nitrophenyl phosphorothiolate was five fold more toxic to rats than its dextrorotatory enantiomer.[1] Also, the levorotatory isomer of O-ethyl S-2-(ethylthio)ethyl ethylphosphonothiolate was six- to ten-fold more toxic to houseflies, mosquito larvae, and honeybees than its enantiomer.[2] Wustner and Fukuto[3] reported that the levorotatory phosphorus isomers of O-2-butyl S-2-(ethylthio)ethyl ethylphosphonothioate were much more active

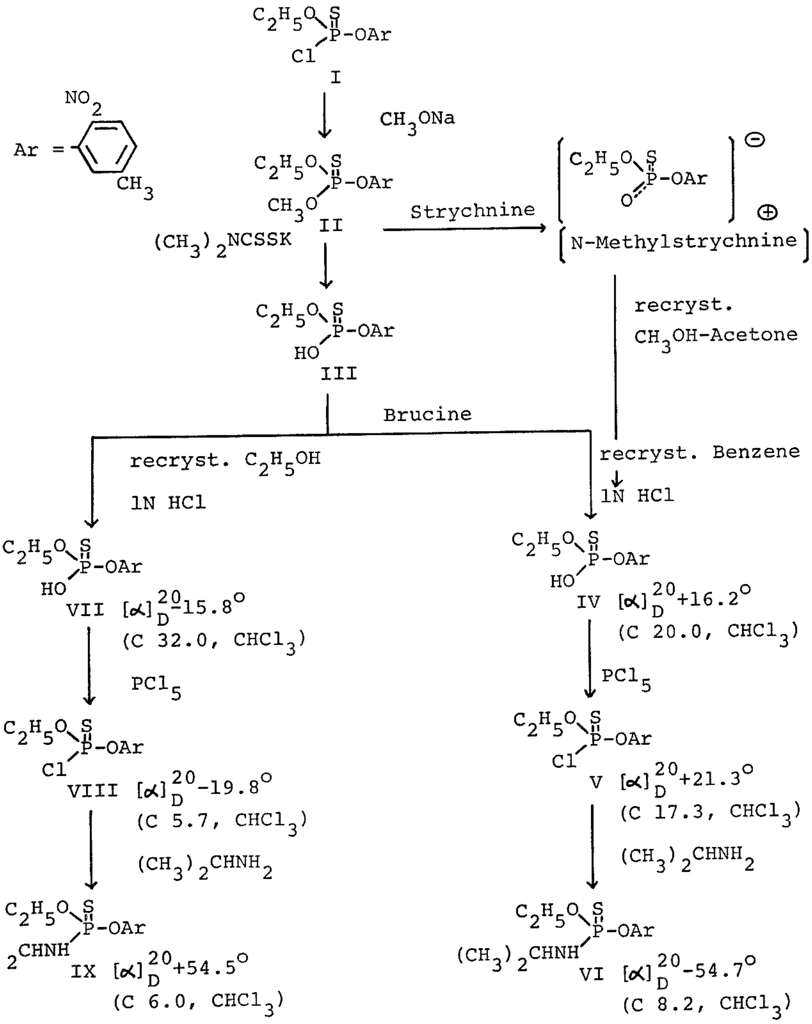

FIG. 1. Synthesis and Resolution of the Optical Isomers of O-Ethyl O-2-Nitro-5-methylphenyl N-Isopropyl Phosphoramidothioate.

as toxicants to houseflies, mosquito larvae and mice than the dextrorotatory compounds.

Certain organophosphoramidates are known to be fungicidal. The phosphorus enantiomers of N, N-diethyl-2-methylimidazol-1-yl phenylphosphinamidothionate showed a difference in mammalian toxicity but not in fungitoxicity.[4] Also, Seiber and Tolkmith[5] described the synthesis of the optical isomers of the herbicide Zytron® (O-2,4-dichlorophenyl O-methyl N-isopropyl phosphoramidothioate). However, very little has been published on the herbicidal activity of the resolved phosphoramidothioates.

This report represents the synthesis and resolution of the optical isomers of O-ethyl O-2-nitro-5-methylphenyl N-isopropyl phosphoramidothioate which contains phosphorus as the sole asymmetric atom. The methods to be described in the following may possess general utility in the preparation of a variety of optically active thiophosphoryl compounds. Moreover, study was conducted to determine the effect of the asymmetry at phosphorus atom on the herbicidal activity against barnyardgrass and rice plant.

