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OPTICALLY ACTIVE ORGANOPHOSPHORAMIDES

O-2,4-DICHLOROPHENYL O-METHYL ISOPROPYLPHOSPHORAMIDOTHIOATE AND SOME RELATED COMPOUNDS

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Abstract—The synthesis of the optical isomers of O-2,4-dichlorophenyl O-methyl isopropylphosphoramidothioate (I) has been carried out for the first time. Optically active I was prepared along with O-2,4-dichlorophenyl S-methyl isopropylphosphoramidothioate (IV), by methylation of the optical isomers of methylammonium O-2,4-dichlorophenyl isopropylphosphoramidothioate (II). The value of the rotation of the stereoisomers of II and IV was found to be notably solvent dependent. This phenomenon has not been previously reported with organophosphorus compounds. The effects observed are consistent with the known hydrogen bonding characteristics of organophosphoramides containing a primary amido group.

INTRODUCTION

IN THE past decade the resolution and reactions of organophosphorus compounds containing an asymmetric phosphorus atom were studied in considerable detail.[1] Accumulating knowledge made it possible to resolve organophosphorus esters of biological interest.[2] The work to be described in the following represents a part of our efforts aimed at preparing optically active organophosphoramides for biological studies.[3] Heretofore, very little has been reported on the biological behavior of such amides.[4] Their action at the molecular level is of fundamental interest since certain amido compounds—containing phosphorus as the sole asymmetric atom—are selectively toxic to organisms that do not contain cholinesterases.[5]

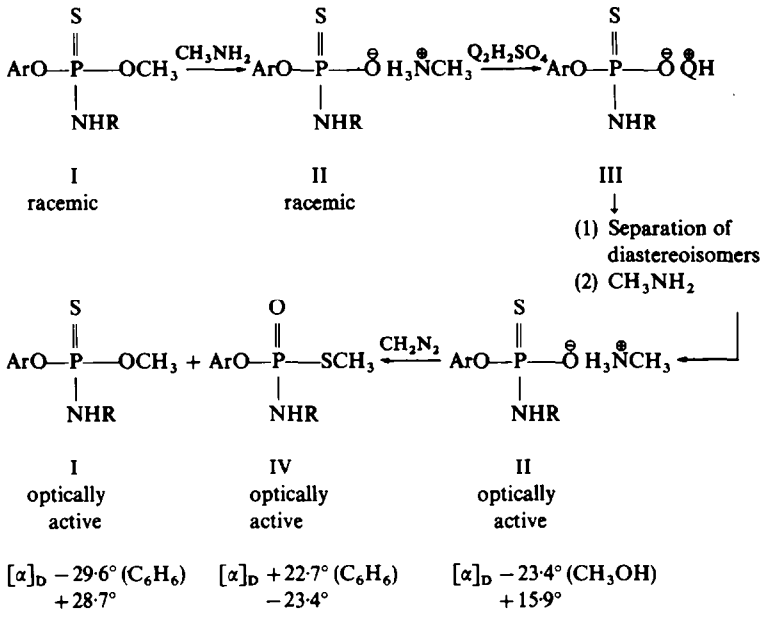
The aim of the work reported here was the synthesis of the optical isomers of a potent selective herbicide, O-2,4-dichlorophenyl O-methyl isopropylphosphoramidothioate (I). Application of a recently discovered resolution method[3] was not successful and a more conventional approach had to be adopted. This involved the stereospecific conversion of optically active methylammonium O-2,4-dichlorophenyl isopropylphosphoramidothioate (II) into the desired enantiomers of I (see Scheme A). In the course of this resolution we encountered strong solvent-dependence in the value and sign of the optical rotation not only of II but also of O-2,4-dichlorophenyl S-methyl isopropylphosphoramidothioate (IV).

RESULTS AND DISCUSSION

A summary of the procedures used to prepare the optical isomers of the phosphoramidothioate (I) is given in Scheme A. The racemic methylamine salt DL-II was prepared by demethylation of I with methylamine, in 55% yield. The enantiomers of II were obtained from the separated quinine salts, by substitution of methylamine for quinine.

