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REARRANGEMENT OF S-PHOSPHORYLISOTHIOUREAS INTO N-PHOSPHORYL-THIOUREAS: STEREOCHEMISTRY AT PHOSPHORUS AND MECHANISM

MARIAN MIKOŁAJCZYK*, PIOTR KIEŁBASINSKI and ANNA SUT

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulphur Compounds, 90-362 Łódź, Boczna 5, Poland

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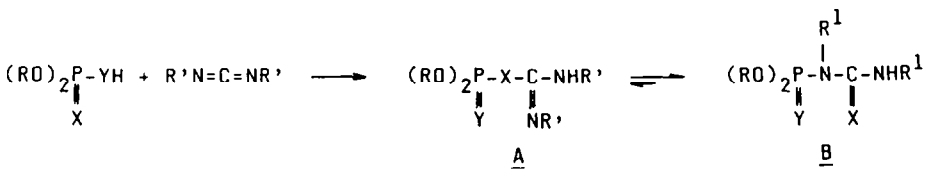
Abstract - Stereochemistry of the rearrangement of S-phosphorylisothioureas into N-phosphorylthioureas has been investigated using two chiral phosphorothioic acid: cyclic 4-methyl-2--oxo-2-mercapto-1,3,2-dioxaphosphorinane (1) and acyclic, optically active O-methyl-O-1-naphthyl phosphorothioic acid (2). Configuration at phosphorus in N-phosphorylthioureas 4 and 9, obtained in the reaction of these thioacids with various carbodiimides, has been established by means of chemical correlation and CD spectra. The title rearrangement has been shown to proceed with full retention of configuration at phosphorus. The stereochemistry of the rearrangement under discussion, as well as the different reactivity of various types of phosphorus thioacids towards carbodiimides have been explained in terms of the mechanism involving pseudorotation of a pentacovalent phosphorus intermediate.

INTRODUCTION

As a part of a general program on the reactions of carbodiimides with thio- and selenoacids[1], we have recently found that the reaction of carbodiimides with phosphorothioic, phosphorodithioic and phosphoroselenoic acids affords in the first step S-(Se)-phosphorylisothio(seleno)-ureas (A) which undergo facile rearrangement to the stable and isolable N-phosphorylthio(seleno) ureas (B)[2] (Scheme I).

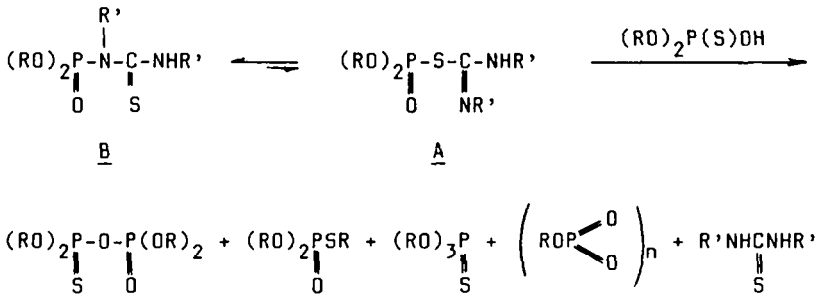
Scheme I



X = S, Se
Y = O, S

Moreover, we have also shown that the phosphorylating properties of these adducts are strongly dependent on their conformation which is, in turn, determined by the nature of the substituents R' connected with the nitrogen atom. Bulky substituents force a special geometry of N-phosphorylthio(seleno)ureas (B) which makes possible their reverse rearrangement to S(Se)-phosphorylisothio(seleno)ureas (A) acting as real phosphorylating agents. Therefore, N-phosphorylthioureas (B)obtained from dicyclohexylcarbodiimide (DCC) and diisopropylcarbodiimide (DP^{i}C), in contrast to those prepared from dibenzylcarbodiimide (DBC) and diarylcarbodiimides, react with a second molecule of thioacid yielding a mixture of the products shown in Scheme II[3].

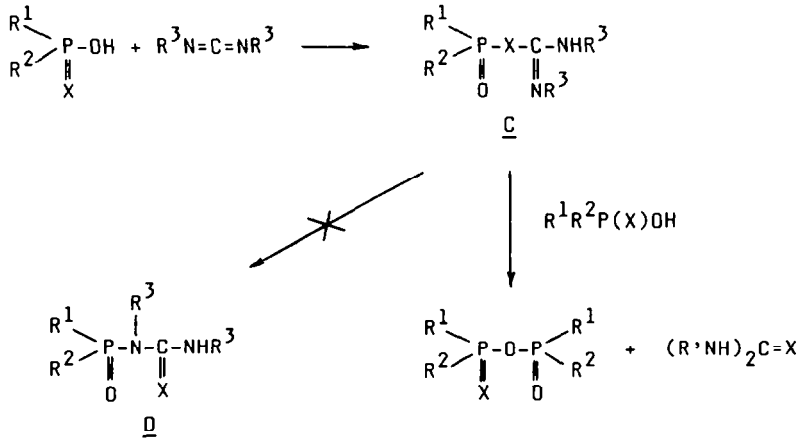
Scheme II



R' = c-Hex, i-Pr

In contrast to the complex course of the reactions described above, the reactions of carbodiimides with phosphoric acids and all kinds of organophosphorus acids containing one or two C-P bonds occur in a much simpler way. In these cases the isourea-type intermediates (C) do not isomerize to N-phosphorylated ureas (D) but react directly with the next acid molecule to give the corresponding anhydrides and ureas (Scheme III).

