Tetrahedron, 1966, Vol. 22, pp. 3055 to 3059. Pergamon Press Ltd. Printed in Northern Ireland

STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT THE THIOPHOSPHORYL CENTRE—I*

OPTICALLY ACTIVE O-ETHYL ETHYLPHOSPHONOCHLORIDOTHIONATE†

J. MICHALSKI and M. MIKOŁAJCZYK
Institute of Organic Chemistry, Polish Academy of Sciences, Łódź 40,
Żwirki 36, Poland

(*Received* 24 *March* 1966)

Dedicated to Professor R. Wizinger-Aust in honour of his 70th birthday

Abstract—The reaction of (−)- and (+)-O-ethyl ethylphosphonothioic acid (I) with phosphorus pentachloride has been shown to give optically active O-ethyl ethylphosphonochloridothionate (II) in high yield. For establishing the relative configuration and degree of stereospecificity of (II) use was made of the pyrophosphonothionates, prepared from I and II. The mechanism of the reaction is discussed.

ALTHOUGH the first phosphorus compound was resolved into optical isomers over 50 years ago, the dynamic stereochemistry of phosphorus centres is a new field which was opened up about 6 years ago. Prior to 1959, it was not known whether displacement reactions at a phosphorus atom are stereospecific. The first major step forward was achieved between 1956 and 1959 when a description of the resolution of asymmetric phosphorus thio-acids[1,2] and of phosphonium salts[3] was reported. Optically active phosphorus thio-acids are one of the most important classes of compounds on which the routes to other types of optically active phosphorus compounds are based, for instance to the optically active phosphinyl chlorides $R'R''P(O)Cl$. The last mentioned have recently been used to study the stereochemistry at an asymmetric phosphorus atom.[4–7] Their usefulness is limited, however, by their rapid racemization or low optical rotation values.

In a search for more convenient models for stereochemical studies, synthesis of phosphonochloridothionates $R(RO)P(S)Cl$ was undertaken. It was expected that the replacement of oxygen by sulphur would result in a system with similar properties but less reactive with nucleophilic reagents. It is interesting to note that, in many essential aspects, the chemistry of thiophosphoryl compounds parallels that of phosphoryl compounds. Nucleophilic displacement reactions of thiophosphoryl

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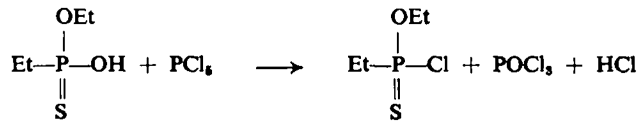
[*] Paper XXXVI in the series "Organophosphorus Compounds of Sulphur and Selenium". For paper XXXV see J. Michalski and B. Pliszka-Krawiecka, *J. Chem. Soc.* in the press.

Preliminary communications: J. Michalski and M. Mikołajczyk, *Chem. and Ind.* 661 (1964); *Chem. Comm.* 35 (1965).

[1] H. S. Aaron, T. M. Shryne and J. I. Miller, *J. Amer. Chem. Soc.* **80**, 107 (1958).
[2] G. Hilgetag and G. Lehmann, *Angew. Chem.* **69**, 506 (1957).
[3] K. F. Kumli, W. E. McEven and C. A. Vander Werf, *J. Amer. Chem. Soc.* **81**, 248 (1959).
[4] M. Green and R. F. Hudson, *Proc. Chem. Soc.* 227 (1959).
[5] J. Michalski and A. Ratajczak, *Chem. & Ind.* 1241 (1960); *Rocz. Chem.* **37**, 1183 (1963).
[6] H. S. Aaron, R. T. Uyeda, H. F. Frack and J. I. Miller, *J. Amer. Chem. Soc.* **84**, 617 (1962).
[7] A. Ratajczak, *Bull. Acad. Polon, Sci., Ser. sci. chim.*, **12**, 139 (1964).

compounds are in general markedly slower than those of phosphoryl compounds.[8] This difference is of great value in stereochemical studies.