Alkylation of thiophosphoric acid derivatives is known to give the thermodynamically more stable S-alkyl derivatives predominately or exclusively, depending on the

SCHEME A (Ar = 2,4-dichlorophenyl, R = isopropyl, Q = quinine)



alkylating agent.[6] It was therefore of no surprise to find that methylation of the methylamine salt II with excess methyl iodide gave the S-methyl isomer of I, O-2,4dichloroproduct. Reaction with diazomethane in ether, on the other hand, gave both the S-methyl isomer IV and the O-methyl isomer I, in the approximate ratio of 10:1. The crude methylation product was separated into its components by a combination of crystallization from hexane, which removed most of the less soluble S-methyl isomer IV, and "dry column" chromatography[7] of the soluble residue (which contained small amounts of 2,4-dichloroanisole and 2,4-dichlorophenol, from impurity in the starting II) on silica gel. When optically active II was the starting material optically active methyl esters were produced. In this way both optical isomers of the desired O-methyl ester I were obtained and a relatively large amount of the optical isomers of the S-methyl isomer IV was formed as by-product. Although the optical purities of the two stereoisomers of II used in the methylation reaction differed significantly, the optical purities of the stereoisomers of the products I and IV were nearly the same. In the case of the S-methyl isomer IV the increased solubility of the racemic mixture over that of the invididual enantiomers was used to optically purify the latter by recrystallization. For the O-methyl isomer I the situation was reversed; the racemic mixture was a low-melting crystalline solid while the individual enantiomers could not be crystallized. Thus each stereoisomer of I could be optically purified by selectively crystallizing out the racemic impurity.

Methylation of L-II, $[\alpha]_D$ −23·7° (methanol), with methyl iodide gave the optically active S-methyl isomer IV, $[\alpha]_D$ +18·8° (benzene) crude and +21·0° (benzene) after one recrystallization. Comparison with the results from diazomethane methylation shows that the stereochemical course was the same for the two methylation reactions.

In Tabel 1 is given a summary of the specific rotations of the L-stereoisomers of I, II, and IV in benzene and methanol, measured at five different wavelengths. In the case of the methylamine salt II, the sign of the rotation changed on interchanging solvents while with IV, the specific rotation at 589 mμ was −23·4° in benzene but 0° in methanol. To prove that IV had not racemized in methanol the sample was recovered by evaporating the solvent and then run again in benzene. The same specific rotation, −23·4° at 589 mμ, was observed. The fact that this sample did indeed have optical activity in methanol was confirmed by determining a portion of the ORD curve below 360 mμ: at 295 mμ a slight positive rotation was observed which increased irregularly to a maximum at 245 mμ ([α] = +69°) and rapidly decreased below 240 mμ.

TABLE 1. SPECIFIC ROTATIONS OF L-I, L-II, AND L-IV MEASURED IN METHANOL AND BENZENE AND AT DIFFERENT WAVELENGTHS

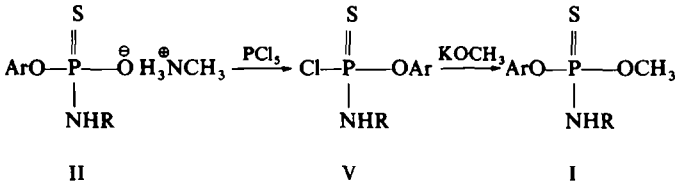
			wavelength (mμ)				
Sample	Solvent (concentration)		589	578	546	436	365
L-I	Methanol	(0·26)	−19·9°	−20·0°	−23·1°	−42·6°	−71·5°
	Benzene	(0·35)	−29·6	−30·6	−35·4	−65·5	−113·0
L-II	Methanol	(0·53)	−23·6	−24·6	−28·2	−51·5	−90·6
	Benzene	(0·55)	+17·3	+18·4	+21·3	+39·2	+66·0
L-IV	Methanol		(0° at all wavelengths)				
	Benzene	(0·56)	−23·4	−23·6	−27·2	−48·0	−78·0

