On the other hand, in the reaction of Br^-, I^-, and SCN^- with 2 we think that each of these anions should be a better leaving group than $PhSO_2^-$, so that k_2'/k_{-1}' will be less than unity in all cases. In this situation step k_2', rather than attack of Nu^- on 2 (step k_1'), will be rate determining and k_{Nu}^S will be given by $k_1'k_2'/(k_{-1}' + k_2')$.

Furthermore, it would be reasonable to expect $k_2'/(k_{-1}' + k_2')$ to be considerably smaller for I^- than for the other two nucleophiles, because k_2' should be effectively independent of Nu^-, while k_{-1}' would probably be much larger for I^- than for either Br^- or SCN^-, since I^- is in all probability a considerably better leaving group than the other two anions. Thus, even though k_1' for I^- attacking 2 was larger than k_1' for SCN^- by about the same amount as in the attack of these two nucleophiles on protonated 1, it would be easy for k_I^S to be significantly less than k_{SCN}^S, simply because $k_2'/(k_{-1}' + k_2')$ for I^- was so much smaller than $k_2'/(k_{-1}' + k_2')$ for SCN^-.

The presence of intermediates on the reaction coordinate in eq 3a and 3b and a change of rate-determining step from attack of Nu^- on protonated 1 to departure of $PhSO_2^-$ from 4 with a change in the leaving group ability of the group to be displaced in the substitution can thus provide a simple and straightforward rationalization for the marked difference in the reactivity pattern for Br^-, I^-, and SCN^- in eq 1b vs. eq 2. We recognize that other more complex explanations are doubtless conceivable. For this reason the difference in the reactivity pattern for the three nucleophiles toward the two substrates can be considered only as suggestive, rather than compelling, evidence for the presence of an intermediate on the reaction coordinate in the substitutions in question.

This is not the first occasion in which kinetic evidence of one type or another has been obtained suggestive of an intermediate being on the reaction coordinate in a simple nucleophilic substitution at sulfenyl sulfur. The work of Ciuffarin provides several additional examples.[5,6] While these, like the present example, are suggestive rather than compelling, and while there have been other cases[7,8] where the evidence seemed to point to synchronous bond making and bond breaking, rather than to an addition–elimination mechanism involving an intermediate, we feel that the present results and those of Ciuffarin,[5,6] together with the known ability of sulfur to expand its valence shell, make it generally desirable to picture nucleophilic substitutions at sulfenyl sulfur as proceeding through an intermediate, except in those specific cases where there is definite experimental evidence that bond making and bond breaking are synchronous.

Experimental Section

Preparation and Purification of Materials. The preparation and purification of phenyl benzenethiolsulfonate (2) and the purification of dioxane and morpholine followed previously described procedures.[3] Sodium thiocyanate, potassium iodide, potassium bromide, lithium perchlorate, and perchloric acid were all reagent grade and were used without further purification.

Procedure for Kinetic Runs. A 1:1 morpholine–morpholine H^+ buffer in 60% dioxane was prepared by adding a known amount of standard perchloric acid to a known amount of morpholine in 60% dioxane. To this was then added the appropriate amount of the catalyzing nucleophile (bromide, iodide, or thiocyanate) along with the amount of lithium perchlorate needed to bring the ionic strength up to the desired value. Four milliliters of this solution was thermostatted in a quartz uv cell in the cell compartment of a Perkin-Elmer Model 402 spectrophotometer. The reaction was then initiated by adding to this solution with efficient mixing 40 μl of a relatively concentrated stock solution of 2 in dioxane. The disappearance of 2 was then followed by monitoring the change in optical density at 272 nm. Plots of log $(A - A_\infty)$ vs. time showed excellent linearity in every case and rate constants were reproducible to within ±3%. A run without added catalyzing nucleophile gave the same rate as previously observed by Kice, Rogers, and Warheit.[3]

Registry No.—2, 1212-08-4; morpholine, 110-91-8; thiocyanate, 302-04-5; iodide, 20461-54-5; bromide, 24959-67-9.

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New Synthesis of S(Se)-Alkylphosphorothio(seleno)lates from the Corresponding Phosphoroanilidates. Stereospecific Cleavage of the Phosphorus–Nitrogen Bond in Chiral Phosphoroanilidates

Wojciech J. Stec,* Andrzej Okruszek, Kvystyna Lesiak, Bogdan Uznanski, and Jan Michalski*

Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, 90-362 Lodz, Boczna 5, Poland

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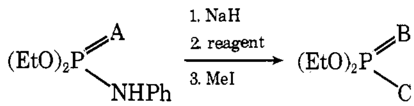
Reaction of sodio derivatives of phosphoroanilidates and their thio and seleno analogues with carbon disulfide or carbon dioxide, followed by treatment of the resulting phosphorothioate or phosphoroselenoate sodium salt with methyl iodide, gave the corresponding S or Se methyl esters. The stereochemistry of P–N bond cleavage was studied using optically active *O*-ethyl ethylphosphonoanilidate and *O*-ethyl ethylphosphonoanilidothioate and diastereoisomeric 2-*N*-phenylamino-2-oxo(-seleno, -thio)-4-methyl-1,3,2-dioxaphosphorinanes. In all cases P–N cleavage proceeds with high stereospecificity and retained configuration around the phosphorus atom. Chemical correlation of absolute configuration at phosphorus in a family of chiral ethylphosphonic acid derivatives is also described.