Scheme III



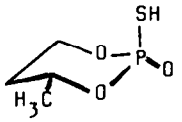
a) R^1=R^2=AlkO, ArO, X=O
b) R'=Alk, Ar, R^2=AlkO, X=O,S,Se
c) R'=R^2=Alk, Ar, X=O,S,Se

It is quite reasonable to assume that the differences in reactivity of various organophosphorus acids towards carbodiimides mentioned above may be, at least partially, dependent on the ability of the initially formed adducts A and C to

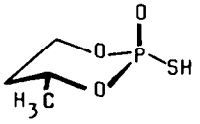
undergo isomerization (reversible or irreversible) to their N-phosphoryl isomers B and D. This raises the questions concerning the mechanism of this rearrangement. The present research was undertaken to determine the stereochemistry of the S-N phosphoryl group migration in S-phosphorylisothioureas.

RESULTS AND DISCUSSION

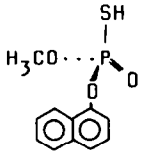
Two types of the model, chiral phosphorothioic acids were used in our studies. The first was a cyclic 4-methyl-2-oxo-2-mercapto-1,3,2-dioxaphosphorinane (1) which exists in two diastereoisomeric forms cis-1 and trans-1 easily available in the diastereoisomerically pure state[4]. The second one was an optically active, acyclic O-methyl-O-naphthyl phosphorothioic acid (2)[5] the absolute configuration of which has recently been established in our laboratory by an X-ray analysis[6].



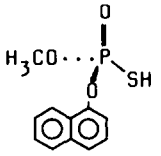
trans-1



cis-1

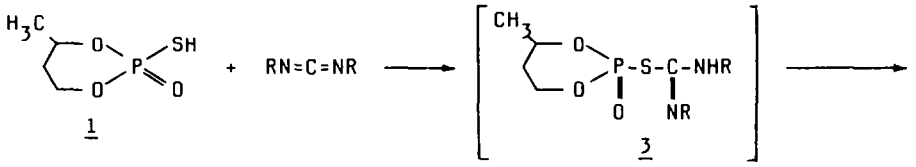


(+)-R-2

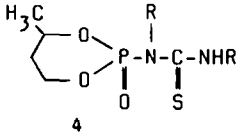


(-)-S-2

In the first set of experiments each diastereoisomer of 1 was reacted with a series of carbodiimides to give the corresponding N-phosphorylthioureas 4 via the isomerization of the transiently formed S-phosphorylisothioureas 3.



1 + RN=C=NR → [3] →



4

a, R = Ph
b, R = $PhCH_2$
c, R = p-$MeOC_6H_4$

Some physical and spectral properties of the adducts 4 obtained in this way are collected in Table I.

The most important observation is that the reactions afforded in all cases the diastereoisomerically pure adducts 4 as can be seen from the ^{31}P-NMR spectra. This unequivocally proves that the rearrangement of 3 to 4 proceeds in a stereospecific manner.

To determine the configuration at phosphorus of the N-phosphorylthioureas 4 and in this way the stereochemistry of the 3-4 isomerization we carried out a series of chemical transformations of known stereochemistry for the diastereoisomeric adducts 4a (R=Ph). This chemical correlation is shown in Scheme IV. In the first step, the two diastereoisomeric phosphoroanilidates 7 have been obtained according to the procedure described by Stec and Łopusiński[7] starting from trans- and cis-4-methyl-2-hydrogen-2-oxo-1,3,2-dioxaphosphorinanes (5).