There is ample analogy for the dependence of sign of rotation on solvent[8] but we are not aware that this phenomenon has been previously noted among optically active organophosphorus compounds. However, it is not at all unreasonable that such an effect should be observed, particularly in phosphoramidates where the asymmetric center is directly attached to groups which may be greatly affected by solvent polarity. Specific conformational effects have been shown to exist with phosophoramidates and phosphoramidothionates containing primary amido groups and to result from hydrogen bonding between the amido proton and the oxygen or sulfur atom at phosphorus.[9] Similar effects may cause the strong dependence of rotation on the nature of the solvent, as observed with the ester IV. That the P═O compound (IV) exhibits a stronger solvent effect than does the P═S compound (I) can be expected from a difference in the strengths of the hydrogen bonds existing in the two compounds. Infrared data indicate that the P═O···H—N bond is stronger than the P═S···H—N bond.[9] Rupture of the O···H bond, on passing to the more polar solvent (methanol), would presumably produce the greatest change in molecular conformation, and hence in optical rotation. In the case of the methylamine salt II, however, the situation is complicated by the presence of ion-pairing in solvents of low polarity and the distribution of the negative charge between the O and S atoms.

We had originally planned to convert the optically active methylamine salt II into optically active I by way of O-2,4-dichlorophenyl isopropylphosphoramidochloridothioate (V). The conversions II → V → I can be readily accomplished at

the racemic level, by chlorination of II with phosphorus pentachloride in carbon tetrachloride under the conditions described by Michalski,[10] and reaction of V with potassium methoxide in methanol (Scheme B).

SCHEME B (Ar = 2,4-dichlorophenyl)



II V I

We found that the treatment of D-II, $[\alpha]_D$ −21·8° (methanol), with phosphorus pentachloride in carbon tetrachloride at −10° for 2 hr afforded a crude product showing a specific rotation of −20·1° (chloroform). However, this product contained only 50% V, by NMR analysis. Increased reaction times gave more complete conversion but also increased racemization. For example, when the reaction was carried out for 72 hours at the same temperature with D-II, $[\alpha]_D$ −18·6° (methanol), the crude product contained at least 90% V, by NMR analysis, but had a specific rotation of only −3·9° (chloroform). Use of intermediate reaction times gave results which were intermediate between those of the 2 hr and 72 hr runs. The signs of the specific rotations of the crude chloridate V, negative in chloroform and positive in methanol, were just the opposite of those of II in benzene and methanol. According to these data the conversion of II to V, under proper reaction conditions, proceeded without racemization but not necessarily with inversion of configuration.

Reaction of the crude chloridate V, $[\alpha]_D$ −11·2° (chloroform), estimated to be at least 75% pure by NMR analysis, was carried out at 0° with potassium methoxide in methanol. The crude product, containing greater than 90% of the expected I, had no detectable optical activity. Lack of configurational stability of V in methanol or racemization of V due to abstraction of the amido proton by methoxide might have caused the loss of this activity. We did not investigate this question.

EXPERIMENTAL

Specific rotations were measured at 25° in 1 dm cells on a Perkin–Elmer Model 141 spectropolarimeter. NMR spectra were determined with a Varian A-60 spectrometer using $CDCl_3$ solvent and TMS internal standard. Solns were evaporated to dryness using a rotary evaporator and reduced press.

DL-*Methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II). A soln of I (125·6 g, 0·4 mole) and $MeNH_2$ (248 g, 8 moles) in MeOH (400 ml) was placed in a loosely stoppered flask and allowed to stand at room temp for 40 hr. The colorless oil resulting after evaporating the soln to dryness under reduced press was dissolved in CCl_4 (500 ml). Crystallization resulted on standing to give 134 g of white powder, m.p. 85°. One more recrystallization from CCl_4 and one from benzene gave 106 g colorless crystals, m.p. 70°, containing solvent of crystallization. After drying several hr 73·0 g (55%) of the title compound was obtained as colorless crystals, m.p. 126–132°. The structure was confirmed by the NMR spectrum: 1·08 [6H, d,* $CH(CH_3)_2$], 2·61 (3H, s, NCH_3), 3·50 (1H, m, CH), 7·20–7·75 (3H, m, aromatic), 7·80 δ (4H, broad and ill-defined, NH_3 and NH). Analytical data was obtained on a sample recrystallized from CCl_4, m.p. 130–132°. (Found: C, 36·4; H, 5·09; N, 8·77. Calc. for $C_{10}H_{17}Cl_2N_2O_2PS$: C, 36·3; H, 5·18; N, 8·4%).