Although the reaction of anions derived from dialkyl phosphoroanilidates with carbonyl and thiocarbonyl compounds, leading to isocyanates, isothiocyanates, and carbodiimides, was described in the early sixties,[1] the fate of the

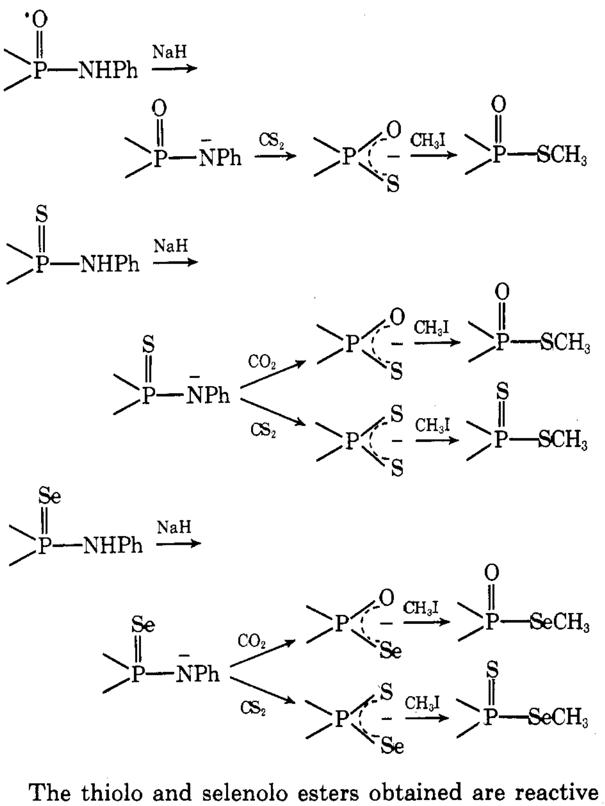
Table I



Expt	A	Substrate: Mp or bp, °C (mmHg)	Substrate: δ_{31P}, ppm	Substrate: Ref	Reagent	B	C	Yield, %	Bp, °C (mmHg)	Product: δ_{31P}, ppm	Product: Ref
1	O	95–96	−2.3	23 mp 96.5°	CS_2	O	SCH_3	82	67–70 (1.5)	−28.5	25 bp 78.5–79° (3 mmHg)
2	S	114 (0.4)	−65.2	24 bp 136–137° (2.5 mmHg)	CO_2			71			
3					CS_2	S	SCH_3	74	50–52 (0.6)	−93.5	26 bp 53–55° (0.7 mmHg)
4	Se	122 (0.25)	−66.5	Anal. Calcd for $C_{10}H_{16}O_2PNSe$: C, 41.12; H, 5.52; P, 10.60; N, 4.79. Found: C, 41.58; H, 5.63; P, 10.96; N, 4.60.	CO_2	O	$SeCH_3$	76	88–90 (1.5)	−19.7	27 bp 100° (4 mmHg)
5					CS_2	S	$SeCH_3$	64	70–72 (0.6)	−83.5	Anal. Calcd for $C_5H_{13}O_2PSSe$: C, 24.28; H, 5.32; P, 12.54. Found: C, 24.17; H, 5.49; P, 12.84.

phosphorus residue and the stereochemistry of its formation has not, to our knowledge, been investigated. By analogy with the Wittig reaction[2] it was reasonable to assume that retention of configuration at phosphorus would accompany the conversion of a chiral anilide or thioanilide into the corresponding phosphorus-containing anion.

In this investigation we have studied the conversion of phosphoroanilidates and their thio and seleno analogues to the corresponding thiolo and selenolo esters summarized in eq 1–5.



(1) (2) (3) (4) (5)

The thiolo and selenolo esters obtained are reactive intermediates in their own right, very useful in synthesis of acid anhydrides or other products resulting from nucleophilic displacement at a phosphorus atom. Special attention has been paid to the stereochemistry of the phosphorus moiety in those cases where enantiomeric or diastereoisomeric compounds could be used.

The possibility of converting phosphoroamidates into phosphorus derivatives containing other functional groups was exploited to a limited extent.

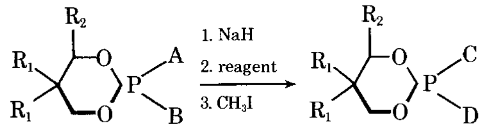
Earlier methods of cleavage of the P–N bond are those involving hydrogen chloride[3] or acidic solvolysis.[4] However, hydrogen chloride reacts stereospecifically only with sterically hindered 2-aminophosphetanes.[5] Acyclic, optically active *N*-benzylphenylmethylphosphinothioamidate reacts with hydrogen chloride with complete loss of optical activity of the resulting phenylmethylphosphinochloridothionate.[5] Recently reported results on methanolysis of methylphenylphosphinoanilidate indicate an acidity-dependent merged dissociative (A-1) and associative (A-2) mechanism for this process.[6] No complete racemization (100% A-1 mechanism) was observed even under strong acidic conditions. In optimal solvolytic conditions 78% stereospecificity, with inversion at phosphorus, was observed. Reaction of phosphorodianilidates with amyl nitrite, leading to the removal of the aniline moiety, has been applied in the field of phosphorylation of nucleosides.[7] It was not explored in cases where stereochemistry at chiral phosphorus molecule could be used.

Taking into account that cleavage of the P–N bond can be applied for preparation of optically active phosphorus derivatives via diastereoisomeric phosphoroamidates, we undertook to study the best conditions under which such reactions proceed.

Results and Discussion

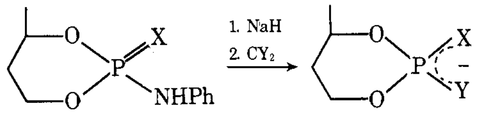
At first the reaction of diethylphosphoroanilidate anion with carbon disulfide, followed by alkylation of the resulting diethylphosphorothioate anion with methyl iodide (eq 1), was used as a simple achiral model. *O,O*-Diethyl-*S*-methyl phosphorothioate was isolated in 82% yield. Reactions of diethyl thio- and selenophosphoroanilidates were also carried out. The anion generated with sodium hydride in dioxane solution was allowed to react with carbon dioxide (eq 2, 4) and/or with carbon disulfide (eq 3, 5). Alkylation of the resulting sodium salts gave corresponding thiolo or selenolo esters in good yields, as shown in Table I. Similar results were obtained when 2-*N*-phenylamino-2-X-1,3,2-dioxaphosphorinanes (X = O, S, Se) were employed in our studies (see Table II). Reactions of *cis*- and *trans*-2-*N*-phenylamino-2-X-4-methyl-1,3,2-dioxaphosphorinanes (X = O, S, Se; Table II, expt 6–14) are of special interest.

