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STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTION AT THIOPHOSPHORYL CENTRE. AN EXAMPLE OF A WALDEN CYCLE INVOLVING PHOSPHORUS

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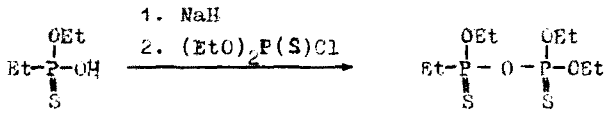
Attempts to devise stereochemical Walden cycles in order to establish inversion of configuration at the asymmetric phosphoryl and thiophosphoryl centres were so far only partly successful (1,2). It was desirable, for the purpose of carrying out stereochemical studies of displacement reaction at the thiophosphoryl centre by Kenyon-Phillips method (3), to have optically active compounds of special properties. With this end in mind the optically active (+)triethyl ethylpyrophosphonodithionate (II), $Et(EtO)P(S)OP(S)(OEt)_2$, was prepared by condensation of (-)sodium O-ethyl ethylphosphonothioate with diethyl phosphorochloridothionate.

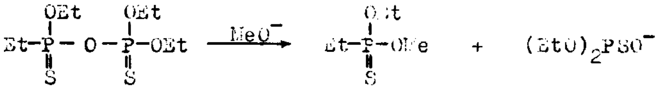


$$Et-\underset{\underset{S}{\|}}{\overset{\overset{OEt}{|}}{P}}-OH \xrightarrow[2.\ (EtO)_2P(S)Cl]{1.\ NaH} Et-\underset{\underset{S}{\|}}{\overset{\overset{OEt}{|}}{P}}-O-\underset{\underset{S}{\|}}{\overset{\overset{OEt}{|}}{P}}-OEt$$

(I), $[\alpha]_D -15.10^\circ$ (II), $[\alpha]_D +30.65^\circ$ *

$[\alpha]_D -14.35^\circ$ $[\alpha]_D +29.85^\circ$

Study of the pyrophosphorodithionate system $>P(S)OP(S)<$ reveals a considerable change of susceptibility of the phosphorus atom to nucleophilic attack when an ester bond is replaced by the direct C-P bond. For instance, the nucleophilic fission of the (+)pyrophosphonodithionate (II) by methoxide anion affords the (+)methyl ethyl ethylphosphonothionate (III) and diethyl phosphorothioic acid.

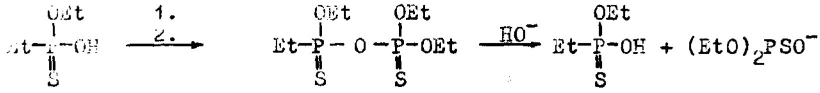


$$\mathrm{Et{-}\overset{OEt}{\underset{S}{P}}{-}O{-}\overset{OEt}{\underset{S}{P}}{-}OEt} \xrightarrow{MeO^-} \mathrm{Et{-}\overset{OEt}{\underset{S}{P}}{-}OMe} + (EtO)_2PSO^-$$

(II), $[\alpha]_D$ +30.65° (III), $[\alpha]_D$ +3.05°

The attack of the reagent is directed on the more electrophilic phosphorus atom containing the C-P bond. This is consistent with the higher reactivity of phosphonothionates than that of phosphorothionates towards nucleophilic reagents (4). The lack of optical activity of the acid fraction is indicative of a unidirectional course of this degradation.

It was reasonable to expect that the attack of the hydroxide anion will follow the same pattern. Hence, alkaline hydrolysis of (+)pyrophosphonodithionate (II) was chosen to prove the inversion at the thiophosphoryl centre. The sample of (+)(II), $[\alpha]_D$ +29.85°, was hydrolysed in an excess of aqueous hydroxide to give, after acidification, (+)O-ethyl ethylphosphonothioic acid (I) and diethyl phosphorothioic acid. (+)O-ethyl ethylphosphonothioic acid (I), $[\alpha]_D$ +12.90°, isolated from the mixture by distillations has a rotation sign opposite to the starting one.

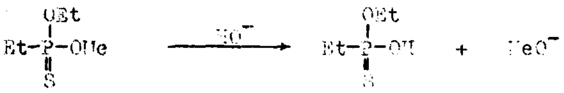


$$\mathrm{Et{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}OH} \xrightarrow[2.]{1.} \mathrm{Et{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}O{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}OEt} \xrightarrow{HO^-} \mathrm{Et{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}OH} + (EtO)_2PSO^-$$

(I), $[\alpha]_D$ -14.35° (II), $[\alpha]_D$ +29.85° (I), $[\alpha]_D$ +12.90°

This shows definitely that reaction of (+)pyrophosphonodithionate (II) with hydroxide anion involves inversion at the asymmetric thiophosphoryl centre since in the formation of (+)anhydride (II) [O-phosphorylation of the (-)acid (I)] no bond is exchanged at the asymmetric phosphorus atom. This reaction sequence comprises the example of a Walden cycle involving phosphorus. The stereospecificity of the hydrolysis is 95%. The decrease of optical activity (10%) of the (+)acid (I) in comparison with the starting (-)acid (I) is most likely to be due to other factors than retention mechanisms.