Table I. Physical and Spectral Data of Adducts 4

Configuration of 1	R	N-(4-methyl-2-oxo-1,3,2-dioxaphosphorinanyl)thiourea (4)[a]			
		Symbol	^{31}P [ppm] ($CHCl_3$, H_3PO_4)	$^4J_{P-CH_3}$ [Hz]	m.p. [°C]
cis	Ph	trans-4a[b]	-7.4	3.0	149-153
trans	Ph	cis-4a[b]	-10.4	2.5	134-136
cis	$PhCH_2$	trans-4b[c]	-1.3	2.75	105-107
trans	$PhCH_2$	cis-4b[c]	-3.5	1.75	118-120
cis	p-$MeOC_6H_4$	trans-4c	-6.3	2.77	142-145
trans	p-$MeOC_6H_4$	cis-4c	-9.9	2.45	74-76

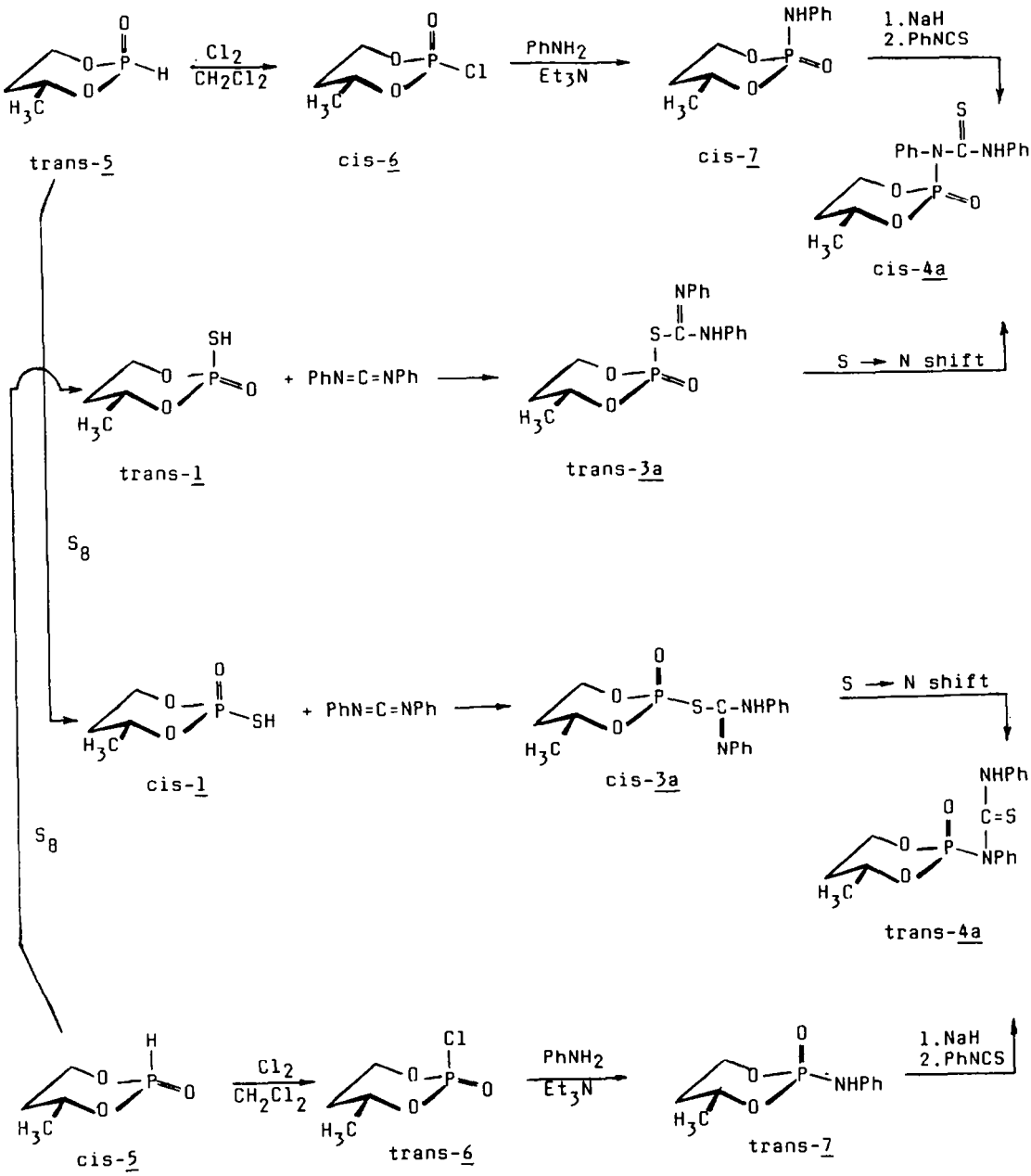
a) for all compounds satisfactory analytical values for C,H,N,P and S (within ± 0.3%) have been obtained after crystallization from benzene;
b) on the basis of the chemical correlation;
c) on the basis of X-ray analysis.