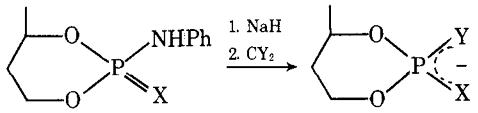
Table II.



Expt	R_1	R_2	Substrate A	Substrate B	Substrate Mp, °C	Substrate $\delta_{^{31}P}$, ppm	Substrate Ref	Reagent	Product C	Product D	Yield %	$\delta_{^{31}P}$, ppm	SS,[b] %	Mp or bp, °C (mmHg)	Product Ref
1	CH_3	H	O	NHPh	167	+2.6	Anal. Calcd for $C_{11}H_{16}O_3NP$: C, 54.77; H, 6.68; N, 5.81; P, 12.84. Found: C, 54.91; H, 6.62; N, 5.91; P, 12.60.	CS_2	O	SCH_3	83	−22.5		81–82	28, mp 81–81.5°
2	CH_3	H	S	NHPh	175–176	−62.5	Anal. Calcd for $C_{11}H_{16}O_2NPS$: C, 51.35; H, 6.37; N, 5.48; P, 12.04. Found: C, 51.63; H, 6.42; N, 5.54; P, 12.31.	CO_2	O	SCH_3	57	−22.5		81–82	See expt 1
3								CS_2	S	SCH_3	68	−90.0		85–86	28, mp 85.5–86°
4	CH_3	H	Se	NHPh	175–176	−62.0	Anal. Calcd for $C_{11}H_{16}O_2NPSe$: C, 43.44; H, 5.29; N, 4.61; P, 10.15. Found: C, 43.14; H, 5.49; P, 10.51; N, 5.00.	CO_2	O	$SeCH_3$	76	−13.8		90–92	Anal. Calcd for $C_6H_{13}O_3PSe$: C, 29.65; H, 5.39; P, 12.74%. Found: C, 29.52; H, 5.58; P, 13.01.
5								CS_2	S	$SeCH_3$	72	−80.0		71–73	Anal. Calcd for $C_6H_{13}O_2PSSe$: C, 27.81; H, 5.08; P, 12.19. Found: C, 27.80; H, 5.15; P, 12.39.
6	H	CH_3	NHPh	O	173–175	+1.0	8, mp 174–176° $\delta_{^{31}P}$ +1.1 ppm	CS_2	SCH_3	O	62	−23.5	100	110–115 (0.2)	29, $\delta_{^{31}P}$, −22.8 ppm
7	H	CH_3	O	NHPh	153–155	+4.5	8, mp 154–156° $\delta_{^{31}P}$ +3.5 ppm	CS_2	O	SCH_3	58	−19.5	100	76–77	29, mp 77–77.5° $\delta_{^{31}P}$ −18.1 ppm
8	H	CH_3	NHPh	S	91–92	−63.0	9, mp 91–92° $\delta_{^{31}P}$ −63.0 ppm	CO_2	O	SCH_3	61	−19.5	100	76–77	See expt 7
9	H	CH_3	S	NHPh	171–172	−59.5	9, mp 171–172° $\delta_{^{31}P}$ −59.5 ppm	CO_2	SCH_3	O	66	−23.5	100	104–106 (0.05)	See expt 6
10	H	CH_3	NHPh	Se	95–96	−62.5	9, mp 95–96° $\delta_{^{31}P}$ −62.5 ppm	CO_2	O	$SeCH_3$	60	−12.5	100	58–59	30, mp 59–59.5° $\delta_{^{31}P}$ −11.7 ppm
11	H	CH_3	Se	NHPh	166–167	−60.0	9, mp 166–167° $\delta_{^{31}P}$ −60.0 ppm	CO_2	$SeCH_3$	O	57	−13.7	100	100 (0.01)	30, $\delta_{^{31}P}$ −14.0 ppm
12	H	CH_3	NHPh	Se			See expt 10	CS_2	S	$SeCH_3$	52	−79.0 (437 Hz)[a]	100	56–57°	Anal. Calcd for $C_5H_{11}O_2PSSe$: C, 24.50; H, 4.53; P, 12.63. Found: C, 24.44; H, 4.50; P, 12.54.
13	H	CH_3	Se	NHPh			See expt 11	CS_2	$SeCH_3$	S	56	−88.0 (510 Hz)[a]	100	95 (0.2)	Anal. Found: C, 24.54; H, 4.67; P, 12.99.
14	H	CH_3	S	NHPh			See expt 9	CS_2	S / SCH_3	SCH_3 / S	66	−88.5 / −95.5	69 / 31	105–110 (0.2)	31, $\delta_{^{31}P}$ −88.5 ppm $\delta_{^{31}P}$ −95.5 ppm

[a] In parentheses values of $^1J_{P-Se}$ are given. [b] SS = stereospecificity.


(6)


(7)

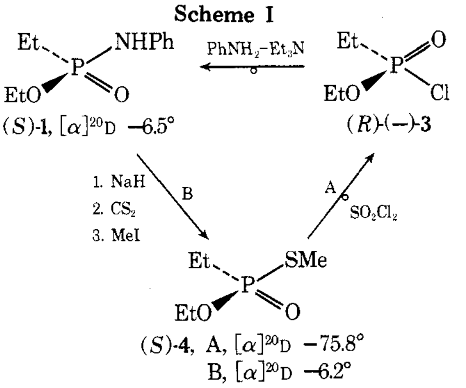
X = O, S, Se; Y = O, S

The synthesis and assignment of cis–trans geometry in the family of starting materials leading to models used in this study were reported recently from this laboratory.[8,9]

In this series of experiments we aimed to define the stereochemistry of the reactions investigated. Reaction mixtures prior to standard work-up preparative procedure were examined with the aid of ^{31}P NMR spectroscopy for determination of the cis–trans isomer ratio.