* d = doublet; s = singlet; m = multiplet.

O-2,4-*Dichlorophenyl isopropylphosphoramidothioic acid, quinine salt* (III). To a soln of II, (19·8 g, 0·06 mole) in 150 ml water and 150 ml MeOH was added a soln of quinine sulfate (25·9 g, 0·33 mole) in 150 ml water and 450 ml MeOH. The resulting clear soln was stirred at room temp in an Erlenmeyer flask exposed to air. After 14 hr ca. 150 ml of the soln had evaporated and a colorless ppt formed. Filtration gave 11·5 g of a diastereoisomer of III as a crystalline solid, m.p. 149–154°, $[\alpha]_D$ −115° (*c*, 0·62, MeOH). After two recrystallizations from benzene 4·8 g, m.p. 111–115°, $[\alpha]_D$ −117° (*c*, 0·70, MeOH), was obtained. A further recrystallization from benzene followed by drying over P_2O_5 at 80° and 10 mm for several hr gave the analytical sample, m.p. 108–112°, $[\alpha]_D$ −115·5° (*c*, 0·85, MeOH). (Found: C, 55·9; H, 5·92; N, 6·80; P, 5·10. Calc. for $C_{29}H_{36}Cl_2N_3O_4PS$: C, 55·8; H, 5·81; N, 6·72; P, 4·96%).

The clear liquor remaining after removal of the crystalline diastereoisomer of III was concentrated under reduced press to remove the remaining MeOH. The liquor was decanted from the viscous syrup ppt which formed. The latter was dissolved in MeOH and brought to constant weight on a rotary evaporator. There was thus obtained 22 g of the remaining diastereoisomeric mixture of III as a crushable foam, $[\alpha]_D$ −99·5° (*c*, 0·83, MeOH). No crystallization could be induced from solns of this foam in a variety of solvents.

L-*Methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II). The diastereoisomer of the quinine salt of III (2 g), m.p. 111–115°, $[\alpha]_D$ −117° (*c*, 0·70, MeOH), was added to a 10% $MeNH_2$ aq (15 ml) with stirring. Agitation was continued at room temp for 5 hr and the resulting mixture filtered to remove a fine ppt of quinine, m.p. 163–170°, $[\alpha]_D$ −184·5° (*c*, 0·71, MeOH). The clear, colorless filtrate was extracted with $CHCl_3$ (2 × 5 ml) and then evaporated to dryness under reduced press to give 0·70 g (70%) of the title compound as a colorless syrup, $[\alpha]_D$ −22·9° (*c*, 0·50, MeOH), which failed to crystallize under several conditions. The NMR spectrum of L-II obtained in this way was identical with that of DL-II.

This reaction was carried out a number of times using different samples of the crystalline diastereoisomer of III. The lowest specific rotation observed for L-II was −23·6° (*c*, 0·60, MeOH). In most cases values of −21 to −23° were obtained, depending on the optical purity of the starting material.

D-*Methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II). A sample of the residual diastereoisomeric quinine salt foam (III; 1·0 g), $[\alpha]_D$ −99·5°, was converted into the methylamine salt by treatment with a 10% $MeNH_2$ aq (10 ml) in the same way as in the preparation of L-II. The resulting residue (0·33 g) from evaporation of the aqueous soln was obtained as an oil-solid mixture, $[\alpha]_D$ +7·2° (*c*, 0·84, MeOH). This mixture was allowed to stand in contact with CCl_4 (5 ml) at 10° for 1 day and the resulting mixture filtered. The solid residue (0·15 g) was mostly DL-II, $[\alpha]_D$ +1·5° (*c*, 1·5, MeOH). Evaporation of the filtrate to dryness gave 0·10 g of the title compound as a slightly yellow syrup, $[\alpha]_D$ +17·2° (*c*, 0·96, MeOH). The NMR spectrum indicated the presence of ca. 5% of 2,4-dichlorophenol in the D-II obtained in this way.