These dioxaphosphorinanes serve also as substrates in the stereospecific synthesis of cis- and trans-1. The two-step synthesis of 7 from 5 results in the net inversion at phosphorus. Then, the two diastereoisomeric anilidates 7 were converted stereospecifically into the corresponding N-phosphorylthioureas 4 by the treatment with sodium hydride followed by phenyl isothiocyanate. Since the conversion of 7 into 4 proceeds without configurational change at phosphorus (it takes place at the nitrogen atom), it is obvious that cis-7 is transformed into cis-4a and from trans-7 trans-4a is obtained. Comparison of the physical and spectral properties of the adducts obtained from 7 and from thioacids 1 revealed that the reaction of cis-1 with diphenylcarbodiimide gives trans-4a and the treatment of trans-1 with diphenylcarbodiimide results in the formation of cis-4a. Additionally, the configuration of the adduct 4b obtained from cis-1 and DBC has been assigned on the basis of an X-ray analysis to be trans[8]. All the experimental facts discussed above lead to the conclusion that the S-N migration of the cyclic phosphoryl moiety proceeds with full retention of configuration at phosphorus.

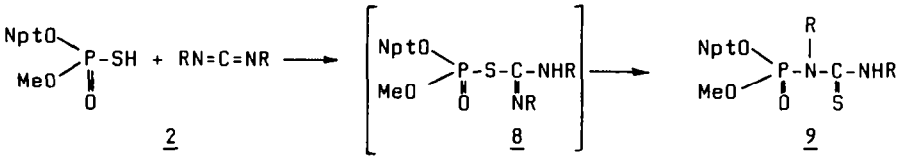
To check whether the same stereochemistry will be observed with an acyclic phosphoryl grouping, optically active (+)-(R)-O-methyl O-1-naphthyl phosphorothioic acid (2) was condensed with four carbodiimides and was found to afford the corresponding optically active adducts 9. Also in this case, the formation of 9 appeared to be entirely stereospecific as seen from the NMR spectra of 9 taken in the presence of chiral shift reagent. This means that the rearrangement of the primary adducts 8 to 9 is stereospecific. Some physical and spectral data of the adducts 9 are summarized in Table II.

Similarly as in the case of the adducts 4 obtained from 1, it was necessary to establish the configuration at phosphorus in the adducts 9 solving in this way the question of the stereochemical course of the 8-9 isomerization. The reactions performed to correlate the thioacid (+)-R-2 with the adduct 9a are shown in Scheme V and VI. At first, we accomplished the conversion of (+)-R-2 into optically active phosphoroanilidate (+)-12 in three steps involving (a) methylation of (+)-R-2 with methyl iodide in the presence of sodium bicarbonate(b) chlorolysis of the phosphorothiolate (+)-10 by means of elemental chlorine in CCl_4 solution and (c) the reaction of the phosphorochloridate (+)-11 with aniline giving the required phosphoroanilidate (+)-12. Then, we

Scheme IV



tried to transform (+)-12 into the corresponding N-phosphorylthiourea 9a by the addition of phenylisothiocyanate to the sodium salt of (+)-12. However, in contrast to our expectations this reaction resulted in the formation of diphenylcarbodiimide (DPC) and the starting thioacid 1 with inverted configuration at phosphorus i.e. (-)-S-2. The partial loss of its optical activity is most probably due to the fact that the phosphorochloridate (+)-R-11 was not obtained in optically pure state. It should be noted that, although the reactions sequence presented in Scheme V constitutes a new Walden inversion cycle for



a, R = Ph
b, R = $PhCH_2$
c, R = c-Hex
d, R = $Cl\text{-}C_6H_4$

Npt = 1-naphthyl

Table II. Physical and Spectral Data of the Adducts 9

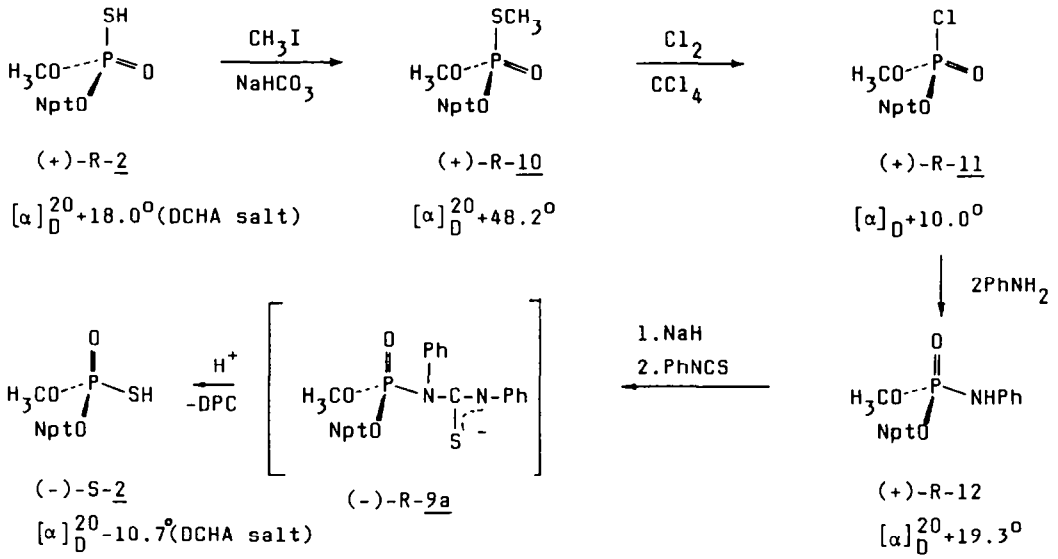
$[\alpha]_D^{20}$ of the DCHA salt of the thioacid 2	R	N-(O-methyl-O-1-naphthyl)phosphoryl-thiourea (9)			
		Symbol	^{31}P[ppm] ($CHCl_3$,H_3PO_4)	$[\alpha]_D^{20}$ [b]	m.p. [°C]
+18°	Ph	9a [a]	-3.5	+64.6°	96-97
+18°	$PhCH_2$	9b	0.8	- 5.1°	oil
+18°	cyclohexyl	9c	-0.1	- 9.5°	oil
+18°	p-$Cl\text{-}C_6H_4$	9d	-3.8	+47°	98-103