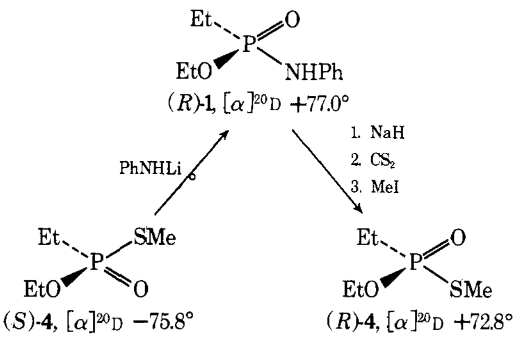
Reaction of a 2-thioanilidate anion (Table II, expt 14) with carbon disulfide, followed by alkylation with methyl iodide, is indicative of an axial preference of the methylthio substituent in diastereoisomeric tetracoordinated dioxaphosphorinanyl ring system or the higher nucleophilicity of sulfur in an axial disposition[10] in the ambident dithiophosphate anion. Detailed inspection of Table II reveals that the reactions under consideration are fully stereospecific and proceed with full retention of configuration at phosphorus (expt 6–13). Preparative yields are reported for products isolated by distillation or crystallization. Both *cis*- and *trans*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinanes (expt 12, 13) were previously unreported and cis–trans assignment, together with stereochemical course of reactions, was elucidated by comparison of spin–spin coupling constants between directly bonded phosphorus and selenium-77. In the light of recent data reported from this laboratory[11] the cis isomer, with equatorially oriented MeSe group, has a higher absolute value of $^{1}J_{^{31}P-^{77}Se}$ (510 Hz) than that of the trans isomer with MeSe group in axial disposition (437 Hz). It is also worthwhile to mention that methylation of ambident phosphoroselenothioate anion (Table I, expt 5; Table II, expt 12, 13) proceeds exclusively on selenium center, in accordance with previous findings reported from this laboratory.[12] Since several discrepancies in stereochemical course of reactions between cyclic and acyclic systems[13] have been reported, we decided to carry out the reaction of enantiomeric *O*-ethyl ethylphosphonoanilidate (1) and its thiophosphoryl analogue 2 with carbon disulfide and carbon dioxide, respectively, and to elucidate definitively the stereochemistry of the reactions in question. Stereochemical correlations are demonstrated in Schemes I–IV. It should be mentioned that the

Scheme I



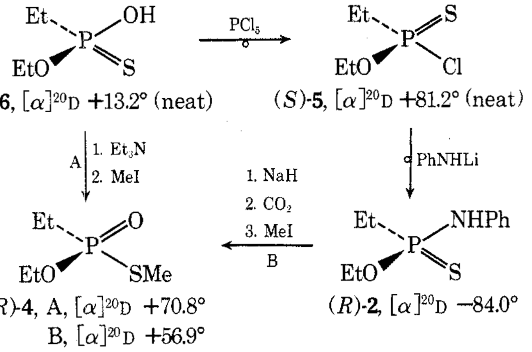
stereochemistry of *O*-ethyl ethylphosphonoamidates and their thiono analogues have not been established previously and it was necessary to perform several transformations which would give a clear picture of the reactions investigated. *S*-(−)-1[14] was obtained in the reaction of optically active (*R*)-(−)-*O*-ethyl ethylphosphonochloridate (3) with aniline in the presence of triethylamine as shown in Scheme I. (*R*)-(−)-3 was obtained from chlorinolysis of (*S*)-(−)-*O*-ethyl-*S*-methyl ethylphosphonothiolate (4) with sulfuryl chloride and was not isolated in a pure form prior to aminolysis. Reaction of the sodium salt of (−)-1 with carbon disulfide followed by alkylation of the resulting *O*-ethyl ethylphosphonothioate anion with methyl iodide gave 4 with the same configuration as the starting thiolo ester used for chlorinolysis, although its specific rotation value was much lower. The transformations described above constitute, according to Cram's classification,[15] a podal, triligostatic, three-reaction cycle in which both chlorinolysis of phosphoryl thiolo esters[16] as well as aminolysis of phosphoryl chloroanhydrides[17] are known to proceed with inversion of configuration at phosphorus. On this basis we conclude that the third reaction, direct 1 → 4 transformation, proceeds with retention at phosphorus center. Although the observed loss of optical activity of 4 in the cycle was most likely caused by fast racemization of chloride 3 prior to its aminolysis,[18] we undertook additional studies in order to establish more definitely the stereospecificity of anilidate → thiolo ester conversion. Direct synthesis of anilidate 1 from thiolo ester 4 was performed. The reaction of (*S*)-(−)-4 with lithium anilide yielded (+)-1 which, after reaction with carbon disulfide, gave 4 of opposite sign of rotation to that of the starting material, with overall stereospecificity above 95% (see Scheme II). The rules of an antipodal, triligostatic, two-reaction cycle of the kind represented in Scheme II led us to the conclusion that nucleophilic exchange (replacement) of a thiomethyl group at a phosphoryl center by lithium anilide proceeds, as in the case of oxo esters,[19] with full inversion of configuration at the phosphorus atom.