In view of the reasonable assumption that the nucleophilic attack of the hydroxide and of the methoxide anions on (+)pyrophosphonodithionate (II) follows the same steric course (5), (+)ester (III) is expected to have a configuration like that of (+)acid (I). Moreover, alkaline hydrolysis of (+)ester (III) affords (-)acid (I).

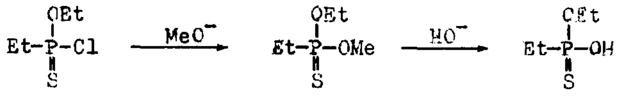


$$\mathrm{Et{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}OMe} \xrightarrow{HO^-} \mathrm{Et{-}\overset{\displaystyle OEt}{\underset{\displaystyle S}{P}}{-}OH} + MeO^-$$

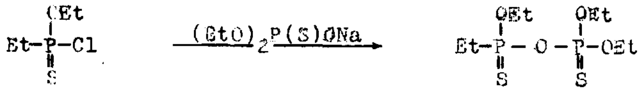
(III), $[\alpha]_D$ +3.05° (I), $[\alpha]_D$ -3.00°

Therefore, alkaline hydrolysis of (+)ester (III) should occur with inversion of configuration.

Besides the reactions outlined above, (-)ester (III) and (+)pyrophosphonodithionate (II) were synthesized starting from the (-)O-ethyl ethylphosphonochloridothionate (IV)(6).



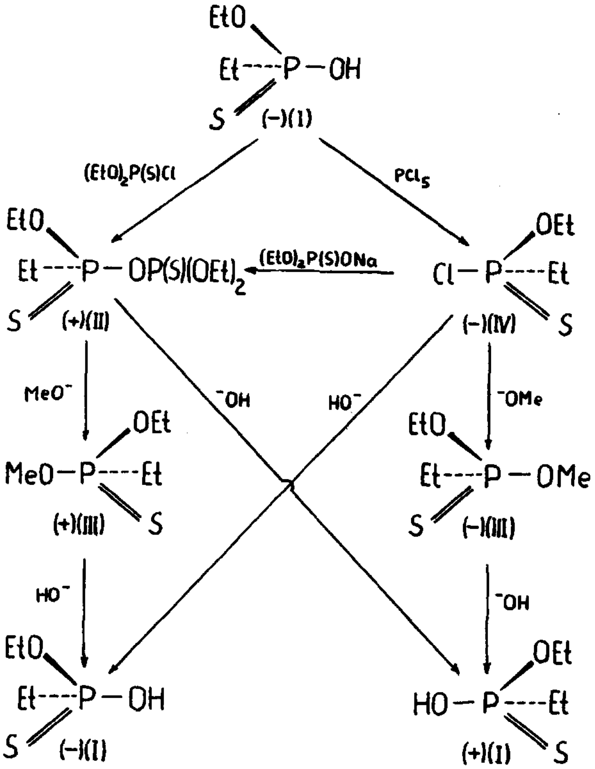
(IV), $[\alpha]_D$ -77.25° (III), $[\alpha]_D$ -2.95° (I), $[\alpha]_D$ +7.63°



(IV), $[\alpha]_D$ -70.00° (II), $[\alpha]_D$ +26.05°

The fact that (-)phosphonochloridothionate (IV) and (+)pyrophosphonodithionate (II) can be converted by methoxide anion into methyl ethyl ethylphosphonothionate (III) of opposite configurations, strongly supports the assumption that (-)(IV) and (+)(II) have also opposite configurations. Hence, the reaction of (-)acid (I) with phosphorus pentachloride and conversion of (-)(IV) into (+)(II) should proceed with inversion.

The interrelations and proposed relative configurations are represented by the scheme given below.


(−)(I)
(EtO)2P(S)Cl
PCl5
(+)(II)
(EtO)2P(S)ONa
(−)(IV)
MeO⁻
⁻OH
HO⁻
⁻OMe
(+)(III)
(−)(III)
HO⁻
⁻OH
(−)(I)
(+)(I)

REFERENCES

(1). M. Green, R.F. Hudson, [J.Chem.Soc., 3883 (1963)] have been showed that alkaline hydrolysis of an optically active diethyl methylpyrophosphonodithionate gives optically inactive O-ethyl methylphosphonothioic acid. This result is strongly in favour of the inversion accompanying the hydrolysis.

(2). A. Ratajczak, Bull.Acad.Polon.Sci., 12, 145 (1964).

(3). E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill Comp., Inc., New York, 1962, p. 117.

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

(5). M. Green, R.F. Hudson, J.Chem.Soc., 540, (1963).

(6). J. Michalski, M. Mikołajczyk, Chem. and Ind., 661 (1964); Chemical Communications, 35 (1965).

* Neat compounds were used for all specific rotation determinations mentioned in the paper.