a) for 9a satisfactory analytical values for C,H,N,P and S(within ± 0.3%) have been obtained
b) measured in $CHCl_3$

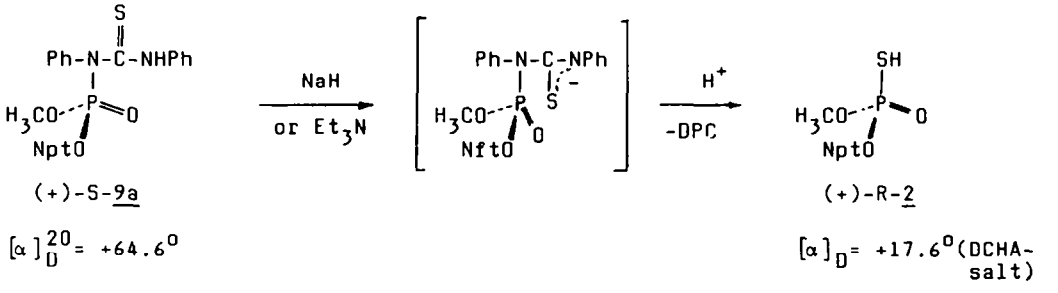
phosphorothioic acids, it does not permit to ascribe the absolute configuration to all the compounds involved, as well as to establish the configuration of optically active 9a which here could not be isolated. This is mainly due to some uncertainties concerning the steric course of the chlorolysis of (+)-10 and aminolysis of (+)-11. By making a reasonable assumption that the thioacid (-)-S-2 arises from the transiently formed anionic form of 9a via the Emmons-Wadsworth type fragmentation, we attempted to perform a similar fragmentation using the adduct (+)-9a already obtained from (+)-R-2 and DPC. It was found that (+)-9a on treatment with sodium hydride or triethylamine affords the same enantiomer of the thioacid 1 from which it has been synthesized and DPC. By analogy with the Emmons-Wadsworth reaction of phosphonoanilidates and cyclic phosphoroanilidates[9], it is quite reasonable to assume that under basic conditions retention at phosphorus is also accompanying the fragmentation of (+)-9a in (+)-R-2. Hence, (+)-9a should have the (+)-S-configuration. Scheme VI shows the reaction discussed above and the configurational relationship between (+)-R-2 and (+)-(S)-9a. The fact that (+)-9a has the S configuration at phosphorus indicates also that the rearrangement of 8a in (+)-9a occurs also with retention at phosphorus. Thus, the migration of both acyclic and cyclic phosphoryl group from sulphur to nitrogen in S-phosphorylisothioureas is a stereoretentive process.

The results discussed above allowed us to comment the stereochemistry of the reactions presented in Scheme V. First of all, the transiently formed N-phosphoryl thiourea 9a, whose fragmentation leads to the thioacid (-)-S-2, must be the (-)-R-enantiomer of 9a e.g. its absolute configuration is opposite

Scheme V



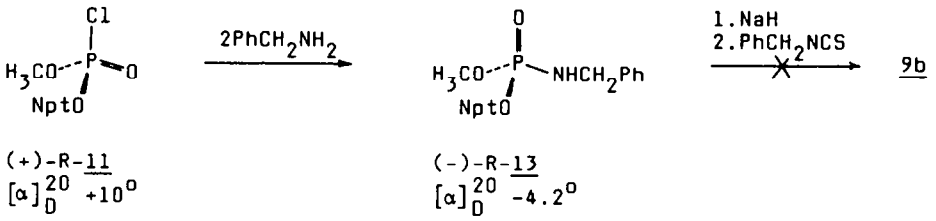
Scheme VI



to that of the starting thioacid (+)-R-2. Conseqently, the phosphoroanilidate (+)-12 which is a source of (-)-R-9a and (-)-S-2, for the reasons discussed above, should also have the R-configuration. This means that one of the two reactions shown in Scheme V of unknown stereochemistry (chlorolysis of (+)-10 and aminolysis of (+)-11) must occur with retention, while the other with inversion of configuration at phosphorus. Taking into account the precise mechanistic studies on the chlorolysis of the phosphorothiolates carried out by Michalski and coworkers[10] as well as the results published by Inch and Hall[11,12] it is quite probable that chlorination of (+)-10 leading to (+)-11 is accompanied by retention and its reaction with aniline by inversion of configuration at phosphorus. Therefore, the R-configuration may be ascribed to (+)-phosphorochloridate 11.