Scheme II

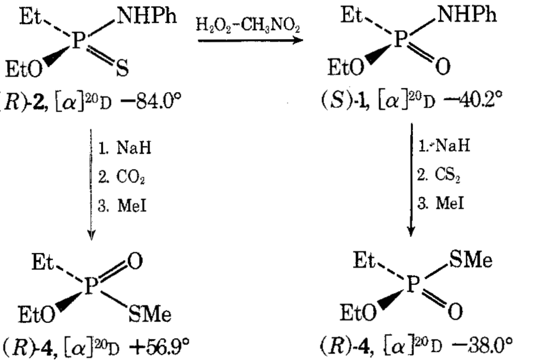


Similar results were obtained for the thioanilidate 2, which was prepared by the reaction of *O*-ethyl ethylphosphonochloridothionate (5) with lithium anilide. The stereochemical correlation with the parent *O*-ethyl ethylphosphonothioic acid (6) is summarized in Scheme III. Since in the podal, diligostatic, four-reaction cycle the chlorinolysis of thio acid 6 with phosphorus pentachloride proceeds with inversion of configuration[20] and the alkylation of 6 does not affect the configuration at phosphorus, we can conclude that one of the remaining reactions must proceed with inversion and the other one with retention of configuration at phosphorus. Although aminolysis of chloride 5 with diethylamine and its lithium salt was previously described,[21] the stereochemical course of these reactions was obscure. Thus, we constructed another reaction cycle which correlates the configuration of anilidate 1 with that of thioanilidate 2 by means of direct oxidation of 2 with hydrogen peroxide (see

Scheme III



Scheme IV



Scheme IV). This antipodal, three-reaction cycle involves one ligand metathesis arising from substitution of sulfur atom by oxygen during the oxidation process. Since both conversion **1** → **4** (as proved above) as well as oxidation of thionophosphoryl amido esters with hydrogen peroxide[22] proceed without any change of configuration at phosphorus, the third reaction (e.g., direct **2** → **4** conversion) must proceed also with retention of configuration. This finding led us to the conclusion concerning the stereochemical course of substitution of the chlorine atom in chloridothionate **5** by the anilide anion (Scheme III). This reaction proceeds with inversion of configuration at phosphorus and stereospecificity exceeding 80%.

Two important conclusions can be drawn from these stereochemical correlations: (1) phosphorylation and thiophosphorylation of lithium anilide with phosphonothiolates or phosphorochloridothionates proceed with inversion of configuration at phosphorus; (2) the Wadsworth–Emmons type conversion[1] of phosphoroanilidates and their thio (seleno) analogues into the corresponding phosphorothio(seleno)lates is highly stereospecific and proceeds with retention of configuration at phosphorus.

Finally we tried to exploit the reaction of amidate anions with carbonyl compounds for the synthesis of chiral organophosphorus compounds via resolution of diastereoisomeric phosphonothioamidates. Reaction of racemic **5** with (−)-*α*-phenylethylamine gave a 1:1 mixture of diastereoisomeric *O*-ethyl-*N*-*α*-phenylethyl ethylphosphonothioamidate (**7**). Pure diastereoisomer **7** was isolated through fractional crystallization from *n*-hexane. However, its reaction with butyllithium, followed by reaction with carbon dioxide in boiling dioxane, failed to give the expected **4**. This means that the method of conversion of phosphoroamidates into phosphoryl thiolo esters described above is limited to "activated" amidates only.

Experimental Section

All melting points and boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use.

^1H NMR spectra were recorded at 60 MHz with a Jeol C-60H spectrometer equipped with Hetero-Spin-Decoupler JNH-SD-HC, with Me_4Si as an internal standard. ^{31}P NMR spectra were obtained on the same instrument at 24.3 MHz with external H_3PO_4 as the reference. Negative chemical shift values are reported for compounds absorbing at lower fields than H_3PO_4. Mass spectra were obtained on a LKB 9000S spectrometer at 70 eV ionizing energy. Optical activity measurements were made with a Perkin-Elmer 141 photopolarimeter in benzene solution, unless specified otherwise. Product purities were determined from integrated ^1H and ^{31}P NMR spectra and GLC (Varian Aerograph 1520) or TLC (Silufol UV 254 plates) analyses.

I. Starting Materials. A. Diethyl phosphoroanilidite was obtained according to Kabachnik and Gilarov[24] from diethyl phosphorochloridite and aniline in the presence of triethylamine in benzene solution: bp 120° (4 mmHg); $n^{20}D$ 1.5203; $\delta_{^{31}P}$ −129.0 ppm; yield 63% [lit.[24] bp 120° (4 mmHg), $n^{20}D$ 1.5254]. Its oxidation with *tert*-butyl hydroperoxide and addition of elemental sulfur or selenium gave corresponding diethyl phosphoroanilidate and its thiono and seleno derivatives. Their colligative and spectral parameters are given in Table I.

B. 2-*N*-Phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane was obtained from the corresponding chlorophosphite[32] and aniline in the presence of triethylamine in benzene solution: mp 65–67°; $\delta_{^{31}P}$ −116.0 ppm (benzene); yield 46%. Anal. Calcd for $C_{11}H_{16}O_2NP$: C, 58.66; H, 7.15; P, 13.75; N, 6.22. Found: C, 58.50; H, 7.22; P, 13.75; N, 6.22. Corresponding 2-oxo-, 2-thio-, and 2-seleno-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinanes were obtained by oxidation of cyclic anilidite with *tert*-butyl hydroperoxide, elemental sulfur, and selenium, respectively, and their characteristics are included in Table I.