This reaction was carried out in the same way with the residual diastereoisomeric salt mixture of III (35 g), obtained in the same manner as described above. Treatment with excess $MeNH_2$ aq gave 12·0 g of an oily solid mixture of D- and DL-II which was allowed to stand in 50 ml of ether overnight at 10°. The crystalline DL-II, 6·5 g, was removed by filtration and the filtrate evaporated to dryness to give 4·5 g of D-II as a slightly yellow syrup, $[\lambda]_D$ +15·9° (*c*, 0·66, MeOH).

Methylation of DL-*methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II) *with diazomethane*. To a stirred and cooled (0°) slurry of the methylamine salt DL-II (3·32 g, 0·01 mole) in ether (35 ml) was added dropwise 100 ml of an ether soln 0·4 molar in diazomethane (0·04 mole). The resulting clear slightly yellow soln was stirred at 0–5° for 3 hr, then boiled briefly to remove excess diazomethane and evaporated to dryness under reduced press. There was thus obtained 3·10 g of crude methylation product as a slightly yellow solid. The NMR spectrum indicated the presence of I and IV in the ratio of 1:10, from the ratio of the O-methyl doublet (centered at 3·8 δ) and S-Me doublet (centered at 2·3 δ). The NMR spectrum also indicated the presence of small amounts of 2,4-dichloroanisole (O-methyl at 3·87 δ) and 2,4-dichlorophenol (OH as a broad singlet at 5·5 δ). The crude product was recrystallized from 30 ml of n-hexane to give 2·05 g of IV as colorless crystals, m.p. 84–85·5°. (Found: C, 38·2; H, 4·55; N, 4·44; P, 9·8. Calc. for $C_{10}H_{14}Cl_2NO_2PS$: C, 38·2; H, 4·48; N, 4·46; P, 9·86%). The structure of this compound was confirmed by its NMR spectrum: 1·21 [6H, d, $CH(C\underline{H}_3)_2$], 2·31 (3H, d, SCH_3), 3·65 (2H, complex ms, NH and CH), 7·20–7·58 δ (3H, m, aromatic).

Evaporation of the hexane filtrate to dryness gave 0·80 g of light yellow oil which was applied to a 50 × 2 cm chromatographic column containing 50 g of dry 100 mesh silica gel, according to the method of Loev and Snader.[7] Benzene was used to introduce the sample and also to develop the chromatogram. The developed chromatogram was removed in sections which were eluted with benzene solutions containing 10% MeOH.

The residues obtained from evaporation of the eluting solvent to dryness were identified by their NMR spectra. Proceeding from the fraction from the bottom of the column (high R_f fraction) there was obtained the following pure fractions: 0·06 g of 2,4-dichloroanisole, 0·15 g of I, m.p. 49–51° (Lit.[11] 51–52°), 0·06 g of 2,4-dichlorophenol and 0·24 g of IV. The NMR data of compound I were as follows: 1·18 [6H, doublet, $CH(C\underline{H}_3)_2$], 3·78 (3H, doublet, OCH_3), 3·5 (2H, complex multiplets, NH and CH), 7·25–7·59 δ (3H, multiplet, aromatic).

Methylation of L-*methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II) *with diazomethane.* Methylation of 3·2 g of L-II, $[\alpha]_D$ −23·3° (*c*, 0·60, MeOH), was carried out in the same way as for DL-II, using 85 ml of 0·4 molar ethereal diazomethane soln. There was obtained 2·93 g of crude product, $[\alpha]_D$ +16·7° (*c*, 0·60, benzene). From this 2·01 g of D-IV, $[\alpha]_D$ +22·1° (*c*, 0·65, benzene) was selectively crystallized out from hexane; a further recrystallization of this solid gave 1·69 g of D-IV as colorless crystals, m.p. 105–106°, $[\alpha]_D$ +22·7° (*c*, 0·60, benzene). Chromatography of the combined hexane liquors from this and another run of the same proportions gave 0·33 g of L-I as a colorless oil $[\alpha]_D$ −27·9° (*c*, 0·40, benzene). After setting several days in hexane solution at −20° a few crystals of DL-I precipitated and the liquor, on evaporation to dryness, gave 0·32 g of L-I as a colorless oil, $[\alpha]_D$ −29·6° (*c*, 0·35, benzene), and −19·9° (*c*, 0·26, MeOH).