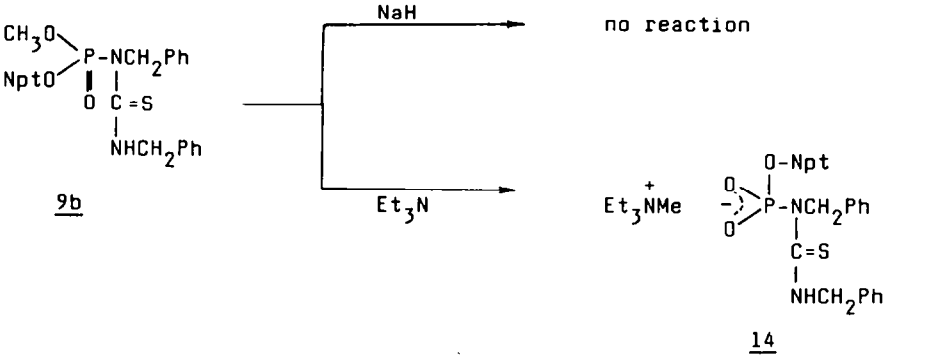
In an extension of this set of experiments, (+)-phosphorochloridate 11 was also treated with benzylamine to give N-benzylamide (-)-13 (with inversion of configuration). However, our attempts to convert it into the corresponding N-phosphorylthiourea 9b using sodium hydride and benzylisothiocyanate were unsuccessful. Similarly, we were not able to transform the adduct (-)-9b, obtained from (+)-R-2 and DBC, into the starting thioacid 1. Whereas with sodium

hydride no reaction was observed, the treatment of (-)-9b with triethylamine resulted in the formation of the achiral demethylation product 14.



(+)-R-11 $[\alpha]_D^{20}$ +10°

(-)-R-13 $[\alpha]_D^{20}$ -4.2°



In this situation we have measured the circular dichroism spectra (CD) for the enantiomeric amide (+)-13 (obtained from the thioacid (-)-S-2) and the adduct (-)-9b. It was found that in the CD-spectrum of (+)-13 there is a strong positive Cotton effect at about 220 nm. The adduct (-)-9b exhibits two positive Cotton effects at about 258 and 225 nm (Figure I). Since both compounds are very similar in structure and exhibit Cotton effects at almost identical wavelengths, it seems reasonable to assume that both (+)-13 and (-)-9b are homochiral; that is they have the same configuration S. This result provides the additional support that the S-N migration in 8b leading to 9b occurs with retention of configuration.

The results described above clearly indicate that the rearrangement of S-phosphorylisothioureas (A) into N-phosphorylthioureas (B) occurs stereospecifically with retention of configuration at phosphorus. In addition, the preliminary results of our kinetic studies revealed that this rearrangement reaction exhibits first-order kinetics[13].

These stereochemical and kinetics data can be explained in terms of the mechanism shown in Scheme VII involving a pentacovalent phosphorus intermediate. In the first step of the rearrangement the nitrogen atom in S-phosphorylisothiourea (A) attacks phosphorus leading to the formation of a betaine-type phosphorane intermediate (E). According to the commonly accepted assumption[15] that the bond forming and bond breaking processes occur only at apical positions of a trigonal bipyramidal intermediate, the phosphorane (E) should undergo pseudorotation to put sulphur in that position. Cleavage of the P-S bond in a new phosphorane (F) formed should result in N-phosphorylthiourea (B) with retained configuration at phosphorus.