C. Isomeric 2-*N*-phenylamino-2-X-4-methyl-1,3,2-dioxaphosphorinanes (X = lone pair, O, S, Se) were synthesized according to procedures described recently from our laboratory.[8,9]

D. *O*-Ethyl ethylphosphonothioic acid [6, bp 57–59° (0.08 mm Hg), $n^{20}D$ 1.4909] was obtained and resolved into optical antipodes according to Aaron et al.[33]

E. *O*-Ethyl ethylphosphonochloridothionate [(*S*)-5, bp 20° (0.05 mmHg), $n^{23}D$ 1.4912, $[\alpha]^{20}D$ +81.2° (neat), $\delta_{^{31}P}$ −106 ppm] was obtained from optically active thio acid (*R*)-**6** [$[\alpha]^{20}D$ +13.2° (neat)] according to the procedure described by Michalski and Mikolajczyk.[34]

F. *O*-Ethyl-*S*-methyl ethylphosphonothiolate [(*S*)-4, bp 55° (1 mmHg), $n^{20}D$ 1.4782, $[\alpha]^{20}D$ −75.8°, $\delta_{^{31}P}$ −61.5 ppm] was produced by S-alkylation of the triethylammonium salt of (*S*)-**6** [$[\alpha]^{20}D$ −14.1° (neat)].[35]

G. Chlorinolysis of 4 and Reaction of Resulting *O*-Ethyl Ethylphosphonochloridate (3) with Aniline. Freshly distilled sulfuryl chloride (2.7 g, 0.02 mol) was added dropwise into a solution of (*S*)-**4** (3.4 g, 0.02 mol, $[\alpha]^{20}D$ 75.8°) in benzene (50 ml) at 5°. Stirring at room temperature was continued for 15 min and a benzene solution of aniline (3.72 g, 0.04 mol) and triethylamine (4.08 g, 0.04 mol) was slowly added at 20° with stirring and external cooling. Stirring at room temperature was continued for 30 min and amine hydrochloride was filtered off and washed with benzene. The solvent was evaporated and the residue was chromatographed (300 g of silica gel 100–200 mesh) in benzene–acetone (1:1). The separation was followed by TLC. *O*-Ethyl ethylphosphonoanilidate [(*S*)-**1**] was isolated after evaporation of solvent, as an undistillable oil with a yield of 3.0 g (70.5%): $\delta_{^{31}P}$ −34.0 ppm (benzene); $[\alpha]^{20}D$ −6.5° (Anal. Calcd for $C_{10}H_{16}O_2NP$: C, 56.20; H, 7.55; N, 6.58; P, 14.50. Found: C, 56.30; H, 7.61; N, 6.72; P, 14.50); ir (film) 1200 ($\nu_{P=O}$), 3155 cm^{-1} (ν_{N-H}); mass spectrum *m/e* (rel intensity) 93 (100), 213 (73), 185 (29), 139 (15), 120 (11), 111 (17.5), 105 (12), 65 (20).

H. Reaction of Lithium Anilide with 4. To a solution of butyllithium (0.08 mol) in ether (80 ml) was added at −10° with stirring and external cooling, under a dry nitrogen atmosphere, 7.5 g (0.08 mol) of aniline. The mixture was cooled to −40° and 12.5 g (0.075 mol) of (*S*)-**4**, $[\alpha]^{20}D$ −75.8°, was added. Stirring at room temperature was continued for 1 hr and the resulting precipitate was filtered off. The filtrate was evaporated, dissolved in benzene, washed with cold, 1% HCl, dried over $MgSO_4$, and evaporated. The residue was chromatographed (200 g of silica gel 100–200 mesh) in benzene–acetone (1:1). The column chromatography was followed by TLC. Evaporation of solvent gave (*R*)-**1** as an undistillable, viscous oil, $\delta_{^{31}P}$ −34.0 ppm (benzene), $[\alpha]^{20}D$ +77.0°, yield 3.1 g (19.5%). The ir and mass spectra were identical with these recorded for **1** described in section IF.

From another fraction of eluate 6 g (48%) of unchanged 4 was recovered.

I. Reaction of Lithium Anilide with 5. To a solution of butyllithium (0.05 mol) in ether (40 ml) was added at −10°, with stirring and external cooling, under a dry nitrogen atmosphere, 4.65 g (0.05 mol) of aniline. The resulting solution was cooled to −40° and 8 g (0.0465 mol) of (*S*)-**5**, $[\alpha]^{20}D$ + 81.2° (neat), was added. The reaction mixture was stirred for 1 hr at room temperature and then evaporated under reduced pressure. The residue was dissolved in benzene (50 ml) and washed with 2% HCl (2 × 50 ml). Water solutions were extracted with benzene (2 × 20 ml). Combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was distilled under reduced pressure, giving 4.5 g (42%) of thioanilidate (*R*)-**2**: bp 115° (0.2 mmHg); $n^{26}D$ = 1.5652; δ_{31P} −85.0 ppm (benzene); $[\alpha]^{20}D$ = −84.0° (Anal. Calcd for $C_{10}H_{16}ONPS$: C, 52.50; H, 7.03; P, 13.50; N, 6.12. Found: C, 51.99; H, 7.28; P, 13.98; N, 6.19); ir (film) 3265 cm^{-1} (ν_{N-H}); mass spectrum *m/e* (rel intensity) 155 (100), 229 (64), 127 (68), 105 (56), 93 (55). As a lower boiling fraction 4.0 g (50%) of unchanged phosphonochloridothionate 5 was recovered, bp 30–35° (0.2 mmHg), $n^{20}D$ 1.4906, $[\alpha]^{20}D$ + 60.2° (neat).

J. Oxidation of 2 with Hydrogen Peroxide. To a solution of (*R*)-**2** (2.3 g, 0.01 mol), $[\alpha]^{20}D$ −84.0°, in nitromethane (50 ml) was added hydrogen peroxide (1 g, 80%). The mixture was gently heated and at 50° an exothermic reaction occurred. Heating at 60° was continued for 30 min. The mixture was evaporated and the residue was purified on silica gel (100–200 mesh) (100 g) with benzene–acetone (1:1) as an eluent. Evaporation of solvent gave 1.9 g (89%) of (*S*)-**1** as an undistillable, viscous oil, δ_{31P} −34.0 ppm (benzene), $[\alpha]^{20}D$ = −40.2°. *The ir and mass spectra were identical with those* recorded for 1 described in section IF.