It is well known that the action of phosphorus pentachloride on phosphorus thioacids leads to an exchange of the hydroxyl-group for halogen.[9] This reaction with optically active O-ethyl ethylphosphonothioic acid (I) is of interest for the following reasons: the possibility of using optically active O-ethyl ethylphosphonochloridothionates (II) as key intermediates for synthesis of other optically active P(S) group-containing organophosphorus compounds; and the stereochemistry of the reaction itself and its comparison with corresponding reactions in carbon chemistry.



$$\mathrm{Et{-}\overset{OEt}{\underset{S}{P}}{-}OH} + \mathrm{PCl_5} \longrightarrow \mathrm{Et{-}\overset{OEt}{\underset{S}{P}}{-}Cl} + \mathrm{POCl_3} + \mathrm{HCl}$$

I (−) or (+) II (−) or (+)

The reaction of (−)- and (+)-O-ethyl ethylphosphonothioic acid (I), with a molar ratio of phosphorus pentachloride was carried out at −10° in solvent. The crude (−)- and (+)-chlorides (II) were purified by distillation in high vacuum. Optically active chlorides (II) of the highest rotation value are obtained in ether solution. The following specimens of the chloride (II), $[\alpha]_D^{20}$ −82·80°, −81·85°, −63·00° were prepared from the (−)-acid (I), with the corresponding rotation values, $[\alpha]_D^{20}$ −14·15°, −14·00° and −11·00°. Other solvents, especially methylene chloride, are less suitable. The chlorides (II) were shown by TLC to be free of any traces of ethyl ethylphosphonochloridate, Et(EtO)P(O)Cl, as impurities. As expected, the optically active chlorides (II) are optically stable. Their optical rotation was found to be unchanged after storage for several days at room temperature.

For establishing the degree of stereospecificity of the reaction and of the configurational changes concerned use was made of the chemistry of pyrophosphonothionate systems. The degree of optical purity of the (−)-chloride (II) can be deduced from its reaction with sodium O-ethyl ethylphosphonate. The properties of (+)-diethyl ethylpyrophosphonothionate (III) formed, are compared with those of III prepared by condensation of (−)-sodium O-ethyl ethylphosphonothioate with racemic O-ethyl ethylphosphonochloridate.

The formation of pyrophosphonothionate (III) in reaction (a) does not affect the asymmetric centre in acid (I). This conclusion is based on the well-established mechanism of condensations of this type.[10,11] The attack of the electrophilic phosphorus atom of (±)-O-ethyl ethylphosphonochloridate is directed on the oxygen of the ambident anion derived from acid (I) and not on sulphur. The asymmetric centre P(S) in the resulting (+)-pyrophosphonothionate (III) has, therefore, the same configuration as the starting (−)-acid (I) and is assumed to have the same optical purity.

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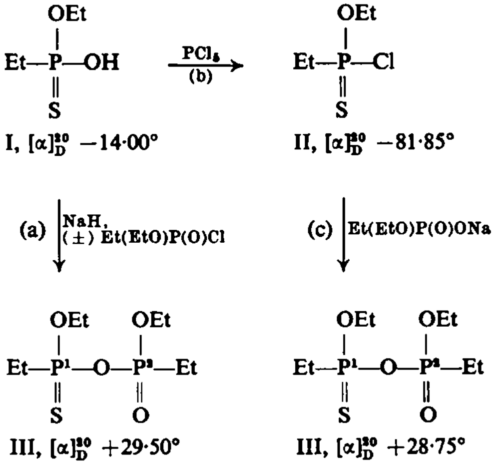
[8] J. R. Cox and O. B. Ramsay, *Chem. Revs.* **64**, 317 (1964).

[9] T. A. Mastryukova, A. E. Shipov and M. I. Kabachnik, *Zh. Obsh. Khim.* **31**, 507 (1961).