Methylation of D-*methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II) *with diazomethane.* Methylation of 4·5 g of D-II, $[\alpha]_D$ +15·9° (*c*, 0·66, MeOH) was carried out in the same way as for DL- and L-II, using 110 ml of 0·4 molar diazomethane soln. There was obtained 4·0 g of crude product, $[\alpha]_D$ −12·1° (*c*, 0·65, benzene). From this 2·15 g of L-IV, $[\alpha]_D$ −23·1° (*c*, 0·60, benzene), was selectively crystallized out from hexane; one further recrystallization gave 1·75 g of L-IV as colorless crystals, m.p. 104–106°, $[\alpha]_D$ −23·4° (*c*, 0·56, MeOH). Chromatography of the hexane liquor, followed by rechromatography of the fraction containing D-I and crystallization of a small amount of DL-I, gave 0·153 g of D-I as an oil, $[\alpha]_D$ +28·2° (*c*, 0·32, benzene).

Methylation of DL- *and* L-*methylammonium* O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II) *with methyl iodide.* A soln of 0·50 g of DL-II in 10 ml MeI was allowed to stand for 3 hr at room temp. To the resulting mixture was added 50 ml benzene. Filtration removed the methylated ammonium iodide mixture and evaporation of the filtrate gave 0·35 g (72%) of crude DL-IV. One recrystallization from hexane gave pure DL-IV, m.p. 85–88°.

In the same way 0·56 g of L-II, $[\alpha]_D$ −23·7° (*c*, 0·53, MeOH), was treated with 10 ml MeI and gave 0·46 g (84%) of D-IV, $[\alpha]_D$ +18·8° (*c*, 0·69, benzene). One recrystallization from hexane gave D-IV, m.p. 100–104°, $[\alpha]_D$ +21·0° (*c*, 0·45, benzene).

Reaction of methylammonium O-2,4-*dichlorophenyl isopropylphosphoramidothioate* (II) *with phosphorus pentachloride*; O-2,4-*dichlorophenyl isopropylphosphoramidochloridothioate* (V). To a stirred and cooled (−10 to −20°) slurry of PCl_5 (2·10 g, 0·01 mole) in dry CCl_4 (15 ml) was added dropwise a soln of DL-II (3·31 g, 0·01 mole) in dry CCl_4 (30 ml). The resulting mixture was stirred at 5° for 30 min additional, then set in a freezer (−20°) for 2 days. Filtration removed 0·75 g $MeNH_2$-HCl and the filtrate on evaporation to dryness several times with CCl_4, to remove the last traces of $POCl_3$, gave 3·03 g of colorless oil. Crystallization from hexane gave 1·68 g (53%) of DL-V, m.p. 46–49° (Lit.[12] m.p. 50·5–51°).

Several attempts were made to convert crude L-II into optically active V by the same procedure, with the following results (specific rotation of L-II starting material in MeOH, reaction temp, reaction time, and specific rotation of the crude product in MeOH and $CHCl_3$): −21·8°, −10°, 2 hr, (not measured), −20·1°; −15·3°, 0°, 4 hr, +12·9°, −19·3; −18·8°, −15°, 18 hr, +8·9°, −11·2°; −18·6°, −20°, 72 hr, +5·3°, −3·9°.

In the three cases in which the reaction was carried out for 18 hr or less, the NMR spectrum showed that the crude product contained, in addition to V, at least one other component which was obtained in diminishing quantity as the reaction was carried out for longer periods of time. The aromatic and CH regions were more complex and in the Me region an imperfect triplet centered at 1·25 δ was obtained, possibly resulting from the overlap of two doublets. In the reaction carried out for 72 hr the NMR spectrum was essentially that of V only. Attempts to crystallize V from the crude products were not successful in any of the cases.

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