K. *O*-Ethyl-*N*-α-phenylethyl Ethylphosphonothioamidate (7). To a solution of racemic 5 (38.5 g, 0.2 mol) in benzene (150 ml) was added, with stirring, a solution of α-phenylethylamine [24.5 g, 0.2 mol, $[\alpha]D$ −37.0° (neat)] and triethylamine (20.4 g, 0.2 mol) in benzene (50 ml). An exothermic reaction was observed and the temperature rose to 40°. Stirring at this temperature was continued for 3 hr and the resulting precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was distilled under reduced pressure, giving 7 as a colorless liquid: bp 120–125° (0.2 mmHg); $n^{22}D$ 1.5450; $[\alpha]^{20}D$ −29.8°; yield 37 g (72%) (Anal. Calcd for $C_{12}H_{20}PNSO$: C, 56.00; H, 7.84; P, 12.05; N, 5.45. Found: C, 56.66; H, 8.26; P, 11.87; N, 6.04); mass spectrum *m/e* (rel intensity) 105 (100), 257 (63.8), 224 (29.6), 178 (21.8), 121 (47.2), 120 (100), 91 (29.1), 77 (49.2). Its ^{31}P NMR analysis (benzene) revealed the presence of two substances, **7a** (δ_{31P} −89.5 ppm) and **7b** (δ_{31P} −89.8 ppm), in the ratio 1:1. The product had solidified during the storage at room temperature. Its recrystallization from *n*-hexane caused an increase in **7a:7b** ratio and after repeated fractional crystallization pure **7a** (11.5 g) was obtained, δ_{31P} −89.5 ppm, mp 51–52°, $[\alpha]^{20}D$ = +12.8° (Anal. Found: C, 55.85; H, 7.95; P, 11.85; N, 5.32). From mother liquors the fraction containing 36% of **7a** and 64% of **7b** (^{31}P NMR analysis) was isolated (yield 15 g, $[\alpha]^{20}D$ −42°).

II. Conversion of Phosphoroanilidates $(RO)_2P(X)NHPh$ (X = O, S, Se) to Corresponding Thiolo(seleno) Esters. General Procedure. To a suspension of NaH (1.44 g, 0.06 mol) in dioxane (100 ml) was added, dropwise, at 50°, a solution of corresponding anilidate (0.05 mol) in dioxane (50 ml). Reaction was accompanied with evolution of hydrogen and formation of a white precipitate. The reaction mixture was stirred at 90° for the next hour[36] and CS_2[37] (20 ml) was added in small portions during 1 hr. An additional 1 hr of stirring at 90° was followed by solvent evaporation, the residue was shaken with 100 ml of benzene–hexane (1:5) solution, and the resulting precipitate was filtered off and washed with hexane. The precipitate was suspended in benzene (100 ml) and 14.2 g (0.1 mol) of methyl iodide was added. The suspension was refluxed for 2 hr and cooled and the precipitate was filtered off and washed with benzene. The filtrate was evaporated and the residue was examined by means of ^{31}P NMR. Pure product was isolated by distillation or crystallization, yield 50–80%. Further details are included in Table I.

III. Conversion of 1 to 4. The procedure described in section II was applied to 1 (3.1 g, 0.0145 mol, $[\alpha]^{20}D$ +77.0°) using CS_2 as the reagent. Pure 4 was isolated in 78% yield [1.9 g, bp 62° (2 mmHg), $n^{20}D$ 1.4782, $[\alpha]^{20}D$ +72.8°, δ_{31P} −61.5 ppm).

IV. Conversion of 2 to 4. The reaction of 2 (3.0 g, 0.013 mol, $[\alpha]^{20}D$ −68.5°) with NaH–CO_2–MeI was performed as described in section II. Pure 4 was isolated by distillation: bp 62° (2 mmHg); $n^{22}D$ = 1.4778; $[\alpha]^{20}D$ = +46.5°; δ_{31P} −61.5 ppm; yield 1.2 g (55%).

V. Attempted Conversion of 7a to 4. To a solution of **7a** (5.14 g, 0.02 mol, $[\alpha]^{20}D$ +12.8°) in dioxane (50 ml) was added at 20°, with stirring, under a dry nitrogen atmosphere, a solution of butyllithium[38] (0.021 mol) in ether (11 ml). An exothermic reaction was observed. Stirring at room temperature was continued for 10 min and dry CO_2 was bubbled through the solution for 1 hr at room temperature and then for 2 hr at 90°. The ^{31}P NMR spectrum showed an absorption band at −101 ppm and no signal in the region characteristic for thio acid (**6**) salt. Thus, the signal at −101 ppm was suspected to correspond to *N*-lithium salt of **7**. It has been proved by its hydrolysis and recovery of starting **7** (82%), bp 123–125° (0.2 mmHg), $[\alpha]^{20}D$ +10.3°.

Registry No.—(*S*)-**1**, 57237-61-3; (*R*)-**1**, 57237-62-4; (*R*)-**2**, 57237-63-5; (*R*)-**3**, 57287-75-9; (*S*)-**4**, 20698-84-4; (*R*)-**4**, 20698-85-5; (*S*)-**5**, 13547-42-7; *rac*-**5**, 13547-40-5; (*R*)-**6**, 4789-36-0; (*S*)-**6** Et_3N salt, 57237-64-6; **7** isomer 1, 57237-65-7; **7** isomer 2, 57237-66-8; diethyl phenylphosphoramidoselenoic acid, 57237-67-9; *O,O*-diethyl *Se*-methylphosphoroselenothioic acid, 50735-57-4; 2-oxo-2-phenylamine-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-68-0; 2-thiono-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-69-1; 2-seleno-2-phenylamino-5,5-dimethyl-1,3,2-dioxaphosphorinane, 57237-70-4; *cis*-2-seleno-2-phenylamino-4-methyl-1,3,2-dioxaphosphorinane, 57237-71-5; *trans*-2-seleno-2-phenylamino-4-methyl-1,3,2-dioxaphosphorinane, 57237-72-6; 2-methylseleno-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane, 52963-22-1; 2-methylseleno-2-thiono-5,5-dimethyl-1,3,2-dioxophosphorinane, 57237-73-7; *trans*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinane, 57237-74-8; *cis*-2-methylseleno-2-thiono-4-methyl-1,3,2-dioxaphosphorinane, 57237-75-9; sulfuryl chloride, 7791-25-5; lithium anilide, 20732-26-7; hydrogen peroxide, 7722-84-1; (−)-α-phenylethylamine, 2627-86-3.