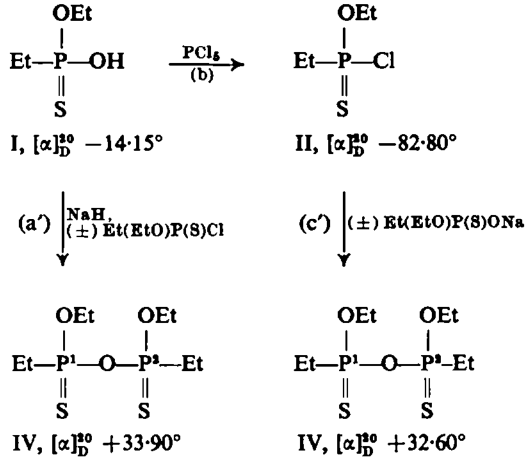
[10] R. A. McIvor, G. A. Grant and C. E. Hubley, *Canad. J. Chem.* **34**, 1611 (1956).

[11] J. Michalski, M. Mikołajczyk and A. Ratajczak, *Chem. & Ind.* 819 (1962); *Bull. Acad. Polon. Sci., Ser. sci. chim.* **13**, 277 (1965).



The comparison of the rotation value of pyrophosphonothionate (III) from reaction (a) with that of III prepared by the reaction sequence (b–c) indicates at least 97·5% optical purity of the chloride (II). Thus, the conversion of the (−)-acid (I) into (−)-chloride (II) should be 98·5% stereospecific if full stereospecificity of the reaction (c) can be assumed. However, some racemization due to the chloride anion exchange[12] is to be expected in this reaction. Reaction (b) seems, therefore, even more stereospecific than indicated above.

A similar reaction sequence has been studied with diethyl ethylpyrophosphonodithionate (IV) as end-product. The results indicate that the minimum stereospecificity of the reaction (b) is 98%.



Since the (+)-pyrophosphonothionate (III) and (+)-pyrophosphonodithionate (IV) prepared by routes (b–c) and (b–c′) are equal in rotation sign to those obtained from reactions (a) and (a′), they must have a configuration at P^1 identical to that of the (−)-acid (I). This may be explained by assuming either subsequent inversions or

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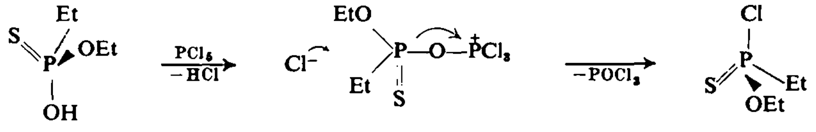
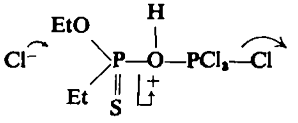
[12] J. Michalski, M. Mikolajczyk, A. Halpern and K. Prószyńska, *Tetrahedron Letters* No. 18, 1919 (1966).

retentions during the reactions (b–c) and (b–c′). The former possibility seems to be valid in this case. By making the very probable assumption that the reactions (c) and (c′) proceed with inversion,[13] the reaction of phosphorus pentachloride with acid (I) should follow the same stereochemical course. This is consistent with result of alkaline hydrolysis of (−)-chloride (II) to (−)-acid (I).[14]

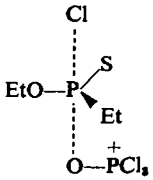
The action of phosphorus pentachloride on acid (I) probably involves in rate-determining step, which is responsible for inversion; a bimolecular attack of the chloride anion on the phosphonium-type intermediate (V), formed in the initial stage of this reaction after hydrogen chloride elimination.

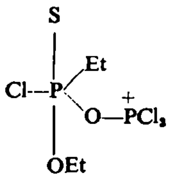

I V II

As proved by TLC, O-ethyl ethylphosphonochloridate is not formed in the reaction considered. This is supporting evidence that the attack of phosphorus pentachloride is directed entirely on the oxygen atom, resembling the phosphorylation of thio-acids by means of acyl halides.[10,11] The arguments advanced by Wiley *et al.*[15] for the mechanism of the reaction of alcohols with phosphine dihalides suggest that a species represented by (VI) is less likely to be involved in the rate-determining transition state.


