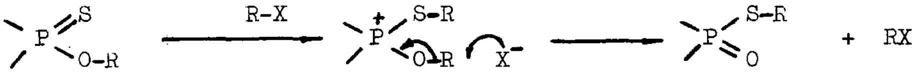
Tetrahedron Letters No.32, pp. 3565-3568, 1968. Pergamon Press. Printed in Great Britain.

CHEMICAL EVIDENCE FOR WALDEN INVERSION AT THIOPHOSPHORYL CENTRE BASED ON PISHSCHIMUKA REACTION. SYNTHESIS OF OPTICALLY ACTIVE N,N-DIETHYLPHOSPHONAMIDIC CHLORIDE

J. Michalski, M. Mikołajczyk, and J. Omelańczuk
Institute of Organic Chemistry, Polish Academy of Sciences, Łódź 40,
Żwirki 36, Poland

(Received in UK 4 March 1968; accepted for publication 13 May 1968)

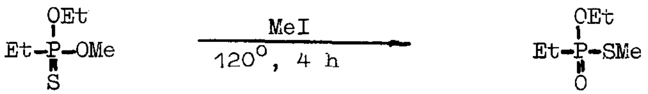
Phosphorus esters containing the P(S) group are very good nucleophiles towards sp^3 carbon. Their reaction with alkyl halides leading to thiol esters is known as Pishschimuka reaction (1).



In accord with the reasonably well established mechanism of the reaction (2) the configuration at the chiral phosphorus atom should be preserved when the optically active thionoester is transformed into thiolo one.

In this laboratory we have found that optically active O-alkyl O-ethyl ethylphosphonothionates can be obtained by the reaction of optically active O-ethyl ethylphosphonochloridothionate, Et(EtO)P(S)Cl, with sodium alkoxides (3). The (-) and (+) O-methyl O-ethyl ethylphosphonothionates, Et(EtO)P(S)OMe, (I), prepared in this manner from optically active phosphonochloridothionates, $[\alpha]_D -76.50^\circ$, $[\alpha]_D +72.60^\circ$, have been found to react with methyl iodide under Pishschimuka reaction conditions to yield optically active O-ethyl S-methyl ethylphosphonothiolates (II)

(a)

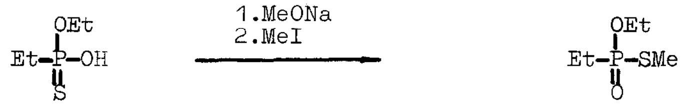


$$\mathrm{Et{-}\overset{OEt}{\underset{S}{P}}{-}OMe} \xrightarrow[120^\circ,\ 4\ \mathrm{h}]{\mathrm{MeI}} \mathrm{Et{-}\overset{OEt}{\underset{O}{P}}{-}SMe}$$

(I), $[\alpha]_D -3.15^\circ$; $+3.00^\circ$ (II), $[\alpha]_D -76.90^\circ$; $+73.75^\circ$

Optically active esters (II) were also obtained by S-methylation of the sodium salt of O-ethyl ethylphosphonothioic acid (III).

(b)

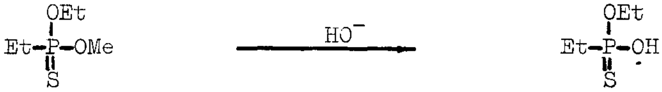


$$\text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{OH} \xrightarrow{\substack{\text{1.MeONa}\\ \text{2.MeI}}} \text{Et}-\overset{\text{OEt}}{\underset{\text{O}}{\text{P}}}-\text{SMe}$$

(III), $[\alpha]_D -13.25^\circ$; $+13.50^\circ$

(II), $[\alpha]_D -86.30^\circ$; $+88.70^\circ$

Reactions (a) and (b) indicate that (-)ester (I) and (-)acid (III) have the same configuration. This is a very important conclusion, for once the **relative** configuration of ester (I) is established it is possible to prove that its alkaline hydrolysis (4) is accompanied by Walden inversion.



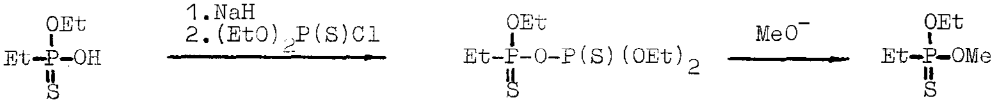
$$\text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{OMe} \xrightarrow{\text{HO}^-} \text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{OH}$$

(I), $[\alpha]_D -2.95^\circ$; $+3.05^\circ$

(III), $[\alpha]_D +7.63^\circ$; -8.00°

The formation of the (+)acid (III) with ca 70% optical activity during hydrolysis may be reasonably explained by competitive attack on sp^3 carbon atom (ca 15%)(5), which would result in the formation of the thioacid (III) of retained configuration

In a similar manner it can be shown that the reaction of optically active dithiopyrophosphonate (IV) with sodium methoxide (4) proceeds with inversion of configuration at the thiophosphoryl centre.



$$\text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{OH} \xrightarrow{\substack{\text{1.NaH}\\ \text{2.(EtO)}_2\text{P(S)Cl}}} \text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{O}-\text{P(S)(OEt)}_2 \xrightarrow{\text{MeO}^-} \text{Et}-\overset{\text{OEt}}{\underset{\text{S}}{\text{P}}}-\text{OMe}$$

(III), $[\alpha]_D -15.10^\circ$

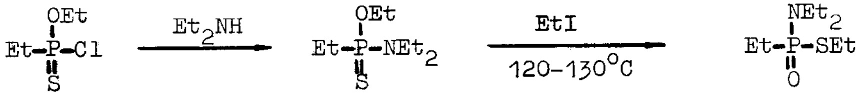
(IV), $[\alpha]_D +30.65^\circ$

(I), $[\alpha]_D +3.05^\circ$

Taking into account the fact that the phosphorylation of (-)acid (III) does not involve any breaking of bonds around the phosphorus atom, formation of (+)ester (I), which has the opposite configuration to that of the original (-)acid (III), establishes the Walden inversion.