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(36) When X = O an anion formation was so fast that additional heating was not necessary.
(37) When X = S, Se in some experiments, leading to phosphoryl compounds, dry CO_2 was bubbled through the reaction mixture at 90° for 2 hr.
(38) Sodium hydride did not react with **7** even in boiling dioxane as proved in a separate experiment.

Organophosphorus Compounds of Sulfur and Selenium. Stereochemistry of Oxidation of Thiono- and Selenophosphoryl Compounds with Hydrogen Peroxide

Wojciech J. Stec,* Andrzej Okruszek, and Jan Michalski*

Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, 90-362 Lodz, Boczna 5, Poland

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The oxidation of 2-R-2-*S*(*Se*)-4-methyl-1,3,2-dioxaphosphorinanes with hydrogen peroxide to 2-oxo derivatives proceeds with net retention of configuration at the phosphorus atom. The same stereochemical course was observed in the case of enantiomeric *O*-ethyl-*O*-methyl ethylphosphonothionate. On the other hand, conversion of optically active phosphine sulfide into the corresponding oxide proceeds with inversion of configuration accompanied by racemization. In contrast the oxidation of enantiomeric phosphine selenide by hydrogen peroxide depends on the reaction conditions. Oxidation reactions of thio- and selenophosphoryl compounds with hydrogen peroxide are rationalized in terms of stability of pentacovalent intermediates, which depends on structure of reactants and reaction conditions.

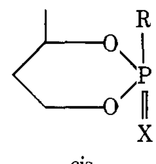
Better insight into the mechanism of oxidation of thio- and selenophosphoryl derivatives to their oxo analogues is of importance for stereochemical correlations, constructing new stereochemical cycles,[1] and better understanding of the metabolic pathways of some phosphoroorganic biocides which are known to involve PS → PO oxidation reactions.[2]

The stereochemistry of conversion of thiophosphoryl compounds into phosphoryl analogues has attracted attention in many research laboratories. It has been demonstrated that oxidizing agents such as potassium permanganate,[3] nitric acid,[4] dinitrogen tetroxide,[4] organic peracids,[5,6] ozone,[6] dimethyl sulfoxide,[7] and hydrogen peroxide[8] can smoothly oxidize thio- and selenophosphoryl compounds. The stereochemical course of the oxidation is dependent on the nature of oxidizing agent, reaction medium, and structure of thio- and selenophosphoryl moieties. Thus nitric acid oxidizes methylphenyl *n*-propylphosphine sulfide and *O*-ethyl-*O*-methyl ethylphosphonothionate with inversion of configuration,[4a] but retention was observed when diastereoisomeric 2-thiono-[4b] and 2-seleno-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans[4c] were used as model compounds. Herriot has also demonstrated the reversal of stereochemistry in oxidation of diastereoisomeric *O*-menthyl methylphenylphosphinothionates by *m*-chloroperbenzoic acid.[5] Net retention was observed in neutral solvents. Addition of trifluoroacetic acid caused a dramatic change in stereochemistry and inversion was observed. The same relationship between stereochemistry and acidity of reaction medium was earlier reported from this laboratory for dinitrogen tetroxide oxidation of enantiomeric phosphine sulfide.[4a] However, dinitrogen tetroxide causes much racemization of the resulting phosphoryl compounds and determination of the particular reaction step responsible for this racemization must await further studies.[9]

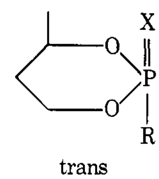
Hydrogen peroxide has also been used as an oxidizing agent[8] and oxidations of diastereoisomeric *O*-menthyl methylphenylphosphinothionate as well as optically active *O*-methyl *tert*-butylphenylphosphinothionate were described as fully stereospecific and proceeding with retention of configuration at phosphorus atom. This result seemed to be in disagreement with our preliminary findings on application of hydrogen peroxide for stereospecific PS → PO conversion. For this reason we undertook more detailed studies on this reaction employing various thio- and selenophosphoryl compounds and different reaction media.

Results

Diastereoisomeric 2-R-2-X-4-methyl-1,3,2-dioxaphosphorinanes (**1–6**), enantiomeric *O*-ethyl-*O*-methyl ethylphosphonates (**7, 8**), and thio, seleno, and oxo derivatives of

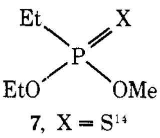


cis

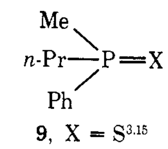


trans

1, X = S; R = OMe[4b,11]
2, X = Se; R = OMe[4c]
3, X = S; R = NMe_2[12]
4, X = Se; R = NMe_2[12]
5, X = O; R = OMe[13]
6, X = O; R = NMe_2[13]



7, X = S[14]
8, X = O[14]



9, X = S[3,15]
10, X = Se[4c]
11, X = O[3,15]

methylphenyl-*n*-propyl phosphine (**9–11**) were chosen as stereochemical models for our studies. Stereochemistry of these compounds has been well established. Information concerning models, reaction conditions (solvent, temperature, and time), and stereospecificities is collected in Tables I–IV.[10]