VI

From the point of view of stereochemical consequences for a second-order nucleophilic displacement at the phosphorus atom, there are three general types of possible mechanisms:[16] (1) inversion mechanism—associated with bipyramidal transition state in which the attacking and the departing groups occupy both axial or both basal positions; (2) retention mechanism—via a transition state with a square pyramid geometry or structure formed by hybridization of an sp^3-orbital with a d$_{xy}$-orbital giving two spd-bonds at 71° and three sp^3-bonds; and (3) racemization mechanism—anticipated for the bipyramidal transition state in which all of the sp^{3}d bonds of the phosphorus atom were energetically equal.


VII


VIII

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[13] J. Michalski, M. Mikolajczyk and J. Omelańczuk, *Tetrahedron Letters* No. 23, 1779 (1965).

[14] J. Michalski and M. Mikolajczyk, *Chem. & Ind.* 661 (1964); M. Mikolajczyk, *Tetrahedron*, in the press.

[15] G. A. Wiley, B. M. Rein and R. L. Hershkowitz, *Tetrahedron Letters* No. 36, 2509 (1964).

[16] R. F. Hudson and M. Green, *Angew. Chem.* 75, 47 (1963).

Since the reaction of phosphorus pentachloride with O-ethyl ethylphosphonothioic acid (I) proceeds with complete inversion of configuration at the thiophosphoryl centre, it follows that the transition states (VII) and (VIII) are to be preferred.

EXPERIMENTAL

Optical activity measurements [Hilger and Watts polarimeter (sensitivity ± 0·01°)]. Neat compounds for all specific rotation determinations.

(±)-O-*Ethyl ethylphosphonochloridothionate* (II) *from* (±)-O-*ethyl ethylphosphonothioic acid* (I). Compound I (3·85 g, 0·025 mole) in CCl_4 (20 ml) was added dropwise at $-5°$ to the stirred suspension of PCl_5, (5·2 g, 0·025 mole) and CCl_4 (25 ml). After the addition had been completed, stirring was continued for 0·5 hr at 0°. Small amounts of unreacted PCl_5 were filtered off. The CCl_4 was removed under red. press. and the residue distilled to give II, 3·1 g (yield 72%), b.p. 49°/2·6 mm, n_D^{20} 1·4930 (lit.[17] b.p. 45°/2·3 mm, n_D^{25} 1·4911). Purity of II was checked by TLC using benzene–AcOEt–$CHCl_3$ (1:1:0·5) as solvent system; R_f 0·865.

(−)- *and* (+)-O-*ethyl ethylphosphonochloridothionates* (II) *from* (−)- *and* (+)-O-*ethyl ethylphosphonothioic acid* (I). The (−)-acid (I), $[\alpha]_D^{20}$ −14·75° (7·7 g, 0·05 mole) in CCl_4 (30 ml) was added dropwise at −10° in 0·5 hr to the stirred suspension of PCl_5 (10·4 g, 0·05 mole) and CCl_4 (60 ml). Stirring was continued for 0·5 hr at +5°. After removal of CCl_4 under red. press., the residue was distilled *in vacuo* to give (−)-chloride (II), 6·7 g (yield 77%) b.p. 22°/0·2 mm, n_D^{20} 1·4931 $[\alpha]_D^{20}$ −73·80° (Found: C, 27·8; H, 6·0; P, 17·4. Calc. for $C_4H_{10}OPSCl$: C, 27·8; H, 5·8; P, 17·95%.)

According to this procedure in other runs optically active chlorides (II), $[\alpha]_D^{20}$ −71·75°, −61·00°, +41·50° were obtained from optically active acids (I) with the corresponding rotation values $[\alpha]_D^{20}$ −14·75°, −14·75°, +8·25°.

Using ether as solvent (−)-chlorides (II), $[\alpha]_D^{20}$ −63·00°, −81·85°, −82·50°, −75·50°, −77·40° were obtained from (−)-acids (I) $[\alpha]_D^{20}$ −11·00°, −14·00°, −14·15°, −14·90°, −15·10°, respectively.