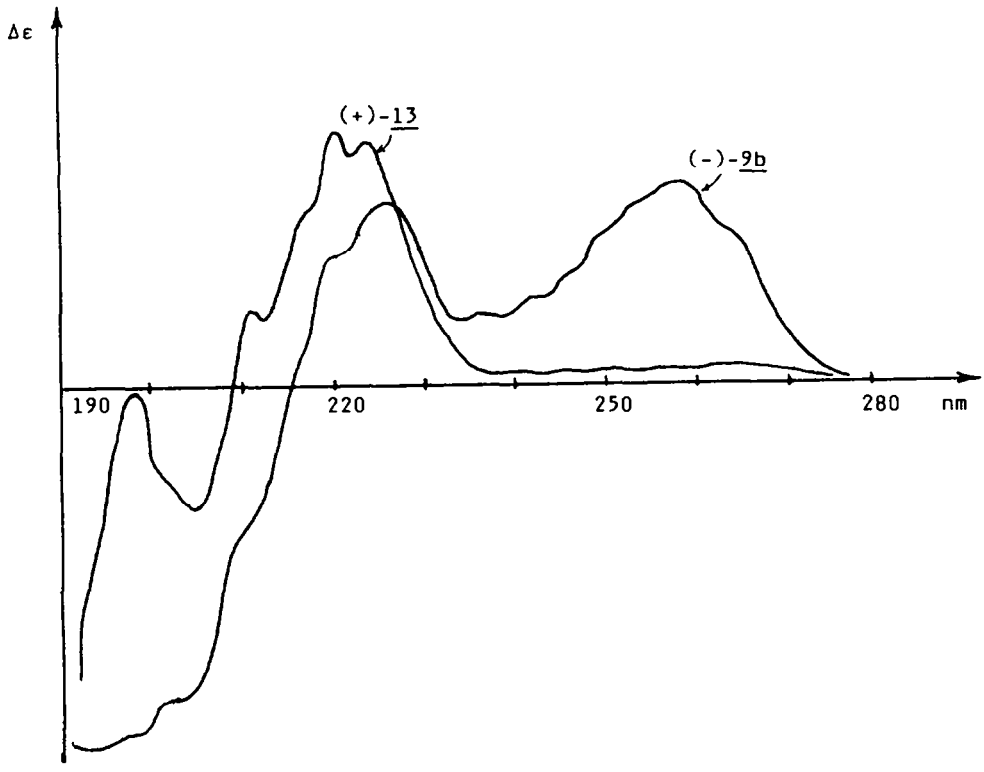
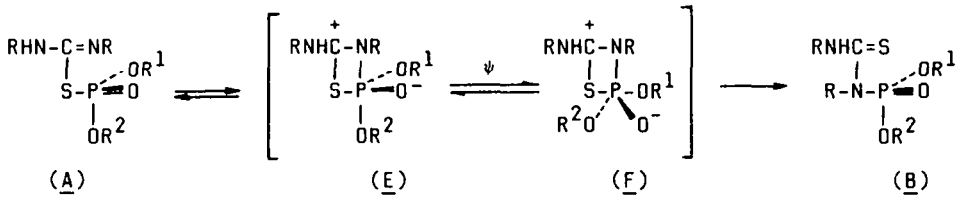


Fig.I. CD-spectra of (+)-13 and (-)-9b

Scheme VII



The pseudorotation process postulated here is essential because it can be accounted for the fact that S-phosphonyl- and S-phosphinylisothioureas, in contrast to S-phosphoryl analogues, do not undergo isomerization to N-phosphonyl- and N-phosphinylthioureas, respectively. The main reasons for this is that the C-P bond provides a constraint to pseudorotation[15] by prefering strongly an equatorial position in a trigonal bipyramidal pentacovalent phosphorus intermediate[16]. It is believed that in this way the different behaviour of various types of phosphorus acids towards carbodiimides may be interpreted.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were measured with a Perkin-Elmer R-12 and ^{31}P-NMR spectra with a FT Jeol FX-60 instrument. Mass spectra were recorded with a LKB 2091 mass spectrometer. Melting points are uncorrected.

Cis- and trans-4-methyl-2-oxo-2-mercapto-1,3,2-dioxaphosphorinanes (1) were prepared from the corresponding cyclic phosphites according to the procedure described previously[4]. Cis- and trans-2-N-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (7) were prepared according to the method of Stec and Łopusiński[7]. Optically active O-methyl-O-1-naphthyl phosphorothioic acid (2) was obtained according to the procedure described by us[5] and O-methyl-O-1-naphthyl-S-methyl phosphorothioate [(+)-R-10] - according to the procedure published by Akintonwa[17]

N-phosphorylthioureas (4 and 9) from carbodiimides and thioacids (1 and 2) - - general procedure. A solution of a thioacid (1 or 2) (0.01 mol) in ether (10 - -30 ml) was slowly added dropwise at room temperature to a solution of the corresponding carbodiimide (0.01 mol) in ether (10-30 ml). After the addition was complete, ether was evaporated to give the desired adduct in a quantitative yield.

Physical and spectral properties of the products (4 and 9) are collected in Tables I and II.