Optically active thionoamides are readily obtained by the aminolysis of optically active O-ethyl ethylphosphonochloridothionates Et(EtO)P(S)Cl (V)(6,7).

The reaction of (-)(V) with diethylamine leads to (+)N,N-diethyl O-ethyl ethylphosphonoamidothionate (VI) which undergo readily the Pishschimuka reaction.



(V),$[\alpha]_D$-77.75°; -50.75° (VI),$[\alpha]_D$+55.15°; +36.00° (VII),$[\alpha]_D$-35.20°; -21.50°

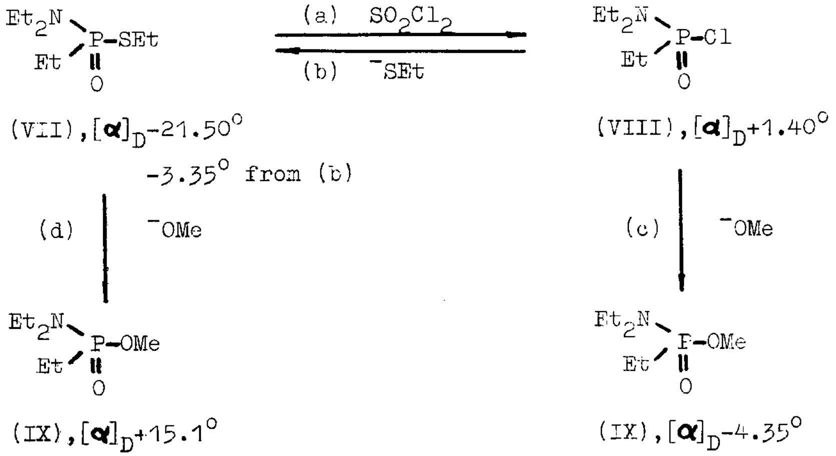
Phosphorus thiol esters react with chlorine to give phosphorochloridates (8).

$$(RO)_2P(O)SR + Cl_2 \longrightarrow (RO)_2P(O)Cl + RSCl$$

The reaction was employed by Green and Hudson (9) and by Michalski and Ratajczak (10) for the preparation of optically active chlorides, RR´P(O)Cl, from the corresponding thiol esters, RR´P(O)SR.

The reaction of the thioloester (VII) with sulphuryl chloride or with chlorine leads to optically active N,N-diethylethylphosphonoamidic chloride (VIII).

In order to elucidate the stereochemistry of the reaction the following transformations were carried out.



(VII),$[\alpha]_D$-21.50°
-3.35° from (b)
(VIII),$[\alpha]_D$+1.40°
(IX),$[\alpha]_D$+15.1°
(IX),$[\alpha]_D$-4.35°

Assuming that the reactions (c) and (d) follow the same steric course (11, 12, 13), it follows that the chlorolysis of ester (VII) occurs with partial inversion of configuration at the phosphorus atom. Reaction (b) allows the relative optical purity of the chloride (VIII) to be estimated at ca 15%. The low optical purity of the chloride (VIII) obtained is probably not caused by racemization occuring during its separation from the reaction mixture but is associated with two competative mechanisms of chlorolysis, an inversion mechanism and a retention mechanism, the first being predominant. It should be pointed out that the optically active chloride (IV) is relatively stable and does not undergo racemization during distillation, as with chlorides of the type Et(EtO)P(O)Cl (10, 11). This makes it useful in studies of the stereochemistry of nucleophilic substitution at a phosphoryl centre P(O).

REFERENCES

(1) P.S. Pishschimuka, J. Russ. Phys.-Chem. Soc., **44**, 1406 (1912).

(2) G. Hilgetag, H. Teichmann, Angew. Chem., **77**, 1001 (1965).

(3) J. Michalski, M. Mikołajczyk, Chem. and Ind., 661 (1964).

(4) J. Michalski, M. Mikołajczyk, J. Omelańczuk, Tetrahedron Letters, 1779 (1965).

(5) J.R. Cox, O.B. Ramsay, Chem. Revs., **64**, 317 (1964).

(6) J. Michalski and M. Mikołajczyk, Chem. and Ind., 661 (1964).

(7) M. Mikołajczyk, Tetrahedron, **23**, 1543 (1967).

(8) C.J.M. Stirling, J. Chem. Soc., 3597 (1967).

(9) M. Green and R.F. Hudson, Proc. Chem. Soc., 227 (1959).

(10) J. Michalski and A. Ratajczak, Chem. and Ind., 1241 (1960); Roczniki Chemii, **37**, 1183 (1963).

(11) H.S. Aaron, J.J. Miller et al., J. Am. Chem. Soc., **84**, 617 (1962).

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

(13) J. Michalski, Bull. Soc. Chim. France, **4**, 1109 (1967).