Reaction of (−)-acid (I), $[\alpha]_D^{20}$ −14·90° with PCl_5 in CH_2Cl_2 affords (−)-chloride (II), $[\alpha]_D^{20}$ −31·60°.

(+)-*Diethyl ethylpyrophosphonothionate* (III) *from* (−)-O-*ethyl ethylphosphonothioic acid* (I). The soln of (−)-sodium O-ethyl ethylphosphonothioate, prepared from 3·08 g (0·02 mole) of I, $[\alpha]_D^{20}$ −14·00°, and NaH (0·5 g), in 30 ml 1,2-dimethoxyethane, was cooled to −5° and 3·4 g (0·02 mole) of (±)-O-ethyl ethylphosphonochloridate in 5 ml dimethoxyethane was added dropwise in 0·5 hr. After standing overnight at room temp the solvent was removed. The residue was taken up in ether (50 ml), filtered to remove NaCl, concentrated and distilled to give 3·9 g (yield 71%) III, b.p. 74–75°/0·05 mm, n_D^{24} 1·4670 $[\alpha]_D^{20}$ +29·50°. (Found: C, 35·0; H, 7·35; P, 21·9. Calc. for $C_8H_{20}O_4P_2S$: C, 35·0; H, 7·35; P, 22·6%.)

(+)-*Diethyl ethylpyrophosphonothionate* (III) *from* (−)-O-*ethyl ethylphosphonochloridothionate* (II). Compound II, $[\alpha]_D^{20}$ −81·85°, (2·8 g, 0·0162 mole) was added to the stirred suspension of sodium O-ethyl ethylphosphonate and 1,2-dimethoxyethane (30 ml) at room temp. After 2 days the reaction mixture was worked up as described above for the first preparation of III to give 3·5 g (yield 79%), b.p. 69–71°/0·02 mm, n_D^{24} 1·4672, $[\alpha]_D^{20}$ +28·75°.

Similarly, 1·4 g (−)-chloride (II), $[\alpha]_D^{20}$ −63·00° added to the sodium O-ethyl ethylphosphonate (1·5 g) in 1,2-dimethoxyethane (15 ml) gave 1·5 g (+)-anhydride (III), b.p. 72–73°/0·03 mm, n_D^{27} 1·4650, $[\alpha]_D^{20}$ +22·50 .

(+)-*Diethyl ethylpyrophosphonodithionate* (IV) *from* (−)-O-*ethyl ethylphosphonothioic acid* (I). To the soln of (−)-sodium O-ethyl ethylphosphonothioate, prepared from I, $[\alpha]_D^{20}$ −14·15° (4·62 g, 0·03 mole) and NaH (0·72 g, 0·03 mole), in 1,2-dimethoxyethane (25 ml) (±)-O-ethyl ethylphosphonochloridothionate (II) was added. The mixture was allowed to stand overnight at room temp. After removal of the solvent, ether was added and NaCl filtered off. Then organic layer was washed with water, dried and evaporated. The residue was distilled to give 4·55 g (yield 53%) IV, b.p. 66–68°/0·01 mm, n_D^{27} 1·4980, $[\alpha]_D^{20}$ +33·90°. (Found: C, 33·4; H, 7·0; P, 21·0. Calc. for $C_8H_{20}O_3P_2S_2$: C, 33·1; H, 6·9; P, 21·4%.)

(+)-*Diethyl ethylpyrophosphonodithionate* (IV) *from* (−)-O-*ethyl ethylphosphonochloridothionate* (II). Starting from II, $[\alpha]_D^{20}$ −82·80° and (±)-sodium O-ethyl ethylphosphonothioate, IV was obtained, b.p. 64–66°/0·005 mm, n_D^{19} 1·5011, $[\alpha]_D^{20}$ +32·60°.

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[17] F. Hoffman, D. H. Wadworth and H. D. Weiss, *J. Amer. Chem. Soc.* **80**, 3945 (1958).