Correlation of configuration

Preparation of O-methyl-O-1-naphthyl phosphorochloridate (11). A solution of chlorine (0.21 g; 2.9 mmole) in CCl_4 (15 ml) was added slowly to a solution of O-methyl-O-1-naphthyl-S-methyl phosphorothioate (10) (0.78g; 2.9 mmole; $[\alpha]_D^{20}$+48.2°) in CCl_4 (15 ml). The resulted mixture was stirred at room temperature for 0.5 h and then evaporated under reduced pressure to give the crude product (11) (0.68g; 90%); $[\alpha]_D^{20}$ +10° ($CHCl_3$, C=1.59); ^{31}P NMR (CCl_4,H_3PO_4): δ=0.2 ppm; ^1H NMR ($CDCl_3$,TMS):δ =1.7(d,3H;J_{P-OCH_3}=14 Hz); 4.7-5.9 ppm (n,7H). This compound was used without further purification to the synthesis of phosphoroamidates (12 and 13). In a similar manner starting from 10 and SO_2Cl_2 phosphorochloridate 11 was obtained in 80% yield; $[\alpha]_D^{20}$ +4°($CHCl_3$,c=1.5).

Preparation of O-methyl-O-1-naphthyl-N-phenyl phosphoroamidate (12). A solution of the freshly prepared (+)-11 (0.9 g,3.5 mmole) in benzene (15 ml) was added dropwise to the solution of aniline (0.65 g; 7 mmole) in benzene (15 ml) and the mixture was stirred overnight at room temperature. Aniline hydrochloride formed was filtered off and the filtrate was evaporated to give 1g (91%) of a crude oily product, which was purified by preparative t.l.c. on silica gel using ethanol-chloroform (1:20) as an eluent. Yield of pure 12: 0.55g (50%);$[\alpha]_D^{20}$ +19.3° ($CHCl_3$, c=0.7); ^{31}P NMR ($CHCl_3$,H_3PO_4): δ=-0.6 ppm; ^1H NMR ($CDCl_3$,TMS): δ=3.9 (d,3H,J_{P-OCH_3}=12Hz); 6.7-8.2 ppm (m,13H). M.S.: m/e=313(M^+,100).

O-methyl-O-1-napthyl-N-benzyl phosphoroamidate (13) was prepared and purified in a similar way. Yield of the pure product: 55%; $[\alpha]_D^{20}$ -4.2° ($CHCl_3$, c=1.13). ^{31}P NMR ($CDCl_3$, H_3PO_4): δ =4.9 ppm; M.S.: m/e=327(M^+,100).

Reaction of 12 with phenyl isothiocyanate.NaH (0.24g; 10 mmole) was added to the solution of 12 (3.13g; 10 mmole) in freshly distilled from sodium dioxane (40 ml). The suspension obtained was stirred for 0.5 h and phenyl isothiocyanate (1.37g; 10.2 mmole) was added. Stirring was continued overnight. The solvent was removed under reduced pressure and the residue was dissolved in water. The aqueous solution was acidified with 10% CH_3COOH and extracted with $CHCl_3$. The organic solution was dried over $MgSO_4$ and evaporated to give 0.15g (59%) of the crude acid (2). The crude acid was dissolved in ether and dicyclohexylamine was added. The precipitated dicyclohexylammonium salt of 2 was filtered off and dried: $[\alpha]_D^{20}$ -10.7°($CHCl_3$,c=1).

Basic Cleavage of 9a to DPC and 2. Triethylamine (0.23g; 2.2 mmole) was added to the solution of 9a (0.52g;1.2 mmole $[\alpha]_D^{20}$+64.6°) in benzene (15 ml) and the mixture was stirred overnight at room temperature. Water was added and the layers were separated. The aqueous layer was acidified with a diluted solution of HCl and extracted with ether. The etheral solution was dried over $MgSO_4$ and evaporated to give 0.237g (80%) of the acid (2), which was transformed into its dicyclohexylammonium salt: $[\alpha]_D^{20}$ +17.6°($CHCl_3$, c=1).

Reaction of trans-7 with phenyl isothiocyanate. NaH (0.24g; 10 mmole) was added to the solution of trans-2-N-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (trans-7) (2.27g; 10 mmole) in dioxane (40 ml). The resulted suspension was stirred for 0.5h and phenyl isothiocyanate (1.37g; 10.2 mmole) was added. Stirring was continued overnight. The solvent was removed and water was added. The solution was acidified with 10% CH_3COOH and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and the solvent was removed to give trans-4a in a 66% yield; m.p.=149-153°. ^{31}P NMR ($CHCl_3$,H_3PO_4): δ=-7.4 ppm. In a similar manner cis-4a was obtained from cis-7 and phenyl isothiocyanate in a 60% yield; m.p.= =134-136°.^{31}P NMR ($CHCl_3$,H_3PO_4): δ=-10.4 ppm.

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16. With this reagrd, it should be noted that our attempts to catch the intermediate of the type E or F in the reaction between 4,4,5,5-tetramethyl-2- -thioxo-2-mercapto-1,3,2-dioxaphospholane and DCC or DBC by means of low temperature FT ^{31}P NMR spectroscopy were negative.

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