The procedures used to prepare the optical isomers of the phosphoramidothioate resolved at the phosphorus atom are given in Fig. 1. Each reaction proceeded almost quantitatively unless otherwise specified. The racemic O-ethyl O-methyl O-2-nitro-5-methylphenyl phosphorothionate II was prepared by reaction of I with sodium methoxide in methanol. Demethylation of II with potassium N,N-dimethyldithiocarbamate in methanol gave the racemic product III, which was purified by DEAE-cellulose column chromatography, by eluting with 0.1 N hydrochloric acid. The racemic compound III was treated with an equivalent of brucine in methanol to form the corresponding brucine salts, which were recrystallized from benzene to give crystals in 30% yield, mp 145~147°C. Treatment of this brucine salt with 1 N hydrochloric acid gave the resolved compound IV, $[\alpha]_D^{20}+16.2°$ After recrystallization, the soluble residue was further recrystallized from ethanol to give crystals in 30% yield, mp 154~155°C. This product was treated with 1 N hydrochloric acid to yield the other enantiomer VII, $[\alpha]_D^{20}-15.8°$ Chlorination of the resolved compounds IV and VII with phosphorus pentachloride in chloroform was carried out for 2 hr at −10~0°C.[6] The crude chloridates were respectively purified by preparative thin-layer chromatography (tlc) in benzene to yield 25 to 30% of V and VIII. Reaction of the chloridates V and VIII was performed at 0°C with isopropylamine in anhydrous ether to give the optically active phosphoramidothioates VI $[\alpha]_D^{20}-54.7°$ and IX $[\alpha]_D^{20}+54.5°$ after purification by preparative tlc in *n*-hexane-acetone (5/2, v/v). Data of elemental analyses are as follows: Found; VI, C, 45.3; H, 5.9; N, 8.6; P, 9.8: IX, C, 45.2; H, 5.8; N, 8.6; P, 9.7. Calcd. for $C_{12}H_{19}N_2O_4PS$; C, 45.3; H, 6.0; N, 8.8; P, 9.7%. Both isomers VI and IX showed identical NMR and IR spectra: 1.15 [9H, m, CH_3, CH $(CH_3)_2$], 2.32 (3H, s, CH_3), 3.30 (H, m, NH), 3.60 (H, m, CH), 4.00 (2H, q, CH_2), 7.00~7.75 δ (3H, m, aromatic); 3300 (NH), 1580 and 1340 (NO_2), 1030 (P-O-alkyl), 650 cm^{-1} (P=S). No impurities were detected in NMR spectra and on tlc.

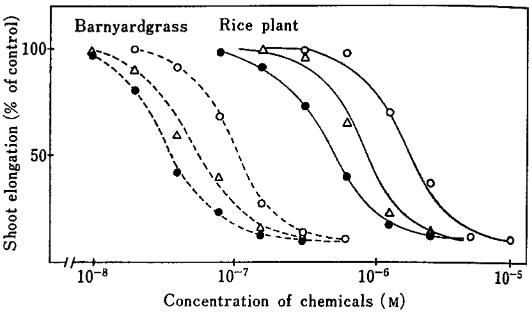

FIG. 2. Inhibitory Effect of the Optical Isomers of O-Ethyl O-2-Nitro-5-methylphenyl N-Isopropyl Phosphoramidothioate on Shoot Elongation of Plant Seedlings.

——, rice plant; ------, barnyardgrass; ○,(+)-isomer; ●, (−)-isomer; △, racemic.

Resolution of the levorotatory isomer was also accomplished with strychnine. An equimolar mixture of the compound II and strychnine in methanol-acetonitrile (1/1, v/v) was allowed to stand for 24 hr at room temperature. The solution was concentrated and then the residue was recrystallized from methanol-acetone (1/18, v/v) to yield colorless crystals, mp 172~174°C. Treatment of this product with 1 N hydrochloric acid gave the optically active thiophosphoric acid, which was subsequently chlorinated with phosphorus pentachloride, followed by reaction with isopropylamine to yield the corresponding phosphoramidothioate, just as with the compound IV obtained from the brucine salt. The value of the optical rotation of this preparation was equal to that of the levorotatory isomer obtained from the brucine salt. Therefore, the optical purities of both the compounds are nearly the same and they must have an identical configuration at phosphorus atom.

Inhibition of shoot elongation of rice plant (*Oryza sativa* L. cultivar. Kinmaze) and barnyardgrass (*Echinochloa crus-galli* Beauv.) by the phosphorus enantiomers VI and IX was tested as reported previously.7) The results are shown in Fig. 2. The phosphorus enantiomers IX and VI gave the 50% inhibition concentrations (I_{50}) of 1.07×10^{-7} M and 3.14×10^{-8} M, respectively, against barnyardgrass, a difference of 3.4 fold. Although rice plant was less sensitive to the enantiomers of the phosphoramidothioate than barnyardgrass, a similar difference between the enantiomers was observed with rice plants: I_{50}; IX, 1.89×10^{-6}M; VI, 5.19×10^{-7} M; a difference of 3.6 fold. The levorotatory phosphorus enantiomer VI was the more potent toxicant against both barnyardgrass and rice plant. The activity of the racemic compound was very close to the mean of the two resolved isomers. It appears that this phosphoramidothioate is the first thiophosphoryl compound with which a difference in herbicidal activity between its phosphorus enantiomers has been demonstrated.

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